The role of phenoxymethylpenicillin, amoxicillin, metronidazole and clindamycin in the management of acute dentoalveolar abscesses – a review

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VERIFIABLE CPD PAPER

IN BRIEF

- Provides an overview of appropriate prescribing of antibiotics in the management of the adult patient with a dentoalveolar abscess.
- Highlights the need for surgical/non-surgical drainage as the primary treatment modality in the management of the acute dentoalveolar abscess.
- Discusses the role of antibiotics as an adjunct to treatment for patients showing signs of systemic involvement.

PRACTICE

Antibiotics are the most widely prescribed category of drugs issued on prescription by general dental practitioners. Despite this there remains little evidence-based literature on what should be prescribed for any given clinical situation, at what dosage and for how long. Given the current climate of evidence-based research, the need to keep antibiotic prescribing to an acceptable minimum, increasing levels of resistance of micro-organisms and widespread hospital infections with 'superbugs', there is a distinct need for appropriate prescribing guidelines. Considering best practice, an extensive review of the literature and a thorough understanding of current empirical treatment regimes, an attempt has been made to recommend suitable antibiotic prescribing for the adult patient suffering from acute dentoalveolar infections based on evidence.

Introduction and background

Since the discovery of the first antibiotic by Alexander Fleming in 1928 and its subsequent production by Florey, Chain and colleagues in 1940,[1] antibiotics have been used extensively in dentistry for the management of dental infections. Following a literature search of MEDLINE, EMBASE and the COCHRANE library (using the search criteria antibiotic and dental) covering over 5,000 references, minimal evidence-based usage of antibiotic prescribing was found for the management of acute dentoalveolar infections. Despite this, antibiotic prescribing by dentists, accounts for 7-10% of all antimicrobials prescribed throughout the community and in 1996 general dental practitioners (GDPs) were responsible for 45% of all prescriptions for metronidazole.[2,3] In 1997 GDPs issued over 3.5 million antibiotic prescriptions.[4]

Studies in the United Kingdom have consistently shown that there is widespread variation in the prescribing habits of GDPs, with many prescribing inappropriately, with inconsistent dose and frequency and often for prolonged periods.[4-10] This was also shown to be the case when patients sought advice and treatment from their general medical practitioners.[11]

In a UK dental survey carried out by a major pharmaceutical company[12] looking at the factors influencing frequency and type of regularly prescribed antibiotic, 75% of dentists gave antibiotics at least once a week with over 15% of those dentists prescribing them on a daily basis. By far the most frequently prescribed antibiotic was amoxicillin, followed by metronidazole and almost 20% of this group of dentists prescribed both amoxicillin and metronidazole in combination.[12]

A postal questionnaire by Lewis *et al.*[13] in 1989 showed that dental practitioners estimate that only the minority of patients (approximately 5%) had an acute infection present when they issued a prescription for antibiotics.

Microbiology

Understanding of the micro-organisms responsible for dentoalveolar infections and their susceptibility to various antibiotic agents has progressed significantly In addition, increasing resistance to antibiotics has led to the need for more appropriate prescribing and to review whether prescribing antibiotics is required at all.

Improved microbiological sampling techniques and better transport media have aided more accurate assessment of the bacteria involved in specific dentoalveolar infections and led to more appropriate antibiotic usage. Culture and sensitivity methods still take time and often antibiotics are prescribed empirically prior to sensitivity results being available, although the choice of antibiotic may be based on previously cultured bacteria and their sensitivities. However the continued development of molecular microbiological techniques, which can provide rapid detection of penicillin resistance in pus, will aid with more accurate prescribing in future.

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Most dentoalveolar infections arise from overgrowth of normal commensals within the oral cavity as a result of changes in local environmental conditions, leading to opportunistic infections.[14] Once bacterial growth exceeds the minimum infective dose, a dentoalveolar infection may arise. Dentoalveolar infections are not caused by a single micro-organism but are mixed infections and there is progression of the microbial species as the infection develops reflecting ecological changes in the affected site.[14-16]

It is widely accepted that dentoalveolar infections affecting the periapical tissues are predominantly comprised of strictly anaerobic Gram-positive cocci and Gram-negative rods mixed with facultative anaerobic flora.[14,15,17,18] The predominance of anaerobic micro-organisms within these infections has previously been underestimated. This is in part due to poor sampling techniques and transport media and in addition to inadequate culture media and failure to use prolonged periods of anaerobic incubation.[19] In mixed infections, strictly anaerobic species exceed facultative anaerobic species by 3-4 times[14,15,17-22] and strict anaerobes usually account for the greater percentage of overall viable bacteria within the mixed abscess flora.[21]

In dentoalveolar infections related to the periodontium eg pericoronitis, acute necrotising ulcerative gingivitis (ANUG) and lateral periodontal abscesses, the predominant organisms are obligate anaerobes derived from the normal commensals of the periodontal tissues.[14,15,17,23-28]

Current prescribing practices

Prescribing of antibiotics for the treatment of dentoalveolar abscesses is usually empirical with wide variation in prescribing habits amongst general dental and general medical practitioners.[4-11]

The definitive treatment of a dentoalveolar abscess is drainage and removal of the cause of the infection.[14,17,18,29-39] In the majority of cases this is the only treatment required. However if the patient is showing signs of systemic illness as a result of their dentoalveolar infection, or are significantly immunocompromised, then adjunctive therapy with antibiotics may be indicated.

An abscess is a localised collection of bacteria, inflammatory cells and tissue breakdown products. Extracellular enzymes derived from the bacteria, or the host, within the abscess have tissue-damaging potential.[14] The host response is to allow drainage of pus by the path of least resistance. Dependent on the anatomical position of the abscess, pus may drain through adjacent soft tissues, via the periodontal ligament, via the tooth or may take a deeper course through tissue or fascial spaces. Spread of pus around the muscles of mastication leads to a reduction in inter-incisal opening and presents clinically as trismus. Trismus must therefore be regarded as a significant indicator of severe odontogenic infection.[40]

In addition bacterial metabolites, along with endotoxins and exotoxins, may enter the blood stream. These affect the thermoregulatory centre in the hypothalamus leading to an increased body temperature, seen clinically as pyrexia.[14] Left untreated the bacteria in the bloodstream may reproduce resulting in septicaemia causing a systemic inflammatory response, leukocytosis and potential end organ damage; this may be fatal. The Office for National Statistics for 2000-2005 report that between 8-16 patients died per year in England and Wales from dentoalveolar abscesses.[41]

Antibiotic treatment is essential to treat septicaemia by killing dividing bacteria in the blood stream. Clinical signs of pyrexia, trismus, significant regional lymphadenopathy, gross facial swelling, closure of the eye, dysphagia, tachycardia and rigors should be regarded as indicators of systemic response to infection and adjunctive antibiotic therapy is always indicated.[7,14-16,29,31-35,37-38,40,42,43]

Where there is systemic involvement treatment involves drainage of the abscess primarily to allow the release of pus, reduce the overall number of microorganisms, decrease the tissue pH, increase oxygen diffusion and allow antibiotics to penetrate.[14] This is followed by removal of the cause of the infection and adjunctive antibiotic therapy. Drainage can be achieved either by removal of necrotic pulp, extraction of the tooth or incision of the soft tissues overlying the abscess.

For the antibiotic to be successful in overcoming the associated systemic symptoms, it must be active against the micro-organisms present, be sensitive to those bacteria and be given in adequate dose, frequency and duration to aid resolution of the systemic symptoms. The minimum inhibitory concentration (MIC) is the least amount of antibiotic required to inhibit further growth of the responsible micro-organisms. The blood concentration should exceed this MIC by a factor of four times to allow the antibiotic to penetrate the tissue in sufficient concentration to kill or inhibit further growth of the infecting microorganism.[14,16,44]

Historically antibiotics have been prescribed in courses for between 5-10 days duration and the patient has been instructed to complete the course. It is now becoming increasingly evident that long courses of antibiotics are not required and indeed may destroy the homeostasis of the oral micro-flora and lead to colonisation resistance.[14] In addition, long courses of antibiotics may increase the selection of resistant micro-organisms and resistance plasmid transfer by conjugation.[14] Antibiotics are prescribed with the intention of eradicating microbial systemic involvement and can be discontinued safely after resolution of these signs. Usually they can be discontinued after 2-3 days.[14,16,31-33]

Resistance

Within the oral cavity there is a complex ecosystem of micro-organisms which is continually changing and diversifying in response to local conditions. This is a relatively stable community and resists colonisation by other micro-organisms leading to colonisation resistance.[45] The importance of the role of these normal micro-flora in preventing disease is becoming increasingly realised.[2,14,17] The homeostasis of the normal oral flora can be disrupted by antimicrobial agents which may interfere with adherence, or kill normal commensals, allowing for major changes in the microbial community enabling overgrowth of resistant organisms. This is the basis by which pseudomembranous colitis (PMC) develops in the colonic micro-flora. Disturbance to the normal colonic micro-flora may allow for selection and

overgrowth of *Clostridium difficile* leading to the production of toxins and the development of PMC.[45]

Following the advances in the 1940s and 1950s in antibiotic therapies the outlook for the control of infectious diseases was good. The adaptability and potential for survival of the micro-organisms was underestimated until bacterial strains were found to be evading antibiotic therapies by selection of resistant strains. This has now progressed to such an extent that certain antimicrobial agents have been rendered useless in the treatment of specific infections.[46] Such is the case with the emergence of methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Staphylococcus aureus* (VRSA), multiple drug resistant *Mycobacterium tuberculosis* and vancomycin resistant *Enterococci*.[46-48]

Such resistant bacteria can spread from patient to patient causing further problems with resistance and treatment. This has now become an international problem and is one of great and increasing concern.[1,2,47-56] It is clear that the widespread and often indiscriminate use of antibiotics, generally prescribed on an empirical rather than a rational basis, has led to increasing numbers of resistant bacteria. It is therefore essential that this situation is firstly recognised and secondly that radical changes in prescribing habits are made to reduce the rate at which new resistance accumulates.[2,15,35,49,51,52] The European Centre for Disease Prevention and Control have recognised the problems of inappropriate prescribing of antibiotics and the first European Antibiotics Awareness Day was launched on 18 November 2008.[56]

Antibiotics in agriculture

Resistance has also been exacerbated by the widespread use of antibiotics used in animal agriculture and farming to promote growth of the animals and prevent disease spread amongst crops. Following the Swann Report in 1969, restrictions on antibiotic use in these industries were made in the UK, but widespread usage continued in other countries. In addition, antibiotics prescribed by veterinary surgeons have resulted in enteric bacteria resistant to the veterinary antibiotic apramicin showing cross-resistance to gentamicin. This led to the Lamming Report in 1992 recommending that veterinary use of antimicrobial agents showing this cross-resistance to agents used in human medicine should be 'discouraged'.[2,34,50]

Resistance changes

In 1946, six years after the introduction and production of penicillin, it was found that approximately 90% of *Staphylococcus aureus* isolates were sensitive to penicillin. By 1952 this had decreased to 75% and by 1998 to approximately only 5% being sensitive.[34,48,52]

Penicillin resistant bacteria are often present in the micro-flora of acute dental infections.[53-55] Eick *et al*.[57] showed that the majority of micro-organisms isolated from pus from dento-alveolar abscesses were Gram negative anaerobes and were highly susceptible to metronidazole and clindamycin, but that 22% of isolated bacteria produced beta-lactamases and were resistant to penicillin.

Last year data published by Kuriyama *et al*.[58] showed that 34% of micro-flora from odontogenic abscesses were resistant to the penicillin group of antimicrobials demonstrating a rising trend in the levels of resistant organisms involved in dentoalveolar infections and questioning the ongoing suitability of penicillins as the first line treatment for such infections.

In a randomised operator-blind comparative clinical trial, testing the efficacy of co-amoxiclav with penicillin V for dentoalveolar infections, after drainage all improved but patients on co-amoxiclav reported significantly greater decrease in pain during the second and third days post drainage. This may be related to the eradication of the beta-lactamase producers with co-amoxiclav that would not be eradicated by penicillin V.[54] All of these data support the contention that phenoxymethylpenicillin should not be the first choice of antibiotic for dentoalveolar infections.

Clindamycin

The spectrum of activity of clindamycin covers a range of micro-organisms and most of those found in acute dentoalveolar infections, including those that are showing resistance to the penicillins.[18,20,53,59-61] In addition, clindamycin is well absorbed orally and has a superior bone penetration when compared with other antimicrobials that have a similar spectrum of activity.[60,62-64] It also has stimulatory effects on the immune system.[59] All these factors suggest it could be a highly appropriate choice for managing the systemic involvement associated with acute dentoalveolar abscesses.

Unfortunately clindamycin has long been associated with causing acute pseudomembranous colitis in patients, which can have fatal consequences. It has therefore not been used as a first line choice of antibiotic for odontogenic abscesses. Its use, however, is now increasing and it has been suggested that this could be the antibiotic of choice for adjunctive management of acute dentoalveolar abscesses.[15,18,40,59,63,65,66]

For the past 15 years it has been used as a penicillin alternative for antibiotic prophylaxis for the prevention of bacterial endocarditis in patients either allergic to penicillin or those who have had a recent course of penicillin,[67,68] highlighting its spectrum of activity in combating the relevant oral flora.

PMC can be caused by an overgrowth of *Clostridium difficile*, which is found in the colon as a normal commensal in approximately 2-3% of healthy adults. This carriage rate increases in the elderly, patients with a history of gastrointestinal disease, the chronically ill, patients on long term antibiotic therapy and those who have been hospitalised.[69-74]

Overgrowth of *Clostridium difficile* following antimicrobial therapy may cause complications ranging from simple watery diarrhoea, which may resolve on discontinuation of the antimicrobial, to PMC which can result in fever, abdominal pain, severe dehydration and death.[69-71] Toxic megacolon and acute peritonitis following perforation of the colon are the most serious complications.[74]

The association of PMC with the use of clindamycin understandably added to the risk of choosing this as a first line antibiotic. However, more recent studies have shown that the chance of developing PMC with the use of clindamycin is no higher than other antimicrobials including amoxicillin[18,48,59,60,69,75] and

in fact is lower than the risk for using co-amoxiclav,[59] with an overall incidence of causing PMC of less than 1%.[66] The risk of developing PMC significantly increases if clindamycin is used in conjunction with other antibiotics and one study shows that the risk more than doubles when used in conjunction with ampicillin.[76]

If clindamycin is used, patients should be warned that if they do develop gastrointestinal symptoms/diarrhoea, they should stop their antimicrobial therapy and contact the person who prescribed it for further investigation. Considering that normal colonisation with Clostridium difficile increases with age, illness and a history of gastrointestinal disease, caution would be advised when prescribing clindamycin to this group of patients.[60] Similarly those patients who have recently been in-patients in hospital or who have been on long term antibiotic therapy may be more likely to develop PMC and this may influence the choice of antimicrobial prescribed.[60]

There have been reports of resistance to clindamycin emerging in community acquired MRSA, although the prevalence seems to be low. As *Staphylococcus aureus* is rarely implicated in dentoalveolar abscesses, for the time being, clindamycin should still be considered in the management of acute dentoalveolar abscesses with signs of systemic illness.[77,78]

Recommendations

In the current climate of evidence-based medicine an attempt has been made to rationalise the use of antibiotic prescribing for adult patients attending with acute dentoalveolar infections. Most can be successfully treated with surgical drainage followed by removal of the cause of the infection. For those patients who have become systemically unwell as a result of their infection, or those who are significantly immunocompromised, the same principles are followed along with adjunctive antibiotic therapy to manage their systemic involvement.

Infections derived from the periodontal tissues are anaerobic in nature and metronidazole is the antimicrobial of choice.[79] Infections derived from periapical tissues are mixed infections, but predominantly anaerobic, and are most appropriately treated with amoxicillin, metronidazole or clindamycin (Fig. 1).

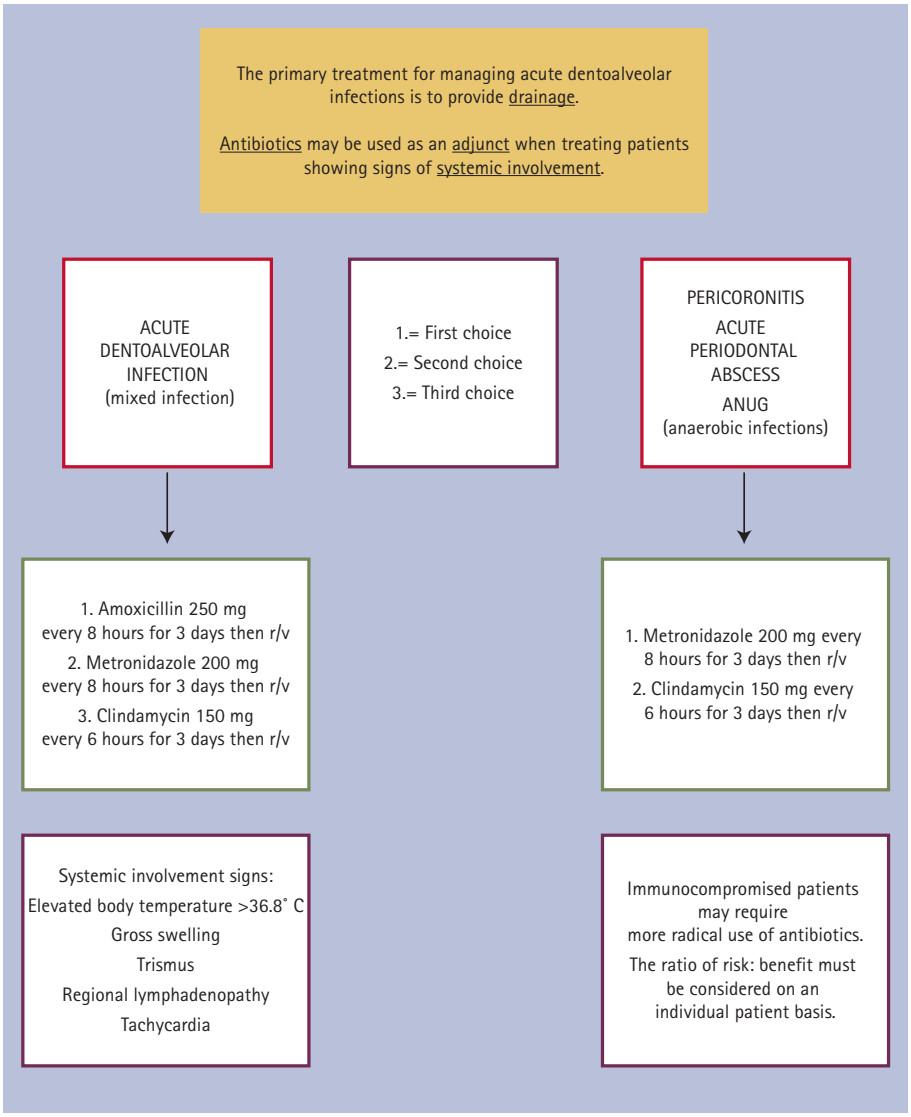

Fig. 1 Guidelines on the usage of antibiotics in the primary care setting

A number of studies have shown that patients respond well when treated with amoxicillin[36,49,52-54,57] despite the evidence of resistant strains and Ingham *et al.*[80] found that metronidazole was as beneficial as penicillin, surmising that this indicated that the anaerobic population of bacteria were most pathogenic. However it may be that effective drainage to reduce the number of bacteria, promote aerobic conditions and optimise a return to health may be the most important part of the process of abscess resolution.

The increasing levels of resistance to penicillin and the emerging interest and usage of clindamycin may make clindamycin a more appropriate choice of antimicrobial in those patients who are at low risk of developing PMC. This has already been advocated by Sandor *et al.*[20]

As antibiotics are prescribed with a view to preventing bacterial multiplication in the blood stream they can be safely discontinued once the systemic signs of infection are eradicated. Following effective drainage, these signs usually resolve within 2-3 days of antibiotic usage and therefore the antibiotic treatment can be stopped at this stage.

With regards to dosage the lowest possible effective dose should be used. In order to achieve sufficient concentration of antibiotic in the tissues, the blood concentration should exceed the MIC by a factor of four. A dose of 250 mg amoxicillin three times daily, 200 mg metronidazole three times daily or a dose of 150 mg clindamycin four times daily will be sufficient to achieve the required blood concentration.

Given the annual costs to the National Health Service involved in prescribing antibiotics, the increasing levels of bacterial resistance, the emergence of bacterial strains resistant to multiple antimicrobial agents and the never ending increase in litigation, care should be taken when prescribing antibiotics for acute dentoalveolar infections associated with systemic illness and emphasis should be placed on the provision of adequate drainage and rational prescribing.

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1. The United Kingdom Parliament. House of Lords Select Committee on Science and Technology – Seventh Report. The path of least resistance. London: Department of Health, 1998.
2. Standing Medical Advisory Committee (SMAC), Department of Health. The path of least resistance. London: Department of Health, 1998.
3. Poveda Roda R, Bagan J V, Sanchis Bielsa J M, Carbonell Pastor E. Antibiotic use in dental practice. A review. *Med Oral Patol Oral Cir Bucal* 2007; **12:** E186-E192.
4. Palmer N O, Martin M V, Pealing R, Ireland R S. An analysis of antibiotic prescriptions from general dental practitioners in England. *J Antimicrob Chemother* 2000; **46:** 1033-1035.
5. Palmer N A, Pealing R, Ireland R S, Martin M V. A study of therapeutic antibiotic prescribing in National Health Service general dental practice in England. *Br Dent J* 2000; **188:** 554-558.
6. Roy K M, Bagg J. Antibiotic prescribing by general dental practitioners in the Greater Glasgow Health Board, Scotland. *Br Dent J* 2000; **188:** 674-676.
7. Palmer N O, Martin M V, Pealing R *et al.* Antibiotic prescribing knowledge of National Health Service general dental practitioners in England and Scotland. *J Antimicrob Chemother* 2001; **47:** 233-237.
8. Dailey Y M, Martin M V. Are antibiotics being used appropriately for emergency dental treatment? *Br Dent J* 2001; **191:** 391-393.
9. Palmer N, Martin M V. An investigation of antibiotic prescribing by general dental practitioners: a pilot study. *Primary Dent Care* 1998; **5:** 11-14.
10. Thomas D W, Satterthwaite J, Absi E G, Lewis M A, Shepherd J P. Antibiotic prescription for acute dental conditions in the primary care setting. *Br Dent J* 1996; **182:** 401-404.
11. Anderson R, Calder L, Thomas D W. Antibiotic prescribing for dental conditions: general medical practitioners and dentists compared. *Br Dent J* 2000; **188:** 398-400.
12. UK Dental Survey. An analysis of 6,000 responses from UK dentists on the 2004 UK dental register. Pfizer. 2005, publication no. DLC-002-05.
13. Lewis M A, Meechan C, MacFarlane T W, Lamey P J, Kay E. Presentation and antimicrobial treatment of acute orofacial infections in general dental practice. *Br Dent J* 1989; **166:** 41-45.
14. Marsh P, Martin M V. *Oral microbiology.* 4th ed. Edinburgh: Wright, 1999.
15. Dirks S J, Terezhalmy G T. The patient with an odontogenic infection. *Quintessence Int* 2004; **35:** 482-502.
16. Pallasch T J. How to use antibiotics effectively. *J Calif Dent Assoc* 1993; **21:** 46-50.
17. Stefanopoulos P K, Kolokotronis A E. The significance of anaerobic bacteria in acute orofacial odontogenic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98:** 398-408.
18. Sandor G K, Low D E, Judd P L, Davidson R J. Antimicrobial treatment options in the management of odontogenic infections. *J Can Dent Assoc* 1999; **65:** 508-514.
19. Lewis M A, MacFarlane T W, McGowan D A. A microbialogical and clinical review of the acute dentoalveolar abscess. *Br J Oral Maxillofac Surg* 1990; **28:** 359-366.
20. Lewis M A O, MacFarlane T W, McGowan D A. Antibiotic susceptibilities of bacteria isolated from acute dentoalveolar abscesses. *J Antimicrob Chemother* 1989; **23:** 69-77.
21. Lewis M A, MacFarlane T W, McGowan D A. Quantitative bacteriology of acute dento-alveolar abscesses. *J Med Microbiol* 1986; **21:** 101-104.
22. Gill Y, Scully C. The microbiology and management of acute dentoalveolar abscess: views of British oral and maxillofacial surgeons. *Br J Oral Maxillofac Surg* 1988; **26:** 452-457.
23. Rothwell B R. Odontogenic infections. *Emerg Med Clin North Am* 1985; **3:** 161-178.
24. Johnson B D, Engel D. Acute necrotizing ulcerative gingivitis. A review of diagnosis, etiology and treatment. *J Periodontol* 1986; **57:** 141-149.
25. Loesche W J, Giordano J R. Metronidazole in periodontitis v: debridement should precede medication. *Compendium* 1994; **15:** 1198-1217.
26. Blakey G H, White R P, Offenbacher S, Phillips C *et al.* Clinical/biological outcomes of treatment for pericoronitis. *J Oral Maxillofac Surg* 1996; **54:** 1150-1160.
27. Rosenberg E S, Torosian J P, Hammond B F, Cutler S A. Routine anaerobic bacterial culture and systemic antibiotic usage in the treatment of adult periodontitis: a 6 year longitudinal study. *Int J Periodontics Restorative Dent* 1993; **13:** 213-241.
28. Walton R E, Zerr M, Peterson L. Antibiotics in dentistry – a boon or a bane? *Alliance for the Prudent Use of Antibiotics Newsletter* 1997; **15:** 1-5.
29. Klein P B. Antibiotic therapy: maximize the benefits, minimize the risks. *Dent Today* 1994; **13:** 42, 44-47.
30. Johnson B S. Principles and practice of antibiotic therapy. *Infect Dis Clin North Am* 1999; **13:** 851-870.
31. Faculty of General Dental Practitioners (UK). The Royal College of Surgeons of England. Primary Dental Care for General Dental Practitioners. 2000.
32. Martin M V, Longman L P, Hill J B, Hardy P. Acute dentoalveolar infections: an investigation of the duration of antibiotic therapy. *Br Dent J* 1997; **183:** 135-137.
33. Pogrel M A. Antibiotics in general practice. *Dent Update* 1994; **21:** 272-280.
34. Haas D A, Epstein J B, Eggert F M. Antimicrobial resistance: dentistry's role. *J Can Dent Assoc* 1998; **64:** 496-502.
35. Palmer N A. Revisiting the role of dentists in prescribing antibiotics. *Dent Update* 2003; **30:** 570-574.
36. Kuriyama T, Absi E G, Williams D W, Lewis M A. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *Br Dent J* 2005; **198:** 759-763.
37. Abbott P V, Hume W R, Pearman J W. Antibiotics and endodontics. *Aus Dent J* 1990; **35:** 50-60.
38. Longman L P, Preston A J, Martin M V, Wilson N H. Endodontics in the adult patient: the role of antibiotics. *J Dent* 2000; **28:** 539-548.
39. Lewis M A O, MacFarlane T W. Short-course high-dosage amoxicillin in the treatment of acute dento-alveolar abscess. *Br Dent J* 1986; **161:** 299-302.
40. Flynn T R, Shanti R M, Levi M H, Adamo A K *et al.* Severe odontogenic infections, part 1: prospective report. *J Oral Maxillofac Surg* 2006; **64:** 1093-1103.
41. Office for National Statistics, Annal, Mortality Statistics: Deaths registered in England and Wales. Series DH2 No 27-32.
42. Baker K A, Fotos P G. The management of odontogenic infections. A rationale for appropriate chemotherapy. *Dent Clin North Am* 1994; **38:** 689-706.
43. Swift J Q, Gulden W S. Antibiotic therapy – managing odontogenic infections. *Dent Clin North Am* 2002; **46:** 623-633.
44. Martindale W. *The extra pharmacopoeia.* 33rd ed. London: Royal Pharmaceutical Society, 2002.
45. Longman L P, Martin M V. The use of antibiotics in the prevention of postoperative infection: a re-appraisal. *Br Dent J* 1991; **170:** 257-262.
46. Molerinari J A. Microbial disease trends and acquired resistance: Part 1. *Compend Contin Educ Dent* 1997; **18:** 106-108.
47. Pallasch T J. Global antibiotic resistance and its impact on the dental community. *J Calif Dent Assoc* 2000; **28:** 215-233.
48. Samaranayake L P, Johnson N W. Guidelines for the use of antimicrobial agents to minimise development of resistance. *Int Dent J* 1999; **49:** 189-195.
49. Standing Medical Advisory Committee (SMAC). Department of Health. Report on impact of clinical prescribing on antimicrobial resistance published. London: Department of Health, 1998.
50. Sweeney L C, Dave J, Chambers P A, Heritage J. Antibiotic resistance in general dental practice – a cause for concern? *Antimicrob Chemother* 2004; **53:** 567-576.
51. Fine D H, Hammond B F, Loesche W J. Clinical use of antibiotics in dental practice. *Int J Antimicrob Agents* 1998; **9:** 235-238.
52. American Dental Association Council on Scientific Affairs. *Antibiotics in Dentistry* 1997; **128:** 648.
53. Lewis M A, Parkhurst C L, Douglas C W *et al.* Prevalence of penicillin resistant bacteria in acute suppurative oral infection. *J Antimicrob Chemother* 1995; **35:** 785-791.
54. Lewis M A O, Carmichael F, MacFarlane T W, Milligan S G. A randomised trial of co-amoxiclav versus penicillin V in the treatment of acute dentoalveolar abscess. *Br Dent J* 1993; **175:** 169-174.
55. Flynn T R, Shanti R M, Hayes C. Severe odontogenic infections, part 2: prospective outcomes study. *J Oral Maxillofac Surg* 2006; **64:** 1104-1113.
56. Lewis M A O. Why we must reduce dental prescription of antibiotics: European Union Antibiotic Awareness Day. *Br Dent J* 2008; **205:** 537-538.
57. Eick S, Pfister W, Straub E. Antimicrobial susceptibility of anaerobic and capnophilic bacteria isolated from odontogenic abscesses and rapidly progressive periodontitis. *Int J Antimicrob Agents* 1999; **12:** 41-46.
58. Kuriyama T, Williams D W, Yanagisawa M *et al.* Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics. *Oral Microbiol Immunol* 2007; **22:** 285-258.
59. Brook I, Lewis M A, Sandor G K *et al.* Clindamycin in dentistry: more than just effective prophylaxis for endocarditis? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100:** 550-558.
60. Addy L D, Martin M V. Clindamycin and dentistry. *Br Dent J* 2005; **199:** 23-26.
61. Stefanopoulos P K, Kolokotronis A E. Controversies in antibiotic choices for odontogenic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **101:** 697-698.
62. Zetner K, Schmidt H, Pfeiffer S. concentrations of clindamycin in the mandibular bone of companion animals. *Int J Antimicrob Agents* 2003; **4:** 166-171.
63. Kirkwood K L. Update on antibiotics used to treat orofacial infections. *Alpha Omegan* 2003; **96:** 28-34.
64. Mueller S C, Henkel K, Neumann J *et al.* Perioperative antibiotic prophylaxis in maxillofacial surgery: penetration of clindamycin into various tissues. *J Craniomaxillofac Surg* 1999; **27:** 172-176.
65. Gilbert D N, Moellering R C Jr, Eliopoulos G M, Sande M A. *The Sandford Guide to Antimicrobial Therapy, Inc.* 2005; **30:** 33.
66. Reese R E, Betts R F, Gumustop B. Clindamycin. *In Handbook of antibiotics.* 3rd ed. pp 435-440. Philadelphia: Lippincott-Williams & Wilkins, 2000.
67. Simmons N A, Ball A P, Cawson R A *et al.* Antibiotic prophylaxis and infective endocarditis. *Lancet* 1992; **339:** 1292-1293.
68. Dajani A S, Taubert K A, Wilson W *et al.* Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *JAMA* 1997; **277:** 1794-1801.
69. Pallasch T J. Clostridium difficile-associated diarrhoea and colitis. *J Calif Dent Assoc* 1999; **27:** 405-409, 411-413.
70. Bignardi G E. Risk factors for Clostridium difficile infection. *J Hosp Infect* 1998; **40:** 1-15.
71. Johnson S, Gerding D N. Clostridium difficile –

associated diarrhea. *Clin Infect Dis* 1998; **26:** 1027-1036.
72. Baxter R, Ray G T, Fireman B H. Case-control study of antibiotic use and subsequent *Clostridium difficile*-associated diarrhea in hospitalized patients. *Infect Control Hosp Epidemiol* 2008; **29:** 44-50.
73. Thibault A, Miller M A, Gaese C. Risk factors for the development of *Clostridium difficile*-associated diarrhea during a hospital outbreak. *Infect Control Hosp Epidemiol* 1991; **12:** 345-348.
74. Andrejak M, Schmit J L, Tondriaux A. The clinical significance of antibiotic associated pseudomembranous colitis in the 1990s. *Drug Saf* 1991; **6:** 339-349.
75. Greenwood D, O'Grady F. *Antibiotics and host defences. The Scientific basis of antimicrobial chemotherapy.* Cambridge University Press, 1985.
76. Brause B D, Romankiewicz J A, Gotz V *et al.* Comparative study of diarrhea associated with clindamycin and ampicillin therapy. *Am J Gastroenterol* 1980; **73:** 244-248.
77. Lewis J S, Jorgensen J H. Inducible clindamycin resistance in Staphylococci: should clinicians and microbiologists be concerned? *Clin Infect Dis* 2005; **40:** 280-285.
78. Limeres J, Tomas I, Alvarez M, Diz P. Empirical antimicrobial therapy for odontogenic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100:** 263-264.
79. Barker G R, Qualtrough A J. An investigation into antibiotic prescribing at a dental teaching hospital. *Br Dent J* 1987; **162:** 303-306.
80. Olson A K, Mac Edington E, Kulid J C, Weller R N. Update on antibiotics for endodontic practice. *Compend Contin Educ Dent* 1990; **11:** 328-332.