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Capnocytophaga in the dental plaque of immunocompromised children with cancer

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Summary. *Objectives.* (i) To compare the prevalence and levels of *Capnocytophaga*, a known systemic pathogen in immunocompromised patients, in the dental plaque of healthy children and children with cancer, and (ii) to determine the susceptibility of strains isolated from cancer patients to a range of antibiotics.

Patients and methods. Thirty-one children with cancer undergoing a first course of immunosuppressive chemotherapy and 30 healthy control children were included in the study. Samples were collected on days 0, 7, 14, and 21 of the cure (and equivalent dates in controls). Susceptibility to antibiotics was tested using an agar dilution method and galleries with predefined concentrations of selected antibiotics.

Results. There was a significant drop in the total anaerobic cultivable flora on day 14 and in the prevalence of *Capnocytophaga* on days 14 and 21 in the children with cancer. The proportion of *Capnocytophaga* in the anaerobic flora, however, was high in certain cancer patients. Beta-lactam/beta-lactamase inhibitor combinations, imipenem, clindamycin, and tetracycline were the most effective against *Capnocytophaga*.

Conclusion. This study showed that *Capnocytophaga* decreased in prevalence and proportion in the dental plaque of cancer patients during chemotherapy but became predominant in some cases. It is recommended that imipenem or beta-lactam/beta-lactamase inhibitor combinations be used to treat *Capnocytophaga* bacteraemia.

Introduction

Capnocytophaga species are gram-negative, capnophilic, gliding bacilli. They are members of the oral commensal flora. Supra- and subgingival plaque represent their main reservoirs [1–3]. *Capnocytophaga* is responsible for up to 3% of nosocomial infections [4–6]. It can cause septicaemia in immunocompromised individuals, particularly if they are neutropenic, and in those with haematological malignancies [7–10].

The strains responsible for bacteraemia and septicaemia may exhibit multidrug resistance [5,7,11]. An increase in the percentage of beta-lactam-resistant strains has recently been reported and has been linked to the presence of beta-lactamase-producing strains [5,12,13].

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The oral cavity may act as a reservoir for *Capnocytophaga*. *Capnocytophaga* populations undergo significant modifications during immunosuppressive chemotherapy and are associated with oral mucosal lesions [1] that frequently occur in patients undergoing chemotherapy [14–17].

The aim of this study was to compare the presence and levels of *Capnocytophaga* in the dental plaque of children with cancer who were undergoing chemotherapy and of healthy control children. The susceptibilities to a range of antibiotics of strains isolated from the patients with cancer were also tested.

Patients and methods

Patients

Children with cancer attending the Department of Paediatric Oncology, C.H.U., Rennes (France) were

recruited the day preceding their first immunosuppressive chemotherapy treatment (D0) and were followed throughout the first three weeks of the treatment. These patients entered into this study with their informed consent (CCPPRB 1995/12-92/DGS 950333).

Children were treated using international protocols, which resulted in rapid, profound neutropenia (< 500 neutrophils/mm^3). During the chemotherapy, the patients systematically received parenteral cotrimoxazole (sulfamethoxazole + trimethoprim: Bactrim™, Produits Roche, Neuilly sur Seine, France, 25 mg/kg/24 h) to prevent *Pneumocystis carinii* infections. In the event of fever (axillary temperature > 37·8 °C once, or ≥ 37·5 °C twice in 8 h), additional antibiotic therapy was begun within 2 h: ceftazidime (50 mg/kg/8 h, Fortum™, Laboratories Glaxo, Paris, France) or ceftriaxone (100 mg/kg/24 h, Rocephine™, Produits Roche, Neuilly-sur-Seine, France) and amikacin (7·5 mg/kg/12 h, Amiklin™, Laboratoires Bristol, Paris, France). If the fever persisted for 48 h, vancomycin (10 mg/kg/6 h, Vancocine™, Laboratoire Lilly France SA, St-Cloud, France) was prescribed. If the fever persisted for over 72 h, imipenem (10 mg/kg/6 h, Tienam™, Laboratoires Merck, Paris, France) together with an antifungal (amphothericin B, 60 mg/kg, Amphocycline™, Laboratoires Bristol, Paris, France), were given.

Oral and dental hygiene instructions were given immediately on diagnosis, and oral hygiene was ensured by mouth washing three times a day with an alcohol-free 2% chlorhexidine solution (ELUDRIL collutoire™, Laboratoires Pierre Fabre, France) after toothbrushing (Inava 7/100, Laboratoires Pierre Fabre, France) without toothpaste [15].

The clinical examinations and samplings were performed by a trained single operator. Dental formulae and tooth emergence and loss were noted. Clinical evaluation included the following assessments: plaque index (PI) [18], gingival index (PI) [19], and oral assessment guide (OAG) for mucosal lesions [20,21].

Control children were also included in this study. They were free of all general and oral pathologies with the exception of minor gingivitis. None had been treated with antibiotics in the 3 months preceding the study and did not receive any antibiotics during the study.

Samples

Supragingival plaque samples were removed as previously described from the buccal surfaces of the last three maxillary teeth and the lingual surfaces of the last three mandibular teeth [1] on day 0, and after 1 (day 7), 2 (day 14), and 3 (day 21) weeks of chemotherapy. The samples were placed in 1 mL of appropriate prereduced transport fluid (reduced transport fluid: RTF [22]) for transportation to the laboratory where they were analysed within 2 h. After serial dilutions, 100 µL of each dilution was spread on Columbia agar containing 5% blood, and on tryptic soy agar with sheep blood containing bacitracin and polymyxin B (TBBP) [23] and tryptic soy agar containing bovine serum, bacitracin, and vancomycin (TSBV) [24] selective media. The Columbia agar plates were incubated at 37 °C under anaerobic conditions (80% N_2, 10% H_2, 10% CO_2). The selective media and duplicates of the Columbia plates were first incubated for 24 h at 37 °C under anaerobic conditions, then in an air +5% CO_2 atmosphere to eliminate both strict anaerobes and aerobes.

Colony counts were performed after 4 and 8 days of incubation. *Capnocytophaga* strains were identified based on colony morphology, Gram staining, catalase and oxidase reactions, enzyme profiles using API ZYM™ galleries (BioMérieux, Lyon, France) [25], and phenotypic individual tests [26,27].

Statistical analyses

The results were analysed using the Mann–Whitney test to compare microbial counts values and Chi-square analysis to compare frequencies of detection of *Capnocytophaga*.

Susceptibility testing

The susceptibilities to cotrimoxazole (sulfamethoxazole 5/6, trimethoprim 1 of 6) of 122 strains isolated at different times from the children with cancer were determined by dilution in agar according to Rummens *et al*. [28]. The susceptibility of these strains was also tested at the concentration (40 µg/mL sulfamethoxazole/1 µg/mL trimethoprim) that corresponded to the serum concentration obtained following parenteral administration of 480 mg of cotrimoxazole (theoretical dose for a child weighing 25 kg). Briefly, after a 48-h incubation period on Columbia agar, the strains were suspended in Mueller–Hinton broth and the concentrations were adjusted by measuring the optical densities at 660 nm in order to standardize the suspensions at 10^6 CFU/

Table 1. Susceptibility of *Capnocytophaga* strains to various antibiotics assessed using ATB 14 269™ (BioMérieux, Lyon, France) (127 strains) and ATB 14 260™ (BioMérieux, Lyon, France) (69 strains) galleries.

	N	Concentration tested (μg/mL)	*R*
Penicillin G	127	0·5–2	59
Amoxicillin	127	2–4	43
Amoxicillin	127	16	34
Amoxicillin + clavulanic acid	127	(4 + 2)–(8 + 4)	0
Amoxicillin + clavulanic acid	127	16 + 2	0
Ticarcillin + clavulanic acid	127	(32 + 2)–(64 + 2)	0
Piperacillin + tazobactam	127	(32 + 2)–(64 + 4)	0
Cefoxitin	127	16–32	0
Cefotetan	127	16–32	14
Cefotaxim	69	32	54
Imipenem	127	4–8	0
Erythromycin	69	1–4	5
Clindamycin	127	2–4	0
Tetracycline	69	8	0
Metronidazole	127	8–16	39
Teicoplanin	69	4	70
Vancomycin	69	4–16	58

N, number of strains tested; *R*, number of strains showing resistance or intermediate resistance.

mL. Ten-microlitre volumes of the suspensions were deposited on Columbia agar plates supplemented with 1% Polyvitex™ (BioMérieux, Lyon, France), 1% haemoglobin, and the appropriate concentration of antibiotic. The agar plates were examined after 24 h, 48 h, and 5 days of incubation. A minimum of 10 colonies was required to record a positive result.

The susceptibility to various antibiotics of strains isolated from children with cancer were evaluated using ATB ANA 14 260™ or ATB ANA 14 269 galleries (BioMérieux, Lyon, France) or both. These galleries contain antibiotics (listed in Table 1) at critical concentrations defined by the Antibiotic Sensitivity Test Committee of the French Society of Microbiology in accordance with the recommendations of the National Committee for Clinical and Laboratory Standards (NCCLS, USA). Both types of galleries were used according to the manufacturer's instructions, except that the growth medium (ATB S Medium™) was replaced by Todd–Hewitt broth (Becton Dickinson, Cockeysville, MD, USA) supplemented with haemin (1%) and vitamin K1 (1%) after the preliminary assessment. Readings were taken by two calibrated individuals after a 24- and 48-h incubation. When the strains tested positive for beta-lactam resistance, the presence of beta-lactamase was confirmed using disks impregnated with nitrocefin (Cefinase™ discs, Becton Dickinson, Cockeysville, MD, USA). The following control strains were used during the antibiotic susceptibility evaluations: *Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, *Escherichia coli* CIP 7624, and *Actinomyces odontolyticus* BC21.

Results

Forty-eight children with cancer were recruited on day 0. Thirty-one of these, aged 3–15 (average age 8·8 ± 3·9 years), were followed up until day 21. Acute lymphoblastic leukaemia (16 of 31), acute myeloblastic leukaemia (4 of 31), and lymphoma (3 of 31) were the most common cancers. All the microbiology monitoring tests (lumbar puncture and faecal, urine, and blood cultures) produced values for all the children throughout the 3-week sampling period that were in line with normal values.

The control population was made up of 30 children aged 3–15 (average age 8·2 ± 3·7 years) attending the Centre Hospitalier Universitaire de Rennes dental school, with age and sex distributions similar to 30 of the children with cancer.

The main results are presented in Table 2.

Table 2. Total anaerobic viable counts and presence of *Capnocytophaga* in the dental plaque.

Day	Group	TAVC (CFU × 10^7)	Prevalence of *Capnocytophaga* (%)	Percent in TAVC range
0	D	3·1 ± 4·4	83·9	0–40·3†
	C	3·3 ± 5·2	82·1	0–28·7
7	D	2·6 ± 4·6	80·0	0–30·0
	C	5·1 ± 1·0	100	+–22·5
14	D	2·5 ± 4·1*	45·2†	0–33·7
	C	5·1 ± 5·7	92·9	0–21·2
21	D	1·6 ± 1·9	38·7†	0–55·5
	C	4·3 ± 7·1	88·5	0–33·3

TAVC, total anaerobic viable count; D, diseased (cancer) children; C, control group; +, percent of TAVC < 0·01%; *, difference with control group statistically significant ($P < 0·05$); †, 92% of TAVC in one case that could not be followed up until day 21.

Values on day 0

On day 0, the diseased (D) and control (C) groups had similar average total anaerobic viable counts (TAVC) and a similar prevalence of detection of *Capnocytophaga* (83·9% and 82·1%, respectively). *Capnocytophaga* represented 92% of the TAVC in 1 of the 17 children who could not be followed up until day 21.

Variations in control group

The control children had similar average TAVC values throughout the study, with a high frequency of detection of *Capnocytophaga* on all sampling days. *Capnocytophaga* made up, on average, 5·2% to 9·6% of the TAVC (up to 33·7% of the TAVC, but rarely over 20%).

Variations in cancer group

The decrease in average TAVC values in the children with cancer on days 7, 14, and 21 was not significant when compared to day 0 ($P > 0{\cdot}05$). The frequency of *Capnocytophaga* significantly decreased on days 14 ($P < 0{\cdot}0001$) and 21 ($P = 0{\cdot}0001$) but not on day 7 ($P = 0{\cdot}1218$) compared to day 0. There were no variations in TAVC values or the prevalence of *Capnocytophaga* based on the type of malignancy.

The difference in average TAVC values between groups D and C was not statistically significant on day 7 ($P = 0{\cdot}2313$). It was significant, however, on day 14 ($P = 0{\cdot}0005$) and almost significant on day 21 ($P = 0{\cdot}0616$). The frequency of *Capnocytophaga* was significantly lower in the cancer group on days 14 ($P < 0{\cdot}0001$) and 21 ($P = 0{\cdot}0002$) compared to the control group.

The influence on detectable *Capnocytophaga* levels of an additional antibiotic treatment during chemotherapy was assessed in the children with cancer. The levels on day 0 were similar to those detected in children who had not received the antibiotic treatment and those who had received antibiotics at least once during the 3-week chemotherapy cure. On day 21, the difference was not statistically significant ($P = 0{\cdot}1160$).

No correlation could be found between detection or not of *Capnocytophaga* and the clinical indices whatever the date of sampling.

Susceptibility to antibiotics

All strains tested were resistant, most of them highly resistant, to cotrimoxazole (91–128 μg/mL to 20–64 μg/mL). The high level of resistance to cotrimoxazole was seen as of day 0 (32 strains of 36 were resistant to 128 or 64 μg/mL; day 7: 21 of 25; day 14: 15 of 17; day 21: 43 of 44). The other strains had minimal inhibitory concentrations (MICs) ranging from 8 to 32 μg/mL. As for 40 μg/mL sulfamethoxazole/1 μg/mL trimethoprim, 116 strains were resistant (day 0: 33 of 36; day 7: 23 of 25; day 14: 16 of 17; day 21: 44 of 44).

The main results obtained with the ATB ANA 14 260™ and ATB ANA 14 269™ galleries are presented in Table 2. All the beta-lactam-resistant strains secreted beta-lactamase based on the nitrocefin chromogenic assay. No differences in susceptibility to the antibiotics based on sample dates were noted.

Discussion

Our study confirmed that *Capnocytophaga* is a member of the commensal flora of supragingival plaque. The genus was detected in 88·5% to 100% of the control subjects.

On day 0, the TAVC values for the children with cancer were similar to those of the healthy children, as was the prevalence of *Capnocytophaga* and its proportion of the TAVC.

The prevalence of *Capnocytophaga* dropped significantly after 2 weeks of chemotherapy. The difference was significant compared to the control group on day 14 and almost significant on day 21. These results show that the growth of this opportunistic pathogen is not favoured in neutropenic patients during a course of immunosuppressive chemotherapy. Further studies are needed to determine whether this decrease can be related to the administration of oral (chlorhexidine) or systemic (antimitotics and antimicrobials) or both agents. No significant correlation was found in this study between the use of antibiotics (other than cotrimoxazole) during chemotherapy and the selection/elimination of *Capnocytophaga*.

Capnocytophaga was, however, shown to be predominant in single samples from two patients with cancer (55% and 92% of TAVC). Although no local or systemic *Capnocytophaga* infections were noted, this predominance might increase the risk of bacterial spreading. The resistance to cotrimoxazole confirmed the previously reported resistance to trimethoprim [28]. In the case of bacteraemia or septicaemia, cotrimoxazole would provide no protection. In fact, cotrimoxazole might induce a positive selective pressure.

The antibiotic galleries provided punctual information. The values used (obtained by antibiotic galleries) were the threshold values established by the National Committee for Clinical and Laboratory Standards (NCCLS) [29] and the Comité Français de l'Antibiogramme (French Antibiogram Committee) [30] and can be used in hospital settings for patients with *Capnocytophaga* infections. The resistance of a large percentage of strains to beta-lactams confirmed the increase in the frequency of resistance strains in recent years [5,7,12,23,28,31–37], especially in neutropenic patients. All the resistant strains isolated produced beta-lactamase. Among the cephalosporins, only cefoxitin was useful against the *Capnocytophaga* strains, which confirmed previous studies [7,12,13,28,31]. The effectiveness of the beta-lactam/beta-lactamase-inhibitor combinations also confirmed recent results obtained with strains isolated from cancer patients undergoing treatment [5,12].

The results obtained with strains isolated from hospital patients also showed a high proportion of resistance to vancomycin (antibiotic administered after 48 h of fever) and confirmed the usefulness of imipenem, for which there is no reported resistance. Recent studies indicate that beta-lactamase-producing strains are generally resistant to broad-spectrum cephalosporins. The use of imipenem for neutropenic patients is thus recommended [5,11] as are beta-lactam/beta-lactamase inhibitor combinations for gram-negative fusiform and *Capnocytophaga* infections [11,12].

The efficacy of erythromycin, tetracycline, and clindamycin against *Capnocytophaga* confirmed the results of previous studies [7,28,31,32,34–36]. Clindamycin and eventually erythromycin might be very useful alternative treatments for *Capnocytophaga* infections in the case of beta-lactam allergies.

What this paper adds

- This paper gives results about the frequency of *Capnocytophaga*, an opportunistic pathogen, in the dental plaque of healthy children and of children under immunosuppressive chemotherapy.
- A high frequency of *Capnocytophaga* strains were susceptible to beta-lactams.
- *Capnocytophaga* strains are susceptible to imipenem, clindamycin and beta-lactam/beta-lactamase inhibitor combinations.

Why this paper is important for paediatric dentists

- Practitioners should prescribe less antibiotics, and especially beta-lactams, to avoid the spreading of resistant strains.
- It is recommended that Imipenem and beta-lactam/beta-lactamase inhibitor associations be used to treat bacteraemia caused by *Capnocytophaga*.

Conclusions

The prevalence of *Capnocytophaga* in dental plaque is identical in healthy patients and patients with cancer previously to immunosuppressive chemotherapy. It drops significantly in patients with neutropenic cancer after 2 to 3 weeks of immunosuppressive chemotherapy. This genus may, however, become predominant in a small number of patients. This could be associated with a higher risk of bacterial spreading. A large number of the strains were resistant to a wide range of antibiotics, especially beta-lactams. It is recommended that imipenem or beta-lactam/beta-lactamase-inhibitor combinations be used to treat bacteraemia caused by *Capnocytophaga*.

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