Tufts University
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Correlation of Severity and Morbidity in Odontogenic Infections and the Administration of Appropriate Empirical Antibiotic Therapy

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Abstract

Aim: Our goal in this study was to develop an infection severity score system that would help physicians to predict the severity of odontogenic head and neck space infections and accordingly provide timely and effective treatment that will hopefully result in reduced patient morbidity, mortality and cost of healthcare.

Introduction: Morbidity and mortality associated with severe odontogenic head and neck space infections remain a concern in healthcare. Identification of morbidity prognostic factors empowers practitioners to provide timely and effective treatment that can reduce adverse outcomes. The purpose of this study was to identify morbidity prognostic factors and effective empirical antimicrobial treatment that can be used by physicians to provide timely and more effective care, thus decreasing morbidity and mortality.

Methods: In this retrospective cross sectional study, 109 patients who had been treated for odontogenic infections were evaluated. The relationships between independent prognostic variables and variables that define morbidity have been tested. The independent prognostic variables that showed a statistically significant association with the morbidity variables were incorporated into a newly developed infection severity score system (SPDA[1]), which predicts the degree of expected morbidity for each patient. Analyzing the culture and sensitivity tests, the effectiveness of different antimicrobial agents that had been used as empirical treatment was examined and the most effective agent to be used was introduced.

Results: The predictor variables (dyspnea, dysphagia, trismus and incorrect administration of initial antibiotics) displayed a statistically significant association with the dependent morbidity variables (need for surgical intensive care, need for re-operation, and spread of infection to a distal facial space). The presence of each risk factor (dyspnea, dysphagia, trismus and incorrect administration of initial antibiotics), increases the odds of Surgical Intensive Care Unit (SICU) admission by 2.382 times (95% CI: 1.48) (p=0.0003) and the odds of re-operation by 3.184 times (95% CI: 1.69, 5.98) (p=0.0003). Furthermore, this study showed that the group of patients who developed severe

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S (space of infection) + P (symptoms on presentation) + D (diabetes) + A (Incorrect administration of empirical antibiotics) = Severity Score (SPDA)

morbidity had a mean SPDA score >15.9, the group of patients who developed moderate morbidity had a mean SPDA score of 12.6, and the group of patients who developed mild morbidity had a mean SPDA < 6.8. Ampicillin/Sulbactam was found to be the most effective empirical antimicrobial agent used for treatment of these infections.

Conclusion: The evaluation and appreciation of the above significant variables into clinical assessment of the patients with odontogenic head and neck space infections and their incorporation into a severity score system empowers clinicians to more appropriately and effectively initiate treatment for these challenging infections.

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Introduction

Odontogenic infections are among the many conditions most commonly treated by Oral and Maxillofacial Surgeons. These infections affect a large portion of the population (34.8%) and can give rise to serious complications if not treated quickly and adequately[1]. Thus, the importance of infections of dental origin is its high incidence and morbidity [2] .The successful management of multi-space odontogenic infections involves identification of the source of the infection, the anatomical spaces encountered, the predominant microorganisms present during each of the various stages of odontogenic infection, the impact of the infectious process on defense systems, the ability to use and interpret laboratory data and imaging studies, and a thorough understanding of contemporary antibiotic and supportive care [3,4,5]. The therapeutic goals, when managing multi-space odontogenic infections are to restore form and function while limiting patient disability and preventing infection recurrence. Odontogenic infections are often the result of pericoronitis, carious teeth with pulpal exposure, periodontitis, or complications of dental procedures. The second and third molars are frequently the source of these multi-space odontogenic infections [6, 7, 8].

Diagnostic imaging modalities are selected based on the patient's history, clinical presentation, physical findings and laboratory results. Periapical and panoramic radiographs are reliable initial screening instruments used to determine etiology. Magnetic resonance imaging and computed tomography are ideal imaging modalities that allow the clinician to assess soft tissue involvement. Information about the soft tissue is needed to distinguish abscesses from cellulites and to determine airway patency [9, 10, 11].

Antibiotics are administered to assist the ability of the immune system to control and eliminate invading microorganisms. Early infections (within the first three days of symptoms) are primarily caused by aerobic *streptococci*, which are sensitive to Penicillin. In late infections (more than three days of symptoms) the predominant microorganisms are anaerobes like *Peptostreptococcus*, *Fusobacterium*, or *Bacteroides*, which are resistant to Penicillin. Clindamycin is also an attractive drug for first line therapy in the treatment of these infections and the addition of Metronidazole to Penicillin is also an excellent treatment choice. The best management of these infections includes appropriate culture for bacterial identification, timely and aggressive incision and drainage, and removal of the etiology [4,12]. It is usually preferable to drain multi-space infections involving the submandibular, submental, masseteric, pterygomandibular, temporal, and/or lateral pharyngeal masticator spaces, as early as possible [6]. Trismus and airway management are important considerations that affect the selection of surgical approaches to drainage. Patients with multi-space infections should be hospitalized and care should be provided by experienced clinicians capable of managing airway problems, administering parenteral antibiotics and fluids, utilizing and interpreting laboratory and diagnostic imaging studies, and controlling possible surgical complications [13].

Although most of these infections can be resolved by removing the source, in severe cases morbidity and mortality can increase significantly [14,11]. The anatomical location of these infections, in combination with incorrect or late treatment, severely increases risk of death due to spread of infection to distal spaces, the emergence of sepsis, and respiratory obstruction [14]. In addition, the anatomical and histological diversity of the oral cavity allows for the coexistence of multiple microbiotas, which contribute to the polymicrobial nature of these infections. More than 20 different species of bacteria have been isolated in some studies [16,17]. Most areas of the human body harbor an indigenous microbial flora that is specific to the anatomic area and the individual person [18,19]. The specific ecosystem helps to play a role in protecting the individual from invasion by pathogenic organisms. Numerous factors may alter the type, frequency, and distribution of these microbes, including the anatomic region, patient immune system, relative humidity, presence/lack of oxygen, local surface characteristics, available nutrition, and any interaction between microbes [6,18,20]. Although there is generally a normal resident flora for any particular anatomic region, a transient flora also may be found to colonize for periods ranging from hours to weeks without being retained permanently.

The oral cavity is warm with relatively constant temperature, is wet and dark, possesses environments with and without oxygen, and provides a constant source of nutrition, housing a unique and diverse bacteria flora [6,18,19,20]. The mouth of the newborn is not sterile but, like the skin, contains a mixture of organisms representative of the mother's vagina, including Streptococci, Enterococci, and Microaerophilic species [18,19]. The high incidence of aerobic organisms occurs because initially there are no crevices that support development of an anaerobic environment. However, that status changes with the eruption of teeth. In adulthood, the flora becomes more constant in composition and contains mostly streptococcal bacterial species (30%–60%), other bacteria, yeasts, fungi, protozoa spirochetes, and viruses. Local diseases, such as caries and periodontitis, can alter the microflora as well [18,19,20]. Environmental agents, such as alcohol, tobacco smoke, medications, and radiation therapy, also change the microflora [6,7,21].

Even though, there are numerous articles in the surgical literature discussing odontogenic infections, they do not identify changes in the microbiology of these infections over time, nor do they make comparisons using case controlled cohorts [12,22,23]. Only one study has attempted to identify such changes and make such comparisons and while not ideal in design (possessing all of the imperfections inherent in a retrospective chart review); it remains the only case-controlled cohort comparison of odontogenic infections over time[8]. The retrospective record review performed by Storoe *et al.* was conducted at the Cleveland Metro Health Medical Center, in Northeastern Ohio. Hospital charts and radiographs were reviewed from two patient cohorts admitted to that institution. An exhaustive statistical analysis was undertaken to analyze and compare the two populations of different admitting time (10 years different) and any changes in their microbiology over the years. No significant differences were found between the two cohorts for age, gender, race, admission temperature, admission white blood cell count, space involvement, or length of stay. Most of the patients in this study had multiple organisms isolated. For the initial analysis, isolates were grouped into four broad categories: gram-positive cocci, other gram-positive bacteria, gram-negative anaerobes, and other gram-negative bacteria. When individual isolates from the cohorts were compared, significant differences were found for a-hemolytic streptococci, bacteroides, melaninogenicus, coagulase-negative staphylococci, eikenella corrodens, staphylococcus epidermidis, neisseria species, and b-lactamase–positive bacteroides. Of the 32 bacterial isolates, 26 (81%) were resistant to one or more antibiotic; 62% of the resistant bacteria were gram positive and 38% were gram-negative. *Staphylococcus aureus* and coagulase-negative staphylococci were the most common gram-positive antibiotic-resistant bacteria isolated. Klebsiella pneumoniae was the most common gram-negative antibiotic-resistant isolate.

Until the mid 1970s, researchers believed that odontogenic infections were caused by a single species of aerobic or facultative bacteria [24]. It is now known that odontogenic infections are polymicrobial in nature [10,12,16,22,25,26,27,28,29,30]. Researchers also observed that bacteria identified from odontogenic infections have changed over the decades [8,11,31,32,33,34,35,36]. Moenning *et al*. reported that the bacterial flora of odontogenic infections is no longer predominately facultative or microaerophilic, with staphylococcus and streptococcus as the primary genera, but is more often a mixed flora, with anaerobes outnumbering aerobes 2:1. The α-hemolytic streptococci are the most frequently isolated bacteria [12,22,28]. However, Bacteroides melaninogenicus has been reported as the most common in some studies [26,37]. In the previouss study, 19 bacterial species were isolated , with α-hemolytic streptococci predominating almost 2:1 over B. melaninogenicus and β-hemolytic streptococci predominating 3:1 over S.epidermidis and almost 4:1 over S.aureus and E. corrodens. Additionally, 24 genera or species were isolated as well, with coagulase-negative staphylococci, α-hemolytic streptococci, and β-hemolytic streptococci having nearly a 1:1:1 ratio predominating equally over all other bacteria by more than a 2:1 ratio. Significant differences between the groups were found for α-hemolytic streptococci, B-melaninogenicus, coagulase-negative staphylococci, E-corrodens, S. epidermidis, Neisseria species, and β-lactamase positive bacteroides, which suggests that there has been a shift in the microbiologic flora involved in odontogenic infections over the years. The α-hemolytic Streptococci were the most common isolates in both groups, which supports previous reports of the frequency with which these bacteria are isolated from odontogenic infections [12,22,28]. It is clear that these common gram-positive cocci remain a threat to patients with odontogenic infections. The significant decreases in neisseria species and E. corrodens over the years are most probably caused by laboratory protocol changes and changes in therapy, respectively. The decrease in E. corrodens isolated may be the result of improved treatment of anaerobic infection with antibiotics that have been developed in the past 10 years. It can be concluded that contrary to previous suggestions, there has been little change in the kinds of bacteria isolated from odontogenic infections over the last 10 years and the α-hemolytic streptococci remain the most frequently isolated bacteria.

From the limited antibiotic sensitivity data available, it was not possible to determine if there have been changes between groups in the kind, number, and frequency of resistant isolates. Despite their limitations, the data suggest some disturbing trends. It was found that 81% of the isolates were resistant to one or more antibiotics. Despite the relatively low overall occurrence, S. aureus was the most frequently identified antibiotic resistant isolate. In addition to its innate virulence, S. aureus is of increasing concern because it, along with other gram-positive cocci, is becoming resistant to most common antibiotics. For example, methicillin-resistant S. aureus that also exhibits intermediate resistance (minimum inhibitory concentration equal to 8 mg/mL) to vancomycin, the antimicrobial regarded as the ‘‘antibiotic of last resort’’ for these bacteria, has been recently reported in Japan and the United States [11].

A contemporary concern is the number of antibiotic-resistant, coagulase-negative staphylococci isolated in odontogenic infections. These bacteria long have been regarded as ‘‘apathogenic’’ members of the normal flora but are increasingly becoming recognized as important causes of infections, especially those acquired in hospitals [36]. Because most of the infections they cause are nosocomial, it should not be surprising to see increasing multiple antibiotic resistances. Against a background of the empiricism with which many clinicians continue to treat these patients, one may predict that there will be more initial treatment failures and a consequent increase in patient morbidity and total cost of care[29,10]

What is considered the indigenous maxillofacial flora begins during birth with the acquisition of the flora of the birth canal and then changes from infancy to adulthood as a result of the specific anatomic region, environmental influences, and host factors. The polymicrobial environment of such infections can increase the probability of bacterial synergism and symbiosis [38]. As the infection matures it shifts toward a chronic stage where it transforms to a strictly anaerobic environment, making the therapeutic management complex and exasperating [10,36]. As a direct result, frequency of complications and the cost of healthcare are increased.

Historically, most common empirical antibiotic treatment for odontogenic infections has been the administration of Penicillin, Ampicillin, or Amoxicillin [17]. However, recent studies have indicated an increased presence of beta-lactamase producing strains associated with odontogenic infections, which increase resistance to the antibiotic treatment.

There are four specific mechanisms by which bacteria acquire resistance genes, which are described below:

SPONTANEOUS MUTATION:

This is the original source for all antibiotic resistance, because bacteria have maintained genes that encode for resistance of naturally occurring antibiotics of other species. For example, the DNA encoding of b-lactamases and penicillin-binding proteins have several homologous sequences [39].

GENE TRANSFER:

Bacteria can undergo conjugation with a transfer of genes as plasmids, which are a composition of cytoplasmic loops of DNA that encode for antibiotic resistance, and transposons, which are able to insert themselves into the genome of the recipient cell. An example of a plasmid-mediated genetic event is acquisition of the ability to produce b-lactamase by some species.

BACTERIOPHAGES:

Viruses infect bacteria and can insert genetic material and take control of the host's genetic and metabolic machinery, which may encod[i]e for antibiotic resistance mechanisms.

MOSAIC GENOME:

Bacteria can absorb directly the fragments of the virally altered genome of dead members of related species to form a ''mosaic genome'' of genetic material from varying sources. This type of gene derivation is responsible for the non–b-lactamase penicillin resistance in streptococcus pneumoniae and meningococci and ampicillin resistance in haemophilus influenzae and gonococci [6,18]. Once the genetic machinery is in place, bacteria exert antibiotic resistance by various pathways that are broadly classified in the four ways described below:

DRUG INACTIVATION OR MODIFICATION:

The destruction or inactivation of the antimicrobial agent is accomplished by the induction of specific drug-inactivating enzymes, such as those that inhibit b-lactams or aminoglycosides. Numerous gram-positive and gram-negative bacteria, such as staphylococcus aureus, enterococcus faecium, escherichia coli, pseudomonas aeruginosa, H. influenzae, bacteroides, and many strains of prevotella have this capability.

ABILITY TO SYNTHESIZE NEUTRALIZING ENZYMES:

The best examples are penicillinase and the methylation of erythromycin and clindamycin. Other antibiotics that are neutralized include vancomycin, sulfonamides, aminoglycosides and rifampin. Bacterial organisms with this capability include S. pneumoniae, S. aureus, clostridium perfringens, bacteroides fragilis, campylobacter species, and neisseria gonorrhoeae.

ALTERATION OF MICROBIAL MEMBRANE PERMEABILITY:

Alterations in membrane permeability can cause decreased uptake or increased efflux of the antibiotic. The types of antibiotics most often affected by this mechanism are the b-lactams, quinolones, tetracyclines, erythromycin, and the aminoglycosides. The gram-negative rods E. coli, P. aeruginosa, and salmonella typhimurium also have this capability.

PORINS SPECIFICITY:

Porins within the transmembrane protein matrix are specific for various antibiotics and the loss of a specific porin confers resistance. Lack of the D2 porin, for example, confers resistance in P. aeruginosa. Increased efflux of the antibiotic before lethal damage occurs is seen in the enterobacteriae with the mar, nor A, and test A genes, which convey resistance by pumping tetracycline out of the cells. E. coli and staphylococcus epidermidis also can resist tetracyclines, macrolides and quinolones by this mechanism[39,40].

ALTERATION OF TARGET SITE:

Enzymes responsible for cell wall synthesis, the transpeptidases, can be altered slightly to produce less affinity for penicillins. These altered penicillin-binding proteins are most often seen in S. aureus and S. pneumonia [41].

ALTERATION IN CONCENTRATION OF RECEPTORS:

Many of the gram-negative rods (E. coli and proteus, enterobacter, and klebsiella species) have the ability to alter the number of drug receptors that bind antibiotics. The sulfonamide family is affected by such a mechanism.

However, infection in general can be characterized by cause and location, and each has its own characteristic flora. Odontogenic infections are generally characterized by a combination of facultative streptococci and oral anaerobes. Within the viridans group of facultative streptococci, the streptococcus milleri group, which consists of S.anginosus, S. intermedius, and S. constellatus, is most frequently associated with orofacial cellulitis and abscess. This is fortunate because only approximately 3% of the strains of these species are resistant to penicillins. On the other hand, other members of the viridans streptococci, such as streptococcus mitis, streptococcus sanguis, and streptococcus salivarius, are more frequently found in endocarditis, and they can be highly penicillin resistant, up to 58% in one study [42]. Among the anaerobes, anaerobic peptostreptococci and members of the genera prevotella and porphyromonas predominate. Although the peptostreptococci remain penicillin sensitive, approximately 25% of strains of prevotella and porphyromonas are penicillin resistant [43]. The penicillin-sensitive streptococci predominate during the first three days of clinical symptoms and the more resistant gram-negative obligate anaerobes appear in significant numbers thereafter. This fact suggests the selection of the penicillins over other antibiotics in early cases.

Another factor is the severity of the odontogenic infection. Flynn *et al.* found a clinical failure rate of 26% for penicillin in hospitalized cases. On the other hand, little or no difference was found between the effectiveness of penicillin and various other antibiotics in outpatient odontogenic infections [44,45]. The clinician must keep in mind the occasional pathogen that is resistant to the usual empiric antibiotic of choice.

In odontogenic infections as well as dog and cat bites, eikenella corrodens is fairly resistant to the penicillins and completely resistant to clindamycin. The fluoroquinolones have become the antibiotic of choice for this pathogen. E.corrodens should be considered a possible pathogen in treatment failure of odontogenic infections and routinely in animal bite wounds [46]. Every clinician who considers treating an infection with antibiotics should determine if the patient has a history of antibiotic allergy. Penicillin allergy is common, and macrolide (erythromycin family) intolerance and drug interactions are frequent. The choice of clindamycin, metronidazole, or newer antibiotics may be prudent when information is unavailable. The penicillins are the antibiotics most frequently prescribed for infections in the oral cavity. It is not surprising that their use is associated with hypersensitivity reactions. Between 1% and 10% of patients who initially take penicillin develop an allergic reaction and persons who do not develop a reaction have less than a 1% chance of developing an allergy with re-exposure [47]. It is judicious to clarify whether the person has a true allergy to penicillin. Cross-sectional studies of penicillin allergy indicate that in many hospital chartings of penicillin allergy, subsequent skin testing proved that more than 60% of patients were not allergic to either penicillin or other β-lactams, which warrants more careful vigilance by doctors who are recording medical histories and allergies of their patients [47,48]. Fortunately, hypersensitivity reaction to clindamycin, often substituted in penicillin-allergic patients, is a rare event. All clinicians should be aware of the potential for cross-allergy between the penicillins and other members of the β-lactam group.

Approximately 10% to 15% of penicillin-allergic patients are also sensitive to the cephalosporins. The cross-allergic group tends to include persons who have had an anaphylactoid reaction to the penicillins. The cephalosporins should be avoided in these patients. The newer β-lactam antibiotics, monobactams (aztreonam) and carbapenems (imipenem and meropenem), have much less frequented cross-sensitivity with the penicillin group. A history of adverse reaction or intolerance of an antibiotic, such as phototoxicity with the tetracyclines or antibiotic-associated colitis with clindamycin, would preclude its subsequent use unless strongly indicated.

In addition, special considerations should guide the choice of the antibiotic treatment prescribed to an immunocompromised patient. The immunocompromised patient is less able to kill invading pathogens by host resistance mechanisms; however, a bactericidal rather than bacteriostatic antibiotic should be selected whenever possible. This strategy should result in a more rapid clinical response.

The bactericidal antibiotics generally interfere with either cell wall synthesis, which causes lysis, or with nucleic acid synthesis, which arrests vital processes. The bacteriostatic antibiotics interfere with protein synthesis, arresting growth and multiplication. Some antibiotics, such as clindamycin are bacteriostatic at low doses and bactericidal at high doses. HIV-infected individuals seem to be able to handle oral bacterial infections almost as well as non-infected persons. This ability is probably caused by the antibody-mediated immunity provided by the B-lymphocytes, which is largely responsible for combating the extracellular bacterial pathogens of most head and neck infections. Resistance to these common infections remains fairly robust until the terminal stages of AIDS, when all types of lymphocytes are severely depleted.

On the other hand, fungal and viral infections, which are resisted by cell-mediated immunity (T cells), are prevalent in poorly controlled HIV-infected individuals. All antibiotic therapy inherently selects for resistant organisms. Studies of patients who are currently taking or recently have taken antibiotics consistently yield a higher incidence and proportion of organisms resistant to that antibiotic [49,50]. These effects persist for a considerable time after antibiotic therapy and may be permanent [50,51]. The previous use of different antibiotics during the course of an acute infection makes the bacteriologic assessment more complex.

In this situation, the clinician has the choice of changing the current antibiotic or increasing its dose, perhaps by using the parenteral route. With penicillins V (oral) and G (intravenous), peak serum blood levels are 5.6mg/mL and 20.0mg/mL, respectively. The dramatic increase in efficacy afforded by the parenteral route of administration may be more advantageous than changing to another antibiotic that is less effective than the penicillins.

The penicillin resistance rate of the endocarditis associated viridans streptococci (S.mitis, S.sanguis, and S.salivarius) can reach 58 % in persons with a history of prior endocarditis[52]. Clindamycin resistance of these bacteria in these patients remains low. In patients with a history of endocarditis, it may be advisable to use clindamycin rather than amoxicillin for endocarditis prophylaxis before oral procedures[52]. This approach, however, has not been tested in a clinical study.

Although abscess cavities are not vascular, some penetration of antibiotics into these spaces does occur. The antibiotic that best penetrates an abscess is clindamycin. The abscess concentration of clindamycin reaches 33% of the serum level[53] .This fact may partially explain the usefulness of clindamycin in odontogenic infections. Bone penetration of antibiotics is another important consideration, especially in osteomyelitis. The antibiotics that best penetrate or even accumulate in bone are the tetracyclines, clindamycin, and the fluoroquinolones.

Cerebrospinal fluid penetration, or the ability of an antibiotic to cross the blood-brain barrier, is also paramount in the treatment of infections that threaten the central nervous system, as in actual or impending cavernous sinus thrombosis. The antibiotics that do not penetrate the cerebrospinal fluid well are clindamycin, the macrolides (including clarithromycin and azithromycin), cefazolin, and most other cephalosporins, aminoglycosides, amphotericin, itraconazole, ethambutol, and saquinavir. Penicillin G in high doses reaches 5% to 10% of the serum concentration in the cerebrospinal fluid when the meninges are inflamed. In odontogenic infections that threaten the central nervous system, the addition of metronidazole (30%–100% penetration) to ampicillin (13%–14% penetration) is more efficacious than using penicillin G alone [54].

The effectiveness of some antibiotics, such as fluoroquinolones and aminoglycosides, is concentration dependent, whereas with other antibiotics, such as the β-lactams and vancomycin, is time dependent. In concentration-dependent antibiotics, efficacy is determined by the ratio of the serum concentration of the antibiotic to the minimum inhibitory concentration (MIC). The MIC is the concentration of the antibiotic required to kill a given percentage of the strains of a particular species, usually 50% or 90%. In time-dependent antibiotics, it is necessary to maintain the serum concentration above the MIC for at least 40% of the dosage interval. With these antibiotics, it is important to know the serum elimination half-life (t 1/2) of the antibiotic to determine its proper dosage interval. For example, the t 1/2 of penicillin G is 0.5 hours. During each half hour, 50% of the remaining penicillin is eliminated from the serum. By five half-lives, or 2.5 hours, only approximately 3% of the peak serum level of Penicillin remains. Because the MIC-90 of viridans streptococci (the concentration that kills 90% of the strains) is 0.2mg/mL and because the peak serum level achieved with 2 million U of intravenous penicillin G is 20 mg/mL, the serum concentration of penicillin after 4 hours (eight half-lives) is approximately 0.15 mg/m. The serum level will have fallen below the MIC-90 roughly for only the last 15% of the dosage interval. Intravenous penicillin G, 2 million U every four hours, should be highly effective against the viridans group of streptococci. Using the same analysis, the peak blood level achieved with amoxicillin, 500 mg orally, is 7.5mg/mL, and its t 1/2 is 1.2 hours. The MIC-90 for the viridans streptococci is 2 mg/mL for amoxicillin. Using an eight hours dosage interval, the remaining serum concentration of amoxicillin should have fallen below the MIC-90 of the viridans streptococci in approximately 2.5 hours, which is only 31% of the dosage interval. Oral amoxicillin therapy may not kill 90% of all the strains of the viridans streptococci. Fortunately for practitioners, the Streptococcus milleri group associated with odontogenic infections is highly sensitive to the Penicillins, whereas the endocarditis-associated strains are less so. The pharmacokinetics of the clinically available antibiotics have been determined during drug development. It is paramount for the clinician to prescribe antibiotics within the accepted ranges for dose and interval.

Once-daily dosing for the aminoglycosides as a means of reducing their ototoxicity and nephrotoxicity has been evaluated in a systematic review[55]. The available well-designed studies indicate that this practice results in a modest increase in therapeutic advantage and possibly a decrease in toxicity. The cost saving of once-daily intravenous dosing makes this approach appealing. Caution is advised in patients with limited volumes of fluid distribution, however.

The efforts of developing new treatments for the infections involving pathogenic bacteria that have developed resistance to the current antibiotic treatments are directed towards the development of new antibiotic agents that are tried and proven effective in clinical trials. A summary of a few of these new agents are listed and described below:

MOXIFLOXACIN (AVELOX) and GEMIFLOXACIN:

These are two new fluoroquinolones whose spectrum includes the viridans streptococci, oral anaerobes, and actinomyces. They are also effective against sinus pathogens, staphylococci, enterobacteriaceae, and B.fragilis. Their broad spectrum is a relative disadvantage when the target is a fairly small range of bacteria. These new fluoroquinolones probably should be reserved for situations in which a narrower spectrum alternative antibiotic is not available.

LINEZOLID (ZYVOX):

This medication is a prototype of oxazolidinones, a new class of antibiotics. It is effective against virtually all gram-positive pathogens but not against the gram-negative oral anaerobes. Its effectiveness against methicillin and vancomycin resistant staphylococci and enterococci indicates that it should be reserved for these highly resistant organisms [54]

TELITHROMYCIN (KETEK):

This agent is the first representative of ketolides, a new class which is related to the macrolides. Its spectrum includes the pathogens against which the macrolides have been historically effective, including S. pneumoniae, mycoplasma, H.influenzae, chlamydia pneumoniae, and legionella pneumophila. Its most frequent use probably is in respiratory tract infections, especially pneumonia [54,56]

QUINUPRISTIN/DALFOPRISIN (SYNERCID):

This is a combination of two pristinamycin antibiotics and is especially effective against vancomycin resistant staphylococci. Its use generally has been reserved for infections caused by these organisms.

Considering the polymicrobial nature of odontogenic infections, the choice of correct initial empiric antibiotics is always a challenge. In odontogenic infections, empiric antibiotics are administered before culture and sensitivity test results are available. In a prospective case series of 34 cases of odontogenic infections, Flynn *et al*. reported therapeutic failure of penicillin in 26% of cases using the following criteria for failure: allergic or toxic reaction (no cases), swelling, temperature, white blood cell count decline after at least 48 hours of intravenous penicillin, and a postoperative CT scan that demonstrated adequate surgical drainage. If inadequate drainage was found on the postoperative CT scan, surgery was repeated. All of the patients with therapeutic penicillin failure (8 of 31 cases initially treated with penicillin) subsequently yielded at least one penicillin resistant strain when culture and sensitivity test results became available. This finding suggests a correlation between infection severity and penicillin resistance [43].

On the other hand, penicillin resistance has not yet been shown to be a significant problem in outpatient odontogenic infections [44,57]. Penicillin V remains the empiric antibiotic of choice for outpatient odontogenic infections. Because of their ineffectiveness against the oral anaerobes, the macrolides are no longer considered among the empiric antibiotics of choice for odontogenic infections. Because the oral anaerobic gram-negative rods are fairly resistant to clindamycin and most cephalosporins, especially those in the first generation, these antibiotics remain second-line choices.

Antibiotic selection is as much of an art as it is a science. It requires the integration of many factors that are host specific, pharmacologic, and even geographic. Much more research is necessary in this field to solve the current problems. There is a need for more timely culture and sensitivity results and better methods to determine when to use antibiotics. There is also a big problem with increasing antibiotic resistance. Currently beta-lactams, typically an amoxicillin and clavulanic acid combination, are used as the primary empirical antibiotic for oral facial infections [17,38].

In an attempt to determine the morbidity predictor factors associated with odontogenic infections, various studies have identified indicators for length of hospital stay and the presence of complications. Flynn *et al*. showed that complications (penicillin treatment failure and re-operation) as well as anatomical extent of infection were statistically significant in predicting length of hospital stay whereas Wang, Ahani, and Pogrel were able to show a positive correlation between age and length of hospital stay as well as white blood cell count and length of hospital stay.

According to these studies, the most common anatomical areas of infection spread were the masticator and submandibular spaces and the most common symptoms were dysphagia and trismus [14,15]. Besides the intense local symptoms, odontogenic infections can spread to adjacent areas and other vital structures, or enter the systemic circulation and cause significant bacteremia with the potential for development of sepsis [17]. In patients with deep neck space infections, airway compromise was more frequent and severe in odontogenic rather than non-odontogenic deep neck space infections. The parapharyngeal, submandibular, and masticator spaces are more vulnerable in odontogenic deep neck space infections than in non-odontogenic infections. The predilection for certain spaces of the neck to be involved in odontogenic deep neck space infection originates from the intimate relationship of the mandibular molars to the adjacent deep neck spaces [37]. The anatomical proximity of these spaces to the upper airway further increases the necessity for early effective treatment to prevent the spread of the infection, which can significantly compromise the upper airway patency.

Consequently, timely and appropriate attendance to severe odontogenic infections is crucial to reduce adverse outcomes. However, diagnosis and management of head and neck infections are common clinical challenges for the healthcare practitioner [15]. Symptoms, signs, and laboratory data are often suggestive of an infectious or inflammatory process [16]. Given the right clinical conditions, however, several noninfectious conditions can mimic these processes. Based on clinical examination and occasionally laboratory data, the examining surgeon must determine the need for advanced imaging studies. Opinions still vary as to whether computed tomography (CT) or magnetic resonance imaging (MRI) is the best imaging modality for acute neck infection [58,59,60,61].

Traditional or single slice acquisition CT uses a gantry that houses an x-ray tube and a row of detectors. Images are produced by data collected from the detectors after a 360 rotation. After each tomographic image the patient table is moved and another image obtained. A time delay of 10 to 15 seconds between each slice is necessary. Spiral CT involves the simultaneous movement of the patient table and the x-ray tube, which results in a volume acquisition of data from which individual tomographic images can be reconstructed. Because a volume data set is acquired, excellent multiplanar reformations are possible when using thin image slices (3mm or less).

Picture archival communication systems are becoming more common in hospitals. Some of these systems allow viewing multiplanar reformation in any plane desired, not just the standard sagittal and coronal planes. In the past, CT reformation programs, such as Dental-Scan, were recommended for true cross-sectional images of the jaws, not only for implant planning but also for evaluation of tumors, osteomyelitis, or other pathologic conditions [62,63]. Picture archival communication systems with multiplanar reformation capability obviate the need for such programs in the evaluation of pathologic conditions. Other advantages of spiral CT in applications to the head and neck include one breath hold, which minimizes artifacts because of swallowing, and improved vascular opacification and lesion enhancement using a smaller contrast bolus [63].

Multi-detector CT is yet another improvement over spiral CT, whereas spiral CT uses a single row of detectors, multi-detector CT uses a matrix of detectors that allows the acquisition of multiple tomographic images per revolution, which greatly increases the speed of imaging.

Miller *et al.* performed a prospective study that compared the efficacy of contrast-enhanced CT (CECT) to clinical examination in detecting the presence of a drainable fluid collection in suspected deep neck infections [64]. The accuracy (frequency of a test to diagnosis correctly the presence or absence of disease) of clinical examination alone in identifying a drainable collection was 63%, the sensitivity (ability of a test to identify correctly a disease when it is truly present) was 55%, and the specificity (ability of a test to identify correctly the absence of disease when it is truly absent) was 73%. The accuracy of CECT alone was 77%, the sensitivity was 95%, and the specificity 53%. When CECT and clinical examination were combined the accuracy in identifying a drainable collection was 89%, the sensitivity was 95%, and the specificity was 80% [61,64].

Computed tomography uses the differences in attenuation of the x-ray beam by different tissues to form an image. The lowest attenuation occurs in air, and the highest attenuation occurs in bone, dentin, enamel, or metal. Fat has a lower attenuation than water, which in turn has lower attenuation than muscle. When edema occurs, there is an increase in water content. Edematous fat increases in attenuation, whereas muscle decreases in attenuation on non-contrasted CT [65]. Increased blood flow occurs in inflamed tissue. After administration of iodinated contrast medium, areas of increased blood flow demonstrate enhancement. Intravenous iodinated contrast is indicated for CT evaluation of a patient with suspected cellulitis or abscess.

It is important to note that upon admission, it is difficult to predict which infection will become complicated to the point of warranting a more aggressive treatment. Unfortunately the available literature regarding such a challenging medical issue is contradictory, lacking specifications, especially when it comes to the factors that play a significant role in combating infections in a timely manner.

The aim of this study was to determine significant variables that predict the morbidity outcome in severe odontogenic infections. Further, this study evaluated the effectiveness of empirical antimicrobial treatment based on culture and sensitivity studies that were conducted along with incision and drainage. A classification of infection severity was developed and its association with the outcome morbidity is evaluated. The new severity score system was used to predict the expected degree of infection morbidity. Our goal in this study was to provide an infection severity score system that would help the physician predict the severity of odontogenic head and neck space infections and accordingly provide timely and effective treatment, which will hopefully result in reduced morbidity, mortality and cost of healthcare.

Specific Aims

1. Identity of any statistically significant association between the clinical factors that are present upon initial evaluation of the patient and morbidity.
2. Develop an infection severity score system that would predict the degree of infection, morbidity and the length of hospital stay, utilizing the signs and symptoms present during the initial evaluation of the patient.
3. Determine any statistically significant association between prolonged hospitalization and the clinical factors that are present upon initial evaluation.
4. Evaluate the effectiveness of different antimicrobial agents that were used as empirical treatment for odontogenic head and neck space infections.

Hypothesis

We hypothesized that a statistically significant positive association would exist among the predictive factors (dysphagia, dyspnea, trismus, fever and incorrect administration of initial antibiotics) and morbidity, as measured by: need for intensive care; need for re-operation; and spread of infection to a distal space. Further, we believed that the presence of specific symptoms (risk factors) during initial evaluation like dyspnea, dysphagia, trismus, and the incorrect administration of initial antibiotics, would increase the degree of morbidity associated with odontogenic head and neck space infections and the length of hospital care.

Materials and Methods

The charts of 109 patients treated for odontogenic infections at Tufts Medical Center were recovered from the hospital's medical records and reviewed. Data were recorded retrospectively on standardized collection forms and a database was developed using Microsoft Excel.

Specific data were collected from each chart included the following:

1. Duration of hospital stay.
2. Past medical history:
    a. Diabetes
    b. HIV
    c. Active chemotherapy
    d. Use of immunosuppressive drugs
3. Clinical presentation at the time of admission:
    a. Evidence and degree of trismus
    b. Presence of dysphagia

c. Presence of dyspnea
d. Body temperature
e. Evidence of swelling

4. Type of empirical antibiotic initiated.
5. White blood cell count test and differentiation performed upon admission.
6. Type of pathogens identified in the culture and sensitivity tests after incision and drainage of the infected space.
7. Specific antibiogram indicated by the sensitivity tests of the pathogens collected from cultures of the area.
8. Any change of antibiotic therapy after indications to do so based on findings of sensitivity tests and cultures of the area.
9. Associated morbidity determined by the following:
   a. Need for re-operation
   b. Need for intensive care
   c. Further spread of infection to distal spaces

In addition, preoperative and postoperative CT Scans were recorded for each patient and the following data were collected:

1. Maxillofacial spaces infected as recorded by the radiologist.
2. In cases of infection spread to more spaces, the postoperative infected maxillofacial spaces were documented based on the determination made in the report of the radiologist who evaluated the postoperative CT scan at that time.
3. Head and neck spaces (listed below) were evaluated for radiographic evidence of infection:
   a. Vestibular
   b. Subperiosteal
   c. Space of the body of the mandible
   d. Infraorbital
   e. Buccal

f. Submandibular

g. Submental

h. Sublingual

i. Pterygomandibular

j. Submasseteric

k. Superficial temporal

l. Deep temporal

m. Lateral pharyngeal

n. Retropharyngeal

o. Pretracheal, Mediastinum,

p. Intracranial

q. Danger Space (space 4)

Study Design

This is a retrospective cross sectional study that evaluated subjects who suffered from odontogenic infections and were treated at Tufts Medical Center over five years (2005-2010). The degree of morbidity associated with odontogenic infections was the primary outcome of this study. Symptoms present upon initial evaluation of the patient were tested for statistically significant association with the variables that define morbidity. This was explored by testing the association between clinical facors (incorrect administration of initial antibiotics, trismus, dysphagia, dyspnea, leukocytosis, fever, chemotherapy, and diabetes) and the factors that define morbidity (need for reoperation, spread of infection to distal maxillofacial spaces, and need for supportive intensive care). Furthermore, the average time of hospital stay per severity group was calculated. We developed a severity score system based on the maxillofacial spaces that the infection spread to (as was determined by the evaluation of the CT scans that had been taken upon admission), the presence of clinical symptoms and signs during initial evaluation of the patient (swelling, fever, trismus, dyspnea, dysphagia), and evidence of positive past medical history for existing immunocompromising diseases (HIV, diabetes, active chemotherapy). The infections were categorized as mild, moderate or severe, and the mean infection severity score was calculated for each category group. The mean infection severity score value was used as a prediction of the degree of infection morbidity.

The secondary outcome examined in this study was the appropriateness and effectiveness of the empirical antibiotic therapy administered as initial treatment for these infections. The most effective antibiotic regimen was determined by correlating the antimicrobial effectiveness of the different empirical antibiotic regimens to the population of bacteria that were isolated from the infected areas and shown on the culture and sensitivity tests. The most effective antibiotic was the one that provided a spectrum of antimicrobial coverage to the highest number of bacteria population and subsequently required a change to a different, more effective antimicrobial agent the least amount of times.

Information regarding the results of culture and sensitivity tests was collected from the hospital charts of the patients. Furthermore, recommendation of appropriate initial antibiotic coverage was made for different infected spaces based on the specific pathogens that presented in these spaces and shown to be antibiotic sensitive on the available culture and sensitivity tests.

Inclusion Criteria:

The subjects included in this study satisfied the following criteria:

- Either sex and of any race
- Older than 16 years of age
- Must have been treated for odontogenic infections at Tufts Medical Center within the 5 year period 2005-2010
- Must have undergone initial CT scan, administration of empirical antibiotics, and white blood cell count test
- Must have undergone incision and drainage after culture and sensitivity tests of the infected area
- Detailed medical history with full examination was conducted and reported in the patients' charts at the time of admission

Exclusion Criteria:

The following subjects were excluded from this study:

- Patients who had charts with missing or incomplete information
- Patients who were treated and the infection was not of odontogenic origin

Sample size and power calculation

nQuery 7.0 was used to calculate the sample size of this study. We tried to achieve a power of greater than 80%, so that the type II error would be less than 20%. The alpha of the study was set to be 5%, leading the type I error to 5%. 109 Subjects were included in the study, providing the study power as 90%.

Statistical Analysis

This is a retrospective cross sectional study which correlated specific clinical symptoms present during the initial evaluation of the patients who suffered from odontogenic infections and the outcome (degree of infection morbidity). The association between morbidity prognostic variables, such as dyspnea, dysphagia, fever, trismus, incorrect administration of initial antibiotics, and the outcome of treatment (need for SICU, need for reoperation, and spread of infection to distal spaces), was tested with two methods: firstly, the frequency odds ratio of the association between each morbidity independent variable and each variable that determines the outcome morbidity was calculated. Chi square tests were applied to examine the statistical significance of the relationship between any one of the independent prognostic variables and the morbidity variables. Second, a new severity score system was created, indicating the number of risk factors among the predictor variables, such as dyspnea, dysphagia, fever, trismus and incorrect administration of initial antibiotics, which showed a statistically significant association with one or more of the morbidity variables. Secondary endpoints were the length of hospital stay and the degree of infection morbidity. Each predictor variable was correlated with the length of hospital stay in an attempt to determine the relative risk (hazard ratio) and show how each prediction variable affects the length of hospital stay.

Severity Score System:
S (space of infection) + P (symptoms on presentation) + D (diabetes) + A (Incorrect administration of empirical antibiotics) = Severity Score (SPDA).

The quantitative values for each one of the three categories (P, D, A) were extrapolated from the correlation results between each predictor variable with the variables that define morbidity. A score of 1 was assigned to each predictor variable showing a statistically significant association with any but only one of the morbidity variables (admission to SICU, need for re-operation, spread of infection to a distal space). A score of 2 was assigned to each predictor variable showing a statistical significant association with only two of the morbidity variables. Each predictor variable that showed a statistically significant association with all the three morbidity variables was given a score of 3 to be used in the above calculation. Furthermore, we scored the category S (spaces involved by the infection), following the scoring system introduced by Flynn *et al.* (2006) (table 9). The mean SPDA score was calculated for each category of infection morbidity, indicating which value is most likely to be associated with mild, moderate, or severe degree of infection morbidity. The statistical significant difference of the SPDA mean value among the three-morbidity category groups was tested with one-way ANOVA and post Hoch tests.

Results

Association between independent Predictor Variables and the Dependent Morbidity Variables:

The incorrect administration of initial antibiotics, showed statistically significant association with the need for admission to the SICU [OR=3.46, p=0.04]. In addition the presence of trismus during the initial evaluation of the patient, showed statistically significant association with the need for admission to the SICU [OR=5.16, p=0.0217). Furthermore, the need for admission to the SICU was statistically significantly associated with the presence of dysphagia [OR=11.12, p=0.0003] and the presence of dyspnea [OR=10.36, p=0.0005) during initial evaluation. The need for reoperation was statistically significantly associated with the incorrect administration of initial antibiotics [OR=4.61, p=0,028], the presence of dyspnea [OR=11.30, p=0.0057] and the presence of dysphagia [OR26.4, p=0.001]. The spread of infection to distal spaces, which was another investigated morbidity outcome, showed statistically significant correlation with the presence of dyspnea [OR=9.17, p=0.0474], dysphagia [OR=60, p=0.001}, fever [OR=9.171, p=0.047], diabetes [OR=11.33, p=0.0208] and the administration of incorrect empirical antibiotics [OR=9.615, p=0.0215]. The results of the above findings are summarized in Figure 1 and Tables 2, 3, and 4.

Effectiveness of Empirical Antimicrobial Therapy:

Clindamycin was the most commonly prescribed antibiotic in this study and was administered as empirical antibiotic agent to 63.3% of patients upon admittance. The combination of ampicillin with sulbactam (A+S) was the second most commonly prescribed antibiotic regimen, accounting for 35.7% of patients. In this study clindamycin was found to be the most common prescribed initial antibiotic for all spaces of infection. However, it was also most likely that patients beginning treatment with clindamycin needed to change to a different antibiotic regimen. On the contrary, ampicillin with sulbactam (A+S) was found to be a more effective antibiotic agent for the treatment of odontogenic head and neck space infections, provided a more specific antimicrobial coverage for pathogenic bacteria involved in these infections, required significantly less need for the patient to begin a different antimicrobial agent, and had more effective antimicrobial spectrum of coverage, as summarized in Figure (1).

The pathogenic population of bacteria that was isolated from different infected head and neck spaces showed significant diversity among these spaces, making the selection of the most appropriate antimicrobial agent even more challenging. The degree of both, the failure of clindamycin to provide a good antimicrobial coverage and the success of ampicillin with sublactam varied when comparing different infected head and neck spaces as shown in our evaluation Figure (1).

Association among Independent Predictor Variables and Length of Hospital Stay:

Each predictor variable was further correlated with the length of hospital stay in an attempt to determine the relative risk (hazard ratio) and showed how each predictor variable affects the length of hospital stay. The predictor variables dyspnea, dysphagia, fever, and trismus showed a relative risk less than 1 and had a positive association with length of hospital stay. However the the results were not statistically significant. The results are summarized in Table 6.

Association among Infection Severity Score, Length of Hospital Stay and Severity of Infection morbidity

Following the results of the association between predictor (independent) variables and morbidity (dependent) variables, we created an infection severity score system (SPDA), which included four categories: space of infection spread, symptoms on presentation, existence of diabetes, and administration of wrong antibiotics. The independent variables that showed statistically significant association with the morbidity dependent variables are the following:

<u>**Category P**</u>:

Dyspnea: showed a statistically significant association with all three dependent morbidity variables (need for re-operation, spread of infection to distal spaces, need of surgical intensive care). Its presence on clinical examination was given a score of 3 to be used for calculation of infection severity (see Table 6).

Dysphagia: showed statistically significant association with all three dependent morbidity variables (need for re-operation, spread of infection to distal spaces, need of surgical intensive care). Its presence on clinical examination was given a score of 3 to be used for calculation of infection severity (see Table 6).

Trismus: showed statistically significant association with only one dependent morbidity variable (need for surgical intensive care). Its presence on clinical examination was given a score of 1 to be used for calculation of infection severity (see Table 6).

Fever: showed statistically significant association with only one dependent morbidity variable (infection spread to a distal space). Its presence on clinical examination was given a score of 1 to be used for calculation of infection severity (see Table 6).

Diabetes: was the only immunocompromising disease, which showed statistically significant association with one of the depended morbidity variables, infection spread to a distal space. Its presence on clinical examination was given a score of 1 to be used for calculation of infection severity. Its value determines category D of the SPDA scoring system (see Table 7).

Administration of wrong initial empirical antibiotics showed a statistically significant association with two dependent morbidity variables (need for surgical intensive care and infection spread to a distal space) and it was given a score of 2 to be used for calculation of infection severity. This value represents category A of the SPDA score system (see Table 8). The Category S (spaces involved in the infection) was scored following the scoring system introduced by Flynn *et al.* (2006)[=] (Table 9).

The mean SPDA score was calculated for each category group of infection morbidity. Each category of infection morbidity was determined based on the clinical severity of the complications associated with odontogenic infections (mild, moderated, severe) and are shown in Figure (2). The mean SPDA for the severe morbidity category was 15.9 (95% CI: 14.18-17.62). The mean SPDA for the moderate morbidity category was 12.6 (95% CI: 10.92-14.28). The mean SPDA for mild morbidity was found to be 6.9 (95% CI:

5.51-8.29). The SPDA mean difference among the three morbidity groups found statistically significant with a p value less than 0.001.

In addition, the mean length of hospital stay was calculated per each morbidity group. For the patients in the severe morbidity group, the average time required to stay in the hospital was 6 days. The average required time spent in the hospital for patients in the moderate morbidity group was 3.9 days. Finally, the average time spent in the hospital for patients in the mild morbidity group was 2.8 days.

In an attempt to determine how the presence of each additional risk factor (dyspnea, dysphagia, trisms, diabetes, administration of wrong antibiotics) can increase the degree of infection morbidity, three logistic regression models were applied to test relationships between the severity score and the outcomes (intubation, SICU and reoperation). Using 0.05 as the significance level, the significant relationships are described in the following. Presence of each additional risk factor (dyspnea, dysphagia, trismus and incorrect administration of initial antibiotics), increases the odds of SICU admission by 2.382 times (95% CI: 1.489, 3.822) (p=0.0003) and the odds of need for reoperation by 3.184 times (95% CI: 1.695, 5.981) (p=0.0003).

Discussion

It is crucial for a clinician to be knowledgeable about signs, symptoms and patterns regarding spread of infection, clinical evolution and the effectiveness of adopted clinical and surgical treatments. Determining which odontogenic infections cause greater risk in terms of morbidity and mortality is difficult and there are few studies that can help clinicians assess and categorize significant variables for such infections. In this study, we focused on the importance of these variables with the intention of helping clinicians lower morbidity and mortality and the overall cost of healthcare for patients.

In this study, CT-Scans were used to determine the spaces that were involved in odontogenic infections, as this method has proven to be extremely reliable [66,67]. Similar to other studies, in our study the submandibular space was found to be the most common space (58.2%) involving odontogenic infections[16,68] . It was also found that the presence of specific predictor variables could increase the morbidity related to odontogenic infections. More specifically, the presence of dyspnea, dysphagia, trismus, and the incorrect administration of empirical antibiotics were shown to increase the need for SICU admission. Only one study was found to investigate symptoms with respect to ICU admission and no significant variables were found. It is worth noting that the study only consisted of 18 patients [68].

In addition, our study showed the presence of dyspnea and dysphagia during initial evaluation increased the need for re-operation. Limited literature is available regarding the need for re-operation, which focused primarily on other variables. The only common variable found significant in previous literature was leukocytosis [66,68].

This study also showed that the presence of diabetes, dyspnea, dysphagia, fever and administration of incorrect empirical antibiotics increased the percentage of infections that spread to a distal space. Due to the lack of published literature on this relationship, we were unable to make any comparisons.

Presence of dyspnea, dysphagia fever, and trismus upon admission, were the only predictor variables that were correlated with an increase in length of hospital stay (LOS). Although none of these variables were statistically significant, they showed a relative risk (hazard ratio) of less than one and seemed to have a positive association with an increase length of stay.

Whether the three variables: fever, dyspnea, and trismus, are significant or not can be argued both ways, therefore we leave this to be clarified with future studies with a greater sample size. Literature on this matter is less scarce but with mixed results and less focused on the variables examined in this study. Other studies have focused more on the patient's immune state and age, and leukocytosis [66,68]. Some studies have found leukocytosis to be significant and some have found it insignificant and more associated with the progression of the patient's state. In general, the consensus seemed to be that incorrect antibiotic administration and an immunocompromised state increases length of hospital stay [52,66,68]. In our study, however, an immunocompromised state was found to be insignificant, possibly due to lack of patients in the immunocompromised category.

Upon examination of cultures and sensitivity tests collected from our patient population, the dominant bacterial population appears to be the gram-negative rods, which were associated with necrotic abscesses as it shown in other studies as well[17]. Unfortunately, the effective antimicrobial spectrum of clindamycin does not extend to this population of bacteria, especially E.corrodens [17]. This could in part explain why patients treated with clindamycin needed re-evaluation and alteration to another antibiotic more frequently. Similar rates of change have been reported in a study by Flynn *et al.* (2006). This mandated the administration of another antimicrobial agent providing better antimicrobial coverage of these bacterial populations, such as A+S, as an initial empirical antibiotic agent. In a related study performed by Stefanopoulos and Kolokotronis, it was found that ampicillin with sublactam (A+S) were effective against all 87 aerobic and anaerobic pathogens tested which suggested it is the antibiotic of choice for severe odontogenic infections [17]. In consensus with the previous studies, our results indicate that A+S is a very effective initial empirical antimicrobial agent that offers good antimicrobial coverage when used as treatment for odontogenic head and neck space infections. In our study this antimicrobial agent showed a very low incidence of need for alteration to another antibiotic agent. Whether these results extend to other hospitals or geographical regions remains to be determined, as the bacterial ecosystems are different. Essentially, these types of studies should become standard at major healthcare centers in order to gain better insight in susceptibility of microorganisms in hopes of improving protocols and also decreasing morbidity and mortality.

A new infection severity score system, which incorporates all the relative risk factors that can predict the degree of infection morbidity, was introduced by this study. Every patient can be scored with this system and a prediction in regards to anticipated degree of infection morbidity and length of hospital stay can be made. The infection severity score system (SPDA) introduced by this study is more valuable in comparison with other systems because it incorporates predictor variables that are not associated only with the infected spaces but with the symptoms of the patient during initial evaluation. Since this model incorporates patient signs and symptoms, its practicality should remain unchanged. It is also valuable when considering the findings of a study published by Storoe et all which found that over a two-decade period, sign and symptoms of patients with odontogenic infections remained unchanged [16].

Limitations

The limitations of this study are related to its retrospective nature and design (cross-sectional study) that may decrease its accuracy and validity. Cross-sectional studies cannot imply causation between the predictor variable and the outcome, nor can they dictate the temporal relationship between the risk factors and the outcome, even when a statistically significant association exists.

These studies can be used to detect risk factors early while also streamlining hypothesis and design of future analytical studies, which can examine further the relationship between causative factors and outcome. Our results were extrapolated from the statistically significant association between clinical factors (risk factors) and the variables that dictate morbidity. Additionally, the small number of patients who developed severe morbidity in our sample group could have affected the accuracy of the results; specifically the association between length of hospital stay and the predictor variables. The relative risk was less than 1, but not statistically significant. A prospective analytical study designed with a larger sample could be conducted in the future to further investigate the relationship between risk factors and severity of infection morbidity.

However, when considering the increased risk of sepsis, respiratory obstruction, and spread of infection inherent in these anatomical locations in combination with incorrect or late treatment, the successful management of multi-space odontogenic infections should involve an effective and timely treatment that removes the infection source, and provide good antimicrobial coverage to the predominant microorganisms found during each progressive infectious stage. This study both identified predictor factors (risk factors) that may increase the severity of morbidity associated with odontogenic infections and incorporated them in an easily calculated severity score system. The use of the severity score system (SPDA) and data suggesting the most effective empirical antimicrobial treatment provides the practicing clinician with enough information to determine appropriate treatment by predicting the degree of infection morbidity, determining which infections may progress in severity. This information could lead to the application of a timely and more effective treatment, that will decrease the infection associated morbidity and mortality, and lower the overall cost of healthcare.

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Apendix A: Tables:

Table 1. Risk Factors and Spread of Infection to Distal Spaces

Predictor Variables	Number of patient	rcentage of Patient with ection spread to a distal space	Odds –Ratio Iantel Maenszel Logit)	hi-sq Value
HIV	2	0.00	0.000	).73
Chemotherapy	1	0.00	0.000	).841
DIABETES	5	25.00	11.33	).02
FEVER	56	7.14	9.17	).04
DYSPNEA	8	37.50	60.00	:0.01
DYSPHAGIA	55	7.14	9.17	).04
Trismus	73	5.48	4.726	).15
WBC >12	61	6.45	3.19	).20
WRONG ADMINISTRATION EMPIRICAL ANTIBIOTICS	28	10.71	9.615	).02

Table 2: Risk Factors and patient who required re-operation			
Predictor Variables	**Percentage of Patient Who required Re-operation**	**Odds –Ratio (Mantel Maenszel Logit)**	**Chi-sq P-Value**
HIV	0.00	0.00	0.55
Chemotherapy	0.00	0.00	0.73
DIABETES	25.00	3.16	0.31
FEVER	14.29	2.77	0.13
DYSPNEA	62.50	26.38	<0.001
DYSPHAGIA	17.86	11.30	0.05
Trismus	13.70	5.55	0.07
WBC >12	12.90	2,66	0.52
WRONG ADMINISTRATION OF EMPIRICAL ANTIBIOTICS	17.86	2.71	0.11

Table 3: Risk factors and percentage of patients who required admission to the SICU			
Predictor Variables	**Percentage of Patient Who required admission to the SICU**	**Odds –Ratio (Mantel- Maenszel Logit) Estimate**	**Chi-sq P-Value**
HIV	0.00	0.00	0.41
Chemotherapy	0.00	0.00	0.64
DIABETES	25.00	1.61	0.68
FEVER	19.64	1.37	0.53
DYSPNEA	62.50	10.35	0.01
DYSPHAGIA	30.36	11.11	0.01
Trismus	23.29	5.16	0.02
WBC >12	22.58	1.58	0.23
WRONG ADMINISTRATION OF EMPIRICAL ANTIBIOTICS	39.29	5.91	0.00

Table 4: Correlation of Risk Factors and Length of hospital Stay		
Prediction Variables	**Relative Risk**	**Value**
HIV	0.593	0.38
Chemotherapy	0.706	0.11
Diabetes	0.816	0.69
Fever	1.486	0.05
Dyspnea	2.242	0.06
Dysphagia	1.346	0.13
Trismus	1.471	0.06
WBC (>12)	0.894	0.61
Wrong Antibiotics	0.673	0.08
Even though the predictor variables of fever, dyspnea, dyspagia, and trismus showed a Relative Risk>1, they did not show any statistical significance (P > 0.05). * Statistical significance, p < 0.05		

Table 5. P (clinical presentation)	
Severity Score	**Clinical Symptoms**
1	Trismus MIO <30mm
1	Fever > 38c
3	Dyspnea
3	Dysphagia
*Severity score for a given subject is the sum of the severity scores for all the symptoms present based on the clinical examination reported	

Table 6 (Existing Immunocompromising Diseases)	
Severity Score	**Immunocompromising Conditions**
1	Diabetes
* Severity score for a given subject is the sum of the severity scores for all the conditions present based on the past medical history recorded	

Table 7. A (Incorrect administration of empirical antibiotics)	
Severity Score	**Antibiotic**
0	Correct antibiotics
2	Wrong antibiotics
* Severity score for a given subject is the sum of the severity scores for all the conditions present based on the past medical history recorded	

Table 8. Severity Score and Anatomic Space	
Severity Score	**Anatomic Space**
S_a: Severity Score 1 (low proximity airway or vital structures) (Each space should be scored with 1 if it is involved)	Vestibular Subperiosteal Space of the body of the mandible Infraorbital Buccal
S_b: Severity Score 2 (moderate threat to airway or vital structures) (Each space should be scored with 2 if it is involved)	Submandibular Submental Sublingual Pterygomandibular Submasseteric Superficial temporal Deep temporal
S_c: Severity Score 3 (high risk to airway or vital structures) (Each space should be scored with 3 if it is involved)	Lateral pharyngeal Retropharyngeal Pretracheal Danger space (space 4) Mediastinum Intracranial infection
*Severity score for a given subject is the sum of the severity scores for all the space involved based on the radiographic examination	

Appendix B: Figures

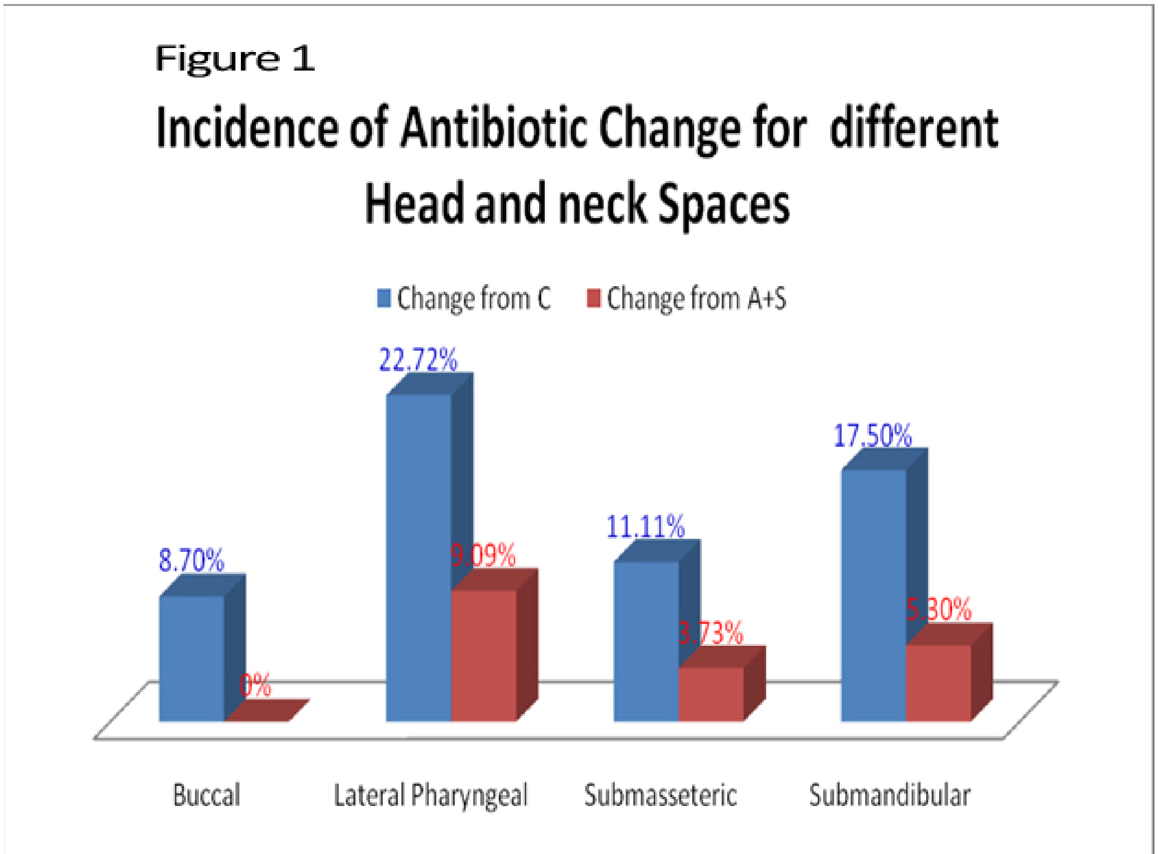
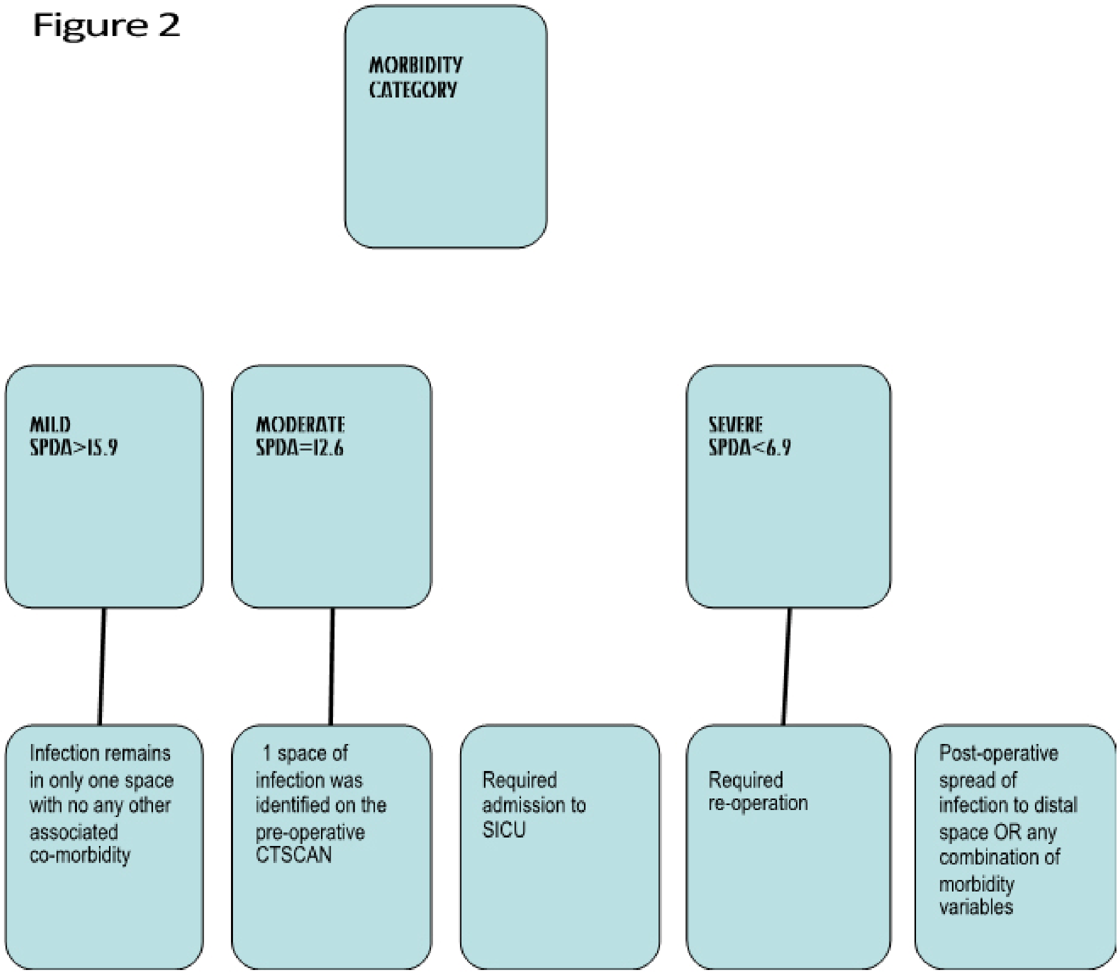


Figure 1. The above chart summarizes percentage of antibiotic change due to lack of coverage once results of culture and sensitivity were received for the four most common spaces involved in odontogenic infections. Clindamycin (C) required a change more often compared to Ampicillin + Sulbactam (A+S) for all four spaces.

Figure 2



Infection degree of morbidity (categories) and its relation to the new severity score system.