Review

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Review

Opportunistic Prevotella and the Odontogenic Infection: A Case Series and Review of the Literature

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Abstract: After 29 years of clinical practice treating odontogenic infections of the head, neck and oral cavity, my co-contributors and I sought to determine by a review of the literature and three clinical cases if *Prevotella* species were significant opportunistic pathogens in odontogenic infections of all kinds in the oral and maxillofacial region. We performed a PubMed review of 40 articles using terms associated with odontogenic infections, pericoronitis, *Prevotella* and antibiotics used to treat common oral and maxillofacial infections. Three cases were reported, and the treatment was discussed. An additional 26 articles were reviewed to describe the pathogenesis of *Prevotella.* Given the opportunity to become virulent—such as post-extraction wound healing of an extraction site adjacent to an intact dentition, excessive plaque and calculus, nearby gingivitis or periodontitis, or an immunocompromised host—we wondered if *Prevotella* could be targeted with antimicrobials mitigating, or even resolving, odontogenic infections in those cases refractory to conservative surgical therapy that includes source control. We found that *Prevotella* is a significant opportunistic pathogen in odontogenic infections. *Prevotella* is susceptible to Metronidazole (Flagyl), and it is effective in mitigating the disease process when basic principles of the treatment of odontogenic infections are employed. Infections not responsive to this empiric therapy should be cultured to determine the opportunistic organism's sensitivity and susceptibility to specific antibiotic therapy.

Keywords: *Prevotella*; odontogenic infection; metronidazole (flagyl); pericoronitis

Introduction

Prevotella species are inhabitants of the periodontal sulcus living in the crevicular fluid and in the dental biofilm attached to hard tissue surfaces (teeth) and mucosa. These obligate anaerobic Gram-negative rods are part of the normal oral microbiome and do not prove to be opportunistic in the immunocompetent host [1].

Principles of source control include decreasing the bacterial load by incision (opening the wound introduces air, changing the environment from anaerobic to aerobic, killing obligate anaerobes), drainage (decompressing the swelling, releasing purulent exudate, and promoting the blood supply), irrigation (washing out bacteria, bacterial toxins and inflammatory by-products), and tooth extraction [2]. Empiric antibiotics are used in immunocompromised hosts, severe infections, and infections refractory to surgery targeted at opportunistic *Prevotella* species.

Mixed infections comprising anaerobic, facultative anaerobic, and aerobic bacteria colonize perialveolar and fascial spaces contributing to odontogenic infections of the head and neck that can progress to life- threatening circumstances, including bacteremia, sepsis, airway compromise and death [3,4]. Pericoronitis, perialveolar infections (sometimes called subperiosteal infections), and multi-space odontogenic infections all show evidence of *Prevotella* species as isolates in the mixed

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oral flora. Antibiotic agents targeting *Prevotella* species will be reviewed with the goal of identifying the narrowest spectrum antibiotics—both bactericidal and bacteriostatic—as well as combination antibiotic agents available to treat opportunistic *Prevotella* and its bacterial collaborators in odontogenic infections.

Odontogenic infections are infections of tooth-related origins usually relating to endodontic or periodontal sources [5,6]. Possible etiologies can include necrotic pulp from carious or fractured teeth, pericoronitis, or deep periodontal pockets where bacteria can harbor and cause infections [7]. Anaerobic and aerobic bacteria are implicated in 50–60% of odontogenic infections, with the most commonly isolated facultative anaerobic organisms being Viridans streptococci, and the most commonly isolated obligate anaerobic bacteria include *Bacteroides spp, Prevotella spp, and Peptostretpococcus spp* [5].

Pericoronitis is an infection of the soft tissue around the crown of a partially erupted tooth and is usually caused by normal microorganisms that inhabit the oral cavity [5]. Bacterial plaque can accumulate underneath the soft tissue which may lead to the inflammatory process [8]. The bacteria that are found at the highest levels in symptomatic pericoronitis include *Actinomyces oris, Eikenella corrodens, Eubacterium nodatum, Fusobacterium nucleatum, Treponema denticola, Eubacterium saburreum,* and various *Streptococcus* species [9]. With proper oral hygiene and strong host defenses, most patients can eliminate the bacteria that are trapped under the operculum without leading to further complications or infections. If the bacteria are not removed under the operculum, pericoronitis can lead to jaw inflammation and phlegmon [10]. If the infection ensues, it may spread, causing a multi-space infection of the head and neck regions.

Management of infections in the oral cavity requires the clinician to have fundamental knowledge of the anatomy of the head and neck region, specifically the fascial planes through which infections can spread. Odontogenic infections typically begin as vestibular space abscesses where the infection is localized and treated easily [5]. The infection, when localized, may present as an abscess, swelling, cellulitis, and trismus. If the infection persists and spreads, the infection will take the path of least resistance, potentially leading to life-threatening complications. Management of odontogenic infection includes controlling the source of the infection by surgical removal, establishing drainage, and mobilizing the host defense system to fight the infection.

Chlorhexidine (CHX) is a broad-spectrum antimicrobial agent commonly used by dental practitioners and the public due to its effectiveness in limiting plaque and biofilm formation. If plaque and biofilm are allowed to flourish and grow, this could result in caries and gingivitis which could progress to periodontitis. The mechanism of action of chlorhexidine is disrupting cellular membranes to kill microorganisms that inhabit the oral cavity. There is some evidence that illustrates that the use of CHX post operatively can reduce the likelihood of post-op infections. Additionally, if CHX is used as a pre-operative rinse, post-operative bacteremia is decreased [11].

The generally accepted standard of care in microbiology labs for susceptibility testing is that if a specimen is considered to be contaminated with indigenous flora, susceptibility testing is not necessary, as the results could be misleading. The minimum bactericidal concentration (MBC) is the minimum concentration of antimicrobial capable of inactivating 99.9% of the bacteria present.

The minimum inhibitory concentration (MIC) of an antibiotic is the lowest concentration of the drug that inhibits the growth of the microorganism [12]. For a bactericidal antibiotic, the minimum bactericidal concentration (MBC) is close to the MIC. For a bacteriostatic antibiotic, the MBC is usually much higher than the MIC, and thus it may not be safe to administer such high doses [12].

Prevotella Pathogenesis

The *Prevotella* species, *P. buccae, P. intermedia, P. loescheii, P. melaninogenica, P. nigrescens* are pleomorphic, strict anaerobes, and form black-pigmented colonies. They can convert glucose into acetic acid and succinic acid, and require vitamin K and hemin for growth. *P. intermedia* is [normally] associated with chronic periodontitis and endodontic infections. Its virulence factors include phospholipase A, IgA/IgG proteases, mercaptans, and hydrogen sulfide [12].

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P. intermedia is one of the microorganisms in the "orange complex," as decribed by Socransky et al. [13] Increasing the colonization of periodontal plaque with microorganisms in this group, which also includes *Fusobacterium nucleatum* and *Peptostreptococcus micros*, leads to more sites being colonized by *Tannerella forsythia*, *Porphyromonas gingivalis* and *Treponema denticola*, which are, in turn, characterized as the "red complex" [12,13].

In 1990, the moderately saccharolytic and predominantly oral species, Bacteroides oralis and B. melaninogenicus, were reclassified in the genus Prevotella [14], and the genus name Bacteroides was restricted to Bacteroides fragilis and closely related species, including B. thetaiotaomicron.

Several strains of *P. intermedia* were found to inhibit the mitogen-or antigen-induced proliferation of B-cells and T-cells, suggesting that immunosupression mediated by periodontal bacteria may contribute to the pathogenesis of periodontal disease [15]. *P. intermedia* can bind to the basement membrane protein, laminin, which is abundant in the periodontal pocket [16]. It ferments glucose and sucrose, hydrolyzes starch, and produces various acids as metabolic end products, including acetic and succinic acids [17].

P. intermedia expresses a 65 kD molecule that acts as a receptor for the Fc region of human IgG, thereby shielding the bacterium from the humoral response of the host [18]. A 38 kD cysteine protease of *P. intermedia* completely degrades IgG, IgA and IgM within 24 h [19]. *P. intermedia* has hemolytic activity that enables it to acquire iron for its metabolism [20]. It also has hemoglobin receptors that can bind hemoglobin with a K_{diss} of $2.5x10^{-8}$ M [21], and has hemagglutination activity associated with its fimbriae [21].

Another virulence factor of *P. intermedia* is interpain A, which degrades the C3 component of complement, synergistically with gingipains [22]. Interpain A can also activate the C1 complex in serum, which results in the deposition of C1q on inert and bacterial surfaces. Endodontic pathogens, particularly *P. intermedia*, can kill infiltrating neutrophils, which may be a mechanism by which endodontic infections get established [23]. *P. intermedia* has the highest DNA degradation ability among periodontopathogenic bacteria, which may explain its ability to escape neutrophil extracellular traps [24].

P. intermedia lipopolysaccharide (LPS) can induce IL-8 gene expression in human dental pulp fibroblasts. This ability appears to be specific to *P. intermedia* LPS, since synthetic LPS and *Salmonella* LPS do not increase IL-8 mRNA levels in the host cells [25]. *P. intermedia* LPS stimulates the production of tumor necrosis factor-alpha (TNF-α) in monocyte-derived macrophages by activating the three types of mitogen-activated protein kinases (MAPKs), ERK1/2, JNK1/2 and p38 [26].

The adhesion of *P. intermedia* to HEp-2, KB and HeLa cells and fibroblasts is inhibited by lactoferrin in a dose-dependent manner [27].

In patients with advanced periodontal disease, systemic administration of metronidazole plus amoxicillin inhibits the growth of *Aggregatibacter actinomycetemcomitans*, *P. gingivalis* and *P. intermedia*, and causes a reduction in the inflammatory lesion [28]. The MIC for metronidazole against *P. intermedia* was found to be about 1 μg/mL [29].

Among other bacteria, *P. buccae* was found in peri-implant bone defects [30], periodontitis [31,32], root canal infections [33], and radicular cysts [34].

Metronidazole

Metronidazole is a commonly used antibiotic and antiprotozoal medication belonging to the nitroimidazole class. It is synthetically derived from azomycin which was originally detected in *Streptomyces spp*. in the 1950s [35]. In 1962, it was used for the treatment of vaginitis due to *Trichomonas vaginalis* and has also been effective in treating patients with gingivitis. Metronidazole is the first choice in the treatment of *Clostridium difficile* [35].

Metronidazole exerts its antimicrobial effects through a stepwise mechanism. It is first taken into the microorganism by diffusion across the cell membranes of anaerobic pathogens [36]. It exerts its antimicrobial effects after the reduction of its nitro group through the transfer of an electron, activating the prodrug and creating reactive intermediates and radicals that are toxic to the

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microorganisms, leading to the inhibition of growth or outright killing by the breaking of DNA strands [35].

Metronidazole is absorbed rapidly by the gastrointestinal tract often bypassing the enterohepatic circulation, as observed in studies with mice and rats [35]. The liver breaks down metronidazole into 5 metabolites. The hydroxy metabolite has a longer half-life than its parent compound. The majority of metronidazole and the metabolites are excreted in the subject's urine and feces, with approximately 12% being excreted unchanged [37].

Metronidazole Disulfiram-Like Reaction

There is a commonly known association of a disulfiram-like reaction with the use of metronidazole and alcohol. Disulfiram is a medication commonly used to treat alcohol dependence. Its mechanism of action is to inhibit the enzyme aldehyde dehydrogenase thus leading to the accumulation of acetaldehyde [38]. Metronidazole has a similar mechanism. While it does not inhibit aldehyde dehydrogenase, it does inhibit alcohol dehydrogenase. When alcohol is mixed with disulfiram or metronidazole there are a range of unpleasant symptoms that accompany the build-up of acetaldehyde. Common symptoms include nausea, vomiting, abdominal pain, flushing of the face, tachycardia, throbbing headaches, and syncope. In more severe cases some of these symptoms may include respiratory depression, cardiovascular collapse, arrhythmias, convulsions, and death [39].

While *Prevotella* has been shown to be highly susceptible to metronidazole, the symptoms associated with the disulfiram-like reactions are a contributing factor for health care providers not wanting to prescribe this antibiotic.

Methods

We performed a comprehensive search of the medical literature to review the information regarding *Prevotella's* relationship to odontogenic infections and the antibiotics used to mitigate its opportunity to become virulent. The PubMed database was searched using the following terms: "*Prevotella* AND Odontogenic Infection AND (OR Amoxicillin OR Clindamycin OR Metronidazole OR Flagyl)". We identified 46 articles from 1996 to 2024 of which 40 were published in English. Twenty-six additional references were used to develop the section on *Prevotella* pathogenesis, and other publications were cited within the paper. A total of 76 references were reviewed and cited. Foreign language papers were excluded from our study. Observational/retrospective studies, literature reviews, and randomized controlled trials were reviewed.

Case Series

CASE 1: Perialveolar Infection

A 25-year-old female presented for extraction of teeth numbers 1, 16, 17, and 32. Her medical history was unremarkable. The surgery was performed with removal of bone, sectioning of teeth and irrigation with dilute Chlorhexidine 0.12% mouthwash and sterile saline. The surgical sites were closed with 4.0 chromic gut sutures. She returned to the office for a post-operative visit one week later that revealed pink healthy healing mucosa in four quadrants. There was no erythema, edema or exudate. The sockets were irrigated with sterile saline alone, and there was no evidence of food impaction. The sutures were removed at this visit. She was told to return to the office if she exhibited any subjective signs of pain or swelling.

21 days after surgery, she returned to the office with concern of yellow fluid in the socket of tooth #17, swelling and mild pain. The floor of mouth and buccal space were not involved. The socket was gently opened with cotton pliers and irrigated with 20 ml of dilute Chlorhexidine 0.12% mouthwash mixed with sterile saline. A prescription was given for Amoxicillin 500 mg, 15 tablets, take one by mouth three times a day until completed. An empiric antibiotic approach with conservative irrigation and drainage was performed as in many perialveolar infections we have treated before.

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29 days after surgery she returned to the office with concern of yellow fluid in the socket of tooth #32, swelling and mild pain. The floor of mouth and buccal space were not involved. The socket was gently opened with cotton pliers and irrigated with 20 ml of dilute Chlorhexidine 0.12% mouthwash and sterile saline. A prescription was given for Chlorhexidine 0.12% mouthwash and the patient was instructed to irrigate the socket twice a day with Chlorhexidine 0.12% mouthwash alone for one week. A new prescription was given for Clindamycin 300 mg, 20 tablets, take one by mouth four times a day until gone.

The patient returned on Day 36 for follow-up and the #32 socket was irrigated with dilute Chlorhexidine 0.12% and sterile saline without evidence of purulent exudate.

On day 45, the patient called the weekend on-call doctor and reported there was exudate coming from the #32 socket again. The doctor explained to the patient that tissue levels of the antibiotic were never achieved and prescribed Amoxicillin 500 mg, 40 tablets, "take one by mouth three times a day until gone."

On day 47, we saw the patient, concerned that there was a resistant bacterium colonizing the #32 space. The #17 space was without evidence of erythema, edema or exudate at this time. Incision and drainage were performed at this site and there was no evidence of purulent exudate. Cultures were taken at the #32 site for anaerobic and aerobic bacteria, a Gram stain and antibiotic sensitivity testing were requested. The socket of #32 revealed caseous material and shiny white collagen-like tissue. The area was irrigated with 60 ml of dilute Chlorhexidine 0.12% mouthwash and sterile saline. The patient continued taking the Amoxicillin.

On day 50, after completing the Amoxicillin prescription, the patient called and reported that the #17 site was draining purulent exudate. The Gram's stain results for the #32 socket reported, "No white blood cells. No organisms seen." The aerobic culture reported at day 51 revealed, "Moderate growth of normal oral flora from the #32 extraction wound." The anaerobic culture reported at day 53 revealed, "*Prevotella buccae* isolated with heavy growth." (Table 1).

Table 1. MBC for *Prevotella buccae* (anaerobic gram-negative rod).

	Anaerobic Gram-negative rods MBC (μg/mL)	
Ampicillin + Sulbactam	1	Susceptible
Clindamycin	256	Resistant
Meropenem	0.25	Susceptible
Metronidazole	0.5	Susceptible

The #17 site was opened with cotton pliers, irrigated with 20 ml dilute Chlorhexidine 0.12% and sterile saline, and the fluid was cultured again. Only one report was filed by the hospital microbiology department, "Moderate growth of mixed oropharyngeal flora was isolated. Final report."

Based on the anaerobic culture and sensitivity results from the day 50 surgery, Metronidazole 500 mg, 40 tablets, "take one by mouth four times a day until gone," was prescribed. The patient continued to irrigate the #17 socket at home with dilute Chlorhexidine 0.12% and water. The patient was followed weekly for improvement and there was no recurrence of the perialveolar infections at the #17 or #32 sockets.

We had never treated a refractory perialveolar infection like this in 18 years of private practice. Therefore, it is important to emphasize careful follow-up and repeated surgical interventions to mitigate these odontogenic infections.

CASE 2: Multi-space Odontogenic Infection

A 23-year-old male patient presented from the hospital emergency department to the lead author's private office to be evaluated for an oral infection. His medical history was unremarkable. Six days prior, he was treated for a carious impacted tooth #32 by a community dental provider and the tooth was removed. An Amoxicillin prescription was given upon discharge. He was given intravenous Clindamycin at the hospital.

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Upon examination, his temperature was 99.4° F and he was trismatic to 1 cm of mouth opening. The perialveolar, buccal and sublingual spaces exhibited moderate edema. There was purulent exudate expressed from the socket of tooth #32. Nitrous oxide-Oxygen sedation was used to facilitate oral opening to approximately 3 cm. Incision and drainage surgery was performed with full thickness mucoperiosteal flap, 5 ml of purulent exudate was removed, and the space was irrigated with dilute Chlorhexidine 0.12% mouthwash and sterile saline. The surgical site was left open for continued drainage. Cultures of the extraction socket of #32 were taken for Gram's stain, aerobic bacteria, and anaerobic bacteria and sent to the hospital. The patient returned to the hospital for intravenous blood testing and observation.

A Complete Blood Count with differential analysis was ordered and the results revealed "White blood cells 12.4K, 86% Neutrophils." The Gram's stain revealed, "Moderate white blood cells, few Gram-positive cocci, few Gram-negative rods, and rare Gram-positive rods." The aerobic culture revealed, "Light growth *Eikenella corrodens*, light growth normal oral flora, rare growth *Streptococcus anginosus (S. milleri* group)."

We recommended the hospitalist send him home with Metronidazole 500 mg, 40 tablets, take one tablet every six hours until gone.

The patient was followed in the private office the next day with improvement of trismus, swelling and pain. He was instructed to rinse with Chlorhexidine 0.12% diluted with water at home for one week. At day 3 post incision and drainage, the anaerobic culture was returned and revealed, "Mixed varieties of *Prevotella* species isolated. Light growth of mixed anaerobic flora including *Prevotella buccae*." CLSI standards lead the microbiology laboratory to not do antibiotic sensitivity testing as no bacteria revealed itself in high quantities outside the expected mixed odontogenic normal flora.

The patient was seen again in the lead author's office at post operative day 8 with resolution of his infection.

CASE 3: Severe Pericoronitis

A 42-year-old male presented to the office with acute pericoronitis, trismus and pain. The patient had an unremarkable medical history. His vital signs were BP 160/110 with a HR of 90. His BMI was 33. Upon oral evaluation, he exhibited a severe pericoronitis associated with tooth #17 which had extended into the left buccal space. There was no floor of mouth raise or purulent exudate present. He was trismatic to approximately 2 cm of oral opening. After he was examined in the private office, he was sent to the hospital for impending surgery and intravenous antibiotics. He was advised to have nothing to eat or drink (NPO) until surgery in the operating room under general anesthesia. We prescribed Unasyn (ampicillin-sulbactam) 3 g intravenously upon arrival at the hospital, due to trismus and the suspicion of an advancing polymicrobial infection.

Surgery was performed in the operating room under oral-endotracheal general anesthesia. A full thickness mucoperiosteal was elevated and tooth #17 was extracted with removal of alveolar bone, and the space was irrigated with Chlorhexidine 0.12% mouthwash diluted with sterile saline, approximately 60 ml. There was serosanguinous fluid in the buccal space without the presence of purulence indicative of cellulitis. The wound was left open to promote drainage. Cultures were taken for aerobic and anaerobic bacteria, and a Gram Stain was requested from the laboratory. The Gram Stain revealed, "Many white blood cells, moderate Gram-positive cocci, and few Gram-negative rods." The aerobic culture revealed, "Moderate growth of mixed skin flora, light growth of *Klebsiella oxytoca*, light growth of *Streptococcus anginosus* (*S. Milleri* group)." Three days later, the anaerobic culture revealed, "Heavy *Fusobacterium*, moderate growth *Parvimonas micra* (*Peptostreptococcus micros*), and moderate growth of mixed varieties of Prevotella species including *Prevotella intermedia*." (Table 2).

The patient was discharged that day with a prescription for Metronidazole 500 mg, 28 tablets, take one tablet four times a day until gone; Augmentin 875 mg, 14 tablets, take one tablet twice a day until gone; Chlorhexidine 0.12% mouthwash, rinse ½ oz. twice a day and spit out, for one week. We also prescribed an opioid-containing analgesic as needed for pain.

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The patient was followed in the office the next day for improvement and his symptoms had subsided by the one-week post-operative examination.

Table 2. Susceptibility Testing for Prevotella intermedia and Fusobacterium species.

Susceptibility		
Prevotella intermedia		
Antibiotic	*Interpretation*	*Value Comment* (µg/mL)
Ampicillin + Sulbactam	Susceptible	<=0.03
Clindamycin	Susceptible	<=0.03
Meropenem	Susceptible	0.06
Metronidazole	Susceptible	0.12
Fusobacterium Species		
Ampicillin + Sulbactam	Susceptible	<=0.03
Clindamycin	Susceptible	0.06
Meropenem	Susceptible	0.03
Metronidazole	Susceptible	<=0.03

Results of the Literature Review and Discussion

The microbiome of the oral cavity is one of the most varied floras in the human body. The variety of bacteria in the oral cavity is a result of the many microenvironments, caused by the various surfaces of teeth, the gingival sulcus, buccal mucosa, and tongue [40]. Each organism has a unique set of conditions that allows the bacteria to survive in that region. Each location in the oral cavity has appropriate nutrients and oxygen tension or physical protection from unfavorable conditions [40]. Plum et al. have proposed that *Streptococcus salivarius* and *Veillonella spp.* often colonize the tongue and buccal surfaces; *Actinomycetes* and *Streptococcus spp* often colonizes the enamel of teeth; and *Fusobacterium, Prevotella, Porphyromonas,* and *Spirochetes* colonize gingival surfaces [41]. *When* managing odontogenic infections, it is important to understand the nature of the flora and the environment – specifically analyzing the organism's oxygen requirement, which will be crucial when identifying the possible bacteria and how to treat the infection. The most common causes of odontogenic infections include caries (65%), pericoronitis (36%) and periodontitis (21%) [42,43]. The teeth most commonly implicated in these infections are those located in the lower posterior segments, according to Sanchez et al. Approximately 61.5% of the cases studied had involvement of the mandibular premolars and molars, followed by the second most frequent causal tooth–the mandibular third molars at 26.6% [44]. The suspected reason for the mandibular molars being the teeth most commonly implicated is due to the teeth lying below the mylohyoid line. The mylohyoid line is a bony ridge to where the mylohyoid muscle attaches and forms the floor of the mouth. The mylohyoid line runs just above the roots of the mandibular molar. Should these teeth develop infections and spread beyond the tooth itself, the infection can extend into the most frequently involved space, the submandibular space, with the potential of spreading further into the deeper neck spaces [2,45,46]. Deep fascial space infections of the neck are most frequently odontogenic in origin and can be life-threatening if the mandibular abscess extends to the adjacent fascial space [47,48]. Severe complications with the spread of odontogenic infection into the deep fascial spaces include descending necrotizing mediastinitis, orbital cellulitis, septic cavernous sinus thrombosis, cerebral abscess, meningitis, necrotizing fasciitis, Lemierre's syndrome, osteomyelitis, endocarditis, and sepsis [40,49,50]. To prevent the dissemination of bacteria into deep fascial spaces, antibiotics are commonly prescribed to aid in treating the odontogenic infection [6].

In line with recent studies addressing the treatment of odontogenic abscesses, the most prevalent anaerobic bacteria were: *Prevotella spp*. *Peptostreptococcus (Micromonas micros*), *Bacteroides*, and different species of *Actinomyces, F. nucleatum* comprised 53% of the anaerobes [40,42,44,49–52]. The aerobic and facultative anaerobes found in high count include: Viridans streptococci, alpha-hemolytic streptococci, *S. aureus, and E. coli.* [40,42,50,53,54] Fungi have also been collected in small cultures [44]. When addressing larger odontogenic infections, the bacteria involved are more pathogenic than those predominantly isolated from smaller odontogenic infections [55].

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Of the cases studied, one-third of the patients were successfully treated solely with incision and drainage. Penicillin has been the antibiotic of choice for uncomplicated dental infections because of its activity against many facultative and anaerobic organisms recovered from these mixed infections [51]. Only in severe abscesses is penicillin prescribed following surgical incision and drainage [53]. The administration of the penicillin drug class is considered to be useful for the empirical management of odontogenic infections, as described by other studies published in Spain [44]. The advantages of such treatment are based upon the bacteria susceptibility to the antibiotic as well as the low cost [44,56–58]. However, some authors have found that PEN-resistant organisms are increasingly isolated from abscesses of odontogenic origin due to the production of β-lactamase which restricts the effectiveness of the penicillin [10,42,54,58–60]. The ability of species to synthesize β-lactamase should be determined before treating with β-lactam antibiotics to avoid potential antibiotic resistance [61]. Patel et al. found *Prevotella* to be the most prevalent in producing β-lactamase, followed by *Capnocytophaga, Veillonella* and *Bacteroides* [62]. The β-lactamase produced protects the bacteria and other surrounding bacteria in the polymicrobial niches against antibiotic activity [63]. There are several mechanisms through which microorganisms can gain resistance to β-lactam antibiotics. These include alteration in penicillin-binding proteins, and barriers to target sites, and the ability to inactivate the antibiotic through production of β-lactamase. *Prevotella*'s resistance to β-lactam antibiotics results from the expression of β-lactamase genes. Kuriyama et al. have found *Prevotella* to have many β-lactamase positive strains. When considering penicillin use, it is important to ascertain whether the patient has allergies to this or other antibiotics.

Other antibiotics that have proven to be effective include penicillinase-resistant penicillin, clindamycin, or a combination of metronidazole plus amoxicillin or a macrolide [51]. Metronidazole has been studied extensively and has been seen to have excellent activity (100%) against all the anaerobic isolates, but possesses little to no activity against aerobes [42,64]. Chan et al. have found there to be a possible decrease in therapeutic effectiveness when metronidazole is used alone [65]. Ciprofloxacin, amoxicillin with a beta-lactam inhibitor like clavulanic acid and clindamycin were also effective [42,66]. Maestre et al. found that *Prevotella* isolates were susceptible to amoxicillin-clavulanic acid, while amoxicillin alone exhibited resistance rates ranging from 17.1% in *P. buccae* to 26.3% in *P. denticola.* In all *Prevotella* species, resistance rates to metronidazole were below 6%, and clindamycin resistance ranged from 0%–21.1% [67]. When looking at *P. buccae*, *P. denticola,* and *P. intermedia,* resistance rates were found to range from 9.1% to 21% for clindamycin, 0% to 5.9% for metronidazole, and 5.9% to 36.4% for tetracycline [67].

In a study from Central India published in 2018, the effectiveness of different antibiotics on anaerobic isolates was examined. Their results found 0/8 susceptible to penicillin, 6/8 susceptible to CLI, 8/8 AMOX + Cl, and 8/8 Metronidazole [42]. For those who have PEN allergies, Sobotka et al. found clindamycin (CLI), erythromycin, tetracyclines, and levofloxacin (LVX) to be adequate alternative regimens [54]. The family of tetracycline antibiotics has been available and commonly prescribed since the mid-1950s [65]. Because of its widespread use and emergence of drug-resistant microorganisms, a culture and sensitivity test should be performed prior to prescribing tetracycline or its derivatives to ensure its effectiveness.

There has been some discussion of the use of combination therapy. Alou et al. found eradication of β-lactamase producing strains to be achieved quicker by the use of combination therapy of amox/clav + tinidazole and by clindamycin + tinidazole than by a β-lactam antibiotic alone.

Based upon literature researched and clinical cases, when a specimen contains a single organism considered to be an opportunistic pathogen, or if there is a clear predominance of growth in a mixed culture, then susceptibility testing is performed on that organism. Occasionally, however, when known empiric therapies are found to be effective, such antibiotics will be prescribed without susceptibility testing. For example, a culture with *Eikenella sp.* and *S. anginosus* found in small quantities among other indigenous flora of the oral cavity, no susceptibilities would be performed. For *Eikenella*, oral therapy with Amoxicillin/clavulanate (Augmentin) is a well-accepted treatment. This would also cover *S. anginosus* as well as much of the indigenous flora. Even for anaerobic infections—these are often polymicrobial and often do not require susceptibility testing—empiric

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therapy including surgery is usually curative [46]. If susceptibility testing is needed for anaerobic organisms such as *Prevotella*, Metronidazole is reliable as the first line of empiric treatment, as resistance in these organisms to Metronidazole is uncommon [45]. Meropenem is used by Kaiser Permanente as it tends to be a standard antibiotic used for anaerobic susceptibility testing.

To aid in the antimicrobial effectiveness, determination of the breakpoint values are important in analyzing susceptibility data for different species of organisms. The breakpoint value is used to categorize bacteria as susceptible, intermediate, or resistant to that specific antibiotic. In the present study, the susceptibility breakpoints were determined by NCCLS (National Committee for Clinical Laboratory Standards) criteria. Breakpoints are determined based on data concerning the clinical outcome, the pharmacology of the agents, which includes the tissue and serum concentrations, the degree of protein-binding, and the susceptibility of bacteria to antimicrobial agents. When antibiotics are administered, concentrations of antibiotics in oral and maxillofacial regions are much smaller than those found in serum samples. This could be a result of the various factors of pharmacokinetics including absorption, distribution, metabolism and excretion. Additionally, in specific sites there may be barriers that limit the ability for the antibiotic to penetrate through membranes resulting in lower concentrations than serum levels.

The Clinical and Laboratory Standards Institute (CLSI) publishes standards for susceptibility testing and an antibiogram for anaerobic organisms (Table 3). The table shows that 99% of *Prevotella* samples tested were susceptible to Metronidazole. Other than Clindamycin and Moxifloxacin, most oral and IV therapies have excellent *Prevotella* coverage. The table also reports that approximately 30% of *Prevotella spp.* are resistant to Clindamycin.

Table 3. Anaerobic Organisms Other Than *Bacteroides spp.* and *Parabacteroides spp.* Reprinted with permission from Clinical and Laboratory Standards Institute from: CLSI. *Performance Standards for Antimicrobial Susceptibility Testing.* 30th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2020. (With permission).

	Ampicillin-Sulbactam			Pipercillin-tazobactam			Imipenem			Meropenem		
Anaerobic Organisms	**# of strains**	**%S**	**%R**	**# of strains**	**%S**	**%R**	**# of strains**	**%S**	**%R**	**# of strains**	**%S**	**%R**
Prevotella spp.	29	97	3	63	100	0	29	100	0	92	98	0
Fusobacterium spp	20	100	0	55	96	2	75	95	4	20	100	0
Anaerobic gram positive cocci	-	-	-	1853	99	1	134	99	0	1647	100	0
Clostridium perfringens	15	100	0	410	100	0	23	100	0	417	100	0
Clostridioides	76	99	0	542	93	0	480	69	4	609	99	0
Clostridium spp.	-			439	94	1	71	99	0	390	100	0
	Penicillin			**Clindamycin**			**Moxifloxacin**			**Metronidazole**		
Anaerobic Organisms	**# of strains**	**%S**	**%R**	**# of strains**	**%S**	**%R**	**# of strains**	**%S**	**%R**	**# of strains**	**%S**	**%R**
Prevotella spp.	63	100	0	29	69	28	92	66	25	92	99	0
Fusobacterium spp	-	-	-	75	77	21	75	68	23	75	95	5
Anaerobic gram positive cocci	1647	100	0	1826	97	3	300	72	21	0	100	0
Clostridium perfringens	402	90	4	425	83	12	23	83	9	425	100	0
Clostridioides	533	6	37	1013	32	38	480	74	25	1343	100	0
Clostridium spp.	390	69	13	461	67	25	71	62	35	461	100	[i]

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What we have observed over 29 years of clinical practice is that *Prevotella* is often resistant to β-lactam antibiotics. We see refractory infection when Amoxicillin is given, and we see those patients that continue to be reinfected after Cleocin is given as well. We see more of these refractory infections, as Amoxicillin has become more popular as an antimicrobial used to treat odontogenic infections. We believe Amoxicillin became popular in light of Viridans group streptococcal (VGS) infective endocarditis (IE) prophylaxis for dental procedures, its minimal side effects, and for its improved absorption from the gastrointestinal tract, providing higher and more sustained serum concentrations. Viridans group streptococci are common to the oral microbiome and have been shown to be antagonistic to periodontal pathogens such as *Prevotella* and other obligate anaerobes. Opportunistic bacterial pathogens have also been shown to begin to mutate after just days of antibiotic administration used for both prophylaxis against surgical wound infections or for the treatment of established oral and maxillofacial infections.

We are surprised that Penicillin has been reported as 100% effective in killing *Prevotella* according to the CLSI table. We also suspect that we did not see *Prevotella* becoming an opportunistic pathogen in light of the old-fashioned "Penicillin plus Flagyl" regimens for odontogenic infections, as the Flagyl (Metronidazole) was bactericidal for *Prevotella*. Metronidazole certainly fell out of fashion because of the Disulfiram-like reaction and its poor tolerance due to gastrointestinal upset. It is of interest to note that many antibiotics in the table are intravenous (IV) only. Community providers need a cost-effective and available oral (PO) medication.

The old "Penicillin plus Flagyl" regimen might be the first empiric line, if *Prevotella* is the suspected actor in a mixed flora multispace odontogenic infection or cellulitis. Surgery and Metronidazole alone seems adequate in treating mild to moderate odontogenic infections in the immunocompetent host.

Conclusions

Prevotella, Eikenella, Fusobacterium and other anaerobic Gram-negative organisms (including Viridans streptococci, *Neisseria, Klebsiella* and other facultative anaerobes) are frequently mitigated by surgery and common orally administered antibiotics used to treat odontogenetic infections, including Amoxicillin, Penicillin, Augmentin, and Clindamycin (Table 4). These organisms live as part of the normal oral microbiome and biofilm—with facultative anaerobic and aerobic organisms—but they can become virulent given the opportunity in odontogenic infections. Although any antibiotic can contribute to pseudomembranous colitis, the use of Clindamycin continues to decrease due to its contribution to this disease.

Perioperative irrigation of dilute Chlorhexidine 0.12% mouthwash during dentoalveolar surgery seems to prevent both perialveolar infections and alveolar osteitis. Repeated use of Chlorhexidine in the presence of mixed flora odontogenic infections and pericoronitis may lead to disruption of a protective microbiome—resulting in the selection of resistant microorganisms—giving an opportunity for *Prevotella* to become virulent. Its use is meant to be adjunctive to surgery and systemic antibiotic administration, killing opportunistic bacteria on contact during surgical procedures.

Infections refractory to surgery and empiric antibiotics should be cultured to identify opportunistic organisms. CLSI guidelines should be followed except in light of recurrent infections where *Prevotella* isolates have been identified. *Prevotella buccae* is resistant to both beta lactam antibiotics and Clindamycin. *Prevotella buccae* and other empiric antibiotic-resistant Prevotella species remain part of the oral microbiome and must be ruled out as an opportunistic pathogen in the mixed contaminated isolate.

The principles of surgery including incision, drainage (removing the source of the infection often including tooth extraction, exposing the area to air which kills exposed obligate anaerobes, and decompressing the swelling), and irrigation (decreasing the bacterial load and removing bacterial inflammatory byproducts) will often cure an odontogenic infection in the immunocompetent host.

Metronidazole is bactericidal at appropriate MBC to treat all *Prevotella* species. Multispace odontogenic infections with mixed flora isolates that include obligate anaerobic organisms can be

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very dangerous. Early surgery prior to infections spreading through fascial spaces causing trismus and airway compromise is necessary, as these infections can cause morbidity and mortality.

If treatment of these infections is late in the course of the disease, radiographs including CT scans and infectious disease specialist consultation may be indicated. A polypharmaceutical approach to serious odontogenic infections of the head and neck may be needed to supplement appropriate surgery of the infected areas. Culture and sensitivity testing can guide antibiotic susceptibility choices and MBCs.

Metronidazole seems to be the only oral antibiotic able to kill *Prevotella buccae* and other antibiotic resistant *Prevotella* species, as well as a majority of obligate anaerobes [7]. Tolerance to the disulfiram-like reaction and stomach upset remain side effects of Metronidazole, limiting its use in some patients. Access to intravenous agents killing *Prevotella* species resistant to oral antibiotics often require hospitalization for administration and access to the drugs (Table 4).

Table 4. The number of resistant isolates and the percentage of resistance against different antibiotics and the prevalence of the corresponding resistance genes in *Prevotella* isolates. A.C.M. Veloo, W.H. Baas, F.J. Haan, J. Coco, J.W. Rossen. Prevalence of antimicrobial resistance genes in Bacteroides spp. and Prevotella spp. Dutch clinical isolates, Clinical Microbiology and Infection, Volume 25, Issue 9, 2019, Pages 1156.e9-1156.e13, ISSN 1198-743X, https://doi.org/10.1016/j.cmi.2019.02.017. (With permission).

	Resistant strains (n[%])			
	Amoxicillin	**Meropenem**	**Clindamycin**	**Metronidazole**
Species				
Breakpoint (mg/L)	**R>2**	**R>8**	**R>4**	**R>4**
P. baroniae (n=2)	1 (50.0)	0	0	0
P. bergensis (n=3)	2 (66.7)	0	2 (66.7)	0
P. bivia (n=17)	9 (52.9)	0	2 (11.8)	1 (5.9)
P. buccae (n=13)	5 (38.5)	0	0	0
P. buccalis (n=3)	0	0	0	0
P. copri (n=2_	1 (50.0)	0	1 (50.0)	0
P. denticola (n=7)	4 (57.1)	0	0	0
P. disiens (n=4)	1 (25.0)	0	2 (50.0)	0
P. histicola (n=2)	1 (50.0)	0	0	0
P. intermedia (n=4)	1 (25.0)	0	0	0
P. jejuni (n=2)	2 (100)	0	0	0
P. melaninogenica (n=21)	14 (66.7)	0	1 (4.8)	1 (4.8)
P. nigrescens (n=4)	3 (75.0)	0	1 (25.0)	0
P. oris (n=2)	2 (100)	0	0	0
P. timonensis (n=6)	1 (16.7)	0	1 (16.7)	0
Prevotella spp. (n=7)	1 (14.3)	0	0	0
Total, n (%)	48 (48.5)	0	10 (10.1)	2 (2.0)

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A quality comprehensive history and physical exam is essential to diagnosing odontogenic infections. We are suggesting the following treatment algorithm based on our case series and literature review:

Mild Odontogenic Infection (e.g., mild pericoronitis, perialveolar infection, chronic or acute suppurative periodontitis, periapical abscess)

a) Surgery alone in the immunocompetent host without comorbid disease
b) Surgery plus Metronidazole in patients who are immunocompromised or have comorbid disease

Moderate Odontogenic Infection (e.g., single fascial space involvement, trismus)

a) Surgery plus Metronidazole
b) Surgery, Metronidazole, Aminopenicillin with β-lactamase inhibitor.
c) Culture and sensitivity guidance to identify specific opportunistic pathogens at appropriate MBC

Advanced Odontogenic Infection (e.g., multiple fascial spaces, airway compromise, reinfection refractory to initial surgical and antibiotic treatment)

a) Surgery, Metronidazole, Aminopenicillin with β-lactamase inhibitor
b) Culture and sensitivity antibiotic guidance at appropriate MBC
c) Additional surgery for reinfection or non-improvement of symptoms
d) Infectious Disease Physician consultation and antibiotic treatment guidance

In patients allergic to β-lactam antibiotics, Clindamycin, Macrolides, Fluoroquinolones, and Aminoglycosides have been effective in mitigating the growth of opportunistic bacterial pathogens in odontogenic infections. These agents have been used in combination to treat the Viridans Streptococci and anaerobic bacteria that contribute to mixed flora odontogenic infections.

We adhere to the principles of antibiotic administration that includes using appropriate MBC, short duration antibiotic therapy to prevent resistant strains of bacteria in oral disease. We look forward to research that isolates *Prevotella* species in odontogenic infections and determines its ability to be mitigated by antibiotics that kill *Prevotella* species resistant to β-lactam antibiotics and Clindamycin. Traditional surgical treatment is always the standard of care in odontogenic infections, with or without adjunctive antibiotics.

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References

1. Kau, S., et al., The facultative human oral pathogen Prevotella histicola in equine cheek tooth apical/ periapical infection: a case report. BMC Vet Res, 2021. **17**(1): p. 343.
2. Bahl, R., et al., *Odontogenic infections: Microbiology and management.* Contemp Clin Dent, 2014. **5**(3): p. 307-11.
3. Fe Marques, A., et al., Septic arthritis of the knee due to Prevotella loescheii following tooth extraction. Med Oral Patol Oral Cir Bucal, 2008. **13**(8): p. E505-7.
4. Al-Nawas, B. and M. Maeurer, Severe versus local odontogenic bacterial infections: comparison of microbial isolates. Eur Surg Res, 2008. **40**(2): p. 220-4.
5. Hupp, J.R., E. Ellis, and M.R. Tucker, *Contemporary oral and maxillo surgery*. Seventh edition. ed. 2019, Philadelphia, PA: Elsevier. xii, 708 pages.
6. Cuevas-Gonzalez, M.V., et al., Antimicrobial resistance in odontogenic infections: A protocol for systematic review. Medicine (Baltimore), 2022. **101**(50): p. e31345.
7. Ardila, C.M. and J.A. Bedoya-Garcia, Antimicrobial resistance in patients with odontogenic infections: A systematic scoping review of prospective and experimental studies. J Clin Exp Dent, 2022. **14**(10): p. e834-e845.
8. Huang, X., et al., Microbial Profile During Pericoronitis and Microbiota Shift After Treatment. Front Microbiol, 2020. **11**: p. 1888.
9. Ribeiro, M.H.B., et al., Microbial profile of symptomatic pericoronitis lesions: a cross-sectional study. J Appl Oral Sci, 2020. **28**: p. e20190266.
10. Kaneko, A., et al., Antimicrobial susceptibility surveillance of bacterial isolates recovered in Japan from odontogenic infections in 2013. J Infect Chemother, 2020. **26**(9): p. 882-889.
11. Arteagoitia, I., C. Rodriguez Andrés, and E. Ramos, Does chlorhexidine reduce bacteremia following tooth extraction? A systematic review and meta-analysis. PLoS One, 2018. **13**(4): p. e0195592.
12. Dưzgünes, N., *Medical microbiology and immunology for dentistry*. 2016, Chicago: Quintessence Publishing Co, Inc. xi, 290 pages.
13. Socransky, S.S., et al., *Microbial complexes in subgingival plaque.* J Clin Periodontol, 1998. **25**(2): p. 134-44.
14. Shah, H.N. and D.M. Collins, Prevotella, a new genus to include Bacteroides melaninogenicus and related species formerly classified in the genus Bacteroides. Int J Syst Bacteriol, 1990. **40**(2): p. 205-8.
15. Shenker, B.J., L. Vitale, and J. Slots, Immunosuppressive effects of Prevotella intermedia on in vitro human lymphocyte activation. Infect Immun, 1991. **59**(12): p. 4583-9.
16. Kalfas, S., et al., *Laminin binding to Prevotella intermedia.* Oral Microbiol Immunol, 1992. **7**(4): p. 235-9.
17. Shah, H.N. and S.E. Gharbia, Biochemical and chemical studies on strains designated Prevotella intermedia and proposal of a new pigmented species, Prevotella nigrescens sp. nov. Int J Syst Bacteriol, 1992. **42**(4): p. 542-6.
18. Labbe, S. and D. Grenier, Characterization of the human immunoglobulin G Fc-binding activity in Prevotella intermedia. Infect Immun, 1995. **63**(7): p. 2785-9.
19. Jansen, H.J., D. Grenier, and J.S. Van der Hoeven, Characterization of immunoglobulin G-degrading proteases of Prevotella intermedia and Prevotella nigrescens. Oral Microbiol Immunol, 1995. **10**(3): p. 138-45.
20. Beem, J.E., W.E. Nesbitt, and K.P. Leung, *Identification of hemolytic activity in Prevotella intermedia.* Oral Microbiol Immunol, 1998. **13**(2): p. 97-105.
21. Leung, W.K., et al., Microbiology of the pericoronal pouch in mandibular third molar pericoronitis. Oral Microbiol Immunol, 1993. **8**(5): p. 306-12.
22. Potempa, M., et al., Interpain A, a cysteine proteinase from Prevotella intermedia, inhibits complement by degrading complement factor C3. PLoS Pathog, 2009. **5**(2): p. e1000316.
23. Matsui, H., et al., Phenotypic characterization of polysaccharidases produced by four Prevotella type strains. Curr Microbiol, 2000. **41**(1): p. 45-9.
24. Doke, M., et al., Nucleases from Prevotella intermedia can degrade neutrophil extracellular traps. Mol Oral Microbiol, 2017. **32**(4): p. 288-300.
25. Nagaoka, S., et al., Interleukin-8 gene expression by human dental pulp fibroblast in cultures stimulated with Prevotella intermedia lipopolysaccharide. J Endod, 1996. **22**(1): p. 9-12.
26. Kim, S.J., et al., Prevotella intermedia lipopolysaccharide stimulates release of tumor necrosis factor-alpha through mitogen-activated protein kinase signaling pathways in monocyte-derived macrophages. FEMS Immunol Med Microbiol, 2007. **51**(2): p. 407-13.
27. Alugupalli, K.R. and S. Kalfas, Inhibitory effect of lactoferrin on the adhesion of Actinobacillus actinomycetemcomitans and Prevotella intermedia to fibroblasts and epithelial cells. APMIS, 1995. **103**(2): p. 154-60.
28. Berglundh, T., et al., The use of metronidazole and amoxicillin in the treatment of advanced periodontal disease. A prospective, controlled clinical trial. J Clin Periodontol, 1998. **25**(5): p. 354-62.

 doi:10.20944/preprints202408.0188.v1

29. Poulet, P.P., D. Duffaut, and J.P. Lodter, Evaluation of the Etest for determining the in-vitro susceptibilities of Prevotella intermedia isolates to metronidazole. J Antimicrob Chemother, 1999. **43**(4): p. 610-1.
30. Augthun, M. and G. Conrads, *Microbial findings of deep peri-implant bone defects.* Int J Oral Maxillofac Implants, 1997. **12**(1): p. 106-12.
31. van Winkelhoff, A.J., et al., *beta-Lactamase producing bacteria in adult periodontitis.* J Clin Periodontol, 1997. **24**(8): p. 538-43.
32. Sharma, G., et al., Fumarate and nitrite reduction by Prevotella nigrescens and Prevotella buccae isolated from Chronic Periodontitis patients. Microb Pathog, 2023. **176**: p. 106022.
33. Le Goff, A., et al., Evaluation of root canal bacteria and their antimicrobial susceptibility in teeth with necrotic pulp. Oral Microbiol Immunol, 1997. **12**(5): p. 318-22.
34. Tek, M., et al., The predominant bacteria isolated from radicular cysts. Head Face Med, 2013. **9**: p. 25.
35. Dingsdag, S.A. and N. Hunter, Metronidazole: an update on metabolism, structure-cytotoxicity and resistance mechanisms. J Antimicrob Chemother, 2018. **73**(2): p. 265-279.
36. Lofmark, S., C. Edlund, and C.E. Nord, *Metronidazole is still the drug of choice for treatment of anaerobic infections.* Clin Infect Dis, 2010. **50 Suppl 1**: p. S16-23.
37. Lamp, K.C., et al., Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. Clin Pharmacokinet, 1999. **36**(5): p. 353-73.
38. Karamanakos, P.N., et al., Pharmaceutical agents known to produce disulfiram-like reaction: effects on hepatic ethanol metabolism and brain monoamines. Int J Toxicol, 2007. **26**(5): p. 423-32.
39. Alonzo, M.M., T.V. Lewis, and J.L. Miller, *Disulfiram-like Reaction With Metronidazole: An Unsuspected Culprit.* J Pediatr Pharmacol Ther, 2019. **24**(5): p. 445-449.
40. Singh, M., D.H. Kambalimath, and K.C. Gupta, *Management of odontogenic space infection with microbiology study.* J Maxillofac Oral Surg, 2014. **13**(2): p. 133-9.
41. Plum, A.W., A.J. Mortelliti, and R.E. Walsh, *Microbial flora and antibiotic resistance in odontogenic abscesses in Upstate New York.* Ear Nose Throat J, 2018. **97**(1-2): p. E27-E31.
42. Shakya, N., et al., Epidemiology, Microbiology and Antibiotic Sensitivity of Odontogenic Space Infections in Central India. J Maxillofac Oral Surg, 2018. **17**(3): p. 324-331.
43. Kwon, G.B. and C.H. Kim, Microbial isolates and antibiotic sensitivity in patients hospitalized with odontogenic infections at a tertiary center over 10 years. J Korean Assoc Oral Maxillofac Surg, 2023. **49**(4): p. 198-207.
44. Sanchez, R., et al., Severe odontogenic infections: epidemiological, microbiological and therapeutic factors. Med Oral Patol Oral Cir Bucal, 2011. **16**(5): p. e670-6.
45. Bigus, S., et al., Antibiotic resistance of the bacterial spectrum of deep space head and neck infections in oral and maxillofacial surgery - a retrospective study. Clin Oral Investig, 2023. **27**(8): p. 4687-4693.
46. Chunduri, N.S., et al., Evaluation of bacterial spectrum of orofacial infections and their antibiotic susceptibility. Ann Maxillofac Surg, 2012. **2**(1): p. 46-50.
47. Sakamoto, H., et al., Necrotizing Fasciitis of the Neck due to an Odontogenic Infection: A Case Report. J Infect Chemother, 1996. **2**(4): p. 290-293.
48. Heim, N., et al., Microbiology and antibiotic sensitivity of head and neck space infections of odontogenic origin. Differences in inpatient and outpatient management. J Craniomaxillofac Surg, 2017. **45**(10): p. 1731-1735.
49. Vata, A., et al., Polymicrobial Bacterial Meningitis in a Patient with Chronic Suppurative Otitis Media: Case Report and Literature Review. Medicina (Kaunas), 2023. **59**(8).
50. Sobottka, I., et al., In vitro activity of moxifloxacin against bacteria isolated from odontogenic abscesses. Antimicrob Agents Chemother, 2002. **46**(12): p. 4019-21.
51. Rush, D.E., et al., Clindamycin versus Unasyn in the treatment of facial cellulitis of odontogenic origin in children. Clin Pediatr (Phila), 2007. **46**(2): p. 154-9.
52. Kuriyama, T., et al., Antimicrobial susceptibility of major pathogens of orofacial odontogenic infections to 11 beta-lactam antibiotics. Oral Microbiol Immunol, 2002. **17**(5): p. 285-9.
53. Warnke, P.H., et al., Penicillin compared with other advanced broad spectrum antibiotics regarding antibacterial activity against oral pathogens isolated from odontogenic abscesses. J Craniomaxillofac Surg, 2008. **36**(8): p. 462-7.
54. Sobottka, I., et al., Microbiological analysis of a prospective, randomized, double-blind trial comparing moxifloxacin and clindamycin in the treatment of odontogenic infiltrates and abscesses. Antimicrob Agents Chemother, 2012. **56**(5): p. 2565-9.
55. Cachovan, G., et al., Radiography-based score indicative for the pathogenicity of bacteria in odontogenic infections. Acta Odontol Scand, 2014. **72**(7): p. 530-6.
56. Poeschl, P.W., et al., Antibiotic susceptibility and resistance of the odontogenic microbiological spectrum and its clinical impact on severe deep space head and neck infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2010. **110**(2): p. 151-6.

 doi:10.20944/preprints202408.0188.v1

57. Kuriyama, T., et al., Bacteriologic features and antimicrobial susceptibility in isolates from orofacial odontogenic infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2000. **90**(5): p. 600-8.
58. Kuriyama, T., et al., Past administration of beta-lactam antibiotics and increase in the emergence of beta-lactamase-producing bacteria in patients with orofacial odontogenic infections. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2000. **89**(2): p. 186-92.
59. Egwari, L.O., et al., Bacteriological and clinical evaluation of twelve cases of post-surgical sepsis of odontogenic tumours at a referral centre. East Afr Med J, 2008. **85**(6): p. 269-74.
60. Boyanova, L., et al., Anaerobic bacteria in 118 patients with deep-space head and neck infections from the University Hospital of Maxillofacial Surgery, Sofia, Bulgaria. J Med Microbiol, 2006. **55**(Pt 9): p. 1285-1289.
61. Eick, S., W. Pfister, and E. Straube, Antimicrobial susceptibility of anaerobic and capnophilic bacteria isolated from odontogenic abscesses and rapidly progressive periodontitis. Int J Antimicrob Agents, 1999. **12**(1): p. 41-6.
62. Patel, M., The prevalence of beta lactamase-producing anaerobic oral bacteria in South African patients with chronic periodontitis. SADJ, 2011. **66**(9): p. 416-8.
63. Alou, L., et al., In vitro killing activity of crevicular concentrations of tinidazole plus common oral antibiotics against high-density mixed inocula of periodontal pathogens in strict anaerobic conditions. J Periodontol, 2010. **81**(1): p. 131-8.
64. Roche, Y. and R.N. Yoshimori, In-vitro activity of spiramycin and metronidazole alone or in combination against clinical isolates from odontogenic abscesses. J Antimicrob Chemother, 1997. **40**(3): p. 353-7.
65. Chan, Y. and C.H. Chan, Antibiotic resistance of pathogenic bacteria from odontogenic infections in Taiwan. J Microbiol Immunol Infect, 2003. **36**(2): p. 105-10.
66. Kuriyama, T., et al., Incidence of beta-lactamase production and antimicrobial susceptibility of anaerobic gram-negative rods isolated from pus specimens of orofacial odontogenic infections. Oral Microbiol Immunol, 2001. **16**(1): p. 10-5.
67. Maestre, J.R., et al., Odontogenic bacteria in periodontal disease and resistance patterns to common antibiotics used as treatment and prophylaxis in odontology in Spain. Rev Esp Quimioter, 2007. **20**(1): p. 61-7.