

ABSTRACT CONTENTS EAOM 2010 LONDON CONFERENCE

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A. Original Research Basic Science

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The ECF sigma factor regulates transport/maturation of gingipains in *P. gingivalis*

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Objectives: The Gram-negative anaerobic bacterium *Porphyromonas gingivalis* (*P. gingivalis*) has been recognized as a major pathogen in the development and progression of chronic periodontitis. To colonize and survive in the gingival crevice, *P. gingivalis* must regulate gene expression in response to the various extracellular changes. Some bacteria utilize sigma factor proteins of the extracytoplasmic function (ECF) subfamily. In this study, we have investigated the ECF sigma factor PGN_0274 to determine its role in this bacterium.

Methods: To elucidate the role of PGN_0274 in *P. gingivalis*, a chromosomal mutant carrying a disruption of PGN_0274 was constructed. Haemagglutination and proteolytic activities (Kgp, Rgp) were measured in the PGN_0274-defective mutant. Real-time PCR analysis was used to assess transcription of kgp and rgp in the PGN_0274-defective mutant. In the PGN_0274-defective mutant, the localization and maturation of Kgp was investigated by SDS PAGE/western immunoblotting analysis.

Results: The PGN_0274-defective mutant formed non-pigmented colonies on the blood agar plates, which is similar to the phenotype of proteinase-defective mutants in *P. gingivalis*. Kgp and Rgp activities of the PGN_0274-defective mutant decreased remarkably compared with the wild-type. In addition, the PGN_0274-defective mutant showed no haemagglutination activity. The results of real-time PCR analysis indicated that kgp was transcribed in PGN_0274-defective mutant as well as the wild-type. These results suggested that PGN_0274-defective mutant did not affect gene expression of kgp at the level of transcription. Immunoblotting analysis using anti-Kgp antiserum showed that Kgp's were poorly secreted into an extracellular portion but the precursor forms of Kgp and adhesins were accumulated within the cells of the PGN_0274-defective mutant. Taken together, our findings indicated that the secretion of Kgp is deranged in the PGN_0274-defective mutant.

Conclusions: These results suggest that PGN_0274 is required for secretion of matured gingipains in the bacterium.

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Association of proteinases of *Porphyromonas gingivalis* with endogenous vesicles

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Objectives: Arginine-gingipain (RGP) and lysine-gingipain (KGP) are major proteinases of *P. gingivalis* and they are important in the pathogenesis of periodontitis. Two types of proteinases were found to exist in the culture supernatant, free from any cellular components and vesicle-bound forms. Since vesicles of gram-negative bacteria may contribute to the transportation of their virulence factors to the host cells, we undertook to investigate the interaction of proteinases and endogenous vesicles.

Methods: Vesicles were collected from the culture supernatants by ammonium sulfate precipitation (40% saturation) and centrifugation. The vesicles were solubilized by a detergent. Proteinase and peptidase activities were determined using chromogenic synthetic substrates.

Results: Although the molecular masses of RGP and KGP in the culture supernatant had previously been determined as 43 kDa and 46 kDa, respectively, the molecular masses of these proteinases solubilized from the vesicles were estimated to be over 1,500 kDa, since they were expelled from the molecular sieving on Sephacryl S-300 gel filtration. Interestingly, the occurrence of the macromolecular size could not be observed in other enzymes tested such as mono-, di- and tripeptidyl peptidases as well as alkaline phosphatase. Therefore, this event may occur specifically in RGP and KGP. When vesicles and culture supernatants containing free RGP and KGP were mixed and incubated, neither RGP nor KGP found to bind to vesicles. Both RGP and KGP bound to the vesicles were more stable than the unbound forms in the heat treatment at 60 °C.

Conclusions: The cellular locations of proteinases of *P. gingivalis* in the culture supernatant, crude extract, vesicle and envelope were determined and molecules of the proteinases bound to the vesicle were confirmed to increase the molecular size.

3

Profile of intracellular IL-2, IL-4, IL-10 and IFN- γ in peripheral blood mononuclear cells from leprosy patients, related to presence of oral infections

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Objectives: The aim of this study was to determine the intracellular profile of interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-10 (IL-10) and interferon- γ (IFN- γ) in peripheral blood lymphomononuclear cells (PBMC) from leprosy patients stratified according to the presence of chronic oral infections.

Methods: Leprosy patients (n = 38) were selected and divided into two groups: group I - leprosy patients with oral infections (n = 19), and group II - leprosy patients without oral infections (n = 19). Non-leprosy patients presenting with oral infections were assigned to the control group (n = 10). Leprosy patients were classified according to Ridley and Jopling (1966). Intracellular IL-2, IL-4, IL-10 and IFN- γ production was evaluated by flow cytometry (FACS). Cell cultures were stimulated with 4 α -phorbol 12-myristate 13-acetate (PMA) and ionomycin (IONO) to evaluate intracellular cytokine staining. These analyses were performed immediately before and 7 days after control of the oral infection.

Results: The percentages of CD3+ cells bearing IL-2, IL-4 and IFN- γ were significantly reduced in leprosy patients with oral infections compared to non-leprosy patients with oral infection ($P < 0.05$, Mann-Whitney test).

Conclusions: The occurrence of oral infections stimulates the expression of intracellular cytokines and when these infections are associated with leprosy they may influence the production of intracellular cytokines and the evolution of leprosy.

Relevance: Analysis of intracellular cytokine production may contribute to the determination of factors that can influence the evolution of leprosy.

4

Atherosclerosis and oral health: mechanisms for *P. gingivalis* survival in endothelial-cells

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Objectives: The periodontal pathogen *Porphyromonas gingivalis* can enter the circulation during brushing or mastication and is thought to be involved in promoting atherosclerosis. *P. gingivalis* is known to invade endothelial cells however the mechanisms by which it evades the host immune-inflammatory response to survive in this location or how it might promote atherosclerosis are poorly understood. We therefore aimed to determine whether *P. gingivalis* infection of endothelial cells influenced the expression of immune-inflammatory molecules including IL8, ICAM-1, and VCAM-1.

Methods: Human microvascular endothelial cell line (HMEC1) was cultured in monolayer and infected with *P. gingivalis* strain W50, or a gingipain knockout of this strain, in the presence or absence of a protease inhibitor. After 18h, cytokine production was quantified by ELISA while adhesion molecule expression and cell viability were quantified by flow cytometry.

Results: Infection of endothelial cells (EC) cells with *P. gingivalis* had no significant effect on EC viability but caused a reduction in EC cytokine and adhesion molecule expression compared to uninfected controls. Inhibition of *P. gingivalis* protease activity partially, but not completely, restored EC cytokine and adhesion molecule expression to uninfected control levels.

Conclusions: *P. gingivalis* infection of endothelial cells reduces the production of immuno-inflammatory response molecules without affecting viability. This effect seems to be partly caused by the activity of *P. gingivalis* proteases. This ability to effectively paralyse innate immune-inflammatory signalling may prevent leukocyte recruitment to the infected site in-vivo and facilitate the long term intra-cellular survival of *P. gingivalis* in EC.

Relevance: Our findings support the postulated association between periodontal disease and cardiovascular disease by identifying mechanisms for long-term intra-cellular survival of *P. gingivalis* in EC. We now need to understand how this promotes atherosclerosis. An improved understanding of these mechanisms may provide opportunities for future therapeutic or preventative intervention.

5

The possible role of *Candida* spp. in oral carcinogenesis

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Objectives: Oral carcinogenesis is a complex multi-factorial process and different carcinogenic factors, principally tobacco use and heavy alcohol consumption, are closely related to the development of oral mucosa malignant transformation. Poor oral hygiene, presence of HPV and local trauma have been investigated for a possible role in oral squamous cell carcinoma (OSCC) aetiology. An association between the colonisation and/or infection of *Candida* spp. and the development of OSCC has also been reported. However, the possible carcinogenetic potential of *Candida* spp. has not been completely elucidated.

Here we report a critical review of the relevant literature on the topic of the possible role of *Candida* spp. in oral carcinogenesis.

Methods: The following databases were searched: MEDLINE, Excerpta Medica database (EMBASE), The Cochrane central register of controlled trials (CENTRAL). Endpoint of literature search was 31 December 2009. The following keywords were used for the search: "oral cancer and candida", "oral carcinoma and candida", "oral premalignant lesions and candida", "oral potentially malignant lesions and candida", "oral carcinogenesis and candida", "oral hyperplasia and candida", "oral dysplasia and candida". The search was repeated using the association for each of the previous terms with the Pubmed entry format "candida" in order to include all the results potentially related to the topic.

Results: 485 citations were generated by the research process and were subsequently screened accordingly to their title, by two independent reviewers. Disagreements were resolved by discussion.

Conclusions: Forty-five articles were eventually selected on the basis of the abstract content and included in the present review.

Relevance: The present review represents the first critical analysis of the literature on this topic.

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In vitro modelling of oral and vaginal candidiasis host-pathogen interactionsN Yadev^{*1}, S Bubeck², C Murdoch¹, SP Saville², J Lopez-Ribot², MH Thornhill¹¹*Unit of Oral & Maxillofacial Medicine & Surgery, School of Clinical Dentistry, University of Sheffield, Sheffield, UK,* ²*Department of Biology, University of Texas San Antonio, San Antonio, Texas, USA*

Objectives: *Candida albicans* is a fungal organism that forms part of the normal microbial flora; colonising oral and vaginal mucosal surfaces predominantly in its yeast form. Under certain circumstances, *C. albicans* can undergo morphogenic transformation from its commensal yeast form to a pathogenic hyphal form, leading to candidiasis. Local host defence mechanisms are key to protecting against infection and maintaining a commensal relationship. However, little is known about the host response to candidiasis.

Methods: A genetically modified strain of *C. albicans* (SSY50B) in which yeast/hyphal transformation is controlled by the addition of Doxycycline was used. Tissue-engineered oral and vaginal *in vitro* models were infected with SSY50B with/without Doxycycline, enabling us to study the effect of yeast-hyphal transformation on the host response. The effect of yeast/hyphae on histological changes, cytokine production, tissue damage and gene-expression was investigated.

Results: Both models produced an inflammatory response to hyphal forms of *C. albicans*. The cytokine response to yeast forms was reduced in the oral models and totally diminished in the vaginal models, suggesting that yeast forms of *C. albicans* are not recognised as a threat by vaginal epithelial cells, whereas oral epithelial cells still recognise and respond to the presence of yeast, though not as strongly as to hyphae. In both models, hyphal forms caused increasing tissue damage over time, whereas the yeast form caused little damage. Different gene response patterns to the two forms of *Candida* were also detected in the models.

Conclusions: These studies reveal the different host response to hyphal and yeast forms of *Candida* as well as differences in the oral and vaginal host response.

Relevance: Identifying factors critical to the commensal and pathological host response to *Candida* could help identify individuals at increased risk of candidiasis and aid in the prevention and treatment of this disease.

7

Histopathological changes in oral mucosa of rats exposed to environmental tobacco smoke

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Objectives: To evaluate the histopathological changes in clinically "normal" oral mucosa of rats exposed to environmental tobacco smoke (ETS).

Methods: 20 female, Sprague Dawley rats, were included in the study. 10 rats were exposed daily to ETS produced by 10 cigarettes, for 4 months. All animals were sacrificed and their tongues were removed, stained using H&E and finally evaluated under light microscope. Epithelial and connective tissues were described and compared statistically using SPSS 17.0: *P* values < 0.05 were considered statistically significant.

Results: Oral mucosa of rats exposed to ETS showed augmented epithelial changes: basal hyperplasia (*P* = 0.001), acanthosis (*P* = 0.0001), nuclear hyperchromatism and picnosis (*P* = 0.010 y 0.014 respectively), and epithelial dysplasia (*P* = 0.0001). Increased chronic inflammatory infiltrate was also observed in this group (*P* = 0.007), as well as a higher number of blood vessels; however the difference was not statistically significant.

Conclusions: ETS was shown to produce tissue alterations in macroscopically healthy mucosa of rats. Cellular and structural changes, clinically imperceptible, may progress into carcinomas if ETS exposure is persistent. Results suggest that visual inspection of the oral cavity is not enough to detect early stages of potentially malignant disorders related to smoking.

Relevance: This was an experimental study using an animal model to demonstrated microscopical oral mucosa changes produced by ETS without clinical alterations.

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Salivary cytokines in leukoplakia and oral cancerV Brailo^{*1}, V Vučičević Boras¹, J Lukač², D Biočina Lukenda³, I Alajbeg⁴, A Milenović⁵, M Balija⁶¹*Department of Oral Medicine and* ⁴*Department of Prosthodontics, School of Dental medicine, University of Zagreb, Gundulićeva 5, Zagreb,* ²*Clinic for Nuclear Medicine and Oncology, Clinical hospital "Sestre milosrdnice", Vinogradska cesta 29,* ³*Study of Dentistry, Medical Faculty, University of Split, Croatia, Šoltanska 2, Split,* ⁵*Clinic for Maxillofacial surgery, Clinical Hospital Dubrava, Avenija Gajka Šuška 6, Zagreb,* ⁶*Croatian Institute for Transfusion Medicine, Petrova 3, Zagreb, Croatia*

Objectives: Oral leukoplakia is a precancerous lesion with malignant transformation rate of 1% per year. Apart from regulating inflammatory response, proinflammatory cytokines interleukin 1 beta (IL-1 β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF- α) take part in the process of carcinogenesis. The aim of the study was to compare salivary and serum concentrations of IL-1 β , IL-6 and TNF- α in patients with oral leukoplakia, oral cancer and healthy controls.

Methods: Eighty eight patients (28 with oral cancer, 29 leukoplakia, and 31 healthy control) were included in this study. Saliva samples were collected between 8 and 12 a.m. by a simple drooling method. Cytokine concentrations were measured by commercial enzyme linked immunoassay.

Results: Salivary IL-1 β and IL-6 were significantly higher in oral cancer patients than in patients with leukoplakia and control group (*P* < 0.05). No differences in concentrations of salivary TNF- α between either of the groups were observed. Serum concentrations of IL-1 β were below level of detection in all but two participants. No significant differences between the groups were observed in serum concentrations of IL-6. Serum TNF- α was significantly higher in control subjects than in oral cancer patients. Cytokine levels were not influenced by periodontal status and smoking.

Conclusions: Patients with oral cancer have elevated levels of inflammatory cytokines in their saliva.

Relevance: Whether this elevation can be used for monitoring the malignant transformation of oral leukoplakia remains to be answered by further follow up studies. Cross sectional study cannot provide that answer but makes solid base for further research by identification and elimination of factors that might influence the values of studied cytokines.

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Immunohistochemical Expression of Notch Signaling in Calcifying Cystic Odontogenic TumorT Kawakami^{*1}, CH Siar², K Nakano¹, M Tomida¹, S Matsuura¹, H Tsujigiwa³, H Nagatsuka³¹*Matsumoto Dental University Graduate School of Oral Medicine, Shiojiri, Japa,* ²*Faculty of Dentistry, University of Malaya, Kuala Lumpur, Malaysia,* ³*Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*

Objectives: Odontogenesis is a complex biological process both with epithelial and mesenchymal tissues, and this process directly reflects the development of odontogenic neoplasms. Calcifying cystic odontogenic tumor (CCOT) is characterized by

odontogenic epithelial islands having ghost cells and calcified foci within the neoplastic epithelial cell nests and sometimes in the ectomesenchymal and/or stromal tissues. Notch signaling is involved in both patterning and cell fate determination during morphogenesis in development. Therefore, we examined Notch related transcription factors and their genes in CCOT.

Methods: The materials were examined by histopathological (HE) method, after that immunohistochemical (IHC) and in situ hybridization (ISH) techniques were applied to determine the transcription factors and/or their mRNA of Notch (NICD) and Jagged.

Results: IHC showed that NICD-positive products existed in the cytoplasm of both of the epithelial and mesenchymal cells. Regarding the epithelial cells including ghost cells, reacted NICD-positive. Furthermore, the ectomesenchymal spindle and/or reticulum cells were stained positive, scattering in the stromal connective tissues. Regarding Jagged, IHC showed positive both for the epithelial components and ectomesenchymal components, which is the nearly the same as that of the NICD-stained specimens. In the dentinoid formation area, the NICD- and Jagged-positive products were present in the cytoplasm of just adjacent cells of the dentinoid tissues and/or the embedded cells. In ISH examination specimens, the mRNA signals of the NICD and Jagged were in the cytoplasm of both the epithelial and mesenchymal cells. In the formation of dentinoid tissue area, the Jagged gene signals were observed in the cytoplasm of the ICH-positive cells.

Conclusions: The results suggest that Notch signaling plays some important roles in cytological differentiation or acquisition of tissue-specific characteristics between odontogenic epithelium and odontogenic ectomesenchymal tissues.

Relevance: The results would help to further elucidate the role of these genes in CCOT and furthermore in odontogenic tumorigenesis.

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Using tissue-engineered oral cancer models to evaluate non-invasive diagnostic technologies

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Objectives: To use 3D tissue-engineered models of normal oral mucosa (NOM) and oral squamous cell carcinoma (OSCC) to develop novel non-invasive imaging techniques. Real-time diagnostic techniques could significantly improve early oral cancer detection and therefore survival rates. Here we aim to investigate whether optical coherence tomography (OCT) is able to differentiate cancerous tissue from healthy tissue in 3D models of NOM and OSCC.

Methods: De-cellularised dermis was seeded with human oral keratinocytes and oral fibroblasts (OF) to produce NOM or with OF and oral cancer cell lines for models of OSCC. Models were cultured submerged for 3 days and then raised to an air-liquid interface for up to 3 weeks. OCT imaging was carried out using an in-house OCT system (swept source light source, 1300nm wavelength).

Results: 3D models with the characteristics of NOM, dysplastic mucosa, carcinoma in situ and invasive OSCC were established. Non-invasive OCT imaging of NOM models showed a clear epithelial/connective tissue interface that was disturbed in severely dysplastic and malignant models. The images obtained with OCT corresponded well to histological assessment of the same models.

Conclusions: When cultured in 3D different oral cancer cell lines produce models with different morphologies and degrees of dysplasia. OCT can provide images of epithelial morphology and basement membrane organisation which could prove to be a useful tool in the diagnosis of dysplastic and OSCC lesions. These models provide us with an important research tool for the development and evaluation of novel non-invasive diagnostic technologies without the need for patient volunteers.

Relevance: OSCC diagnosis currently relies on histological analysis of biopsies. These are invasive, and take time to analyse causing anxiety for patients and delays in treatment. A non-invasive, real-time point-of-care method for assessing potentially malignant lesions could overcome these problems and facilitate widespread, regular screening.

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Is Response to Chemoprevention in Oral Leukoplakia Determined by p53 Expression?

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Objectives: We previously performed a randomized clinical trial (RCT) for chemoprevention of oral leukoplakia by administering low-dose of beta-carotene (10mg/d) and vitamin C (500mg/d) supplements for one-year. Although the RCT did not support use of these agents for either clinical remission or for cancer prevention, it is unclear

whether or not clinical responses reflect expressions of biomarkers and lifestyles. The objectives are to characterize baseline expression of p53 and Ki67 between those responding or non-responding to our intervention and to elucidate any relationship between dietary factors and clinical responses.

Methods: Non-smoking subjects (n=23) were allocated to experimental group and among 16 who completed the trial there were 4-responders (1CR and 3PR) and 12-non-responders (9NC, 1PD and 2Ca) at median 65-months period. Serial paraffin-embedded sections of 3-μm thickness were immuno-stained, the percentage of positive cell nuclei for each marker were estimated as labeling index (LI), and analyzed (Student's t-test, $P < 0.05$).

Results: Expression of p53 was greater in basal layers than in para-basal layers. Mean para-basal LI of p53 was higher in non-responders (24.8%) than in responding subjects (11.2%)($P=0.048$). Ki67 LIs were not significantly different. Mean serum beta-carotene level at baseline was higher in responding (1.0μmol/dl) than in non-responding subjects (0.7μmol/dl) ($P=0.46$). However, uptake of serum beta-carotene levels between baseline and after one-year supplement was higher in non-responding (4.7μmol/dl) than in responding subjects (2.0μmol/dl)($P=0.21$). Number of portions of green-yellow vegetables consumed was higher in responding (3.0/d) than in non-responding subjects (2.2/d)($P=0.07$).

Conclusions: Results suggested that expression of p53 was inversely related to clinical response to the supplements. Clinical responses could be influenced by intake of green-yellow vegetables.

Relevance: This study was set to assess the validity of biomarkers and lifestyle factors in chemoprevention. Further studies to elucidate whether taking high amount of micronutrients from natural foods might be protective in cancer prevention are indicated.

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Micronucleus cytome assay in potentially malignant lesions and oral cancer

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Objectives: The Buccal Micronucleus Cytome (BMCyt) assay is a biomarker to study DNA damage, chromosomal instability, cell death and the regenerative potential of human buccal mucosa tissue. This study aimed to compare the cellular kinetics and buccal mucosa profile in Potentially Malignant Lesions and oral cancer using the BMCyt assay.

Methods: BMCyt assay was used to measure ratios of buccal cell populations and micronuclei (MNI) in Potential Malignant Disorders such as leukoplakia (L), lichen planus (LP) and Squamous Cell Carcinoma (SCC). The samples for this study were collected from three areas: from the lesions (sample A), from a 3 cm region around the lesions (non-clinical abnormalities = sample B) and from the opposite side of the lesion (without lesion = sample C).

Results: The results comparing the areas A, B, C showed no statistical significance for micronuclei, pyknotic cells and binucleated differentiated cells. Statistical significance ($P < 0.05$) was observed in LP for nuclear bud, karyolysis and karyorrhexis when comparing samples A and C, and karyolytic cells between B and C; SSC presented significant differences in karyolysis and karyorrhexis cells when comparing B and C, and karyolytic cells between A and C.

Samples from area B showed higher frequencies ($P < 0.05$) of condensed chromatin cells and nuclear bud in L than in LP, karyolysis and karyorrhexis in SCC than in LP, and more in L than SSC in condensed chromatin cells. The area A presented higher frequencies of nuclear bud and karyolysis in LP than in SCC and in SCC than in L.

Conclusions: These changes may reflect genomic instability and differences in the cellular kinetics and/or structural profile of the buccal mucosa.

Relevance: The BMCyt assay is a non-invasive method and can be used to identify changes in potentially malignant lesions and squamous cell carcinoma.

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Micronucleus and Sister Chromatid Exchange Analyses in Peripheral Lymphocytes of Patients with Oral Leukoplakia – A Pilot Study

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Objectives: The purpose of this study was to determine the genetic instability by investigation of frequencies of micronuclei (MN) and sister chromatid

exchange (SCE) in peripheral blood lymphocytes of patients diagnosed with oral leukoplakia.

Methods: Thirty biopsy proven newly-diagnosed and untreated patients with oral leukoplakia of the same severity scores, fifteen newly-diagnosed and untreated patients with oral cancer and fifteen healthy controls participated in this study. The clinical features of the lesions, the tobacco & alcohol habits and level of education of the patients were recorded. SCE and MN analyses were performed on peripheral blood lymphocytes of patients with oral leukoplakia, patients with oral cancer and healthy controls.

Results: Mean SCE (5.97 ± 1.18) and MN (27.07 ± 9.75) frequencies values of the healthy controls were significantly lower than those of patients with oral leukoplakia (7.92 ± 2.01 and 38.76 ± 14.25) and patients with oral cancer (7.93 ± 1.61 and 52.60 ± 17.41).

Conclusions: These pilot data indicate that patients with oral leukoplakia with higher frequencies of MN and SCE compared with those of controls should be frequently followed up because of the potential risk for developing malignancy. Furthermore, the routine analysis of the genomic instability along with aetiological factors will assist the prognosis of oral leukoplakia.

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Oral Cancer Diagnosis by Mechanical Phenotyping

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Objectives: Oral squamous-cell carcinomas are among the ten most common cancers and have a 50% lethality rate after five years. The identification of a cellular marker for functional changes may represent a significant improvement not only for early diagnosis but also for prognosis and treatment of oral cancer. Optical cell rheology using a microfluidic optical stretcher (OS) is a novel approach to determine the complex cellular polymer network as a whole. Therefore measurable differences in viscoelasticity may be recommended as a cytometric marker for diagnosis of malignancy.

Methods: Normal oral epithelial cell lines OKF-4TERT1 and OKF-6TERT1 and oral cancer cell lines HN, BHY, CAL-27 and CAL-33 (DSMZ GmbH, Germany) were measured and compared to primary cultured oral cells, which were obtained by tissue biopsy from the oral mucosa of four voluntary donors and five cancer patients.

Individual cells were trapped by two laser beams at low laser power and subsequently stretched out by an elevated optical stress σ at a high laser power. The peak stress ranged between $\sigma_0 = 1\text{--}5$ Pa and was calculated accordingly; the duration of the stretch was $0.8\text{--}2$ s. The response of the cells in the OS was monitored via video microscopy and analysed by custom-made algorithms.

Results: The temporal development of the deformability displayed typical viscoelastic behavior on the timescale of seconds. Comparing normal and cancer cell lines, the cancer cells deformed more rapidly upon stress application and the extension reached a plateau after about 0.2s. The normal cells exhibited a more retarded behaviour, where the deformation increased at a slower rate. The mean compliances at $t = 0.5$ s for all normal and all cancer cell lines were $D_n(0.5\text{ s}) = (7.18 \pm 0.43) 10^{-3}$ Pa⁻¹ and $D_c(0.5\text{ s}) = (18.2 \pm 1.1) 10^{-3}$ Pa⁻¹, respectively. The cancer cells were > 2.5 -times more deformable and could clearly be distinguished from the normal cells ($P < 0.05$).

Conclusions: Our results indicate that mechanical phenotyping is a sensible approach for identifying malignant oral epithelial cells.

Relevance: The ability to obtain cells in a minimally invasive manner by brush biopsies in combination with mechanical phenotyping using an optical technique has many potential applications in Oral Cancer diagnosis.

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Expression of a GHRH receptor (SV1) in squamous cell carcinomas of the oral mucosa

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Objectives: Growth hormone-releasing hormone (GHRH) is secreted by the hypothalamus and upon binding to specific GHRH receptors in the pituitary stimulates growth hormone production and release. In addition to its neuroendocrine action GHRH plays a role in tumorigenesis. Consistently with this latter role, the splice variant I (SV1) of GHRH receptor, which is widely expressed in non-pituitary normal tissues and cancers, can mediate the proliferative effects of GHRH and even in the absence of GHRH it is capable of eliciting mitogenic signals in the tissues in which it is expressed.

Methods: The aim of the present study was to investigate the expression of the GHRH tumoral receptor SV1 in squamous cell carcinomas (SCC) and epithelial dysplasias of the oral cavity by immunohistochemistry.

Results: Positivity was scored according to the staining intensity and involved cytoplasmic localization. According to our results 12 out of 28 (42.8%) oral cancer specimens were positive for SV1 expression as opposed to only 3 out of 34 (8.8%) epithelial dysplasias ($P < 0.001$). A trend was found between SV1 expression and well differentiated SCC.

Conclusions: This is the first report demonstrating the involvement of SV1 in the pathogenesis of SCCs of the oral cavity

Relevance: Our work implies that the progression from a state of dysplasia into malignancy is accompanied by expression of SV1 receptor. Our findings also suggest that treatment with GHRH antagonists should be further explored and be under consideration for the management of SCCs of the oral cavity. Further experiments are ongoing in order to confirm and extend our findings.

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Differential Proteomics defined Keratin-13 and -17 in oral malignancy

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Objectives: Oral squamous cell carcinoma (OSCC) is thought to develop via dysplasia and carcinoma in situ (CIS) as a "Two-hit theory", which was proposed by Knudson. However, differential diagnosis is sometimes difficult between these lesions. We looked for a histological biomarker using daily surgical diagnosis to distinguish the borderline lesion of oral malignancy and early cancer. The aim of the study was to identify the potential biomarker involved in early change of the borderline lesion of oral cancer.

Methods: A comparative proteomics approach was employed to identify the differentially expressed proteins in the CIS, OSCC and control. We have successfully identified proteins from the samples obtained by laser micro-dissection and mass spectrometry (LC-MS/MS), as well as immunohistochemistry.

Results: Sufficient amounts of proteins were clearly detected from a formalin fixed and paraffin-embedded tissues ($n = 15$); 94 from CIS, 167 from OSCC and 151 from control tissues by means of LC-MS/MS analysis. Of those proteins, 38 were up- and 19 were down-regulated in OSCC compared to control. Keratin (K13, K17) was one of most significantly altered proteins and its expression in the OSCC ($n = 20$) and CIS ($n = 20$) was confirmed using immunohistochemistry. In cooperation with other biomarker such as cell proliferation marker Ki67, phospholipase A2, cyclooxygenase-2, and Aourora A, the observation suggests that Keratins 13 and 17 might be potential biomarkers for early diagnosis for CIS and OSCC.

Conclusions & Relevance: This study demonstrates that a comprehensive strategy of proteomic identification combined with further validation should be adopted in the discovery of cancer biomarkers.

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NF-κB-expression in oral premalignant and malignant lesions: An immunohistochemical study

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Objectives: NF-κB is a key protein complex for many cellular processes, such as inflammation, cell death and proliferation. Altered expression has been reported in various diseases, including viral infections and cancer. The purpose of this study is to evaluate the immunohistochemical expression of NF-κB in oral epithelial malignant and premalignant lesions.

Methods: Forty five oral cases comprising 4 normal mucosal controls, 11 hyperplasias, 21 dysplasias of various degrees and 9 squamous cell carcinomas (SCC) were investigated. Immunohistochemical staining with NF-κB p65 was performed. Both cytoplasmic and nuclear staining of NF-κB p65 was noted. Intensity and percentage of positive epithelial cells were graded in a semi-quantitative manner, in a scale of 0-3 for each parameter. A combined score was also calculated (0-6). Statistical analysis of the results was performed by using the chi-square test.

Results: NF-κB p65 was detected in both cytoplasm and nuclei of epithelial cells with more prominent cytoplasmic expression. Immunohistochemical expression was noted in all investigated categories to a variable extent. The average percentage, intensity and total scores were 2.75, 1.5, 4.25 for normal mucosa, 2.82, 1.7, 4.5 for hyperplasias, 2.9, 2.43, 5.33 for dysplasias and 2.78, 2.44, 5.22 for SCC, respectively. No statistically significant difference was noted between the scores of normal tissues and hyperplasias or between the scores of dysplasias and SCCs. Statistically significant difference for intensity and total scores ($P = 0.0329$ and $P = 0.04$ respectively) was recorded between hyperplasias and dysplasias.

Conclusions: There is an increased expression of NF-κB in oral dysplasias and SCCs as compared with normal oral mucosa and hyperplasias. Nevertheless, the degree of dysplasia does not seem to affect the expression of NF-κB.

Relevance: The elucidation of the role of molecular markers such as NF- κ B in the progression of oral premalignancy and malignancy may have significant diagnostic and therapeutic implications.

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CYP1B1 Leu432Val polymorphism in oral cancer risk patients from the Basque Country (Spain)

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Objectives: Cytochrome P450 subfamily 1B polypeptide 1 (CYP1B1) is a gene located on chromosome 2 that encodes an enzyme that activates several polycyclic aromatic hydrocarbons and heterocyclic aromatic amines. Functional polymorphisms have been described for this gene. Several studies have suggested that the functional polymorphism CYP1B1 codon 432 (Leu432Val) could be a carcinogenic susceptibility factor associated with tobacco consumption. Due to the high incidence of oral and larynx cancer in our region together with the high tobacco consumption, the aim of this study was to determine the distribution of CYP1B1 Leu432Val polymorphism in our environment and analyze its relationship with the risk of developing oral cancer.

Methods: We analyzed 398 samples: 46 patients who had suffered an oral carcinoma (Group OC), 38 patients who had suffered a larynx carcinoma (Group LC), 68 patients with oral lichenoid disease (Group OLD) and 246 resident population (Group RP). DNA was extracted from oral cytological samples from each patient using a phenol-chloroform-isoamylalcohol method. The genotypes were determined by PCR using a Taqman assay.

Results: The most frequently observed genotype in the resident population was Leu/Val (38.6% Leu/Leu, 42.7% Leu/Val and 18.6% Val/Val). When comparing the genotypic distribution no significant differences were observed between the resident population and the other groups ($P=0.724$). No significant association between CYP1B1 Leu432Val polymorphism and the risk of oral cancer was found (Leu/Val OR 1.188 95% CI 0.467-3.02 and Val/Val OR 0.679 95% CI 0.312-1.48).

Conclusions: The presence of CYP1B1 Leu432Val genotype shows no relation to their risk of oral carcinoma in our region.

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EGFR cell distribution correlates with survival in oral carcinomas

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Objectives: The aim of this study was to analyze the expression of epidermal growth factor receptor (EGFR) in oral squamous cell carcinomas (OSCC) and the possible relationships of this marker with clinical, pathological and survival variables.

Methods: We studied a series of primary OSCC ($n=63$) diagnosed consecutively at the Complejo Hospitalario Universitario de Santiago de Compostela (period 1995-2003). We analyzed the clinical and pathological parameters, EGFR expression (low/moderate/strong intensity; $>10\%$ of the tumour cells) and EGFR cell distribution (membrane + cytoplasm or membrane), by immunohistochemistry using tissue microarrays (two 1.5mm core disks of each case) (Chi-square test; $P<0.05$). The overall survival and disease-free survival were also studied (Kaplan-Meier method; Cox regression method; $P<0.05$).

Results: EGFR expression was observed in 95.2% ($n=60$), with moderate/strong expression in 79.3% ($n=50$) and negative/weak expression in 20.7% ($n=13$). Simultaneous membrane and cytoplasmic expression occurred in 35% ($n=21$) of cases. This simultaneous expression was associated with the presence of vascular invasion ($P=0.04$). We found an independent prognostic value for stage classification (hazard ratio 24.05, CI 95% 4.66-124.19, $P<0.001$) and EGFR cell distribution (hazard ratio 4.09, CI 95% 1.65-10.15, $P=0.002$). Even in the early stages (stages I/II), simultaneous membrane and cytoplasmic EGFR expression correlated with lower overall survival (hazard ratio 4.92, CI 95% 1.08-22.41, $P=0.039$).

Conclusions: EGFR overexpression is frequent in OSCC. Simultaneous membrane and cytoplasmic EGFR expression is associated with lower overall survival.

Relevance: The significant and independent value of EGFR cell distribution in overall survival may add to the classical prognostic parameters such stage or differentiation grade, which is of vital importance for an appropriate OSCC treatment plan. Moreover, the high expression of EGFR confirmed in this research warrants the study of targeted therapies to these receptors and their pathways in OSCC.

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Genetically altered fields in oral precancer: DNA-FCM and a-CGH

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Objectives: Field cancerization is an accepted model for oral carcinogenesis. So far genetically altered fields have just been reported near carcinomas. We aimed to study the distant mirror fields of oral precancer by DNA-content flow cytometry (DNA-FCM) and by high-resolution oligonucleotide array-Comparative Genomic Hybridization (a-CGH).

Methods: 5 leukoplakias without dysplasia (OLs), 9 dysplastic leukoplakias (DOLs) and 14 corresponding histologically healthy mirror fields (MFs) were analyzed. DNA aneuploidy (DNA Index, $DI \neq 1$) was detected by DNA-FCM at high resolution (mean DNA-diploid $CV = 1.2 \pm 0.2\%$) on DAPI stained nuclei suspensions. DNA aneuploid and diploid nuclei were FCM-sorted to obtain genomic DNA for a-CGH performed by 105K microarray using an Agilent platform.

Results: MFs, OLs and DOLs showed an increasing prevalence of DNA-aneuploidy (7.1% in MFs, 20% in OLs, 66.7% in DOLs). MFs and OLs showed near-diploid DNA-aneuploid sublines, conversely high DNA-aneuploid sublines were predominant in DOLs. The average number of chromosome aberrations (Ch-Ab) was 3.1 in MFs, 3 in OLs and 11.9 in DOLs. The presence of dysplasia was associated with an increasing mean number of Ch-Ab in the corresponding MFs (from 1.8 to 3.8). Of note Ch-Ab were also observed in DNA-diploid sublines reflecting the complementarities of the 2 techniques. The most frequent Ch-Ab in MFs was the gain of 20q13.33-qter (42.9%). Often the same aberrations were observed in both MFs and corresponding OLs/DOLs.

Conclusions: In the present 14 MFs DNA-aneuploidy and Ch-Ab were respectively observed in 7.1% and 57.1%. Since chromosome loss was observed at very low frequency, the progression from normal to precancer seems to be under the control of a gain of function of several genes.

Relevance: The presence of DNA-aneuploidy and Ch-Ab in MFs indicates an early onset of field effect in oral carcinogenesis. Array-CGH integrated with DNA-FCM.

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Enhancement of DNA Vaccine Potency by In Vivo Electroporation

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Objectives: In a previous investigation we developed a highly reproducible carcinogenesis model by combining DMBA application with physical wounding of the hamster lingual mucosa. Using this animal model, we demonstrated the presence of a novel hamster oral papillomavirus (HOPV).

Recently it has become clear that more potent methods for DNA vaccine delivery need to be developed to enhance the efficacy of DNA vaccines. In this study, we used HOPV hamster model to compare the anti-tumour effectiveness of different procedures of DNA vaccine delivery, intramuscular injection alone or with electroporation (EP).

Methods: Forty hamsters were divided equally into four groups. These groups were designated as GC (no treatment), GV (vaccination without EP), GE (EP without vaccination), GVE (vaccination followed by EP). The animals in GC were injected intramuscularly with vector only, while those in GV were injected with DNA plasmids encoding the E7-gene. The animals of GVE were injected DNA plasmids followed by EP, while those in GE were only injected vector followed by EP. Three weeks after the initial DNA injection, all animals were boosted with the same plasmids they had received initially. The lingual tips of hamsters were painted three times a week with DMBA for 8 weeks. The middle portion of the lingual tip was then excised under anesthesia. Thereafter, the tips were painted daily with DMBA until the animals were sacrificed.

Results: The all hamsters of GC and GE groups showed lingual carcinoma. Some delays in cancer development in the hamsters of GV and GVE group were observed. In particular, in GVE group, 4 hamsters showed no lesions.

Conclusions: These results suggested that immunization with E7 DNA vaccines followed by EP in vivo delayed carcinoma development of papillomavirus-associated oral cancer.

Relevance: In vivo EP is a potent method for DNA vaccine delivery, therefore, it contributes to papillomavirus-induced oral cancer prevention strategy.

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Selected transcriptome profiles of oral cancer suggestive of field cancerisation using second generation sequencing

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Objectives: To characterize differential gene expression between oral cancerous tissues and the normal mucosal tissues of oral cancer patients and oral mucosal tissues of cancer free patients using second generation sequencing.

Methods: Five fresh frozen oral cancer tissue samples from smoking patients, with 2 samples of proximal normal were included in this study. An additional 8 samples consisting of normal oral mucosal tissues from the alveolar mucosa of non-cancer patients who had their wisdom tooth removed where 4 were smokers and another 4 were non-smokers was also included. The tissues and socio-demographic information were obtained from the Malaysian Oral Cancer Data and Tumour Bank System (MOCDBS) at the Oral Cancer Research and Coordinating Centre (OCRCC). Manual macrodissection was used to obtain >70% tumour or normal epithelial tissue. High quality poly A+ RNA was extracted from the macrodissected tissues and second generation sequencing was done using the Illumina Genome Analyzer. Validation of second generation sequencing was done using commercial and custom microarrays.

Results: Among the differentially expressed genes, KRT76 which encodes a filament protein that is responsible for the structural integrity of epithelial cells was the most down-regulated gene when comparing all tumours to all normals (excluding proximal normals). KRT76 is the second most down-regulated gene when comparing differential expression between proximal normal and normal non-cancer samples. Further comparison of all tumors against all normals, including the proximal normals, still indicates down-regulation of KRT76, but to a much lesser degree. A similar pattern was also observed for other down-regulated genes such as the KRT2, KRT3, ANKS1B, CPLX2, FGB, HIST1H3A, HIST1H3G, HIST1H4I, LOR and ZFH2.

Conclusions: This pattern of partial cancerisation of proximal normal samples is suggestive of the possible presence of 'field cancerisation'.

Relevance: The "field cancerisation" theory was postulated by Slaughter whereby the occurrence of multiple independent primary tumours was explained by the fact that the upper aerodigestive tract is chronically exposed to carcinogens. Various conventional molecular methods including microarray based technologies have been applied. Nevertheless, there have been no reports utilizing second generation sequencing to elucidate differentially expressed genes in relation to 'field cancerisation' in oral carcinogenesis. Using second generation sequencing to discover genes involved in 'field cancerisation' may be useful in predicting the outcome of different management strategies for oral cancer patients.

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Immunohistochemical analysis of cytokeratin 17 in oral squamous cell carcinoma

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Objectives: Cytokeratin (CK) 17 is expressed in basal cells of oral normal mucosa and squamous cell carcinoma cells, however, little is known about the CK17 expression pattern in oral squamous cell carcinoma (OSCC). The aim of this study was to evaluate the relevance of various CKs including CK17 to clinicopathological parameters of OSCC.

Methods: In 44 samples from patients with primary OSCC, the expression of CKs in tumor cells was immunohistochemically examined by anti-CK14, anti-CK16, anti-CK17, anti-CK18, anti-CK19, and anti-CK20 monoclonal antibodies. A comparison of CK expression patterns with clinicopathological parameters (tumour region and size, lymph node states, mode of invasion by Yamamoto-Kohama criteria, differentiation grade, and clinical stage) was carried out. The stained sections with more than 10% reactive cells in tumour cells were defined as positive, and less than 10% as negative.

Results: Of 44 samples, CK14 was detected in 42 samples (95.5%), CK17 in 29 (65.9%), CK16 in 25 (56.8%), CK19 in 17 (38.6%), CK18 in 13 (29.5%), and CK20 in 12 (27.3%). Next, to clarify the clinically pronounced CKs from 6 kinds of CKs, the

frequencies of each CK expressions were examined between cases. CK17 was significantly expressed in N0 cases ($P < 0.05$) more than N-positive cases. Moreover, CK17 was significantly expressed in YK-1, YK-2, and YK-3 cases ($P < 0.01$) more than YK-4 cases. CK20 was significantly expressed in T3 and T4 cases ($P < 0.01$) more than T1 and T2 cases. There were no significant differences between CK14, CK16, CK18, and CK19 and any clinicopathological parameters.

Conclusions: The expression of CK17 was associated with metastasis of neck lymph nodes and characteristic of tumour invasion. The expression of CK20 was associated with clinical progression of OSCC.

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Possible involvement of Δ Np63 in proliferation and differentiation of OSCC

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Objectives: Δ Np63, a homologue of the tumour suppressor protein p53, is predominantly expressed in the basal layer of normal epidermis. It is known that Δ Np63 is involved in the proliferation and maintenance of epithelial stem cells. However, the role of Δ Np63 in cancer cells remains unclear. In the present study, we thus examined the expression and function of Δ Np63 in oral squamous cell carcinoma (OSCC).

Methods: Eighty-one patients with OSCC were enrolled in this study. The expression of Δ Np63 and differentiation markers in the OSCC specimens and OSCC cell lines was investigated by immunohistochemical staining, RT-PCR-based method, and western blotting. The differentiation markers examined were as follows: cytokeratin 5 (CK5) and cytokeratin 14 (CK14) as markers of basal cell of epithelium, neurotrophin receptor p75 (p75NTR) as a marker of epithelial stem cell, and BMI1 as a marker of stemness gene. MIB1 was also used as a marker of cell proliferation activity. The expression of these markers in the OSCC cell transfected with Δ Np63 siRNA was analyzed by Real-time PCR method. The proliferation activity of the OSCC cell was examined by MTT assay and BrdU incorporation assay.

Results: In the well-differentiated OSCC, immunoreactivities for Δ Np63 were detected only in the outer layer of the cancer nest. Meanwhile, in the moderately and poorly differentiated OSCC, Δ Np63 was expressed in almost all cancer cells. The expression patterns of CK5, CK14, and MIB1 were similar to that of Δ Np63. Δ Np63 and these differentiation markers were expressed in almost all cell lines. However, by the transfection with Δ Np63 siRNA, the expression of CK5, CK14, p75NTR, and BMI1 was significantly down-regulated. Furthermore, the cell proliferation activities were significantly inhibited in the cells transfected with Δ Np63 siRNA.

Conclusions: These results suggest that Δ Np63 is possibly involved in the proliferation and differentiation of OSCC.

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Genetic polymorphisms and risk of oral cancer

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Objectives: This study was done to investigate the role of single nucleotide polymorphisms (SNPs) within genes of phase I (CYP1A1) and phase II (GSTM1, GSTT1, GSTP1) of the xenobiotic metabolism and its association with oral cancer risk.

Methods: An unmatched case-control study was conducted using 207 newly diagnosed oral cancer patients and 117 non-cancer subjects selected from the OCRCC database. Peripheral blood was obtained from consented individuals and the CYP1A1, GSTM1, GSTT1 and GSTP1 genotypes were determined using polymerase chain reaction (PCR) and restriction enzyme digestion (RFLP). Simple and multiple logistic regression yielding odds ratio (OR and aOR) were employed to measure the association between genetic polymorphisms and risk of oral cancer.

Results: In comparing cases and controls for CYP1A1, GSTM1 and GSTT1 polymorphism, the OR was 0.84 (95% CI 0.534 - 1.330), 0.99 (95% CI 0.627 - 1.554) and 0.87 (95% CI 0.541 - 1.388) respectively. However, the adjusted OR for GSTP1 polymorphism, as compared to the wild-type, was 0.43 (95% CI 0.221 - 0.837). It was noted that polymorphism of GSTP1 conferred a 57% reduction in risk of oral cancer as compared to individual with GSTP1 wild type genotype. Meanwhile individual with combination of betel quid chewing habit and/or GSTP1 polymorphism has 1.6 times the risk of oral cancer although it was not statistically significant (95% CI 0.974 - 2.635).

Conclusions: Analysis suggested that polymorphism of GSTP1 seems to have protective effect on the risk of oral cancer.

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Verrucous carcinoma: A histopathologic re-appraisal of 63 diagnosed cases

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Objectives: Oral verrucous carcinoma (VC) constitutes an uncommon, exophytic, warty, slow growing variant of squamous cell carcinoma (SCC) with pushing margins. Typically, VC involves older males with chronic smokeless tobacco use being the primary aetiological factor. Microscopically, differential diagnosis should be made among other lesions with similar histological characteristics including verrucous hyperplasia (VH) and papillary SCC, while the possibility of a hybrid VC-SCC should be considered. The purpose of this study was to re-evaluate the histopathological features of 63 cases originally diagnosed as VCs in light of recent changes in classification and microscopic criteria of verruciform lesions.

Methods: The archives of the Laboratory of Oral Pathology, School of Dentistry, Athens, were reviewed from 1970 to 2009 and all cases with a histological diagnosis of oral VC were retrieved. The microscopic slides were re-examined according to the following criteria: architecture of the epithelium (shape of projections, keratin production, tumor thickness), dysplastic cellular characteristics (mitoses, atypia, pleomorphism), stroma infiltration (broad pushing borders, small or larger islands) and inflammatory response.

Results: Among 27,446 diagnosed cases, 63 (0.29%) had received a diagnosis of VC. Microscopic re-evaluation of these cases confirmed the diagnosis of VC in 40 (63.5%) cases. Eleven (17.5%) cases were reclassified as VH, 7 (11.1%) as VC-SCC hybrid tumours, 2 (3.2%) as keratoacanthomas and 1 (1.5%) as papillary SCC, while in 2 (3.2%) cases the material was insufficient to render diagnosis.

Conclusions: Careful reassessment of the microscopic features resulted in reclassification of a significant percentage of cases originally diagnosed as VC. The microscopic resemblance of VC to other verruciform lesions of the oral cavity may cause difficulties in rendering an accurate diagnosis.

Relevance: The differences in the prognosis and appropriate management of VC and other verruciform lesions presenting with similar clinical and microscopic features necessitates careful histopathological analysis by an experienced pathologist.

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Immunohistochemical localization of p75NTR in oral leukoplakia and OSCC

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Objectives: Neurotrophin receptor p75 (p75NTR) is involved in the proliferation, differentiation, and apoptosis in the various cells. Recent studies have revealed that p75NTR is associated with the development of cancer in a variety of organs. In this study, the expression of p75NTR was immunohistochemically examined in oral leukoplakia (OL) and oral squamous cell carcinoma (OSCC).

Methods: 112 patients with primary OL and 81 patients with primary OSCC, who were diagnosed in our department, were enrolled in this study. In the immunohistochemical analyses, the primary antibodies used were anti-p75NTR polyclonal antibodies and anti-MIB1 monoclonal antibody.

Results: In the normal oral epithelium and OL, p75NTR was localised in the basal epithelial cells, meanwhile MIB1 was located in the parabasal layers. The positive rate of MIB1 was significantly increased in association with the severity of epithelial dysplasia in the OL, although that of p75NTR was invariable. In the well-differentiated OSCC, immunoreactivities for p75NTR were detected only in the outer layer of the cancer nest. In the moderately and poorly differentiated OSCC, p75NTR was expressed in all cells. The expression patterns of MIB1 were similar to that of p75NTR in the OSCC. The p75NTR positive rate in the group with cervical lymph node metastasis was significantly higher than that in those of non-metastasis. Furthermore, the cumulative survival rate of patients with p75NTR-high expression tumours was significantly lower than that of patients with p75NTR-low expression tumours.

Conclusions: In the normal epithelium and the OL, p75NTR was mainly expressed in the undifferentiated epithelial cells without the proliferation activities. Meanwhile in the OSCC, p75NTR was possibly involved in the proliferation and differentiation. Furthermore, it was suggested that p75NTR could be useful as a prognostic factor of OSCC patients.

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Ki-67 is not a prognostic factor for oral cancer

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Methods: We studied 79 tumors from 65 patients. Immunohistochemistry study with Mib-1 monoclonal antibody was used to detect Ki-67 expression in tumor tissue and adjacent non-tumor tissue. The influence of different variables on survival was studied with univariate and multivariate analyses

Results: Ki-67 expression was significantly higher in well-differentiated versus poorly-differentiated carcinomas. The survival time of these patients was affected by the clinical presentation, T, N, stage, and surgical treatment. Ki-67 expression had no impact on survival. An association was found between the parabaasal expression of Ki-67 in adjacent non-tumor epithelium and Ki-67 expression in the tumor.

Conclusions: Ki-67 lacks prognostic value, probably because it is a marker of the total fraction of proliferating cells, corresponding not only to cells in constant proliferation but also to proliferating cells destined for terminal differentiation.

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Survivin expression in different conditions related to intra-oral carcinogenesis stages

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Methods: Three groups were analyzed. The first group consisted of cytologic material obtained from patients of the Heart Institute Patient Center and the Smoking Cessation Program of the University Hospital, University of São Paulo Medical School (INCOR-HCFMUSP). Patients smoked more than 20 cigarettes/day/10years and had no history of malignant oral neoplasm or clinical signs at the site evaluated were collected from the left side of the tongue and floor of the mouth. Medical history was taken, extra and intra-oral examination were carried out. Smears of 30 patients, two of each selected location, were performed using cytobrush. The second group consisted of tissue samples from 21 patients with white lesions clinically classified as leukoplakia. The third group consisted of 42 tissue samples from patients diagnosed with oral squamous cell carcinoma. Groups 2 and 3 were formed by material from the Laboratory of Oral Pathology, São José dos Campos Dental School. Quantitative immunohistochemistry analysis of survivin expression was made. One smear of floor of the mouth and tongue was stained and evaluated by the method of Papanicolaou. Statistical analysis was performed by Fisher's exact test, Mann-Whitney and X2.

Results: Survivin was positive in 100% of cytological material from the smokers, 85.7% of oral leukoplakia and 83.3% of oral squamous cell carcinoma. Fisher's exact test showed no association between the expression of survivin and daily cigarette consumption and duration of smoking on the tongue or floor of the mouth respectively: tongue ($P = 0.68$) ($P = 0.21$) and floor of the mouth: ($P = 0.69$) ($P = 0.69$). Survivin expression was higher in mouth floor, Mann-Whitney test ($P = 0.001$). Survivin expression was not statistically correlated to cigarette consumption, although it was more intense in the mouth floor.

Conclusions: The survivin expression in the oral mucosa of heavy smokers, oral leukoplakia and oral squamous cell carcinoma indicated that survivin is a protein that participates in all steps of oral carcinogenesis.

Relevance: The present research attempts to provide information of the effects of smoking in oral mucosa. Survivin expression studies using oral cytological smears were not found. This may be useful to highlight important aspects of oral carcinogenesis steps.

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Genetic polymorphisms and risk of oral cancer

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Methods: An unmatched case-control study was conducted using 207 newly diagnosed oral cancer patients and 117 non-cancer subjects selected from the OCRCC database.

Peripheral blood was obtained from consented individuals and the CYP1A1, GSTM1, GSTT1 and GSTP1 genotypes were determined using polymerase chain reaction (PCR) and restriction enzyme digestion (RFLP). Simple and multiple logistic regression yielding odds ratio (OR and aOR) were employed to measure the association between genetic polymorphisms and risk of oral cancer.

Results: In comparing cases and controls for CYP1A1, GSTM1 and GSTT1 polymorphism, the OR was 0.84 (95% CI 0.534 - 1.330), 0.99 (95% CI 0.627 - 1.554) and 0.87 (95% CI 0.541 - 1.388) respectively. However, the adjusted OR for GSTP1 polymorphism, as compared to the wild-type, was 0.43 (95% CI 0.221 - 0.837). It was noted that polymorphism of GSTP1 conferred a 57% reduction in risk of oral cancer as compared to individuals with the GSTP1 wild type genotype. Meanwhile individuals with combination of betel quid chewing habit and/or GSTP1 polymorphism has 1.6 times the risk of oral cancer although it was not statistically significant (95% CI 0.974 - 2.635).

Conclusions: Analysis suggested that polymorphism of GSTP1 seems to have protective effect on the risk of oral cancer.

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Optimized microRNA analysis for oral mucosal lesions

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Objectives: To develop a robust diagnostic method to extract microRNAs (miRNAs) from cytological scrapings of the oral mucosa in order to assess comparative expression levels of a number of miRNAs.

Methods: Oral epithelial scrapings were preserved in either RNA Protect Saliva Qiagen Inc.), RNA Later (ABS) or in lysis buffer for 24 hours, 7 days or immediate RNA extraction. Samples were compared to known RNA from human heart. Total RNA was extracted using mirVana miRNA Isolation kit (Ambion), quantified by spectrophotometer (Nanodrop), and quality analyzed using Experion (Bio Rad). Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to quantify mature miRNA (miR-24; miR-16; miR-19b; miR-26b) using Taqman miRNA assays (ABS) and Ct values at a threshold of 0.35. Three reverse transcription methods were compared: (i) reverse transcribing with miRNA specific RT primers; (ii) megaplex RT reaction using pooled miRNA primers; or (iii) the latter with an additional pre-amplification step.

Results: RNA amounts varied significantly, however this did not effect miRNA specific RT-PCR product production. The quality of the isolated RNA varied significantly with most samples generating poor quality RNA (RQI 2.5-5). Nevertheless, specific RT-PCR were generated from all extracts. Neither storage material nor time had little effect on the Ct value of RT-PCR. All methods resulted in miRNA specific RT-PCR products. The pre-amplified RT megaplex miRNA primer pool resulted in the most reproducibly lowest Ct levels.

Conclusions: These results would indicate that RNA Protect Saliva and pre-amplified RT megaplex miRNA primer pool is a robust method for analyzing miRNA variation in oral epithelial cytological samples, independent of RNA degradation.

Relevance: MicroRNAs (miRNAs) are small non-coding RNA genes that mediate gene expression at the post-transcriptional level with evidence that deregulation of specific miRNAs occurs in human diseases. These results allow for quantitative comparative analysis of miRNA in potentially malignant lesions.

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Expression of cyclooxygenase-2 in keratocystic odontogenic tumors in a Dutch population

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Objectives: The World Health Organization's recent classification of Head and Neck Tumors reclassified the keratocyst as a benign neoplasm, recommending the term 'keratocystic odontogenic tumor' (KCOT). Markers known to be rapidly induced in response to growth factors, tumor promoters, cytokines, bacterial endotoxins, oncogenes, hormones and shear stress, such as COX-2, may shed new light on the biological mechanisms involved in the development of this benign but yet aggressive neoplasm. The purpose of this study is to investigate the expression of cyclooxygenase-2 (COX-2) in KCOTs.

Methods: One hundred and sixteen biopsy specimens of KCOTs obtained from the Department of Oral and Maxillofacial Surgery/Oral Pathology of the VU University Medical Center, Amsterdam, were evaluated. The mean age of the patients was 41.6 years old, ranging from 12 to 84. The KCOTs were most frequent in the 2nd and 3rd decades, with a male:female ratio of 2.3:1 and predominantly located in the angle/ramus of the mandible. Formalin-fixed, paraffin-embedded blocks were sectioned and used for hematoxylin-eosin (H&E) staining and incubated with an anti-COX-2 monoclonal antibody (Dako) for immunohistochemical examination. Detection of the COX-2 antibody was performed with the EnVision kit. Cellular staining pattern for

COX-2 was cytoplasmatic and the staining intensities were semi-quantitatively evaluated as: negative (-), mild (±) or intense (+).

Results: Mild to strong expression of COX-2 was observed in 83(71.6%) of the cases, 29.3% (34) of which were mild positive and 42.2% (49) were strong positive. COX-2 stain was detected mainly in the lining epithelium. Changes in the staining pattern were observed in areas of an associated inflammatory infiltrate.

Conclusions: The expression of COX-2 in keratocystic odontogenic tumours seems to confirm previous reports noting a greater suprabasal staining for proliferation markers, such as Ki-67 and proliferating cell nuclear antigen (PCNA) and more significant staining with p53 as compared to the other odontogenic cysts. These results further strengthen the current concept that the KCOT should be regarded as a benign cystic neoplasm.

Relevance: Both genetic and molecular research regarding odontogenic tumors, and KCOTs in particular, has led to an increasing amount of knowledge and understanding of their physio-pathological pathways. Although prognostic factors based on clinicopathologic and immuno-histochemical findings for determining the potential for recurrence of KCOT still remain unclear, its use for determining the potential for recurrence of KCOT after surgical treatment may become important to successfully manage this neoplasm's aggressive behavior. Future management of KCOTs will probably be based on thorough knowledge of the biological basis of this tumor, thereby enabling a more tailored treatment approach.

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Guanylate-binding protein-1 localization in non-neoplastic and neoplastic salivary glands

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Objectives: Guanylate-binding protein-1 (GBP-1) is a molecular weight of 67 kDa protein that is induced by interferon-gamma and thought to be a key mediator of angiostatic effects of inflammation. GBP-1 closely relates prognoses of colorectal or prostatic carcinomas. Therefore, this pilot examination is designed to clarify the GBP-1 localization in non-neoplastic salivary glands and salivary gland neoplasms.

Methods: We selected non-neoplastic samples (n=10) including chronic sialoadenitis (n=5) and non-inflammatory salivary glands (n=5) excised at neck dissection and salivary gland tumours (n=10) comprising myoepitheliomas (MEs) (n=2), myoepithelial carcinomas (MCs) (n=2), adenoid cystic carcinomas (AdCCs) (n=2), mucoepidermoid carcinomas (MECs) (n=2) and acinic cell carcinomas (AcCCs) (n=2). Four-micron-thick paraffin sections were routinely treated and stained with a GBP-1 mouse monoclonal antibody (clone 4D10MB01, Abnova, Taiwan).

Results: In non-neoplastic samples, membranous and granular-positive reactions to GBP-1 were present in terminal, intercalated and interlobular ducts, while mucous cells were mostly negative. Myoepithelial cells showed cytoplasmic positivity. Endothelial cells and some inflammatory cells were positive. In neoplastic samples, benign myoepithelial cells showed cytoplasmic positive reactions, while anaplastic and invasive myoepithelial cells exhibited negative or decreased reactions. The parenchyma of AdCC, AcCCs and MECs were membranous-positive, but mucous cells in MECs were mostly negative. Concerning stroma, vascular GBP-1 expression somewhat decreased in the invasive front of a microcystic variant of AcCC and a intermediate grade MEC. Interestingly, stromal venules of a solid type AcCC were negative.

Conclusions: This study demonstrated that GBP-1 was constantly produced by not only the stroma of the salivary gland, but also the parenchyma. Although it is unknown whether GBP-1 is a prognostic predictor, this protein looks to be a biomarker of malignant transformation of myoepithelial cells.

Relevance: To distinguish malignant myoepithelial tumour cells from benign ones is important in the diagnosis of pleomorphic adenoma/myoepithelioma.

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Changes of Salivary Glands and Components due to Cigarette Smoke

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Objectives: Passive smoking is the involuntary inhalation of cigarette smoke (CS). It has been demonstrated that there is a strong positive correlation between cigarette smoking and the increased incidence and severity of periodontal disease and caries. We examined the effect of CS exposure on saliva and salivary glands (SGs).

Methods: CS-exposed rats were intermittently housed in an animal CS exposure chamber with whole-body exposure to CS for three times daily, until euthenizing at 31-days. Whole saliva was collected before CS exposure (0-day), and 15 and 30-days after the start of CS exposure. Saliva secretion was stimulated by administration of isoproterenol and pilocarpine after anesthesia. Whole saliva was collected over a 15-minute period after the stimulation. Amount of total salivary protein, salivary cotinine level, amylase and peroxidase activities were measured by each detection kit or

tetramethylbenzidine. SGs were excised on 31-days and fixed in fixative solution. Then paraffin sections were prepared and histopathological evaluation was performed.

Results: The increase in body weight of the CS-exposed rats was less than that of the control rats. Salivary flow rates did not differ at 0, 15 or 30-days after the start of CS exposure. However, the amylase and peroxidase activities and total protein content in the saliva were significantly lower in 15-days CS-exposed rats than in 15-days control rats. Salivary cotinine was detected in 15 and 30-days after the start of CS exposure. Histological examination of the SGs of CS-exposed rats showed vacuolar degeneration, vasodilation and hyperemia. In particular, vacuolar degeneration of the central part of the submandibular glands were remarkable.

Conclusions: These results suggest that CS exposure has adverse impacts on salivary composition and SGs, which could aggravate the oral environment.

Relevance: This study suggests others examining the adverse impact of CS in smokers are warranted. This study helps improve our knowledge of the oral environment of passive smokers.

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Tumors of minor salivary glands: Clinico-pathological study of 197 cases

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Objectives: Salivary gland tumors are relatively uncommon lesions accounting for <3% of all head and neck tumors. Tumors of minor salivary gland origin (MSGT) constitute <25% of all salivary gland tumors. The purpose of this study was to investigate the demographics and the relative frequency of the various histological subtypes of MSGT in a Greek population.

Methods: All cases with a histological diagnosis of MSGT were retrieved from the files of the Laboratory of Oral Pathology, School of Dentistry, Athens, between 1970-2009 and re-evaluated. Information regarding age, gender and anatomical location of the tumors was collected from the patients' records.

Results: Among 27446 cases, 197 (0.71%) diagnosed as MSGT were identified. The female:male ratio was 1:1.49 and the age ranged between 11-88 years (mean age 46.2 years). Among all MSGT, 139 (70.6%) represented benign (BMSGT) and 58 (29.4%) malignant (MMSGT) neoplasms. The gender ratio was 1:1.48 for BMSGT and 1:1.52 for MMSGT, respectively. Mean age was 43.8 years for BMSGT and 52 years for MMSGT. Pleomorphic adenoma ranked as the commonest BMSGT (85%), while mucoepidermoid carcinoma (27.6%) and adenocarcinoma NOS (27.6%) were the most common MMSGT. Finally, for both categories, palate was the most popular site of involvement accounting for 59% of BMSGT and 53.4% of MMSGT cases.

Conclusions: MSGT are a heterogeneous group of lesions with differences in demographics and clinical features and a striking range of histological diversity, accurate diagnosis of which is critical for appropriate management.

Relevance: Most studies of salivary gland tumors encompass both major and minor salivary gland tumors. Studies focusing exclusively on MSGT in a specific population may help to the better characterization of these uncommon entities.

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Mannose binding lectin gene (MBL-2) polymorphism in oral lichen planus

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Objectives: The aim of the present study was to assess the relevance of genetic diversity of MBL in OLP.

Methods: The study sample comprised 90 individuals, 45 OLP patients and 45 healthy volunteers. MBL-2 gene was amplified using real-time PCR.

Results: Frequency of A/A genotype was 55.6% in OLP and 53.3% in healthy volunteers. Likewise, A/0 heterozygote genotype was found in 42.2% and 35.6%; 2.2% and 11.1%, had the recessive 0/0 genotype respectively. Frequencies of the "A" and "0" alleles were 77% and 23% in the OLP group and 71.2% in control group. There were no statistically significant differences regarding genotype frequency ($P=0.546$) or allele frequency ($P=0.497$).

Conclusions: In conclusion, no significant association was found between polymorphism of MBL-2 gene and OLP.

Relevance: TNF- α may be associated with the aetiopathogenesis of oral lichen planus (OLP) and it has been suggested that polymorphism of mannose-binding lectin (MBL) increases the *in vitro* production of TNF- α .

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Expression of miR-125b, miR-203 and miR-21 in oral lichen planus

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Objectives: Oral lichen planus (OLP) is a chronic inflammatory disease of unknown origin, affecting up to 2% of the population. We have previously shown increased expression of the tumour suppressor protein p53 and decreased expression of its sibling p63 in OLP compared to normal controls. We have also shown increased expression of Smad proteins, which are important factors in the TGF- β -pathway, in OLP lesions compared to normal oral mucosa. MicroRNAs (miRNAs) are small noncoding RNAs which account for 1-3% of the genome, and regulate up to 30% of human genes at the posttranscriptional level by interfering with translation of mRNA or inducing degradation. A single miRNA can target around 200 different mRNAs. MiR-125b is a negative regulator of p53 and p53-induced apoptosis, miR-203 is epithelial specific and regulates Np63 and miR-21 regulates TAp63, and has also been indicated to be involved in regulation of the TGF- β pathway.

Methods: 4mm punch biopsies were collected from 20 patients, clinically and histologically diagnosed with OLP. From 20 sex and age matched controls punch biopsies from the buccal mucosa were collected. Biopsies were embedded in Tissue Tek OCT, snap frozen and stored at -80°C. After sectioning and staining, laser micro dissection was used to collect epithelium, from which RNA was extracted. For microRNA analysis miR-specific RT primers for each miR was used.

Results: Sufficient amounts of total RNA could be extracted from all laser dissected epithelia, and miRNA analysis was successfully performed.

Conclusion and Relevance: The aim was to map expression of miRNAs known to target p53, p63 and the TGF- β pathway, factors previously shown to be dysregulated in OLP. As miRNAs are known to have important roles in certain diseases, it is important to analyse their expression in correlation to their targets and thus map their potential impact also in this specific disease.

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ELISA method for detection of antibodies against p63 in patients diagnosed with oral and/or genital and skin lichen planus

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Objectives: Lichen planus is a chronic inflammatory disease. Autoimmunity has been implicated in the etiology of this disease, and recently we detected antibodies directed against all six p63 isoforms in sera from two OLP patients using western blot.

Methods: Sera from an additional 46 patients and 43 controls were collected. We developed a novel ELISA technique for screening of sera for detection of p63 isoforms.

Results: In addition to the two previous patients, we found three other patients with auto-antibodies against p63 isoforms. This novel groups of patients were all women with a mean age of 70 years and were diagnosed with severe disease symptoms both orally and in vulva and vagina.

Conclusions: The detection of another three patients with autoantibodies against p63 supports the hypothesis that p63 can be involved in development of this disease and further suggests that p63 could play a role in the generalised forms of the disease.

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No difference in micronuclear scores in both circulating lymphocytes and Buccal Epithelial Cells between Patients with Oral Lichen Planus and Oral Lichenoid Stomatitis

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Objectives: We earlier demonstrated that oral lichen planus (OLP) is associated with high frequencies of micronuclei and sister chromatid exchanges in circulating lymphocytes when compared with healthy controls. The aim of the present study was to compare the micronuclei scores in both circulating lymphocytes and buccal exfoliated epithelial cells of patients with OLP with those with oral lichenoid stomatitis (OLS).

Methods: Twenty-two OLP (histopathologically confirmed with no dysplasia) patients (47.6 ± 14.4 ; 4 male, 18 female) and twenty-one OLS (dental materials associated) patients (51.3 ± 12.4 ; 6 male, 15 female) were enrolled in the study. They were all non smokers, newly-diagnosed (confirmed by histopathology and allergy testing to dental materials) with similar disease severity scores and with no previous history or a family history of cancer. The periodontal status, the subtype, localization, severity degree of the lesions were recorded. MN analyses were performed on peripheral blood lymphocytes and on buccal exfoliated epithelial cells of OLP and OLS patients.

Results: No significant differences were observed between OLP and OLS patients in regards of age, gender, localization, subtype and disease scores ($P < 0.05$). The evaluation of MN scores of circulating lymphocytes {; median (min-max) : 2.3 ± 1.6 ; 2 (0-7) for OLP patients; 1.6 ± 1.7 ; 1 (0-6) for OLS patients} and buccal exfoliated cells (22.4 ± 24.8 ; 14.5 (3-95) for OLP patients; 26.4 ± 24.9 ; 16 (3-93) for OLS patients) between the two study groups revealed no significant differences ($t = 1.217$; $P = 0.232$ and $z = 0.366$; $P = 0.714$).

Conclusions: MN test does not distinguish OLP from OLS. Though the two conditions have different aetiologies, cell and tissue damage appear to generate micronuclei in a similar fashion. As MN are increased in precancer and cancer this could be a surrogate marker to indicate that both OLP and OLS have the potential to change to cancer.

Conflict of interest and source of funding statement: The authors declare that they have no conflict of interests. The study was self-funded by the authors and their institution.

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pS6k and ki-67 expression in oral premalignancy: An immunohistochemical study

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Objectives: Phosphorylated form of S6 kinase (pS6k) is the most downstream target of Akt-mTOR pathway, which participates in cell cycle progression, cell size, differentiation and survival control. Activation of Akt-mTOR pathway exerts an oncogenic activity and is a frequent event in oral cancer. The purpose of this study was to evaluate the immunohistochemical expression of pS6k in oral premalignant lesions and its correlation with cell proliferation.

Methods: Formalin fixed oral leukoplakia tissues corresponding to hyperplastic epithelium ($n=11$), dysplastic epithelium of various degrees ($n=28$) and control normal mucosa ($n=5$) were used. Immunohistochemical analysis for pS6k and ki-67 was performed for each epithelial layer individually. pS6k immunostaining was evaluated in a semiquantitative manner according to intensity (0-3), percentage (0-3) of positive epithelial cells and total combined score (0-6). The percentage of ki-67 positive cells was also assessed. Statistical analysis was performed using Mann - Whitney U test and Spearman's rank test.

Results: pS6k nuclear expression was detected in all cases with variations in percentage, intensity and total score. Statistical analysis showed increased pS6k total score in dysplasias compared to hyperplasias ($P=0.02$). Moreover, percentage of positive cells in each layer individually was significantly higher in dysplasias compared to hyperplasias ($P<0.05$). Concerning ki-67 proliferation index, no statistically significant difference was noted between dysplasias and hyperplasias for all epithelial layers ($P=0.26$), whereas significantly higher expression was noticed in the basal layer of dysplasias compared to hyperplasias ($P=0.01$). Finally, positive correlation between expression of ki-67 and pS6k was noticed in hyperplasias and dysplasias ($P=0.05$).

Conclusions: In oral premalignant lesions, an increased expression of pS6k was noticed in dysplasias compared to hyperplasias, which correlated positively with cell proliferation, indicating that aberrant expression of pS6k is an early event in oral carcinogenesis.

Relevance: These findings identify the Akt-mTOR pathway as a potential therapeutic target for oral premalignant lesions.

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Phospho-4E-BP1 expression in oral lichen planus. An immunohistochemical study

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Objectives: Oral lichen planus (OLP) is an immunologically-mediated disease with a premalignant potential. Molecular characterization is a prerequisite for the understanding of carcinogenesis mechanisms. Activation of the oncogenic PI3K/AKT/mTOR pathway results in 4E-BP1 phosphorylation thus releasing eIF4E and allowing

cap-dependent translation. The purpose of this study is to evaluate the expression of phospho-4E-BP1 in OLP in comparison with oral malignant and premalignant lesions.

Methods: A total of 78 oral cases comprising 44 OLP, 5 normal mucosa (NM), 20 leukoplakias (5 hyperplasias and 15 dysplasias) and 9 squamous cell carcinomas (SCC) were investigated. Immunohistochemistry for phospho-4E-BP1 (Thr37/46) was performed. Intensity and percentage of positive epithelial cells were graded on a scale of 0-3 each. A combined score was also calculated (0-6). Statistical analysis was performed by Mann-Whitney test.

Results: Phospho-4E-BP1 was detected in the cytoplasm and mainly the nuclei of epithelial cells. The average percentage, intensity and total scores were 2.2, 2.2, 4.4 for NM; 2.34, 1.59, 3.95 for OLP; 3, 2.76, 5.76 for leukoplakias; and 3, 2.4, 5.4 for SCC. The percentage of phospho-4E-BP1 positive cells was statistically significantly lower in OLP compared to SCC and leukoplakias ($P=0.0011$ and $P=0.00001$, respectively). Staining intensity was also lower in OLP compared to SCC and leukoplakias ($P=0.0069$ and $P=0.00001$, respectively), but higher compared to NM ($P=0.0462$).

Conclusions: To our knowledge this is the first attempt to investigate the activation of the oncogenic PI3K/AKT/mTOR in OLP. Although the expression of phospho-4E-BP1 was lower compared to oral leukoplakias and SCCs, higher levels compared to NM indicate that the pathway may be active in a proportion of OLP cases.

Relevance: Further investigation of the importance of this pathway in OLP could serve as a useful tool to understand and characterize the premalignant nature of this entity.

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Immunohistochemical expression of PCNA and Ki-67 in oral lichen planus

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Objectives: The aim of the study was to detect PCNA and Ki-67 tissue antigens in correlation with the severity of clinicopathologic alteration of oral mucosa in OLP, to assess the expression intensity of these antigens in the clinical forms lichen ruber planus (LRP) and lichen ruber erosivus (LRE).

Methods: Patients ($N=92$) with the clinical and histopathologic diagnosis of OLP were selected. The control group included patients ($N=47$) with oral leukoplakia, verified as leukoplakia simplex. The PCNA and Ki-67 tissue antigens were detected by the APAAP and LSAB immunohistochemistry methods after treatment in a microwave oven.

Results: The reaction of study antigens was mosaic-like, intracellular and focal prominent in particular cell groups. PCNA antigen was detected in the basal and parabasal cell layers, and in inflammatory infiltrate of lamina propria. The Ki-67 antigen was detected in basal cells and in some inflammatory cells of lamina propria. The reaction was negative in other epithelial layers. High intensity of PCNA antigen expression was observed in OLP lesions, without any notable difference in the expression intensity between the two clinical forms of the disease. The intensity of PCNA antigen expression positively correlated with the extent of inflammation and intralesional hyperkeratosis. The expression of Ki-67 tissue antigen manifested with mild to moderate reaction. Reaction of greater intensity was observed in erosive lesions of oral lichen. The reaction positively correlated with the extent of inflammation and intralesional hyperkeratosis.

Conclusions: According, the immunohistochemical reaction of PCNA and Ki-67 antigens was found to alter according to the clinical status of OLP patients and could be related to the modified nature of OLP lesions.

Relevance: Assessment of the PCNA and Ki-67 antigens expression could prove important for elucidation of pathologic processes in oral precancerous lesions such as oral OLP and oral leukoplakia.

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Differential gene expression patterns in patients with recurrent aphthous stomatitis

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Objectives: The objective of this study was to compare patterns of gene expression in ulcerated and non-ulcerated oral mucosal tissue in patients with recurrent aphthous stomatitis (RAS).

Methods: Participants recruited through fliers from the University of Florida campus signed a consent, completed a questionnaire and had a punch biopsy of an aphthous lesion (onset <72hr) and adjacent normal mucosa. The tissue was snap frozen and stabilized with RNAlater Ice prior to RNA extraction (Qiagen RNeasy Fibrous tissue kit). Microarray analyses were performed using the GeneChip® Human Genome U133 Plus 2.0 Array. Data were analyzed using unsupervised and supervised statistical

analyses. Biocarta Pathway and Pathway Express were used to identify significant gene sets.

Results: We analyzed oral mucosal tissue from 7 RAS patients (4 males and 3 females) aged 21–36 years. Estimated range of time since RAS onset was 8–50 hours. All aphthae were 5mm or smaller in diameter. Hierarchical cluster analysis of 2,815 probe sets with a coefficient of variation > 0.5 showed a major node separating normal and ulcerated tissue except for two small aphthae 5–2mm in diameter.

Of the 54,675 probes representing over 38,500 genes, several hundred probe sets were consistently differentially expressed in ulcerated vs. adjacent tissue. These included genes involved in local proliferative processes and wound healing, such as metalloproteinases (MMP1,3,10 and PAPP-A), TIMP1, INHBA, IGF1R, S100A7, IL1B and CLU that had higher expression in all (7/7) aphthous tissues. However, pleiotrophin gene expression was lower in all (7/7) ulcers (permutational paired t-test $P=0.016$). Leave-one-out cross-validation and Monte Carlo simulations demonstrated the ability of significant probe sets to distinguish between ulcerated and non-ulcerated groups. Of 313 gene sets from Biocarta Pathway, 49 were differentially expressed. These included pathways involved in inflammatory processes, cell proliferation and apoptosis.

Conclusions: We identified differentially expressed genes in aphthae vs. adjacent normal tissue involving multiple pathways. Our expression pattern partially overlaps with that seen when comparing aphthae and normal mucosa from healthy controls (Borra et al., 2004). Replication of these findings in a larger sample is needed to confirm this pattern of expression, because of the possibility of false positive findings from multiple comparisons. This study was sponsored by NIH/NIDCR grant # R03DE016356, U24DE016509, and 1UL1RR029890.

Relevance: Recurrent aphthous stomatitis is the most common intraoral ulcerative disease. The aetiology is unknown, although it likely involves a complex interplay of local, systemic and genetic factors. Microarray analyses provide a global insight into the complex molecular level processes that occur in aphthous tissue.

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An evaluation of the genetic relationship between Orofacial Granulomatosis and Crohn's Disease

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Objectives: The association between Orofacial Granulomatosis (OFG) and Crohn's Disease (CD) is well established with reports of OFG preceding CD, reflecting intestinal disease and even as an early clinical marker of treatment failure in intestinal CD management. Specific gene mutations are well known to confer a risk for CD and can be prognostically significant. Despite the close association between OFG and CD, there is no published data on CD susceptibility genes in OFG. This pilot study investigates a population of 59 well characterised OFG patients for CD susceptibility genes.

Methods: Fifty nine biopsy proven OFG patients from Newcastle upon Tyne, UK, were recruited. Thirty three of these patients had a diagnosis of CD. Oral phenotypic data was recorded and details of CD was recorded in those patients with the disease. DNA was extracted from blood samples provided by these patients and genotyped for risk alleles strongly associated with CD using Applied Biosystems Taqman assays. Population controls were obtained from the 1958 British Birth Cohort.

Results: There was no association in the NOD2, ATG16L1 or IRGM loci. However, there was marginal evidence of a trend towards association at the IL23R locus. The pure OFG and OFG-CD showed an observed allele frequency of 3.6% and 0% respectively compared with 6.4% in the control group.

Conclusions: The potential role of IL23R in the pathogenesis of CD is beginning to evolve. This pilot study suggests a possible similar pathogenesis in OFG as there appears to be a lower incidence of the "protective" allele in OFG patients with and without CD.

Relevance: As this is a small pilot study, one must be cautious not to over interpret genetic associations which require greater patients numbers. Nevertheless, these results suggest a genetic association between OFG and CD which could have exciting implications for future management of both conditions.

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Genetic variations in NOD2/CARD15 in orofacial granulomatosis and major aphthous stomatitis

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Objectives: Genetic studies of a large cohort of patients with Crohn's disease (CD) have identified homozygous mutations in the CARD15 gene, which encodes NOD2,

and accounts for 10–15% of patients with CD. The goal of our study was to examine if similar mutations are observed in patients with orofacial granulomatosis (OFG) and major aphthous stomatitis (mRAS).

Methods: DNA was isolated from buccal swabs with isohelix DDK in patients with OFG (n=9; female=5), CD with OFG (n=4; female=2) and mRAS (n=10; female=7) and from 15 healthy controls. The diagnosis of OFG and mRAS were based on disease history and clinical characteristics. Allele and genotype mutations on exon 4 (Arg 702 Trp), exon 8 (Gly 908 Arg) and exon 11 (Leu 1007 insC) were screened after DNA-sequencing.

Results: Genetic variations of CARD15 were found in 3 patients with OFG and 4 patients with mRAS but not in the healthy controls. Although the patient material is small it indicates that OFG and mRAS may have the same extent of genetic variations in CARD15 as seen in CD patients.

Conclusions: Our study showed that genetic variations in NOD2/CARD15 may be associated with OFG and mRAS but there was no association between variations in NOD2/CARD15 and the severity of symptoms. Since these mutations occur mainly in the leucine-rich repeat domain, they interfere with the ability of NOD2 to recognise ligand and a reduced capacity to activate NFκB in response to stimulation with muramyl dipeptide. How these mutations give rise to susceptibility to OFG and mRAS is not known, although they may result in a disturbance in the normal immunological unresponsiveness of the mucosal immune system to components of the commensal intestinal microbiota.

Relevance: If there is a similar genetic variation in NOD2/CARD15 in patients with CD, OFG and mRAS, it could lead to an identification of an etiological denominator of these diseases.

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Antibiotic prophylaxis in rats treated with pamidronate plus dexamethasone and subjected to dental extraction: A study of the changes in the jaws

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Objectives: Osteonecrosis of the jaws is a well-known, devastating side effect of long-term bisphosphonate use. An analysis is made of the prophylactic effect of antibiotic treatment in Sprague-Dawley rats treated with pamidronate plus dexamethasone and subjected to oral surgery in the form of dental extraction.

Methods: A total of 120 animals were included in a randomized prospective study composed of the following groups: group I (60 animals: dexamethasone 1 mg/kg and pamidronate 3 mg/kg daily for 7, 14 and 21 days. All were subjected to right mandibular or maxillary molar extraction 8, 15 and 22 days after the start of dosing) and group II (the same as before, with the addition of penicillin 0.1 ml/kg/day for 3 days before and 4 days after extraction). The rats in both groups were sacrificed 14 and 28 days after extraction. A clinical and histological evaluation was made.

Results: In group I, osteonecrosis was documented in 18 cases (34.6%)(affecting the upper and lower jaw in 10 and 8 cases, respectively). In group II, osteonecrosis was documented in 5 cases (9.61%)(affecting the upper and lower jaw in 3 and 2 cases, respectively) – the difference between the two groups being statistically significant ($P=0.002$).

Conclusions: The adoption of preventive measures (antibiotic prophylaxis) in invasive dental procedures results in a significant reduction in osteonecrosis of the jaws associated with bisphosphonate use.

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Effects of tacrolimus on organotypic model mimicking oral mucosa

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Objectives: Tacrolimus ointment has shown efficacy in treating T-cell mediated inflammatory oral mucosal diseases including lichen planus. However, the safety of topical tacrolimus has been questioned based on a possible association with malignant transformation. The aim of this study was to evaluate the safety profile of tacrolimus treatment on oral mucosa using an in-vitro model.

Methods: Spontaneously immortalized keratinocytes and fibroblasts were obtained from healthy human gingival biopsy samples and grown in 3-dimensional organotypic cell culture model (raft culture). First, the cells were grown as monolayers and then the epithelial cells were added on fibroblasts and collagen gel. The cultures were raised to air-liquid interface for stratification and differentiation. Raft cultures of ten days were

exposed for tacrolimus (Prograf® 5mg/ml, Fujisawa GmbH, München, Germany) for two days at concentrations of 0.1%, 0.03% and 0.005% with medium alone as control. The effects of tacrolimus on proliferation (Ki-67), apoptosis (Caspase 3, TUNEL), cell adhesion (Syndecan-1, CD44s, CD44v6) and epidermal growth factor receptors (EGFR + ERBB2-4) were evaluated by immunohistochemistry and TUNEL method.

Results: Thinning of the epithelial but not the connective tissue layer of raft cultures was observed after tacrolimus exposure. Proliferation as assessed by Mib-1 index was at the same level both in control and treatment cultures. Apoptosis was almost absent in all cultures. EGFR + ERBB2-4, as well as the cell adhesion molecules syndecan-1 and both CD44 and variant 6, showed constant staining patterns in both control and treatment epithelium.

Conclusions: Despite the slight thinning of epithelium no changes in proliferation, apoptosis, cell adhesion or expression of EGFR + ERBB2-4 were detected after tacrolimus exposure in raft cultures.

Relevance: Our results suggest that the short term tacrolimus exposure of oral mucosa using an in-vitro model does not induce changes in factors known to be involved in malignant transformation.

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Using polymersomes to deliver chemotherapeutic agents to oral cancer cells

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Objectives: Polymersomes are synthetic block co-polymers that self-assemble in water to form membrane-enclosed nanovesicles. Polymersomes have the potential to encapsulate and carry chemotherapeutic drugs into cells thereby reducing the off target toxicity that often compromises anti-cancer treatment. Here, we assess the in-vitro efficiency of polymersomes to penetrate and deliver their load to head and neck cancer cells (HNSCC) cultured as both monolayers and as tumour spheroids (small solid expanding tumour masses).

Methods: HNSCC cells were grown as monolayers or as tumour spheroids. Polymersomes were loaded with a fluorescent tracking molecule or chemotherapeutic agents and applied to the monolayers or spheroids for increasing lengths of time. The cell viability, uptake and retention of polymersomes were analysed over time. The effectiveness of chemotherapeutic-loaded polymersomes to kill HNSCC cells was analysed.

Results: Polymersomes loaded with fluorescent rhodamine were internalised by HNSCC within 2 minutes of administration and maximal delivery was achieved within 30 minutes. In addition, polymersomes loaded with only 20% paclitaxel demonstrated similar killing of HNSCC grown as monolayers compared to the same concentration of free drug. When delivered to tumour spheroids, polymersomes are internalised by over 80% of tumour cells within 120 hours and importantly are shown to penetrate into the hypoxic regions of the tumour model. We are currently increasing the amount of paclitaxel encapsulated by polymersomes and are also attempting to load polymersomes with paclitaxel and cisplatin for combination therapy.

Conclusions: Polymersomes can rapidly deliver chemotherapeutic agents into tumour cells and kill them in a dose-dependent manner. They can also enhance drug delivery into the drug resistant hypoxic centre of solid tumour masses.

Relevance: Polymersomes could provide a safe and efficient method of delivering drugs for the treatment of head and neck cancers, offering significant advances in drug delivery with the goal of improving treatment of cancer patients.

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CAR-3 role in development of a targeting drug delivery system

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Objectives: CAR-3, an epitope of a mucin-like protein, has been localized in some human carcinomas, but no data is available on CAR-3 in oral tissues. In the recent development of “disease specific” nanoparticles, one goal is to bind monoclonal antibodies (Mab) onto nanoparticles surfaces without altering their biological functions. Our aims are: to assess CAR-3 presence in oral tissues (normal and pathological) and to investigate the absorption of AR-3 (the monoclonal antibody directed against CAR-3) onto a novel drug delivery system made of hydroxyapatite nanocrystals (HA-NC).

Methods: Immunohistochemistry using AR-3 has been performed on neoplastic and normal specimens of oral mucosa. HA-NC were prepared from an aqueous solution of (NH₄)₃PO₄ by slow addition of Ca(CH₃COO)₂ keeping the pH at a constant value of

10 by addition of a (NH₄)OH solution. After biomaterial physical-chemical characterisation, AR-3 (1 mg/mL) has been isothermally adsorbed onto HA-NC. To identify the amount of adsorbed AR-3, spectrophotometrical (280 nm) and Western Blot analysis were carried out.

Results: Immunohistochemistry localised CAR-3 at the surface of epithelial cells and at the level of extracellular matrix of oral carcinoma, while most part of normal samples resulted negative. Highly biocompatible plate-shaped HA-NC were obtained, with low crystallinity, a length of 20 nm and a specific surface area of 120 ± 6 m²/g. The AR-3 molecules adsorbed onto HA-NC were indirectly spectrophotometrically quantified, showing an high rate of absorption.

Conclusion: This study may be useful to develop new chemotherapeutic strategies based on immunological tools. Functionalisation can act as a strategy to fine-tune the bioactivity of HA-NC, as a targeted delivery system for drugs with controlled release properties.

Relevance: Final perspective is to obtain “personalised medicine” with a significant reduction of pharmacological dose, avoiding toxicity against healthy cells. Furthermore, inexpensive, but safe materials, such as HA-NC, have to be explored to reduce the cost of nanotechnology-based therapy.

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Antineoplastic effects of Sulindac in in-vivo oral carcinogenesis model

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Objectives: The NSAID Sulindac exerts antineoplastic effects in various malignant neoplasms, including oral squamous cell carcinoma (SCC) cell lines. Our aim was to explore the effects of sulindac on the chemoprevention and management of oral premalignant lesions using the hamster cheek pouch oral carcinogenesis model.

Methods: Thirty healthy Syrian golden hamsters (5 weeks old) were randomly divided in 3 experimental groups (A1, A2 and B) and 2 control groups (C1 and C2) (n = 6 each). All animals right buccal pouches were treated with 0.5% DMBA for 9 (A1, C1) or 14 (A2, B, C2) weeks and were subsequently sacrificed. The animals of groups A1 and A2 received 500ppm sulindac in their diet for the whole length of the experiment, while the animals of group B received sulindac from the 10th week. The animals of groups C1 and C2 did not receive sulindac. The treated buccal pouches were removed and examined macroscopically and histopathologically.

Results: All 12 animals of groups A1 and C1 developed epithelial dysplasia which was more frequently severe in group C1 ($P < 0.05$). While all 6 animals of group C2 developed invasive SCC (4 superficial and 2 deep), only 5 animals in group B developed invasive SCC (3 superficial and 2 deep), the last one showing only mild dysplastic changes. In group A2, 3 animals developed SCC (all superficial), the remaining ones showing carcinoma in situ (n = 2) or severe dysplasia (n = 1). The proportion of animals developing SCC in group A2 was significantly lower compared to group C2.

Conclusions: Sulindac appears to partially prevent the transformation from oral premalignant lesions to SCC. Sulindac did not prevent the development of precancerous lesions but resulted in less severe dysplastic changes.

Relevance: Sulindac may play a potential role in the chemoprevention and treatment of oral premalignant and malignant lesions.

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The Effect of Ethanolic Extract of Propolis on Radiation-Induced Mucositis in Rat

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Objectives: The aim of this study was to assess the efficacy of ethanolic extract of propolis in radiation-induced mucositis in rats.

Methods: This study was performed in Babol Dental Faculty and Shahid Rajaie Hospital of Abol, University of Medical Sciences in 2008. It was carried out on 21 male Wistar rats aged 7-11 weeks and weighing 160 ± 20 grams. The rats were divided into 3 groups. Groups A and B received intra-peritoneal injections of 100 or 200mg/kg ethanolic extract of propolis, and the control group (group C) received 10% ethanol (10 ml/kg, i.p) just before X-ray irradiation. After being injected, all the rats were irradiated in the head and neck region using an X-ray device at a dose rate of 15 Gy for 9 minutes and 39 seconds. The daily injections continued for the next 10 days, while the lips and tongues of the rats were examined daily to assess the intensity of lesions induced by irradiation.

Results: In the control group, the first signs of ulcers appeared on the first day, while they appeared on the fifth day in group B and fourth day in group A ($P < 0.001$). The severity of ulcers was greatest in the control group and least in group B ($P < 0.001$).

Conclusions: Our findings show that propolis is effective against radiation-induced mucositis in an animal model, but further research and evaluation is required.

Relevance: This study emphasises the need for further research into propolis in the management or prevention of radiation induced mucositis in oral cancer therapies.

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The effect of low level laser (LLL) irradiation on the structure of poly methyl-methacrylate (PMA) of the denture base

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Objectives: Earlier studies have demonstrated the antifungal and antibacterial effect of LLL irradiation on the oral mucosa and on the surface of dentures in the treatment of denture stomatitis. The aim of this *in vitro* study was to examine whether the LLL irradiation causes structural changes in the PMMA of the denture base.

Methods: The effect of laser-induced structural changes on the denture base material was investigated by semiconductor diode laser, BTL-2000 (BTL-2 Dravotnicka Technika, Prague, Czech Republic). Poly methyl-methacrylate (PMMA) was synthesized in the process of free-radical polymerization of methyl-methacrylate monomers in the xylene solution at nitrogen atmosphere pressure and under isothermal conditions. Thin PMMA films were made from 5 wt.% PMMA solutions in tetra-hydrofuran by solvent evaporation at room temperature. One cm² sized samples weighing approximately 10 mg were cut from thus prepared films and exposed to LLL irradiation. The samples were divided into five groups among which the first one was not treated and was used as the reference group. The second group was treated with a red probe, 685 nm wavelength, P=30 mW, for one minute whereas the fourth group was treated with the same probe three times longer than the second group. The third group was treated with an infrared probe, 830 nm wavelength, P=50 nW, and the fifth group was treated with the same probe three times as long. The samples were analyzed using the SEC (Size Exclusion Chromatography) method. Based on average molecular weight as well as on the calculated polydispersion indices, the deviations between the groups are negligible and are set within the framework of repetition.

Results: The results have shown that radiation did not cause any significant disintegration of macromolecular polymer chains.

Conclusions: Since the polymer structures used in prosthodontics are reticulated and therefore have greater stability than the linear ones, the result suggests an enhanced stability of their structure, rather than polymer degradation.

Relevance: Low-power laser irradiation may be a simple and alternative approach in the disinfection of dentures and as a noninvasive adjunct method in the treatment of denture stomatitis.

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Alkaloid-dependent upregulation of AlphavBeta6 integrin promotes oral submucous fibrosis

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Objectives: Oral submucous fibrosis (OSF) is a premalignant, fibrosing disorder of the mouth, with a malignant transformation rate of 7-13%. OSF is strongly associated with areca (betel) nut chewing and, worldwide, over 5 million people are affected. Given that integrin $\alpha v\beta 6$ has been implicated in both tissue fibrosis and oral cancer (OSCC) progression, we examined its expression and function in OSF.

Methods: Immunocytochemistry was used to investigate $\alpha v\beta 6$ expression in OSF and OSF-associated OSCC. Keratinocyte-derived cell lines with high and low $\alpha v\beta 6$ expression (VB6 and OKF6 respectively) were used to examine the functional role of $\alpha v\beta 6$ in TGF- $\beta 1$ activation and cell migration. Co-culture assays with keratinocytes and fibroblasts were performed to study possible pro-fibrotic paracrine interactions. The effect of betel nut constituents on keratinocyte $\alpha v\beta 6$ expression was also examined.

Results: High $\alpha v\beta 6$ expression was not detected in normal oral epithelium, but was found in approximately 50% of OSF cases. VB6 cells showed $\alpha v\beta 6$ -dependent activation of TGF- $\beta 1$, which induced transdifferentiation of human fibroblasts into myofibroblasts, and resulted in upregulation of genes associated with tissue fibrosis. These experimental *in vitro* findings were confirmed using human clinical samples where we showed that the stroma of OSF contained myofibroblasts, and that TGF- $\beta 1$ -dependent Smad signalling was detectable both in keratinocytes and myofibroblasts. We found that arecoline, the major alkaloid in areca nut, upregulated keratinocyte

$\alpha v\beta 6$ expression through the M4 muscarinic acetylcholine receptor. Increased $\alpha v\beta 6$ expression also promoted keratinocyte migration and invasion, raising the possibility that it may support malignant transformation. Over 80% of oral cancers arising on a background of OSF had moderate/high $\alpha v\beta 6$ expression.

Conclusions: These data suggest that the pathogenesis of OSF may be epithelial-driven, and involve arecoline-dependent upregulation of $\alpha v\beta 6$ integrin.

Relevance: It is possible that targeting $\alpha v\beta 6$ may prevent the progression of OSF.

$\alpha v\beta 6$ expression in OSF may identify patients with high risk of malignant transformation. A prospective study examining SCC development in OSF patients would be informative.

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Salivary cytokines as possible biomarkers of periodontal disease

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Objectives: The aim of this study was to compare salivary concentrations of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF- α) between patients with periodontal disease and healthy controls. Furthermore, we aimed to find whether salivary levels of proinflammatory cytokines correlated with clinical measurements of periodontal disease.

Methods: Test group consisted of 33 patients, 16 patients had generalized chronic periodontitis and 17 patients had generalized aggressive periodontitis. Control group consisted of 28 healthy participants with no clinical signs of periodontal disease and healthy oral mucosa. Plaque index (PI), bleeding on probing (BOP), probing depth (PD) and clinical attachment level (CAL) were taken by a single examiner with a standardized periodontal probe. Saliva samples were collected between 8 and 12 AM by simple drooling method. Concentrations of salivary IL-6 and TNF- α were measured by commercial chemiluminescent enzyme linked immunoassay. Statistical analysis was performed by use of Mann-Whitney test, analysis of covariance and Spearman's rank correlation.

Results: No significant differences with regard to the age and gender were detected between the tested groups. All clinical measurements were significantly higher in the patient group. Also, significantly higher number of smokers was observed in the patient group. No significant differences in the salivary IL-6 and TNF- α were observed between patients and healthy controls. No significant correlations between salivary IL-6 and TNF- α and performed clinical measurements of periodontal disease were observed.

Conclusions: No difference in the level of proinflammatory cytokines between healthy controls and individuals with periodontitis was found. Primary source of proinflammatory cytokines in the oral cavity is from gingival crevicular fluid. Therefore our results can be partially explained by the dilution of these cytokines in the whole saliva.

Relevance: These results cast doubt upon the use of salivary IL-6 and TNF- α as possible biomarkers of periodontal disease.

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Chronic khat-chewing effect on oral mucosa: a histopathological-immunohistochemical correlation study

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Objectives: To evaluate the correlation between the histopathological findings and the immunohistochemical expression of p53 and cycline D1 in oral mucosa exposed to chronic khat-chewing.

Methods: Ninety biopsies were incised from the buccal mucosa of 54 Yemeni males where khat-chewing side (KCS) and non-chewing side (NCS) of 36 chronic khat-chewers (CKSs) were biopsied, yielding 72 biopsies, while 18 non-chewers (NCs) had only left buccal mucosa biopsied, yielding 18 biopsies. Three 5 micron sections of each biopsy were obtained and one was routinely processed and stained for histopathological examination while the other two were processed and stained for p53 and cycline D1 antibodies respectively for immunohistochemical examination. Data regarding khat-chewing, chewing side, smoking and frequencies of hyperkeratosis, dysplasia and staining with p53 and cycline D1 were statistically described and analyzed (x2 or Fisher's Exact test, $P < 0.05$).

Results: One hundred percent and 61% of biopsies taken from (KCS) and (NCS) of (CKCs) were hyperkeratotic in contrast to only 38.9% of biopsies taken from left sides of (NCs), while 72.2%, 69.4% and 38.9% of these biopsies respectively revealed some degree of dysplasia. Hyperkeratosis was correlated with khat-chewing** and smoking**, in contrast to dysplasia which was correlated with smoking*** more than with khat-chewing*. Forty-two percent and 72% of hyperkeratotic cases were cycline D1

and p53 positive respectively, while 50% and 81% of dysplastic cases were cycline D1 and p53 positive respectively. While p53 staining was highly correlated with dysplasia*** and hyperkeratosis**, cycline D1 was highly correlated with dysplasia*** only.

Conclusions: The data supports the assertion that both khat and cigarette smoke are oral cancer risk factors, chronic exposure of the oral mucosa to khat-chewing and/or smoking causes genotypic disturbances of p53 and cycline D1. The established phenotypic changes (mainly dysplasia) appear to progress through such disturbed pathways.

Relevance: Proper educational programmes should be established to address khat-chewing and smoking habits.

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HSP expression as recovery reaction in orthodontic periodontal tension sides

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Objectives: Heat shock protein(HSP) are induced by not only heat shock but also via orthodontic tooth movement induced mechanical stress in the related periodontal ligament. It is important to examine the immunohistochemical (IHC) profile change of the Heat shock protein (HSP) in the periodontal ligament cells after receiving the mechanical stress for orthodontic treatment.

Methods: To provide a continuous mechanical stress on periodontal ligament, rubber dam sheet was placed between upper molars of 8-week-old ddY-mice, for exposed to mechanical stress. At 20-minutes, 1-hour, 3-hours, 9-hours and 24-hours after insertion of the sheet, relevant parts of the mice tissue were excised and placed in fixative solution. The examination of HSP27, p-HSP27, Runx2, Msx2 and alkaline phosphatase (ALP) expressions by IHC was performed. Control animals were not subjected to mechanical stress.

Results: In the experimental group, strong expressions of HSP were seen in the periodontal fibroblasts of the tension side at 20-minutes after mechanical stress. Expressions of HSP became stronger in parallel with passage of time. The HSP expression peaked at 24-hours after mechanical stress. The p-HSP27 expressions followed with the HSP. The expression pattern of HSP was nearly the same as that of Runx2 and ALP.

Conclusions: Application of mechanical stress on the periodontal fibroblasts resulted in strong expressions of HSP at the tension side with the passage of time. Some positive expressions at the pressure sides were found to be in low level in the control group. Our results suggested that HSP works as a chaperon of osteoblast-activating factors at the tension sides in the cells, and that HSP works as a recovery reaction for damaged periodontal cells exposed to mechanical stress.

Relevance: The results would help to further elucidate the histopathological changes of the periodontal ligaments after receiving orthodontic mechanical stress.

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Expression of Runx2 in Dental Root Pulp Cells due to Orthodontic Mechanical Stress

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Objectives: Orthodontic treatment causes dynamic histological changes of the periodontal tissues. Mechanical stress during orthodontic treatment may cause some histopathological changes in dental pulp cells, especially the activation of odontoblasts. Therefore, we examined immunohistochemical (IHC) expression of Runx2 as a regulating factor for odontoblasts in mouse dental pulp after orthodontic mechanical stress.

Methods: To provide a continuous mechanical stress on the periodontal ligament, an elastic separator was bent and placed between upper first and second molar of 8-week-old ddY mice. According to mechanical stimulus time, the experimental group was divided into 5-subgroups: 20-minutes, 1-hour, 3-hours, 9-hours and 24-hours. Upon completion of each time period, relevant parts of the mouse tissues were excised and fixed in fixative solution. The examination of Runx2 and alkaline phosphatase (ALP) expressions by IHC was performed after histopathological examination. Control animals were not subjected to mechanical stress.

Results: Histopathologically, there were no significant changes in both control and experimental specimens. In IHC-control specimens, localized Runx2 expression was detected in some pulp cells at the periphery of the dental root pulp cavity. Furthermore, weak expression of ALP was also observed in some cells. In IHC-experimental 60-min specimens, Runx2 and ALP expressions appeared in some pulp cells and some odontoblasts. Both immunohistochemical expressions became stronger over time in the examination group specimens ranging from 3-hours to 24-hours.

Conclusions: Application of mechanical stress on the periodontal ligament resulted in expressions of Runx2 and ALP in the odontoblasts, appearing comparatively shortly after orthodontic mechanical stress in mice which may directly reflect the activation of odontoblasts to form secondary dentine, although further evaluation of the appearance and the nature of Runx2 and ALP expression are necessary.

Relevance: The results would help to further elucidate the histopathological changes of the dental pulp, especially the formation of pathological secondary dentine, after receiving orthodontic mechanical stress.

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Mutations of keratin genes in patients with white sponge nevus

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Objective: White sponge nevus (WSN) is a rare autosomal dominant disorder that primarily affects the oral mucosa. Clinically, soft, white and spongy plaques characterise this disease. In some cases, the nasal, esophageal and anogenital mucosa may also be affected. Mutations in the genes encoding mucosal-specific keratins K4 and K13 have been shown to underlie the cause of WSN. The aim of this study was to characterize the mutations in the keratin genes assumed to be responsible for WSN in five Swedish patients.

Methods: DNA was isolated from buccal swabs with isohelix DDK in patients with WSN. ($n = 5$; 4 from the same family (in three generations) The diagnosis of WSN was based on disease history and clinical characteristics. In the adults ($n = 4$) a biopsy from the oral mucosa was performed to verify the diagnosis. From a newly born child, the diagnosis was based on clinical grounds only. Keratin 4 and 13 genes were amplified by using the polymerase chain reaction and directly sequenced.

Results: Sequencing analysis of the patients in one family revealed the presence of a heterozygous T-to-C transition mutation (rs60906702) in exon 1 of the keratin 13 gene. In the second family, a heterozygous mutation in exon 1 of keratin 4 gene was observed. This mutation has not previously been reported.

Conclusions: We identified heterozygous missense mutations in both the keratin 13 and 4 genes, presumably related to the development of WSN. Thus, these results confirm the hypothesis that mucosa keratin defects are the cause of WSN.

Relevance: The location of genetic variations in patients with WSN may serve as a starting point for the development of novel treatment strategies of this oral mucosal disease.

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A novel spectrophotometer in the colorimetric analysis of oral mucosa

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Objectives: Visual examination of oral mucosa colour is one of the most important parameters to identify pathological lesions, but up to now objective colorimetric parameters are not available.

In our study, for the first time, a novel fiber optic spectrophotometer is applied in order 1) to verify the manageability of the instrument; 2) to assess colorimetric differences among different sites of normal appearing oral mucosa, in the same and in different subjects; 3) to assess colorimetric differences between pathological and healthy mucosa of the same patient.

Methods: Fibre Optics Reflectance Spectrometry technique was used to identify colorimetric and spectrophotometrical data, employing a portable spectrophotometer. Healthy subjects and patients affected by different kind of oral lesions were enrolled in the study. All of them received: 1) a spectrophotometric analysis at different oral mucosal sites: healthy subjects were measured at standard sites, while patients were measured at lesion site and normal contralateral mucosa; 2) a questionnaire concerning demographic data, skin phototype, oral hygiene, smoking and nutritional habits. To identify colorimetric variations, colorimetric CIE Lab coordinates were used.

Results: A correct and reliable analysis procedure was obtained to satisfy repeatability of measurements. Although all normal oral mucosa sites resulted localized in the same red-yellow area of the CIE Lab graphic, the instrument was able to determine and quantify even slight intra-individual colorimetric differences. Colorimetric coordinates correctly reflected the chromatic features of oral lesions.

Conclusions: This novel fiber optics spectrophotometer has shown high manageability. Further studies are now in progress to investigate possible relationships between colorimetric coordinates and specific skin phototype or histopathological data.

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Etymology in Oral MedicineT Shembesh*¹, C Spencer², L Cascarini³¹Department of Oral Medicine, KCL Dental Institute, Guy's Hospital Campus, London, UK, ²Department of General Surgery, Queen Mary's Hospital Sidcup, Kent, UK,³Department of Oral & Maxillofacial Surgery, Northwick Park Hospital, London, UK**Objectives:** We aimed to improve understanding of the history and origin of some of our professional vocabulary.**Methods:** Free text and [Mesh] terms, exploding terms where appropriate and adapted to each database. PubMed, BNI 1985 to Present, CINAHL 1981 to Present, EMBASE 1980 to Present, MEDLINE 1950 to Present, PsycINFO 1806 to Present as well as a hand search of key bibliography and the British Library's catalogue.**Results:** The following terms have been identified as having an interesting origin and their etymology explored: Oral, cancer, aphthous, colchicine, herpes, shingles, lupus, lichen, pemphigus, halitosis, ranula, candida & thrush.**Conclusions:** Many terms in medicine and pathology originate from the same or similar root word. This helps develop associations in the reader's mind and makes understanding and learning new medical vocabulary and their correct use easier and indeed a more enjoyable experience. However, it is how the word is used ultimately that determines its meaning regardless of its etymological origin.**Relevance:** Knowledge of the etymology of medical terms facilitates familiarity with many root words and prefixes especially for those without knowledge of Latin (L.) and Greek (G.). It also seems to appeal to doctors and dentists who naturally have a 'Why is it called that?' kind of thinking.

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In vivo micro-vascularoscopy – A longitudinal study on gingival tissue

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Objectives: A micro-vascularoscopic imaging system has recently been developed, allowing non-invasive real-time capillary imaging in vivo. Longitudinal validation studies are necessary to assess tissue capillary architectural change with time to identify variation in normal vascular behaviour and lay the foundation for future disease interpretation. In the same work, intra-oral image re-localisation reproducibility may also be assessed.**Methods:** Five male volunteers underwent healthy gingival margin imaging weekly for four weeks and monthly for three months (Research Ethics Committee approval BDM/09/10-28). Two locations were imaged per subject, both 'freehand' and with a vacuum-formed 'localising stent'.

After visual analysis of each image series for matching characteristics, objective assessment followed utilising custom-designed imaging software. Having measured shifts in the field of view to quantify localisation differences, we digitally assessed changes in capillary density and distribution to determine vascular morphological change.

Results: Analysis showed remarkably few changes in gingival capillary architecture with time. The standard error for capillary morphological variability over three months was 12.1% (n = 5).

Instrument re-localisation was highly reproducible with time. Images could be visually matched over time in 95% of stent and 58% freehand series.

Instrument movement varied by a mean of 92µm within the 1020µm field of view.

Conclusions: The instrument produces accurately re-localisable images, and given the confirmed stability of normal healthy vascular architecture, any observed capillary architectural change is therefore likely to reflect disease processes.**Relevance:** *In vivo* micro-vascularoscopy has the potential to revolutionise clinical diagnosis in the fields of oral medicine, surgery and pathology. It is recognised that angiogenesis and changes in local vascularity are elementary features of both inflammatory responses and in progression of the neoplastic process. Visualisation of micro-vascular changes and responses within intra-oral structures may permit reduced reliance on surgical biopsy, particularly for monitoring chronic conditions, thus saving resources and improving patient care.

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FT-Raman spectroscopy ex vivo analysis of inflammatory fibrous hyperplasia from buccal mucosaJ Dias Almeida¹, LF Carvalho², RA Bitar³, AA Martin³, H da Silva Martinho⁴¹Department of Biosciences and Oral Diagnosis – São Paulo State University, ²Federal University of ABC and Department of Biosciences and Oral Diagnosis, São Paulo State University, ³Laboratory of Vibrational Biomedical Spectroscopy, Vale do Paraíba University, ⁴Center for Natural Sciences and Humanities, Federal University of ABC, Brazil**Objectives:** The aim of the present study was to use FT-Raman Spectroscopy to identify biological and biochemical alterations that exist between oral inflammatory fibrous hyperplasia and normal tissue from the buccal mucosa.**Methods:** 92 spectra of inflammatory fibrous hyperplasia (IFH) from 19 patients were compared to 27 spectra of normal mucosa (NM) from 6 patients. Samples of IFH andNM were obtained from biopsies. Tissue samples were stored in liquid nitrogen (77K) prior to FT-Raman spectra recording. The spectral differences were analyzed using multivariate Principal Components Analysis (PCA). PCA was performed over the range 500 to 1800 cm⁻¹ by computing the covariance matrix.**Results:** Relation between the data of IFH and NM was more evident when the PCA of all spectra was calculated and when the Principal Components (PC) PC3 vs. PC5 were analysed. Results showed great differences in the normal group. This was confirmed by the analysis of the Loading Plot of the PCs that showed great modifications between NM and IFH. This was identified by inverted peaks in Raman band 500 e 1110 cm⁻¹; 1300, 1580 and 1730 cm⁻¹. These bands correspond mainly to molecular vibrations of lipids, collagen (I and III) and proteins. The predictive value of diagnostic model was calculated by linear discriminate analysis which showed 0.87 ROC curve.**Conclusions:** Biological and biochemical similarities and differences between I inflammatory fibrous hyperplasia and normal tissues were confirmed by Raman Spectroscopy.**Relevance:** Inflammatory fibrous hyperplasia (IFH) is considered a non-neoplastic proliferative process that generally occurs in association with trauma. This pathology has typical histopathological features in both epithelial and conjunctival tissues. Raman spectroscopy of pathological tissues has become a reality that can contribute to knowledge enhancement about biochemical alteration making the differential diagnosis of oral pathologies possible.

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Optimized microRNA analysis for oral mucosal lesions

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Objectives: To develop a robust diagnostic method to extract microRNAs (miRNAs) from cytological scrapings of the oral mucosa in order to assess comparative expression levels of a number of miRNAs.**Methods:** Oral epithelial scrapings were preserved in either RNA Protect Saliva Qiagen Inc.), RNA Later (ABS) or in lysis buffer for 24 hours, 7 days or immediate RNA extraction. Samples were compared to known RNA from human heart. Total RNA was extracted using mirVana miRNA Isolation kit (Ambion), quantified by spectrophotometer (Nanodrop), and quality analyzed using Experion (Bio Rad). Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to quantify mature miRNA (miR-24; miR-16; miR-19b; miR-26b) using Taqman miRNA assays (ABS) and Ct values at a threshold of 0.35. Three reverse transcription methods were compared: (i) reverse transcribing with miRNA specific RT primers; (ii) megaplex RT reaction using pooled miRNA primers; or (iii) the latter with an additional pre-amplification step.**Results:** RNA amounts varied significantly, however this did not effect miRNA specific RT-PCR product production. The quality of the isolated RNA varied significantly with most samples generating poor quality RNA (RQI 2.5-5). Nevertheless, specific RT-PCR were generated from all extracts. Neither storage material nor time had little effect on the Ct value of RT-PCR. All methods resulted in miRNA specific RT-PCR products. The pre-amplified RT megaplex miRNA primer pool resulted in the most reproducibly lowest Ct levels.**Conclusions:** These results would indicate that RNA Protect Saliva and pre-amplified RT megaplex miRNA primer pool is a robust method for analyzing miRNA variation in oral epithelial cytological samples, independent of RNA degradation.**Relevance:** MicroRNAs (miRNAs) are small non-coding RNA genes that mediate gene expression at the post-transcriptional level with evidence that deregulation of specific miRNAs occurs in human diseases. These results allow for quantitative comparative analysis of miRNA in potentially malignant lesions.**B. Original Research Clinical**

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Eating disorders (anorexia nervosa and bulimia nervosa) and imbalance in oral bacterial microfloraGN Back-Brito¹, AJ Mota¹, SS Takamune², LAS Bernardes², EFGB Prado²,TA Cordas², FG Nóbrega¹, CY Koga-Ito*¹¹Department of Biosciences and Oral Diagnosis, São José dos Campos Dental School, Univ Estadual Paulista- UNESP, São Paulo, Brazil, ²Department of Psychiatry, Faculty of Medicine, University of São Paulo- USP, São Paulo, Brazil**Objectives:** Eating disorders (ED) may cause several systemic and oral alterations, although, there are not previous studies on the oral microflora of these patients. The aim of this study was to evaluate the microbial diversity in the oral cavity of these patients by culture and molecular Methods.**Methods:** Thirty-two anorexic and 27 bulimic paired with 59 control individuals were included in the study. Investigation by culture method was performed by plating oral rinses samples for staphylococci, enterococci, mutans streptococci, lactobacilli, enterobacteria/pseudomonas quantification. Species of staphylococci, enterococci and enterobacteria/pseudomonas were identified by API system. Counts of microorganisms

obtained with culture methods results were compared by ANOVA/Mann-Whitney test (5%).

Results: There were significant differences among counts ($P < 0.05$) of staphylococci, enterococci, mutans streptococci and lactobacilli between the ED group and the control, but no differences were observed for the prevalence of enterobacteria/pseudomonas ($P = 0.312$). Few differences between the groups were observed for the species diversity of the studied microorganisms. Investigation by culture-independent method was performed by ribotyping analysis by the sequencing of 16S rRNA bacterial genes of 3,000 clones for TA group and 1,500 clones for the control group. A total of 70 species were detected, 42 of them were observed only in the TA group, 35 only in the control group and 7 species were common to both groups. Species that were unique to ED included those in the genera *Achromobacter*, *Anaeroglobus*, *Bordetella*, *Neisseria*, *Rothia*, *Selenomonas* and *Capnocytophaga*. Cultive-dependent methodology indicated quantitative differences genera, except for enterobacteria/pseudomonas.

Conclusions: Eating disorders may cause modifications in the bacterial composition of oral microflora.

Relevance: Imbalance in the oral microflora caused by ED may be correlated to increased predisposition to specific infections.

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Microbiology of erosive-ulcerative oral mucosal lesions of unknown cause

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Objectives: To determine the possible infectious associations of erosive-ulcerative oral mucosal lesions of unknown cause

Methods: The study group comprised 23 patients with an age range of 20-65 yrs who presented with a spectrum of erosive-ulcerative oral mucosal lesions that could not be easily clinically categorized, and did not have a history or clinical features of likely oral lichen planus, pemphigoid, pemphigus, recurrent aphthous stomatitis, malignancy or trauma. Laboratory investigation included plates and cell cultures of Vero, McCoy and identification of serum antibodies to Herpetic and Chlamydia infections in IFA, RIF and PCR.

Results: The most frequent reasons of erosive-ulcerative oral mucosal lesions were Herpetic, Chlamydia and Candida infections. There was serological evidence of existing or past infection with Herpes Simplex viruses 1 or 2 in 29% of patients, while serologically detectable past or present Chlamydial infection was observed in 27%. Culture studies revealed Candidal infection in 18%, protothytes in 7%, and mixed infection in 46% of patients. All patients showed decreased cellular and humoral immunity and dysbacteriosis.

Conclusions: Detailed micobiological studies are rarely helpful in the diagnostic process of patients with erosive-ulcerative oral mucosal lesions of unknown cause.

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Diagnosis of HIV+ from a first oral sign

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Objectives: The purpose of this study is to present several HIV patients with oral signs as first indicator of their HIV+ infection, examined in the Stomatology Service of the General University Hospital of Valencia between 2001 and 2009.

Methods: A retrospective study was made by registering the age, sex, previous medical cases and current pathology of the patients examined in the Stomatology Service of the General University Hospital of Valencia for showing oral lesions.

Results: In 8 patients oral lesions were found which were considered suspicious of an unknown underlying immunodeficiency. The HIV diagnosis was later confirmed by corporal fluids testing.

The sample was made up of 8 males between 25 and 59 (42.88 ± 11.39 years). The pathologies found were: Kaposi's Sarcoma (3), Candidiasis (2), Syphilis (2), Lymphoma (1), oral hairy Leukoplakia (1) and acute necrotic ulcerative gingivitis (1). Two of the patients presented more than one pathology at the same time.

Conclusions: This study concludes that an HIV immunodeficiency or the AIDS disease diagnosis can be established from a first oral sign, when the related lesion is a diagnostic criterion for the illness.

Relevance: HIV infection affects 33.4 million people in the world. In 2008, there were 2.7 millions of new cases and 2 million people died because of AIDS. Around 140,000 persons in Spain live suffering from the HIV and in 2008, 1583 cases were diagnosed. The knowledge of this kind of pathologies can be useful for the dentist to detect a potential underlying immunodeficiency and helps to establish an early diagnosis from a first sign in the oral cavity.

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Prevalence of HPV infection in genital and oral sites in HIV-infected patients

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Objectives: Investigate the prevalence and distribution of HPV genotypes in oral and genital mucosa (healthy or with lesions) in a cohort of patients. Determine the associations between HPV infection and history of HIV infection

Methods: The evaluation was performed in a cohort of 142 patients (45 female, 97 male). The data recorded were: duration and risk factors of HIV infection, type and duration of HAART, CD4 count, viral load, presence of lesions in oral and/or genital mucosa. Furthermore, data recorded in the medical charts was also considered. HPV genotypes were looked for in oral and genital mucosa (anal and vaginal in female, anal and penile in male) by means of scraping. Each specimen was analysed for cytologic abnormalities and HPV detection and genotyping by PCR. CD8+CD38+ T cells were analysed by flow cytometry. Logistic regression was used to explore possible risk factors for dysplasia and for oncogenic, high risk HPV (HR-HPV) genotypes.

Results: The mean age of 142 patients was 42 years (range 24-61). In approximately 20% of patients (29/142) HPV infection was detected in the oral cavity. The most common HPV genotype in oral cavity was HPV-6 (6/29) and HPV-16 (5/29). Another genotype isolated in the oral cavity was SIBX3 (4/29), a putative HPV genotype. Patients with HPV infection in the oral cavity were 8 out of 45 female and 21 out of 97 male. All males had a history for having sex with men (MSM). Oral lesions were observed in 60 patients (42%): 7 (11%) showed clinical papilloma, and 20 (30%) HIV related lesions (candidosis, HHV manifestation and periodontal disease). High-Risk and Low-Risk HPV infection in oral and genital mucosa were present in 75% and 23% of patients, respectively.

Conclusions: Considering the more common HR-HPV infection detected in this cohort of patients, it seems to be crucial to screen and follow up all HIV positive subjects for HPV infection at different mucosal sites.

Relevance: These data suggest screening HIV infected patients in order to assess HPV co-infection in oral and genital mucosa.

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Comparison of oral candidiasis prevalence in renal transplants and controls

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Introduction: The aim of this study was to analyse the prevalence of oral candidiasis in a group of renal transplant patients (RTPs) compared with healthy controls (HCs).

Details: The study included 500 RTPs (307 men, 193 women, mean age 53.63 years) and 501 HCs (314 men, 187 women, mean age 52.25 years). Demographic and pharmacologic data were recorded for all subjects.

Methods: Seven (7.4%) percent of the RTPs presented oral candidiasis compared to 4.19% of HCs ($p \leq 0.03$). The most frequent oral candidiasis in RTPs was erythematous candidiasis associated with denture use, followed by angular cheilitis and pseudomembranous candidiasis. Analysis showed that age, smoking habits, dose and level of mycophenolate mofetil and presence of dentures all affect the prevalence of oral candidiasis significantly. The multiple logistic regression model only indicated denture use as a predictor for oral candidiasis.

Conclusions: This study showed that the prevalence of oral candidiasis in the RTP Group was significantly higher than in the HC Group. We report a lower prevalence of oral candidiasis in RTPs than previous reports.

Relevance: The presence of oral fungal infections in RTPs emphasizes the importance of regular oral screening in these patients. Immunosuppressant treatment depresses the cell-mediated immune response. For the clinician, this means a greater risk of oral infection and other associated complications.

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Evaluation of diagnostic aids for the detection of oral potentially malignant disorders

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Objectives: Early detection of oral cancer is crucial in improving survival rate. A variety of new and emerging diagnostic aids and adjunctive techniques are currently available to potentially assist in the detection of oral possibly malignant disorders (OPMDs). The accuracy (sensitivity and specificity) of three adjunctive tests, namely Toluidine blue staining, Autofluorescence, and Chemiluminescence was evaluated in relation to conventional oral examination and surgical biopsy (gold standard).

Methods: A total of 99 patients, 55 males and 44 females, age 25 to 82 years (mean age 58 ± 13 years), who presented to the Oral Medicine Clinics at King's and Guy's Hospitals, London with oral white and red patches suspicious of precancer, were enrolled. There were 59 Whites, 19 Asians, 19 Afro-Caribbean and 2 of mixed ethnicity. 47 patients were current smokers, 22 ex-smokers, while 20 were alcohol misusers. In a detailed investigation these patients underwent all three chair-side tests followed by surgical biopsy.

Results: 58 patients had oral leukoplakia/ erythroplakia, 4 chronic hyperplastic candidiasis and the rest frictional keratosis (12) or lichen planus (24). Out of the 99 lesions, 82 (83%) showed loss of fluorescence, 70 (71%) were positive (aceto-white) with Vizilite and 36 (36%) retained toluidine blue. Following surgical biopsy 35 had oral dysplasia (20 mild, 9 moderate and 6 severe). The sensitivity (se) and specificity (sp) for the detection of a dysplastic lesion were: autofluorescence (se 80%, sp 1%), vizilite (se 77%, sp 16%) and toluidine blue (se 34%, sp 84%).

Conclusions: While these adjuncts were useful in confirming the presence of most of the OPMDs, their ability to discriminate high-risk from low-risk lesions is unclear.

Relevance: Developing methods to identify patients with potentially malignant disorders at risk of developing cancer remains a significant issue. Accurate and reliable tests are needed if we are to propose programmes for screening for oral cancer.

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Leonardo da Vinci Partnership – A Lifelong Learning Programme to Raise Awareness of Dental and Medical Professionals within Europe for the Early Detection of Oral CancerS Warnakulasuriya*, A Gould¹, M Mignogna², S Leuci², I Thermidou³, A Ravidis³*¹King's College London, UK, ²Federico II, University of Naples, Italy, ³Saint Savvas Hospital, Athens, Greece*

Objective: To create cooperation among institutions at a European level in order to raise awareness of oral cancer among dental and medical professionals. To develop educational material for purposes of screening and for the early detection of oral cancer and precancer.

Methods: In order to understand gaps in knowledge and performance, we undertook:

1. A review of literature on dentist's awareness, opinions and behaviors in published studies regarding early detection and prevention of oral cancer in Europe.
2. A review of literature on oral cancer screening programs in Europe.
3. Catalogued and reviewed all available teaching resources (including e-learning) on screening for oral cancer.

Results: Dentists encounter oral cancer patients infrequently during their life-time performance. The diagnostic dilemma is complicated by oral mucosal disorders that may be mistaken for cancer. The reviews of literature confirm fundamental gaps in knowledge and understanding of early signs and symptoms. There are inequalities in screening performance within as well as between European countries, largely based on available resources for training. In the United Kingdom there has been a resolute drive to develop e-learning material (primarily funded by the Department of Health) that could be adopted for European use.

Conclusions: The Leonardo da Vinci Partnership will address the failures to implement screening for oral cancer by recommending strategies on involvement of medical and dental professionals and producing e-learning material that could be translated to European languages.

Relevance: A three to five year educational agenda within Europe will lead to key improvements in dentists' and doctors' performance in the early detection of oral cancer.

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Quality of life and clinical function after oral cancer treatmentT Pereira¹, J Fantom-Neto², GP Pastor², JC Berto², CM Navarro³*¹Department of Dental Materials and Prosthodontics, Araraquara Dental School, Sao Paulo State University (UNESP), Brazil, ²Department of Otolaryngology Head and Neck Surgery, Hospital Amaral Carvalho, Jau/SP, Brazil, ³Department of Oral Diagnosis and Surgery, Araraquara Dental School, Sao Paulo State University (UNESP), Brazil*

Objectives: The purpose of this study was to investigate treatment modalities that influence health related quality of life (HRQOL) and to evaluate the postoperative function of patients who underwent treatment for intraoral cancer.

Methods: The University of Washington Head and Neck Questionnaire (UW-QOL) and clinical examination were used, and the outcome was compared against patient's age, gender, TNM stage, site, surgical and adjuvant therapy. The patients were submitted to clinical examination and interview (questionnaire) between April and December 2008. Fifty patients underwent surgery and 29 were submitted to adjuvant radiotherapy or chemotherapy (Rt/Ct).

Results: The anatomical site and the tumour size did not influence the treatment modality. Adjuvant Rt/Ct was associated with worse HRQOL related to pain, swallowing, chewing, taste and saliva. Tongue mobility was significantly worse in patients submitted to adjuvant Rt/Ct treatment. Patients significantly presented problems with speech and more difficulty eating hard foods when they suffered adjuvant Rt/Ct.

Conclusions: The adjuvant Rt/Ct for oral cancer has a clear and direct influence on well-being and associated quality of life. The adjuvant Rt/Ct resulted in worse HRQOL domains compared with surgery exclusively. Chewing and deglutition were the domains mainly affected in patients undergoing Rt/Ct.

Relevance: Understanding the side effects mainly of the adjuvant therapy and how patients experience them as well as the functional and quality of life implications is important to treatment evaluation and patient decision making.

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A Survey of the Awareness and Impact of Oral Mucositis (OM) in Patients Undergoing Chemo- and Radiotherapy Treatment for Head and Neck Cancer

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Objective: To understand awareness of oral mucositis (OM) and impact on quality of life (QoL) in patients receiving chemotherapy and/or radiotherapy for head and neck (H&N) cancer.

Methods: A web-based survey of H&N cancer patients between 07/2009 and 06/2010 via the website www.mouthcancerfoundation.org.

Results: A total of 265 patients undertook the survey. The most common diagnoses were tongue (46.7%) and tonsillar cancer (21.0%). 36.9% of patients received radiotherapy and 61.3% combined chemotherapy and radiotherapy. 79.8% (130) of patients experienced OM. The most common duration (9–12 weeks) occurred in 23.4% of patients. Only 14.1% experienced OM for less than 1 month, 68.5% experienced OM for at least 2 months and 12.5% for more than 1 year. 75.5% of patients reported a pain score of at least 7/10 due to OM with the majority reporting an impact on QoL with difficulty eating (91.3%), swallowing (81.7%), drinking (68.3%) and talking (68.3%) being very common.

Significant numbers of patients reported embarrassment eating with others (42.9%), embarrassment regarding appearance (23.0%) and need for strong (opioid) analgesia (50.0%). A small proportion of patients had a delay/change in cancer treatment (10.9%) as a result of OM. 74.8% (122) patients had been informed about OM prior to treatment but nearly all patients (95.3%) contacted a doctor/nurse as a result of OM and the majority of patients received a prescription (86.6%) and/or advice (71.4%). Patients also consulted pharmacists (5.5%), the internet (35.4%), patient groups (10.2%) and dentists (10.2%), and also purchased OTC (11.0%) or herbal/alternative (7.9%) treatments.

Conclusions: The burden of OM in H&N cancer is high and effects on QoL are common. Although many patients are informed about OM, when it occurs they require further advice/treatment.

Relevance: The potential impact of OM and need for on-going patient support is a key for clinicians involved in H&N cancer.

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Oral & Pharyngeal Verrucous Carcinoma Epidemiological and Clinical Features in four DecadesR Czerninski*, A Zini², O Moshel³, HD Sgan Cohen²*¹Department of Oral Medicine, ²Department of Community Dentistry, ³Hebrew University-Hadassah School of Dental Medicine, Jerusalem, Israel*

Objectives: Verrucous Carcinoma (VC) is associated with chewing tobacco and HPV. As tobacco chewing is very rare in Israel, and HPV related cervical cancer has a very low rate in Israel, we wished to characterize VC over 4 decades to identify other risk groups

Methods: Data (gender, age, ethnicity, country of origin tumor site.) were derived from the Israel National Cancer Registry (INCR) and included all registered data during 1970–2006. Analyses of associations between variables were conducted employing Log-Rank test, and Chi Square. Kaplan-Meier five year survival plots were calculated. Level of statistical significance was chosen at $P < 0.05$.

Results: Of 11,842 oral and pharyngeal cancer cases, 4874 were SCC of which 4012 were cancers of the oral cavity, pharynx and lips. Of these, 163 (4.0%) were VC (88 males and 75 females). The average age was 66.83 (62.3 yrs for male, 72.5 yrs for female). The most prevalent sites were: lips (24%), tongue (19%) and cheek mucosa (14%). Most lip and cheek mucosa lesions were among males, while gum, floor of the

mouth, or palatal lesions were found among females ($P = 0.002$). Five year survival (5YS) rate was 71.2%; survival was higher among those below 58 yrs of age and decreased with age ($p = 0.017$). Lowest 5YS was found for gums (52.6%) and highest for the naso-pharynx (85.7%) ($p = 0.043$).

Conclusions: Age can be an important factor in VC. Clinicians should pay close attention to verrucal lesions, on lips, tongue and buccal mucosa at older ages. VC might have a low survival than earlier reported and should be treated with caution.

Relevance: The clinician should be aware of VC despite its rarity.

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Narrow band imaging and high definition television in evaluation of oral and oropharyngeal squamous cell cancer: A prospective study on 80 patients

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Objectives: To prospectively evaluate the diagnostic gain of these technologies in the evaluation of oral (O) and oropharyngeal (OP) squamous cell carcinoma (SCC).

Methods: Between April 2007 and September 2009, we analyzed 80 patients divided into 2 groups. Group A included 26 patients previously biopsied and diagnosed as affected by OSCC and OPSCC and subjected to pre- and intraoperative HDTV white light (WL) and HDTV NBI endoscopy. Group B included 54 subjects already treated for an OSCC or OPSCC and followed-up by HDTV WL and HDTV NBI.

Results: Nine of 26 (34%) patients in Group A showed adjunctive findings with NBI compared to standard WL. All of these findings received histopathologic confirmation. Eleven of 54 (20%) patients in Group B showed positive NBI findings. All lesions were histologically confirmed as neoplasms. Sensitivity, specificity, positive, negative predictive values, and accuracy for HDTV WL were 47%, 100%, 100%, 87%, and 68%, respectively, and for HDTV NBI were 95%, 100%, 100%, 93%, and 97%, respectively. Overall, 20 of 80 (25%) patients had a diagnostic gain in applying NBI and HDTV: 6 patients received a diagnosis of recurrence and 1 of persistence after previous treatments; 5 showed a metachronous tumour; in 4 a synchronous tumour was diagnosed; 3 lesions were upstaged; 1 patient affected by an unknown primary with positive neck nodes was demonstrated to harbour it in the anterior tonsillar pillar.

Conclusions: NBI and HDTV technologies seem to be very promising diagnostic tools in the evaluation of OSCC and OPSCC.

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Economic Impact of Oral Cancer: Duration of hospitalisation and ambulatory follow-up after complete resection of oral squamous cell carcinoma in 63 patients

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Objectives: Oral cancer is a debilitating disease. Every effort should be made to minimize the consequences of therapy and to keep the patient's appearance socially acceptable. This can lead to rather long hospitalisation and frequent follow-up visits. Our aim was to investigate the overall economic impact of hospital care of patients who had undergone primary radical resection of their tumour until death. Most investigators consider only the costs of 5-year survivors but the total costs are rarely examined.

Methods: Between 1991 and 2008, 201 patients underwent radical resection for oral squamous cell carcinoma (OSCC), excluding the lip. Of these, 63 patients had died. The medical records of the latter group were retrospectively reviewed.

Results: The mean duration of hospitalisation was 66 days, in some cases including periods for intensive care, tracheotomy, reconstructive procedures, radio- and/or chemotherapy or complications (e.g. flap failure, kachexia). The mean number of post-op follow-up visits was 31, including visits for prosthodontic rehabilitation. Although a number of variables were examined only tumour size, tumour recurrence and tobacco and alcohol consumption showed significant differences. The overall cost of a patient with OSCC was approximately 45.000 Euros, from the beginning of therapy until death after 48 months.

Conclusions: OSCC often necessitates numerous therapeutic interventions and supportive care by hospital specialists. This will be reflected in the costs of hospital care. Because OSCC severely affects the quality of life (facial appearance, speech, mastication, deglutition, dentition, smell, taste, sensitivity etc.) it is our obligation to ameliorate these deficits as much as possible.

Relevance: The global financial crisis is affecting health care also. The public should be aware of the burden of self-inflicted diseases. Considering the fact that OSCC is in most cases a preventable disease, every effort should be made for prophylaxis and early detection.

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Oral cancer knowledge: a survey administered to patients in Dental Departments at a large Italian hospital

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Objectives: We aimed to describe knowledge regarding oral cancer (OC) risk factors and symptoms among patients attending Dental Departments within Italian University hospitals and assess whether smoking habits and family history of OC affected OC knowledge.

Methods: 2200 questionnaires were sent to four hospitals in order to assess patients' knowledge regarding clinical and epidemiological aspects of OC. Information on socio-demographic and personal risk behaviours was also collected. OC knowledge was evaluated overall and stratified by smoking status and oral cancer family history: heterogeneity was assessed by use of the χ^2 test.

Results: A total of 1201 questionnaires were collected (response rate, 55%). Patients socio-demographic characteristics were similar by study site. The majority of participants correctly identified cigarette smoking as a risk factor for OC (86%) and vegetable consumption (74%) and good oral hygiene (77%) as possible protective factors; however it was less widely known that heavy alcohol consumption (55%) and pipe smoking (19%) were OC risk factors. Less than 15% of patients reported having received OC counselling by a dentist or physician. In stratified analyses, current (34%), former (11%) and never smokers (50%) reported similar OC knowledge. Individuals with a positive family history for oral cancer (17%) were significantly more likely to identify risk factors for oral cancer correctly such as cigarette smoking (94% vs. 85%, $P = 0.0011$), possible signs of oral cancer (83% vs. 72%, $P < 0.005$), and report having received oral counselling by physicians (13% vs. 7%, $P < 0.001$), dentists (24% versus 12%, $P < 0.001$) or other health care personnel (27% versus 8%, $P < 0.001$). Family history of OC did not affect smoking status.

Conclusions: Patients were knowledgeable about most risk factors and clinical signs of OC; positive family history of OC was associated with improved knowledge. Oral health care providers infrequently talk about OC to their patients.

Relevance: Better communication between oral health care personnel and patients is needed.

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Clinical study of the osteonecrosis of the jaws in 67 patients treated with intravenous bisphosphonates for malignant diseases

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Objectives: To analyze the characteristics of patients who received intravenous bisphosphonates and developed osteonecrosis of the jaw (ONJ), compared with other patients who were also treated with intravenous bisphosphonates and did not develop the disease and a control group, and to identify possible risk factors for ONJ.

Methods: The study sample consisted of 156 patients divided into three groups: group A, composed of 67 patients who were treated with intravenous bisphosphonates and developed ONJ; group B, consisting of 53 patients having received intravenous bisphosphonates did not develop ONJ; group C, comprised 36 healthy patients. We, first performed a descriptive statistical study by χ^2 test and Fisher's exact test for qualitative variables and an analysis of variance (ANOVA) for continuous ones. For patients in group A, bivariate and multivariate analysis was conducted and had further Kolmogorov-Smirnov, Kruskal-Wallis and Mann-Whitney tests. Statistical significance level was set at $P < 0.05$.

Results: The DMF index and the number of missing teeth were significantly higher in patients with ONJ ($P < 0.05$). Cytostatic drugs, corticosteroids, hormone therapy are associated with an increased risk of developing ONJ ($P < 0.05$). The extent of bone exposure was higher in Group A, though not statistically significant; female patients between 60 and 70 years of age, diagnosed with breast carcinoma had more predisposition for ONJ.

Conclusions: In patients treated with intravenous bisphosphonates for malignant diseases, poor oral health status along with a long exposure to intravenous bisphosphonates and administration of adjuvant therapies such as cytostatics, corticosteroids and hormones, may be related to increased risk of developing osteonecrosis of the jaw.

Relevance: The study examined variables associated with ONJ in a large series and found significant associations and those that indicate poor prognosis of ONJ.

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Primary intraoral malignant melanoma. Clinicopathological analysis of seven cases

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Objectives: The purpose of this study was to analyze the demographic, clinical and histopathological features of 7 cases of primary intraoral malignant melanoma and to compare them with similar published studies in order to contribute to the better understanding and diagnosis of this rare tumor.

Methods: The study material comprised 7 cases of primary intraoral malignant melanoma registered in the files of the Departments of Oral Pathology, Dental School, Athens (6 cases) and 251 Hospital of Hellenic Airforce, Athens (1 case). Age, gender, location and clinical characteristics were retrieved from the clinical files. The microscopic slides were reviewed and the histopathological parameters were recorded.

Results: Patients' age ranged from 37 to 86 with an average of 64.2. Five patients were women and two were men. The location of the lesions were the maxilla (3 cases), the palate (2 cases), both maxilla and palate (1 case) and the mandible (1 case). The clinical appearance of the lesion was specified as a tumor in 3 patients, a colour alteration in 3 patients and an ulcer in 1 patient. The colour of the lesions ranged from brown or black to blue or red. Histologically, all cases showed an invasive pattern, which was combined with in-situ growth in 3 cases; the cell constituency showed significant variation, including epithelioid, plasmacytoid and clear cells. One case was classified as amelanotic melanoma.

Conclusions: Primary intraoral malignant melanoma is a rare oral mucosal neoplasm with a predilection for maxillary and/or palatal involvement. The variation in clinical presentation and histopathological features may cause difficulties in the diagnosis.

Relevance: Primary intraoral malignant melanoma has a poor prognosis, thus early diagnosis and treatment, based on the knowledge of the salient features of the disease, is of paramount importance.

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A retrospective study of 128 cases of initial lesions of Oral Squamous Cell Carcinoma (OSCC)

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Objectives: The purpose of this study was to analyze the clinical features of Oral Squamous Cell Carcinomas in stage I diagnosed in the Service of Stomatology (University General Hospital. Valencia, Spain), and its evolution after treatment.

Methods: In this retrospective study we included 128 patients with a history of OSCC in stage I, diagnosed from 1993 to 2010. We studied the clinical aspects and location of the lesions as well as the age, sex, and the presence of toxic habits in the individuals. Recurrence and survival data were also recorded after the treatment.

Results: Of 128 patients, 75 (59.4%) were men and 52 (40.6%) women. The average age was 61 ± 14 years (range 27-95). Most of the patients had no smoking (62.5%) or no alcohol (68%) habits. The most frequent lesions found were ulcers (49.2%), being the 70.3% of them located in the floor of the mouth and in the lateral and ventral tongue. A 78.1% of the patients did not complain of pain. Only a 20.3% of them had a recurrence after the treatment and the survival rate was 92.2%.

Conclusions: The most commonly clinical presentation observed on stage I of OSCC was ulceration located on the tongue or on the floor of the mouth. The high rates of survival of these lesions diagnosed and treated on stage I highlights the importance of establishing an early diagnosis.

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Patients with oral carcinoma of the scaly cells in T3 and T4 stages

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Objectives: The aim of this study was to analyse the clinical characteristics of patients diagnosed with oral carcinoma of the scaly cells (OSCC) in T3 and T4 stages at the time of diagnosis, treated by the Stomatology Service at the General University Hospital of Valencia (Spain) from 1993 to March 2010.

Methods: A retrospective analysis was carried out on 71 patients analysing the following clinical variables: age, sex, presence of habits such as tobacco and alcohol consumption, type of location of the lesions, bone and paraesthesia affection.

Results: From the seventy-one analysed patients, the average aged obtained was 62 ± 14 years old, of which 43 (60.6%) were males and 28 (39.4%) were females. Thirty-five patients (49.3%) were smokers and 36 (50.7%) were non-smokers. Twenty-seven (38.0%) habitually drank alcohol and 6 patients (8.5%) presented with erythroplasia and 21 (29.6%) in the form of tumours, with the most frequent being in the form of ulcers (57.7%), located on the lower mouth, ventral surface and sides of the tongue and

on the gums. There was bony involvement in 58 patients (81.7%) and paraesthesia in 9 (12.7%).

Conclusions: According to this study, oral carcinoma of the scaly cells in T3 and T4 stages appear more frequently in males during the sixth decade of life. It is clinically apparent usually as an ulcer on the tongue or gums, most frequently producing bony involvement and/or paraesthesia effects.

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Proliferative verrucous leukoplakia with more than one malignancy

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Objectives: The aim of this study was to evaluate the clinical characteristics of patients with proliferative verrucous leukoplakia (PVL) who developed more than one cancer.

Methods: We reviewed 85 case histories of patients with PVL who were diagnosed and treated at the Department of Stomatology, University General Hospital of Valencia between 1992 and 2010. All the patients fell within the criteria used to define PVL and had been under observation for at least a year. We took as our study group the patients who had developed more than one cancer. We registered sex, age, tobacco habits, type and localisation of lesions, time of follow-up, and survival rates.

Results: From the 85 patients with PVL, 30 (35%) developed carcinoma and, of these, 18 developed more than one cancer (60%), with a mean average of 3.3 cancers per patient. Fifteen of the patients were female (83%) and 3 were male, and the mean average age at the time of diagnosis was 68 years. Presence of cancer was not correlated with tobacco consumption. All cancer was localised to the gingivae with erythroplakias and verrucous leukoplakias being the most commonly occurring clinical presentation. The follow-up period ranged between 1 and 14 years, with a mean average of 7 years. The five year survival rate was 55%.

Conclusions: Proliferative verrucous leukoplakia has a high tendency to develop more than one cancer, especially in women with erythroplakia and verrucous lesions localised to the gingivae.

Relevance: The relentless growth pattern associated with PVL and its propensity to develop into carcinoma merit close clinical supervision and monitoring.

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Oral metastasis from distant primary tumors: a study of 22 patients

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Objectives: The objective of our study was to analyze the clinical characteristics of a group of patients with metastasis in oral cavity from distant primary tumors.

Methods: The study group consisted of 22 patients with metastasis in the oral cavity from the Stomatology Service of the University General Hospital of Valencia, for the last 15 years. We analyzed their clinical characteristics, their evolution and treatment.

Results: The average of our patients was 59.04 years, with a distinct male predilection (18'8% females: 81.2% males). There were 54.54% of non-cigarette smokers. The areas more affected were soft tissues (57.89), the jaws (5.26%) or a mixed form, soft and hard tissues (36.84%). The most frequent clinical types were exofitic lesions (72.72%), ulcers (4.54%) and there sometimes were no lesions (22.72%).

31.8% of patients related sensitive defect of orofacial nerves. There was a known primary malignancy in 50%, there were not known primary malignancies in 31.81% and a synchronic malignancy was diagnosed in 18.81%. The most known primary tumor was lung (33.33%), prostate (20%), oesophagus (20%), liver and breast cancer (4.54%).

Conclusions: We found that the majority of our patients were males who were over 55 years old, had oral metastasis which were predominantly soft tissue lesions (50%) continued by mixed forms (soft and hard tissues). The primary tumors most frequent were lung, prostate and oesophagus.

Relevance: The relevance of this study is that we found oral metastasis more commonly in soft tissue and mixed forms (soft and hard tissue) than in hard tissues, as well as a high frequency of cases with no known primary tumors.

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Oral squamous cell carcinoma. Clinicopathological presentation and prognostic factors

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Objectives: The purpose of this study was to study social, clinical, and pathological features of 100 patients with oral squamous cell carcinoma (OSCC) and to evaluate variables that can impact the survival rate of patients.

Methods: A total of 100 patients with OSCC were recruited retrospectively. Data on patient age, gender, habits, clinical and histopathological aspects of the lesion, TNM and stage of the tumour and survival were collected and analyzed. Survival curves were generated using Kaplan-Meier method, and multivariate analysis was made using Cox regression.

Results: The average age of the patients at diagnosis was 63.3 years, with a male to female ratio of 3:2. Location of cancer on the tongue and floor of the mouth was found in 57% of the patients and the most common lesion type was ulceration. Fifty per cent of the patients were diagnosed at advanced stage. The overall 3-year survival rate was 75%. The clinical factors with a prognostic value were the tumour size, lymph node status and distant metastasis.

Conclusions: Despite several diagnostic and therapeutic advances, survival rate is low in OSCC. Tumour grading and regional lymph node metastasis may serve as useful indicators for prognosis.

Relevance: This study emphasizes the importance of early diagnosis in the survival rate of the patients.

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Langerhans cells and T cells in leukoplakias – a retrospective study

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Objectives: Activation of the immune system is crucial in host response to tumour cells. The aim of this retrospective study was to compare presence and distribution of Langerhans cells (LCs) and T cells in oral leukoplakias (LPL) that transform into squamous cell carcinomas (SCC) with LPL that do not develop into SCC.

Methods: Tissue specimens from patients with LPL biopsied and a histopathological diagnosis of hyperkeratosis with dysplasia were retrieved from our archives (LPL/LPL; n = 10). Also, specimens biopsied at least twice with a histopathological diagnosis of hyperkeratosis with dysplasia at the first occasion and a histopathological diagnosis of SCC at the second occasion were collected (LPL/SCC; n = 10). Immunohistochemistry was performed using monoclonal antibodies against CD1a+ (LCs), CD3+ T cells Ki67+ and p53+ cells. Digitized images of sections were obtained and quantitative analysis of number of positive cells/mm² were conducted. Statistical analysis: Mann-Whitney U-test.

Results: LPL/LPL compared to LPL/SCC: Epithelium: LCs: median values: 87/43; $P \leq 0.05$. T cells: 93/167; $P > 0.05$. Ki67+ cells: 613/352; $P > 0.05$. p53 Connective tissue: LCs: 59/40; $P = 0.05$. T cells: 594/876; $P > 0.05$.

Conclusions: The number of LCs is significantly decreased in LPL that transform into SCC compared to LPL that do not transform into SCC. This implies that impaired immunosurveillance may be of importance in the malignant transformation process. No significant differences could be detected between the groups in CD3, Ki67 and p53 expressing cells. Further investigations are presently underway.

Relevance: Investigation of immunosurveillance in premalignant oral mucosal disorders can result in new knowledge about malignant transformation and immune activation.

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Squamous odontogenic tumour (SOT) AND SOT-like proliferations:

A comparative immunohistochemical study

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Objectives: The proliferating and anti-apoptotic related proteins, as well as keratins known to be expressed in simple and odontogenic epithelia, were evaluated in SOT-Like Proliferations (SOT-LP) arising in the cystic wall of odontogenic cysts in comparison to Squamous Odontogenic Tumor (SOT) islands, in order to determine their possible neoplastic capacity.

Methods: Ten cases of SOT-LP arising in the cystic wall of 7 radicular and 3 residual cysts and two cases of intraosseous SOT, were evaluated using a routine streptavidin-biotin peroxidase immunohistochemical method with antibodies against Ki67, Bcl-2 and cytokeratins (CK) 8/18 and 19. The number and localisation of Ki-67, Bcl-2, CK8/18 and CK19 immunoreactive cells were estimated in the SOT-LP, in related cystic epithelium and SOT islands.

Results: All cases of SOT-LP and SOT showed <5% Ki-67 nuclear expression at the basal and suprabasal epithelial layers. Weak Bcl-2 immunostaining was observed in < 5% of basal cells in the cystic epithelium and SOT-LP, in contrast to SOT cases in which Bcl-2 was expressed by >25% of tumour cells. In all cysts and SOT-LP islands, CK8/18 and CK19 were expressed more intensively at the superficial epithelial layers and the central areas respectively. In SOT cases, CK8/18 immunostaining with variable intensity was observed mainly centrally, whereas almost all cells of the tumour islands showed intense CK19 expression.

Conclusions: SOT-LP showed a similar immunohistochemical profile regarding the expression of proliferating and anti-apoptotic related proteins with the cystic epithelium in all cases; a finding suggestive of their reactive nature.

Relevance: Although SOT-LP show common histopathological features with SOT, they most probably represent a reactive proliferation of the cystic epithelium and their presence in the cystic wall is not indicative of a neoplastic capacity.

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A non-invasive method for early detection of aneuploid cells in potentially malignant oral lesions

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Objectives: Chromosomal numerical aberrations are an early event in oral carcinogenesis. We aimed to develop a non-invasive method for early detection of aneuploid cells (ACs) obtained by oral brush samples from potentially malignant lesions, malignant lesions and from heavy smokers.

Methods: The study group included 259 individuals: 90 heavy smokers (31 with lung cancer and 59 without lung cancer), 57 with oral lichen planus (OLP), 35 patients with oral leukoplakia and 15 with squamous cell carcinoma (SCC), 62 patients were selected as control group. Cells were obtained by use of a disposable brush and were simultaneously analysed for morphology and Fluorescence in-situ hybridisation (FISH) using a multiparametric cell scanning system. Dual FISH was performed using centromeric probes for chromosome 2 and 8.

Results: Over 2% of ACs was detected in all cases with SCC, in 45% of the leukoplakia cases, in 24% of patients with OLP, in 12% of the smokers without lung cancer and in 23% of the heavy smokers with lung cancer. 5% of the control subjects had over 2% ACs in the samples examined. In leukoplakia, the proportion of ACs increased with the severity of the histopathologic diagnosis. Five patients, 2 with oral leukoplakia and three with OLP developed SCC; in these patients a significant proportion of the cells were aneuploid. Most of ACs had normal morphology.

Conclusions: ACs can be detected in the early stages of oral carcinogenesis, and in high risk patients. We suggest that the supplement of a brush sample and the simultaneous morphological and FISH analysis of the cells collected, enable early detection of potentially malignant conditions and monitoring of high risk patients.

Relevance: The presence of aneuploid cells in oral samples obtained non-invasively, can predict the malignant potential of oral lesions for early detection of oral cancer.

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Direct Visualization of Oral-Cavity Tissue Fluorescence and Toluidine Blue Staining: New Adjunctive Aids for Oral Medicine Practitioners in Early Oral Cancer Diagnosis and Potentially Malignant Disorders Follow-Up?

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Objectives: Oral squamous cell carcinoma is believed to arise from oral potentially malignant disorders (PMD) in the 50% of the cases. Early identification of 'high risk' PMD could greatly reduce mortality and morbidity due to oral cancer. Unfortunately, conventional clinical examination and histopathological confirmation remain the 'gold standard' for the detection of oral cancer.

Aims: The purpose of this study are i) to assess the additive value of VELscope® and toluidine blue in the evaluation of clinical features of PMDs, previously identified by visual conventional examination; and ii) to establish the sensitivity, specificity and diagnostic accuracy of VELscope® and toluidine blue in discriminating 'low risk' and 'high risk' PMDs.

Methods: A total of 100 patients, with suspected PMD, were accrued to the study at the Unit of Oral Medicine. All patients undergone i) conventional visual exam; ii) clinical examination by means of VELscope® iii) exam with toluidine blue. All clinical examinations were performed in blindness by two different investigators. Each investigator reported the subjective assessment of the lesion clinical features, with or without the adjunctive techniques. All PMDs visualized were recorded either as VELscope Positive (VsP) or VELscope Negative (VsN) and toluidine positive (TbP) or negative (TbN). All visualized lesions were then biopsied and classified using the binary grading system ('low risk'/'high risk').

Results: The adjunctive techniques helped to enhance the brightness and edge visibility in the majority of cases. The 91.3% of the bioptic samples, histologically identified as

carcinoma were sampled as VsP and TbP lesions, whereas the 90% and 85% of 'low risk' PDM were respectively VsN and TbN. Using histology as the gold standard, VELscope and toluidine blue achieved a sensitivity both of 91.3%, a specificity of 90.1% and 85.6% and a diagnostic accuracy of 90.5% and 86.9% respectively, when discriminating 'low risk' and 'high risk' PDMs.

Conclusions and Relevance: Data collected suggests that the new adjunctive techniques can identify high risk PDM and enhance visualization of the clinical features of the PMDs.

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Sampling methods for HPV-DNA detection in OSCC: Biopsy Vs Brushing

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Objectives: The lack of uniformity among studies regarding Human Papillomavirus (HPV) DNA detection in oral lesions still represents the main limitation for the elucidation of the role of HPV in oral carcinogenesis. The aim of this investigation was to compare HPV DNA frequency and type-specific distribution in samples obtained by brushing and biopsy of OSCC. The correlation between HPV detection rate by each method of sampling and demographical (age, gender), behavioural (smoke and alcohol) and clinical-pathological variables (site of lesion, degree of keratinization and histological grading) was examined.

Methods: HPV DNA was detected in brushed cells and formalin-fixed paraffin-embedded biopsies from 76 immunocompetent adults consecutively diagnosed with OSCC from January 2007 to December 2009. HPV DNA detection was performed by a double method (nested PCR amplification followed by direct DNA sequencing and the commercial assay INNOLiPA HPV Genotyping). Data was statistically analyzed (univariate and multivariate statistics, $P < 0.05$).

Results: HPV DNA was detected in 17% of brushed specimens and 11% of biopsies ($P = 0.025$). No statistical difference was noted between two methods regarding High Risk HPV types frequency (brushing 11.8% vs biopsy 11%; $P = 0.797$). A concordance between methods was found in 59/76 patients, of which 57 were negative and 2 shown a type specific concordant results for HPV. Any demographical, behavioural and clinical variable was associated with HPV detection in both types of specimens, excepting for moderate grading (G2) in brushed cells (OR = 6.95; 95%CI: 1.42-34.04).

Conclusions: Brushing demonstrated more reliability for HPV detection than biopsy, especially when highly sensitive procedures of viral DNA identification were used.

Relevance: A small fraction of OSCC seems to be linked to HPV in the Mediterranean area. Other studies with a major sample size and using more sensitive methods (laser micro-dissection of tumor tissue, cytological sampling by mouthwash) are just beginning to validate this report.

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A case series analysis of 248 oral cancers from Yemen

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Objectives: This study gives a detailed description of tongue, gum and floor of the mouth (FOM) squamous cell carcinoma (SCC) in 248 Yemeni patients.

Methods: A computer-based archive of the National Center of Oncology (NCO) (Sana'a, Yemen) was obtained. The available data regarding age, sex, province and histological differentiation for cases diagnosed, in 2007-2008, with (SCC) of the tongue, gum and (FOM) (n=248) were extracted. (Data regarding habits are currently extracted from the hard files).

Results: Of the retrieved cases, 128 (51.6%) were male. The overall mean age of the patients was 58.21 (13.43); for the male and female, it was 58.96 (14.19) and 57.41 (12.59) respectively. The minimum age at onset was 30 (n=4, 3males) while the maximum age was 110 (n=1male). Approximately 64% of patients (67% of males and 61% of females) were more than 50 years in age. The site distributions of cancers (in males and females respectively) were the tongue, 62.9% (34.7% and 28.2%), the FOM, 22.2% (11.3% and 10.9%) and the gum, 14.9% (6% and 8.9%). Regarding histological differentiation, 74.6%, 16.9%, 3.6% and 2.8% of cases were well, moderately, poorly differentiated and undifferentiated respectively. Most of the cases were referred from Al-Hodiada (26.6%), Hajja (12.9%), Taiz (10.1%), Al-Mahweet (7.3%) and Dhamar (6.9%) provinces. The other 17 provinces contributed with small proportions separately.

Conclusions: Since the (NCO) is the only cancer treatment and registry center in Yemen, our retrieved data might represent the whole picture in Yemen. Along with poverty, oral cancer is prevalent in provinces where almost all males and, to a less

extent, females practice at least one of the bad habits of khat-chewing, smoking and shammah (dry smokeless tobacco) use.

Relevance: To exactly evaluate the burden of oral cancer in Yemen, Cancer registry should be more precise and include all the practiced habits.

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Impact of diagnostic delay on the survival of head and neck carcinomas patients: a systematic review

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Objectives: To evaluate the existing knowledge on the relationship between diagnostic delay and survival of head and neck cancer patients.

Methods: A systematic review based upon systematic search on MEDLINE (1966 to January 2010) and EMBASE (1980 to January 2010), for English language articles. Search terms ("Head and neck cancers") AND ("delay" OR "prognostic" OR "survival").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]. The same terms were used as free-text words. The retrieved reports share neither the concept of diagnostic delay nor the statistical analyses or follow-up periods, thus rendering impossible the use of meta-analytical tools.

Results: 729 articles were accessed and 10 met the inclusion criteria. Oral and oropharyngeal cancer: Total delay was not related to survival, but referral delay reached a significant relationship that disappeared when tumour proliferative activity was considered.

Pharyngeal cancers: The reports linking diagnostic delays and prognosis of pharyngeal carcinomas are scarce and show glaringly opposing results. Laryngeal cancers: Delays in the diagnosis of larynx carcinomas seem to be an independent prognostic factor for survival.

Conclusions: There is not enough scientific evidence that permits the inclusion of diagnostic delay as an independent prognostic factor for survival of the head and neck cancer.

Relevance: In this review, because of the important value of tumour stage as a prognostic factor for survival, diagnostic delay has demonstrated a weak association with survival of head and neck carcinomas, with the exception of laryngeal carcinomas, where both patient- and clinician-related delays significantly worsen survival rates.

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Oral cancer in the United Arab Emirates. A descriptive analysis

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Objectives: To investigate the risk factors among oral cancer patients in the UAE.

Methods: Patients with oral and oro-pharyngeal squamous cell carcinoma registered with the Oncology Centre at Tawam Hospital between 2003 and 2009 were studied. Site and stage of tumour were assessed and after ethics committee approval and informed consent, information regarding risk factors was obtained from contactable patients via interviews.

Results: Seventy-six patients (mean = 11 per year, average age 53y) mainly of Arabian and Near Eastern nationalities were registered. 13 patients (17%) had oro-pharyngeal cancer. Most tumours were large at diagnosis (76% stage 2 or higher; n=58), and dentists referred only 1 patient, although most reported visiting a dentist at least every few years.

Fifty-four (71%) patients were contactable and agreed to participate. 78% (42/54) were males and 61% (33/54) reported never smoking (cigarette, cigar, pipe or shisha), 89% (48/54) never chewing betel and 80% (43/54) never drinking alcohol.

Only 2 patients (4%) reported using a mouthwash, while 91% (49/54) reported reasonable levels of vegetable consumption (more than 3-4 times per week) and 69% (37/54) similar levels of fruit consumption.

Conclusions: The aetiological factors associated with head and neck cancer in the UAE appear unique with low levels of nicotine, betel chewing, alcohol consumption, mouthwash use and relatively high levels of vegetable and fruit consumption. Further, the majority were oral, not oro-pharyngeal, contra-indicating HPV as being aetiological. Thus, there may well be unique genetic susceptibility factors for UAE oral cancer sufferers.

Relevance: Oral cancer is a global health problem with considerable geographical variation previously linked to life-style habits. The results of the present study indicate that these life-style factors are not the predominate feature in head and neck cancer sufferers in the UAE and further study assessing other, perhaps genetic, factors need to be undertaken.

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Diagnosing Sjögren's Syndrome from different perspectives

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Objectives: Sjögren's syndrome (SS) is characterised by keratoconjunctivitis sicca (KCS) and xerostomia. It is associated with other inflammatory rheumatoid conditions in secondary SS (sSS) but as primary SS (pSS) is without concomitant autoimmune disorders. The prevalence of subjective signs of KCS and/or xerostomia is 12-20% in Iceland, while the full clinical picture of SS has a prevalence of 0.2%. According to the EU-US diagnostic criteria, extended clinical, laboratory and imaging investigations, including histopathological evaluation are required for the confirmation of the pSS diagnosis. These international criteria may be more suited for clinical research, than for clinical practice. Aim: This study aimed to identify one specific test or combination of tests that would have the greatest predictive value for diagnosing pSS in clinical practice. A further aim was to reduce costs, give a speedier diagnosis and reduce patient discomfort whilst undergoing evaluation for pSS.

Methods: A consecutive series of 36 female patients with symptoms of xerostomia/xerophthalmia was studied. An extended anonymised data file was designed to include all clinical and experimental data including oral and ocular symptoms, measurements of salivary flow and tear production and function. The presence of antinuclear antibodies (ANA) and precipitating antibodies to SSA (Ro) and SSB (La) antigens was recorded. Salivary gland investigation was performed using standard scintigraphic methods.

Results: 12 patients fulfilled the EU-US criteria for pSS, 6 had sSS and 18 patients had only sicca symptoms without any concomitant rheumatic disorder. Antibodies against SSB had the highest predictive value for pSS, followed by SSA and then impaired salivary function of the parotid gland evaluated by scintigraphy; low unstimulated salivary flow and, lastly, a positive Schirmer test. 24 patients had abnormal scintigraphic findings. The combination of positive ANA and abnormal scintigraphy were found in 58% of all cases of pSS, while the combination of positive ANA and abnormal salivary flow were found in 56% of the total SS cases (pSS and sSS).

Conclusions: These data suggest that a stepwise evaluation of patients suspected of having pSS could begin with tests of tear and salivary function followed by serology. When the diagnosis remains in doubt, scintigraphy and biopsy could be considered. Selecting a combination of routine tests in daily clinical practice could be both time- and cost- saving.

Relevance: The diagnosis of Sjögren's syndrome has considerable importance for the patient from medical and dental perspectives. It is sometimes important for dental insurance purposes and should make clinicians aware of, for example, the need for enhanced caries prevention

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Classification of xerostomia patients by using a flow chart

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Objectives: The classification standard for diagnosing xerostomia patients was proposed by the Japanese Society for Oral Mucous Membrane (JSOMM). A flow chart to classify patients was designed.

Methods: Subjective and objective assessment of xerostomia (XS), sialometry by either stimulated whole saliva (SWS) collection or unstimulated whole saliva (UWS) collection, salivary gland scintigraphy were used for diagnostic items. In the diagnostic flow chart, psychogenic cases were first excluded by subjective and objective symptoms and the sialometry. Next, after considering salivary gland scintigraphy the classification was directed to the XS including Sjögren's syndrome (SS) or XS induced by excessive oral evaporation. SS was diagnosed by the revised Japanese criteria (1999). The rest of cases were diagnosed as non-SS XS. This non-SS group was examined for XS associated with systemic and metabolic diseases, XS associated with neurogenic or neuropsychiatric disorders, drug-induced XS, and subsequently further examined for radiation-induced XS, XS associated with aging, GVHD, sarcoidosis, AIDS, malignant lymphoma. If there was no relevance, it was diagnosed as an idiopathic XS. Subsequently, 241 patients' records were classified according to this chart as a retrospective study.

Results: The diagnostic classification of the 241 examples by this flow chart resulted in having 136 (57%) of SS and 85 (35%) of non-SS XS. The latter group further classified into 51 idiopathic (60%), 14 drug-induced (16%), 11 systemic and metabolic (13%), 4 sarcoidosis (5%), 3 associated with aging (4%), 1 GVHD (1%), and 1 neurogenic or neuropsychiatric disorder (1%).

Conclusions: The flow chart proved to offer a concrete classification of xerostomia patients. A retrospective analysis showed that over half of the patients tested were xerostomia associated SS cases.

Relevance: The classification standard is valid to diagnose xerostomia patients by using the flow chart.

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An electrical device for evaluating minor salivary gland function

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Objectives: The purpose of this study was to evaluate the function of minor salivary gland using a newly developed electrical device applying impedance measurement.

Methods: Eight patients with xerostomia, including 3 patients with Sjögren's syndrome, and 33 healthy controls were investigated. A filter paper (10mm X 10mm) was placed on the lower lip to absorb saliva secreted over 30 seconds. The filter paper was fastened to a clamp on the device, and a 1KHz sinusoidal alternating current (1.20V) applied. Depending on the impedance of the filter paper, the device shows lower potential difference when the amount of the saliva absorbed by the filter paper is small. The flow rate of saliva ($\mu\text{l}/\text{cm}^2$) was estimated from a standard curve drawn from mean values of quantitative tests on healthy volunteers.

Results: The average potential difference in healthy controls was $0.43 \pm 0.03\text{V}$ [mean \pm SD]. In contrast, patients with xerostomia showed $0.28 \pm 0.03\text{V}$, significantly lower than the control (Mann-Whitney's U-test $P < 0.001$). Quantitative tests gave potential difference values of 0.38V at $0.5\mu\text{l}/\text{cm}^2$ volume, 0.41V at $1.0\mu\text{l}/\text{cm}^2$ and 0.51V at $3.0\mu\text{l}/\text{cm}^2$. Therefore, the normal range of minor salivary gland flow rate in the lower lip was estimated as $1.5 \pm 1.0\mu\text{l}/\text{cm}^2/30\text{sec}$.

Conclusions: The electrical device was shown to be able to estimate minor salivary gland flow rate.

Relevance: This device may be useful as an objective test in screening for patients with xerostomia.

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Importance of salivary flow in Systemic Lupus Erythematosus disease

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Objectives: Correlate symptoms of dry mouth with salivary flow alterations, pH, clearance and taste disturbance through the conventional salivary flow test in SLE patients.

Methods: Whole saliva was collected 54 SLE patients, by drooling for 5 minutes into a graduated receptacle (not stimulated saliva). The volume was measured and the flow rate (mL/min) calculated. In sequence, the subjects were oriented to chew silicone for 5 minutes and drool the saliva into another graduated receptacle (stimulated saliva). The volume was measured and the flow rate (mL/min) calculated. According to the International Standard, the accepted range of normal flow for unstimulated saliva is above 0.1 mL/min, while the minimum volume accepted for stimulated saliva is 0.5 mL/min.

Results: Total absence of unstimulated salivary flow was observed in 16.7% of patients. After the mechanical stimulation, 5.56% of patients returned to normal flow. In 3.7% of patients, there was no significant difference between unstimulated and stimulated salivary flow and remained totally absent in 1 subject. The symptoms of mouth and eye dryness and taste disturbance were correlated with hyposalivation in stimulated salivary flow. In the unstimulated salivary flow the saliva presented an acidic pH, viscosity disturbance and clearance. After mechanical stimulation the pH returned to normal in 37%, but both viscosity and clearance were elevated. The palliative therapies for these subjects with mouth dryness were artificial saliva and lubricant oral gel, which improved the symptoms.

Conclusions: The conclusions were that the reduction of salivary flow and disturbance of saliva quality are frequently found in SLE patients. In some cases, before the clinical and laboratory diagnosis of SLE, some patients presented with symptoms of mouth dryness. Both the salivary flow test and investigation of xerostomia symptoms should be performed routinely in these patients.

Relevance: The importance of salivary flow and multidisciplinary treatment in SLE patients.

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Viscosity, wettability and lubrication of hyaluronic acid (HA) solutions containing lysozyme and/or peroxidase

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Objectives: Saliva substitutes are the only regimen for xerostomic patients with totally abolished salivary glands. The alleviating effects of today's commercially-available substitutes are short-lived and, therefore, of limited benefit to patients. The purpose of

this study was to investigate viscosity, wettability and lubrication of HA solutions with lysozyme and/or peroxidase, to verify their potential as the main component of a saliva substitute.

Methods: Human saliva was collected from 20 healthy donors, aged 25 to 35 years, between 9:00 a.m. and 11:00 a.m. Solutions containing HA were prepared using simulated salivary buffer (0.021 M Na₂HPO₄/NaH₂PO₄, pH 7.0, containing 36 mM NaCl and 0.96 mM CaCl₂). Hen egg white lysozyme and bovine lactoperoxidase was dissolved in HA solutions with different concentration. Viscosity was measured using cone-and-plate digital viscometer at six different shear rates and wettability on acrylic resin and Co-Cr alloy was determined by contact angle. Lubrication was estimated by the measurement of friction coefficient.

Results: The viscosity of HA solutions was decreased in order of HA, HA with lysozyme, HA with peroxidase and HA with lysozyme and peroxidase. The contact angle of HA solutions showed no significant difference according to tested materials and addition of lysozyme and/or peroxidase. Lubrication of HA solutions showed no significant difference according to addition of lysozyme and/or peroxidase. Viscosity was increased in order of stimulated parotid saliva, stimulated whole saliva, unstimulated whole saliva and stimulated submandibular-sublingual saliva, but contact angle was decreased in the same order. The contact angle of human saliva on acrylic resin displayed much lower value than that on Co-Cr alloy. Contact angles on acrylic resin by HA solutions containing lysozyme and/or peroxidase were much higher than those by human saliva.

Conclusions: The addition of lysozyme and/or peroxidase had a modest effect on the viscosity, but not contact angle and lubrication, of the HA solution. The viscoelastic properties HA solutions containing lysozyme and/or peroxidase compared with human saliva were objectively confirmed, suggesting HA as a candidate molecule for the development of effective salivary substitutes.

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Minor salivary glands' malignant neoplasms: Report of 16 cases

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Objectives: The aim of this study was to determine various parameters related to minor salivary gland malignant neoplasms in 16 cases. These parameters were: sex and age of the patient; location of the lesion; clinical appearance; histological type of the lesion and clinical stage; treatment procedures and survival rates.

Methods: We reviewed 16 cases with intraoral minor salivary gland malignant neoplasms in patients diagnosed and treated at the Department of Stomatology, University General Hospital of Valencia between 1999 and 2010.

Results: In the present study, six patients were male and ten female. The mean age was 56.2 years (47.2 in males and 61.6 in females) with an age range between 20-84 years. The palate was the most common site of involvement (62.5%). The most common clinical appearance was swelling (68.75%). Adenocarcinoma was the most common histological type (50%), followed by mucoepidermoid carcinoma (25%) and adenoid cystic carcinoma (25%). The clinical stage ranged between I and IV, the most frequent being stage IV (43.75%). Fifteen patients were treated with surgery as the primary option and the other one was treated only with radiotherapy. Adjuvant radiotherapy was administered to patients with positive or close resection margins (10 patients). The mean follow-up was four years. Two cases relapsed; one was retreated with chemotherapy and the other with a second surgical intervention. These two patients died due to their tumour, making the survival rate 87.5%.

Conclusions: In this study we found a good survival rate and positive response to treatment. This could be due to the slow growth of the tumours, low rate of regional lymph node involvement and near absence of distant metastasis.

Relevance: Minor salivary gland malignant neoplasms account for 2-4% of head and neck malignant neoplasms, 10% of all oral cavity malignant neoplasms and 15-23% of all salivary gland malignant neoplasms.

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A validated clinical oral dryness score

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Objectives: To develop a Clinical Oral Dryness Score (CODS) for routine use in assessment of dry mouth patients and determine its relationship with salivary flow rates.

Methods: CODS was determined from 10 features of oral dryness, each scoring as 1 point on a scale of 0-10. Features included dental mirror sticking to the buccal mucosa and tongue, frothy saliva, tongue shows loss of papillae. CODS, unstimulated whole mouth saliva (UWS) flow rate and stimulated parotid saliva (SPS) flow rate were

measured in 100 patients and 50 healthy controls. Patients included those suffering from primary and secondary Sjögren's syndrome, SNOX (sialadenitis, nodal osteoarthritis and xerostomia) and drug-induced hyposalivation.

Results: The reliability and reproducibility of CODS was validated by comparing independent scores from 3 clinicians who assessed the same 20 patients. The intra-class correlation coefficient (ICC) for total score was 0.89, 0.94, and 0.96 between examiners 1 & 2, 1 & 3 and 2 & 3 respectively.

Conclusions & Relevance: The CODS is a reliable method for routine assessment of the severity of dry mouth.

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Measurement of mucosal wetness in patients with xerostomia

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Objectives: To determine the validity of using direct measurement of mucosal wetness in the assessment of patients complaining of dry mouth (dmp).

Methods: Wetness of the buccal, anterior tongue, lower labial and anterior hard palate was measured in 100 dmp patients and compared with 50 healthy control subjects. Patients were diagnosed as primary and secondary Sjögren's syndrome, SNOX (sialadenitis, nodal osteoarthritis and xerostomia) or drug-induced hyposalivation. Mucosal wetness was sampled with standardized filter strips and moisture measured (Periotron) and expressed as a thickness (microm). A Clinical Oral Dryness Score (CODS) was determined from 10 features of oral dryness, each scoring as 1 point on a scale of 0-10. Unstimulated whole mouth saliva (UWS) flow rate and stimulated parotid saliva (SPS) flow rate were determined.

Results: In control subjects' wetness was greatest on the anterior tongue (65 ± 17.2 microm; mean \pm SD) and least on anterior hard palate (11 ± 11.7 microm.). In dmp mucosal wetness was reduced by 50% on the buccal, tongue and labial surfaces. Dmp were grouped according to UWS flow rate and each group showed similarly reduced wetness on the labial and buccal surfaces. In contrast the tongue showed a graded reduction in wetness which correlated with UWS flow rate. The CODS in all UWS flow rate patient groups was increased compared with control subjects. Dmp with normal UWS flow rates had reduced wetness of the tongue and buccal surfaces compared with control subjects with similar UWS flow rates.

Conclusions: Measurement of mucosal wetness provides a direct assessment of the mucosa in dmp. There are dmp without salivary hypofunction (UWS < 0.2ml/min) who show reduced amounts of saliva on some mucosal surfaces.

Relevance: Measurement of mucosal wetness is relatively quick to perform and therefore could be incorporated into the clinical assessment of dmp.

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Ultrasound in the diagnosis of Sjögren's Syndrome and correlation with systemic markers

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Objectives: Ultrasound (US) is established as a simple non-invasive imaging technique for diagnosis of salivary gland changes in Sjögren's Syndrome (SS), identifying a characteristic pattern of multiple small hypoechoic foci scattered throughout all gland parenchyma. Few studies have compared the efficacy of US diagnosis against the currently agreed American-European Consensus Group diagnostic criteria for SS (Vitali et al 2002). None have examined the correlation between the degree of US-assessed salivary gland involvement and other markers for SS. The aim was to examine relationships between US-identified changes and other features of SS.

Methods: US examination was performed, using the Philips iU22 US machine with 12-5MHz linear probe, on 363 adult patients referred with a complaint of xerostomia. US-identifiable gland changes were categorised and the severity scored by 4 experienced radiologists working to a standardised reporting template.

US images were scored in 4 categories: gland echogenicity, parenchymal consistency, number of glands involved and for the presence of distinct hypoechoic and/or hypervascular foci. The total score was compared to ENA, ANA, Rheumatoid factor, IgG, ESR, CD4, CD8, CD4:CD8 ratio, whole salivary flow and stimulated parotid flow.

Results: 143/147 patients with SS were identified correctly by US. 17/216 patients without SS were also shown to have pan-glandular honeycomb-pattern change. Sensitivity for US-detected salivary gland change was 97.28%, specificity 92.13% and accuracy 94.21%. Negative predictive value of US was notably high (98%). Changes were more marked in primary SS and in those who were ENA or ANA positive. Positive correlation was seen with Rheumatoid factor, and negative correlations with CD4 count and salivary flow rates. The accuracy of US compares very favourably with previous imaging by traditional sialography.

Conclusions: Ultrasound is sensitive, specific and non-invasive in its use for diagnosis of SS. Other observed correlations suggest US may indicate severity of involvement in this autoimmune disease

Relevance: Ultrasound may be the preferred imaging modality for Sjögren's syndrome.

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Oral Health, Salivary Secretion and Metabolic Control in Type-1-diabetic ChildrenV Groule¹, I Bendtsen Falch², AML Pedersen¹¹Department of Oral Medicine, Institute of Odontology, University of Copenhagen, Denmark, ²Department of Pediatrics, Roskilde Hospital, Denmark**Objectives:** To investigate associations between oral health and salivary gland function in well- and poorly controlled children with type 1-diabetes.**Methods:** In this cross-sectional study, caries, gingival index, counts of mutans streptococci, lactobacilli and *Candida albicans*, oral hygiene and oral dryness (visual analogue scale), unstimulated (UWS) and chewing-stimulated (SWS) whole saliva and unstimulated labial saliva (LS) flow rates (Periotron 8000®) were measured, and labial salivary gland biopsies obtained from 30 children with type 1-diabetes (mean age 14.4 ± 1.3 yrs) and 10 healthy children (aged 15.3 ± 1.0 yrs).**Results:** There were no differences between the diabetic children and the healthy controls with regard to age, gender, caries, bacterial counts, oral hygiene, oral dryness, SWS and LS. Gingival scores were, however, significantly higher and UWS and *Candida albicans* counts lower in diabetic children. Labial salivary gland biopsies revealed focal periductal lymphocytic infiltrates in 35% of the diabetic children and in 20% of the healthy children, but the degree of inflammation did not differ (focus score mean 0.5 and 0.3, respectively). In the diabetic children, oral dryness was negatively correlated with UWS ($P=0.052$) and borderline significant initial caries lesions with LS ($P=0.06$). There were no differences between the well-regulated diabetic children (i.e. HbA1C < 8.7%, $n=24$) and poorly regulated (HbA1C > 8.7%; $n=6$) with regard to age, gender, caries, gingival scores, lactobacilli, *Candida albicans*, UWS and LS. However, mutans streptococci counts were higher; SWS were lower and focal lymphocytic inflammation more prevalent among the dysregulated (67%) diabetic children. Oral dryness, salivary flow rates and focus scores were not associated with age, gender or disease duration (mean 5.5 ± 3.4 years).**Conclusions:** Children with type 1-diabetes of relatively short duration display changes in oral health and salivary gland function and structure, in particular when glycemic control is poor, which stresses the importance of early preventive dental visits.**Relevance:** The results are of relevance for the clinical management of children with type 1-diabetes.

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Changes in parameters of Sjogrens syndrome (SS) assessed after 10 years on a combined SS clinicP Shirlaw, E Hullah, F Barone, G Panayi, B Kirkham, G Larkin, C Pitzalis¹, R Cook, B Jacob, SJ ChallacombeDepartment of Oral Medicine, Clinical & Diagnostic Sciences Group, King's College London Dental Institute and Guys & St Thomas' NHS Foundation Trust, London UK, ¹Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK**Objectives:** Sjogrens syndrome is a progressive cell mediated and antibody mediated autoimmune disease. Few longitudinal studies have been undertaken to evaluate significant clinical or laboratory markers which might indicate disease progression, or risk of lymphoma. The objective of this study was to undertake such a study.**Methods:** 100 patients diagnosed with primary or secondary Sjogrens Syndrome, SNOX syndrome or drug related xerostomia were assessed at 5 and 10 years for whole salivary flow (WSF), stimulated parotid saliva flow (SPF), Schirmers, and clinical oral dryness score (CODS), ESR and CRP, and lymphocyte subsets.**Results:** In SS, the mean WSF at 0.06 ml/min was not significantly different after 5 years, but the mean at 10 years was decreased. In SNOX, WSF was not significantly changed at 5 or 10 years. These trends were mirrored in SPF in both SS and SNOX. The mean CD4 counts showed a decrease at 5 and 10 years but was related to marked drops in individual patients. The mean fatigue score increased in both SS and SNOX. Mean Schirmer test values were unchanged at 5 and lower at 10 years. No significant changes in CODS was found, possibly due to improved self management**Conclusions:** Overall, little significant change was found in most parameters measured after 5 years, but significant reductions in some were seen at 10 years. Longitudinal studies may help identify prognostic markers in SS. Quantifying the severity of disease assists in assessing and monitoring clinical improvements in therapy but no single value was correlated with disease progression.**Relevance:** Sequential audit of disease severity by clinical and laboratory markers indicates progression of disease and may direct the need for further intervention.

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Efficacy of Biotène Oral Balance in secondary Sjögren's syndrome patientsA Ardita^{*1}, A Adem¹, T Argjend²¹Dentistry Department, Faculty of Medicine, University of Tirana, Tirana, Albania,²Rheumatology Clinic, University Hospital "Mother Theresa", Tirana, Albania**Objectives:** The objective of the present study was to evaluate the efficacy of Oral Balance® saliva substitute in alleviating dry mouth symptoms in a sample of patients with secondary Sjögren's Syndrome.**Methods:** Twenty-one consecutive secondary Sjögren's Syndrome (sSS) patients with dry mouth complaints and hyposalivation were included in this study. Patients used a lactoperoxidase-system-containing gel (Biotène Oral Balance®) for 4 weeks. The effects on subjective oral symptoms were recorded by means of a 7-item questionnaire which contained questions regarding dry mouth sensation and its effect on chewing, swallowing, taste, speech, burning sensations and denture retention. The severity of symptoms was assessed using a visual analogical scale (VAS). Oral symptom scores and unstimulated whole salivary flow (UWS) were recorded at baseline and after 4 weeks' use of the product.**Results:** Two patients withdrew from the study because of adverse effects caused by the product (nausea and unpleasant taste). Nineteen patients (all women, mean age 53.0 years) participated throughout the entire study. Wilcoxon signed-ranked tests indicated significant improvements in oral symptom VAS scores post-treatment for 5 of the 7 items on the oral dryness questionnaire, although no increase in salivary flow rate was found. However, the improvement in certain variables before and after treatment did not take a positive course in all cases, and some symptoms even worsened in a few subjects after treatment. Patients with lower UWS at baseline tended to have greater improvement in oral symptoms.**Conclusion:** The study suggests that use of Oral Balance gel is effective in alleviating the symptoms of dry mouth in sSS patients, but a randomised controlled trial is needed to assess the placebo effect.**Relevance:** Saliva substitutes appear to be useful aids in the management of sSS patients. Saliva substitutes are not available in Albania and this is the first study involving Albanian patients.

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Acupuncture for prevention of radiation-induced xerostomiaFPF Braga^{*1}, DA Migliari¹¹Department of Oral Diagnosis, School of Dentistry, University of Sao Paulo, Sao Paulo, Brazil**Objectives:** To evaluate the effectiveness of acupuncture in minimizing the severity of radiation-induced xerostomia in patients with head and neck cancer.**Methods:** Twenty-four patients receiving >5000cGy radiotherapy (RT) involving major salivary glands bilaterally were assigned to preventative acupuncture group (PA, $n=12$) treated with acupuncture twice a week, lasting 20 minutes each session, before and during RT, and control group (CT, $n=12$), without acupuncture. The acupoints used in our preventative protocol were selected according to the principles of traditional Chinese and occidental orthodox medicine, and included local, distal and auricular points. Clinical response of acupuncture was evaluated objectively by measuring resting (RSFR) and stimulated (SSFR) whole salivary flow rates, and subjectively by patients' self-evaluation xerostomia questionnaire using a visual analogue scale (VAS) after RT; a repeated-measures analysis of variance by using a mixed-effect modeling procedure and ANOVA, $P<0.001$, were used.**Results:** The related-factors of age, gender, treatment by chemotherapy and neck dissection surgery were also investigated between groups and no statistically significant differences were found ($P>0.05$). All patients showed some degree of impairment in the salivary gland functioning. However, statistically significant differences between groups were evidenced for both objective and subjective analyses ($P<0.001$). Patients in the PA-group who were treated with preventative acupuncture showed significantly improved salivary flow rates (RSFR=498.2%; SSFR=301.4%), and decreased xerostomia-related symptoms (VAS=209.8%) as compared with patients in CT-group who did not receive acupuncture.**Conclusions:** Although preventative acupuncture treatment did not completely prevent the oral sequelae of RT, its significant potential to minimize the severity of radiation-induced xerostomia was evidenced, suggesting that acupuncture can be a useful therapy in the management of patients with head and neck cancer undergoing RT.**Relevance:** To demonstrate the benefits of acupuncture focused in a preventative manner to reduce the severity of xerostomia in patients treated with RT.

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Assessment of disease severity and treatment responses in oral mucosal diseases

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Objectives: Few oral medicine treatments are evidence based, even those regarded as standard therapies. This reflects lack of any method to routinely assess disease severity and thus of quantifying response to therapies. Objectives: to construct and evaluate oral disease severity scores (ODSS) for a variety of conditions seen in routine clinical practice. Conditions selected included recurrent aphthous stomatitis (RAS), lichen planus (LP), Pemphigus & pemphigoid (PV and MMP), Sjogren's syndrome (SS), and Orophacial granulomatosis (OFG).

Methods: Apart from SS, ODSS were designed to have a maximum score of 60 and capture over 95% of known clinical presentations. For RAS six parameters of ulcer number, size and site, with duration of ulcers and ulcer free periods and pain, each out of ten. For Bullous diseases, LP and OFG, 17 intraoral sites were examined and each scored out of three and added to an analogue pain score. For SS, visual criteria of dryness were established with a score out of 10. Clinicians were trained and calibrated for each ODSS. Results: Over 600 patients were assessed both for initial disease severity and for subsequent response to therapy. With RAS (n=100), significant responses could be demonstrated with local steroid therapy, though 10% of patients remained recalcitrant to therapy. With LP (n=100) local steroids resulted in significant improvement in the majority of patients over one year.

Results: Over 600 patients were assessed both for initial disease severity and for subsequent response to therapy. With RAS (n=100), significant responses could be demonstrated with local steroid therapy, though 10% of patients remained recalcitrant to therapy. With LP (n=100) local steroids resulted in significant improvement in the majority of patients over one year. With PV and MMP, (n=100) responses with systemic therapy were achieved in 95% of patients after one year. With OFG (n=200) elimination diets or systemic therapy resulted in significant improvement in 83% of patients. For SS, little change in the ODSS was found after 10 year.

Conclusions: Quantitative assessment of disease severity in routine clinical care is possible. ODSS can be useful or may be deemed essential in determining evidence-based assessment of treatment efficiency. Relevance: Audit of responses is now possible on a routine basis.

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Eosinophil cationic protein in saliva: a marker for disease activity in oral lesions?

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Objectives: Eosinophil cationic protein (ECP), one of the secretory proteins of eosinophils present in higher levels in serum, sputum and nasal secretions during allergic and inflammatory reactions. Determination of ECP is successfully used in diagnosis, clinical assessment and disease monitoring. The aim is to investigate whether salivary ECP is a feasible marker of inflammation to monitor disease activity in various oral lesions.

Methods: Nineteen patients with clinically and/or histopathologically diagnosed oral lesions (mean age: 44.15 ± 11.22) and 20 healthy subjects (mean age: 32.85 ± 09.26) were enrolled. Oral lesions were recurrent aphthous stomatitis (n = 6), gingivitis (n = 1), white sponge nevus (1), lichen planus (n = 6), leukoplakia (n = 3), pemphigus vulgaris (n = 1), herpes zoster virus infection (n = 1). Saliva and blood samples were collected, processed and stored at -200. ECP was analysed using fluorescence enzyme immunoassay.

Results: The mean ECP values in saliva and serum (66.91 ± 3.57 µg l⁻¹, 22.17 ± 8.40 µg l⁻¹, respectively) were higher in patients with oral lesions than those of healthy subjects (43.11 ± 21.71 µg l⁻¹, 16.82 ± 12.25 µg l⁻¹). However, the correlation was not statistically significant (P > 0.05). Patients with oral lesions had higher ECP levels in saliva than serum. The highest salivary ECP levels were detected in patients with lichen planus (151.4 µg l⁻¹), gingivitis (141.4 µg l⁻¹), leukoplakia (137.0 µg l⁻¹) and recurrent aphthous stomatitis (130.6 µg l⁻¹), whereas oral white sponge nevus presented the lowest salivary ECP level (23.40 µg l⁻¹).

Conclusions: Relatively high levels of salivary ECP in patients with oral lesions might be explained as migration of eosinophils to oral cavity that results in exacerbation of inflammatory response. Elevated levels of salivary ECP seems to correlate with the clinical presentation of oral lesions.

Relevance: Non-invasive measurement of inflammatory markers in saliva for oral disease monitoring may offer a valuable objective parameter with more accurate outcomes than serum.

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Recurrent Aphthous Ulcerative Disease, Recurrent Herpes Labialis and Benign Migratory Glossitis among 17–25 yr olds

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Objectives: To investigate the prevalence of Recurrent Aphthous Ulcerative Disease (RAUD), Recurrent Herpes Labialis (RHL) and Benign Migratory Glossitis (BMG) among 17 - 25 year olds.

Methods: A total of 528 individuals between 17 and 25 years of age were recruited into the study. Data was collected via an anonymous written questionnaire regarding age, gender, country of birth, time living in Australia, other countries lived in, cultural background, smoking, alcohol use, family history, and Self Reported Lifetime (SLP) and Two-year (STP) prevalence's of RAUD, RHL and BMG.

Results: The SLP prevalence of RHL was 3.1% and 2.6%, RAUD was 11.7% and 10.5%, BMG was 0.9% and 0.7%, White Patches was 2.2% and 2.3% for males and females respectively, with no gender related statistical significance. Prevalence of RHL increased with a history of alcohol consumption. Prevalence of RAUD increased with tobacco smoking and family history. Spending a majority of childhood in Australia was associated with a lower experience of RAUD but a higher experience of BMG.

Conclusions: Tobacco smoking and family history are associated with increased prevalence of RAUD. Alcohol consumption is associated with an increased prevalence of RHL. A childhood spent in Australia is associated with a lower RAUD but higher BMG prevalence.

Relevance: Recurrent Aphthous Ulcerative Disease (RAUD), Recurrent Herpes Labialis (RHL) and Benign Migratory Glossitis (BMG) have been identified as the most common oral mucosal lesions among children and adults. There is very little data on the prevalence of these conditions among the 17-25 years age group. Risk factors such as smoking, stress, alcohol consumption and sexual activity peak in this age group and may play a role in the onset of these diseases.

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Oral lichen planus: a retrospective study of 520 Romanian patients (Bucharest)

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Objectives: The purpose of this study was to describe the clinical characteristics of oral lichen planus (OLP) in 520 Romanian patients.

Methods: A total of 520 medical charts of patients suffering from OLP in the Department of Oral Medicine and Oral Pathology, Faculty of Dental Medicine, Carol Davila University of Bucharest, Bucharest, Romania, were retrospectively analysed from January 1990 to December 2008.

Results: Of the 520 patients, 400 (76%) were women and 120 (24%) were men. The mean age at presentation was 52 years for women and 64 for men, with an overall age range of 10-82 years. The reticular form of the disease was the predominant type in 58.4% of the patients as initial presentation. In 37.7% of patients were also observed erosive lesions sometimes concomitantly with reticular lesions. The atrophic form was the predominant type in 3.8% of 520 patients. Erosive lesions were significantly more symptomatic (pain, burning, bleeding). More than 23% of the patients had skin involvement. An association between OLP and hepatitis C virus infection and diabetes was found. Interestingly, 19% of patients showed an association between OLP and gallbladder diseases. Six patients had a malignant transformation at a site previously diagnosed as OLP.

Conclusions: The clinical features of patients in this survey share many similarities with those reported previously.

Relevance: To the best of our knowledge no similar study has been conducted in a Romanian population or in Eastern Europe. Regarding the association between OLP and gallbladder diseases, when compared with the general population, the prevalence of gallbladder diseases in OLP group was higher: 19% versus 8.4% (Acalovschi M. Epidemiology of gallstone disease. In: M Acalovschi, G Paumgartner, eds. Hepatobiliary Diseases: Cholestasis and Gallstones – Falk Workshop. London: Kluwer Academic Publishers, 2001: 117–30).

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Investigative analysis between oral lichen planus and daily medicine intake

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Objectives: To investigate whether daily systemic and/or topical medication contributes to the development of OLP lesions.

Methods: The study group comprised 110 OLP patients while there were 76 subjects in the control group, matched by age, race and sex. Data collected for analysis included medical records, drug intake and topical medication. Criteria for analysis of drug intake included: (1) ATC-code drug classification; (2) number of different drugs used daily in the categories of monopharmacy (1 drug), minor polypharmacy (2–4 drugs), and major polypharmacy (> 5 drugs); and (3) drugs implicated in lichenoid reactions (DILRs).

Results: Sixty (54.5%) of the 110 OLP patients reported daily medication prior to the appearance of the OLP lesion while 52 (68.4%) of the 76 of control group reported daily intake medicine. No statistical difference was found between the two groups in terms of systemic diseases, number of medicated individuals in the categories of mono- and polypharmacy, nor use of DILRs (P > 0.05). Regarding the clinical forms, site of involvement, distribution and symptoms of the disease, a statistically significant difference was only found for the clinical erosive form of OLP, seen more frequently in

non-DILR ($P = 0.04$) in nonmedicated OLP patients ($P = 0.03$) than in DILR OLP patients. Daily use of topical oral medication was reported by 2 (1.8%) of the OLP patients and by 1 (1.3%) of the control group.

Conclusions: It seems that the use of systemic medication does not lead to a significant increase in the incidence of OLP lesions. Lichenoid drug reactions are likely to occur only in a small numbers of patients.

Relevance: To add some knowledge to the issue of lichenoid drug reaction

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Oral contact allergic reactions and oral lichen process

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Objectives: Dental materials, oral hygiene products, food additives and salivary components may cause contact allergic reactions in the oral cavity with varied clinical presentation. The concept of contact allergy aggravating or inducing oral Lichenoid reactions is somewhat controversial. We sought to identify clinically relevant contact allergens that may be important in the management of patients with oral lichen planus. **Methods:** We retrospectively reviewed patients with oral lichen planus who had patch tests performed at the Unit of Oral Pathology and Medicine of Milan University Dental Hospital (Italy) from 2003 to 2009.

Results: Patch tests were performed on 65 patients (45 males; mean age 57 years, range 41-83), with a clinical and histopathologic diagnosis of oral lichen planus following the criteria proposed by Al-Hashimi et al. 2007. Of these, 13 (20%) had positive patch test results. These patients with positive results had clinically relevant reactions. Of the patients with positive metal reactions, 5 had improvement after removal of the metal prosthesis or restorations. Six others noted that their most troublesome areas were adjacent to metal dental restorations. One patient had a reaction to flavourings.

Conclusions: Although we did not find any significant association between the patients and positive patch test reactions. Due to the premalignant character of these lesions, replacement of positively tested materials and follow up of these patients is advised.

Relevance: It would be advisable to include hypersensitivity to dental components when evaluating the pathogenesis and management of patients with oral lichen planus.

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Implant treatment in patients with oral lichen planus

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Objectives: The aim of this prospective controlled study was to evaluate the influence of oral lichen planus (OLP) on several peri-implant parameters, immediate/late postoperative complications and patient satisfaction.

Methods: Two homogeneous groups of 18 partially edentulous patients diagnosed of oral lichen planus (OLP group) and 18 partially edentulous patients with no oral disease (control group, CG) were treated by means of 56 and 60 endosseous Nobel Biocare System implants, respectively. Clinical parameters were evaluated immediately after implant placement (pain, wound healing) and after a mean follow up of 54.10 months in the OLP group and 51.9 months in the CG (bleeding, pocket depth). Complications were assessed along the evaluation period.

Results: No differences were observed between both groups with respect to pain (14.18 ± 8.06 versus 13.40 ± 7.15 ; $P = 0.77$). After 8 weeks a complete wound healing was observed in 77.8% of the OLP patients and 66.7% in the CG. Complete healing was achieved in 100% of both groups at week 10. Satisfaction with implant treatment scored similar high rates in both groups (9.33 ± 1.08 versus 9.44 ± 0.85), however 16.7% of the OLP patients noted an aggravation of their OLP. Bleeding index and pocket depths were similar in both groups but those who displayed desquamative gingivitis showed statistically significant higher scores. Number of visits due to the presence of complications were more frequent in the OLP group ($P < 0.01$).

Conclusions: There were no significant differences with respect to clinical parameters analyzed such as pain, wound healing, bleeding, pocket depth and satisfaction between both groups. Number of visits is higher in patients with OLP.

Relevance: This is the first study analyzing some clinical characteristics related to implants in patients with OLP. Within the limits of the study it seems that the response of the peri-implant tissues is similar to normal subjects.

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The Body Mass Index (BMI) and other life style factors in patients with oral lichen planus

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Objectives: Lichen Planus is a common inflammatory skin disease with unknown aetiology, which affects most frequently the oral mucosa.

This study examined various life style factors in relation with the distribution and clinical forms of 100 patients with oral lichen planus (OLP), seen in our clinic last year.

Methods: A clinical oral examination and a questionnaire-based interview was taken from our patients with OLP. The data were analysed, using a SPSS version and the chi-square test. The life style factors included: BMI; smoking and drinking habits, vegetables and fruits intake, stress, family and work status.

Results: The BMI in our group was higher in 60.9% of our male and 34.9% of our female patients, compared to 21% of men and 11.9% of women from total Greek population.

The BMI was statistically different among our males and females ($P = 0.047$). Our patients with BMI > 25 had more tongue lesions ($P = 0.066$) and clinical forms ($P = 0.074$) than patients with normal weight.

Tongue lesions are more often seen in patients who drink wine occasionally or every day ($P = 0.032$), in non smokers ($P = 0.027$), in patients with no activities at their free time ($P = 0.012$) and slightly in patients whose caffeine intake was > 200 mg/daily ($P = 0.091$).

Patients under stress had more often tongue and buccal lesions ($P = 0.014$) and with higher stress score had more than 2 clinical forms ($P = 0.008$).

The frequency of vegetables or fruits daily consumption was not statistically related with the OLP parameters.

Conclusions: The life style seems to play an important role in OLP manifestations. Further and larger studies should be undertaken to look for the long term effect of these life style factors into the pathogenesis and malignant potential of this disease.

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Preliminary outcome of patch testing in biopsy-proven oral lichenoid reaction

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Objectives: To determine whether a positive patch test result to the standard dental materials and standard European series, with subsequent removal of the adjacent restoration, leads to clinical improvement in oral lichenoid reactions (OLR).

Methods: The clinical case notes of patients with histologically confirmed lichenoid lesions who underwent cutaneous patch testing for potential contact hypersensitivity to an adjacent dental restoration were retrospectively analysed. The following criteria were assessed: patient demographics and pre-existing atopy, symptoms, clinical presentation and histopathological nature of lesion, patch test technique and results, adverse reactions and clinical response to removal of the offending restoration.

Results: The cohort comprised of 18 females and 9 males (mean age 54.7 ± 14.2 years). 41% reported atopy. Fifteen of 18 individuals (83%) with symptomatic lesions were patch test positive. The most common allergens were ammoniated mercury (73%) and amalgam (47%). Of these individuals, 67% showed an improvement in clinical signs and symptoms within 3 months of replacement or coverage of the associated restoration. Conversely, only 44% of individuals with asymptomatic lesions tested positive. No adverse effects to patch testing were recorded.

Conclusions: This study, although limited by sample size, suggests that a positive cutaneous patch test result to amalgam or its components is of predictive value in identifying patients with OLR who are likely to respond to restoration replacement or coverage.

Relevance: To date, published literature regarding OLR and mucosal contact hypersensitivity is limited. This data indicates that a subset of patients with OLR, if selected and patch tested using defined criteria, respond favourably to amalgam replacement or coverage.

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Characterization of oral involvement in acute-graft-versus-host disease

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Objectives: Acute graft-versus-host-disease (aGVHD) is a major complication of allogeneic hematopoietic cell transplantation (HCT). The purpose of this study was to characterize the oral features associated with aGVHD.

Methods: Patients that underwent allogeneic HCT at Dana-Farber/Brigham and Women's Cancer Center (Boston, MA) between 1995 and 2009 and developed prominent oral aGVHD were identified. Data was collected from patient medical records using a standardized form and analyzed descriptively.

Results: Fourteen cases were identified, of which 5 (36%) only demonstrated oral features; the remaining 10 had variable involvement of skin (9/14, 64%), liver (4/14, 29%), and gut (2/14, 14%). Oral mucositis preceded aGVHD in 9 (64%) patients. The median time to onset of oral aGVHD was 31(range 11-91) days. Intraoral sites affected by non-specific ulcerations included the tongue (12/14, 86%; dorsum in 6/14), buccal mucosa (12/14, 86%), labial mucosa (10/14, 71%), palate (8/14, 57%; hard palate in 5/14), and floor of mouth (5/14; 36%); 3(21%) cases presented prominent lip ulceration and crusting. Salivary gland disease features included severe hypofunction (1/14; 7%) and palatal mucocoeles (1/14; 7%). In addition to systemic therapies, topical solutions of dexamethasone (7/14; 50%), morphine (3/14; 21.5%), tacrolimus (1/14; 7%) were utilized for ancillary support. Of the 9 (64%) patients that survived beyond day100, 2 (14%) developed oral cGVHD.

Conclusions: Oral features of aGVHD include extensive non-specific ulcerations of keratinized and non-keratinized mucosa and are often observed in the context of concurrent skin, liver and gut involvement. Intensive topical therapies may be helpful in reducing symptoms and promoting healing. Concurrent salivary gland disease appears to be infrequent.

Relevance: This is the first report to comprehensively characterize the oral features of acute GVHD. Oral medicine specialists should be aware of this potential complication of allogeneic HCT, and can play an important role in both its diagnosis and management.

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Oral lichen planus: A retrospective study of 110 Brazilian patients

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Objectives: This retrospective patient record study investigated the profile of OLP in a group of Brazilian patients seen between 1989 and 2009.

Methods: 1822 clinical records from the Stomatology Discipline were analyzed and data such as gender, age, race, clinical presentation of OLP, site affected, presence of symptoms and extraoral manifestations of the disease, smoking habit, and consumption of alcoholic beverages were obtained.

Results: Among the 1822 records of patients with oral mucosal lesions, OLP was identified in 6.03%. Of these, 76.36% were females, with a mean age of 54 years, and 85% were whites. The reticular form was the most frequent (81.81%). Extraoral lesions were observed in 32.72% of the patients and painful symptoms were reported by 50.90%. The cheek mucosa was the site most affected (92.72%) and multiple oral lesions were observed in 77.27% of the patients. Among patients with OLP, 18.18% reported a smoking habit and 29.09% the consumption of alcoholic beverages.

Conclusions: This retrospective study showed a relatively high prevalence of OLP in the population studied, with a predominance of the disease among middle-aged white women and bilateral involvement of the cheek mucosa. Reticular lesions were the most frequent, followed by the erosive form which is mainly associated with painful symptoms. No relationship with tobacco or alcohol consumption was observed.

Relevance: Oral lichen planus (OLP) is a chronic autoimmune disease characterized by multiple clinical presentations and a relatively high prevalence in the population.

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Disease severity scoring and efficacy of treatment of oral lichen planus

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Objectives: Few studies of Oral Lichen Planus (OLP) have utilised an oral disease severity score (ODSS) in the assessment of disease severity and in the routine assessment of response to treatment. Aim: to evaluate the use of a standardised quantitative assessment tool (ODSS) to reflect disease severity in routine clinical care of patients with OLP as well as its role in establishing evidence for treatment outcome.

Methods: Retrospective study of a target of 100 patients with biopsy confirmed OLP scored at the first visit and on subsequent visits with a mean follow up of two years recording (A) Number of sites involved (17 sites) (B) Activity at each site (Mild / Moderate / Severe) (C) Self assessed pain score (0-10). Most patients were treated with local steroid (Betnesol 500 mcg) mouthwashes.

Results: The mean age of patients was 52 +/- 12 (SD) at first visit. The mean severity score at entry to treatment was 31 (range 12 to 65). After 6 months treatment the mean score was 21 (range 5 to 55) and after 12 months it was 15 (range 5 to 45). The mean

improvement in the score was 32% + 15 but 12% of patients showed no change in the score after 12 months. The mean improvement in the activity score was over 50%. Analysis of site responses indicated that gingival sites responded less well than non-gingival sites.

Conclusions: ODSS applied to OLP demonstrates that this is a useful, easy to use method for assessing both initial severity of disease which may indicate local or systemic therapy, and for monitoring treatment responses in a routine clinic.

Relevance: ODSS can be/should be used routinely on oral medicine clinics.

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Use of systemic medication in patients with oral lichen planus

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Objectives: The aim of this study was to describe the medication profile of patients diagnosed with oral lichen planus (OLP) compared to a control group without OLP and to evaluate if the use was different, indicating a drug-related etiology for some patients diagnosed with OLP.

Methods: A study group of 567 prospective patients diagnosed with OLP (mean age = 56.6 years; females n = 369) were compared to a control group without OLP (n = 1008; mean age = 55.5 years; females n = 398). OLP patients were also classified according to the clinical type. The individual drugs were recorded and classified based on the ATC code. Other variables such as gender and age were analyzed between groups and Fisher's exact test was used in the analysis.

Results: 272 patients (47.9%) of the OLP group used no medication at all compared to 546 patients (54.1%) in the healthy control group. Women used more medication than men and this difference was a statistically significant in OLP and controls ($P < 0.001$). The medication profile was similar for OLP and controls. However, statistically significant differences were found between OLP and healthy patients for drugs for the urinary and genital organs and sex hormones ($P < 0.05$), musculoskeletal system ($P < 0.01$), hormones, excluding sex hormones and insulin ($P < 0.01$) and respiratory system ($P < 0.05$) where OLP patients used these drugs more frequently. No statistically significant differences in medication were found between the different clinical types of OLP and control group.

Conclusions: The overall drug consumption medication patterns were similar between groups, but some drug groups were used more often by OLP patients. The results indicate that some patients diagnosed with OLP may have had drug-related lichenoid reactions, or that some drugs may predispose to the development of OLP.

Relevance: The results argue for further investigation into the possible association between OLP and medication use.

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Malignant transformation of oral lichen planus and oral lichenoid lesions

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Objectives: To report a clinicopathological analysis of 23 cases of oral lichen planus (OLP) and oral lichenoid lesions (OLL) associated to oral squamous cell or verrucous carcinoma (SCC, VC).

Methods: Data from 23 patients (21 females, 91%; 2 males, 9%) with a diagnosis of oral SCC or VC developed within a context of OLP or OLL, were retrieved and analyzed. The patients had been treated at the Unit of Oral Pathology and Laser-Assisted Oral Surgery of the University of Parma, Italy, between 1990 and 2010. The Patients were subclassified according to the WHO diagnostic criteria for OLP and OLL (OLP group: 12 patients, all females; OLL group: 11 patients, 2 males and 9 females). Age at diagnosis of OLP/OLL ranged from 36 to 87 years (mean age: 64.1 year). Complete follow-up was available for all patients.

Results: Nine (75%) and 3 (25%) patients of the OLP group developed SCC and VC, respectively. All the malignancies reported among the OLL group were SCC. Carcinomas were diagnosed after a mean period of 125 months from the diagnosis of OLP and after a mean period of 21.6 months from the diagnosis of OLL. In 7 cases, OLL and SCC were diagnosed at the same time. Sites of occurrence of SCC and VC among OLP patients were buccal mucosa (5 cases), palate and gingiva (4 cases), tongue (2 cases) and floor of the mouth (1 case). Among OLL patients, SCC development was reported on the tongue and buccal mucosa in 6 and 5 cases, respectively. In all cases, tumours were treated primarily by surgery. Recurrence or second primary tumours (SPT) were observed in 5 out 12 cases among OLP patients. No recurrences or SPT were reported among OLL patients.

Conclusions: The present report highlights the possible premalignant character of OLP and OLL.

Relevance: All cases of OLP or OLL should be carefully managed.

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Interventions for treating oral lichen planus: an updated Cochrane reviewT Kobkan¹, C Marco*², L Giovanni³¹Department of Oral Medicine, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand, ²Department of Oral Medicine, School of Dental Sciences, University of Newcastle upon Tyne, Newcastle upon Tyne, UK, ³Unit of Oral Pathology and Oral Medicine, Department of Medicine, Surgery and Dentistry, University of Milan, Milan, Italy

Objectives: Oral Lichen Planus (OLP) is a common chronic inflammatory disease associated with cell-mediated immunological dysfunction. Various treatment regimens have been attempted to improve OLP lesions, but a complete cure has not yet been accomplished. The objectives of this review were: to analyse the current available evidence to test the null hypothesis that there is no difference between the effectiveness of proposed treatments and placebo or between different treatments in the management of OLP.

Methods: All randomised and quasi randomised controlled trials which compared an active treatment with placebo or with another active treatment were considered in this review with no language restriction. The Cochrane Oral Health Group's Trials Register was searched for relevant studies as well as MEDLINE and EMBASE. All studies meeting the inclusion criteria then underwent validity assessment and data were extracted. For dichotomous outcomes, the estimates of effects of an intervention were expressed as risk ratios (RR) together with 95% confidence intervals. For continuous outcomes, mean differences (MD) and 95% confidence intervals were used to summarise the data for each group. Meta-analyses were done only with studies of similar comparisons reporting the same outcome measures. Risk ratios were combined for dichotomous data, and mean differences for continuous data, using random-effects models. Statistical analysis was performed by Review Manager 5.

Results: 25 trials were selected. In 10 trials active intervention was compared with placebo. Local steroids were the active intervention in 13 studies. Local calcineurin inhibitors were employed in 9 trials. All but one study comparing an active treatment with placebo included pain among the outcomes considered and 6 of them used a visual analogue scale (VAS). The studies comparing pimecrolimus with placebo showed not significant results and even pooling data together did not result in statistically significant effect on clinical manifestation. The other treatments tested against placebo showed statistically significant effects on oral signs, of different clinical relevance.

Conclusions: At present there is no reliable evidence to support the use of any specific treatment for OLP. Even high potency steroids such as clobetasol propionate or calcineurin inhibitors such as tacrolimus/pimecrolimus that are widely used lack evidence of strong effectiveness.

Relevance: A fundamental step forward should be to set up and validate an objective outcome instruments for OLP. This appears to be a mandatory priority for any future research on the field.

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Serum levels of IL-17 in patients diagnosed with Oral Lichen Planus or Oral Lichenoid Lesions: a preliminary studyLA Gueiros¹, C Ribeiro^{1,2}, A Tavares de Carvalho¹, J Jorge Jr², PA Vargas², M Ajudarte Lopes², O Paes de Almeida², JC Leão¹¹Departamento de Clínica e Odontologia Preventiva, Universidade Federal de Pernambuco, Recife, Brazil, ²Departamento de Diagnóstico Oral, Faculdade de Odontologia de Piracicaba, Universidade Estadual de Campinas, Piracicaba, Brazil

Objectives: The aim of this study was to evaluate the serum level of IL-17 protein by enzyme-linked immunosorbent assay (ELISA) in patients diagnosed with oral lichen planus (OLP) or oral lichenoid lesions (OLL).

Methods: Twenty nine patients with oral lichen planus-like lesions were classified as OLP or OLL according to the WHO modified criteria for diagnosing OLP. Blood samples were collected and IL-17 serum levels were determined by ELISA (human IL-17 DuoSet ELISA kit, R&D Systems, Minneapolis, USA).

Results: The study sample comprised of 9 males (31%) and 20 females (69%), aged from 23 to 50 years, with a mean of 49.62 years of age. The mean IL-17 serum level was higher in OLL patients (32.23ng/mL, ranging from 9.69 to 191.93 ng/mL) than in OLP (25.13 ng/mL, ranging from 9.69 ng/mL to 124.14 ng/mL), however, this tendency was not statistically significant ($P > 0.05$).

Conclusions: Based upon the results of the present study it is suggested that the evaluation of serum levels of IL-17 does not seem to be a reliable method to predict the diagnosis of OLP or OLL. However, since the level of IL-17 in OLP patients was not previously reported, a larger sample should be analyzed in order to allow an adequate comprehension of IL-17 role in lichenoid lesions.

Relevance: The role of inflammatory response and cytokine pattern of immune-mediated lesions are important aspects of their pathogenesis. Th-17 cytokine pattern has been evaluated in many distinct inflammatory diseases and can be associated with induction of pro-inflammatory responses. Understanding the role of IL-17 and Th-17 response in lichenoid lesions can be an important issue in the comprehension of these diseases.

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Temporal variation of the different clinical forms of histopathologically-proven oral mucosal lichen planus (OMLP)

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Objectives: To assess temporal changes in the clinical appearance of a larger cohort of patients with histo-pathologically confirmed OMLP.

Methods: Patients with biopsy-confirmed diagnosis of OMLP at Royal Melbourne Dental Hospital between the years 1989 to 2000 were included in this study. Clinical photographs were analysed and classified into reticular, erythematous, plaque-like or ulcerative. Appearance changes were noted as 'improved', 'worsened', 'unchanged' or 'variable'.

Results: Over the 12 year period, 266 females and 125 males were diagnosed with OLP. On average, the patients were followed up for a 6.3 years. 757 distinct mucosal lesions were found among these 391 patients at initial presentation with the most frequent lesions being reticular ($n = 370$), then erythematous ($n = 247$), ulcerative ($n = 75$) and lastly plaque-like ($n = 75$). The majority of patients showed no change in the clinical form of OMLP ($n = 279$, 71.4%) and only a small proportion of the initial lesions exhibited more severe forms of OMLP at subsequent follow-ups ($n = 41$, 10.5%). No statistically significant correlations could be found on whether OMLP was likely to improve, worsen or remain unchanged depending on the age ($P > 0.05$) or gender ($P > 0.05$).

Conclusions: The clinical appearance of OLP did not change or improve in the vast majority of patients during this 12-year period. Further, this study supports the notion that ulcerative OLP lesions, non responsive to treatment, warrant a high degree of suspicion.

Relevance: Oral lichen planus is a chronic inflammatory disease that has various clinical presentations including reticular, erythematous, plaque-like, ulcerative and bullous. The present study shows that these clinical forms would appear to behave differently over time and the changing nature of these lesions is likely to be indicative of differing rates of malignant transformation in patients with OMLP.

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Efficacy of mycophenolate mofetil in severe mucocutaneous lichen planus using severity scoring

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Objectives: Ulcerative oral lichen planus (LP) is a chronic inflammatory condition often challenging to treat and the aim is to assess treatment methods of severely affected patients.

Methods: A retrospective analysis of patients presenting to a combined oral medicine/dermatology clinic identified ten (9F 1M, mean (SD) age at onset 37.5(12.3) yrs with biopsy confirmed ulcerative LP treated with mycophenolate mofetil (MMF) (1.5-2.5gm daily) for a minimum of 6 months. Eight patients had previously taken systemic agents (which included prednisolone ($n = 8$), azathioprine ($n = 5$), acitretin ($n = 3$), thalidomide ($n = 2$), ciclosporin ($n = 1$)) which had been discontinued. Disease severity at each visit during a mean (SD) follow-up period of 9.2(5.2) yrs was recorded using pain, site and activity scores. These were combined to form an oral disease severity score (Escudier M et al. Br J Dermatol 2007;157:765-70). The clinical presentation of LP was VVG ($n = 7$); peno-gingival ($n = 1$); oral ($n = 1$) multi-site other ($n = 1$). Oral lesions included desquamative gingivitis ($n = 10$), ulceration ($n = 8$) and fibrotic oral scarring ($n = 5$).

Results: Five of seven patients with VVG LP expressed the HLA DQB1*0201 allele. During therapy with MMF, three were taking concomitant low dose prednisolone (two for 6-9 months, one long term) and one patient was weaned off azathioprine over 9 months. Mean (SD) baseline oral severity score was 39.1(11.9) with significant improvement at 21-24 months, mean score 22.2(10.4) ($P = 0.01$). The mean (SD) duration of MMF treatment was 44.9(27.5) months. Eight patients remained on treatment (4 = remission; 1 = well controlled; 3 = partial control) while two patients were in remission 22-24 months after discontinuing MMF. Mild side effects were reported by two patients.

Conclusions: Topical steroids may ameliorate symptoms but have limited ability to minimise long-term sequelae. Systemic agents have been tried with varying success and may be limited by longer-term adverse effects. MMF is an immunosuppressive agent that reversibly inhibits T cell proliferation thus potentially reducing disease activity in LP.

Relevance: Our series demonstrates the efficacy, favourable side effect profile and potential longer term disease modification with MMF treatment.

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Clinical trial of dexamethasone vs. cyclosporine for oral lichen planusM Georgaki*¹, N Nikitakis¹, S Diamanti^{1,2}, A Sklavounou¹¹Department of Oral Medicine and Pathology, Dental School, University of Athens, Greece, ²251 General Greek Airforce Hospital, Athens, Greece

Objectives: Oral lichen planus (OLP) is a common, frequently symptomatic, disease. Various treatments have been used for symptomatic OLP, including corticosteroids

and immunosuppressants. The aim of this study was to compare the effectiveness of topical dexamethasone vs. ciclosporin treatment for symptomatic OLP.

Methods: Twenty five patients with biopsy-proven symptomatic (erosive or atrophic) OLP were randomly assigned treatment with dexamethasone 2mg/5ml tid (14F-4M, age range: 33-82, mean: 61.8) or ciclosporin 100mg/ml tid (4F-3M, age range 44-81, mean: 59.6) for 4 weeks. The patients were followed up every week for the first month and once a month for the following 6 months, and assessed parameters included clinical scoring (0-5 Thongprasom's scale), pain (0-10 VAS scale), dysphagia and speech difficulties (none, mild or severe). Possible side effects, including fungal infections, were also recorded.

Results: The average clinical scores at 0, 1, 2, 3 and 4 weeks of treatment were 4.16, 3.15, 2.56, 2.46 and 2.07 for the dexamethasone group (DG) and 3.42, 3.5, 2.85, 3 and 2.5 for the ciclosporin group (CG). At the same time, the average pain scores were 4.08, 2.83, 2.26, 1.42 and 1.3 for DG and 4.00, 3.55, 4.15, 3.12 and 2.12 for CG. After 4 weeks, the percentage of patients in DG reporting dysphagia and speech difficulties decreased from 83.33% to 6.25% and from 27.77% to 0%, respectively; the corresponding decreases for CG patients were from 85.71% to 16.67% and from 28.57% to 14.28%. Regarding the side effects, 35.29% of DG patients developed candidiasis as compared to 16.66% of CG patients.

Conclusions: Despite the small number of enrolled patients and the ongoing follow-up, dexamethasone topical treatment appeared to be associated with more pronounced clinical improvement than ciclosporin treatment after one month of treatment.

Relevance: This study may contribute to a better understanding of the differences in effectiveness of OLP topical treatments.

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The utility of an antifungal agent in the management of Oral Mucosal Lichen Planus (OMLP)

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Objectives: To assess the benefits of topical antifungal additional to topical corticosteroid in the management of OMLP.

Methods: Twenty Patients with OMLP were enrolled, the and randomly assigned to either Group A; treated with both topical antifungal (miconazole gel) and corticosteroid (betamethasone dipropionate ointment), or group B treated with corticosteroid alone. Clinical signs (erythema, ulceration, and size) and symptoms (pain, burning, and stinging) were assessed. Three cytological smears (periodic acid-Schiff, potassium hydroxide, and calcofluor white) were performed and an oral rinse samples taken, colony forming units (CFU's)/mL enumerated and antifungal susceptibility assessed for amphotericin B, nystatin, fluconazole, miconazole, and ketoconazole.

Results: No significant differences in the signs and symptoms of OMLP between the group treated with a topical corticosteroid alone and the group for which a topical antifungal agent was added to the topical corticosteroid ($P > 0.05$), other than the level of erythema observed. A reduction in erythema was seen in both patient groups, however a greater reduction in the degree of erythema was observed in the group treated with a corticosteroid alone. The level of carriage of oral yeast did not correlate with the signs and symptoms of OMLP ($P > 0.05$).

Conclusions: The benefit of topical corticosteroids used alone in reducing the degree of erythema of lesions of OMLP was demonstrated in this study. No benefit was observed when the antifungal agent was added to the corticosteroid preparation. Further, the concentration of oral yeast neither correlated nor influenced clinical outcome.

Relevance: The role of oral candidosis in the clinical presentation and treatment of OMLP has been poorly understood. This study shows that additional treatment with antifungal agents is not associated with better outcome for patients with OMLP.

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Erythema multiforme with oral involvement. Review of 14 cases

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Objectives: To retrospectively analyse the clinical characteristics, precipitating factors and treatment modalities of all cases diagnosed as EM at the Oral Pathology and Medicine Department, Dental School, University of Athens, Greece, between 2007–2009.

Methods: Fourteen cases diagnosed as EM were retrieved from the files of the Oral Medicine Clinic. Medical charts were analyzed with regards to age, gender, previous drug use and HSV infection, clinical manifestations, recurrences and treatment outcome.

Results: Mean age of the patients was 40, 28 years (SD ± 19.27 , min-max:14-69) while the female-to-male ratio was 1,3:1. Eight cases were diagnosed as recurrent, HSV-associated EM while 3 cases were drug-induced. One patient was diagnosed with persistent HSV/Epstein-Barr Virus associated EM. In 6/14 cases oral mucosal involvement was accompanied by target skin lesions while in 3 cases histopathological investigation was performed to rule out other vesiculobullous disorders. Nine patients

responded to treatment with systemic corticosteroids, while 2 of them were placed in anti-viral prophylaxis with no recurrences noted so far. One patient with persistent EM was treated with thalidomide due to the refractory nature to steroids and anti-virals.

Conclusions: Acute onset or recurrent nature of disease, localization of the lesions primarily at the anterior areas of the mouth and preceding HSV infection or drug use are supportive of EM diagnosis with only oral involvement. Prophylactic antiviral treatment may prove useful to prevent recurrences but persistent EM, although rare, must be considered for other therapies, such as thalidomide.

Relevance: EM with only oral involvement may be often encountered at the setting of an Oral Medicine Clinic and in such cases diagnosis may prove to be a real challenge. Detailed medical history and careful clinical assessment may be diagnostic but histopathological investigation may also be needed.

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Oral Pemphigus vulgaris: a retrospective study of 56 patients with 17-years follow-up

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Objectives: Pemphigus vulgaris (PV) is a potentially life-threatening chronic autoimmune disease affecting the mucosa and skin and resulting in epithelial acantholysis, bullae formation, and chronic ulceration. Although PV onset frequently involves the oral cavity and the disease can remain limited to the mouth, only few cohorts of predominantly oral PV have been reported. Treatment experiences in Oral Medicine settings are limited and no standardised treatments are available. The aim of the study was to report the clinical presentation and management of 56 patients with predominantly oral PV primarily treated in an outpatient Oral Medicine clinic.

Methods: A retrospective study was conducted based on the records of 56 patients (24 males and 32 females) with histologically and immunologically proven PV who attended the Department of Oral Medicine, University of Turin (Italy), between 1992 and 2009. Diagnostic delay, male:female ratio, average age at diagnosis, oral mucosal and cutaneous involvement, duration and adverse effect of systemic immunosuppressive therapy were studied.

Results: The mean diagnostic delay was 5.45 months. The male:female ratio was 1.33:1 while the mean age at diagnosis was 55.70 years for women and 52.17 years for men. The oral lesions affected mainly the buccal mucosa and gingivae. One third of patients had cutaneous involvement. Three patients were treated only with topic therapy whereas the others received systemic corticosteroid therapy with doses ranging from 1 to 2 mg/kg/daily for variable lengths of time. Thirty patients were treated with adjuvant azathioprine (1-2 mg/kg/daily). Sixteen patients (29%) achieved a complete remission (no lesions for more than 1 year) and 3 patients were in partial remission (no lesions for less than 1 year). One patient had a new exacerbation of the disease after dental procedures. The mean duration of systemic therapy in patients undergoing complete remission was 45 months. The most frequent adverse effects of systemic therapy were, Cushingoid facies, weight gain, ocular problems and cardio-circulatory diseases. One patient died following a pancytopenia possibly related to the immunosuppressive therapy.

Conclusions: Our cohort is one of the largest reported from Italy with predominantly oral PV and most of the patients were treated on an outpatient basis without the need of hospitalisation. Diagnostic delay was around 6 months and around one third of the patients achieved complete remission after therapy. The treatment of pemphigus vulgaris remains largely empirical and side-effects of treatment are common and can be dramatic.

Relevance: Our retrospective study highlights the frequent exclusive oral localisation of PV and the need to standardise treatment modalities to improve patients' outcome and reduce the occurrence of unwarranted and sometimes very severe side-effects.

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Periodontal status in oral mucous membrane pemphigoid

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Objectives: To evaluate the periodontal status of mucous membrane pemphigoid (MMP) patients and compare it with that of healthy controls.

Methods: A prospective hospital-based study was undertaken to examine and evaluate the potential impact of gingival MMP lesions on the human periodontium of 29 patients. Parameters evaluated included plaque score, gingival index, bleeding index, probing depths, recession, clinical attachment level (CAL), mobility, furcation involvement, number of missing teeth and Machtei criteria.

Results: The study group comprised 29 patients (25 female and 4 male) mean age 54.17 (± 14.47). The control group comprised 30 patients (21 female and 9 male) mean age 51.70 (± 12.98). Mean values for plaque index, bleeding percentage, gingival index and probing depth were found to be higher for MMP patients, and these differences were

found to be statistically different. The mean value of CAL was found to be significantly higher in MMP patients in comparison with the control group.

Conclusions: These results showed that periodontal status is worse in MMP patients than comparable healthy control subjects.

Relevance: These patients should be encouraged to accept and undergo long-term periodontal follow up.

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Erythema Multiforme: a clinical review of 27 cases

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Objectives: The aim of this study was to analyse the clinical features, etiopathogenic factors, and treatment of a series of 27 cases of erythema multiforme (EM) seen in the Service of Stomatology of Valencia University General Hospital.

Methods: Data was collected with regard to the clinical manifestation, antecedent of viral infection, and the use of drugs as possible etiological factors. Data concerning drug treatment and patients' response to topical and systemic corticotherapy was also evaluated.

Results: A total of 27 patients were studied (19 males and 8 females), with a mean age of 46.3 ± 20.08 years. A relationship was clearly suspected between drug use and lesion outbreak in 6 patients (22.2%). Conversely, in 10 patients (37%) the triggering factor could have been herpes virus infection (herpes labialis). 14 cases (51.8%) were classified as presenting minor EM, 7 cases (25.9%) presented major forms of the disease and 3 cases (11.1%) were classified as corresponding to Stevens-Johnson syndrome. Systemic and/or topical corticosteroids proved effective in controlling the outbreaks in all of the patients.

Conclusions: The oral mucosa is the most affected mucosal region in EM, with a predilection for lip mucosa, erosive forms, and bloodstained crusts. Systemic corticosteroids are effective in controlling the outbreaks, although their use as maintenance therapy is not clearly suggested.

Relevance: Erythema multiforme (EM) is an acute disorder of the skin and mucosal membranes manifesting in the oral cavity (60-70% of all patients) as polymorphic erosive, ampulla, and bloodstained crusts. The etiology is unclear, although an autoimmune mechanism is involved. Infections and drugs have been implicated in the etiopathogenesis. With the exception of corticosteroids, no specific treatment for EM is available.

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The evaluation of oral health-related quality of life and anxiety values in patients with active or inactive minor recurrent aphthous stomatitis

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Objectives: Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal lesions. Lesions appear as single or multiple ulcers on non and keratinized oral mucosa. They are characterized by pain during chewing and generally heal only after 7-10 days. As the etiology is unknown, there is no curative treatment. To learn more about the patients' quality of life and anxiety levels would be useful in understanding the efficacy of treatments. The aim of the present study was to evaluate the oral health-related quality of life and anxiety values in patients with active or inactive minor recurrent aphthous stomatitis and to compare them to healthy controls.

Methods: One hundred patients with minor RAS were included in the study. Data were collected by questionnaires regarding STAI, OHIP-14, OHR-QoL and SF-36.

Results: Our findings suggested that patients with active minor RAS have a decreased quality of life and increased anxiety levels, due to pain during eating and chewing.

Conclusions: It has been concluded that, traditional treatment of RAS patients should be accompanied by psychological support.

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Impact of Behçet's Syndrome on quality of life

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Objectives: The aim of this study was to assess the impact of the type and number of symptoms on the quality of life of patients with Behçet's Syndrome.

Methods: A questionnaire was mailed to the 650 members of the Behçet's Syndrome Society in the United Kingdom (UK). Participants provided information on their socio-demographic characteristics (sex, age, ethnicity, marital status and education), disease duration, current symptoms (mouth ulcers, genital ulcers, skin lesions, fatigue, joint problems, stomach/bowel problems, eye problems, pathergy reaction, headaches and other neurological problems) and health-related quality of life (using the EQ-5D scale, which assesses 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression). EQ-5D responses were converted into utility scores using the UK preference weights. Linear regression models were fitted to test the associations of each symptom and the number of symptoms with the EQ-5D index.

Results: 447 adults returned the questionnaires (68.8% response rate), of whom 400 were adults with confirmed diagnosis of Behçet's Syndrome. Of them, 362 had information on the variables selected for this analysis: mean age of 49.8 years (Standard Deviation: 12.4, range: 19 to 81), 76% females and 94% White British. The mean EQ-5D index was 0.47 (SD: 0.38, range: -0.59 to 1). Seven symptoms were negatively related to the EQ-5D index after adjustment for socio-demographic characteristics, disease duration and symptoms control (all $P < 0.033$). However, only joint problems, neurological problems, pathergy reaction and stomach/bowel problems remained significantly related to the EQ-5D index after further adjustment for other symptoms (all $P < 0.033$). Furthermore, the number of symptoms was significantly related to the EQ-5D index after adjustment for socio-demographic characteristics, disease duration and symptoms control. The EQ-5D index decreased by -0.05 units (95% Confidence Interval: -0.07 to -0.04) for every additional symptom reported.

Conclusions & Relevance: Behçet's Syndrome has a significant adverse impact on quality of life.

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The evaluation of the incidence of recurrent aphthous lesions in patients with haematonic deficiencies

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Objectives: Recurrent aphthous stomatitis (RAS) is a disease of unknown cause. It is a disorder characterized by recurring ulcers confined to the oral mucosa in patients with no other signs of disease. Immunological disorders, haematological deficiencies (HD) and allergic or psychological abnormalities have all been implicated as causes of RAS. Many articles reported that HD might be twice as common in some groups of patients with RAS as in healthy control subjects. HD is found in up to 20% of patients with RAS. Although a relationship is implied between HD and RAS, there is no evidence whether any RAS history was included in patients with HD. This study aims to determine the incidence of RAS in the patients with HD.

Methods: Fifty-eight patients with HD who were referred to the Department of Internal Medicine, Faculty of Istanbul Medicine, University of Istanbul were evaluated. Folic acid, vitamin B12, ferritin, iron were recorded. Patients who had at least one deficiency of these values were included in this study. Family history of anaemia and intra-oral examination regarding RAS status of the patients were evaluated.

Results: Active aphthous lesions were observed only in 3 patients (5.17%) on clinical examination. Furthermore, nineteen patients (32.75%) reported RAS history in the last one year of their anaemia without any apparent active lesion in intra-oral examination.

Conclusions: We conclude that HD could not be a major aetiological factor of RAS and these results suggest that haematological tests are not routinely essential for all patients with RAS.

Relevance: Therefore, we suggest that large groups of patients should be evaluated to determine the aetiology of RAS.

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Research of Methylene tetrahydrofolate Reductase Gene Polymorphism in Recurrent Aphthous Stomatitis Patients

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Objectives: Recurrent aphthous stomatitis (RAS) is a chronic inflammatory disease of the oral mucosa characterized by pain and recurrent ulcers affecting approximately 20% of the population. Although the aetiological factors are still not known, previous studies have demonstrated deficiencies of iron, ferritin, folate and vitamin B12 may lead to RAS. Methylene tetrahydrofolate reductase (MTHFR) is an enzyme, which has an important role in folate and 1-carbon metabolism. This enzyme biologically reduces 5, 10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, which is the active form of the folate in the blood circulation and has important roles in DNA synthesis, repair and methylation. A germ-line mutation has been discovered in the 677 nucleotide (C677T) of the MTHFR gene. This mutation decreases the specific activity of the enzyme and the folate level in the blood circulation. Many authors have reported

patients with TT genotype having lower concentrations of plasma folate compared to other genotypes. In this study, we aimed to evaluate the impact of MTHFR C677T gene polymorphism on serum folate levels in RAS patients and the relationship of this polymorphism with RAS.

Methods: Ninety patient with RAS and 87 control subjects were included in this study. Complete blood count and levels of serum iron, total iron binding capacity (TIBC), ferritin, folic acid and vitamin B12 were investigated. The distribution of MTHFR gene polymorphisms were determined by polymerase chain reaction, restriction length polymorphism techniques.

Results: Levels of serum iron, TIBC, ferritin, vitamin B12 and hematocrit were similar in RAS and control group. Low levels of serum folic acid occurred in 17.8% of RAS patients and 8% of control subjects while hemoglobin levels were low in 11.1% of RAS patients and 3.4% of control subjects. No differences were observed in the distribution of MTHFR genotypes and allele frequencies in the cases versus controls. The frequency of mutant allele (T) was 48.9% in RAS patients and 43.6% in controls. The homozygous mutation (TT) in the MTHFR gene was identified in 10% of RAS patients and 9.1% of controls. Serum folic acid levels were significantly lower in the TT genotype in RAS patients versus TT genotype control subjects.

Conclusions: Routine hematologic screening including complete blood count, serum levels of serum iron, ferritin, folic acid and vitamin B12 and total iron binding capacity should be evaluated in all patients with RAS. Lower serum folic acid levels with MTHFR 677 TT genotype could be a possible risk factor for RAS. But we need further investigations including higher numbers of patients to obtain more accurate results.

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Oral Disease Severity Scores (ODSS) and Treatment in patients with Recurrent Ulcers

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One challenge in clinical Oral Medicine is the quantification of otherwise subjective severity and activity of diseases whose nature is to recur or relapse and remit. The aim was to evaluate the use of a standardised quantitative assessment tool (ODSS) in order to show disease severity and to establish evidence for treatment outcomes in the care of patients with recurrent oral ulceration.

Methods: An ulcer scoring system has been devised encompassing ulcer size, number, duration, frequency, site, pain severity, and ulcer free period. Six different parameters were scored with a maximum total score of 60. In this trial, 200 patients presenting with ROU (120 MiRAS, 40 MjRAS, 20 HerpRAS and 20 others) were scored before and after 6 months of topical (betnesol 500mcg mouthwash) or systemic therapy and a smaller number after one year. Patient scores were plotted onto pre-designed graphs, enabling the assessor to view the trend of the patient's progress.

Results: The mean ODSS score dropped from 34.5 to 27.2 over six months and to 23.2 over 12 months ($P < 0.02$). The mean in MjRAS reduced from 45 to 36, and in MiRAS from 31 to 24. Improvements were seen in number, size and particularly in ulcer free periods. Patients with major RAS appear to respond better to drug therapy than those with minor RAS. Atypical ulcers and ulcers associated with smoking-cessation appear to be more resistant to therapy.

Conclusions: Quantifying the severity of ulcer characteristics assists in assessing and monitoring clinical improvements in RAS therapy, in particular highlighting the particular aspects of the disease modified by an agent. This can inform better therapy choices to target an individual patient's specific condition.

Relevance: ODSS offers a powerful aid in research and clinical trials for continuous monitoring of therapeutic responses. A unified simple scoring system such as this can allow multi-centre therapeutic trials and is also applicable in routine clinical practice.

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Quality of life in patients treated with mucoadhesive patches for recurrent aphthous stomatitis

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Objectives: To evaluate the efficacy of a mucoadhesive patch for recurrent aphthous stomatitis (RAS) in pain alleviation, ulcer duration and quality of life. Mucoadhesive patch releases natural active agents (citrus oil and magnesium salt) with analgesic and antibacterial effect, covers ulcer preventing from oral fluid and trauma for about eight hours.

Methods: Fifty patients with RAS, over the age of 18 and otherwise healthy, were recruited into the study. Demographic data included age, gender, profession, education status, smoking habits, alcohol consumption, oral hygiene status, frequency and duration of RAS, level of pain and functional limitations related to RAS. Patients were informed about the study and asked to fill questionnaires concerning their ulcer experience and measurement of quality of life. A mucoadhesive patch was applied to RAS. After a week patients were re-called to fill the questionnaires.

Results: Patients presented with RAS predominantly appearing once a month, single, in labial mucosa and tongue, healing in at least 5-7 days, causing discomfort in eating and speaking, with pain that lasted 5-15 days. An interesting statement was that most patients continuously traumatized ulcers with their tongue. Significant reduction in pain and discomfort due to oral functions with application of adhesive patch was recorded. Ulcers covered with a patch healed more rapidly than usual. No mucosal adverse effect of the patch was observed. Adhesiveness, taste and application of patch only one or twice were found highly acceptable by subjects. Patients were willing to use the patch again if necessary.

Conclusions: Adhesive patch with high patient acceptance was found effective in the symptomatic control of pain. Improvement in patients' quality of life was detected.

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Evaluation of the efficacy of Colchicine with and without Betnesol mouthwash in management of RAS

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Objectives: Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal diseases. Although the clinical characteristics of RAS are well defined, there have been few clinical trials of the efficacy of treatments. Topical steroids such as Betnesol mouthwash are the standard therapy for management of RAS. In addition systemic therapy such as Colchicine can be considered in severe cases, but to date there are no clinical trials reporting efficacies for either. This could be partly due to the lack of a standardized disease severity scoring system in routine clinical practice. In this clinical trial the efficacy of Colchicine with or without Betnesol mouthwash in management of RAS was compared.

Methods: 105 patients with RAS (major, minor) were randomized in this trial into 3 groups: (1): 35 patients on Colchicine 500mcg OD and Betnesol mouthwash QDS, (2): 35 patients on Colchicine 500mcg OD, (3): 35 patients on Betnesol mouthwash QDS during ulcers attacks and BD in between. An Ulcer Severity Score (USS) established in the department (Tappuni et al 2006) was used for assessing the initial severity and monitoring any response to the treatment, using six parameters including number, size, site, duration of ulcers, ulcer free periods and pain.

Results: 50 patients have completed 12 months of the trial. The severities of the ulcers were scored on the first visit (before treatment) and at 3 monthly intervals thereafter for 12 months. The mean of Ulcer Severity Score (USS) of the whole group before any treatment was 34.5 and after 12 months of treatment ($n = 50$) was 15.5. The mean score for patients on Colchicine and Betnesol dropped from 33.7 to 14.8, for patients on Colchicine dropped from 34.1 to 15.6 and patients on Betnesol mouthwash dropped from 33.7 to 15.0.

Conclusions: This study suggested that significant reductions in the USS are found with all three modes of therapy, with reductions in the size, number, duration, of ulcers and pain and an increase in the ulcer-free period. While Colchicine tablet 500mcg alone reduced recurrence of ulcers but had a little effect on improving symptoms of ulcers and Betnesol mouthwash reduced the symptoms of ulcers but could not prevent recurrences, the combination of Colchicine and Betnesol mouthwash has significant clinical benefit in the managements of RAS.

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Low-level laser therapy in the treatment of recurrent aphthous stomatitis

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Objectives: Recurrent aphthous stomatitis (RAS) is a common condition. It is characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous halos and yellow or grey bases. They appear in childhood or adolescence. There is no curative treatment available. The current treatments aim only to ensure adequate food intake, by palliating pain symptoms, reducing lesion duration, and, in cases where ulcers are constant or frequent, minimizing recurrence. Low-level laser therapy (LLLT) with a diode laser, has been reported for biostimulation in the treatment of different diseases. The aim of this study is to evaluate the influence of LLLT on the treatment of RAS.

Methods: 40 RAS patients with active oral ulcers were included in this study and divided into study and control groups. LLLT was applied on active oral ulcers in 20 patients in the study group. An application, mimicking the original LLLT protocol, without the active laser beam, was applied to 20 patients with active oral ulcers in the control group. The pain was measured by using the Visual Analogue Scale (VAS). Overall pain was assessed by using a 200 mm horizontal, ungraded VAS, onto which patients are asked to place a mark. The left side is marked "no pain" and the right side marked "worst pain imaginable". A ten-point verbal rating scale was also used.

Patients were asked to quantitatively express their degree of pain from zero being "no pain" and ten, representing worst pain imaginable". VAS values were recorded before and after the application of diode laser.

Results: The mean value of VAS was $8.41 (\pm 0.67)$, before the application of the laser and $1.21 (\pm 0.57)$ after application of laser in the study group. In the control group, the mean value of VAS was $7.96 (\pm 0.53)$ before application of the placebo laser and $6.48 (\pm 0.94)$ after application of placebo laser.

Conclusions: LLLT is shown to be effective in relieving pain due to active oral ulcers. Since the major goal of current treatments is to minimise symptoms and pain, we aimed to assess the effect of LLLT on pain levels.

Relevance: LLLT with diode laser can be considered as a useful method for the treatment of RAS. Independent studies comparing and analyzing the effect of LLLT and other management regimes for RAS are necessary.

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Outcome Predictors related with the Effects of Parafunctional Habit Control and Topical Lubricant on Discomfort associated with Burning Mouth Syndrome

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Objectives: The high prevalence of oral parafunctional habits and dry mouth symptoms in patients with burning mouth syndrome (BMS) suggests that inflammation at the subclinical level due to repetitive microtrauma may cause burning mouth sensations. The concomitant prescription of topical lubricants with oral habit control can be an effective initial approach for patients with BMS. In this study, we have investigated outcome predictors affecting the effects of this initial approach on discomforts associated with BMS.

Methods: One hundred-forty patients (12 men and 128 women, mean age 59.9 ± 10.7 years) with a complaint of burning or painful sensation in the mouth without any visible signs were included in the present study. Clinical evaluation procedures included oral examination, interview, panoramic radiography, a comprehensive questionnaire, a simplified psychological test (Symptom Checklist 90-Revised, SCL-90R), blood tests, and a measurement of salivary flow rate. Various kinds of oral parafunctional habits were also inquired. All patients were instructed not to touch the tongue tip to the teeth or restorations and to avoid tongue thrusting, tongue or mucosal biting, clenching, and lip pressure or sucking. A glycerin-containing carboxymethylcellulose (CMC) solution was prescribed to the patients. Follow-up evaluation was scheduled after 2 weeks, and subjective symptoms were examined using the same questionnaire. The patients were sub-grouped according to several variables, such as symptom area and duration, symptom severity, psychological status, salivary flow rates, and current medications. The changes of symptoms were analyzed and compared between sub-groups. The research protocol was approved by the Institutional Review Board of the University Hospital (#CR110007).

Results: The visual analog scale (VAS) scores of burning, bad taste, taste alteration, and effect of oral complaints on the daily life were significantly decreased after the 2-weeks' initial approach. The subjects showing T-scores < 50 in each dimension of SCL-90-R displayed greater decrease of symptoms compared with those showing $50 < T$ -scores. The subjects showing the flow rate of stimulated whole saliva (SWS) > 0.5 mL/min displayed greater decrease of symptoms compared with those showing $SWS \leq 0.5$ mL/min. The flow rate of unstimulated whole saliva did not affect the treatment outcome. The subjects not taking psychiatric medications displayed greater decrease of symptoms compared with those taking psychiatric medications. The subjects having more severe degree of symptoms (VAS > 5) at the first visit displayed greater decrease of symptoms compared with those having less severe degree of symptoms (VAS < 5). The symptom area and duration did not affect treatment outcome.

Conclusions & Relevance: Psychological status, current taking of psychiatric medications, the flow rate SWS and initial symptom severity can be treatment outcome predictors in the initial approach using topical lubricants with oral habit control, in patients with BMS.

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The frequency of psychological disorders in patients with complaints of mental and organic origin

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Objectives: This study was designed to compare the frequency of psychological disorders as well as type and intensity of stressful events between two groups of patients with mental- origin complaints (MOC) and organic origin complaints (OCC).

Methods: 132 patients with MOC were compared with 132 patients with OCC. Both groups filled Scl-90 and holms-rahe questionnaires, for determination of the psycho-

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logical damages type and for type and severity of stressful events respectively. The type of complaints, severity of mental complaints (by visual analysis scale (VAS)) and type of the psychological disorders were recorded. Descriptive analysis was used to demonstrate data and ANOVA test, T-test and chi-square perason test to compare subgroups.

Results: The mean age was $43 \pm 14/75$ years in the MOC group (MOCG) and $31 \pm 10/66$ years in the OCC group (OCCG). 84/132 of MOCG and 70/132 of OCCG were female. The most prevalent mental complaints in MOCG were pain without dental etiology (33/3%), burning (16/6%) and tooth pain (12/1%). The severity of complaints was moderate (VAS) in MOCG. The most prevalent clinical diagnosis were AFP (34/1), variable atypical sensory disorders with mental origin (25%) and burning mouth syndrome (18/1%). Furthermore 53/8% of patients in MOCG and 28% in OCCG were predisposed to psychological disorders (due to the scl-90). 31.1% of MOCG and 2.1% of OCCG had psychological disorders with a significant difference ($P < 0.05$). The most prevalent psychological disorder (due to psychologist's examination) was anxiety disorder (40/2%) and the most stressful event reported in both groups was changes in life conditions (10/8%, 20%).

Conclusions: This study showed that 100% of patients with MOC had psychological disorders.

Relevance: Dentists must refer such patients to Oral Medicine Specialist to prevent unnecessary or harmful interventions to patients and to conduct the patients in correct treatment processes.

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Burning mouth syndrome

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Objectives: Burning mouth disorder may be defined as burning sensation in oral mucosa concern with the absence of clinical signs. Multiple conditions have been implicated as local or systemic in the causation of burning sensation. The international associations for the study of pain define it as: "A distinctive nosological entity characterized by unremitting oral burning or similar pain in the absence of detectable mucosal change." The purpose of this preliminary study was to characterize different profile of patients with burning mouth syndrome.

Methods: A total of 184 patients (147 female, 37 male) who complained of burning sensation, seeking for treatment in sole oral medicine office in Rasht, Guilan province, North of Iran, from 2001 to 2009. After oral exploration, the absence of visible oral lesions was verified in each case. An inquiry was made about the overall health of the patients and any medications being taken as well as the location and duration of burning mouth syndrome (BMS). All patients underwent routine hematologic screening: serum iron, total iron-binding capacity, vitamin B12, folic acid, fasting glucose and thyroid profile.

Results: 37 participants were male; therefore, the female, male ratio was about 4:1. The mean age was 55.85 years with the age range 20-87 years old. 69.6 percent were older than 50 years old. Moreover, their employment status denoted that 65.8% were house wives and 10.3% retired, versus 23.9% deal with job. Urban and rural life accounted for 87% and 13% respectively. Furthermore, type II was more prevalent 91.8% in comparison to other types. According to location, 74.4% complained burning in whole mouth, tongue, lip and gingival were as followed. Neurologic disorders were more common (29.3%) among patients.

Conclusions & Relevance: Since the purpose of this study was to characterize the features of BMS, findings coincide with other studies. Ironically, age, gender, lifestyle (urban, occupation) make patients prone to BMS.

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Validity and reliability of patient-centred outcome measures in oral dysaesthesia

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Objectives: To investigate the validity and reliability of an oral health related quality of life measure in patients with oral dysaesthesia.

Methods: Forty-five individuals newly diagnosed with oral dysaesthesia (37 females, 8 males, mean age 61 years, range 38 – 83) were enrolled in this study. Individuals were interviewed using Visual Analogue Scale (VAS), and the Oral Health Impact Profile (OHIP-14). Psychometric testing was carried out and both construct validity and internal reliability were examined.

Results: Patient rating of pain experienced, using VAS, correlated with OHIP-14 scores ($P < 0.05$), demonstrating construct validity. The Cronbach's alpha for OHIP-14 was 0.788 demonstrating good internal consistency. Item-total correlations were for items 3 (0.089) and 12 (0.183) were below the recommended minimum of 0.20. The Cronbach's alpha for OHIP-14 increases to 0.808 with the exclusion of items 3 and 12 from the 14 item questionnaire.

Conclusions: OHIP-14 performs relatively well in patients with oral dysaesthesia, demonstrating validity and reliability. However, the exclusion of items 3 and 12 from the questionnaire should be considered in future studies with this patient population.

Relevance: The negative impact of oral dysaesthesia on the quality of life of patients has been documented in the literature. This study gives direction to clinicians and researchers regarding the suitability of an oral health related quality of life measure for future research projects.

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Study of risk factors and clinical and radiological variables in patients with temporomandibular joint (TMJ) osteoarthritis or osteoarthritis

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Objectives: To describe etiological, clinical and radiological variables in patients with temporomandibular joint (TMJ) osteoarthritis or osteoarthritis, comparing the two groups with each other and with a group of patients with temporomandibular disorders (TMD).

Methods: Based on the axis I Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD), a total of 35 patients were studied (32 females and 3 males, 10.7:1) with a mean age of 53 ± 18 years. Twenty-one (60%) presented osteoarthritis (mean age 54.7 ± 20.2 years) and 14 osteoarthritis (mean age 51.7 ± 16.9 years). The groups were compared with each other and with a group of patients with TMD including myofascial pain (10.4%), disc displacement and reduction (14.6%), disc displacement without reduction (3.0%), joint pain (8.5%), osteoarthritis (4.9%), osteoarthritis (9.1%), multiple diagnoses (31.1%), and no RDC/TMD diagnosis (18.3%). Descriptive statistics were presented as the mean and standard deviation, and percentage, while comparisons of variables were made using the Fisher exact test, the chi-squared test and ANOVA.

Results: No significant differences were found between patients with osteoarthritis and patients with osteoarthritis. Age was significantly older in patients with osteoarthritis (54.7 ± 20.2) or osteoarthritis (51.7 ± 16.9) than in the TMD group (38.6 ± 18.2) ($F = 8.83$; $F = 8.03$; $P = 0.003$; $P = 0.005$). The time to first visit (30.2 ± 46.0 months) and the percentage of patients with loss of posterior occlusal contact (71.4%) were significantly greater in the osteoarthritis group than in the patients with TMD ($F = 3.95$; $P = 0.04$; Fischer $P = 0.009$). Maximum interincisal aperture (32.5 ± 6.4mm), left lateralization (5.0 ± 3.7mm), the number of posterior occlusal contacts (5.2 ± 3.0) and the presence of parafunctional habits (42.9%) were all significantly smaller in the osteoarthritis group than in the subjects with TMD ($F = 4.45$, $P = 0.03$; $F = 5.78$, $P = 0.02$; $F = 6.17$, $P = 0.01$; Fischer $P = 0.04$).

Conclusions & Relevance: Osteoarthritis and osteoarthritis show no significant differences between each other, though osteoarthritis does present differential features in terms of risk factors and mandibular mobility with respect to the TMD group.

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Illness perception and clinical variables in chronic orofacial pain patients

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Objectives: Patients beliefs about their disease have been shown to determine coping strategies. The aim of the study was to investigate the relationship between patients pain beliefs as measured on the Brief Illness Perception Questionnaire (B-IPQ) and clinical characteristics of their facial pain severity, interference with daily function, pain-related disability, depression and anxiety.

Methods: 54 consecutive non dental chronic (>3 months) orofacial pain patients attending a facial pain clinic were asked to complete the B-IPQ, Brief Pain Inventory (severity and interference with daily function), Chronic Graded Pain Scale (pain-related disability) and Hospital Anxiety and Depression scale. 38 patients were female and 16 were male with an average age of 47.7 ± 17.1 years. They were 23 new and 31 follow up patients. Average duration of pain was 52.0 ± 40.5 months. Correlations were measured by Pearson's correlation coefficient.

Results: Belief that pain could have a serious consequence on one's life, identity, concern and emotional impact were significantly associated with pain severity, interference with daily function and pain-related disability ($P < 0.05$) but not with depression. Lower personal control was significantly associated with anxiety while duration of pain was significantly associated with interference with enjoyment of life ($P < 0.05$). Overall illness perception score was significantly lower in follow up patients ($P < 0.05$).

Conclusions: Beliefs about facial pain are associated with pain severity, interference with daily function and pain-related disability in chronic orofacial pain. With treatment patients' beliefs appear to change and may reflect their new coping strategies.

Relevance: Since psychological and physical component of chronic pain are closely associated, changing patients' beliefs about pain into more positive ones, might result in better treatment outcomes.

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New Patient Satisfaction after an Initial Consultation at the Eastman Dental Hospital Orofacial Pain Unit

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Objectives: We investigated factors that were predictive of patient satisfaction after an initial consultation visit and proposed treatment plan at an orofacial pain unit.

Methods: We included 50 consecutive new patients referred to the Eastman Dental Hospital Orofacial Pain Unit. Patients filled out pre-visit questionnaires (Brief Pain Inventory (BPI); Graded Chronic Pain Scale Questionnaire (GCPS); Hospital Anxiety and Depression Scale (HAD) and a patient treatment goal questionnaire) and a post-visit satisfaction questionnaire devised by our unit. We sent questionnaires to patients by mail, and those who did not respond to the initial mailing after 2 weeks were re-sent the questionnaire. We contacted by telephone those who did not respond to the second questionnaire after 2 weeks. Statistical analyses included regression analysis, analysis of variance (ANOVA), Fisher's exact test, chi-squared test, and t-test where appropriate.

Results: Twenty-two patients (44%) responded to the initial mailing, 10 (20%) responded to the second mailing, 12 (24%) were contacted by phone and 6 (12%) did not respond. Older patients were statistically more responsive than younger patients ($P < 0.001$). Non-responders to the mailing had non-statistically higher BPI and GCPS scores. Among responders, mean overall patient satisfaction was 8.1 ± 2.2 on a 10 point scale, with no differences based on diagnosis, treatment plan, pain severity and duration, and high anxiety or depression. Treatment goal of reducing pain medication was predictive of overall patient satisfaction ($P = 0.047$). Patients who had seen at least one specialist prior reported higher scores in understanding the reasons for their condition ($P = 0.01$) and understanding what to do to treat their condition ($P = 0.028$).

Conclusions: Younger patients and those with more severe and chronic pain were less likely to respond to the post-visit questionnaire. Among responders, medication reduction and previous consultation were predictive of patient satisfaction outcomes.

Relevance: Patient satisfaction after consultation at an orofacial pain unit is generally high after an initial visit.

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Management of temporomandibular disorders: Thinking outside the 'capsule' (a multidisciplinary approach)

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Objectives: To present the case for a multi-disciplinary approach to the management (assessment and treatment) of patients with Temporomandibular Disorder (TMD).

Methods: Over a six month period 173 new patients were seen in a multi-disciplinary facial pain clinic. Of these, after careful assessment, 63 were identified with a primary diagnosis of TMD. A variety of validity scales were used to assess patients at the initial visit and any subsequent visits including the Brief Pain Inventory (BPI) and the Hospital Anxiety and Depression (HAD) scale. At the time of assessment identified co-morbidities were also noted.

Results: Of the 63 patients, 13 were found to have depression and/or anxiety, 16 other chronic pain conditions, four migraines, 25 had previously used acute analgesics and 16 had used antidepressants. At the assessment visit all patients received reassurance and comprehensive information. In 10 jaw exercises were recommended, 25 were made occlusal splints and 16 were prescribed an antidepressant. 53 had more than one treatment modality. 28 were discharged at the first visit. Of those needing further treatment 6 were referred to clinical psychology, 2 to liaison psychiatry, 5 to the complementary and alternative medicine clinic and 3 to a restorative specialist.

Conclusions: Clinicians involved in the treatment of TMD should be aware that conservative management should include a comprehensive assessment and a treatment plan which takes into consideration the associated features and co-morbidities of TMD.

Relevance: Patients with TMD are often assessed and treated only from a physical approach. It is proposed that co-morbidities should be taken into consideration to achieve holistic and consequently effective treatment.

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Acupuncture and burning mouth syndrome: an open label study

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Objectives: The treatment of Burning Mouth Syndrome (BMS) is possible, but not still satisfactory. Acupuncture is an ancient Chinese non-pharmacological therapy used for

treating a variety of conditions. It uses a puncture needle to target several acupoints in the body to sustain circulation of qi and restoration of yin and yang, with the purpose of maintaining body health. The aim of this prospective open-label study was to evaluate the effect of acupuncture on symptoms in patients suffering from BMS.

Methods: A total of BMS 10 patients received acupuncture. Treatments lasted 8 weeks (12 sessions) and were provided 2 times per week for the first 4 weeks and weekly for 4 more weeks. Low to moderate needle stimulation was applied until a throbbing sensation was obtained (de qi sensation). The acupuncture points were concentrated on face and/or in meridians related to the face (according the Chinese medicine). The primary outcome was the VAS analogue scale for pain. Secondary outcomes were the SF-36 (Short Form-36 Health Survey) and the HAD scale (Hospital Anxiety and Depression scale). A Wilcoxon test was used to evaluate clinical data.

Results: The study group was composed of 9 women (median age, 68 years) and 1 man (median age 64.5 years). All patients had a history of oral complaint for more than 6 months (average, 25.0 ± 15.7 months; range, 6 to 58 months). No side effects were observed. Following the 8 weeks of treatment, none of the 10 patients reported a significant reduction of pain, as showed by VAS scale. Regarding quality of life, we found that subjects receiving acupuncture treatment seemed better able cope with their symptoms, although they often still had the same degree of oral burning sensations.

Conclusions: This prospective open-label acupuncture protocol failed to demonstrate symptom reduction in BMS patients

Relevance: The results of this evaluation failed to suggest any relevance of acupuncture treatment in BMS.

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Effect of Oral Capsaicin Gel on Burning Mouth Syndrome

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Objectives: To investigate the effectiveness and safety of repeated topical application of oral capsaicin gel for relief of burning symptoms in patients with burning mouth syndrome (BMS).

Methods: This double-blind crossover study included 22 female patients with BMS (age mean 58.4 ± 9.2 years). The patients were randomized for topical application of either 0.01% or 0.025% oral capsaicin gel on the dorsal part of tongue three times a day for 14 days, followed by 14 days wash-out period, and finally treatment with the other concentration of oral gel three times a day for 14 days. A visual analogue scale (VAS) was used to score the severity of pain at trial entry, 14 days after use of first oral gel, 14 days after wash-out, 14 days after use of second gel and finally after 14 days wash-out.

Results: The severity of pain was not associated with the duration of BMS symptoms which was mean 3.7 ± 2.5 years. The VAS scores were significantly lower after treatment with the first capsaicin gel compared to baseline (mean $41.8 \pm SD27.4$ and 55.4 ± 24.2 mm, $P=0.005$); and after use of the second capsaicin gel and after 14 days wash-out (40.6 ± 30.6 and 46.4 ± 31.5 mm). The VAS scores increased in both periods, where the gel was not used. There were no differences in VAS scores, when comparing use of the first and second gel. Three patients dropped out after one week due to gastrointestinal side-effects such as nausea and itching and another found the consistency of the gel unpleasant.

Conclusions: Topical application of oral capsaicin gel is therapeutically effective and safe for the short-term treatment of BMS. Further studies are needed to investigate especially the gastrointestinal side-effects which may limit its long-term use.

Relevance: BMS is a major diagnostic and therapeutic problem and the condition has a major negative impact on quality of life. Our search for effective and safe therapeutic approaches for this pain condition is important.

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Effects of oral function on pain perception

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Objectives: In humans, pain plays a crucial role in transmitting hazardous signals to the body, but it causes discomfort. Various studies have shown that the pain perception is often reduced by playing sports, concentrating on other things or having a comfortable feeling. In this study, we examined the effects of listening to the music and oral function (biting, chewing and taste) on pain perception.

Methods: Fifty subjects (43 males and 7 females, mean age: 31.5 yrs) participated, whose ankles were exposed to CO₂ laser. Laser stimulation was given every 10 seconds on the 5 points on the ankle. In all subjects, the actual effects of oral function and music on pain perception were assessed using visual analog scale (VAS). The effects of oral function and music on pain using functional magnetic resonance imaging (fMRI) were investigated with ten of above subjects without missing teeth (8 males and 2 females,

mean age: 40.0 yrs). Mechanical pain stimulation was given to their ankles with a plastic needle-point flower holder. We analyzed the blood oxygenation level-dependent (BOLD) signals in the cingulate cortex which is one area of the pain transmittance route. Functional images followed by anatomical images were acquired using a 3.0-T Horizon MR scanner.

Results: In the VAS levels, we found a significant pain reduction when the subjects listened to music (Shaffe's test, $P < 0.0001$), whereas no significant differences were seen on oral function. However, the fMRI study revealed that biting and listening to the music attenuates BOLD signals in the cingulate cortex during mechanical pain stimulation in 6 subjects.

Conclusions: The finding suggested that listening to music is able to reduce pain perception, whereas oral function doesn't seem to have actual pain-reducing effect despite its effect on BOLD signals.

Relevance: It is important to find a helpful tool for attenuating pain perception.

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Efficacy of ALA in the treatment of Burning Mouth Syndrome

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Objectives: In order to control symptoms of Burning Mouth Syndrome (BMS) has been suggested the use of an antioxidant drug with potentials effects for the treatment of neuropathies: the Alphalipoic Acid (ALA). We have two main objectives:

- 1.-Evaluate the efficacy of ALA in controlling symptoms of BMS
- 2.-Evaluate other variables that could modify the response to this treatment

Methods: A double-blind trial has been performed in a group of 59 patients: 32 in placebo and 27 in the cases group. ALA has been used at 600mg/day doses during two months and the improvement of symptoms has been assessed via VAS and by the influence of other variables that could modify the response to treatment.

Results: 64% of the patients receiving ALA showed some kind of improve, that has maintained in 60% of the patients up to one month after finishing the treatment. It has been found that patients with depression and long term evolution of symptoms have lower probability of improvement.

Conclusions: ALA is effective in the treatment of BMS, and this effect can be maintained at least two months after finishing treatment. There are some variables that modified the response to this treatment that could predict the indication to this treatment in a particular patient.

Relevance: These results united to the great placebo effect found (27%) makes us wonder the possible existence of two populations in this disease: one of which would benefit easily when being treated with ALA (suggesting a neuropathy) and the other one in which it would be more important the psychological treatment (where the symptoms would be relate with patient's psyche).

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Transdermal Opioid Analgesia for Chronic Facial Pain

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Objectives: Chronic facial pain patients frequently use opioid analgesics in addition to specific CNS pain medication. Transdermal opioids give predictable continuous dosing for two to seven days and can avoid peak and trough effects of oral dosing. This case series reviews a mixed diagnostic group of chronic facial pain patients offered transdermal opioid patches through the Oral Medicine clinic in Glasgow.

Methods: Twelve patients with stable pain were prescribed transdermal opioids as part of their facial pain management and completed a structured questionnaire about their experience. Ten patients had used Fentanyl, one Buprenorphine and Fentanyl. One was unsure which drug had been used.

Results: Efficacy: Of patients reporting a beneficial response, the average reported reduction in pain score was 3.8 (n=10, range 6-1) compared to the pre-patch oral analgesic regime.

Tolerability: Five of twelve patients continue to use the patch in their pain regime, using them for an average of 15 months (range 7-21). Six discontinued the patches within a short period (<1-3 months) due to lack of efficacy or side effects (nausea, drowsiness, agitation, sweating). Ten patients would recommend patches to another chronic facial pain patient, including five not continuing patches themselves.

Conclusions: This series suggests that patches are not suitable for all chronic facial pain patients but they can be a useful adjunct to improve pain control. Standard opioid side effects were experienced resulting in some patients discontinuing treatment despite a good effect on pain. As a retrospective study it was not possible to use analgesic use as an endpoint but this would be desirable in a prospective case series.

Relevance: This patient group can be difficult to manage and transdermal opioid use can allow the analgesic regime to be simplified allowing 24 hours drug delivery. The pain score reduction suggests that this is beneficial where the side effects are tolerable.

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Low level laser therapy in BMS patients: a preliminary reportVD Pellegrini^{*1}, EFP Silva¹, IT Kato², RA Prates², NN Sugaya¹¹Department of Stomatology, Universidade de Sao Paulo, ²Instituto de Pesquisas Energeticas e Nucleares, Sao Paulo, Brazil**Objectives:** The objective of this trial was to assess the efficacy of a low level laser therapy (LLLT) to manage burning mouth syndrome (BMS) patient's symptoms.**Methods:** Two groups of BMS patients were constituted: laser group (LG) received LLLT irradiations and control group (CG) that received non active laser irradiations with the same probe. An infrared diode (GaAs) laser (790nm), output power of 120mW, spot area of 0,03cm² was utilized. Allocation was randomized by a computer generated sequencer. Patients were blinded to treatment type. The researcher that delivered irradiations was blinded to the results. The researcher who collected results through a visual analogue scale (VAS) was blinded to patient's allocation. Four sessions of irradiation were provided (6J/cm²), 2 per week, in consecutive weeks. Control assessments were done at the start, after irradiations, and 7, 14, 30, 60, 90 days after last irradiation.**Results:** Seventeen patients were followed in this preliminary trial, presenting 33 oral sites with burning sensation: 16 women, one man; mean age 62.5 years and mean duration of symptoms of 36.2 months. Ten patients were allocated to LG and 7 patients to CG. Thirteen out of 20 sites in LG presented symptomless at 90-day follow-up, while 2 out of 13 sites in CG presented symptomless at that endpoint. Statistical analysis applied to percentages of improvement/worsening relatively to VAS scores showed a better result in LG (Mann-Whitney, $p \leq 0.05$) when compared to CG, at 14-day and 90-day follow-up control.**Conclusions:** LLLT showed to be beneficial to BMS patients encouraging the extension of the research aiming a greater number of patients and improvement of the treatment protocol.

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Use of Gamma Knife Radiosurgery for Trigeminal NeuralgiaM Tomida¹, M Hayashi², N Kouyama², Y Katayama², Y Kawakami², N Nakamura¹, N Asanuma¹¹Department of Oral Physiology, Matsumoto Dental University, Nagano, Japan,²Department of Physiology, Tokyo Women's Medical University, Tokyo, Japan**Objectives:** Gamma knife surgery (GKS) has been used for treating intractable pain control, such as trigeminal neuralgia (TN). However, little is known about an objective evaluation and side effects on sensibility without pain. The purpose of this study was to examine the period of time necessary for complete pain relief of patients using GKS for TN and to assess the side effects of other sensibility induced by GKS.**Methods:** We included 10 patients (4 men and 6 women; mean age 67 years) with TN who were investigated by questionnaire for symptom and visual analog scale (VAS) of pain, and were examined threshold of touch sensation using Semmes-Weinstein monofilaments, cold sensation and allodynia before and after GKS. MR and CT images were obtained after a Leksell head frame was applied to head parallel to the trigeminal. These images were uploaded into a computer system and the retro Gasserian area was correctly marked on the images of computer equipped with gamma planning software. All patients were irradiated a maximum dose of 90 Gy at the retro Gasserian using a 4mm collimator.**Results:** The mean value of the scale for pain was 8.5 ± 1.3 (SD) in 8 patients having facial paresthesia before GKS. At 3 months after GKS, pain completely disappeared in 7 patients. All patients experienced a significant pain reduction without side effects, such as observed on the peripheral nerves, within 6 month after GKS. Allodynia, facial paresthesia or cold sensation numbness disappeared after GKS according to complete pain relief.**Conclusions:** These results suggest that GKS is not only a useful tool in treatment for TN, but also may provide a great contribution in various diseases as an epoch-defining method.**Relevance:** It is helpful for patients with severe pain to find a new technical treatment to reduce pain.

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Orofacial granulomatosis as an adverse reaction to cosmetic fillers: study of 20 cases

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Objectives: Subcutaneous or submucosal infiltration of cosmetic materials is a very common practice, due to the ease with which such materials can be deposited, and their presumed innocuousness. However, in recent years there have been reports of foreign body granulomatous reactions occurring many years after infiltration. The present study describes 20 patients with orofacial granulomatosis induced by filler materials.**Methods:** Data were collected on the clinical manifestations, histopathological findings, treatment and course of the lesions of 20 patients. Once clinical suspicion

was established, the patients were questioned about the filler material they received, its location, and the time elapsed from infiltration. Patient follow-up was carried out, recording any outbreaks or relapses, and the treatments received.

Results: One male and 19 females presented orofacial swelling an average of 7.7 years after the infiltration of silicone (n=12), hyaluronic acid (n=2), collagen (n=3), methacrylate (n=1) and polyalkylimide (n=2). The mean duration of follow-up in our series was 19 months, with final complete remission of the lesions in all cases. A biopsy of the lesions was performed in 18 patients. Foreign body granulomas were observed in all these cases, with the presence of giant multinucleated cells, and important chronic inflammatory infiltration. The outbreaks were treated with prednisone (Dacortin®) or deflazacort (Zamene®) 30-90 mg/day for 10-15 days.**Conclusions:** Systemic corticosteroids are able to control granulomatous reactions, which manifest in the form of outbreaks and tend to undergo spontaneous remission over the years.**Relevance:** In the United States, these cosmetic procedures were estimated to total 8.3 million in the year 2003, and 12 million in 2004. As a consequence of this great increase in the number of procedures performed, different side effects have been reported in the literature, including particularly foreign body reactions described by the authors as orofacial granulomatosis or granulomatous adverse reaction.

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Orofacial granulomatosis - a case series study of 120 patientsBE McCartan¹, CM Healy², L Fitzpatrick², CE McCreary³, SR Flint², SC Rogers³, ME Toner²¹Royal College of Surgeons in Ireland, ²Trinity College Dublin, ³University College Cork, Ireland**Objectives:** To analyse the patient history, examination findings and investigations of a large panel of OFG patients.**Methods:** Records were retrieved for OFG cases who had attended oral medicine clinics in two Dublin institutions over a 21 year period (1988-2008). Patients in whom Crohn's disease was identified were excluded. Details of patient history, examination and investigation were collated.**Results:** Details on 120 OFG cases were available: 57 male, 63 female, median age 28 years, range 5-84 years. The median duration of symptoms was 12 weeks and 77% presented with lip swelling. Thirty-five patients felt there was a food trigger for their symptoms, with chocolate, carbonated drinks and beer most commonly implicated. On examination, some degree of lip/facial swelling was found in 94% of patients. The upper and lower lips were affected equally commonly. Cobblestoning was identified in 64% of patients and was present statistically significantly more frequently in males. 29% had mucosal tags, 36% oral ulceration, 34% granulomatous gingivitis and 16% tongue fissuring. Biopsy reports were available for 71% of patients and a definitive diagnosis of OFG was made in 56% of these, with a further 8% being reported as suspicious of OFG. Urticarial testing was carried out in 97 patients and 55% reacted to one or more of benzoic acid, cinnamaldehyde and cinnamyl alcohol, while on 17% of patients who had standard patch testing carried out (n=41) reacted to one or more of these agents.**Conclusions:** There are few case series of OFG in the literature, and most of these are of small numbers only. This series demonstrates the frequency of oral complaints and findings in OFG. Patient histories and testing suggest an important role for food substances in the aetiology of OFG.**Relevance:** This is the largest case series of OFG to date of which we are aware.

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Clinical presentation of oro-facial granulomatosis (OFG) with and without concurrent Crohn's diseaseH Campbell^{1,2,3}, ME Escudier^{*4,5}, P Patel^{1,6}, C Nunes^{1,6}, T Poate^{4,5}, K Barnard^{4,5}, P Shirlaw^{4,5}, M Lomer^{1,5}, SJ Challacombe^{4,5}, J Sanderson^{1,6}¹Nutritional Sciences Division, Kings College London (KCL), ²Department of Nutrition and Dietetics, Guy's and St Thomas' NHS Foundation Trust (GSTFT), ³NIHR comprehensive Biomedical Research Centre at GSTFT and KCL, ⁴Department of Oral Medicine, KCL, ⁵Mucosal Biology Research Group, KCL, ⁶Department of Gastroenterology, GSTFT**Objectives:** To define the common presentation of OFG and establish differentiating features between those with and without a concurrent diagnosis of Crohn's disease.**Methods:** A retrospective notes review of 207 patients with orofacial granulomatosis (OFG). Data were extracted for age of onset, sex, clinical features, blood parameters, concurrent Crohn's disease (established by standard criteria) and treatments used.**Results:** Ninety seven patients (47%) were female. Median age of disease onset was 24 years. Referrals were mainly sourced from maxillo-facial surgeons (31%) and gastroenterologists (19%). The buccal mucosa (74%) and lower lip (68%) were the most common sites involved followed by gingivae (63.5%) and upper lip (61%). Forty six (22%) had concurrent Crohn's disease. Ulcers (46% vs. 15%, $P = < 0.001$) and mucosal scarring (20% vs. 5%, $P = < 0.001$) were more common in patients with concurrent Crohn's disease as was abnormal C reactive protein (73% vs. 49%,

$P=0.016$), abnormal full blood counts (46% vs 23%) and low haemoglobin (31% vs 11%). The sulcus (27% vs 13%, $P=0.019$) and fauces (4% vs 0%, $P=0.008$) were significantly more likely to be affected in Crohn's disease.

Half of the patients with concurrent Crohn's disease were diagnosed with Crohn's disease prior to onset of OFG. Conversely 42.5% had OFG symptoms prior to diagnosis of Crohn's disease. The remaining patients (7.5%) presented with symptoms and were diagnosed with Crohn's disease within the same year. The predominant treatment used (86%) was the cinnamon and benzoate free diet. Topical treatments including antifungal and steroidal creams, ointments, mouthwashes and intralesional steroid injections were used in 64% of cases. Azathioprine was used in 39% of patients and anti TNF α therapy in 7.5% of patients. Only 3% of patients required cheiloplasty. **Conclusions:** OFG affects young adults and most commonly presents with buccal and lower lip involvement. Abnormalities in inflammatory markers and haematinic deficiencies and oral presentation of ulceration and scarring are all factors which can contribute to clinical decision making when considering further gastrointestinal involvement. Initial presentation of OFG is not necessarily predictive of further development of Crohn's disease.

Relevance: Orofacial granulomatosis (OFG) is a rare chronic inflammatory disease of unknown aetiology sharing histological features with gut Crohn's disease

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Experience with anti-TNF α therapy in the management of orofacial granulomatosis (OFG)

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Objectives: To investigate the role of infliximab (IFX) and adalimumab (ADA) in the management of patients with OFG.

Methods: A review of patients receiving induction and maintenance IFX for OFG +/- Crohn's disease (CD) for active oral disease failing other therapies was performed. Clinical response defined by global physician assessment, aided by oral disease activity scores, was assessed at 2 months, 1 and 2 years. ADA was considered for patients failing IFX. Adverse events were recorded. Predictors of need for anti-TNF- α therapy were determined by comparison with OFG patients not requiring anti-TNF- α from our overall OFG database ($n=207$).

Results: Fourteen patients (9 males) were treated with IFX (OFG only ($n=7$), OFG with CD ($n=7$)). Nine patients received concomitant immunosuppression. Median duration of treatment was 18 months. Short term response was achieved in 10/14 (71%) patients. Eight of 14 (57%) and 4/12 (33%) patients remained responsive at 1 and 2 years respectively. Two patients who failed IFX responded to ADA. Factors predicting need for anti-TNF- α therapy were oral sulcal involvement, intestinal CD and a raised CRP. Oral sulcal involvement predicted response at 1 and 2 years. Intestinal CD did not predict response. The only significant adverse event was an IFX infusion reaction. **Conclusions:** IFX provided good short term response for most OFG patients however a significant proportion lost response long term. Adverse events were uncommon. Patients failing IFX may respond to ADA.

Relevance: Orofacial granulomatosis (OFG) can be challenging to treat and experience with anti-TNF- α therapy is limited. We report our experience with infliximab (IFX) and adalimumab (ADA) for OFG in 14 patients, the largest reported series to date.

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The relevance of patch testing and a clinical review of the cinnamon and benzoate free diet in orofacial granulomatosis (OFG)

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Objectives: To (i) determine the current clinical impact of the cinnamon and benzoate free diet (ii) assess if patch testing is predictive for dietary response (iii) identify other patient reported sensitivities and (iv) investigate differences between patients presenting with and without co-existing CD.

Methods: Case notes of patients with OFG ($n=207$) were reviewed. Data were extracted for age of onset, gender, treatments, patch test results, reported sensitivities and diagnosis of CD. A clinical response to the diet was as reported by the patient. The chi square test examined the significance of relationships between, dietary benefit and patch test results between patients with OFG and those with a concurrent diagnosis of CD. Data is reported as n/N (%) to allow for missing data.

Results: Ninety seven (47%) patients were female and 46/203 (23%) had coexisting CD. The predominant treatment 172/199 (86%) was a cinnamon and benzoate free diet with 86/157 (55%) demonstrating clinical benefit. Only 45/199 (23%) patients had exclusive dietary treatment and, of those, co-existing CD did not affect whether

patients benefited from diet or not (73/128, 57% patients without CD versus 13/29, 45% with CD; $P=0.233$). Atopic symptoms were reported in 110/197 (56%) patients and 31/97 (16%) had food hypersensitivity. Patch tests were done in 112/198 (57%) patients and 40/112 (36%) had one or more positive results. The most common sensitivities were to fragrances 10/40 (25%) and cinnamates 9/40 (22.5%). Benzoate sensitivity was seen in 6/40 (15%) patients. A higher incidence of positive patch tests was seen in patients who demonstrated clinical benefit from the diet versus those who did not (23/43, 53% versus 15/45, 33% respectively) but this did not reach statistical significance ($P=0.056$). No statistical difference was seen in the incidence of positive patch tests to cinnamates and benzoates for patients who did or did not benefit from dietary intervention (6/43, 14% versus 5/45, 11% respectively; $P=0.687$) nor whether they had CD or not (6/22, 27% versus 34/90, 38% respectively; $P=0.357$).

Conclusions: In clinical practice, a cinnamon and benzoate free diet can improve OFG symptoms and may avoid more invasive treatments in many patients with OFG irrespective of concurrent diagnosis of CD. Patch testing is not predictive of dietary benefit in OFG.

Relevance: A cinnamon and benzoate free diet has proven beneficial in up to 72% of patients with OFG (White et al, 2006).

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The varied response of orofacial granulomatosis (OFG) to azathioprine (AZA)

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Objectives: To report our experience with AZA for patients with OFG treated in a specialist oral medicine/gastroenterology service.

Methods: A review of patients receiving AZA for OFG +/- CD for active oral disease failing other therapies was performed. Patients were identified via patient notes and clinical and demographic features were recorded. Clinical response was defined by global physician assessment, aided by oral disease activity scores (ODAS), and was assessed at 4 months, and at more than 1 year follow up. Adverse events were recorded.

Results: 66 (39 males) of 207 (32%) patients with OFG (OFG only ($n=39$), OFG with CD ($n=27$)) attending the oral medicine/gastroenterology clinic received AZA between 1997 and 2009. Of 66 patients, 45 patients were analysed at 4 months and 31 at the 12 month period. The remainder were not included due to poor adherence, insufficient follow up data or acute neutropaenia ($n=1$). Mean follow up was 15 months. Response at 4 months was achieved in 17/45 (38%) patients; 6/27 (22%) were OFG alone and 11/18 (61%) were OFG with CD (a significant difference $P=0.01$). At 12 months or more follow up 3/17 (18%) OFG alone patients remained responsive vs 10/14 (71%) with OFG/CD ($P=0.004$). A significant reduction was observed in ODAS at 4 months for site ($P=0.029$) and severity ($P=0.02$) in all 45 patients. This significance was maintained for the patients with OFG/CD ($P=0.013$ and 0.004) but not for the OFG alone group ($P=NS$). A similar number of patients suffered late unwanted effects (nausea, depression and arthralgia) to AZA between the groups (21% for OFG alone vs 11% for OFG/CD $P=NS$).

Conclusions: AZA is disappointing when used as treatment for pure OFG and emphasizes the importance of dietary therapy. Conversely, in those with concurrent CD, AZA appears as effective as those with intestinal CD. This is in keeping with other studies suggesting that OFG alone and OFG with CD are different disease entities.

Relevance: Orofacial granulomatosis (OFG) is a chronic inflammatory disorder presenting with swelling of the lips, mucosa and other oral sites. It may occur alone or in combination with intestinal Crohn's disease (CD). There is currently no consensus on management of OFG but exclusion diets, topical and systemic immunosuppressants, and surgery have been used with varied success. Azathioprine (AZA) is effective in the management of CD but experience with its use in OFG is limited.

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Jaw osteonecrosis in long-term oral bisphosphonate therapy: series of 14 cases

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Objectives: In 2003 the first cases of jaw osteonecrosis (BRONJ) in patients receiving intravenous bisphosphonate (BPH) treatment for malignant disease were reported. Many case series documented the incidence of BRONJ secondary to oral BPH used in the treatment of osteoporosis.

This study was performed to elucidate the relationship between oral BPH and the development of BRONJ as well as to describe the characteristics of patients.

Methods: The study group included fourteen patients, all females (medium-age 73,28 years). The patient data included: toxic habits (smokers, ex-smokers, alcohol habit), comorbidities, characteristics of BPH treatment (molecules, duration of treatment, duration of suspension), aetiological factors, clinical BRONJ features (symptoms, site, number of expositions, size, staging) and also clinical complications (oro-sinusal communications, intra-and extra-oral fistula, pathological fractures, paraesthesia).

Results: The patient group consisted of 1 smoker (7,14%), 2 ex-smokers (14,28%) and no patients with alcohol habits. Alendronate was the most frequent BPH used for osteoporosis treatment (92,85%). The average BPH-duration was 82,28 months (range 18-240); at the time of diagnosis 9 patients were on-therapy, 5 off-therapy (range 1-6 months). Ten patients (71,42%) showed a history of dental extractions and 4 (28,57%) exhibited unknown aetiological factors.

Three patients (21,42%) had maxillary BRONJ, 11 (85,71%) mandibular BRONJ, one had both jaws involvement. The average number of expositions was equal to 0,85 (range 0-2). The major size of bone lesions was 0,84cm (mean, range:0,5-2). The range of reported symptoms was: painless (28,57%), low-pain (42,85%), hard-pain (28,57%). Staging included 2 patients on stage I, 2 on IIa, 6 on IIb and 4 on III. The reported clinical complications were: 4 (28,57%) intra-oral fistula, 2 (14,28%) extra-oral fistula, 2 (14,28%) pathological fractures with paresthesia.

Conclusions: The benefits/risks of oral BPH use must be weighed individually and in consultation with the prescribing physician, before determining the need for temporary/permanent cessation of medication.

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Osteoporosis diagnosis in postmenopausal women on oral bisphosphonates requiring dental extractions

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Objectives: The aim of this study was to evaluate the criteria for oral bisphosphonate (OB) prescription in a series of postmenopausal women referred for dental extractions. **Methods:** The study sample was characterized by 33 osteoporotic postmenopausal women aged 69.6±7, and 7 years on OB treatment referred for dental extractions. Bone densitometry values, Osteoporosis Self-assessment Tool (OST) results, Mental Index (MI) (thickness of the mandibular cortex below the mental foramen measured bilaterally on cone-beam CT images), and serum cross-linked C-telopeptide of type I collagen (CTX) were recorded in every patient.

Results: Only five patients (15%) had undergone bone densitometry before starting OB. The number of participants at low, intermediate, and high risk for osteoporosis according to OST results was nine (27.3%), 23 (69.7%) and one(3%) respectively. Using the cut off threshold of 3mm for MI, only one patient (3%) was considered at risk of osteoporosis. CTX was recorded in 23 patients, with an average value of 197.75 pg/ml; eight patients (34.7%) had < 100 pg/ml; three (13%) had 100-150 pg/ml; and 12 (52.1%) had > 150 pg/ml.

Conclusions: Despite all patients in the present series receiving OB, the majority did not appear to fit the criteria for diagnosis of postmenopausal osteoporosis

Relevance: To date there are no valid criteria to identify patients at increased risk for maxillary osteonecrosis due to bisphosphonates, and many of these patients are referred for dental treatment. Subsequently, standardised guidelines for OB prescription in postmenopausal women could help clinicians to improve osteoporosis management and to reduce the prevalence of osteonecrosis related to dental procedures in patients on OB.

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Prevalence of osteonecrosis of the jaws after a 3-years intravenous bisphosphonate therapy in patients with breast carcinoma

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Objectives: Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a rare adverse effect of high-dosage and long-term bisphosphonate therapy. Incidence of BRONJ is reported from 0.8% up to 12%.

In 2000-2008 65 hormone receptor-positive, premenopausal breast cancer patients were treated with infusions of 4mg zoledronic acid (Zoledronat®) over three years in a controlled prospective study at the Department of Obstetrics and Gynecology, Medical University of Graz, Austria.

None of the 65 women claimed existing teeth or jaw complaints in the gynaecological follow-up examinations.

The prevalence of BRONJ in this study population is to be detected.

Methods: In an ongoing clinical study at the Department of Oral Surgery and Radiology, Medical University of Graz that started in March 2010 this group of patients is investigated concerning subclinical so far unnoticed osteonecrosis of the jaws.

Results: In the first three months 28 patients were examined. 4 patients with clinically evident osteonecrosis of the jaws and 2 patients representing stage 0 according to AAOMS (American Association of Oral and Maxillofacial Surgeons) were detected. (The entire study population is to be presented at the EAOM 2010).

Conclusions: Incidence is probably higher than expected. This implicates the urgent need for thorough dental follow up examinations.

Relevance: The findings of this study may be relevant for oncologists and dentists by numbering the prevalence of BRONJ for a well-defined study population.

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Osteonecrosis of the jaws in orally symptomatic postmenopausal female patients with osteoporosis

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We aimed to collect and analyze clinical data from a cohort of 76 female patients treated with bisphosphonates (BP) for postmenopausal osteoporosis and referred to the Unit of Oral Diagnosis and Day Surgery for diagnosis and treatment.

Methods: Each patient received a throughout oral, dental and periodontal examination. Relevant clinical data regarding the BP treatment and comorbidities, oral findings and dental treatment plan, past and present dental therapies were recorded. All individuals had been recalled every three months for clinical examination, oral hygiene instructions and professional scaling; when needed periodontal, restorative and dento-alveolar surgical treatments were provided with strict protocols, according to the international guidelines.

Results: Over the last 4 years period, 76 consecutive patients aged 51 to 91 yrs (mean = 68,6 yrs) and treated with BP for postmenopausal osteoporosis were referred (alendronate n = 47, clodronate n = 16, risendronate n = 10, ibandronate n = 3 - mean treatment time = 190 wks); at the referral time osteonecrosis of the jaws (ONJ) has been identified in 7 patients (stage I n = 3, stage II n = 4 - mandibula n = 6, both jaws n = 1). The duration of BP therapy in ONJ patients ranged from 24 to 432 wks. The triggering events for ONJ were identified as dentoalveolar surgery (n = 2), local trauma from dentures (n = 3) and periodontal infection (n = 2). In the ONJ group, 5 patients were never smokers and 2 had systemic comorbidities. Treatment and control of the ONJ cases was obtained with repeated antibacterial treatments and in 4 patients with surgical debridement of the affected areas. Closure of the exposure and complete remission has been obtained in 4 cases. At present none of the non-ONJ patients submitted to invasive dental treatments developed ONJ signs and/or symptoms.

Conclusions: ONJ could be a harmful side effect of BP treatments in postmenopausal osteoporosis patients as well as non-oncologic patients. Oral prevention and appropriate protocols for invasive oral surgery could minimize the risk of ONJ.

Relevance: BP related ONJ prevalence in non-oncologic patients could be further reduced with focused management of oral health and diseases.

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Radiologic evaluation of bisphosphonate-related osteonecrosis of the jaws

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Objectives: Bisphosphonates are the drugs of choice for the management of patients with metastatic lesions including osteoporosis, Paget's disease, multiple myeloma, bone cancer, breast cancer and cancer induced hypocalcaemia. Osteonecrosis of the jaw (ONJ) is a major complication associated with long-term use of bisphosphonates. It is defined as the exposure of mandibular and/or maxillary bone, which demonstrates no tendency to heal for upto eight weeks following diagnoses by a health care professional. It is often associated with the development of mucositis and abscesses. The objective of this study is to evaluate the radiologic findings of the ONJ.

Methods: 20 patients who were treated with bisphosphonates for neoplastic diseases and presented with exposed bone and prulent discharge of the jaws, were included in this study. Each case was examined radiographically by ortopantomograph.

Results: Radiological examinations of the patients revealed osteolytic lesions and sclerotic changes in the jaws. Radiolucencies of differing sizes were present in all ONJ patients.

Conclusions: Orthopantomographic imaging can help determine the borders of the bone exposed into the oral cavity amongst patients treated with bisphosphonates.

Relevance: Orthopantomographic imaging is a useful diagnostic tool for the evaluation of the degree of bone necrosis before and during ONJ management.

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Clobetasol transmucosal absorption: a pharmacokinetics study on healthy subjects

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Objectives: Clobetasol propionate is a super-potent topical corticosteroid used in oral medicine to treat chronic inflammatory diseases. Besides excellent therapeutic properties, local adverse effects are reported, but also occasional systemic reactions related to adreno-cortical suppression can be found (for example, moon face or hirsutism). To our knowledge, no data on clobetasol transmucosal absorption is available, thus this study aims to investigate, under standard conditions, the amount of drug in circulating blood following topical application in healthy subjects.

Methods: Blood samples were collected at 0, 4, 8, 24 hours and at the 7th day from 14 healthy volunteers who applied 0.05% clobetasol propionate gel, 3 times/day for 1 week. In 5 of them a 3cm wide erosion on buccal mucosa was provoked using a dermatologic curette. A new high-performance liquid chromatography/ mass spectrometry method was employed to detect clobetasol plasma concentrations. At the end of the study, all subjects received an oral cavity examination and a questionnaire concerning clobetasol adverse effects and subjects compliance.

Results: At 4 hours, minimal concentration clobetasol (in the order of nanograms) was detected with a considerable increase in the subsequent samples. A significant difference was reported between subjects with erosion and those with normal mucosa. After 1 week, some volunteers complained of mild local adverse effects, mainly esophageous burning, while one subject showed Candida infection of the tongue.

Conclusions: Clobetasol systemic absorption seems to rise with the increasing number of applications. Higher keratinization of smokers' mucosae appears to hinder transmucosal drug penetration, while loss of integrity of the epithelial barrier seems to promote it.

Relevance: These results confirm the systemic absorption of oral topically applied clobetasol, reinforcing recommendations of careful monitoring of patients to promptly intercept sporadic adverse reactions. Further studies will be useful to better establish an accurate dose-response curve and to correlate clobetasol blood concentration with endogenous cortisol levels.

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Curcumin in the treatment of oral submucous fibrosis

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Objectives: Oral Submucous Fibrosis (OSMF) is a chronic insidious disease of the oral mucosa with pale blanched mucosa, palpable fibrotic bands associated with burning sensation, progressive inability to open the mouth and protrude the tongue. OSMF is prevalent in betel nut chewers with high incidence amongst Asians. The objective of this research is to assess the efficacy of CURCUMIN-an alkaloid extracted from TURMERIC plant in the treatment of OSMF by recording the clinical and histopathological(H/P) changes before and after treatment.

Methods: Patients (n=50) with varying grades of OSMF were divided into 2 groups-A&B (n=25), each treated for 90 days with 2 preparations-group A(curcumin paste for topical application) and group B(curcumin capsules for systemic ingestion), pre & post treatment clinical(mouth opening, tongue protrusion, relief of burning sensation, mucosal colour changes, fibrotic band status) and H/P changes were observed and statistically analysed(mean \pm s.d & percentage improvement).

Results: Significant clinical and H/P changes were observed,

- 1.Average increase in mouth opening was 5mm(21.47%) in group A and 7mm(29.8%) in group B
- 2.Average increase in tongue protrusion was 4mm(17.2%) in group A and 6mm(26.7%) in group B
- 3.Relief of burning sensation was 84%(group A) and 64%(group B)
- 4.Reversal to normal pink mucosa was 28%(group A) and 44%(group B)
- 5.Reggression of fibrotic bands was significant in group B
- 6.H/P sections post treatment showed marked epithelial cell proliferation, decrease in lymphocytes, reduced submucosal collagenisation
- 7.No toxic reactions were observed in the study.

Conclusions: The therapeutic efficacy of curcumin is established and effects were more pronounced in group B.

Relevance: The use of curcumin, a turmeric plant extract in treatment of OSMF is a non-toxic, non-invasive, economical method which holds good promise in the treatment and cure of OSMF in future.

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The effects of a new local haemostatic agent in bone healing: Apreliminary report

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Objectives: When a tooth is removed, the remaining empty socket consists of cortical bone covered by torn periodontal ligaments, with a rim of oral epithelium left at the coronal portion. The socket fills with blood, which coagulates and seals the socket from the oral environment. The events that occur during normal wound healing of soft-tissue injuries also take place during the repair of an injured bone. However, in contrast to soft tissues, osteoblasts and osteoclasts are also involved to reconstitute and remodel the damaged ossified tissue. Ankaferd blood stopper (ABS) is being used as a new haemostatic agent and it comprises a standardized mixture of plants. Each of these plants has some effect on the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics and cell mediators. Therefore, it can accelerate bone healing. The aim of this preliminary report is to determine the benefits of ABS application into tooth extraction sockets during bone healing process.

Methods: 42 extraction sites from thirty-two patients were included in this study. The patients were randomly selected and divided into two groups. After tooth extraction, ABS was applied into the sockets in twenty extraction sites of fourteen patients as the study group. In control group, no application was done into the socket in 20 extraction sites of thirteen patients. Clinical and radiographic examination were carried out at 1 week, 1 month and 3 months later in both groups. Bone levels were radiographically measured and recorded in each control session.

Results: Mean bone levels of the sockets were 1.2 mm, 1.1 mm and 0.6 mm at 1 week, 1 month and 3 months later respectively in the study group while the mean bone levels of the sockets were 1.2 mm, 1.2 mm and 0.8 mm at 1 week, 1 month and 3 months later respectively in the control group.

Conclusions: A very recent *in vitro* study has shown that exposure to ABS resulted in a very rapid formation of a network within the plasma and serum. During the first week of healing, osteoclasts accumulate along the crestal bone. It is not until 4 to 6 months after extraction that the cortical bone lining in a socket is fully resorbed and this is recognized radiographically by a loss of a distinct lamina dura. As bone fills the socket, the epithelium moves toward the crest and eventually becomes level with the adjacent crestal gingiva. According to these results, bone healing was very little faster in the study group when compared with the control group.

Relevance: ABS can be used in the socket to accelerate bone healing after tooth extraction is performed. Usage of ABS may provide a better and faster healing process.

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Photodynamic therapy on peri-implantitis: comparative effectiveness – an *in vivo* trial

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Objectives: Aim of this prospective *in vivo* study was to compare the effects of photodynamic therapy (PDT) using a diode laser with a 810 nm wavelength together with a toluidine blue O application (TBO) versus the use of conventional explorative surgical therapy (CT) on anaerobic microbial reduction at rough implant surfaces of peri-implantitis affected sites.

Methods: Twenty subjects, who showed clinical and radiographic signs of oral peri-implantitis, were randomly divided into two groups. Both underwent mucoperiosteal flap surgery performing scaling at implant surfaces and debridement of the granulation tissues. The CT group was then irrigated with a 0.2% chlorhexidine solution, only. In the PDT group, TBO was applied inside the peri-implant sites and then irradiated with diode laser for 20s, repeated five times, for a total exposure length of 100 seconds. Microbiological samples and inflammatory parameters were obtained before-immediately after treatment, at the 12th and 24th week post-treatment examinations.

Results: After treatment of PDT group the total anaerobia bacterial counts showed a mean bacterial reduction of 94.45% compared to 82.64% seen in the CT group ($P < 0.05$). However, values measured at the 12th and 24th week observations showed a gradual increase of the anaerobic bacterial counts. A. actinomycetemcomitans showed, overall, a lower bacterial counts percentage reduction ($P < 0.003$) in comparison to *P.gingivalis* ($P < 0.0001$) and *P. intermedia* ($P < 0.0003$). At the latter observation, the PDT resulted, though, in a significantly greater decrease of bleeding scores compared to the CT modality ($P < 0.03$).

Conclusions: These findings suggest that PDT initially may result in an additional benefit in comparison to the CT modality regarding the anaerobic decontamination of rough implant surfaces, although the extent of the reduction was not homogeneous on the overall bacterial species.

Relevance: The PDT bactericide benefit seems only to be temporarily maintained, as a partial re-colonization took place at the 3 and 6 months post-treatment registrations.

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A Comparison of Oral High Dose Amoxicillin with Parenteral Penicillin in Treatment of Acute Oral InfectionsZ DalirSani¹, F Babazadeh², M Shiezhadeh³¹Oral Medicine, Dental Research Center of Mashhad University of Medical Sciences, Department of Oral Medicine, Mashhad School of Dentistry, ²Dept of Oral & Maxillofacial Surgery, School of Dentistry & Dental Research Center of Mashhad University of Medical Sciences, ³Dept of Prosthodontics, Dental School, Mashhad University of Medical Sciences, Iran**Objectives:** Regarding the difficulties and side effects of parenteral penicillin and considering the positive effects of high dose oral amoxicillin on acute odontogenic infections based on a previous pilot study, we decided to look for a practical and useful alternative treatment for parenteral penicillin. This study was planned to compare therapeutic effect of oral high dose amoxicillin with parenteral penicillin in the treatment of acute odontogenic infections.**Methods:** In this clinical trial study, approved by the ethical committee of Mashhad University of Medical Sciences, 56 patients with acute odontogenic infection were randomly divided into 2 groups. After obtaining informed consent, Patients in the control and case groups were treated, respectively, by parenteral penicillin G and oral amoxicillin (2g three times a day). All of the patients were visited after 24 hour, 48 hour and 1 week intervals and the body temperature, pain intensity, size of the swelling and skin redness were recorded. Our criteria for improvement and response to treatment in this study were absence of fever, pain and redness as well as the maximum reduction in swelling. Data were analyzed by Mann-Whitney and Fisher's exact tests through SPSS software ($P = 0.05$).**Results:** 25 patients of the control and 26 patients of the case group recovered (after 1 week) and no significant difference was found between the two groups ($X^2 = 0.0219$, $P = 0.0639$).**Conclusions:** Our study showed that high dose oral amoxicillin was as effective as parenteral Penicillin G without its side effects such as pain and anaphylaxis.**Relevance:** High dose oral amoxicillin could be considered as an alternative treatment in acute odontogenic infection.

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Resistant factors of the conservative therapy to BRONJY Goto^{*}, S Kawano¹, J Hayashida¹, T Ikari², S Kurahara², T Toyoshima¹, T Minamizato¹, T Kiyosue¹, R Matsubara¹, K Oobu¹, Y Takenoshita², Y Mori², Y Shiratsuchi¹, S Nakamura¹¹Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Fukuoka, Japan,²Section of Oral and Maxillofacial Surgery, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Fukuoka, Japan**Objectives:** Treatment strategies for bisphosphonate-related osteonecrosis of the jaws (BRONJ) are not established definitively. We have mainly provided conservative therapies including sequestrectomy and debridement for patients with BRONJ. The purpose of this study was to assess the resistance factors hampering conservative therapy.**Methods:** Thirty-two patients with BRONJ (2 males and 30 females; mean age, 72.0years; range 46-88years), who were clinically diagnosed from 2004 to 2010 in the Department of Oral and Maxillofacial Surgery in Kyushu University Hospital, were evaluated concerning clinical parameters (sex, age, route of administration, duration of bisphosphonates therapy), systemic factors, local risk factors, treatment methods, drug holidays, outcome of the treatment, and duration to cure.**Results:** Oral bisphosphonates (OB) were used in 15 patients. OB combined with corticosteroids (OC) were used in 5 patients. Intravenous bisphosphonates (IB) were used in 12 patients. The treatment methods for BRONJ were local irrigation in all cases, antibiotic therapy in 29, sequestrectomy in 13, debridement in 11, and hyperbaric oxygen therapy in 6. As for outcomes of management, 15 cases (46.9%) were completely cured and 17 (53.1%) were under treatment at this time. The rates of complete cure were 10 of 15 patients (66.7%) in OB, 3 of 5 (60.0%) in OC and 2 of 12 (16.7%) in IB. The average duration of therapy to complete cure was 446.9 days. The duration in the patients with corticosteroids therapy (1167.3 days) was significantly longer than that in the patients without (269.0 days).**Conclusions:** It is difficult to cure cases of BRONJ caused by IB or OC, though the conservative therapy for BRONJ is useful.

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VEGF-gene polymorphisms and bisphosphonate-induced osteonecrosis of the jawsPG Arduino^{*}, E Menegatti¹, C Scully², M Scoletta¹, C Battaglio¹, A Chiecchio¹, M Mozzati¹, D Berardi¹, A Vandone¹, M Donadio¹, S Gandolfo¹, R Broccoletti¹¹University of Turin, Turin, Italy, ²UCL Eastman Dental Institute, London, UK**Objectives:** Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is a term recently emerged to describe a significant complication in a subset of patients receiving this class of agents. BRONJ has generated vast interest in the medical and research

communities yet it remains an enigma, given its unknown pathogenesis. Like many other complex trait diseases, it can be caused by a combination of environmental and genetic risk factors. To date, only one study has investigated BRONJ genetic susceptibility, reporting a possible association with polymorphisms of the cytochrome P450 CYP2C8. So far, nobody has investigated vascular endothelial growth factor (VEGF) gene polymorphism in BRONJ in Italian patients.

Methods: Polymorphisms (+936 C>T, -2578 C>A, -634 G>C) in the VEGF gene were investigated. The study involved 178 participants. A total of 23 Italian patients with BRONJ were enrolled (Group A). There were 155 control subjects, comprised of 30 patients exposed to intravenous bisphosphonates but without any clinical evidence of BRONJ (Group B; no symptoms or clinical signs of BRONJ) and 125 healthy blood donor volunteers (Group C).**Results:** The frequency of the CAC (+936/-2578/-634) haplotype was significantly increased in females patients with BRONJ compared with female healthy controls (OR = 2.11, 95% CI = 1.14-3.89, $P = 0.024$). These findings support the hypothesis that the CC homozygotes of -634G>C of VEGF gene and the AA homozygotes of -2578C>A could influence the expression of VEGF in female patients who developed BRONJ.**Conclusions and Relevance:** These preliminary results suggest a possible role for this VEGF gene polymorphism in the susceptibility of BRONJ in select patients, but further studies are necessary.

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Ozone therapy in endodontic treatment of chronic apical periodontitisA Gusiyska¹, A Kisselova^{*2}¹Department of Operative Dentistry and Endodontics, Medical University – FDM, Sofia,Bulgaria, ²Department of Imaging and Oral Diagnostic, Medical University – FDM, Sofia, Bulgaria**Objectives:** The effect of focal dental infection on general health has been a subject of controversy for decades. Elimination of microorganisms from the root canal system is realized by instrumentation and irrigation with sodium hypochlorite, as a basic solution, which is now a widely accepted in endodontic protocols. Ozone is one of the most contemporary and powerful antimicrobial agents available for use in medicine or dentistry. Ozone is a reactive gas that shows important antimicrobial properties, which increase properties of NaOCl as an oxidizing and hydrolyzing agent.

We aimed to observe influence of ozonated NaOCl in the process of healing of periapical lesions used in a final stage of treatment of chronic apical periodontitis. The follow-up of results were taken by radiographs using a parallel technique with bite registration.

Methods: The subjects of this study were twenty seven clinical cases with radiolucency and radiographical evidence of periapical lesions. The diagnoses were determinate by systematic clinical observations and radiographic analyses using periapical index (PAI) by Orstavik. All of the teeth were isolated with rubber dam. Preparation was done by strict endodontic protocol. When completely finished strict endodontic chemo-mechanical protocol, we apply ozonated NaOCl – 5.25%, stimulated with ultrasound. Ozone gas was generating by Biozonix.**Results:** An initial radiograph revealed extensive lesions in the periapical bone above the teeth. After follow-up, radiographs demonstrated disappearance of the bone radiolucency. Our positive results are connecting with resolution of the periapical radiolucency with increased bone density.**Conclusions:** Ozone therapy should be used after the conventional cleaning, shaping, and irrigation of root canals, and the ozonated liquid in the canal system should be contribute to final decontamination of endodontic and periapical space. Follow-up radiographs showed resolution of the periapical lesions with rapid bone regeneration-increased bone density.**Relevance:** We speculate that ozonated NaOCl has a high level of biocompatibility with periapical tissues and may be a valuable adjunct to root canal therapies.

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Aetiology and management of halitosis: experiences at a breath odour clinicJD Cameira-Nunes^{*}, JM Sioli¹, A Ortiz¹, MJ Cobos-Fuentes¹, I Gallardo¹, A Martinez-Sahuquillo¹¹Department of Stomatology, University of Seville, Spain

Halitosis is an unpleasant and often offensive odour emanating from one's breath. It has a high prevalence, independent of gender, age and socio-economic status. It is a reason for consultation which has become increasingly more frequent and it usually has much impact on the quality of life.

Objectives: To determine the aetiology in patients complaining of halitosis, and the previous resorting to health professionals.**Material and methods:** Transversal analytical study. The observation was carried out by a multidisciplinary team: dentist, ORL, gastroenterologist, internal medicine specialist and psychologist. The protocol consisted of: clinical history (including data on previous resorting to health professionals), specific diagnostic tests and other

complementary ones when necessary. The sample was composed of 616 patients who presented themselves with halitosis complaints.

Results: The prevalence of real halitosis was 77% (n=474) of the patients. The aetiologies found were: oral causes (78%), respiratory tract (9%), combination of both (5%), digestive causes (4%), systemic (2%), neuropsychological (1%) and not identified (1%). In patients with pseudo-halitosis (23%, n=142), 68% had carried out an upper endoscopy without presenting digestive complaints, and 61% had consulted more than five health professionals.

Conclusions: A complete and specific clinical history, focusing on related conditions and diseases and a multidisciplinary approach are crucial factors for therapeutic success, saving time and expense.

Relevance: A variety of psychological and systemic conditions frequently confuse health professionals, considerably increasing the charges and wasted time in consultations, fruitless examinations and treatments.

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Er:YAG laser in the treatment of bisphosphonates-related osteonecrosis of the jaws (BRONJ)

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Objectives: To report the experience with 144 patients affected by BRONJ and treated with Er:YAG laser, conventional surgery and medical treatment alone or in combination with Nd:YAG low-level-laser therapy (LLLT).

Methods: One hundred and forty-four patients (106 females, 73.6% and 61 males, 26.3%) affected by BRONJ were referred to the Oral Pathology and Laser-assisted Unit of the University of Parma, Italy between 2004 and 2010. Bisphosphonates had been administered for multiple myeloma (53 patients), bone metastases (63 patients) and osteoporosis (28 patients). One hundred and ten out of 144 patients (76.3%) had single BRONJ localization and 34 (23.6%) had multiple lesions. The mandible was involved in 96 patients (66.6%) and the maxilla was involved in 34 cases (23.6%). In 14 cases (9.7%) both the jaws were affected. Overall BRONJ sites were 165. One-hundred and sixteen out of 165 sites were treated and subclassified as follows: group 1: 15 sites - local and systemic medical therapy; group 2: 31 sites - medical therapy and LLLT; group 3: 18 sites - surgical therapy alone; group 4: 52 sites - surgical therapy (including Er:YAG laser) and LLLT.

Results: Clinical improvement (complete healing of the lesion or passage to a lower stage of the disease) was observed in 4 out of 15 sites in group 1 (26.6%), 19 out of 31 sites in group 2 (61.6%), 9 out of 18 sites in group 3 (50%) and 47 out of 52 sites in group 4 (90.3%). A follow-up of at least 3 months was available for all patients.

Conclusions: Surgical approach with Er:YAG laser may be useful in the treatment of BRONJ. LLLT in combination with medical or surgical treatment seems to provide better results than medical or surgical therapy alone.

Relevance: A possibly effective therapy based on the use of Er:Yag laser as well as on Nd:YAG LLLT is described.

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Oral mucosal lesions and oral hygiene habits in young orthodontic patients

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Objectives: The aim was to detect the prevalence and type of oral mucosal lesions and oral hygiene habits in patients during orthodontic treatment and in controls who were not orthodontic appliances wearers but who were referred to orthodontists due to malocclusion.

Methods: The study comprised 111 young patients. The experimental group involved 60 patients (33 boys and 27 girls) while control group involved 51 patients (27 boys and 24 girls). The patients age ranged between 6 and 18 years, (mean age 13.25 in the experimental group and 11.86 in the control group).

A complete medical history was obtained and clinical examination performed in all participants. Data was recorded in a questionnaire created for the purpose of this study. Pathologic oral mucosal changes (inflammation, erosions, contusions, ulcerations and hematomas) detected during clinical examination were evaluated using clinical tests. Topography of lesions was determined by the WHO scheme. The degree of oral hygiene, gingival and adjacent mucosal inflammation were determined and verified by clinical indices.

The study was approved by the Ethical Committee, School of Dental Medicine, University of Zagreb. As all the subjects were under 18 years of age, a written consent was obtained from their parents.

All data were analyzed by using Chi² tests. Due to low frequency of observed variables, Fisher's Exact Test was used in a certain number of cases.

Results: Among all detected lesions, inflammation was the most frequent mucosal lesion identified in the control group. Better oral hygiene was observed among all subjects of the experimental group but with no statistical difference detectable ($P > 0.05$). There was no statistical significant difference in oral hygiene status with respect to, age, gender, type of dentition and orthodontic appliances. A statistically significant difference was observed with respect to oral hygiene status and inflammation intensity ($P < 0.05$).

Conclusions: Inflammation was the most frequent oral lesion in both groups of patients. The poorer the oral hygiene, the more intensive the inflammation was.

Relevance: Raising the patient's awareness about oral hygiene and increasing his/her motivation to follow up all given instructions leads to a successful treatment and achieving the desired therapeutic effects.

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Periodontal disease in diabetics and Serum C-reactive protein (CRP) values

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Objectives: To evaluate C-reactive protein values in diabetic patients with periodontal disease.

Methods: 250 patients randomly selected from the dental out-patient department of BIRDEM. A questionnaire survey and clinical examination of periodontal status, including gingival bleeding, gingival inflammation and oral mucosa, to determine the subject's periodontal health and treatment needs were undertaken. Periodontal pocket depth measurement was undertaken with a blunt periodontal probe. Probing depths of < 3 mm and below were regarded as healthy periodontium and > 3 mm as diseased - periodontitis (Sensor probe - Dentec Type CP- 12, marking 3- 6 - 9 - 12 mm). Blood samples were collected for C- reactive protein (CRP) values.

Results: CRP values for 32.8% males and 28.4% females were within the normal range (< 6 mg l⁻¹), 6.4% males and 11.6% females presented with a moderately high levels, (6- 20 mg l⁻¹), 4% males and 10.4% females presented with high level (21-50 mg l⁻¹) and 2.8% males and 3.6% females had a very high level (> 50 mg l⁻¹) of CRP values. This association was statistically significant ($P = 0.0166$). Gender distribution among diabetic subjects with CRP values was (< 6 mg l⁻¹) & (> 6 mg l⁻¹), 82 males (32.8%) & 71 females (28.4%) were within the reference range (< 6 mg l⁻¹) and 33 males (13.2%) and 64 females (25.6%) were above the reference range (< 6 mg l⁻¹). This study demonstrates a preponderance of female diabetics with higher C-reactive protein values (statistically significant at $P = 0.0025$).

Conclusion: High CRP values with periodontal disease are a predictor of coronary heart disease. Regular dental examination and routine scaling is essential for diabetic patients.

Relevance: This study is of interest to prevent coronary heart disease in diabetic subjects with periodontal disease but more studies with larger group of patients are required to confirm this diagnosis.

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Ultrasound therapy in osteoradionecrosis of the jaws: a pilot study

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Objectives: The study aimed to evaluate the effect of low-intensity ultrasound (US) in the treatment of osteoradionecrosis (ORN) of the jaws.

Methods: Patients were selected among those who underwent surgery for total removal of a tumour in the head and neck, received adjuvant radiotherapy, and developed ORN in the jaws. ORN diagnosis was based on clinical and radiographic aspects. Ten patients were evaluated and completed the proposed treatment protocol: a maximum of 40 US applications of 20 minutes over the facial area corresponding to the region affected by ORN. Ultrasound applications were provided at least twice a week up to 40 sessions. The apparatus used comprised a transducer composed of a PZT ceramic disc (lead zirconate titanate) that emitted longitudinal waves with a frequency of 1.5MHz and power of 30mW. The parameters used for evaluation of results were: pain, oedema, wound repair and radiographic appearance. Patients were examined every three months as a follow-up regimen.

Results: Eight men and two women with ORN (9 mandible, one maxilla) comprised the sample, presenting an average age of 52.7 years. ORN duration ranged from 4 to 120 weeks (mean 48 weeks). All patients presented good response becoming symptom-free (7 with pain complaint) and showing mucosal repair. Three patients showed complete repair with US applications solely (6 to 18 applications). Seven patients underwent surgical intervention after the 40 US applications (provided from 6 to 25 weeks).

Conclusions: We concluded that the therapy with low-intensity US is effective in the treatment of jaws ORN, showing no adverse side effects and being well accepted by patients.

Relevance: ORN is a serious complication of anticancer treatment that presents with no satisfactory therapeutic management so far. US therapy showed a rather interesting therapeutic effect, even in long lasting cases, encouraging further research.

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Influence of oral hygiene on plasma cell gingivitis

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Objectives: Plasma cell gingivitis (PCG) is a rare benign disorder of the gingiva, characterized by sharply demarcated erythematous and oedematous gingivitis. This is usually considered as a hypersensitive reaction. Identifying and avoiding the source of possible allergens could eliminate these lesions. The aim of the study was to review files of PCG patients attending the Oral Medicine Section of the Turin Dental School, and to assess the role of plaque control in managing PCG.

Methods: A retrospective hospital-based study was undertaken to examine and evaluate the potential impact of oral hygiene on the gingival PCG lesions on the human periodontium of 8 patients. Parameters evaluated included plaque score, gingival index, bleeding index, probing depths, recession, clinical attachment level (CAL) and a modified clinical score describing gingival lesions.

Results: The study group comprised 8 patients (5 female and 3 male) mean age 17.4 (range to 7 to 54). Professional oral hygiene statistically improved parameters evaluated, also for those patients unresponsive to topical immunosuppressive therapy.

Conclusions: No definitive standard of care has been set for PCG and furthermore no definitive consensus guidelines have yet been provided. However, our results show that PCG could be markedly reduced by scaling, root planning and improved plaque control, showing a possible relationship between PCG and presence of bacterial plaque. Therefore, these patients should be encouraged to receive regular professional oral hygiene therapy.

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Taste perception evaluation in children undergoing bone marrow transplantation (BMT)

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Objectives: The oral cavity is frequently implied by the typical side effects of antitlastic therapy, i.e. radiotherapy, chemotherapy and conditioning regimens used for Bone Marrow Transplantation (BMT). Taste disorders may cause anxiety, depression and nutritional deficiencies significantly impacting on quality of life. This project intends to verify the presence of taste dysfunction in children undergoing BMT.

Methods: Forty children (aged between 5 and 12) followed up at the Department of Pediatrics of Brescia, being candidates for BMT for leukemia, solid tumors or immunodeficiencies, were enrolled. All children underwent an initial standardized examination of the oral cavity and a structured interview in order to understand individual preferences and regular nutrition practices. The study was carried out using a taste perception test, that was first validated performing a standardized assessment of taste in a 100 healthy children sample. The test was composed in two phases: the first one was the identification of the stimulus (bitter, sour, salty, sweet, water) and the second one was the valuation of stimulus intensity. Stimulus consisted in 16 sterile solutions containing sapid substances in different concentrations and 1 solution containing water as placebo, at the temperature of 24 °C; stimulus intensity was evaluated through an analogical scale from 0 to 10 (where 0 corresponds to a neutral Stimulus (water), and 10 to the maximum intensity). The test was repeated at different time points: before chemo and/or radiotherapy, during chemo and/or radiotherapy (once a month) and after engraftment (every three months for a year). The data were collected and, through statistical analysis, mean and standard deviation of threshold values and intensity, in four administrations, for each taste and for placebo, were obtained.

Results: During the chemo and/or radiotherapy, threshold and intensity values were altered for all the sapid solutions compared to the value in healthy children.

Conclusions: According to these results, the authors propose guidelines in order to choose the best supportive care (oral disinfection, anti-infective and anti-GvHD prophylaxis, food) and tasteful nutrition to improve the quality of life.

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Factors related to periodontal disease among type 1 and type 2 diabetes mellitus patients: a case-control study

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Objectives: Diabetes mellitus is associated with the increased incidence and severity of periodontal disease. The aim of this study was to link periodontal disease status with microvascular complications in patients with type 1 and type 2 diabetes.

Methods: Periodontal screening recordings were performed in 103 young patients with type 1 diabetes, and 103 adults with type 2 diabetes, as well 44 young patients and 38 adults as control subjects. We evaluated age, sex, duration of diabetes and metabolic control parameters, and screened for nephropathy and retinopathy. All four groups were compared using a univariate general linear model.

Results: We found a lower prevalence of severe periodontitis and a higher prevalence of reversible gingivitis in the type 1 diabetes group than in the corresponding control group. The prevalences of mild and severe periodontitis were similar for type 2 diabetes patients and controls, but a lower prevalence of gingivitis was found in the type 2 diabetes group. A high prevalence of lost teeth was observed in the type 2 diabetes group and its controls (58% lost teeth in both groups, average 16 sites), while the prevalence of tooth loss was low in the type 1 diabetes and control groups (10% lost teeth in both groups, average 27 sites).

Conclusions: The higher prevalence of periodontal disease among type 1 and type 2 diabetes mellitus patients may be related to the duration of the disease and poor metabolic control. The pre-clinical period of type 2 diabetes may be related to these results.

Relevance: The two-way condition between periodontal diseases and diabetes mellitus are still unclear, but early diagnosis could improve better treatment of both diseases and avoid aggressive periodontitis as a microvascular complication in diabetes patients.

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CO2 and diode laser for excisional biopsies of oral mucosal lesions: A pilot study

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Objectives: The present pilot study evaluates the histopathological characteristics and suitability of CO2 and diode lasers when performing excisional biopsies in the buccal mucosa, with special emphasis on the extent of the thermal damage zone created.

Methods: 15 patients agreed to undergo surgical removal of their fibrous hyperplasias with a laser. These patients were randomly assigned to one of three groups; one diode and two CO2 laser groups. The CO2 laser was used in a continuous wave mode (cw) with a power of 5 watt, and in a pulsed char free mode (cf). Power settings for the diode laser were 5.12 watt in a pulsed mode. The thermal damage zone of the three lasers, and intraoperative and postoperative complications were assessed and compared.

Results: The collateral thermal damage zone on the borders of the excisional biopsies was significantly smaller with the CO2 laser for both settings tested, compared to the diode laser, regarding values in μm or histopathological index scores. The only intraoperative complication encountered was bleeding that had to be controlled with electrocauterization. No postoperative complications occurred in any of the three groups.

Conclusions: The CO2 laser seems to be appropriate for excisional biopsies of benign oral mucosal lesions. The CO2 laser offers clear advantages in terms of smaller thermal damage zones over the diode laser. More study participants are needed to demonstrate potential differences between the two different CO2 laser settings tested.

Relevance: Different lasers, including diode and CO2 lasers, have been marketed as being suitable for soft tissue surgery. Regarding excisional biopsies of the oral mucosa, the CO2 laser offers clear advantages over the diode laser when a histopathological interpretation of the lesion is needed. This seems especially important for biopsies of premalignant lesions or conditions such as oral leukoplakias or lichen planus.

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Chronic khat-chewing effect on oral mucosa: a clinicopathological correlation study

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Objectives: To evaluate the clinical and histopathological effects of chronic khat-chewing on oral mucosa and the potential correlation between these effects.

Methods: A population of 1190 Yemeni males were interviewed regarding their khat-chewing and smoking habits. Seventy-nine individuals of them were eligible to our study including 54 chronic khat-chewers (CKCs) and 25 non-chewers (NCs). They had their oral cavities examined investigating the presence of mucosal lesions. Fifty-four out of the 79 participants, including 36 CKCs and 18 NCs, agreed to undergo a histopathological evaluation. Biopsies were taken from the buccal mucosa of the khat-chewing side (KCS) and non-chewing side (NCS) regarding for CKCs and only from the left buccal mucosa regarding NCs. These biopsies were routinely processed and examined for the presence of keratosis and dysplasia. Data were statistically described and analyzed (χ^2 or Fisher's Exact test, $P < 0.05$).

Results: Clinically, CKCs had white lesions confined primarily to the buccal mucosa. This included KCS 100% and NCS, 22.2%, while only one of NCs had a white lesion on the left buccal mucosa. These lesions were strongly associated with khat-chewing

habit rather than smoking. Histopathologically, 38.9% of the biopsies taken from NCs and 100% and 61% of the KCS and NCS biopsies respectively were hyperkeratotic, while 38.9% of NCs biopsies and 72% and 69.4% of the KCS and NCS biopsies respectively revealed some degree of dysplasia. While hyperkeratosis was correlated to khat-chewing and smoking equally, dysplasia was correlated with smoking more than with khat-chewing. Hyperkeratosis was increasingly correlated with the clinical findings in contrast to dysplasia.

Conclusions: Chronic khat-chewing causes oral white lesions that clinically appear innocuous (frictional), however, smoking and to less extent chronic khat-chewing, predispose oral mucosa to dysplastic changes supporting the claim of considering them as oral cancer risk factors.

Relevance: Khat-chewing and smoking habits should be addressed with proper educational programmes.

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A survey of Medical Professionals with regards to oral health

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Objectives: To determine the confidence of Medical Professionals in relation to the diagnosis of oral pathology within their Patients. Moreover, to determine the extent of training received by Medical Professionals with regards to oral health. In addition, whether Medical Professionals feel they would benefit from further training with regards to oral health.

Methods: A self-administered, internet based, anonymous questionnaire was sent to 474 Medics at Heart of England NHS Foundation Trust.

Results: Respondents (N=55) were asked details regarding their speciality, grade, confidence and practise with regards to diagnosing oral pathology, knowledge of systemic disease with oral manifestations, previous oral health education and any desire for future oral health training. Most respondents didn't routinely examine the mouths of their inpatients. Most Practitioners lacked confidence with regards to diagnosis of oral pathology. There appeared to be a good understanding of which patients are at risk of developing oral pathology and which systemic diseases have oral manifestations. Only 9.6% (N=5) of respondents have referred patients to an Oral Medicine department, while 50% (N=26) report there are unaware of Oral Medicine as a service. 81.5% (N=44) of respondents deny having had any formal training with regards to oral health, however 72.7% (N=40) feel they would benefit from future training in oral health.

Conclusions: Responses suggest that Medics don't often perform oral examinations on their patients and most lack the confidence to do so. However, Medics have a good grasp on which patients are at higher risk of developing oral pathology. Moreover, it appears that Oral Medicine is a little known and little utilised speciality within the secondary care medical setting. There appears to be a lack of training within the Medical profession with regards to oral health, but a strong desire for appropriate training in the future.

Relevance: There may be a significant role for Oral Medicine Specialists in providing any such training.

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Epicutaneous testing of dental materials: A preliminary study

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Objectives: The role of contact allergy in oral soft tissues disease processes is unknown. Type 4 hypersensitivity reactions may be seen related to most dental materials used from amalgam and gold to polymers. Release of metal ions is thought to cause the allergic reactions; micro-particles of the corrosion products of the metal and/or ionic metal hydroxides/oxides may be the allergens. This study was performed to detect the prevalence of contact allergy to flavourings, preservatives, dental acrylates, medications, and metals in patients with oral diseases using patch testing.

Methods: Between the years 2002 and 2009, 228 patients with oral diseases had undergone a patch test. Patients were tested with a 45-item oral antigen screening series. Data were analyzed retrospectively.

Results: The most often allergens detected include nickel sulfate (5.26%), mercury (4.82%), palladium chloride and cadmium sulfate (1.75%). The most frequent oral manifestations were angioedema (2.63%), burning mouth (7.89%), burning mouth syndrome (59.64%), oral lichen planus (25.43%), leukoplakia (3.07%), recurrent aphthous stomatitis (1.31%).

Conclusions: Positive reactions to metals were frequent in all the different clinical variants, and no specific association between a clinical presentation and a particular allergen was found. Skin patch testing may be helpful in selected cases. The readings need to be taken at days 3, 7, and 14, or even later to avoid missing delayed reactions.

Relevance: Skin patch tests, applying a series of dental materials in non-toxic concentrations on the skin, have been used to identify sensitization. Patch testing

and the resultant avoidance therapy are useful adjuncts in the management of oral mucosal diseases.

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Microbiopsy: a first-level diagnostic tool for dentists facing oral lesions

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Objectives: The high prevalence of oral abnormalities from a routine dental visit makes it impractical to send every oral lesion to specialized centres for histologic evaluation, this could contribute to increase the diagnostic delay which is a key-issue in oral oncology. Our previous study had demonstrated the reliability of microbiopsy to detect oncological alterations as a first-level test in suspicious lesions assessed by oral medicine practitioners; now we aimed to assess the feasibility of microbiopsy by general dentists to select cases needing further evaluations.

Methods: 50 volunteer general dentists were briefly instructed on the sample technique. In the following months they sampled any intraoral lesions displaying an epithelial component. Practicability features of microbiopsy by general dentists were compared to data from our previous study.

Results: In a 12-months period, 108 lesions were sampled from 92 patients. When compared to our previous study, no differences were observed for inadequate samples rate (8/108; 7.4% versus 6/164; 3.7%) and presence of basement membrane zone (BMZ) in the specimen (80/100; 80% versus 110/158; 69.6%). The present series confirmed the lack of significance of clinical aspect and site of the lesion respect to the presence of BMZ in the specimen. Local anaesthesia was needed in just 13/108 (12%) samplings and did not improve adequacy nor the BMZ presence. The present series had a significantly lower prevalence of positive lesions (8/100; 8% versus 83/158 52.5%). Positive lesions (for either dysplasia or carcinoma) were referred to specialists for further assessments while the others have been followed-up.

Conclusions: Results on adequacy and presence of BMZ demonstrated that microbiopsy can be reliably used by general dentists to select cases needing referral to specialists.

Relevance: The extensive use of microbiopsy as a first-level diagnostic test by general dentists could reduce the diagnostic delay in oral oncology.

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Gingival enlargement: A new proposal for classification and approach

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Objectives: Gingival enlargement (GE) is a neglected area in dentistry, since there is little data about this entity. Most classifications of GE are based on aetiology. Although this may be the most exact, it seems this classification is not useful in clinically so it does not serve as a good approach. We want to present a new proposal for GE approach based on 27 years of clinical experience in oral medicine and a broad literature review.

Methods: An approach called "the Four D" approach" will be introduced. There are four axes: Duration, Distribution, Description and Dental mobility. Duration of GE is the first step to classify and diagnosis and is subdivided to acute (< 1 month) and chronic (> 1 month). Distribution deals with the spread of GE and is further classified to focal, multi focal and disseminated GE. Description is a detailed explanation of clinical characteristics which helps in assumption of the origin of GE. This step in turn will serve as an important guide in diagnosis. Dental mobility determines whether there is periodontal involvement (e.g. periodontitis, some genetic disorders and malignancies).

Results: Classification of GE can be facilitated by using the "Four D approach" as each kind of GE fits in one of the subdivisions of each axis, which facilitates ascertaining the correct nature of the GE.

Conclusions: It is the first approach to GE which may be useful for the classification and diagnosis of GE.

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Oral mucosal lesions in institutionalized elderly patients in Mashhad

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Objectives: To determine frequency of oral mucosal lesion in the Iranian elderly population.

Methods: 237 Institutionalized elderly residents (> 60 years old) were enrolled in this cross-sectional study. Demographic and clinical findings were recorded in provided check lists. SPSS software 13.5 and chi-square test were employed for analyzing the data.

Results: 98% of cases had at least one mucosal lesion. Mean age of the cases was 79.59 ± 8.88 (M: 77.15 ± 10.40 ; F: 80.30 ± 8.29). The most common lesions were fissured tongue (66.5%), atrophic glossitis (46.8%), varicosities (42.0%) and xerostomia (38.2%). No sex predilection was observed except for xerostomia ($P = 0.026$). Denture stomatitis and fissured tongue were the most common denture related lesions. The number of lesions ranged from 0 (4 cases) to 10 (one case), with the most cases having 4 lesions. Xerostomia and atrophic glossitis had a significant correlation with advance in age.

Conclusions: This study shows a high prevalence of oral lesions in a sample of Iranian elderly population.

Relevance: This study highlights the need for serious attention to the oral health status of this age group.

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Common oral mucosal diseases, systemic inflammation and cardiovascular diseases in a large US survey

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Background: Periodontitis has been associated with raised serum biomarkers of inflammation, sub/clinical markers of atherosclerosis, and increased risk of and/or mortality from cardiovascular disease (CVD). There remains little information regarding the association between other common oral mucosal diseases, systemic inflammation and CVD.

Objective: To assess this association in a cross-sectional survey of a nationally representative sample of the non-institutionalized civilians in the United States.

Methods: 17,223 men and women aged 17 years or older received oral examination as part of the Third National Health and Nutrition Examination Survey (NHANES III). The primary and secondary outcome measure was the association of oral mucosal diseases with raised serum levels of C-Reactive Protein/Fibrinogen and increased prevalence of CVD respectively. Adjustment for common confounding factors was performed.

Results: Having any oral mucosal disease was significantly associated with systemic inflammation (serum levels of CRP ≥ 10 mg/dL) (Odds ratio 1.40, 95%CI 1.03 to 1.91). Individuals with any oral mucosal disease were 1.42 times (95%CI 1.08 to 1.88) more likely to have history of heart attack and 1.35 times (95%CI 1.05 to 1.74) more likely to report angina than unaffected individuals. All associations were independent of age, sex, ethnicity, years of education, poverty-income ratio, body mass index, smoking status and diagnosis of periodontitis.

Conclusions: Common oral mucosal diseases are independently associated with raised markers of systemic inflammation and history of CVD.

Relevance: The present study reports for the first time the possible association between oral disease other than periodontitis with systemic inflammation and CVD. As some of the oral disorders considered are common, these findings might have important implications for the health of the public. Further research is needed to confirm these preliminary results.

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Information Leaflets Improve Oral Health Related Quality of Life in Patients with Oral Diseases

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Objectives: Patient information leaflets (PIL's) are regularly used in oral medicine clinics, but not yet in Croatia. Aims: to assess the impact of chronic (recurrent) oral diseases on quality of life (QoL); to assess the impact of PIL's on patients' knowledge on their oral diseases; to assess the impact of PIL's on patients' QoL improvement; to compare integral and brief versions of QoL questionnaire.

Methods: Study included 47 patients previously diagnosed and controlled for: oral lichen planus, burning mouth syndrome, recurrent aphthous ulcers and Sjogren's syndrome. There were also subjects complaining for geographic tongue. Two versions of OHIP were used as measures of oral health related QoL, and appropriate inventories for each diagnosis were used to assess knowledge on the disease. Subjects were assessed immediately prior to and 3 weeks after handing PIL. PIL's were compiled from the EAOM website and several clinical institutions. QoL and knowledge before and after intervention were compared using Student's test for paired samples. Pearson's correlation was used to compare integral and brief versions of OHIP.

Results: Twenty six participants completed the study. PIL's significantly reduced oral diseases' deteriorating effect on QoL (OHIP 55.54 ± 27.22 before and 44.7 ± 23.83 after PIL ($P = 0.0003$)). Knowledge increase was anticipated, but was not statistically

significant (19.61 ± 3.72 before and 21.04 ± 4.21 after PIL ($P = 0.0926$)). OHIP 14 was as reliable as OHIP 49 (r was 0.9199 before and 0.9219 after PIL).

Conclusions: Introducing PIL's in Croatian oral medicine practice is essential as the patients' overall well being, affected by oral diseases, will benefit.

Relevance: This study represents an objective measure of the value of patient information leaflets and emphasizes importance of introducing them to every oral medicine clinic.

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Patient and health care practitioner perspectives on UK Oral Medicine practice

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Objectives: Oral Medicine service demand has increased two fold in 5 years at EDH (new referrals 6526, 2004: 12613, 2009), despite a perceived lack of knowledge with regards to oro-facial disease referral amongst health care professionals. We aimed to assess the awareness and understanding of the specialty amongst referred patients, medical and dental professionals/students.

Methods: Questionnaires assessing awareness of oral medicine practice were distributed to three patient groups: New, Short-term discharged after 3 visits) and Long-term (visited unit more than 3 times). A different questionnaire was distributed to medical students, junior doctors and maxillofacial trainees. The latter results were compared against those from oral medicine trainees.

Results: Surveys were completed by 77:32:57 new: short-term: long-term patients respectively. The survey response rate was 98%. Of the "new" patients 50% had no knowledge of oral medicine practice. Satisfaction with the service was high in both the short-term (100%) and long-term (89.5%) groups. Surveys were completed by 22:8:6:13 medical students:junior doctors:OMFS:Oral medicine trainees respectively. 68% of medical students and 50% of junior doctors reported an awareness of oral medicine. There was wide variation in the referral patterns between each of the studied groups. Oral medicine and OMFS trainee groups were confident in their appropriateness of referral to the specialty, unlike medical students (16.7%) and junior doctors (29.2%).

Conclusions: In this sample there was limited awareness of oral medicine or the conditions managed amongst medical practitioners and the general public. Improving the specialty profile could play a significant role in development in the UK.

Relevance: Oral Medicine is a recognised specialty in the UK, however access to the service is restricted by the poor awareness of the conditions treated. This study concludes that medical practitioners remain unsure of Oral Medicine spectrum of practice.

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Vitamin B₁₂ deficiency in 30 patients – developing a standardised management approach

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Objectives: The association between vitamin-B12 deficiency and oral symptoms and signs has long been recognised. Measurement of serum vitamin B12 is inexpensive and frequently undertaken in Oral Medicine practice. The causes of vitamin-B12 deficiency are diverse. Within our unit we recognised that we did not have a standardised approach to the management of patients with a low serum vitamin-B12. The aim of this study was to review past cases and the literature to inform management of future patients with vitamin-B12 deficiency.

Methods: Within the context of the published literature, review was undertaken of the records of 30 patients who presented with oral symptoms and were found to have a serum vitamin-B12 $\leq 130 \mu\text{g/L}$.

Results: Vitamin-B12 deficiency ($< 50-130 \mu\text{g/L}$) was identified in patients with diverse oral diagnoses. Anaemia ($n=2$), macrocytosis ($n=3$), other haematitic deficiencies ($n=6$) or potentially relevant drugs ($n=4$) were infrequently identified. All patients were intrinsic factor antibody negative. Neuro-psychiatric states other than depression ($n=6$) were absent. No relevant gastrointestinal factors were identified, but information about diet and testing for coeliac disease was incomplete. All patients received vitamin-B12 supplementation and approximately half reported an improvement in their presenting symptoms.

Conclusions: Vitamin-B12 deficiency is regularly identified in patients with oral symptoms and signs. The cohort of patients retrospectively reviewed in this study confirmed the importance of testing haematitics at the same time as the full blood count. The causes of the vitamin-B12 deficiencies in this cohort were obscure. This study together with review of the literature has lead to formulation of a systematic approach to management of patients with oral symptoms and signs who are identified to have a vitamin-B12 deficiency.

Relevance: To help inform a systematic approach to management of patients with oral symptoms and signs who are identified as vitamin-B12 deficient.

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Testing Marginal Homogeneity to compare demographic and behavioural profiles of patients affected by oral mucosal lesions: Evidence from a hospital-based study in Palermo (South-Italy)

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Objectives: Diagnosis of the wide variety of lesions that occur in the oral cavity is an essential part of dental practice. The objective of this study was to explore the demographic and behavioural profiles of patients affected by oral cavity diseases on a wide spectrum.

Methods: Data from 3,154 patients with at least one Oral Mucosal Lesion (OML) was collected at our Unit. In an Exploratory Phase, the application of Multiple Correspondence Analysis (MCA) to geometrically characterize which OMLs are more or less similar in terms of their demographical and behavioral profiles in a sub-space of low-dimensionality was performed. In the Confirmatory Phase, the execution of global test was carried out to analyse the evidence of a difference between demographic and behavioural profiles for each cluster of diagnoses of OMLs detected in the MCA map, following the quasi-likelihood approach based on Generalized Estimating Equations (GEE) for marginal modeling of multivariate responses.

Results: Only 1,839 patient records were complete for all variables, with 41 different types of OMLs. 60.3% of the complete records had one of the 5 more frequent diagnoses (Oral candidosis 18.4%; Lichen Planus 13.8%; Oral Fibroma 9.1%, BMS 7.3% and Hyperkeratosis 6.2%). Results of MCA showed, on the first principal MCA axis, similar profiles for the couples Carcinoma-Leukoplakia, Halitosis-RAS and for BMS-ONJ, as confirmed by the GEE approach used to test SMH hypothesis.

Conclusions: Our results are substantially in agreement with data reported by previous studies. MCA map can be considered a graphical algorithm for all physicians not experienced with oral medicine in order to suspect the possible presence of OMLs.

Relevance: Our study, after evaluating the associations of associative non-causative variables with OMLs, stresses the need for a careful medical history collection which can provide a correct diagnosis.

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The efficacy of autofluorescence imaging (VELScope) in the visualisation of oral mucosal lesions

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Objectives: The aim of this study was to assess the efficacy of direct fluorescence visualisation (VELScope™) in the detection of oral mucosal lesions and its ability to highlight malignant and potentially malignant lesions.

Methods: 112 patients referred for assessment of an oral white lesion were initially examined under routine incandescent operator light. The location, size, ease of visibility, border distinctness and presence of satellite lesions were recorded. Clinical examination was repeated using VELScope, noting parameters such as loss of autofluorescence and presence of blanching. An incisional biopsy was performed to provide a definitive histopathological diagnosis.

Results: VELScope examination enhanced the visibility of 41 lesions. Its use resulted in a change in the provisional diagnosis in 22 cases. VELScope helped uncover 5 clinically undetected lesions and altered the biopsy site in 4 cases. VELScope examination alone showed a sensitivity of 30% and a specificity of 63%, with a positive predictive value of 19% and a negative predictive value of 75%. Its accuracy at identifying dysplasia was 55%.

Conclusions: VELScope is useful at aiding visualisation of abnormalities of the oral mucosa that may not be clearly discernable to the naked eye, but cannot provide a definitive diagnosis as to the presence or otherwise of dysplastic tissue change. Loss of tissue autofluorescence is not useful in diagnosing oral epithelial dysplasia in its own right without relevant clinical interpretation.

Relevance: The current evidence suggests that conventional oral examination is unreliable and deficient in differentiating between benign, dysplastic and malignant lesions, thereby resulting in delayed patient referral and poorer prognosis. Thus, any technology which highlights oral premalignant lesions in a highly sensitive and specific manner will undoubtedly aid clinicians in early diagnosis and treatment of these conditions.

C. Case Reports/Series

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Oral tuberculosis – a first sign of systemic disease

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Introduction: Tuberculosis is an infectious, chronic granulomatous disease that can involve almost any organ in the body, but primary lesions are usually confined to the lungs. Oral lesions are an infrequent occurrence in tuberculosis and tuberculosis of the oral cavity is usually a consequence of active pulmonary tuberculosis. Although primary tuberculosis in the oral cavity has been documented, it is a rare occurrence. The tongue and gingivae are common sites, followed by soft palate, floor of the mouth, lips and buccal mucosa.

Case detail: A 20-year-old girl presented with a solitary, large ulcer on the right buccal mucosa, with intensive redness and mild pain and with a large mass of plaque and calculus on lower and upper right molars of three months duration. Elsewhere in the mouth oral hygiene was good. There was no history of oral trauma, no fever or weight loss. General examination was unremarkable. The initial diagnosis was of malignancy. A biopsy was taken and histopathology showed multiple granulomas with epithelioid histiocytes, caseation, and Langhans cells.

Conclusion: With a possible diagnosis of tuberculosis, the patient underwent systemic investigations and lung foci were discovered. She was put on antituberculous therapy, and after eight months complete resolution of the disease was achieved.

Relevance: Through the differential diagnosis of oral ulcerations, the dentist can play a role in the early detection of tuberculosis, especially when oral lesions are not associated with any apparent systemic infection.

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White Sponge Nevus. A Case series of 26 patients

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Objectives: The aim of this study was to analyse the clinical characteristics of a series of patients with white sponge nevus (WSN) seen in the Service of Stomatology of Valencia University General Hospital from 1999 until 2010.

Methods: We analyzed epidemiological data, family history and clinical features of 26 patients with WSN belonging to 10 different families.

Results: There were 17 males and 9 females with an average age of 27.3±23.65 years. The lesions consisted of whitish plaques with a spongy aspect, usually asymptomatic. The most frequent location was cheek mucosa, appearing in all of the 26 patients studied, followed by lateral edge of tongue (9 patients), floor of the mouth (7 patients) and less frequently in labial mucosa and gingiva. Histopathologic samples were obtained from 8 of the 10 families studied, in at least one member of each family, finding an acanthotic epithelium with parakeratosis and intracellular edema of the spinous layer without showing any signs of cellular dysplasia appearing in any of the biopsied cases. No other pathology of oral mucosa was found in any patient.

Conclusions: White sponge nevus is a relatively frequent pathology, diagnosed in early ages, with a marked family trend exhibiting a dominant autosomal hereditary pattern, which does not carry risk of malignancy.

Relevance: The clinical features of WSN are similar to those of pre-malignant lesions such as leukoplakia or lichen planus, so the knowledge of the entity is important in the differential diagnosis of oral white lesions to avoid diagnostic mistakes, wrong prognosis and overtreatment.

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Cervical tuberculous lymphadenitis: incidental finding in neck dissection specimens

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Introduction: Head and neck cancers generally metastasize to cervical lymph nodes, thus neck dissection are performed routinely during surgical excision of primary malignancies. These specimens are then histologically examined for metastatic tumour as well as for the extent and staging of the tumour. Incidental findings of three cases of tuberculous lymphadenitis are reported here from the neck dissection specimens.

Details: Three cases of tuberculous lymphadenitis were found in a 60 year old lady with a primary left buccal mucosa squamous cell carcinoma, a 39 year old gentleman with a large ameloblastoma of the anterior mandible and in a 68 year old male with squamous cell carcinoma of the right lateral border of tongue. In all three cases, there was no previous history of tuberculosis nor was pulmonary tuberculosis diagnosed during routine preoperative chest radiographs. Antituberculosis treatment was started for all patients after recovery from the surgery.

Conclusions: In neck dissections, pathologists not only have to examine whether there is any evidence of metastasis from primary tumour but also need to be aware of the

presence of any other lesions such as tuberculous lymphadenitis. Patients have to be referred on for further management of the tuberculosis if detected.

Relevance: With the increase number of immigrants in Malaysia and elevated cases of HIV/AIDS, many patients may have contracted tuberculosis unknowingly. Clinicians should have a high level of suspicion for the possibility of tuberculosis in patients having swelling of the cervical lymph nodes even though the chest radiograph appears to be negative. Universal infection control precautions are mandatory and should be practiced in the operation theatre as tuberculosis is an occupational risk for health care workers.

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Non – HIV Kaposi sarcoma with oral involvement

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Introduction: Kaposi Sarcoma is the most frequent tumor associated with AIDS, the cervico-facial area being the most affected zone. The etiology is unknown, but it seems that HHV type 8 is an important co-factor.

The tumor onset is characterised by a red macule that increases in size, becoming nodular-exophytic. Histologically the tumor is a fibrosarcoma or an angiosarcoma.

Details: A 71 years old male patient was examined in the Maxillo-Facial Surgery Hospital, for phonatory, breathing and food-intake difficulties. The patient's medical history revealed silicosis (1970), renal lithiasis with partial nephrectomy (1977), chronic hepatitis (1980) and pulmonary tuberculosis treated between 1990–1992.

The cutaneous lesions started, shortly after the onset of tuberculosis and were diagnosed in a Dermatological Hospital. These tumors gradually extended over the lower limbs, upper limbs and subsequently affected the oral mucosa.

The clinical examination revealed multiple Kaposi Sarcomas on the upper and lower limbs, dorsum of the nose and vermillion of the upper lip. The oral examination showed multiple red-violaceous grouped tumors on the soft and hard palate and one large isolated tumor on the upper labial mucosa.

Relevant blood tests were within normal limits and WDRL, HIV and IDR were negative. The Pneumology consultation revealed no active pulmonary lesions but multiple sequelae of the previous disease. Surgical excision of the main lesions was performed. The postoperative recovery was favorable and there were no local recurrences during 6 months of follow-up.

The histopathology report confirmed the diagnosis of Kaposi Sarcoma. For the treatment of the skin lesions, the patient was transferred to the "Scarlat Longhin" Dermatological Hospital in Bucharest.

Conclusions: Non-HIV Kaposi Sarcoma can be encountered in clinical practice. Other immunosuppression mechanisms may favour disease onset.

Relevance: In some cases oral Kaposi Sarcoma lesions are encountered in non-HIV patients. Sometimes the lesions can be widespread, producing significant disturbance.

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A Rare Case of Fungal Osteomyelitis Affecting the Maxilla, Mimicking Advanced Periodontal Disease

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Introduction: Osteomyelitis was originally described by Nelaton in 1844 as an infection of the bone and bone marrow. The condition is usually caused by bacteria and the common site of presentation within the head and neck is the mandible. Reports of fungal osteomyelitis within the literature are rare. Osteomyelitis affecting the maxilla is unusual, due to its extensive blood supply.

Case detail: A 55-year-old Afro-Caribbean male, presented to his dentist with a 2-month history of painful, mobile maxillary teeth. Medically he suffered with diabetes and hypertension. Intra-oral examination revealed mobility of the alveolus and associated teeth. The teeth were non tender to percussion and were associated with multiple sinuses. Further investigation included radiographs (OPG), which showed generalised severe bone loss. A CT scan showed extensive bone destruction. A provisional diagnosis of osteomyelitis was made, which was confirmed by incisional biopsy. Histological examination confirmed the presence of fungal hyphae within the bone marrow space, and the diagnosis of fungal osteomyelitis was made. The condition was discussed with patient and managed with a three-month course of antifungal medication (Voriconazole). During this period he was regularly reviewed. At 3 months his maxilla and teeth were much firmer; sinuses had resolved and radiographs showed evidence of bony healing.

Conclusion: This case demonstrates the importance of careful examination and diagnosis. Although originally a provisional diagnosis of advanced periodontal disease was made, this was re-evaluated according to the patient's signs and symptoms.

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Non-exposed variant of bisphosphonate-associated osteonecrosis of the jaws: a case series

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Objectives: To report a case series of patients with the non-exposed variant of bisphosphonate-associated osteonecrosis of the jaws - a form of jaw osteonecrosis that does not manifest with necrotic bone exposure/mucosal fenestration.

Methods: Among 332 individuals referred to 5 clinical centres in Europe because of development of jawbone abnormalities after/during exposure to bisphosphonates, we identified a total of 96 patients who presented with the non-exposed variant of osteonecrosis. Relevant data were obtained via clinical notes, radiological investigations, patients' history and referral letters.

Results: The most common clinical feature of non-exposed osteonecrosis was jaw bone pain, (88/96, 91.6%), followed by sinus tract (51%), bone enlargement (36.4%), and gingival swelling (17.7%). Subsequent progression to frank bone exposure was observed in 53.1% (51/96) of the patients within 4.6 months (mean; 95% CI 3.6–5.6). No radiological abnormalities were identified in 29.1% (28/96) of patients.

Conclusions: Clinicians should be highly vigilant to identify individuals with non-exposed osteonecrosis, who could account to approximately 30% of patients with bisphosphonates-associated osteonecrosis.

Relevance: The impact of these findings on epidemiological data and clinical trial design could be significant.

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Leukoplakia and oral cancer

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Introduction: Leukoplakia is defined as an oral mucosal white keratotic lesion, the most prevalent sites being the buccal mucosa, gingivae and vermillion border of the lip. Peak age of occurrence is 60, with higher incidence in those who smoke who also show a lower peak age of presentation. Leukoplakia is a potentially malignant lesion, with transformation rate in the order of 2%.

Details: A 55-year old male presented, complaining of roughness of the cheeks, with a 20 year intensive (30 cigarettes a day) smoking history. A white, thick, striated patch was noted on both buccal mucosal surfaces. Biopsy results revealed a classic histopathologic picture of leukoplakia, with an intact basement membrane. Only after initial biopsy did the patient admit a family history of oral cancer- in particular his mother and brother.

Conclusions: With all the relevant tests carried out, the patient was advised on smoking cessation and underwent surgical therapy for both cheeks. The left buccal surface was histological clear for signs of cancer, but the right side had a cancer transformation, and patient was referred to the Oncology Department for the next treatment phase.

Relevance: In the prevention of the oral cancer, all leukoplakias must be thoroughly examined and reviewing the family history and disease relevant points is essential.

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Verrucous leukoplakia associated with HPV

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Introduction: Oral leukoplakia can arise from either keratinized or non-keratinized epithelium, is often associated with tobacco use, but many times an etiologic factor cannot be identified. A high risk type of oral leukoplakia – proliferative verrucous leukoplakia (PVL) is a white lesion associated with human papillomaviruses (HPV). These are a group of genetically related organisms infecting the squamous epithelium, inducing the proliferative changes in cells. Oral PVL-associated with HPV can progress to oral squamous cell carcinoma (OSCC). HPV with DNA types 16 and 18 have the strongest malignant potential.

Details: A 35 year-old-female was referred with white, verrucous leukoplakia lesion of the hard plate on the left upper molar region. Lesion was painless and the patient was

unaware of it. She was a heavy smoker. Biopsy was taken and revealed acanthosis, parakeratosis and altered layers of basal cells. The basement membrane was intact.

Conclusions: Although the dysplastic changes were minor the sample was found positive for Ki-67 and altered p53 expression. It was further tested for HPV (PCR) and type 16 was found, and complete removal of the lesion was recommended.

Relevance: PVL, a high-risk type of oral leukoplakia is a unique white lesion in which HPV can play a major role inducing the proliferative changes, resulting in both benign and malignant lesions. It is always wise to test PVL for the presence of HPV.

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Oral verrucous carcinoma

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Introduction: Verrucous carcinoma (VC) is a well-differentiated form of locally aggressive squamous cell carcinoma that could arise from cutaneous surfaces and/or oral mucosa. Most patients have a long history of premalignant lesions like lichen planus (LP).

Details: A 28-year-old female attended for periodontal treatment, and on the first examination was diagnosed with chronic periodontal disease and lichen-like lesions on both buccal aspects of the right mandibular alveolar ridge around teeth 46 and 47. During periodontal treatment incisional biopsy was taken from three sites in the mouth. Two buccal samples were diagnosed as lichen planus without carcinomatous transformation, but the sample from the alveolar ridge was diagnosed not as LP, but as VC. Microscopically, the tumour showed a heavily keratinized lesion with compressive invasion pattern, cell atypia, and free surgical margins.

Conclusions: In the case of VC whenever feasible, the surgical removal is recommended over radiotherapy. A free surgical margin is an important prognostic factor for determining recurrences. After the marginal mandibulectomy the patient received radiotherapy.

Relevance: VC can sometimes clinically mimic other white lesions and histological examination is of the highest importance. Even if oral VC is less frequent and has excellent prognosis, VC presents a potential for local recurrence that should be considered during the planning of surgical treatment of this neoplasm in the oral cavity.

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Oral metastases as first manifestation of renal cell carcinoma: presentation of clinical cases

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Introduction: Oral metastases represent 1% of all oral cancers and rarely they may be the first manifestation of a primary tumor arisen elsewhere. Renal cell carcinoma, breast cancer, lung cancer, prostate cancer can metastasize to the oral cavity, but only few cases are reported in the literature as being the first appearance of the disease. Prognosis is generally poor since at the moment of the diagnosis, the primary tumor has already had widespread metastases.

Details: We present 8 unpublished cases of oral metastasis of renal cell carcinoma, 7 of which were the first sign of the primary tumour: mean age was 63.5 yrs (range 78–45 yrs); 6 were males and 2 females. Both bone and soft tissues were involved: 3 cases were localized in the parotid gland, 2 were within the gingiva, 2 in the mandible (condyle and body) and 1 on the tongue. Clinical signs and symptoms were various and related to the involved organs: swelling, teeth mobility, epulis-like lesions, halitosis, chin numbness, pain, facial palsy were the most common. Radiologic features were often non specific and did not contribute to the diagnosis. Differential diagnosis included many benign oral conditions (i.e. abscesses, osteomyelitis, periodontal pathologies, granulomatous gingivitis, pyogenic granuloma, giant cell granuloma, epulis), primary oral tumors (squamous cell carcinoma, lymphoproliferative disorders and salivary gland tumors) and at least in one case metastases.

Conclusions: Since clinical and radiologic features of the oral lesions are non-contributory for the diagnosis, this can be difficult without the biopsy which is mandatory. Pathology often reveals poorly differentiated clear cell carcinoma and therefore our diagnoses were made via the aid of immunohistochemistry (vimentin and CD10) especially when the primary tumor had not been identified.

Relevance: Metastatic renal cell carcinoma, even if it is rare, should be considered for differential diagnosis in those patients presenting with a new head or neck lesion.

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A case of histiocytic sarcoma localized in the maxillary gingiva

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Introduction: Histiocytic sarcoma (HS) is a rare neoplasm which is usually on aggressive tumor with a poor response to therapy. The World Health Organization

defines HS as a malignant proliferation of cells showing morphologic and immunophenotypic features similar to those of mature tissue histiocytes. We report a case of HS arising from maxillary gingiva.

Details: A 71-year-old Japanese male was referred to Matsumoto Dental University Hospital for gingival swelling and bleeding. The patient first noticed that his left maxillary gingiva was gradually swelling and bleeding two months before. A 10x5mm solitary mass was observed at the left gingiva of the maxillary first molar. Based on the clinical diagnosis of a maxillary tumor, the lesion was removed together with the left maxillary first molar. The lesion was fixed in 10% natural-buffered formalin after surgical excision, and was embedded in paraffin according to standard methods. Macroscopically, the tumor, measuring 10x5x5mm, showed polypoid feature colored with dark red. Microscopical examinations revealed that the tumor was composed atypical histiocytic cell proliferation with necrosis. Large and round tumor cells showed that had eosinophilic cytoplasm with round to irregular nuclei and one to several distinct nucleoli. Immunohistochemically, tumor cells were positive for EMA, vimentin, LCA and CD68, and negative for AE1/AE3, S100, CD1a, CD3, CD20, CD21, CD30 and CD56. Ki-67 labeling index was 38%, accompanied with positive reaction to p53. The patient has shown no evidence of recurrence and metastases in lymph nodes or in any distant organs since the operation. Finally, we made a diagnosis of Histiocytic sarcoma.

Conclusions: This present case is histologically malignant, but it looks likely to be clinically benign. Long-term follow-up is recommended to detect recurrence and/or metastasis.

Relevance: It is important to recognize that localized HS of the unique biological type infrequently occurs in the oral region.

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Extranodal nasal-type NK/T-cell lymphoma of palate and paranasal sinuses

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Introduction: Extranodal nasal-type natural killer (NK)/T-cell lymphoma represents a rare entity originating in the nasal cavity, palate or midfacial region. Initial signs and symptoms often include non-specific rhinitis and/or sinusitis, nasal obstruction, epistaxis, facial swelling and pain. Other clinical features include swelling of the soft or posterior hard palate and the formation of a deep necrotic midline palatal ulceration resulting in an oronasal fistula. Differential diagnosis includes deep fungal infections, Wegener's granulomatosis, tertiary syphilis, other non-Hodgkin's lymphomas, cocaine abuse and malignant epithelial midline tumours. We report a case of extranodal nasal-type NK/T-cell lymphoma highlighting clinical and histological differential diagnosis and management.

Details: A 40-years-old man presented with chief complaints of headache, facial pain, nasal stuffiness and fever. Clinical examination revealed a large deep necrotic ulcer in the palatal midline associated with oronasal fistula. Endoscopic rhinoscopy revealed crusts in the nasal cavities, moderate perforation of the nasal septum cartilage and contraction of the middle and inferior concha. CT-scan showed a space-occupying dense soft tissue mass involving the maxillary sinuses, ethmoidal cells and sphenoidal sinus. Laboratory investigation revealed increased erythrocyte sedimentation rate. A wide surgical excision of the lesion was performed. Histological and immunohistochemical evaluation rendered the diagnosis of extranodal nasal-type NK/T cell lymphoma. The patient was treated with CHOP chemotherapy radiotherapy and autologous bone marrow transplantation. Rehabilitation involved the fabrication of an obturator.

Conclusions: Extranodal nasal-type NK/T-cell lymphoma is a rare, very aggressive, site specific malignant lymphoma; it progresses fast and has a poor prognosis, which can be improved by early diagnosis and combined treatment.

Relevance: Extranodal nasal-type NK/T-cell lymphoma is a rare pathologic entity which has to be included in differential diagnosis of destructive palatal midline lesions.

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Orofacial manifestation of Langerhans cell histiocytosis (LCH)

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Introduction: Histiocytoses are a group of acute and chronic, localized and generalized diseases for which oral manifestations may be the first signs. Little is known about the aetiology. They are diseases in which cells from the mononuclear system (MCH), previously known as reticulo-endothelial system, are found in affected tissues. These cells may be either altered or proliferating histiocytes.

Details: In 1977 at department of periodontology we examined patient with loosening of teeth. He was diagnosed for non-specific reticulosis that time at department of dermatovenereology. Intraoral evaluation revealed gingival overgrowth and movement

of teeth. Vestibular mucosa displayed yellow infiltrates with necrosis and ulcerations in distal areas. Radiographic examination showed osteolytic focus in jaws and helped confirm the diagnosis LCH.

Conclusions: Due to the character of the disease the patient is reviewed in the department of periodontology together with other specialties to provide multi-disciplinary care. In regard of prevalence the resumption is of significant under-diagnosis.

Relevance: Secondary signs (hypothyroidisms, exophthalmos, diabetes insipidus and hypogonadism) assist in the diagnosis of this disease.

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Management of an unusually aggressive, non-malignant leukoplakia

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Introduction: White patches are common in Oral Medicine nevertheless their management has been historically a source of controversy. We present a case of leukoplakia of the gingivae associated with mobility of mandibular teeth that has been treated over 6 years requiring a multidisciplinary approach to management.

Details: We present a case of a 56 year-old male non-smoker who attended the Oral Medicine Clinic regarding a white plaque affecting the mandibular gingivae that progressed slowly and relentlessly over 6 years from homogenous to proliferative. Its progress was mirrored in the development of severe periodontal disease only affecting teeth in close relation to the lesion. With progression of the lesion, the periodontal disease proved resistant to treatment and this resulted in mobility of the involved mandibular teeth. However, the aggressive nature of the lesion was not reflected in several biopsies reported as hyperkeratosis with no dysplasia. More recently, a further pathological specimen from an extensive gingivectomy revealed verrucous leukoplakia with severe dysplasia and the recommendation to treat as a low-grade carcinoma. This prompted referral to the Head and Neck Cancer Multi-Disciplinary Team (MDT) to discuss management options for this unusual case.

Conclusions: It was decided the patient should undergo extraction of the posterior teeth, excision of the leukoplakia, laser ablation of any residual lesion, provision of an immediate denture following initial healing and in the absence of disease at further follow-up, the possible placement of dental implants.

Relevance: This case highlights the difficulties encountered by the Oral Medicine physician in the diagnosis and management of white plaques, the pitfalls of biopsies in the diagnosis of leukoplakia, and the importance of a multidisciplinary approach to the treatment of complex patients. This case is also unusual in that it presented as a white plaque associated, from the beginning, with gradual tooth mobility in the absence of malignancy.

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Graft vs. Host Disease or Acute Relapse? Cutaneous and Gingival Extramedullary Manifestations of Acute Myeloid Leukaemia following Haemopoietic Stem Cell Transplantation

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Introduction: White patches are common in Oral Medicine nevertheless their management has been historically a source of controversy. We present a case of leukoplakia of the gingivae associated with mobility of mandibular teeth that has been treated over 6 years requiring a multidisciplinary approach to management.

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Glomus tumor of the upper lip: Report of a rare case

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Introduction: Glomus tumors (GTs) constitute mesenchymal neoplasms composed of cells resembling the modified smooth muscle cells of the normal glomus body. They are rare entities and usually occur in young adults. The majority appear in the distal extremities, particularly in the subungual region, hand, wrist and foot, affecting the skin or superficial soft tissues. Clinically, GTs are small (<1cm), red-blue lesions and may be associated with a long history of localized painful symptoms. Surgical excision is usually curative although a 10% recurrence is reported. The aim of this paper is to report a rare case of glomus tumor of the upper lip.

Details: A 16-year old patient presented with a slow-growing, slightly symptomatic mass of the upper labial mucosa close to the vermillion border. Clinical examination revealed a small dimensioned (0.4x0.4cm), reddish, soft tumor covered by normal mucosa. An excisional biopsy was performed and histopathological examination demonstrated numerous capillary blood vessels surrounded by nests of neoplastic cells. The latter were round with eosinophilic or amphophilic cytoplasm and dense nuclei with regular contour and indiscernible nucleoli. Mitotic activity or pleomorphism was not observed. Immunohistochemically, the tumor cells exhibited strong positivity for Smooth Muscle Actin (SMA). Based on the histological and immunohistochemical characteristics of the tumor, a final diagnosis of GT was rendered.

Conclusions: GTs represent soft tissue benign neoplasms which have been infrequently reported to affect the head and neck region. Microscopic differential diagnosis includes sweat gland tumors, melanocytic nevi, paragangliomas and vascular neoplasms, such as hemangiopericytomas. Involvement of the oral cavity, including the upper labial mucosa, is a very rare occurrence.

Relevance: Rare soft tissue neoplasms, including glomus tumor, may affect the oral cavity causing significant diagnostic difficulties and potential confusion with apparent therapeutic implications.

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Metastatic melanoma of tongue – A case report and literature review

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Introduction: The incidence of melanoma in the skin has increased considerably. This neoplasm is characterized by a high metastatic rate, however the metastases in the tongue are rarely reported. The authors report a case of primary melanoma of the skin with metastases in lymph nodes, brain and tongue.

Details: A 72 year-old white man presented complaining of a nodule in his tongue. His medical history revealed treatment for peri-umbilical melanoma with micro metastases in the inguinal lymph nodes. 15 months later without any other clinical signs of disease, a dorsal tongue lesion arose. The differential diagnosis of salivary gland neoplasm, lymphoma and metastasis melanoma was made. An incisional biopsy report was consistent with solid malignant epithelioid arrangement infiltrating into skeletal muscle. Immunohistochemical evaluation showed reactivity with anti-HMB45, anti-Melan A and anti-S100, and negative for the anti-PAN cytokeratin which confirms the diagnosis of metastasis melanoma. Immunostaining for Ki67, MCM2, MCM5 and geminin revealed intense proliferative activity. The patient was surgically treated. Two months later he showed signs of confusion, and a diagnosis of brain metastasis. He died thirty days after tongue biopsy.

Conclusions: The above case report demonstrates the importance of assessing the patient medical history, clinical examination and immunohistochemistry analysis in diagnosis.

Relevance: Metastatic melanoma lesions in the tongue are rare. This case demonstrates that the lesions in the other organs or systems can metastasize to the oral cavity.

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Long term follow-up of mesothelioma presenting in the tongue

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Introduction: This patient was initially referred by their dentist for excision of what were thought to be two fibroepithelial polyps on the tongue. However, histology identified malignant cells from an unknown primary. Investigations, that eventually identified the primary as a mesothelioma, included immunohistology, tumour markers and imaging. Data on this was presented to the 2009 BSOM meeting. We now report the longer term progress of this case.

Details: Initial presentation was of two painless lesions on the dorsum of the tongue. The diagnosis of mesothelioma was made using a panel of special stains, CT of the

thorax and MRI. Despite little in the way of systemic symptoms, there was extensive mesothelioma involvement of the left pleura and she was started on chemotherapy with cisplatin and pemetrexed. Six months later she developed 3 small tongue lesions at new sites. Histology of these again found mesothelioma and she received a second more intense course of palliative chemotherapy. This induced left axillary lymphoedema and cellulitis and a few weeks later she developed two more lingual metastases. It is planned to laser ablate these and any future lingual recurrences.

Conclusions: Metastasis of mesothelioma to the oral cavity is very rare and this is the first reported case where oral metastases were the presenting lesion. Unfortunately, excision and palliative chemotherapy have not been successful in preventing lingual recurrence and this has had a considerable impact on this patient's quality of life. This update reminds us of the importance of multi-disciplinary management of complex cases and the difficulties of managing oral metastases.

Relevance: These lesions mimicked the appearance of a fibroepithelial polyp and highlight the importance of biopsy and histopathological diagnosis even in presumed benign lesions. In addition this case emphasises the importance of the general dental practitioner in screening for oral neoplasms of all types.

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Squamous odontogenic tumour: a case report

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Introduction: Squamous odontogenic tumour (SOT) is a rare benign odontogenic tumour composed of well-differentiated squamous epithelium in a fibrous stroma. The aim of this report is to describe a case of SOT located between the mandibular incisors.

Details: A 31-year-old man was referred for evaluation of a mandibular lytic lesion detected in a routine radiographic exam. On intraoral examination, no color mucosa alteration, swelling, hypoesthesia, hyperesthesia or anesthesia of gingival tissue were observed. Panoramic radiography revealed a unilocular radiolucency located at the apex of the lower incisors, which presented sharp margins and measured about 3.0 cm in diameter. Although the teeth involved were displaced, they responded positively to a cold pulp test. The differential diagnosis included ameloblastoma, keratocystic odontogenic tumor, simple bone cyst and central giant cell lesion. Under local anaesthesia, an incisional biopsy was performed. Microscopically, the lesion was composed of islands of benign neoplastic squamous epithelium in a mature connective tissue stroma without the presence of peripheral columnar cells, palisading nuclei, or stellate reticulum. According to the microscopic findings, a diagnosis of SOT was established. Surgical excision was performed under local anaesthesia, confirming the diagnosis of SOT. After 12 months of the treatment, no radiographic or clinical evidence of recurrence was observed.

Conclusion(s): Although a slow growing painless swelling is the most common symptom in patients with SOT, this lesion may be a finding in a routine radiographic exam.

Relevance: Radiographic exam is essential to complement the extraoral and intraoral exams, since several bony lesions may be evidenced occasionally, such as this SOT.

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Verrucous carcinoma: report of a case

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Introduction: Verrucous carcinoma (VC) is a rare and low grade variant of oral squamous cell carcinoma, representing from 1% to 10% of this tumour. Most of the VC are related to tobacco smoking and occurs usually in men over 55 years. Additionally, HPV genotypes 16 and 18 have been identified in some VC. The objective of this paper is to report a case of oral VC.

Details: A 67 years old male patient, retired, with a chief complain of a painless lesion on the hard palate, with one month of evolution was referred to the Oral Medicine unit, of UFPE, Recife, Brazil. The patient was a heavy drinker and smoked around 20 cigarettes/day for 58 years. On physical examination, it was observed an irregular, exophytic, sessile, nodular and white lesion located on the junction of hard and soft palate, which presented firm consistency and verruciform surface. The lesion measured 5.0 cm in diameter. Verrucous carcinoma was the main hypothesis of diagnosis. Under local anaesthesia, an incisional biopsy was performed and the surgical specimen sent for histopathological analysis. Microscopically, there was a thickened well-differentiated squamous epithelium with intense keratinization and papilliferous surface, which caused intrastromal invaginations. Moreover, a chronic inflammatory infiltrate was observed in the adjacent connective tissue. Based upon the clinical and laboratory findings a final diagnosis of VC was established.

Conclusion(s): Although it is a low grade neoplasm, VC may be diagnosed in advanced clinical stage. In addition, it occurs predominantly in older and heavy smoker patients.

Relevance: It is important to establish preventive actions in patients with high risk for oral squamous cell carcinoma. Thus, these actions would prevent such lesions or contribute for the early diagnosis, especially in low grade neoplasms, such as VC.

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Linear naevus sebaceous syndrome (LNSS)

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Introduction: Linear naevus sebaceous syndrome (LNSS) is a rare genetic neurocutaneous disorder characterised by epidermal naevi and variable congenital anomalies affecting multiple organ systems including the CNS. It is thought to result from genetic mosaicism involving a lethal autosomal-dominant gene. Sebaceous naevi essentially consist of overgrown epidermis, sebaceous glands, hair follicles, and connective tissue. They typically involve the scalp, face and neck. Malignant change in the naevi is a major concern. Both diagnosis and management of the disorder can be challenging and involve a multidisciplinary approach.

Details: A 10.5 month old child with known LNSS was referred for assessment of oral swellings. Initial diagnosis had been made at 6 months by a pediatric dermatologist in view of an extensive raised papillary sebaceous naevus on her face and mild developmental delay. Oral examination revealed a 1 x 2.5cm lesion involving the dorsum of the tongue at the level of the junction of the hard and soft palate assumed to represent an epithelial naevus. The rest of the oral tissues appeared normal. Since the child appeared unaffected by the oral lesion the decision was made to monitor it.

Close monitoring of the skin and oral mucosa has continued and the patient is now seven years old. The tongue lesions have continued to enlarge but have not markedly interfered with speech or eating. Two deeply pigmented naevi on the nape of the neck developed and have undergone excision in view of concerns about possible malignant change. At her most recent oral medicine appointment the mother reported new skin lesions and extensive multiple irregular shaped naevi over the left shoulder were noted. An urgent referral to the dermatologist was arranged.

Conclusions: The patient continues to be reviewed regularly for monitoring of her neurological, ophthalmological and developmental status. Her cranio-facial naevi are reviewed regularly and it is anticipated that she will undergo further surgery for prophylactic purposes and cosmetic and social reasons. Her oral lesions also continue to be monitored for progression and for any effect on function. The recent development of the extensive naevi is of a major concern due to her young age and the risk of malignant change.

Relevance: This report highlights an uncommon genetic condition with significant morbidity and malignant potential which may present with oral manifestations.

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Inflammatory myofibroblastic tumor with delayed tooth eruption and multiple cervical root resorption in an 11-year old girl: A case report

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Introduction: Inflammatory myofibroblastic tumour (IMT) is a rare lesion characterized by myofibroblastic cells and variable mixture of inflammatory cells. Proposed pathogenic factors include viral infection, autoimmunity and/or reactive non-neoplastic or neoplastic origin. Only 17 cases have been reported in the mouth. IMT can present with variable clinical manifestations. IMT is classified as a benign lesion but local aggressiveness may be associated with chromosomal aberrations. Diagnosis of IMT is based on histopathological and immunohistochemical findings. More documentation on oral IMTs is necessary to gain insights of details of IMTs appearing in the oral cavity.

Details: An 11-year-old previously healthy girl had a complicated eruption of the left maxillary canine tooth and first premolar. A panoramic tomography showed large resorption of the mesial side of the root d24. Because of lack of space d24 was extracted and granulation tissue was enucleated. Twelve weeks later, a significant bone deficiency was observed and the position of d23 was still in under-occlusion. The patient was referred to University Central Hospital, where a cystic osteolytic area in the same region was observed. The lesion was treated by enucleation and curettage and the damaged teeth with resorption were extracted and sent for histopathological examination. A compact cellular spindle cell proliferation with collagenous stroma with storiform architecture was observed. The tumour tissue was strongly positive for SMA, vimentin and ALK1. Calponin, myoglobin and HHF35 showed moderate immunostaining in myofibroblasts.

Conclusions: Diagnosis of IMT is challenged by the rarity of the lesion, rapid growth possibly clinically simulating malignancy and even difficulties to identify myofibro-

blasts. In the case presented, the first sign of IMT was delayed eruption of two permanent teeth followed by resorption of three teeth.

Relevance: This case underscores the importance of histopathological examination of the soft tissue found in any resorption cavities especially in the case of multiple resorptions.

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Dry mouth as an initial sign of botulism: a case report

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Introduction: Botulism is a rare neuromuscular disease that affects humans and other animal species caused by a potent neurotoxin produced by the anaerobic, spore-forming Gram-positive bacteria *Clostridium botulinum*. There are four different recognised clinical types of botulism, but the food-borne (or classic), wound and infant forms are the most clinically significant. Clinical features as well as medical history and physical examination are essential in the early diagnosis and management of this potentially lethal disease. However, because of the rarity of the disease, several differential diagnoses are usually provided by health practitioners.

Details: A 30 year-old man (AL) without any known underlying disease was referred to the Oral Medicine Unit, University of Parma, by the Emergency Services for a severe and diffuse xerostomia associated with dysphagia. Signs and symptoms had been present for two days, with difficulty in eating and speaking. He also reported blurred vision. At clinical examination the oral mucosa appeared extremely dry, sticky and inflamed. The lips were dry, cracked and signs of angular cheilitis were also present. These features were also diffuse through the pharynx. He was a non-smoker and did not report any alcohol, drug or other substance abuse. From the clinical interview he reported that both he and his identical twin were affected by abdominal pain and difficulty in eating. In particular the patient's twin (AC) had a more severe ocular involvement (anisocoria, diplopia, photophobia, blurred vision) and nausea associated with the above reported oral symptomatology. In addition he complained of generalised weakness. All the hematological, toxicological and virological examinations performed were negative. The neurological examination showed a reduced bilateral photomotor reflex to direct and consensual stimulus. No extra-ocular muscle dysfunction was observed on examination, but the patient experienced diplopia. In addition a low hyposthenia under resistance (4/5) was recorded on the superior right arm with difficulty in fine motility. During hospitalisation, an autonomic symptomatology became evident with constipation, xerostomia and xerophthalmia in both the twins suggesting the hypothesis of food-borne botulism, further confirmed by an electrophysiological study and by the detection of Neurotoxicogenic Clostridia in faecal samples in one of the two patients as well as in home-canned food.

Conclusions: Dentists are not usually involved in the diagnostic process of botulism because oral involvement is clearly associated with other more evident clinical signs, often more characteristic of the pathology. However, as in this case, sometimes the presence of particularly severe oral manifestations, in combination with other data, may suggest that oral medicine practitioners could assist other health specialists in the detection of rare diseases such as botulism.

Relevance: In this case report we describe severe and diffuse oral involvement due to food-borne botulism infection.

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Minor salivary gland MALT lymphoma: first sign of Sjögren Syndrome

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Introduction: Patients with Sjögren syndrome (SS) have an increased risk of developing salivary gland extranodal marginal zone B cell lymphoma of MALT type.

Details: A 60 years old female was referred to our center for a small submucosal node (2-3 mm) on the left of the upper lip incidentally detected by the patient herself. On palpation the lesion was a freely movable mass. The patient complained of no symptoms. Her past personal and family history were unremarkable. A benign minor salivary gland neoplasm was hypothesized (e.g. canalicular adenoma) and an excisional biopsy was performed under local anesthesia. The conventional hematoxylin and eosin stain showed an intense benign lymphocytic infiltration replacing the salivary gland parenchyma without any sign of clonality. The patient was referred to the hematologist for further evaluations which revealed the presence of ANA, Ab anti-SSA and anti-SSB, but no hematological disorders. In the same time the patient started suffering xerostomia and entered a diagnostic protocol for SS which led to the confirmation of diagnosis. Seven months later another similar node appeared near on the lower lip and

the patients. An additional excision was performed thus revealing an atypical lymphoid infiltrate suspicious of involvement of the extranodal marginal zone B cell lymphoma of the MALT type. The patient was then referred to the hematologist for staging of her lymphoma. As no other involvements were observed (endoscopy, CT total body, bone marrow biopsy), a wait-and-see policy was adopted.

Conclusions: Prolonged autoimmune inflammation as in SS may play a part in the development of lymphoma; conversely in the present case the finding of intense benign lymphocytic infiltration similar to MALT lymphoma brought to the identification of SS.

Relevance: These findings highlight an unusual diagnosis of SS related MALT lymphoma preceding the typical symptoms and clinical signs of SS.

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An unusual location for a salivary gland stone

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Introduction: Sialolithiasis refers to calculus formation in salivary glands. It may lead to salivary flow obstruction and subsequent sialadenitis. Sialolithiasis most frequently involves the submandibular salivary glands (80%-90%) and is less frequently found in the parotid glands (10%-20%). Very rarely sublingual and accessory salivary glands may undergo this process (2%). We describe an unusual presentation of sialolithiasis involving a minor salivary gland located in the ventral surface of the tongue.

Details: A 51-year old healthy, non-smoking, female was referred by her dentist with a one year history of an asymptomatic, firm lump involving her tongue's ventral surface. Although it had slowly increased in size over this period, it had not swelled in association with eating or the smell or sight of food. Extra-oral examination was unremarkable. A non-tender, hard, mobile, pale swelling of ~4x6 mm was found on the tongue's ventral surface. A differential diagnosis of minor salivary gland stone, submucosal foreign body or minor salivary gland tumour was considered. The diagnosis of a sialolith was confirmed by ultrasound examination and excisional biopsy with histopathological analysis.

Conclusions: There may be up to 750 accessory salivary glands in the mouth. However, minor salivary gland stones are rarely reported in the literature. It has been suggested that they frequently spontaneously resolve by calculus ejection. As in the case presented, the mean age of patients affected is 50 years (range 9-90 years). They are most commonly found in the upper lip (49.2%), followed by the buccal mucosa (37.3%) and are reported to involve the tongue or palate only very rarely (1.6%).

Relevance: Although uncommonly encountered minor salivary gland calculi should be considered as part of the differential diagnosis of small mobile submucosal swellings. As in the major salivary glands ultrasound examination may be helpful in the diagnosis of minor salivary gland calculi.

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Bullous lichen planus on the lip associated with skin lesions

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Introduction: Oral lichen planus is a relatively common disorder whose cause is still unknown. Bullous lichen planus (BLP) is a rare variant of LP, characterized by the development of vesicles and bullae. BLP to be distinguished from lichen planus pemphigoides, bullous pemphigoid, pemphigus vulgaris, erythema multiforme, and herpes simplex virus infection. It is uncommon on the lips and associate with skin lesion.

Details: We reported a 21-year-old Caucasian female has described blisters and ulcer on the lip since 2008. March 2010, presented with erythema and ulcer in all lower lip, and erythematous plaque on the forehead. The histopathological analyses of lips lesion showed bullous lichen planus and immunofluorescence exam showed negative.

Conclusions: The patient has been treated with prednisone with disappearance of the cutaneous and oral lesions.

Relevance: The importance of differential diagnoses of the BLP with the others vesiculobullous lesions.

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Lacrimal canalicular duct scarring in patients with lichen planus

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Introduction: We report 7 women with erosive lichen planus (LP) who were noted to have scarring around the punctum of the lacrimal duct which we believe is related to their LP. Only a few cases of lacrimal canalicular obstruction secondary to scarring from LP have been reported (Durrani OM, Ophthalmology 2008; 115: 386-389).

Interestingly 3 of our cases had vulvo-vaginal-gingival (VVG) syndrome which is a severe subgroup of LP (Setterfield J Am Acad Dermatol 2006; 55:98–113).

Details: The average age was 65 years (range 51–83). All 7 had erosive LP affecting at least the vulval and oral mucosa and 3 of them had vulvo-vaginal-gingival (VVG) syndrome; 5 complained of epiphora, 1 photophobia, 1 eye irritation and 2 were asymptomatic. All 7 cases had scarring around the punctum of the lacrimal duct, 1 had cicatrizing conjunctivitis and bilateral ectropion. Two patients underwent lacrimal duct dilatation procedures without improvement, 1 improved with Celluvisc and Prednisolone 0.5% eye drops and 4 declined any intervention.

Conclusions: Given the strong association between ulcerative lichen planus, particularly of the VVG variant and multi-site scarring sequelae, it is perhaps not unexpected that ocular inflammation may lead to sub-conjunctival fibrosis and lacrimal duct stenosis. We believe this complication has been under reported.

Relevance: Eyes should be considered during the multidisciplinary assessment of patients with severe erosive LP.

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A follow-up of six malignant oral lichen planus patients

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Introduction: Lichen planus (OLP) is a chronic inflammatory disease that can persist in some patients for a long time. The oral form may persist for up to 20 years. The most important complication of OLP is the development of oral squamous cell carcinoma (OSCC). There is some controversy regarding its malignant potential.

The reported frequency of malignant transformation varies between 0.3% to over 5%. The forms that more commonly undergo malignant transformation are erosive and atrophic forms.

Objective: The aim was to assess the course of 6 malignant oral lichen planus cases.

Details: This is a prospective study in which we describe six OLP who developed oral carcinoma. All patients, four women and two men, had clinically and histologically confirmed OLP by WHO criteria in the period from 1989 to 1993. OLP and malignant change diagnoses were realized in the Dental School of the Oviedo University. Surgical treatment of oral carcinoma were realized in the Oral and Maxillofacial Surgery of University Hospital of Asturias (HUCA).

The age of individuals at diagnosis of OLP were: 51, 66, 57, 41, 56, 48 (mean = 53.1). The age at diagnosis of carcinoma were: 53, 73, 64, 45, 64, 58 (mean = 59.3).

Malignant OLP localizations were: buccal-sulcus, buccal, lingual mucogingival reflection, two margin of the tongue and dorsum of the tongue. The clinical forms of OLP that developed malignancy were: three reticular-atrophic, two reticular-plaque, one reticular-atrophic-erosive. One female patient developed several dysplastic lesions and a gingival OSCC. One man developed two verrucous carcinomas (buccal and upper gingival).

Conclusions: Fifteen years later, there were three patients who survived. One of the female patient has recurrent OSCC which is terminal.

Relevance: All cases of OLP must be routinely evaluated to monitor for any suspicious changes suggestive of malignancy.

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Bevacizumab associated mucous membrane pemphigoid

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Introduction: We describe a case of drug-induced mucous membrane pemphigoid following the administration of intravitreal bevacizumab (Avastin® - humanized monoclonal antibody to vascular endothelial growth factor) for the treatment of age-related macular degeneration.

Details: An 82 year old Caucasian woman was originally referred from Department of Ophthalmology, with a history of oral, cutaneous, vulval and anal blistering and ulceration, commencing within 24 hours of the first administration of bevacizumab and subsequent flares after each further administration.

Histopathology with direct immunofluorescence confirmed the clinical diagnosis of mucous membrane pemphigoid.

As further bevacizumab was necessary to preserve sight, management was initiated with Dapsone 25mg/day with 500 IU Vitamin E (G6PD and Hb normal) and topical fluticasone propionate 400mcg mouthwash twice daily. The patient responded well to therapy and maintains satisfactory symptom control.

Conclusions: To date, there are no reports of bevacizumab-induced mucous membrane pemphigoid; however the temporal association between the onset of symptoms and recurrent disease deterioration with further therapy suggests bevacizumab as the causative agent.

Relevance: Clinicians must be vigilant to the development of new oro-facial drug reactions.

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Oral pemphigus vulgaris with subsequent oesophageal involvement

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Introduction: While the clinical and epidemiological features of oral mucosal and cutaneous pemphigus vulgaris (PV) have been well documented there remain few reports of the possible frequency of PV of the oesophagus and its possible association with oral involvement. Although previously considered to be rare, recent reports have suggested that up to 87% of patients with PV may have symptoms or endoscopic features of oesophageal disease and that the latter may be poorly responsive to conventional corticosteroid-sparing immunosuppressive regimes.

Details: The clinical and immunological features of a 53 year old Asian female who developed likely oesophageal PV subsequent to oral disease are presented. During week six of responsive therapy with azathioprine and decreasing prednisolone, and despite falling levels of circulating desmoglein antibodies, the patient developed upper gastrointestinal symptoms and haemoptysis. Oesophagogastrroduodenoscopy demonstrated upper oesophageal blistering consistent with PV. Increased corticosteroid dose was required to resolve the oesophageal symptoms.

Conclusions: Despite a lack of significant oro-cutaneous lesions at the time, and with decreasing serological markers of likely active disease, blistering of the oesophagus due to PV occurred. This may suggest that the immunological targets for oesophageal disease differ from those of the oral mucosa or skin, or that conventional first-line systemic therapy is unlikely to be effective for oesophageal lesions. Mild upper gastrointestinal symptoms should always be investigated and not be dismissed as secondary to corticosteroid therapy.

Relevance: This case report highlights that oesophageal PV can occur in the absence of other mucocutaneous lesions or when therapy of oral mucosal lesions is seemingly effective.

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An unusual case of oral pemphigus- vulgaris or foliaceus?

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Introduction: Pemphigus is a potentially serious and rare vesiculobullous autoimmune skin disease affecting 0.1 to 0.5 patients per 100,000 population per year and usually involves the oral mucosa. Pemphigus vulgaris is the most common form in which 50 to 70% of patients present with oral lesions. Other forms are pemphigus foliaceus, pemphigus erythematosus and pemphigus vegetans which rarely affect the mouth.

Details: A 42 year old female presented to her GP in 2005 with erythematous and sore gingivae and was referred to a maxillofacial surgeon. A biopsy suggested pemphigus but the patient did not respond to topical steroids. In 2006 the oral lesions had spread to involve the tongue and the patient was referred to oral medicine where another biopsy was taken which suggested pemphigus foliaceus. Systemic treatment was commenced. The patient also has psoriasis managed with systemic medication. We present a case of pemphigus which may represent oral pemphigus foliaceus.

Conclusions: This may be a rare case of oral pemphigus foliaceus, but the management was the same as for oral pemphigus vulgaris.

Relevance: Despite the uncertain diagnosis management does not change. The patient responded to systemic immunosuppressant treatment despite the unusual clinical and histopathological appearance of the oral lesions.

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Paraneoplastic pemphigus with clinical features of erosive lichen planus associated with Castleman's disease: the first case from the UK

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Introduction: Castleman disease (CD) is a rare lymphoproliferative disorder. Paraneoplastic pemphigus (PNP) is an autoimmune mucocutaneous disorder associated with neoplasms of lymphocytic origin, including CD. Castleman's disease has been found in approximately 10% of PNP patients frequently with lichen planus-like features.

Details: In July 2007 a 54 years old lady with a previous diagnosis of oral lichen planus (OLP) was urgently referred because of extensive oral ulcerations. A diagnosis of erosive OLP was made and systemic treatment with Prednisolone (30 mg/day) resolved the lesions within a month. In September 2007 during steroid tapering a dramatic exacerbation was seen with the appearance of new oral erosions accompanied by an erythematous skin rash mainly evident on the legs, cicatricial alopecia and nails lesions. Direct immunofluorescence studies were equivocal, however, indirect immunofluorescence demonstrated intercellular binding at a dilution of 1:160 consistent with

pemphigus vulgaris (PV). Desmoglein 1 and 3 ELISA were both negative while two skin biopsies suggested a lichenoid inflammation. The prednisolone was increased to 100 mg/daily. Azathioprine was added and the dose of prednisolone was tapered but at this time a CD4 lymphopenia was noted. The patient was HIV negative, and the lymphopenia was not considered worthy of further investigation. Over the next 18 months the patient was treated with intravenous immunoglobulins, micophenolate mofetil, hydroxychloroquine sulphate, dapsone and finally systemic cyclosporine that cleared up most of the skin and oral complaint. Because of the possible diagnosis of PNP, a CT scan was arranged that revealed a solitary mediastinal mass located between the ascending aorta and the right pulmonary artery. Given the position, a complete primary surgical excision was performed. Histology demonstrated the morphological features of the hyaline vascular variant of CD. The patient had an uneventful post-operative recovery, and an impressive improvement of the oral and skin lesions was seen.

Conclusions: CD is an extremely rare disorder, but its association with PNP is not uncommon.

Relevance: This is the first case described in a patient from the UK.

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Differential outcomes of two patients presenting with laminin 5 mucous membrane pemphigoid

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Introduction: Mucous membrane pemphigoid (MMP) is an autoimmune subepithelial blistering disease that occurs predominantly in the mucous membranes, and which has a propensity for scarring and tissue destruction. One of the sub-categories of this condition is laminin 5 MMP (L5-MMP). Published literature has suggested that L5-MMP has an increased relative risk for malignant tumours. Egan et al cohort concluded that of those patients with L5-MMP 28.6% had solid cancers and a relative risk for malignancy of 6.8. This condition has also been reported as carrying a high mortality rate especially in those individuals who develop a solid cancer at the time of blistering. We report 2 cases of L5-MMP and its initial investigations and continual management.

Details: We present two patients that were referred to the Guys Oral Medicine Department for persistent oral ulceration. Immunofluorescences for both showed staining to base and were subsequently diagnosed with L5-MMP. Interestingly Case 1, a 69 year old female had no cutaneous, genital or ocular involvement. An elevated carcinoembryonic antigen led to further investigation and evidence of colonic carcinoma with liver metastases. Case 2, a 46 year old male however did have extensive cutaneous involvement and currently no evidence of malignancy.

Conclusions: The mechanism underlying the association of L5-MMP and cancer is not fully understood, but there is emerging evidence that laminin 5 expression in cancer cells promotes their growth, invasion and metastasis. Hence patients who present with a positive L5-MMP should be carefully checked and screening for internal malignancies should be performed.

Relevance: Clinicians who manage patients presenting with bullous disease should be aware of the diagnosis of L5-MMP. Upon positive diagnosis the clinician should immediately attract their attention to screening for a malignancy and therefore investigate the patient appropriately. The presented cases also show the difficulty and complexity in managing such patients.

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Oral Pemphigus vulgaris: a case report

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Introduction: Pemphigus vulgaris (PV) is part of a group of autoimmune blistering dermatologic condition and sometimes causes chronic ulceration of the oral mucosa. The fact that blisters on the oral mucosa are sometimes the first manifestation of the disease implies that dental professionals must be sufficiently familiarized with the PV to ensure early diagnosis and treatment.

Details: A 27-year-old Brazilian woman was referred to the Oral Lesions Clinic of the Department of Oral Pathology, University of Fortaleza, School of Dentistry with a two month history of painful ulceration on her tongue. On intra-oral examination, ulcers were observed on the cheek, both lower and upper lip, floor of the mouth and gingiva. On extra-oral examination she had some skin lesions. Nikolsky's sign was positive and clinical diagnosis of PV was made. Incisional biopsy was performed and the diagnosis of PV was confirmed. Histological findings were characterized by suprabasilar cleft with Tzanck cells and mild inflammation in the underlying connective tissue. Initially, for a period of 10 days, 60mg prednisolone once daily was prescribed to the patient. Prednisolone was decreased by 10 mg in the following week. On the 17 days follow up, almost all of the lesions had healed. At the end of 9th week, prednisolone was decreased to 20 mg daily. We referred the patient to the clinical dermatologic public center but she could not be evaluated. In the examination after 01 year of treatment, the ventral

surface of the tongue had healed without scarring, but she was not taking the prednisone and small lesions on the cheek, gingival and labial mucosa was present again.

Conclusions: PV is an uncommon cause of chronic ulcerations in oral mucosa.

Relevance: PV has great relevance for dentists, since 50% of the patients with this disorder present the first clinical sign in the oral cavity.

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First-line combination treatment for oral pemphigus vulgaris: A case report

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Introduction: Pemphigus vulgaris (PV) is a relatively uncommon autoimmune mucocutaneous blistering disease. Oral lesions may precede skin involvement for several months and present as blisters that rupture to form persistent ulcers, as well as desquamative gingivitis. Treatment of choice is the use of systemic corticosteroids, ideally in combination with other steroid sparing immunosuppressive drugs.

Details: A 46 year old male presented complaining of numerous painful ulcers in his oral cavity for the past 7 months. The condition began as a solitary ulcerative area of the retromolar mucosa, for which the patient had originally received a clinical diagnosis of squamous cell carcinoma. A biopsy had been performed excluding malignancy but failing to render a final diagnosis. Clinical examination in our clinic revealed several ulcerative lesions throughout the oral mucosa, along with redness of both eyes, nasal mucosal and genital ulcerations. An incisional biopsy and light microscopic and direct immunofluorescence examination confirmed the diagnosis of PV. The patient was initially treated with systemic corticosteroids (Prednisolone 50mg daily) plus immunosuppressant (Mycophenolate mofetil 500 mg daily). In four weeks, the patient presented with an improved clinical appearance and symptomatology; however, development of candidiasis was noticed and systemic antifungal medication was administered. After four weeks, there was significant clinical improvement with only residual oral mucosal lesions, but a duplication of the liver enzymes was recorded. Continuation and progressive tapering of the steroid treatment along with gradual replacement of mycophenolate mofetil by azathioprine was initiated. The patient remains under close observation.

Conclusions: PV treatment, especially management of the frequently persistent oral lesions, demands experience and flexibility for adjustments according to the clinical response and the potential side effects. Close follow-up is required.

Relevance: Knowledge of the efficacy and side effects of the available combination schemes is necessary for adequate management of oral PV.

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Childhood oral mucous membrane pemphigoid: a case report

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Background: Mucous membrane pemphigoid (MMP) is an autoimmune disease characterized by chronic vesiculo-bullous eruptions, predominantly on mucous membranes (oral, ocular, urogenital, anal, nasopharyngeal, oesophageal and/or laryngeal) and may cause serious complications, such as blindness due to scars formation. MMP occurs mostly in elderly people with an average age of 60 years and it is uncommon in children under 20 years of age. There are only 19 cases reported so far in the English literature.

Case report: We present a 13-year-old girl who presented gingival bleeding, pain, eating difficulty and peeling of the gum 16 months ago. Clinical examination revealed desquamative gingivitis. The diagnosis was confirmed by histological and direct immunofluorescence findings. Symptoms resolved on treatment with occlusive topical corticosteroids.

Conclusion: Because of the rareness of MMP in children, delayed diagnosis and treatment have been shown in most cases reported. Desquamative gingivitis is usually the first presentation of oral MMP in childhood and must be considered in differential diagnosis. Occlusive therapy with topical corticoids is particularly recommended in children because has fewer side effects systemic corticoids or dapsone.

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Successful steroid therapy of Stevens Johnson syndrome with oral manifestations

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Introduction: Stevens-Johnson syndrome (SJS) is a disease with typical skin and mucosal manifestation. Red, brick-like efflorescence with blister in the centre, a so

called iris lesion, is characteristic for the illness. Although etiology has not been fully elucidated, several studies have pointed out the important role of soluble Fas ligand mediated apoptosis, clonal expansion of cytotoxic CD8⁺ T lymphocytes, and TNF- α during development of the disease. SJS is mostly induced by external factors, e.g. various drugs (sulfonamide, phenobarbital, carbamazepine, rituximab, and others), or infections (*Herpes simplex*, *Mycoplasma pneumoniae*, and others).

Details: A nineteen-year-old patient was examined at the Department of Periodontology for hemorrhagic crusts on lips, erosions with exudation on both buccal mucosa, and an edematous tongue. Hypersalivation and severe pain were present. After two days skin efflorescence on knees, back and glans penis erupted. Patient was treated at the Clinic of Dentistry and 1st Clinic of Dermatovenereology. Steroid therapy improved and stabilized SJS disease in the patient.

Conclusion: Interdisciplinary approach to the treatment in specialized centres is highly recommended.

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Chronic macrocheilia associated with complex aphthosis - a rare entity

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Introduction: Macrocheilia is a multifactorial and disabling symptom, often posing a diagnostic and therapeutic challenge. A patient with the uncommon association of chronic lower lip swelling and complex aphthosis is presented.

Details: A healthy 23-year-old Chinese male presented with an asymptomatic non-fluctuating lower lip swelling associated with a history of painful recurrent oral ulcers since age 8. These were accompanied by occasional genital ulcers without any ulcer-free period. Examination showed a soft, everted and oedematous lower lip with multiple small aphthous ulcers on the lower labial mucosa. No mucous exudates were expressed on palpation of the lower lip. The rest of the oral mucosa and skin was normal.

A diagnosis of complex aphthosis was made based on the above. Differential diagnoses for the lip swelling included orofacial granulomatosis, sarcoidosis, Crohn's disease, cheilitis glandularis and chronic infections like tuberculosis or leprosy.

Two biopsies of the oral cavity were performed. The first biopsy of an oral ulcer showed non-specific ulceration. A second biopsy of the swollen lower lip revealed non-keratinising stratified squamous epithelium with prominent vascular ectasia and a dense superficial and deep perivascular infiltrate of plasma cells and lymphocytes. No granulomas or features of cheilitis glandularis were present. Herpes culture of the oral ulcers was negative. The patient declined further haematologic screening for recurrent aphthous ulcers. The lip swelling was attributed to chronic inflammation from the recurrent oral ulcers.

The oral ulcers responded well to colchicine. The patient declined further treatment for the persistent lip swelling.

Conclusions: Macrocheilia presents a challenging clinical problem that affects one's quality of life. Common causes include infection, inflammatory processes, post-traumatic swelling, malignancy and developmental disorders. Some cases are idiopathic. This case illustrates that chronic inflammation from recurrent oral aphthous ulcers can result in macrocheilia.

Relevance: This case report highlights the approach to macrocheilia and the rare association of recurrent aphthous ulcers and chronic lip oedema.

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Cluster headache: Report of a case

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Introduction: Cluster headache is a rare form of primary headache affecting predominantly males, characterized by short-lasting attacks (20-180 minutes) of excruciating unilateral periorbital pain. The frequency of attacks of headache varies from 1 every other day to 8 times per day. The attacks are accompanied by ipsilateral autonomic signs, such as conjunctival injection and lacrimation, nasal congestion and/or rhinorrhea, forehead sweating, eyelid oedema, ptosis and miosis. There are periods of headache attacks lasting for several weeks or months with pain-free intervals of weeks, months or years. The objective of this work is to present a case of cluster headache and to overview its treatment and differential diagnosis from other headache disorders.

Details: A 66-year-old male presented with a 10 days history of intense headache attacks. Headache attacks were lasting for 30 minutes and were characterized by excruciating left unilateral periorbital pain, accompanied by photophobia, echophobia and unilateral left nasal congestion and rhinorrhea. The patient had 2 headache attacks per day occurring at midday and during night interrupting sleep. He reported a history of similar headache attacks which occurred 10 years before and lasted for a few weeks. Cluster headache was diagnosed on the basis of history and symptomatology. The patient was treated with sumatriptan, prednisolone and verapamil. His symptoms ended 48 hours after the initiation of treatment.

Conclusions: Cluster headache is a rare form of headache with a characteristic unilateral occurrence and accompanying autonomic signs and should be considered in the differential diagnosis of intense headaches.

Relevance: Oral medicine practitioners dealing with orofacial pain disorders should be aware of the diagnosis and management of this rare type of primary headache.

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Not all episodic unilateral facial pain is trigeminal neuralgia

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Introduction: All patients with facial pain need to have a careful history taken. More than one facial pain may be present at any one time. One needs to be open to changing the diagnosis when more facts become apparent.

Details: Sixty one year old female was referred by the oral surgeons after she had failed to get complete relief of pain on her medications. She had first developed pain three years previously. It was strictly unilateral on the left side affecting maxillary and mandibular divisions. She would get two or three episodes of pain a day each lasting at the most 2 minutes. The pain was sharp and shooting of moderate severity and provoked by light touch activities. There was also a background pain over the same area which was more aching and constant. The episodic pain was associated with rhinorrhea, aural fullness, eyelid oedema, hot, phonophobia and photophobia. It responded well to carbamazepine but better to lamotrigine. She gave a history of episodic migraine.

Conclusions: Re-evaluation of the history made it possible to reject the diagnosis of trigeminal neuralgia and to institute appropriate treatment and avoid surgical interventions.

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A case of pyostomatitis vegetans associated with ulcerative colitis

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Introduction: Pyostomatitis vegetans (PV) is a rare oral disorder often associated with gastrointestinal and/or cutaneous diseases. PV is characterized by multiple pustules on an erythematous base. It is now generally accepted that most cases of PV are associated with inflammatory bowel disease (IBD), mainly ulcerative colitis (UC). The aetiology of PV is unknown. Management of PV consists mainly of topical or systemic corticosteroids, with medical and/or surgical treatment of any IBD.

Details: A 19-year-old female patient presented with mucosal lesions in oral cavity. She had been diagnosed with ulcerative colitis (UC) 3 years previously, and her condition was acceptably controlled with mesalazine. She developed oral lesions showing necrotic yellowish "plugs" and corrugated sloughing mucosal tissues. The histopathological features were suggestive of PV. DIF and IIF investigations were negative. Gastroenterology (GE) suspected that the oral lesions might have been due to adverse reaction to mesalazine and ordered a one week drug holiday, including topical steroid spray. GE switched mesalazine with mesalamin and introduced Decortin 30mg for treatment of the UC. Eight weeks later lesions expanded onto the lips and soft palate. In the meantime, GE tapered Decortin to 20mg. As her condition worsened further, she developed crusting lesions on her scalp, right retroauricular region. She was admitted to hospital and received antibiotics i.v. The patient was seen by a dermatologist who corroborated our original idea that we are dealing with extraintestinal manifestations of UC. We suggested 60mg prednisone for 14 days, followed by 40mg for next 14 days. This regimen was accepted by GE and one month later her condition finally started showing marked improvement.

Conclusions: This was a case of PV that became secondarily infected, most probably because of systemic steroids that were prescribed in a dose not sufficient to control UC, and yet sufficient for immunosuppression.

Relevance: This case contributes greatly to widen knowledge about this rare disease.

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A liver transplanted child with immunological features of orofacial granulomatosis and adverse food reactions

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Objectives: The objectives with this case presentation of a pediatric liver transplanted (PLT) patient were to characterise the inflammatory infiltrate of the oral mucosal lesion and to examine the immune status of peripheral blood cells, phenotypically by flow cytometric analysis and functionally by testing the reactivity of CD4⁺ T cells and Tregs towards food allergens *in vitro*.

Methods: Oral mucosal biopsies and blood were collected under general anaesthesia from a liver transplanted 10-year-old boy. The following primary antibodies were used for immunohistochemistry: goat antihuman CD1a, CD3, CD4, CD8, CD20. Flow

cytometry was used to assess the percentage of CD4⁺ T cells, activated CD4⁺ T cells expressing HLA-DR, naive CD4⁺ T cells being CD45RA⁺/RO^{neg} and putative CD4⁺ Tregs, expressing FoxP3. CD4⁺ T cells were isolated and stimulated with 100 mg/l well of food allergens (codfish, oat, albumen, peanut, rye and OVA). CD4⁺CD25⁺ T cells were removed from the CD4⁺ T cell fraction prior to stimulation with food allergens, to investigate the functionality of putative Tregs.

Results: In the oral mucosal ridges of the PLT patient, a substantial infiltrate of CD20 expressing dendritic cells was observed. The patient had lower number of FoxP3⁺ Tregs and higher number of activated CD4⁺HLA-DR⁺ T cells in the blood, compared to controls. The putative Tregs were functional i.e. had suppressive capacity, since removal of CD4⁺CD25⁺ (expressing FoxP3) led to increased proliferation towards certain food allergens. The T cell reactivity towards food allergens correlated well with observed reactivity from patient patch test.

Conclusions: This PLT patient presented with an inflammatory infiltrate similar to what has been reported for OFG patients. These results also underscore that food hypersensitivity may be associated with oral granulomatous-like lesions observed in PLT patients.

Relevance: This research may lead to a better understanding of the common denominator of OFG and PLT patients.

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Allergic reaction to azithromycin-a case report

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Introduction: Macrolides are considered the safest group of antibiotics, with a very low prevalence of allergic reactions (0.4-3%). Azithromycin, one of the macrolide antibiotics, has several unique pharmacokinetic properties that provide short-course therapeutic regimens due to its long elimination half-life (over 40 h) and wide antibacterial spectrum. We present a case report of a young patient who developed a bullous eruption on oral labial and buccal mucosa and lips after ingestion of the third dose of azithromycin.

Details: A 13,5-year-old boy presenting with intra-oral pain and a bullous eruption on the labial mucosa which had occurred overnight, was referred to our Department by the dermatologist. No cutaneous lesions were present.

Conclusions: After taking steroid therapy, lesions started to regress. However on the fourth day, a new bullous eruption appeared on labial mucosa with lower intensity. This could be explained by the finding that azithromycin has a long plasma half-life and is detectable in neutrophil lysates 28 days after the last dose, resulting in a higher risk of adverse effects. Diagnosis was based on the past medical history, family history and clinical appearance.

Relevance: To our knowledge and according to the available literature, this is the first described case of an oral eruption after azithromycin treatment. In spite of the fact that azithromycin remains one of the best tolerated macrolides, potentially severe adverse reactions may sometimes occur.

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Oromandibular dystonia as psychosomatic disorder following botulinum toxin A injection

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Introduction: Oromandibular dystonia (OMD) is a form of focal and/or segmental dystonia that affects the orofacial region and involves the jaw openers, tongue, facial, and platysma muscles. Botulinum toxin A (BTX) is commonly used for treatment of OMD but requires repetitive injections due to its short action.

Details: A patient with dysmimesis and dysarthria of more than one year was referred to our hospital for diagnosis and treatment. The symptoms were induced and worsened under stressful conditions. She was diagnosed OMD as psychosomatic disorder, and received oral medications, including muscle relaxant, and psychosomatic therapy (client-centered psychotherapy), but showed no improvement. A single low-dose BTX (10-units) injected intramuscularly into the both masseter muscles resulted in amelioration of symptoms over a period of more than two years. This is in contrast to the reported shorter clinical effect of BTX of about only 3-4 months.

Conclusions: In this case, a single low-dose BTX seems to have improved the symptoms of OMD when combined with psychosomatic therapy and medication. While oral medication is the first choice treatment for OMD, the next choice is BTX muscle injection, which should be used as soon as possible, preferably within 1 year of development of symptoms. But a lack of understanding of the OMD by dentists can also prolong the suffering of patients. Patients with OMD often visit dentists first because the initial symptoms appear in the maxillary-facial region.

Therefore, including OMD in the dental school oral medicine curriculum would be beneficial.

Relevance: The following criteria define psychosomatic disorders (Psychother Psychosom 1995, 63:112-123): 1) Psychological or behavioral influences are thought to play a major part in the aetiology of physical disorders. 2) These mental disturbances are usually mild, non-diagnostic and often prolonged (such as worry, emotional conflict, and apprehension), and are not themselves listed in the ICD-9.

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Cocaine related oronasal communication : A series of four cases

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Introduction: Cocaine is an illegal substance of abuse that is absorbed through the mucosal membranes. It exerts sympathomimetic activity at central nervous system level, since it inhibits presynaptic catecholamine and serotonin reuptake. Contact with the nasal mucosa can cause congestion, epistaxis, erosion and destruction of the nasal septum. Four cases of medio-palatal perforation in cocaine's users are presented.

Details: Patients came to stomatologists because of the inconveniences caused by oronasal communication. Their cases were studied, diagnosed and treated. Histopathology in two of the four cases did not reveal any evidence of vasculitis or of active cocaine consumption. Treatments performed were reconstructive surgery and/or sealing prostheses.

Conclusions: The documented consequences of intranasal cocaine abuse include lesions in different zones of the digestive and respiratory mucosal membranes, such as irritation and dryness of the oral and nasal mucosa, destruction of the nasal septum and, more rarely, perforation or destruction of the midzone of the hard palate, giving rise to oronasal communication.

Relevance: The assessment of the biopsy of the area from the edge of the oronasal communication (vasoconstriction, vasculitis, infarction and polynuclear cell infiltration areas and neural hyperplasia) could be useful in revealing the persistence of active addiction and also as a complementary tool to plan a possible surgical or prosthetic lesion's restoration. From the management perspective, while the ideal treatment of such cocaine-induced perforations is surgical reconstruction, failure due to flap or graft necrosis secondary to continued drug abuse is common. An alternative in such cases would be the fitting of a sealing prosthesis.

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Imatinib associated oral hyperpigmentation and horizontal melanonychia

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Introduction: Imatinib is a tyrosine kinase inhibitor used in the management of chronic myeloid leukaemia (CML) and gastro-intestinal stromal tumours. Little is known about the ability of Imatinib to induce pigmentation of the oral mucosa. This report illustrates such a case.

Details: A 48-year-old Caucasian male was referred by his dentist regarding asymptomatic palatal discoloration thought to be ecchymosis due to a history of CML. The patient had received Imatinib (Gleevec®) for 9 years following a sibling allograft bone marrow transplant. Clinical examination showed extensive, ill-defined, grey discoloration of the mucosa of his hard palate and horizontal melanonychia of his toe nails. The finger nails were spared. A palatal punch biopsy was undertaken. Histopathological examination showed prominent accumulation of pigment granules, stained similarly to melanin, within stromal cells of the lamina propria. Increased numbers of melanocytes, hyperpigmentation of basal keratinocytes, haemosiderin and inflammation were not seen.

Conclusions: Although oral lichenoid reactions attributable to Imatinib have been described, the oral mucosal pigmentation induced by this drug should not be regarded as post-inflammatory and is effected by accumulation of melanin-like material in stromal cells.

Relevance: Clinicians should be aware of this rare phenomenon whilst managing patients treated with Imatinib.

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Traditional Chinese medicine for treating orofacial localized scleroderma

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Introduction: Scleroderma is a connective tissue disease characterized by thickening or hardening of the skin and fibrosis of the involved tissues. Scleroderma affecting only

the oral mucosa and adjacent skin is very rare. We present two cases with localized scleroderma that were treated with traditional Chinese medicine.

Details: One patient received oral *Salvia miltiorrhiza* and topical Asiaticoside, and the other only took oral *Salvia miltiorrhiza*. At 9-month follow-up, the patient treated with combined medication demonstrated remarkable reduction in the size and hypopigmentation of the lesion. Patient treated only with *Salvia miltiorrhiza* showed softening and mild lightening of the lesion, but the size remained unchanged.

Conclusions: *Salvia miltiorrhiza* together with Asiaticoside may represent a valid and safe alternative for treating localized scleroderma. Further randomized controlled studies are warranted to optimize the therapeutic approach to this rare condition.

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Recurrent multiple oral warts treated successfully with systemic cidofovir

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Introduction: The development of human papilloma virus (HPV) induced multiple oral warts (MOW) in the oral cavity and perioral region that recur upon surgical excision may present a significant management challenge. Cidofovir has antiviral activity against HPV. Systemically administered cidofovir has been used successfully in the treatment of respiratory papillomatosis. A literature search using pubmed failed to reveal any reports of systemically administered cidofovir employed successfully in the treatment of recurrent HPV-induced MOW.

Details: A 37-year-old male Caucasian patient was referred to the Oral Medicine Department, Newcastle Dental Hospital for a second opinion with regard to the management of MOW. The patient had undergone surgical excision of multiple papillomata present intraorally and periorally which then recurred completely. Histopathological examination confirmed that these lesions were HPV-induced MOW. As surgery had caused significant postoperative discomfort and subsequently failed, he was keen to discuss medical management. His medical history was significant and relevant in that he had chronic sarcoidosis which had been treated with high dose prednisolone over several months. Clinical examination of the head and neck and intraorally revealed warts in a perioral and oral distribution. His immunological parameters indicated systemic immunosuppression. Following case conference and referral to the Infectious Disease Department, Royal Victoria Infirmary, he received 4 courses of intravenous cidofovir at monthly intervals.

The treatment outcome was favourable with a 75% lesion reduction at 6 months post-treatment with no drug induced complications noted.

Conclusions: This case indicates that systemic cidofovir therapy was a safe and effective therapeutic option in the management of recurrent HPV-induced MOW.

Relevance: Recurrent HPV-induced MOW may present a significant management challenge. Systemic treatment with cidofovir should be considered as a potential therapeutic option however further studies are needed to demonstrate conclusively its efficacy and safety.

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Coronal osseous dysplasia and complex odontoma around an impacted third molar

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Introduction: Osseous dysplasia (OD) is the most common fibro-osseous lesion of the tooth-bearing area of the jaws. It is located periapically and characterized by non-encapsulated cellular fibrous tissue with foci of bone or cementum-like material. According to the latest classification by the World Health Organization, OD occurs in four clinical forms: periapical osseous dysplasia, focal osseous dysplasia, florid osseous dysplasia and familial gigantiform cementoma.

We report an unusual case of coronal OD in an impacted third molar tooth that was associated with a complex odontoma (CO).

Details: A 36-year old female presented with odontalgia of the upper second premolar and first molar. Radiographic examination revealed, apart from the features relevant to these teeth, a mixed radiolucent - radiopaque lesion at the coronal and distal site of the impacted lower left third molar. The lesion was totally excised along with the impacted third molar and adjacent second molar. Microscopic examination revealed a lesion with features of OD coronally and CO at the distal site of the impacted molar.

Conclusions: To our knowledge, there is one case report of an OD around an impacted upper canine and an ipsilateral impacted upper third molar in the same patient, the latter associated with an irregular dental structure, consistent with an odontome and dentigerous cyst. A fibro-osseous lesion diagnosed as an ossifying fibroma around an erupted ectopic molar has also been described.

Relevance: Although OD is classically considered to originate from the periodontal ligament, residual dental follicle may be also be involved in its pathogenesis.

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Localized tongue amyloidosis in a patient with Neurofibromatosis type II

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Introduction: In this presentation, a case of localized amyloidosis (AL) in a patient with Neurofibromatosis type II (NF2) is described. Amyloidosis is a rare disease, resulting from amyloid fibrils deposited locally or systematically. Oral mucosa is usually affected secondary to systemic AL, while localized involvement is rare. NF2 is caused by chr22q abnormalities and characterized by multiple schwannomas, meningiomas, gliomas of cranial/spinal nerves.

Details: A 30-year-old female patient with NF2 and mental retardation presented with a painless, nodular mass on the dorsum of the tongue covered by normal mucosa. The onset/duration of the lesion was unclear. Family history was negative for congenital malformations. Karyotype analysis revealed the presence of ring chromosome 22 or its loss (mosaicism). Imaging and histopathology showed spinal (thoracic) and cranial (cerebellum/parietal) meningiomas, schwannomas (orbital/inner ear), and accompanied unilateral blindness/deafness.

The initial differential diagnosis of tongue lesion included tumours, median rhomboid glossitis, or multiple neurofibromatosis. However, the histologic examination revealed amorphous, fibrillary, multinodular, depositions, positive to Congo-Red staining. The complete blood examination revealed mild anaemia and increased Thyroxine T4 due to multinodular colloid goiter of the thyroid, normal values for κ and λ chains, immunoglobulins, electrolytes, creatinine/urea, protein electrophoresis, and absence of pathognomic autoantibodies and immunocomplexes. Bence-Jones protein was not detected in urine as well. Imaging of kidneys, heart, liver and spleen was also normal. The absence of organ or hematologic pathology in this patient with NF2 suggested the diagnosis of localized tongue AL.

Conclusions: Oral mucosa examination should be included in cases of neurocutaneous diseases. Also, oral manifestations can be the only sign of AL with better prognosis, but a careful follow up is necessary.

Relevance: To our knowledge this is the first case with synchronous presence of localized oral AL and NF2. Further genetic investigation is needed for the direct association between these entities.

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Tongue Lipomatosis: A Case Report

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Introduction: Lipomata are benign tumours of fat and when found in the oral cavity they most commonly present as a solitary asymptomatic nodule of the buccal mucosa or vestibule.

Details: In 2009, a 66-year-old Caucasian male presented to New York University College of Dentistry complaining of progressive asymmetric tongue enlargement. Medical history was pertinent for hypertension, type 2 diabetes, atherosclerosis, aortic valve insufficiency, hypercholesterolemia, hyperthyroidism, gastro-oesophageal reflux, sleep disturbance and a past history of bladder cancer and cardiac bypass surgery. Medications included ramipril, metoprolol, amlodopine, insulin, simvastatin, fenofibrate, methimazole, pantoprazole, aspirin, and zolpidem. He reported a past 30 pack year cigarette history, and current <14 drinks/week alcohol history. He reported neither dysphagia, dysarthria, nor dyspnoea. There were no extra-oral findings, and intra-oral examination revealed macroglossia confined to the oral tongue, normal mucosa, and a bilateral yellowish multinodular submucosal appearance. A differential diagnosis included lipomatosis and amyloidosis. Submucosal lobulated adipose tissue sprung out during incisional biopsy, and histopathology was consistent with lipoma without any capsule. The patient elected not to undergo surgical excision and is currently under surveillance.

Conclusions: The history and histopathologic features suggest an unusual and rare presentation of Madelung's disease (bilateral symmetric lipomatosis), often associated with diabetes and excessive alcohol intake.

Relevance: Lipomatosis of the tongue is rare condition.

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Low-Level Laser Therapy in Bisphosphonate-Related Osteonecrosis of the Jaws – A Case Report

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Introduction: Bisphosphonates are standard of care in the treatment of metastatic bone disease in women with breast cancer and are also used to prevent and treat therapy-

induced osteoporosis in the adjuvant setting. Osteonecrosis of the jaw (ONJ) is a major complication associated with long-term use of Bisphosphonates. It is defined as exposure of mandibular and/or maxillary bone, which shows no tendency of healing for at least 8 weeks after diagnoses by a health care professional, often associated with the development of mucositis and abscesses. Treatment of ONJ is a complex procedure and it includes antibiotics and surgical debridement. But the results are still controversial. Its treatment is a challenge for oral and maxillofacial surgeons, dentists, oral pathologists and oncologists. Low-level laser therapy (LLLT) with diode laser have been reported for bio stimulation in the treatment of ONJ.

Details: We describe our experience of LLLT with diode laser of ONJ of a 44 year old woman who was treated with zoledronic acid for multiple bone metastasis. She was operated 13 years ago because of breast cancer, however, multiple bone metastasis were diagnosed two years ago in her clavicles, pelvis and cervical vertebrae. Her complaints were pain, swelling and paresthesia in her left lower lip. According to the intraoral and radiographic examinations and symptoms of the patient, ONJ was described as Stage 0 which includes patients exposed to Bisphosphonate and who present with non-specific symptoms or clinical and radiographic abnormalities. LLLT with diode laser two times a week, in addition to antibiotherapy was applied during a six month period. Clinical symptoms such as pain, swelling and paresthesia were completely healed. She had no signs or symptoms of ONJ since then.

Conclusions: The effectiveness of LLLT with diode laser in ONJ was presented in this report.

Relevance: LLLT with diode laser can be considered as a useful method for the treatment of ONJ. Further, more independent studies analyzing LLLT usage for ONJ treatment and the value and its comparisons with other methods are necessary.

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Surgical laser application in BRONJ treatment: A 15 Months follow-up study

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Introduction: Bisphosphonate related osteonecrosis of the jaws (BRONJ) is a rare but often severe adverse effect of a high- dosage and long-term BP therapy.

Recommendations for the treatment of BRONJ range from a strictly conservative management(1,2) to extended surgical interventions up to entire jaw resections and subsequent reconstruction(3,4).

Nevertheless, all regimes are associated with a high incidence of recurrence of clinically apparent necrosis and progression of disease.

Application of a hard laser for debridement of necrotic bone seems to be an efficient technique(5).

Details: Between October 2008 and March 2009 five cases of BRONJ (stage 1 and 2) were treated with surgical laser application (ErCrYSGG-Laser, 2780nm, H mode [bone ablation]: 6W, 30% water, 70% air, 30 pps, 1mm distance). The aim was to achieve a stable mucosal closure.

A stable mucosal coverage could be reached in all five cases. No case of recurrence of clinically apparent necrosis over a 15 months recall time-period was observed.

Conclusions: Laser surgery can be considered a promising technique for the effective treatment of BRONJ.

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Ectopic thyroid in submandibular and sublingual region: report of a case

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Introduction: Ectopic thyroid is defined as thyroid cells that are located at sites other than anterior or lateral to the second, third, and fourth tracheal rings. Seventy percent of patients with displaced thyroid, lack thyroid tissue at its normal anatomical location and this ectopic tissue is prone to functional insufficiency and may come to attention only after compensatory enlargement. Because most of the time there is no other functioning thyroid tissue, the removal of ectopic thyroid frequently is followed by severe hypothyroidism.

Details: We introduce a 31 year-old female with a firm, nontender mass with smooth surface, mildly mobile mass in both left submandibular and sublingual regions with extensions to the right side. She did not have eutopic thyroid tissue.

Conclusions: No treatment is required for a patient with a lingual and sublingual thyroid or parathyroid glands. A hypothyroid patient with obstructive symptoms is best managed with hormone replacement therapy, which induces glandular shrinkage. If obstructive symptoms can not be relieved, then excision is required and, if it is the only thyroid tissue, the patient will require lifelong hormone replacement therapy.

Relevance: Ectopic thyroid should be considered in the differential diagnosis of sublingual masses.

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Pyostomatitis vegetans. Report of a case and review of the literature

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Introduction: Pyostomatitis vegetans is a rare condition of unknown pathogenesis, usually considered a specific marker of idiopathic inflammatory bowel disease, in particular Crohn's disease. Since the introduction of the term by McCarthy in 1949, less than 60 cases have been reported in the literature. We present an additional case of pyostomatitis vegetans and review the pertinent literature.

Details: A 58-year-old male presented for diagnosis and treatment of "white lesions that looked like pus on the gingiva that peel off on tooth brushing. The lesions did not cause significant discomfort and did not respond to topical antifungal treatment prescribed for "thrush. His medical history was non-contributory.

Clinical examination showed yellow-white mucosal pustules on an erythematous base present on both lingual and buccal surfaces of the maxillary and mandibular gingiva, floor of mouth and palate. The lesions had the appearance of snail-tracks and bled lightly on scraping. With the working diagnosis of pyostomatitis vegetans a complete blood count was ordered that revealed anaemia, eosinophilia and increased ESR. Incisional biopsy from the maxillary gingiva was consistent with pyostomatitis vegetans. On further questioning the patient stated that a year ago he was investigated with colonoscopy, having blood in his faeces and was then diagnosed with "haemorrhoids, while he was suffering from frequent diarrhoeic episodes. Based on these findings, the patient was referred to a GI specialist for evaluation of idiopathic inflammatory bowel disease.

Conclusions: The correlation between PV and idiopathic inflammatory bowel diseases dictates thorough evaluation of these patients, taking into account that the GI symptoms can be subtle and difficult to diagnose.

Relevance: Evaluation and diagnosis of oral lesions may contribute to diagnosing systemic diseases.

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Idiopathic loss of deciduous teeth and associated alveolus

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Introduction: A case of unexplained loss of deciduous teeth and the associated alveolus is presented and discussed.

Details: A 5 year old boy presented with a three month history of gingival pain in the lower left dental quadrant together with spontaneous exfoliation of the lower left B. There was a recent history of non-specific ulcerative disease of this site that had lasted for approximately 10 days. There were no notable features in the medical and social histories. There was no history of recurrent infection, bruising or hypermobility.

Clinical examination revealed no cervical lymphadenopathy or facial swelling. Introrally there was mobility of the lower left CD and the associated alveolus. The surrounding soft tissues were mildly erythematous. Radiographic examination demonstrated possible bony sequestration of the labial aspect of the alveolus in the affected region. A full blood cell count revealed no neutropenia or lymphopenia.

A broad differential diagnosis was considered that included Langerhan's cell disease, premature tooth exfoliation, leukaemia and post-herpetic osteonecrosis.

Surgical removal of the mobile teeth and alveolus was performed and the area debrided. Post-operative healing was uncomplicated with complete resolution of painful symptoms. Histopathological examination revealed non-specific inflammation of the soft tissue and necrotic alveolar bone. At 6 weeks post-presentation no further oral disease was observed.

Conclusions: Spontaneous dental exfoliation and bony necrosis in a child is rare and diagnostically challenging.

Relevance: Sudden unexplained dental exfoliation and/or bony sequestration warrant rapid and detailed investigation. Factitious causes should be considered if there is no identifiable local or systemic causes.

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The management of Lesch-Nyhan syndrome – a case report

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Introduction: Lesch-Nyhan syndrome (LNS), first described in 1964 is a rare (prevalence 1 in 380,000), usually X-linked recessive disorder, resulting in deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT). Overproduction of uric acid, behavioural problems and neurological disability characterise the syndrome. Persistent and self-injurious behaviour pose difficult management issues.

Details: A 14 year old boy with LNS presented with a recent history of self-trauma to the right buccal mucosa. He takes allopurinol daily and is unusual for LNS in that he has a normal mental capacity. Dentally he is in the permanent dentition phase, is

caries-free and maintains good oral hygiene with assistance. The site of soft tissue trauma has varied with time. Previous management of LNS induced oral self injury has been extraction of the whole dentition. However in this case the provision of more than 20 different appliances, medical management of areas of trauma with antimicrobials and anti-inflammatory agents has prevented recurrence of the severe trauma previously inflicted.

Close liaison with the paediatric dental team, Oral Medicine specialist and technician has overcome the difficulties of providing appliances to this boy and prevented him becoming edentulous.

Conclusions: This resource intensive management plan will require life-long dental input but it is hoped that he will maintain an intact dentition whilst preventing further mucosal trauma.

Relevance: This case highlights that dental clearance is not the only option in the management of patients with LNS.

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Dental extractions in children with osteogenesis imperfecta managed with bisphosphonates

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Introduction: Osteogenesis imperfecta (OI) is a connective tissue disorder with a number of different types. Clinical features include bone fractures, blue sclerae and associated dentinogenesis imperfecta (DI). The latter often requires long-term specialist care secondary to increased dental need. Since the late 1990's bisphosphonates (BST) have been used in the management of OI. Osteonecrosis (ONJ) of the jaw has been reported in adults receiving BST. Existing literature on the dental implications of BST in paediatric patients is deficient and inconclusive.

Details: Five children attended the Department of Paediatric Dentistry at the Eastman Dental Hospital with OI on IV pamidronate requiring dental extraction. Age range 5-8 years, males:females 4:1. The duration of the BST treatment prior to extraction varied from 12 months to 6 years. Each patient had at least one dental extraction whilst receiving BST treatment. Three of the 5 had DI as well as OI. Four cases required general anaesthesia (GA), 1 local anaesthesia (LA), 1 had both GA then LA. There were no additional precautions/modifications carried out as advised by the multidisciplinary team involved in the care of these patients including antibiotic therapy. No patients had evidence of ONJ at 4 months - 60 months post-extraction.

Conclusions: There was no evidence of ONJ in this on-going case series. This may be related to a decreased dose of pamidronate compared to adults or increased vascularity in childhood.

Relevance: ONJ and bisphosphonates is a current, relevant topic and there is no established pathway to optimise dental treatment in paediatric patients. Guidelines based on an expanded case series are necessary to inform primary and secondary care.

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Bisphosphonate-related osteonecrosis of the jaw combined with jaw metastasis of prostate adenocarcinoma: A case presentation

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Introduction: It has been mentioned in the literature that osteonecrotic zones in patients under intravenous bisphosphonate therapy should be thoroughly investigated to exclude a potential distant metastasis or other bone pathology in the necrotic area. However, it has not been reported that an osteonecrotic zone of the jaws was actually diagnosed with a distant bone metastasis due to prostate cancer.

Details: The patient in the present case presentation had been under medical treatment with zoledronate (i.v.) for a prostate carcinoma with distant bone metastases throughout the skeleton including the skull for the past 4 years. No metastases had been documented in the jaws. Upon sequestrectomy of the bisphosphonate-related osteonecrosis of the jaw (BRONJ) in the region of teeth #17-19, the histopathologic examination of the removed bone revealed a metastasis from the known adenocarcinoma of the prostate in the specimen.

Conclusions: Routine bone biopsies for the diagnosis of BRONJ are not recommended in the literature. Furthermore, osteonecrosis of the jaw is not always caused by bisphosphonates: other conditions may also lead to bony necrosis, including systemic medication use (e.g., antiangiogenic drugs); radiation; bacterial, viral and deep fungal infection; direct chemical toxicity; trauma; and other aetiologies. Regarding these differential diagnoses for BRONJ and also the findings in the case presented, routine histopathologic analysis of all removed segments of bony sequestrum should be recommended.

Relevance: To the best of our knowledge, this case describing the manifestation of BRONJ in combination with distant bone metastasis of a prostate carcinoma is the first reported in the literature. To exclude potential distant metastasis in patients diagnosed

with BRONJ, analysis of all removed segments of bony sequestrum should be recommended. Whether to take an ex-/incisional biopsy in cancer patients suffering from BRONJ, or to take a more conservative approach without extensive removal of necrotic bone, should be carefully considered by the responsible surgeon.

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Lateral periodontal cysts in periapical sites: Report of two cases

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Introduction: Lateral periodontal cyst (LPC) is an uncommon developmental odontogenic cyst, which arises in the alveolar bone between or lateral to the roots of erupted teeth and constitute less than 1% of cystic jaw lesions. On rare occasions, odontogenic cysts with histological features of LPC may be identified in periapical sites, masquerading as a lesion of pulpal origin. We report two atypical LPC cases occurring in periapical sites.

Details: Case 1. A 70-year-old female attended the dental office. Examination disclosed an almost circular radiolucency with sclerotic borders involving the periapical areas of the left lateral incisor (non-vital) and canine (vital). Despite root canal therapy of the lateral incisor, the lesion persisted, necessitating surgical removal.

Case 2. A 52-year-old male presented with an asymptomatic intraosseous lesion apical to the mandibular right first and second premolars, which were vital. The lesion appeared as a well-circumscribed radiolucency with radiopaque margins. Surgical removal was performed.

Histopathologic assessment of each lesion was consistent with a LPC, revealing thin, non-keratinized epithelial lining containing focal thickenings and clear cells and minimal inflammation of the cyst wall.

Conclusions: The presented cases illustrate the fact that the lateral periodontal cyst may not always be confined to the interdental region and may masquerade as a periapical lesion of purported endodontic origin.

Relevance: LPCs should be always included in the differential diagnosis of periapical radiolucencies especially when the teeth are vital. An ectopic periapical location with or without coincidental pulpal necrosis and/or periodontal disease should not preclude the diagnosis of LPC.

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Meet the girls: A Case Report

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Introduction: Salivary Gland Aplasia (SGA) of one or more of the major salivary glands is an extremely rare autosomal dominant congenital abnormality. Even though the incidence is not well described, some reports suggest a M:F 2:1. Cases of familial SGA have been previously described. These are transmitted as complex, pleiotropic, autosomal dominant character with high penetrance with mutations in FGF10.

Details: A family of three sisters aged between 3 and 9 years were referred to the Oral Medicine Department at Birmingham Dental Hospital regarding intraoral dryness, recurrent parotitis and possible dental decay. On intraoral examination the major salivary gland ducts were difficult to detect in two of the girls. Diagnosis of SGA was confirmed following US and MRI scans.

Conclusions: The diagnosis of SGA is reached by the clinicopathological findings together with imaging studies such as US, CT and MRI scans. Severity of the clinical presentation depends on the number of salivary glands involved and their relative contribution to salivation. Therefore, as the condition does not always cause severe symptoms or clinical signs, underdiagnosis can occur.

Relevance: The aim of this presentation is to describe an unusual UK familial case of SGA and to discuss the prevention and management of the oral complications due to this rare condition.

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Unexplained thrombocytopenia as a cause for spontaneous gingival bleeding

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Introduction: Gingival bleeding is a common finding, typically associated with inflamed tissues and periodontal disease. Such haemorrhage is easily provoked by probing or brushing but rarely occurs spontaneously, suggesting an underlying haematological disorder, often thrombocytopenia. Spontaneous bleeding rarely occurs until platelet numbers fall below 30x106/ml. A new case of thrombocytopenia, first diagnosed in the Oral Medicine clinic, is presented.

Details: A 39 year old female was referred by her GDP with a 4 day history of spontaneous bleeding from her gingivae. At the time of her consultation she also complained of lethargy, malaise, loss of appetite resulting in unintentional weight loss of 12.5kg and a persistent cough, over the last 5 months.

Examination revealed a swollen lower lip with petechial haemorrhages and gingival spontaneous bleeding with exophytic areas of soft tissue hyperplasia anteriorly. Several pupurae were present in the mouth, particularly two large blood blisters on the left buccal mucosa.

A differential diagnosis of a platelet disorder, leukaemia or other coagulopathy was made and urgent haematological and coagulation screening investigations were ordered. Results reported platelets of $2 \times 10^6/\text{ml}$ and low haemoglobin. After 1 month, the patient remains admitted under investigation, for an underlying cause of her thrombocytopenia, having had a negative viral screen. Interestingly, a PET-CT scan has shown mediastinal and upper abdominal adenopathy suggesting lymphoma or more likely, sarcoidosis as an underlying cause.

Conclusions: Patients with serious medical problems may present first to the dental surgeon with oral symptoms. It is important that such cases are referred early for investigation, particularly with a mind to the likelihood of coagulopathy and its underlying causes as an explanation for gingival swelling and bleeding.

Relevance: Spontaneous gingival haemorrhage should be regarded as a suspicious sign but a premature biopsy can have the potential to cause significant problems until the coagulation status of the patient is known.

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First Report of New Oral Findings in a Case with Noonan Syndrome

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Introduction: Noonan syndrome was described in 1963 as a multisystem disorder characterized by short stature and low-set ears. Noonan syndrome is one of the most common autosomal dominant disorders seen in children with congenital heart disease (2-5). The disorder may be characterized by a wide spectrum of symptoms and physical features that vary greatly in range and severity. Affected individuals have distinctive facial features including hypertelorism, ptosis, flat nasal bridge, open bite, high arched palate, short neck, and often with chest, breast and spine deformity. Noonan syndrome

is difficult to be diagnosed by facial appearance alone. A mutation in the PTPN 11 gene has been reported in about 50% of individuals with Noonan syndrome. Noonan syndrome is relatively common with an estimated incidence of between 1 per 1000 and 1 per 2500 live birth.

Details: Medical History: A 19 yr old girl was admitted to the Oral Medicine Department of Dental Faculty, Tehran University of Medical Sciences in Iran. She had not been diagnosed as having Noonan syndrome by ten and family history was negative for any other similar cases. The patient has passed high school courses; no obvious sign of mental retardation was detected. At age 6 and 12 she underwent surgical operations for spine deformity. The patient referred by chief complaint about gingival bleeding and crowding of teeth especially in lower jaw. By an overall examination, clinical features compatible with what is now called Noonan syndrome were found. Physical examination revealed a short stature, low-set rotated ears, loss of intertragic notch, short broad neck, chest deformity, lack of breast growth, low-set breast position especially in right side, Kyphoscoliosis and clinodactyly of right hand. Facially the patient exhibited hypertelorism, ptosis, strabismus, sporadic freckle and nevi especially on forehead, protruded lower lip, small mandible, depressed chin, flat nasal bridge, tendency for exophthalmia associated with lowset hair line. Based on physical examination and consultation with audiologist, the patient did not suffer from hearing loss. The result of her Echo and Electrocardiography taken by the cardiologist, showed no sign of heart disease. Complete blood count and the blood biochemistry test revealed just light hypo chrome microcytic microcytic anemia. Oral examination revealed an anterior open bite, severe anterior gingival enlargement, dental crowding associated with diastema, tapered incisors, narrow high-arched palate and prominent rugae. Study casts of the jaws were prepared for examination. Tapered incisors and malocclusion, prominent rugae and high-arched palate were noticeable. On radiographic survey what we observed were a bilateral taurodontism on mandibular second molars, impaction of right maxillary canine and missing of left maxillary canine, and an idiopathic osteosclerosis between left maxillary first and second premolars area.

Conclusions: The high frequency of cardiac, ophthalmic, growth, orthopedic and oral manifestations associated with Noonan syndrome, emphasizes the need for early diagnosis.

Relevance: The present case was diagnosed as Noonan syndrome but the report describes some new oral manifestations including, bilateral taurodontism, missing canine and prominent. Based on what we found in the present case we believe that they can be related to Noonan syndrome and can be considered as other suggestive oral features of Noonan syndrome.

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