

An evidence-based assessment of the clinical guidelines for replanted avulsed teeth. Part II: prescription of systemic antibiotics

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Abstract – Background: Current clinical guidelines recommend prescribing systemic antibiotic therapy (SAT) for patients having an avulsed permanent tooth replanted. The principles of evidence-based dentistry can be used to assess whether this is the best approach based on currently-available evidence. The objective of this study was to use the principles of evidence-based dentistry to answer the PICO question: (P) for a replanted avulsed permanent tooth, (I) is prescribing SAT, (C) compared with not prescribing SAT, (O) associated with an increased likelihood of successful periodontal healing after tooth replantation? **Materials and methods:** A literature search was performed across four internet databases (Ovid Medline, Cochrane Library, PubMed, ISI Web of Science), for relevant citations ($n = 35\,702$). Limiting citations to those in English and removing duplicates produced a set of titles ($n = 14\,742$) that were sieved according to evidence-based dentistry principles. Relevant titles were selected for abstract assessment ($n = 782$), identifying papers for examination ($n = 74$). Inclusion criteria were applied and three papers (326 total teeth) met the final criteria for meta-analysis. **Results:** Meta-analyses found no statistically significant difference between prescribing or not prescribing antibiotics for acceptable periodontal healing without progressive root resorption (common odds ratio = 0.90, SE = 0.29, 95% confidence intervals = 0.51–1.58). **Conclusion:** The evidence for an association between prescribing SAT and an increased likelihood of acceptable periodontal healing outcome is inconclusive. This investigation of antibiotic use as defined in the clinical guidelines indicates there is inconclusive clinical evidence from studies of replanted avulsed human teeth to either contradict or support the guideline. Pending future research to the contrary, dentists are recommended to follow current guidelines in prescribing SAT when replanting avulsed teeth.

The current emphasis in dentistry proposes that clinical guidelines in patient management are evidence-based (1). Current guidelines recommend systemic antibiotic therapy (SAT) for patients with avulsion of a permanent tooth, which is reimplemented (2–7). Doxycycline administered at the appropriate dose (based on patient weight and age) twice daily for 7 days is recommended, or, in patients susceptible to tetracycline staining, penicillin V (doses based on patient weight and age) taken four times daily for 7 days (4, 5, 7). Other guidelines recommend SAT but do not specify type, dosage or duration (2, 6, 8). Therapeutic doses of penicillin for 4–7 days postreplantation have been suggested to help prevent periodontal healing complications and assist pulpal revascularization (9).

The purpose for giving SAT is to prevent or abolish bacterial infection. Thus the time of initiating SAT is important. A wide-open apex of a replanted tooth may allow SAT to reach bacteria in the pulp. In particular, SAT may affect the occurrence of inflammatory

resorption (2, 10–12), speculated to occur by reducing the bacterially-associated inflammatory reaction in the periodontal ligament and preventing bacteria from entering the apical foramen (10, 11, 13). Bacteria may contaminate the root surface by substance contact during the injury, in the storage media or in handling. The socket may be contaminated by salivary exposure, bacterial ingress from periodontal tissues, or during replantation (14). Administration of SAT does not appear to affect existing inflammatory resorption or influence the development of ankylosis and replacement resorption (10).

Studies on replanted animal teeth suggest improved outcomes following SAT (10, 12, 13). A study of dried, replanted monkey teeth found no inflammatory resorption in treated teeth following SAT and also no inflammatory resorption of teeth following immediate endodontic treatment; no added benefit was seen when SAT was given for teeth with immediate endodontic

therapy (10). This may indicate that SAT confers no added benefit with early pulp extirpation. But it should be noted that there were only eight teeth per group, the teeth were extracted and air-dried for 1 h prior to replantation, the endodontic treatment was commenced before extraction and completed extra-orally with gutta percha obturation prior to replantation, and SAT was given intramuscularly (10). This combination of factors is unlikely to occur in human cases.

Additional support for SAT was provided by a further study in monkey teeth where SAT was associated with decreased initial inflammatory reaction and decreased resorption of alveolar bone (13). Less inflammation was noted in teeth receiving endodontic treatment plus SAT compared with teeth receiving endodontic treatment only (13). Again, these results cannot be extrapolated directly to human avulsed teeth as the study methods differ from current clinical management (13).

Studies in humans have not found improved periodontal or pulpal outcomes associated with SAT (11, 15–18). A recent Cochrane review found no appropriate scientific evidence to either recommend or discourage the use of prophylactic SAT to prevent complications and failures of dental implants (19). Not only is any benefit of SAT on periodontal healing outcome following replantation yet to be established but also a debate exists on which antibiotic regime to use. Systemic doxycycline has been reported as advantageous (20, 21). In addition to its antibacterial action, tetracycline may decrease root resorption by affecting osteoclast motility and reducing the effectiveness of collagenases (12, 22). However, tetracycline use is contraindicated in children under 8 years of age as it leads to yellow intrinsic staining of the developing dentition (23).

Systemic administration of doxycycline was superior to amoxicillin in reducing inflammatory resorption in 30 replanted teeth in five beagle dogs, and both antibiotics were more effective than control procedures (no SAT) (12). The study avoided drying of periodontal ligament cells by replanting teeth within 5 min, reducing the likelihood of replacement resorption (12). However, the study conditions did not simulate the human situation: although pulps were extirpated, dental plaque was introduced into canals as a bacterial source (12). The benefit of SAT under these conditions cannot be construed as evidence for a similar effect in human avulsed teeth. A further dog study by the same investigators found no statistically significant difference in occurrence of complete healing, inflammatory resorption or replacement resorption for extracted and replanted teeth between groups with systemic tetracycline, systemic amoxicillin or controls (22). Endodontic treatment was completed prior to extraction and bacterial infection of sockets was assumed prior to replantation after 60 min of extra-oral dry time (22). The lack of significant effect of either antibiotic suggests tetracycline is no more beneficial than amoxicillin in decreasing inflammatory resorption and challenges the benefit of SAT.

Locally-applied, topical antibiotics may be more beneficial than SAT. Topical doxycycline prior to replantation significantly reduced development of inflammatory resorption in replanted monkey teeth,

while systemic doxycycline had no effect (24). This study has not been replicated in human teeth, although the approach has been used (25). In replanting an avulsed tooth it is unlikely that a general dentist would have topical antibiotics available, challenging the clinical relevance of this strategy.

This is the second paper by the present authors using the principles of evidence-based dentistry to assess whether the clinical guidelines for managing replanted permanent avulsed teeth (2–7) reflect the best approaches according to currently-available evidence. The first paper found clinical evidence for an association between pulp extirpation performed after 14 days following replantation and the development of inflammatory root resorption, supporting the current clinical guidelines for early pulp extirpation within 10–14 days (26). While the clinical guidelines recommend prescribing SAT, there appears to be little clinical evidence of benefit. The present study aimed to assess the evidence for this recommendation in managing replanted permanent avulsed teeth and to determine whether prescribing SAT is associated with an increased likelihood of successful periodontal healing.

Materials and methods

The PICO question

The research question was expressed as a PICO question: (P) for a replanted avulsed permanent tooth, (I) is prescribing SAT, (C) compared with not prescribing SAT, (O) associated with an increased likelihood of successful periodontal healing after tooth replantation?

Searching the literature

The evidence-based assessment process has previously been described by the authors (26). A search was performed across four databases: Ovid Medline (27), Cochrane Library (28), PubMed (29) and ISI Web of Science (30), for citations relevant to the PICO question; 35 702 citations resulted (Table 1). Limiting to articles written in English and deleting duplicates reduced the list to 14 742 citations.

Limitation criteria

Inclusion/exclusion criteria were applied to titles of papers, retaining human studies of permanent anterior teeth (Table 1). Excluded were animal or laboratory studies, studies on primary or permanent posterior teeth, reviews, position papers, letters, editorials and meeting abstracts. This sieve retained 782 papers with abstracts that were searched via libraries and databases, reapplying the criteria and adding more exclusions (intentional extraction, transplantation, luxations). Abstracts addressing exarticulation and avulsion were retained.

Developing an evidence hierarchy

Evidence categories were assigned to papers based on the abstracts and ranked as previously (26). For locatable

Table 1. Sequence of steps, procedures, and results of evidence-based assessment

Sequence of steps	Procedure	Limitation criteria applied	Results of search and sieve (no. of papers)
1. Initial search (Ovid Medline, PubMed, Cochrane Library, ISI Web of Science)	Keywords, Boolean operators	None	35 702
2. Initial removal of duplicate citations	Keywords, Boolean operators	Written in English No duplicate citations across database results	22 034
3. Development of single set of citations	Search strings, keywords, Boolean operators	No duplicate citations in databases	14 742
4. Preliminary sieve	Paper titles examined	Human studies Actual studies Permanent anterior teeth Relevant to PICO question	782
5. Secondary sieve	Abstracts examined	Above criteria reapplied Clinical studies and case series	74
6. Appraisal and ranking of evidence	Papers examined	Relevant prospective and retrospective clinical studies	30
7. Final assessment for meta-analysis	Data extraction and critical appraisal	Prescription and non-prescription of systemic antibiotic therapy in same study Periodontal healing outcomes described in relation to systemic antibiotic therapy Replantation conforms to current clinical guidelines Teeth representative of typical avulsed tooth	3

articles without abstracts, the introduction and Materials and methods sections were read to determine study relevance and assign an evidence category. Examining titles and abstracts of the 782 papers, 384 were found to be irrelevant to the PICO question, 138 were case reports and 74 (63 clinical studies, 11 case series) were retained (Table 1).

Full texts of the 74 papers were retrieved and examined: 38 papers were irrelevant (two case series; eight case reports; one position paper; three prevalence studies; 17 on trauma but not avulsion; five on intentional extraction/transplantation; two on management of ankylosis or replacement resorption); three papers were grey literature. Data were extracted from the remaining 33 papers; each study was appraised using forms developed previously (26).

For inclusion of a paper, SAT use and the reporting of periodontal healing outcomes were required. Excluded then were 27 papers describing clinical studies (17 did not specify SAT use; one described SAT inadequately; three prescribed SAT for all patients without comparison groups; three did not report periodontal healing outcomes in relation to SAT; one reported pulpal healing; two had unsuitable cohorts with extended extraoral times or management dissimilar to current clinical guidelines). Four papers (15, 16, 31, 32) describing one prospective observational cohort study were combined as a single report; and two papers describing retrospective clinical audits (11, 33), provided data on SAT prescription or otherwise in relation to reported periodontal healing outcomes (Table 1).

Studies investigating the effect of systemic antibiotic therapy

One prospective (16) and four retrospective studies (11, 17, 18, 33) investigated SAT in relation to periodontal

healing outcomes, using diagnostic criteria (Table 2). Following 34 teeth for at least 1 year, Sae-Lim and Yuen (11) concluded SAT did not appear to affect periodontal outcomes. Andreasen et al. (16) studied 400 replanted avulsed teeth and reported no significant relationship between SAT and periodontal healing outcome. Administering penicillin immediately postimplantation for 110 teeth, Andreasen and Hjørting-Hansen (17) found no replantation outcome was favoured by using SAT. Following 11 teeth in 6–19 year olds, Crona-Larsson et al. (18) found no beneficial effect of systemic antibiotics. Administering penicillin immediately postimplantation for 110 teeth, Andreasen and Hjørting-Hansen (17) found no replantation outcome was favoured by using SAT. Studying 21 teeth, Andersson and Bodin (33) could not demonstrate a relationship between rate of root resorption and SAT.

Systemic antibiotic therapy used in studies

The SAT use described in the studies varied (Table 2). The study by Sae-Lim and Yuen (11) assessed the effect of the local protocol for SAT, which included penicillin or erythromycin for severe forms of oro-facial trauma but did not report dosages or duration. Andreasen et al. (16) administered penicillin as 500 000 units orally four times daily for 4 days. Andersson and Bodin (33) prescribed antibiotics for patients for 7 days, but did not name the antibiotic type or dose.

Direct comparison of prescription and non-prescription of systemic antibiotic therapy

Characteristics of the three studies (11, 16, 33) directly comparing prescription and non-prescription of SAT and describing periodontal healing outcomes are

Table 2. Descriptions of five studies indicating effect of systemic antibiotic therapy on periodontal healing outcomes

Study	No. patients	Age (years)	No. teeth	Systemic antibiotic therapy	Follow up	Diagnosis of periodontal healing outcome
Sae-Lim and Yuen (11)	-	7–48	34	Penicillin or erythromycin, duration not specified	Min 1 year	Radiographic
Andreasen et al. (16)	322	5–52	400	Penicillin for 4 days immediately after the injury	Up to 20 years	Radiographic, high percussion note, reduced mobility, infraocclusion
Andreasen and Hjorting-Hansen (17)	82	6–24	110	Penicillin given immediately after replantation	2 months–40 years	Radiographic, high percussion note, reduced mobility, infraocclusion
Crona-Larsson et al. (18)	108	6–19	11	Type, dose, duration of antibiotics not specified	Min 1 year	Radiographic
Andersson and Bodin (33)	18	7–29	21	Type, dose, duration of antibiotics not specified	Av 5 years	Radiographic (root resorption index)

Table 3. Periodontal healing outcomes in three studies reporting on prescription and non-prescription of systemic antibiotic therapy providing teeth for meta-analysis

Study and type	Meta-analysis (no. teeth)	Systemic antibiotic therapy (no. teeth)	Periodontal healing outcome with systemic antibiotic therapy (no. teeth)	No systemic antibiotic therapy (no. teeth)	Periodontal healing outcome with no systemic antibiotic therapy (no. teeth)
Retrospective clinical audits:					
Sae-Lim and Yuen (11)	34	26	Positive periodontal outcome (10) Negative periodontal outcome (16)	8	Positive periodontal outcome (2) Negative periodontal outcome (6)
Andersson and Bodin (33)	21	19	No resorption (6) Non-progressive resorption (8) Progressive resorption (5)	2	No resorption (1) Non-progressive resorption (0) Progressive resorption (1)
Prospective cohort study:					
Andreasen et al. (16)	271	202	Periodontal healing (49) Periodontal necrosis (153)	69	Periodontal healing (20) Periodontal necrosis (49)
Totals	326	247		79	

shown in Table 3. Data on SAT use were not available for all teeth, reducing sample sizes to a total of 326 teeth (SAT: 247; no SAT: 79) for meta-analysis. Immature teeth could not be separated from mature teeth within the available data. Favourable periodontal healing outcomes [defined in the articles included as: positive periodontal outcome (11), periodontal healing (16), no root resorption (33), non-progressive root resorption (33)], following SAT varied markedly between studies, occurring in: 10 of 26 teeth (11); 49 of 202 teeth (16) and 14 of 19 teeth (33). Favourable periodontal healing outcomes without SAT also varied, occurring in: 2 of 8 teeth (11); 20 of 69 teeth (16) and 1 of 2 teeth (33).

Classification of periodontal healing outcomes

In pooling teeth for meta-analysis (Table 3), the periodontal healing outcomes were reclassified by the present investigators. No data with respect to periodontal healing complications (development of inflammatory resorption, replacement resorption) were found in relation to use of SAT. Acceptable periodontal healing was defined as positive periodontal outcome (an intact periodontal ligament space) (11), periodontal healing (mobility equal to that of the control tooth and no radiographic sign of root resorption) (16) and no root

resorption or non-progressive root resorption (33). Unacceptable periodontal healing was defined as negative periodontal outcome (the presence of inflammatory resorption, ankylosis/replacement resorption, marginal periodontal breakdown or extraction/progressive resorption) (11), periodontal necrosis (radiographic signs of root resorption or clinical signs of ankylosis) (16) and progressive root resorption (33).

Statistical analysis

Meta-analyses and forest plots were created using Revman 4.2 statistical software (34, 35), examining data as dichotomous (i.e. the outcome did or did not occur), and calculating odds ratios (ORs), standard errors (SE) and 95% confidence intervals (CI) as described previously (26). Study ORs were weighted, common odds ratios (CORs) were calculated for an overall estimate of effect, and the random effects model (DerSimonian and Laird technique) was used in combining study results, as described previously (26, 34). The overall effect of prescribing SAT vs not prescribing SAT on the periodontal healing outcome was determined by the z statistic ($\alpha = 0.05$). Between-study heterogeneity was assessed using the Chi-squared test as Cochran's Q (34). Inconsistency due to heterogeneity (as opposed to sampling error) was assessed by the I^2 statistic (values

exceeding 56% show marked heterogeneity and values less than 31% show less significant heterogeneity), followed by sensitivity analysis for sources of heterogeneity (36).

Results

Acceptable periodontal healing was determined after pooling data from three studies (11, 16, 33; Table 3) and assembling 326 teeth (SAT: 247; no SAT: 79). Acceptable periodontal healing occurred as follows: SAT: 73 teeth (30%); no SAT: 23 teeth (29%).

Odds ratios and study weightings

Study ORs for the effect of SAT on acceptable periodontal healing (Fig. 1) were not statistically significant: 2.80 (SE = 1.51; CI = 0.15–53.71) (33); 0.78 (SE = 0.31; CI = 0.43–1.45) (16) and 1.88 (SE = 0.91; CI = 0.31–11.17) (11). A non-significant COR of 0.90 (SE = 0.29; CI = 0.51–1.58) suggested prescribing SAT was not associated with increased likelihood of acceptable healing. Study weights and contributions to the overall estimate of effect were: 0.44, 3.7% (33); 10.27, 86.2% (16) and 1.21, 10.1% (11). The non-significant overall effect ($z = 0.37$; $P = 0.71$) indicated a lack of effect of prescribing SAT on acceptable periodontal healing. No between-study heterogeneity was seen ($\chi^2 = 1.41$; $P = 0.49$; $I^2 = 0\%$).

Forest plot

In plotting the effect of SAT on acceptable periodontal healing, all study lines (11, 16, 33) cross the vertical line (of no effect) at 1, indicating non-significant ORs (Fig. 1). Diamond position slightly left and crossing the vertical line favours no prescription of SAT, but without statistical significance.

Answer to the PICO question

Meta-analysis of the currently-available evidence on acceptable periodontal healing indicates that: (P) for a replanted avulsed permanent tooth, (I) prescribing SAT, (C) compared with not prescribing SAT, (O) is not

associated with an increased likelihood of successful periodontal healing after tooth replantation.

Discussion

This meta-analysis investigating the clinical evidence from studies of SAT for replanted human avulsed permanent teeth in accord with current guidelines (2–7) found no clinical evidence clearly contradicting or supporting the guidelines. There was also no evidence from human, replanted avulsed teeth concerning the type, dose or duration of SAT.

The meta-analysis showed no significant association between prescribing SAT and periodontal healing outcome, supporting previous reports (11, 16–18). No individual study OR or COR for an acceptable periodontal healing outcome was statistically significant. The COR (0.90) for acceptable healing with SAT slightly favoured non-prescription, but was not statistically significant. This analysis was based on 326 teeth, which is a larger sample than any previous study reporting outcomes on the use of SAT for avulsed teeth.

The decision to prescribe SAT may be determined by other factors for individual patients, such as their immune status, medical conditions (e.g. congenital cardiac defect) or other associated injuries. If pulp extirpation is delayed, as in immature teeth without extended extraoral times, SAT may be more appropriate than in cases where the pulp is extirpated within 14 days, helping to avoid development of inflammatory resorption. Prescribing SAT aims to reduce the likelihood that a replanted avulsed tooth will develop inflammatory resorption. In the present study, a lack of data on prescription of SAT precluded meta-analysis for this particular healing complication. Future meta-analysis may be able to address the influence of SAT on development of inflammatory resorption and provide evidence to support the clinical guidelines.

No heterogeneity between studies as shown by the I^2 statistic was noted for the meta-analyses. Given the small sample sizes in two of the studies included, the power to detect heterogeneity was reduced and other heterogeneity (not statistically detectable), may have been present. The difficulty in combining studies for meta-analysis due to

Review: Prescribing systemic antibiotics for replanted avulsed teeth

Comparison: 01 Systemic antibiotics vs no systemic antibiotics for replanted avulsed teeth

Outcome: 02 Acceptable periodontal healing vs unacceptable periodontal healing

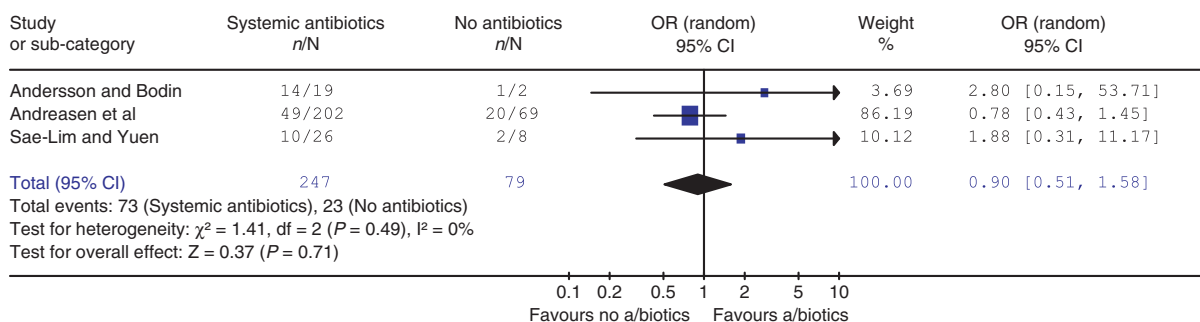


Fig. 1. Influence of systemic antibiotic therapy on an acceptable periodontal healing outcome for replanted avulsed teeth.

variable reporting of healing outcomes has been discussed previously (26).

The present analysis is limited by the few studies available for meta-analysis. Many relevant studies were excluded on the basis that prescription of SAT was not reported. Ideally, such studies should report details for each avulsed tooth including extraoral time, tooth maturity, SAT (including type, dosage, time of initiation and duration), clinical management and periodontal healing outcomes. The inclusion of such information in future studies would enable the accumulation of a large data base and allow the development of well substantiated clinical guidelines for management of replanted avulsed teeth.

In assessing the effect of SAT on outcomes, the present analysis was limited by the lack of details in many papers of the type, dosage and duration of antibiotics prescribed. In combining data from the three studies selected it was assumed that antibiotics prescribed were similar in effect. In prescribing SAT the clinician expects that the patient will be compliant, take antibiotics at the prescribed intervals and complete the course of antibiotics. However, such expectations may not be fulfilled; none of the studies investigating the effect of SAT on success of replantation assessed patient compliance. The lack of SAT after replantation for some patients may reflect other patient or tooth-related factors that were not reported. No study reported randomized prescription of SAT, and no study reporting the effect of SAT on periodontal healing outcome described the reasons for prescribing SAT or otherwise. The present authors have addressed previously the appropriate use of the random effects model for meta-analyses based on cohort studies (26).

The importance of a structured history (data collection) form for emergency trauma management has been reported (37). Lack of detail in studies reporting clinical outcomes may reflect lack of data collection or recording. Many relevant studies did not report whether the patient was prescribed SAT. Without using a structured history this information was rarely recorded (37), even though the recording of prescribed drugs in patient records is a legal requirement in many countries. A publication is more likely to report the prescription of SAT if this has been recorded in all patient records.

The lack of randomized clinical trials (the gold standard for evidence-based research) on replanted avulsed permanent teeth is a limitation of the present study, and the appropriateness of using cohort studies as the primary studies for meta-analysis has been discussed previously by the present authors (26). Retrospective cohort studies were included in the present study due to the lack of prospective studies, providing a further limitation on the meta-analysis. Use of only one assessor and the exclusion of articles not published in the English language as well as publication bias have been previously discussed by the authors (26).

Conclusion

This evidence-based study of data from three papers and pooling 326 replanted avulsed teeth concludes that the likelihood of successful periodontal healing is unaffected

by prescribing SAT. The evidence for an association between the prescription of SAT and acceptable periodontal healing is inconclusive. Pending future research to the contrary, it is recommended that dentists follow the current guidelines for prescribing SAT in the management of replanted avulsed teeth.

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