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Factors associated with hospitalization outcomes in patients with orofacial sepsis.



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JOHANNESBURG

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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Dentistry.

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Johannesburg,
3 April 2023.

DECLARATION

I, Ruan Scheepers declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Dentistry at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



3rd day of April 2023

ABSTRACT

Background: Orofacial infection is an easily preventable disease which if left untreated may spread to the deep neck spaces, resulting in life-threatening complications. The purpose of this study was to review the clinical features of patients admitted with orofacial infections in patients presenting to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH). The objective was to identify anatomical, patient and hospital- level factors that influence the clinical outcome of orofacial infections.

Methods: This was a prospective cross-sectional study performed in the Department of Maxillofacial and Oral Surgery at CMJAH and CHBAH over a 12-month period. All patients over the age of 18, admitted with the diagnosis of orofacial infections were included in the study. Data were collected at admission and during the course of patient stay in hospital. The data were categorised as demographic, health status, clinical presentation at admission, special investigations performed, anatomical and treatment variables. A multivariable linear regression analysis was used to examine the association between hospital stay (outcome variable) and the predictor variables. Comorbid bivariate conditions were tested using simple linear regression analysis and were included in the final multivariable linear regression model. A Spearman's correlation coefficient was calculated to determine the strength of association between length of stay and comorbidity burden, fascial space involvement and individual comorbidities.

Results: A total of 152 patients were eligible for inclusion in the study. Fifty-seven-point 2 percent (57.2%) were male, mean patient age was 35±12.8 years, 13.8% were HIV positive and 9.9% of patients were diabetic. Furthermore, 75% of patients had multiple facial spaces involved in the infection, with trismus being the most prevalent presenting clinical finding (80.9%). Hospital outcome and duration of hospital stay was correlated with C-reactive protein (CRP) level, white blood cell count (WBC), comorbid conditions such as hypertension, diabetes mellitus (DM) and metastatic cancer, multiple-fascial spaces involved and clinical signs such as third molar

involvement and dysphagia at admission.

Conclusions: Orofacial infections involving 3rd molars and multiple fascial spaces should be treated aggressively to enhance clinical outcomes, in particular those presenting with comorbidities such as diabetes. Future prospective studies, involving larger sample sizes, are recommended to further substantiate and provide statistical support for the role of cost-effective biological factors such as CRP and comorbidities in predicting clinical outcomes and length of stay for patients with orofacial sepsis.

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"Rejoice always, pray continually, give thanks in all circumstances; for this is God's will for you in Jesus Christ"- 1 Thessalonians 5:16-18 NLT

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Chapter 1: Introduction

Hospitalisation is often indicated for maxillofacial and oral surgery (MFOS) patients, such as those with orofacial sepsis, head and neck pathology and facial gunshot wounds. Recently, hospitalisations due to orofacial infections have become more common, possibly attributable to a larger comorbid burden, or even reduced access or fear of seeking treatment, as seen recently after the occurrence of the COVID-19 pandemic (Yew *et al.*, 2021).

The origin of orofacial sepsis is generally categorized as odontogenic and non-odontogenic, with the former being the more prevalent. During a four-year prospective study by Flynn *et al.,* (2006), caries was responsible for 66%, pericoronitis 22% and periodontal disease 22% of all odontogenic infections. These results were reinforced by findings by Guralnick *et al.*(1984).

Pyogenic infections of the face and neck, infections of the oral mucosa, oropharyngeal candidiasis, sialadenitis, and parotitis are examples of non-odontogenic diseases (Chow, 2010). Non-odontogenic cellulitis can typically be associated with trauma, sinus pathology, skin infections, or idiopathic causes (Abramowicz, 2017). Septic fractures were reported to be the second most prevalent cause of sepsis. Bacteria may enter the subcutaneous tissue once the protective barriers of the skin and/or mucosa are breached after trauma. Pathogens either enter by exposure (fracture with periodontal ligament space exposed) or direct injection causes via breech of skin by a foreign body or animal bite. The flora responsible for the sepsis is often determined by the location and mechanism of injury.

Orofacial microbial aetiology may be predicted by the bacteria and oral flora in the vicinity of where the infection arises. Bacteria are adapted to a different location depending on the oxygen supply (aerobic *vs* anaerobic), pH of the site, the host defences and the presence of antimicrobial agents (Kim *et al.*, 2012).

Causative organisms for mid-facial fractures frequently come from cutaneous flora and the nasal or paranasal sinuses. Gram negative anaerobic infections have been linked to contamination with foreign objects or debri (Bertossi *et al*., 2017). Soil contamination predisposes patients to *Clostridium tetani* and *Actinomyces* contamination.

Odontogenic infection can be used to explain the mechanisms and principles of spread of infection in the head and neck region. A carious tooth, breaching the pulp, leads to formation of a mixed bacterial colony (De Paz., 2007). The pulpal wall becomes colonized by a mixed anaerobic biofilm. Purulent infection develops once bacteria and toxic products breach the periapical tissues. The infection may remain localized or spread mainly via haematogenous or lymphatic spread (Shafer, 1983). In cases where the roots are in close proximity to the maxillary sinus, spread may occur through the cortical plate resulting in sinusitis. When the roots are positioned close to the buccal cortical plate, purulent material typically spreads buccally. The abscess may remain localized and develop a fistulous tract in the mucosa or skin, or it may travel across the fascial planes and develop abscess collections in possible anatomical spaces (Killey *et al*., 1975).

In early stages of infection, treatment can easily be conducted on an outpatient basis, in a primary healthcare centre. Treatment at this stage is relatively simple and quick. Once the infection has spread beyond the local tissue, infection can lead to fatal complications. Due to the anatomical region of the maxillofacial infection, spread via the circulatory system to vital organs such as the brain or heart, may compromise life sustaining functions. Complications such as airway obstruction, necrotizing fasciitis, mediastinitis, cavernous sinus thrombosis and sepsis, may arise and therefore necessitate hospitalisation. The aforementioned complications may result in delayed recovery and prolong the length of hospital stay (LOS) and may necessitate intensive care admissions. This not only increases the load on an already stretched healthcare system but may also affect the patient financially as a result of loss of income.

Orofacial sepsis cases are important in the healthcare setting and are examples of easily preventable disease. Due the financial, economic, and healthcare burden, it is important to optimize treatment. An adequate clinical examination is important in developing a proper risk profile, by examining the intrinsic as well as extrinsic factors present. These factors may be used to identify high-risk patients. Identification of high-risk groups and timeous intervention, including proper diagnosis and adequate dental care, may reduce adverse outcomes associated with prolonged hospital stay.

A paucity of knowledge regarding epidemiology of hospitalization outcomes exists with regard to patients with a primary diagnosis of orofacial sepsis in South Africa. Against this background, this study aims to identify measurable indicators that can be used to predict the outcome of treatment and LOS of an orofacial sepsis patient.

Chapter 2: Literature review

2.1 Orofacial sepsis

Patients suffering with odontogenic infections are commonly seen in outpatient dental clinics. These infections are usually limited to the oral cavity or superficial anatomic spaces on first presentation to the clinic. At this stage such infections can be controlled by the elimination of the aetiological factor, antibiotics, intraoral surgical incision and drainage. In cases where patients were not able to attend to the infection early, such infections may spread to deep neck spaces and may become life threatening. Late presentation, incorrect diagnosis, or ineffective initial treatment may all contribute to the progression of orofacial sepsis, requiring hospital admission and urgent surgical intervention (Bertossi *et al.*, 2017; Jevon *et al.,* 2020).

One of the diseases regularly treated by oral health care professionals is odontogenic infection. Odontogenic infections involve the alveolar processes, jaws, or face that arises from dental origin, periodontal origin or oral mucosa (Nhongo *et al.*, 2022). Dental trauma, dental caries, extensive restorations, unsuccessful root canal treatment, pericoronitis, and periodontal disease are frequently linked to odontogenic infections. The infection begins locally around a tooth and may either be limited there or it may spread to nearby or distant locations. The progression of the disease is reliant on factors such as the virulence of the bacteria, patient immunity, and the regional anatomical structures.

Periapical infection arises due to the ingress of microorganisms in the pulpal tissue. When the microorganism reaches the periapical tissue via the apical foramen, the body initiates an inflammatory process that may lead to the formation of an abscess. The infection often stays contained to the intraoral region, but in rare circumstances, patients may suffer spread to distal locations, which may lead to serious complications such infection of the paranasal sinuses, airway obstruction, thrombosis of the cavernous sinus, cerebral abscess, or even death (Agbara *et al*.,

2018). Another frequent odontogenic illness, pericoronitis, is brought on by a build-up of bacteria and food particles between the gingiva covering the partly erupted crown of the third molar. Pericoronitis commonly present as a chronic mild persistent inflammation surrounding the mandibular third molar area. However, if neglected, pericoronitis can develop into a dangerous infection accompanied by fever, oedema, and an abscess that could spread. The fast spread of infection can sometimes lead the symptoms to become severe, necessitating hospitalization for intravenous (IV) antibiotics and extraction of the associated tooth. Airway obstruction is a possible life-threatening complication if left untreated, due to the proximity of the structures to the oropharynx.

Clinically odontogenic infections can present in a wide variety of ways. It is dependent on the aetiological agent and whether the infection is localised or disseminated. The clinical signs and symptoms of all infections include pain and soreness, redness, and swelling (the cardinal signs of inflammation). Localized discomfort, cellulitis, sensitivity to tooth percussion, and temperature changes can all be symptoms of superficial infections. Swelling, fever, and occasionally dysphagia, trismus, or difficulty breathing may be present in deeper lying regions or infections that develop along the fascial planes. Recent reports concluded that the submandibular (75.3%) was the most commonly affected fascial space. The buccal (18.8%), parapharyngeal (15.3%), submental (14.1%), sublingual (11.8%), pterygomaxillary (4.7%), and infratemporal (3.5%) spaces were also commonly involved. However, the temporal space and the canine fossa (1.3% each), were infrequently involved (Bridwell *et al.*, 2021; Eshghpour *et al.*, 2021; Zawiślak *et al.* 2021). Facial spaces most involved in single space infections are the buccal space (60%), followed by the canine space (13%). In cases involving multiple spaces, the submandibular and the buccal spaces are the ones most commonly involved (Zawiślak *et al.,* 2021).

Signs and symptoms of the acute periapical infection often include discomfort and swelling. The characteristic periapical radiolucency can be seen on dental radiographs because of the bone resorption caused by the chronic inflammatory response, which is often asymptomatic and occurs around the root apex. An acute dental infection may develop from the periapical disease, which has been there but without symptoms (Bertossi *et al.*, 2017; Zawiślak *et al.,* 2021).

Table 2.1: Clinical presentation of odontogenic infections

Type of infection	**Clinical presentation**
Dentoalveolar infection	Periodontal, periapical and subperiosteal abscesses, resulting in alveolar ridge swelling.
Submental space infection	Firm midline swelling beneath the chin. Commonly caused by infection of the mandibular incisors.
Submandibular space infection	A swelling of the submandibular triangle of the neck around the angle of the mandible. Usually caused by involvement of mandibular molar teeth. Patients usually present with a degree of trismus.
Sublingual space infection	Swelling of the floor of the mouth resulting in elevation of the tongue, possible dysphagia and speech characterised with a defect of resonance (hot-potato speech).
Retropharyngeal space infection	Usually originate from molar infections, and present with a high potential to spread to the mediastinum. Stiff neck, sore throat, dysphagia, raspy voice are commonly seen in these cases.
Buccal space infection	Originate from maxillary premolar or molar teeth, resulting in swelling of the cheek.
Masticator space infection	Mandibular 3rd molar involvement, whereby the patient presents with swelling involving the mandibular ramus. A degree of trismus is present.
Canine space infection	Swelling of the anterior cheek with loss of the nasolabial fold and possible extension to the infraorbital region. Infection originate from the maxillary incisors and canine.

(Bertossi *et al.*, 2017; Yew *et al.*, 2021; Zawiślak *et al.,* 2021)

2.2 Ludwig's angina

Ludwig's angina is a life-threatening illness that can be fatal and is characterized by a brawny swelling brought on by a cellulitis that is progressing quickly. Abscess development and lymphatic involvement are often absent in such cases. Anatomically the submandibular space is segmented by the mylohyoid muscle, into the sublingual space and the submylohyoid space. The root apices of the mandibular teeth are generally located inferior to the attachment of the mylohyoid to the mandibular, the mylohyoid ridge, allowing infection to enter the submylohyoid space (Bridwell *et al.*, 2021). The infection spreads posteriorly and superiorly, tracking to the sublingual and submandibular spaces (Dowdy *et al.*, 2012). Involvement of these spaces may result in tongue swelling up to two to three times the normal size. This may lead to elevation of the tongue against the hypopharynx, and if untreated and allowed to progress this eventually leads to airway obstruction. Further complications include oedema involving the epiglottitis, true and false vocal cords, and aryepiglottic folds (Dowdy *et al.,* 2012). Dowdy *et al.,* (2012) reported a rapid progression of oedema of the airway structures, within 30–45 min of initial presentation. The infection can also spread via the styloglossus muscle into the parapharyngeal space, retropharyngeal space, and finally into the superior mediastinum (Kim, *et al.*, 2012; Dowdy *et al.,* 2012; Bridwell *et al.*, 2021).

The aetiological agent in these cases can be attributed to infected lower molars or mandibular pericoronitis. Patients who exhibit hoarseness, stridor, respiratory distress, reduced airflow, cyanosis, and the "sniffing" position—an upright position with the neck pushed forward and the chin raised—indicate that their upper airways are about to become compromised which will put them at risk for a life-threatening event (Bridwell *et al.*, 2021). Infection of the carotid sheath and arterial rupture, mediastinitis, empyema, pericardial and/or pleural effusion, osteomyelitis of the mandible, subphrenic abscess, and aspiration pneumonia are further complications of Ludwig's angina (Bermejo-Martín *et al.*, 2014; Bridwell *et al.*, 2021).

2.3. Spread of infection

The alveolar ridge or tissues near the tooth of origin are often the places where odontogenic infections occur, and they are typically mild. The infectious process begins at the root apex and extends to the surrounding tissue. If left untreated, the infection will begin to erode through the bone, taking the path of least resistance (the weakest area of the bone) (Bertossi *et al.*, 2017). In the mandible, the lingual aspect provides least resistance, but in the maxilla, the narrow buccal plate represents the simplest path. Muscle attachment in relation to the area where the infection perforates, play an important role in the manner in which the infection spreads.

Most commonly odontogenic infections develop in vestibular abscesses, aiding the penetration of bony structures of the head and neck. However, due to muscle attachments in the area, the infection may spread into fascial spaces, resulting in more severe infections. Occasionally, spread beyond the barriers of the fascial spaces may occur, which could result in life-threatening complications. Gravity, breathing, and negative intrathoracic pressure facilitate the spread of infection downwards along the fascial planes of the head and neck (Bertossi *et al.*, 2017). There is a consistent tendency in the spread of infection into the space, even though the pattern of spread differs between patients. Other routes that infection may be spread along include: haematogenous or lymphatic spread (Bertossi *et al.*, 2017). Bacteria from an odontogenic infection can enter the bloodstream, resulting in a bacteraemia ensuing in distant effects. In immune-compromised individuals, the bacteraemia may progress into septicaemia, a more serious blood infection accompanied by symptoms such as rigor, high fever, tachycardia, severe nausea, vomiting and mental changes (Agbara *et al.*, 2018).

The absence of valves in the facial, angular, or ophthalmic veins makes them vulnerable to haematogenous spread into the cavernous sinus and the cranium (Burnham *et al.,* 2011). Blood flow may occur in either direction in veins that lack valves, the direction of flow is dependent on

the prevailing pressure gradients. As a result, the cavernous sinus may be exposed to contaminated venous drainage, which may lead to cavernous sinus thrombosis. Dental infections, however, accounts for less than 10% of septic cavernous sinus thrombosis cases (Agbara *et al*., 2018), and most of these cases are related to structures in the danger triangle. The prevalence of cavernous sinus thrombosis has been reduced due to the use of effective antimicrobial agents in recent years.

Head and neck infections may spread via the lymphatic system. This happens as a result of the organisms entering the lymphatic system and moving through the lymph from a primary node close to the infected area to a secondary node farther away. The lymphatic fluid flows via small vessels, interconnected to lymphatic nodes, and finally drains into the venous system at the junction of the internal jugular and subclavian veins in the neck. After entering the vascular system, the infection could spread to other tissues or organs via haematogenous spread.

Lymphocytes, produced by the lymph nodes, act as antimicrobial filters to combat infections which may spread through lymphatic channels. Infectious spread is halted, if the infection is successfully controlled in the primary node.

2.4. Microbiology

The pathogenesis of odontogenic infection is polymicrobial, consisting of various facultative anaerobes, such as the s*treptococci viridans* group and the *streptococcus anginosus* group, and strict anaerobes, especially anaerobic *cocci, Prevotella* and *Fusobacterium* species (Bertossi *et al.*, 2017; Umeshappa *et al.*, 2021). The most commonly isolated bacterial species in odontogenic infections are strictly anaerobic gram-negative rods and gram-positive cocci, in addition to facultative and microaerophilic streptococci (Umeshappa *et al.*, 2021). Anaerobic bacteria outnumber aerobes 3:1 (Khemaleelakul *et al.,* 2002). The apical abscess has been shown, by

culture and molecular microbiology studies, to consist of mixed microbial colonies, with an overwhelming dominant anaerobic component (Bertossi *et al.*, 2017). Anaerobes (75%) include *Peptostreptococci*, *Bacteroides*, and *Prevotella* organisms, and *Fusobacterium nucleatum*. Aerobes (25%) include a-hemolytic *streptococci*.

Table 2.2: Bacteria phyla and genera typically cultured in dental abscesses

Firmicutes	*Streptococcus*, *Dialister*, *Filifactor*, and *Pseudoramibacter*
Bacteroidetes	*Prevotella*, *Porphyromonas*, *and Tannerella*
Fusobacteria	*Fusobacterium* and *Leptotrichia*
Actinobacteria	*Actinomyces* and *Propionibacterium*
Spirochaetes	*Treponema*
Synergistetes	*Pyramidobacter*
Proteobacteria	*Campylobacter* and *Eikenella*

(Chunduri *et al.*, 2012; Bertossi *et al.*, 2017)

Numerous bacterial combinations have been found in apical abscesses. In one report, *Firmicutes* (52%), *Fusobacteria* (17%), *Bacteroidetes* (13%), and other mixed species (18%) were the most prevalent phyla found in acute infections, while *Firmicutes* (59%), *Bacteroidetes* (14%), and *Actinobacteria* (10%) dominated chronic asymptomatic apical periodontitis infections (Bertossi *et al.*, 2017; Ogle., 2017). *Fusobacteria* members were far more common in acute infections but significantly less common in chronic illnesses. It was discovered that the bacterial populations in acute abscesses are more varied than those in chronic infections. In the study by De Oliveira *et al.,* (2007), *Prevotella* species were reported as the most isolated species, found in 10% to 87% of dentoalveolar abscesses.

In clinical practice, the aim is to identify a single species or major group of species, responsible for the infection. Yet, studies show that no single species can be responsible, but rather a set of

species organised in a multispecies biofilm community is involved. Thus, it is a heterogenous cause (Machado de Oliveira *et al.*, 2007). A microbial profile is demonstrated by the range of species present. Culture studies have reported a mean number of species ranging from 2 to 8.5 per pus specimen (Ogle., 2017).

Clinically, the bacterial load is just as significant as the species of bacteria present. The host's defence mechanisms may be overwhelmed by a high bacterial load. Total bacterial loads per abscess case have been reported to range from 104 to 109 cells (Khemaleelakul *et al.,* 2002). A higher bacterial load may enhance the variety of organisms, which may subsequently lead to a number of synergistic interactions between the individuals in the community and boost the infection's virulence factor. As a result of the synergistic action of bacteria within a multispecies bacterial biofilm community, even bacteria of low-virulence and/or in low numbers may affect the virulence of other members of the community (Peters *et al.*, 2012). The presence of a high load of a virulent strain might make the entire population more infectious and cause a more severe illness. This emphasises the importance of decreasing the total bacterial load and reducing the infectious bioburden on the individual. This is clinically obtained by tooth extraction, root canal therapy, incision and drainage, mechanical debridement, and copious irrigation of the infected area.

2.4.1 Anaerobes

Anaerobes are the most prevalent bacteria in odontogenic infections. These bacteria require an oxygen free environment to grow and thrive. Catalase is usually absent, but certain species have the ability to produce superoxide dismutase, which safeguards them from oxygen (Khemaleelakul *et al.,* 2002; Ogle., 2017). A maximum of 0.05% of oxygen can be tolerated in the case of strict anaerobes. Whereas moderate anaerobes can grow between 2% to 8% oxygen and facultative anaerobes have the ability to grow under aerobic conditions but can also thrive in an oxygen free

environment.

In the early stages of odontogenic infections, the bacteria that make up the infection mimic that of the normal oral flora. However, due to ecologic interactions and environmental conditions, over time anaerobes ultimately become the predominant group in the endodontic and periapical infections (Ogle., 2017).

In general, the occurrence of acute signs and symptoms including pain, sensitivity to pressure, and cellulitis can be attributed to the presence of gram-negative anaerobic bacilli and anaerobic gram-positive cocci. The development of an abscess, accumulation of foul-smelling pus, and tissue destruction is seen in anaerobic infections. Dental abscesses arising due to only anaerobe bacteria, occur in only about 20% of cases. The majority arise due to a mixed infection, with strict anaerobes outnumbering facultative anaerobes by a ratio that varies between 1.5 and 3:1 (Khemaleelakul *et al.,* 2002; Riggio *et al.*, 2007; Ogle., 2017).

Facultative anaerobes isolated in odontogenic infections belong to the *Streptococci viridans* and the *anginosus* groups. *Staphylococcus aureus* has also been identified as a causative organism in acute dental abscess.

2.4.2 Aerobes

Aerobic bacteria are thought to be responsible for only a small percentage (5%) of odontogenic infections. (Khemaleelakul *et al.,* 2002). The predominant species involved are *Streptococcus* species that form part of the normal oral flora. These aerobic *Streptococci* species are present in early stages of the infection resulting in the development of cellulitis. However, this rapidly

transforms into a mixed infection that is dominated by anaerobic bacteria. The aerobic bacteria serve as the infection's primary causative organisms and pave the way for anaerobic bacteria to invade when the local tissue condition changes to a more hypoxic state that promotes anaerobic growth (Peters *et al.*, 2012; Ogle., 2017).

2.5. Management

The advent of antibiotics, improved health standards, better understanding of medical conditions and the improved access to primary healthcare have all contributed to the reduction in the mortality and morbidity of odontogenic infections. Three stages can be appreciated in odontogenic infections, namely a soft mildly tender swelling, that is usually present in the first three days; followed by a hard, red and severely painful swelling (usually day 2-5) and finally abscess formation (day 5-7) (Ogle., 2017; Jevon *et al.,* 2020).

To best manage odontogenic infections with the most favourable results, seven guidelines have been put forward, as presented in Figure 2.1 (Flynn *et al*., 2006 Jevon *et al.*, 2020). A comprehensive clinical examination and meticulous history-taking is pertinent in assessing the severity of any infection. A thorough history will aid in identifying factors such as the capacity of the immune system to fight disease processes and the quantity of systemic defences against infections (Flynn *et al.*, 2006).

A comprehensive examination is important in identifying signs outside of normal parameters. Further haematological and clinical parameters, such as C-reactive proteins (CRP), white blood cell count (WBC), fever, respiratory rate, number of anatomical spaces involved, anatomical position and compromised airway, have been used as prognostic indicators (Stathopoulos *et al.*, 2017; Heim *et al.*, 2019; Muna *et al.,* 2022). CRP, anatomical position, and fever have been investigated as predictor factors for the length of hospital stay (LOS) in odontogenic infections.

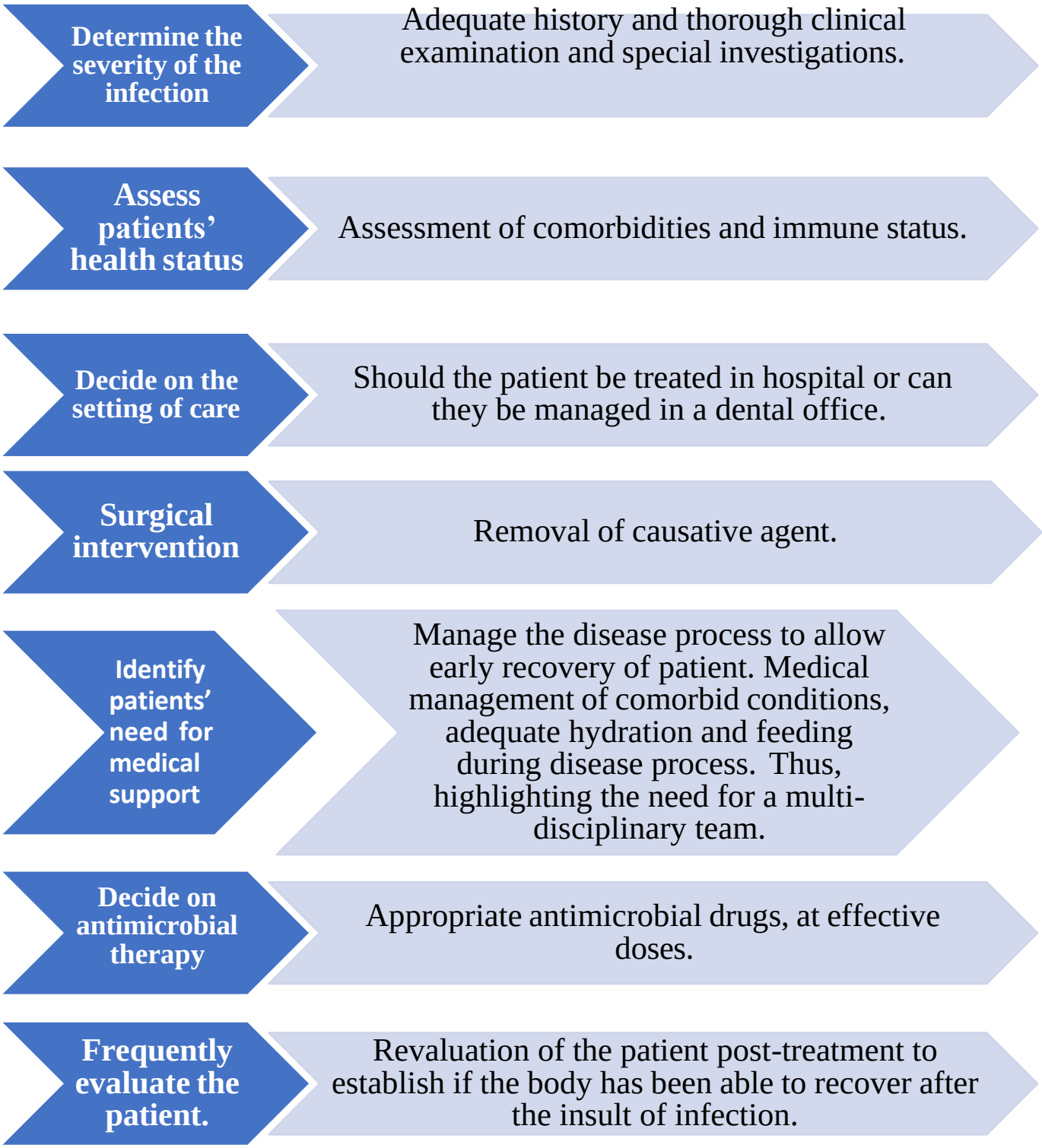


Figure 2.1 Guidelines for management of odontogenic infections

Numerous fascial spaces, also known as potential spaces between regional fasciae and organs and the musculoskeletal structures, exist in the head and neck region. A patient without trismus and/or dysphagia, and systemically healthy, presenting with infections in low-risk areas (Table 2.3) can be treated initially in a primary care dental office. However, infections that spread to higher-risk spaces should be controlled more aggressively and may require treatment in a hospital setting.

Table 2.3: Risk accompanying fascial space involvement.

Risk	Low	Moderate	High	Life threatening
Facial spaces	Buccal	Submental	Lateral pharyngeal	Mediastinum
		Sublingual		
	Vestibular	Submandibular	Pretracheal	
		Temporal		Intracranial infection
	Infraorbital	Submasseteric	Retropharyngeal	
		Pterygomandibular		

(Zheng *et al.*, 2012; Agbara *et al.*, 2018; Jevon *et al.,* 2020)

An analysis by these authors also concluded that there was a negative correlation between severity and number of days prior to consultation, confirming that rapidly progressing cases presented sooner than slowly progressing cases.

In deciding on the setting of care a few factors need to be considered. Young, healthy patients with no signs of worsening, who presented or present early may be treated as an outpatient (Agbara *et al.*, 2018; Jevon *et al.,* 2020; Kim *et al.,* 2021). On the other hand, an elderly and/or immunocompromised patient, with multi-space infections or involvement of spaces of moderate or higher risks, with fast progressing or well-established infection, should be managed in a hospital environment.

Systemic inflammatory response syndrome (SIRS) is a defence response of the body to a noxious stressor, to enable the body to identify and remove the insult. Sepsis is when SIRS is present, with a suspected source of infection. SIRS can be diagnosed with the presence of any two of the following four criteria (Sainuddin *et al.*, 2017; Chakraborty *et al.,* 2022):

- Body temperature of 38°C and higher or below 36°C.
- Tachycardia, 90 beats per minute or higher.
- Tachypnoea: greater than 20 breaths per minute
- Leukocyte count greater than 12000 or less than 4000 per microliter.

Table 2.4 provides established admission guidelines for patients presenting with odontogenic infections.

Table 2.4: Objective scoring criteria for decision making on admission of odontogenic infections.

Systemic inflammatory response syndrome (SIRS) Odontogenic infection with SIRS indicates that the patient has sepsis, and that fluid management and IVI antibiotics are necessary and requires admission to hospital (Chakraborty and Burns, 2022).
Trismus Patient is unable to open the normal range (40-60mm). This can be further subdivided in moderate (<20mm) and severe (<10mm). Moreover, patient may present with false trismus where the patient guard against wide opening due to pain (Flynn *et al.*, 2006; Sainuddin *et al.*, 2017).
Difficulty in swallowing (dysphagia) Dysphagia is a good predictor of a compromised airway, thus remains a vital criteria. Dysphagia is classified as mild, able to swallow anything, moderate, unable to swallow liquids and in severe cases the patient will be unable to their own swallow saliva (Attrill *et al.*, 2018).
Threatening airway or swelling encroaching vital structures A compromised airway is an emergency and requires immediate airway management and monitoring with aggressive treatment of infection (Attrill *et al.*, 2018).
Involvement of anatomical spaces

Collection in one facial space may be subdivided in moderate, high or life-threatening risk levels (Table 2.3). Involvement of more than one space requires immediate admission (Zheng *et al.*, 2012; Sainuddin *et al.*, 2017; Stathopoulos *et al.*, 2017; Kim and Kim, 2021).
Comorbidities and Immunocompromised patients Diabetes mellitus (DM), known or suspected alcohol use, cigarette smoking, and immunocompromised states such as HIV positivity, immunosuppressive medication use, or chemotherapy are also considered. Certain comorbidities have been shown to delay healing and lengthen hospital stays and increase probabilities of complications (Zheng *et al.*, 2012; Botha *et al.*, 2015; Kim and Kim, 2021; Juncar *et al.,* 2020).
Dehydration Dehydration in odontogenic infection patients might be brought on by decreased oral intake due to discomfort, dysphagia, or trismus. The risk of complications is increased when sepsis is present. A systolic blood pressure of less than 90 mmHg, a decrease in skin turgor, or an increased serum urea content are indicative of dehydration (Sainuddin *et al.*, 2017).
Involvement of orbital content
Any orbital involvement necessitate admission (Kim and Kim, 2021).

Antimicrobial management is a good adjunct to surgical treatment of orofacial infections. It is of essential importance that antimicrobial treatment alone is not able to clear the infection. Over-prescribing of antimicrobial substances has become a problem in the contemporary world, leading to complications such as microbial resistance and hypersensitivity to antimicrobial substances. Both the use of Clindamycin alone and Penicillin in combination with Metronidazole has been demonstrated to be an efficient antibacterial strategy in treating orofacial infections (Bhagania, 2018). In a comparative study by Bhagania *et al*, (2018) they established that Clindamycin has the additive benefit of resulting in a shorter in-hospital stay and has a slightly higher success rate in clearing the infection.

Recent published guidelines by the Scottish Dental Clinical Effectiveness Programme (SDCEP) on antibiotic use in dental practice has identified Penicillin-based antibiotics as the initial choice of

treatment for odontogenic infections. Metronidazole is efficient against anaerobic bacteria and may be added as an adjunct (NHS, 2022). In the hospital setting, the protocol for antibiotics prescription may vary in accordance with the local hospital antimicrobial protocol. Bacterial culture and consultation with the microbiologist is of great value in deciding on antibiotic choice, especially for severe cases and cases which are not responding to empirical antibiotics (Kim, Chuang and August, 2017).

The Maxillofacial and Oral surgery (MFOS) department's antibiotic protocol at Wits recommends the oral use of Amoxycillin for minor cellulitis on an outpatient basis (Appendix 3). Patients admitted for single space infections are treated with Penicillin G intravenously. Clindamycin is prescribed for patients allergic to Penicillin. In cases where there is no clinical improvement after 72 hours, Metronidazole is added.

Mild cases can be treated on an outpatient basis. Delayed treatment can result in more severe spread of infection beyond the initial border and can progress to surrounding soft tissues and bone, resulting in life-threatening maxillofacial emergencies requiring hospital admission. Untreated, localised odontogenic infections can spread rapidly through various fascial planes, compromising multiple fascial compartments (Kim *et al.*, 2012).

It was reported that the mean length of in-hospital stay in patients admitted with sepsis is 4.5 days. This dramatically increased to 6.5 days for severe sepsis and a mean of 16.5 days was reported for patients with septic shock (Paoli, 2018).

A fatal outcome is infrequent, however, spread of infections may cause other fatal complications, including mediastinitis, septic shock, and massive haemorrhage. These complications often result in poor hospitalization outcomes.

Airway compromise is a chief reason for death in severe odontogenic infections. The practice of safe airway maintenance, removal of the source of infection, prompt aggressive surgical drainage

and medical support has seen a reduction in mortality rates in patients with odontogenic infections. The mortality rate was reported to be 8-10% for Ludwig's angina (Ugboko *et al*., 2005), most often due to hypoxia or asphyxia rather than overwhelming sepsis. Ugboko *et al.,* (2005) attributed the higher mortality rate in their study to late presentation, presence of uncontrolled underlying disease especially diabetes mellitus (DM), and economic constraints with inability to procure more effective prescribed antibiotics. This appears to be a general trend seen not only in African counties but also in other developing countries around the world.

A clinical examination provides the clinician with a good indication of the risk of airway compromise. Severe involvement is seen when the floor of mouth is raised and 'full' (indurated with lifting or without fluctuance, displacing the tongue posteriorly). Other locations of severe airway compromise are found when the tonsillar pillar is oedematous and swollen with or without uvula displacement, and when the lateral pharyngeal space (lingual surface of mandible posterior to the third molar) is tender or oedematous and the patient cannot swallow.

Radiographs of the lateral neck and CT scans can also be used to determine whether the airway is compromised. A maximum incisal opening of less than 25 mm and blunting of the inferior border of the mandible at the body, are recognized as findings strongly related with the necessity for CT imaging and are major markers of more serious odontogenic infections (Miller *et al*., 1999).

Other complications include septic shock, mediastinitis, pleural empyema, upper airway obstruction, disseminated intravascular coagulation, acute respiratory distress syndrome, necrotizing fasciitis, pericarditis, and death. Furthermore, there are intrinsic as well as extrinsic factors, which may affect the patients' hospital LOS. Identification of high risk groups and timeous intervention, including proper diagnosis and adequate dental care, may reduce adverse outcomes associated with prolonged hospital stay.

A paucity of knowledge regarding epidemiology of hospitalization outcomes exists with regard to patients with a primary diagnosis of orofacial sepsis in South Africa. Against this background, this

study was undertaken to assess outcome of patients hospitalised for orofacial sepsis.

Chapter 3: Material and Methods

3.1. Null-Hypothesis

It is not possible to predict the outcome and longevity of in-hospital stay of a patient with orofacial sepsis by considering comorbid factors and clinical investigations at admission.

3.2. Aim

The aim of this study was to investigate clinical outcomes in patients hospitalized for orofacial sepsis, and to identify possible patient and hospital-level factors associated with such outcomes.

3.3. Objectives

- To determine the strength of the correlation between location of abscess and duration of hospital stay.
- To determine the strength of association between delay in treatment and LOS in the hospital.
- To record complications of the orofacial sepsis.
- To record types of antibiotics used
- To determine the demographics of the referral health care practitioners.

3.4. Data source and patient selection

Prospective analysis was done of patients treated at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Hospital (CHBH) over a 12-month period. All patients over 18 years of age, with a primary diagnosis of orofacial sepsis were included in the study.

3.5. Data extraction

Data was recorded using a data collection sheet (Appendix 1). Each patient was allocated a data collection sheet at admission, data was updated daily as the treatment progressed and the data collection sheet was collected at discharge. The data sheet was assessed to record the patients' information over the course of the hospital stay.

Data was categorized as demographic, health status, clinical presentation at admission, anatomical variables, treatment variables and special investigations. The demographic variables included on the data collection sheet were age and gender. The data collection sheet also aimed to determine the demographics of the referral healthcare worker; being a professional nurse, dentist or medical doctor; from hospital or clinical setting, and whether the referral practice had an active dental or surgery department. It data sheet contained time-related variables including time spent from onset of symptoms to seeking treatment, LOS in hospital, date of admission and time between admission and surgery.

A checklist of medical comorbidities was included in order to record health status–related variables. The list was adapted from the study of Kim *et al.,* (2012) who investigated the relationship between hospital stay and charges. The datasheet aimed to interrogate the aetiological agent of the infection, such as dental caries, third molar involvement, pericoronitis, root remnants, etcetera. It also recorded any clinical signs the patient may present, such as dyspnoea, dysphagia, trismus, commonly associated with orofacial infections (Flynn, 2006).

The data collection sheet also recorded the admission criteria, such as temperature at admission and respiratory rate. Other data obtained included special investigations such as blood tests, which included CRP and WBC, and a pus swab. Obtaining data from patients admitted to other departments in the hospital with severe compromised airways posed some difficulty.

The researcher requested assistance from the registrars and staff, in order to collect the data from such patients.

Anatomical variables recorded the fascial spaces involved by cellulitis or abscess. Lastly the recorded treatment variables included the type of treatment received by the patient. These include surgical as well as non-surgical treatment. Surgical treatment included details on tooth extractions and surgical drainage of facial spaces. Non-surgical treatment recorded medication administered, dose and route administered.

3.6. Independent variables

Age, gender, type of admission (elective *vs* emergency), and the burden of concomitant conditions are among the independent factors addressed in the current study.

3.7. Outcomes

Three outcomes, namely length of hospital stay, treatment outcome (route of discharge) and occurrence of infectious complications were analysed from the dataset.

LOS indicates the number of days that a patient stayed in the hospital since admission. The infectious complications evaluated included septicaemia, bacterial infections, septic fracture and mycoses.

3.8. Predictor variables

The predictor variables were composed of a heterogeneous set of patient- and hospital-related variables. Patient-related factors include anatomical spaces involved in sepsis, delay in onset of

treatment and the comorbid burden. All the comorbid conditions were analysed individually. We also assessed the comorbidity burden where patients had none, one or multiple comorbidities.

Hospital-related factors such as: the level of care from which the patients were referred, whether a hospital or clinic, the referring practitioner, namely medical doctor, dentist or professional nurse, presence of an active surgical department (general/MFOS) or dental department and what treatment the patient received, if any, prior to referral referred.

Age was a continuous variable. All other demographic, health status related, and hospital related variables were recorded as categorical variables as provided in the dataset.

Statistical analyses

A multivariable linear regression analysis was used to examine the association between hospital stay (outcome variable) and the predictor variables. Each comorbid bivariate condition was tested by using simple linear regression analysis and were included in the final multivariable linear regression model. A $p < 0.05$ was considered to be statistically significant. A Spearman's correlation coefficient was calculated to determine the strength of association between LOS and comorbidity burden.

Descriptive summary statistical analysis was performed on all identified patients. The T-test was performed to determine the significant difference between delayed and immediate treatment. To determine if the LOS is the same for immediate and delayed treatment we performed a Welch Two Sample t-test and a Mann-Whitney test to look at the distribution of the days admitted for delayed and immediate treatment.

Spearman's rank correlation was calculated to determine the effect of facial space involvement and comorbidity burden on LOS. With the use of a Welch Two Sample t-test we determined the effect of each facial space involvement on the LOS as well as each individual comorbidity's effect on LOS.

Chapter 4: Results

Table 4.1: Association of length of stay, clinical characteristics and treatment outcome

Variable	**Categories**	**Number of patients**	**Percentage**
Gender	Male	87	57.2
	Female	64	42.1
Age group	<60	140	92.1
	>60	12	7.9
Hospital factors			
Referral from:	Referred from hospital	31	20.4
	Referred from clinic	47	30.9
	No referral. walk in patient	74	48.7
Referred by:	Medical Doctor	43	28.3
	Dentist	30	19.7
	Professional nurse	5	3.3
Referring hospital	Active dental department	59	38.8
	Active surgical department	23	15.1
	Active MFOS dept	0	0.0
	On treatment	38	25.0
Hospital:	CMJAH	73	48.0
	CHBAH	79	52.0
Length of stay		8 +/- 7.4	
Time lapsed before treatment		10.3 +/- 12.4	
Time from admission to first surgery	less than 12 hours	81	53.3
	12-24 hours	45	29.6
	longer than 24 hours	26	17.1

Clinical characteristics			
Admission Temperature	<37	144	94.7
	>37.5	8	5.3
Pulse rate at admission	90 +/- 14.66		
Respiratory rate at admission	20 +/- 4.37		
Comorbidity count	None	84	55.3
	Single	31	20.4
	Multiple	39	25.7
	Smoking	44	28.9
Involved spaces	Single	28	18.4
	Multiple	114	75.0
Clinical features	Fever	4	2.6
	Trismus	123	80.9
	Odynophagia	21	13.8
	Dyspnoea	23	15.1
	Dysphonia	3	2.0
	Dysphagia	31	21.1
	Periorbital oedema	3	2.0
	Mobile mandibular section	2	1.3
	Rhinorrhoea	1	0.7
Infectious complications	Osteomyelitis	5	3.3
	Wound breakdown	4	2.6
	Necrotizing fasciitis	1	0.7
	Septic shock	1	0.7
	Loss of occlusal integrity, open bite, non-healing fracture, osteomyelitis	2	1.3

	Soft tissue loss	1	0.7
Cause of infection:	Decayed tooth	106	69.7
	3rd molar involvement	44	28.9
	Septic hardware	7	4.6
	Septic fracture	17	11.2
	Root remnants	3	2.0
	Soft tissue infection (human bite, sinusitis, foreign body, post-surgery	11	7.2
	Acute alveolitis	6	3.9
	Periodontitis	2	1.3
Biological Values:			
CRP		142.63 +/- 101	
WBC count		14.01 +/-6.5	
Treatment			
Antibiotic regimen	single regimen antibiotics used	136	89.5
	Additional antibiotic needed	16	10.5
Treatment	I&D only	9	5.9
	I&D with extraction	120	78.9
	I&D with fracture repair	18	11.8
	I&D with removal of hardware	8	5.3
Discharge	Routinely	148	97.4
	RTH	3	2.0
	Death	1	0.7

Multiple Linear Regression

LOS to hospital are positively skewed based on a histogram/boxplot of the raw data (Figure 4.1). Various common transformations were attempted.

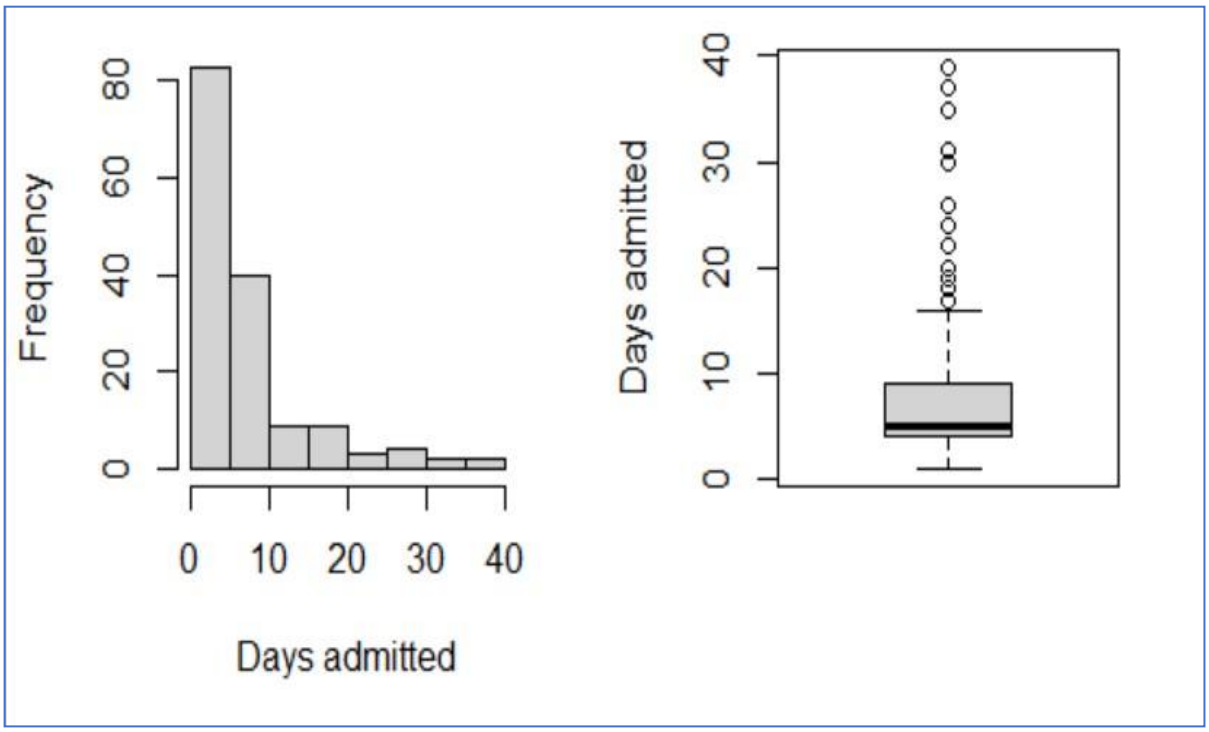


Figure 4.1 – Distribution of Length of stay Variable

The transformation which resulted in the most symmetric distribution of the data was the log (base 10) transformation. Although this transformation still failed a formal test for normality (Shapiro-Wilks test (W = 0.70381, p-value <0.001), the data appeared symmetric based on the histogram and boxplot (Figure 4.2) which means that it is likely that the parametric regression method using the transformed variable will be robust to the assumption of normality.

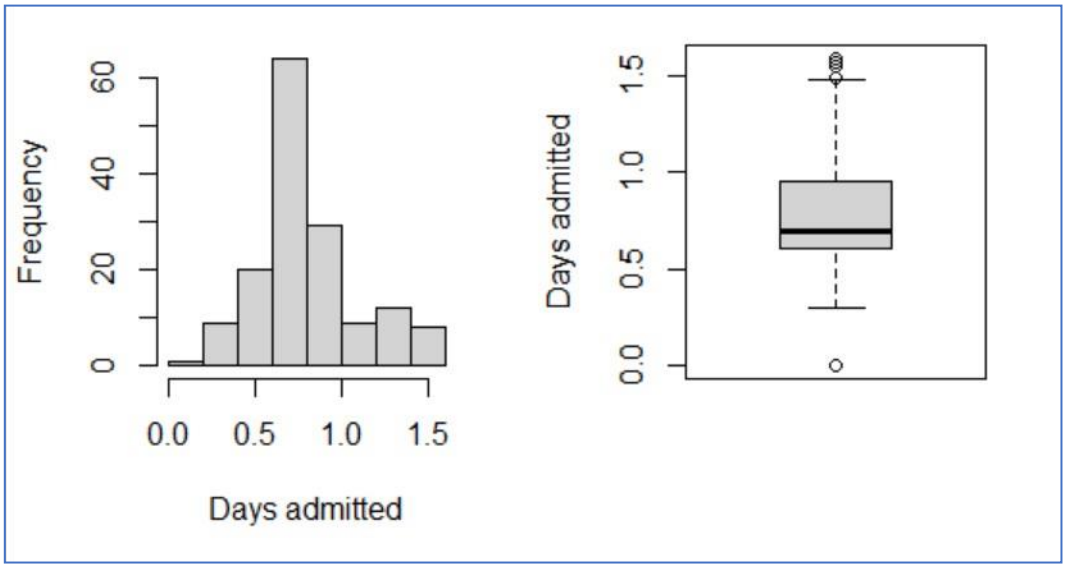


Figure 4.2 - Distribution of log10 of length of stay

Results of a multiple regression model:

A model was fitted using the following variables and interactions as requested:

Comorbidity burden, facial space involvement, third molar involvement, CRP and WBC.

Model selection was done using Akaikie Information Criterion, and the drop1 function. The best model which was obtained with *almost* significant effects for all terms was a model including space involvement, 3rd molar involvement and CRP. The basic diagnostic plots are shown in Figure 4.3.

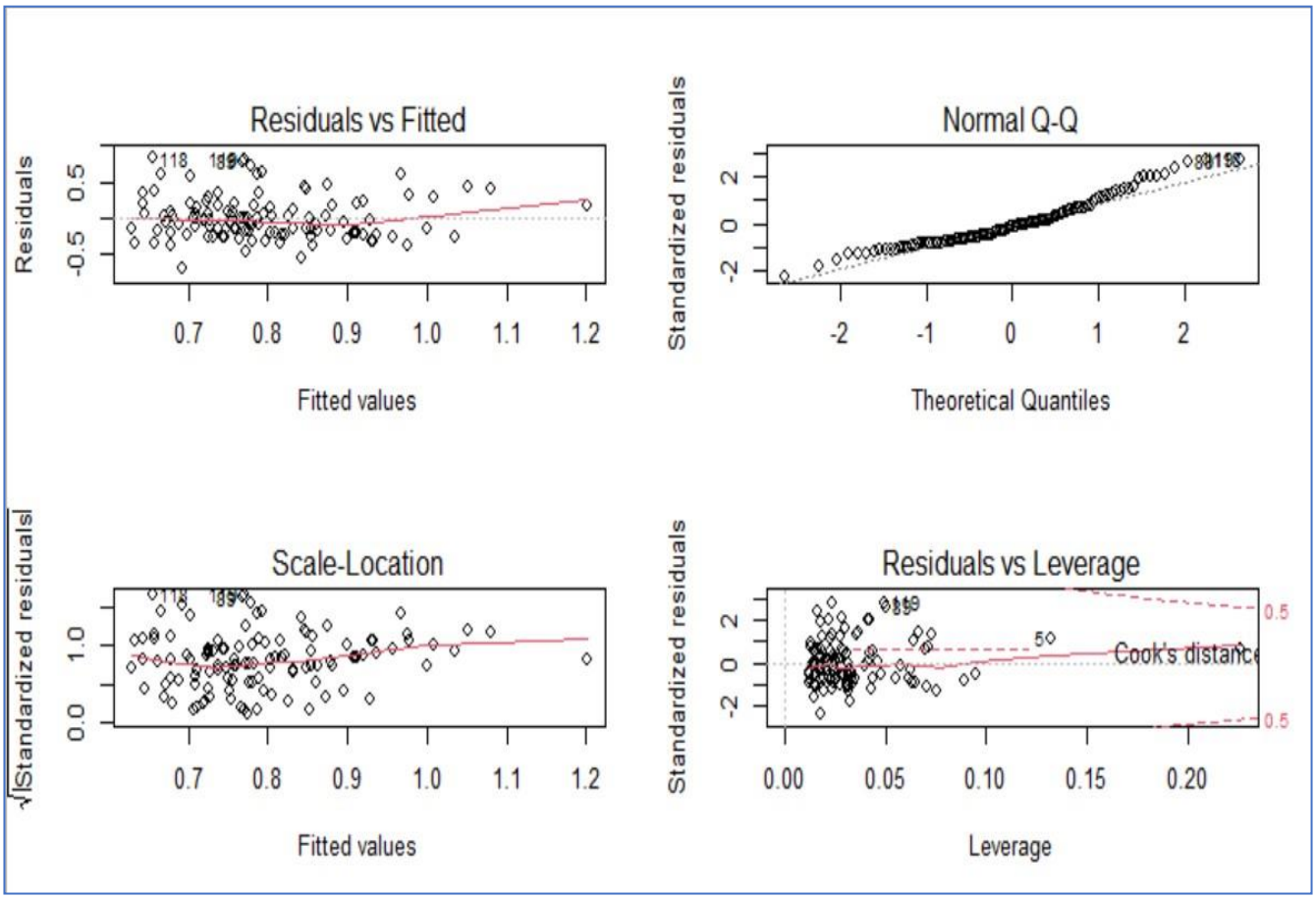


Figure 4.3 - Basic diagnostic plots of "best" model

4.1. Patient and demographic data

A study population of 152 cases were identified over the course of 12 months at CHBAH and CMJAH. These patients were diagnosed with orofacial sepsis and treated in hospital. Of these patients 57.2% were biologically male and 42.8% female. The mean age was 35±12.8 (range 18-76), with 12 patients being over the age of 60 years. Only patients older than 18 were included in the study. The study population was composed of a younger population age, with the majority of patients falling within the age group of 26-30. From the patients admitted, 48% were admitted at CMJAH and 52% at CHBAH.

The mean duration of stay, which was eight days, was not associated with sex (Mann-Whitney: U=499.0, p=0.14) or age (Pearson: r= 0.09, df=69, p=0.421).

4.2. Health status

Table 4.2: Comorbidity burden and predictor value.

Comorbidity	Number of cases	Percentage	t-value	df	p-value
Tuberculosis	3	2	t = -0.474	2.09	0.68
HIV/AIDS	21	13.8	t = -1.711	27.68	0.098
Chronic nephritis	3	2	t = 1.299	2.71	0.293
Alcohol abuse	5	3.3	t = 0.753	4.64	0.488
Cigarette use	44	28.9	t = 0.525	108.11	0.0601
Rheumatoid arthritis	2	1.3	t = 5.119	149	0
Chronic blood loss anaemia	3	2	t = -0.502	2.03	0.665
Congestive heart failure	4	2.6	t = -0.975	3.14	0.398
Coagulopathy	4	2.6	t = -1.039	3.16	0.372
Diabetes Mellitus	15	9.9	t = -1.298	16.44	**0.0212**
Hypertension	12	7.9	t = 3.249	59.3	**0.002**
Liver disease	4	2.6	t = -0.561	3.59	0.608
Metastatic cancer	3	2	t = -4.59	2.2	**0.037**
Asthma	2	1.3	t = 1.813	1.89	0.219
Single	31	20.4			0.414
Multiple	37	24.3			0.748
None	84	55.3			0.335

Table 4.2 shows the comorbidities patients presented with on admission. Among the population

84 (55..3%), of patients presented without any comorbidity. Twenty point four (20.4%) had a single comorbidity, of which 18 (58%) were cigarette users. The study population has a very low comorbidity burden, with an average burden of one per patient.

The most common comorbidity patients presented with, were HIV (13.8% of cases, p=0.09), DM (9.9% of cases, p=0.212) and hypertension (7.9% of cases, p=0.002). There were two patients who presented with a comorbidity load, with the value of 5. Both patients were admitted due to decayed teeth. Only hypertension and metastatic cancer had a statistically significant predictive value on LOS.

Of the patients treated, 21 were diagnosed to be HIV+, all of which were on ARV treatment. Of these, seven patients had an undetectable viral load. The highest viral load was 307 000, with a CD4 count of 167. The viral load was shown to present as a predictor value for LOS (t-test with a p=0.05). The longest LOS of all HIV+ patients was 26 days. This patient presented with 4 facial spaces involved and a comorbidity load of 4. The patient also required an additional antibiotic administered due to antibiotic resistance. The average LOS of HIV+ patients was 8+/-7 days.

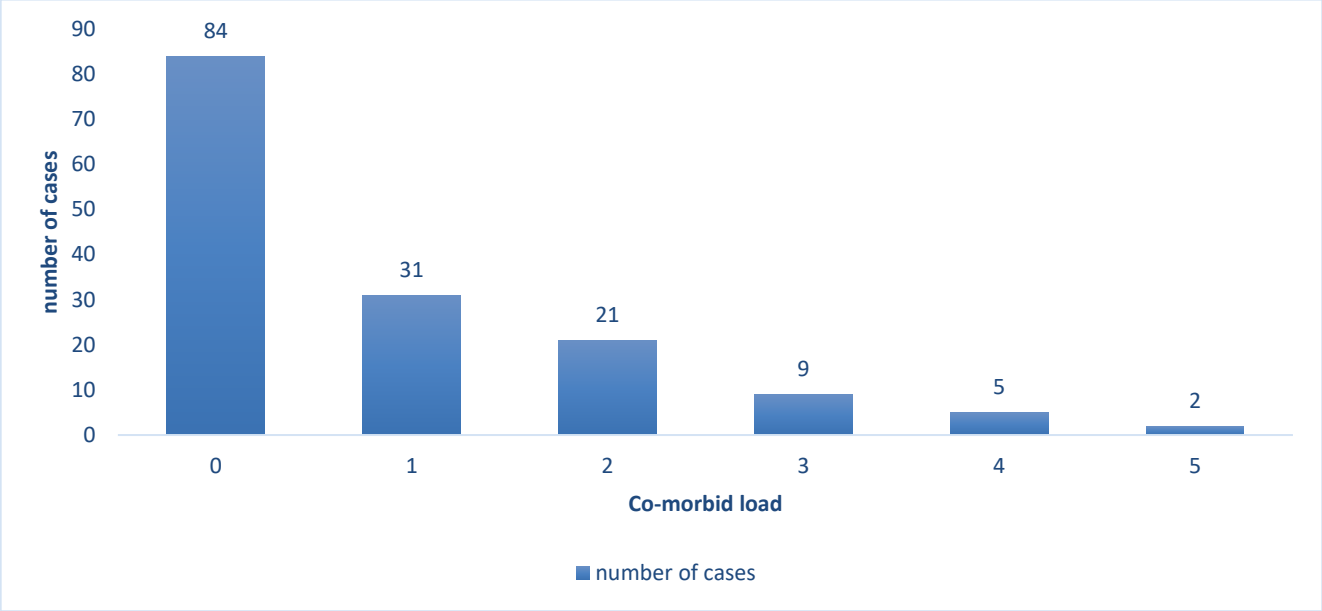


Figure 4.4: Prevalence of co-morbid count of patients admitted for orofacial sepsis.

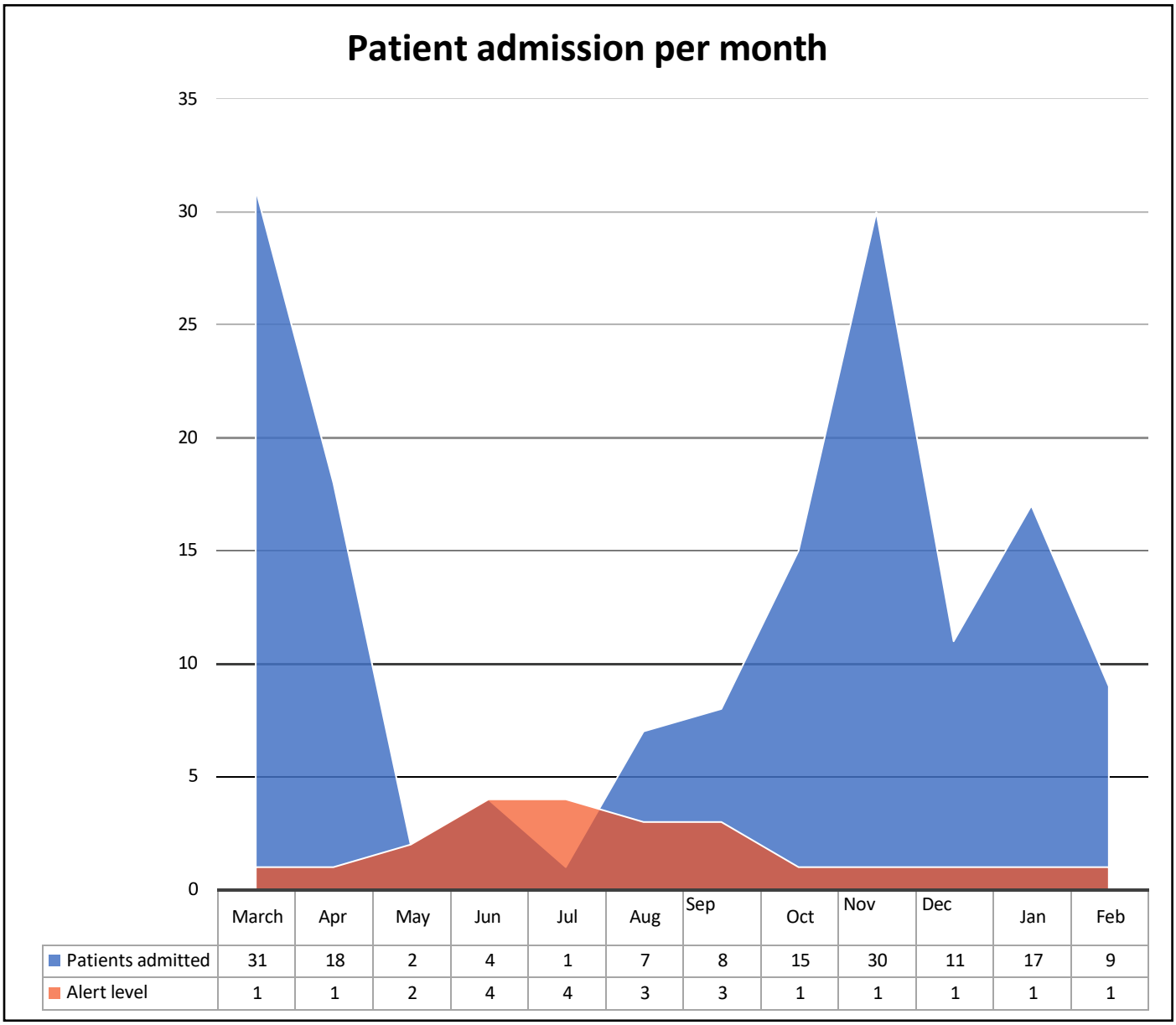
4.3. Hospital course

Descriptive statistics pertaining to hospital course is depicted in Table 4.1. Of the patients who participated in the study, 74 (48.7%) presented directly to the hospital OPD clinic for treatment. The remainder of the patients presented as referrals from local hospitals ((31 patients, (20.4 %,)) and clinics (47 patients, (30.9%,)) respectively. Neither the referral nor the OPD patients presented with a statistically significant predictor value (df=32, t=9.5 and p=0.552). Of the 78 referring institutions, 59 (75.6%) are active dental departments, and 23 (29.4%) are active general surgery departments. The majority of the patients were referred by medical doctors (43 patients, (55.1%)), 30 patients (38.5%) were referred by dentists and 5 (6.4%) by a professional nurse.

Thirty-six patients were referred on treatment, of which only two patients did not receive antibiotic treatment but received analgesics. Both of these cases were seen by a professional nurse. Medical doctors who had seen 19 cases, (52.8%), tended to prescribe 2g Co-amoxiclav in 18 cases and Flucloxacillin in one case. Dental practitioners tended to prescribe either 500mg Amoxicillin combined with 400mg Metronidazole (56.2%), or 2g Co-amoxiclav (25%) or 500mg Amoxicillin (18.8%). Patients referred on treatment did not provide a statistically significant predictor value (p=0.475) for LOS.

The mean number of days from initiation of symptoms to admission was 10.3 +/-12.4 days. The LOS was not the same for treatment delay in treatment (Levene's test, F=5.0618, df1=1; df2 = 150, p=0.02591). Time lapsed from admission to surgery was divided into three groups: immediate (within 12 hours) (53.3%), between 12 and 24 hours (29.6%) and delayed (longer than 24 hours) (17.1%). The mean LOS was not the same for immediate and delayed treatment (Welch Two Sample t-test, t=2.9446, df=111.07; p=0.0039). The distribution of LOS for immediate and delayed treatment were not equal (Mann-Whitney test (Wilcoxon rank sum test

with continuity correction in R, W=3795.5, p=0.000624). Therefore, there was a significant difference in the LOS between immediate and delayed treatment. Assumption of normality is suspect due to the skewness in LOS. An assumption of equal shape is suspect due to heterogeneity of variance. Thus, delay in seeking treatment and initiation of treatment may be associated with longer LOS.



	March	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb
Patients admitted	31	18	2	4	1	7	8	15	30	11	17	9
Alert level	1	1	2	4	4	3	3	1	1	1	1	1

Figure 4.5: Number of patients admitted for orofacial sepsis per month vs the national lockdown restriction level.

4.4. Clinical presentation, aetiology, and location of infection

Significant information relating to the characteristics of infections are demonstrated in Table 4.3. The aetiology of the infection was investigated, by preforming a multiple linear regression, to determine the predictor value. The most common cause of infection was due to decayed teeth (69.7%, p=0.486). Of these, 44 involved the lower 3rd molars (p=0.001, b*=0.256), which presented as a statistically significant predictor value for LOS.

Table 4.3: Aetiological factors of orofacial sepsis and predictor value for length of hospital stay.

Aetiology	Number	Percentage	p-value
Decayed tooth	106	69.7	0.486
Septic hardware	7	4.6	0.84
Trauma	7	4.6	0.551
Septic fracture	10	6.6	0.331
Root remnants	3	2.0	0.998
Soft tissue infection (human bite, sinusitis, foreign body, post-surgery	11	7.2	0.461
Acute alveolitis	6	3.9	0.529
Periodontitis	2	1.3	0.6
3rd molar involvement	44	28.9	**0.001**

On investigating the presenting symptoms, 80.9% of patients presented with trismus (p=0.068). On performing a multi linear regression model dysphagia (21.1%) presented as a statistically significant predictor value (p=0.02). Forty-eight (31.6%) of patients presenting with more than one clinical sign at admission, a multiple linear regression was preformed to relate to LOS (p=0.066, standard error=0.89).

Table 4.4: Clinical signs and symptoms and the predictor value of length of hospital stay.

Presenting symptom	**Number of cases**	**percentage**	**p-value**
Trismus	123	80.9	0.068
Dysphasia	31	20.4	0.02
Dyspnoea	23	15.1	0.319
Odynophagia	21	13.8	0.293
Periorbital oedema	3	2.0	0.665
Dysphonia	3	2.0	0.167
Mobile mandibular section	2	1.3	0.407
Chest pain	1	0.7	0.14
Rhinorrhoea	1	0.7	0.142
Multiple signs at admission	48	31.6	p=0.066

There was 2±1.5 infected anatomical spaces on average per subject (range 1-10). The majority (75%) had multispace involvement, with the submandibular space (56.6%) being the most commonly involved space. The LOS was not the same at each facial space involvement (Welch Two Sample t-test). Ludwig's angina was diagnosed in 17 (11.2%) (p=0.027) cases and the mediastinal spread was seen in 3 (2%) of the cases. The LOS had a positive correlation to the number of involved facial spaces (Spearman's rank correlation ratio S=442421, p=0.0024).

Table 4.5: Anatomical space involved as predictor value for orofacial sepsis.

Facial space involved	Number of cases	Prevalence	p-value	t-value	df
Periosteal	4	2.6	0.307	t = 1.2	3.43
Buccal	55	36.2	0.484	t = 0.702	126.92
Submandibular	86	56.6	0.549	t = 0.601	117.78
Masseteric	26	17.1	0.18	t = -1.367	34.59
Submasseteric	28	18.4	0.692	t = 0.399	52.45
Pterygomandibular	18	11.8	0.486	t = -0.708	21.76
Parapharyngeal	11	7.2	0.285	t = -1.123	11.14
Submental	54	35.5	0.36	t = -0.92	108.65
Sublingual	28	18.4	0.265	t = -1.132	36.67
Cervical	6	3.9	0.243	t = -1.318	5.18
Infraorbital	9	5.9	0.497	t = -0.708	8.71
Infratemporal	6	3.9	0.293	t = -1.169	5.25
Temporal	7	4.6	0.867	t = -0.174	6.34
Thoracic	3	2.0	0.282	t = -1.454	2.02
Canine space	4	2.6	0	t = 5.059	11.42
Frontal	2	1.3	0.943	t = -0.09	1.04
Ludwig's angina	17	11.2	**0.027**	t = -2.425	17.21

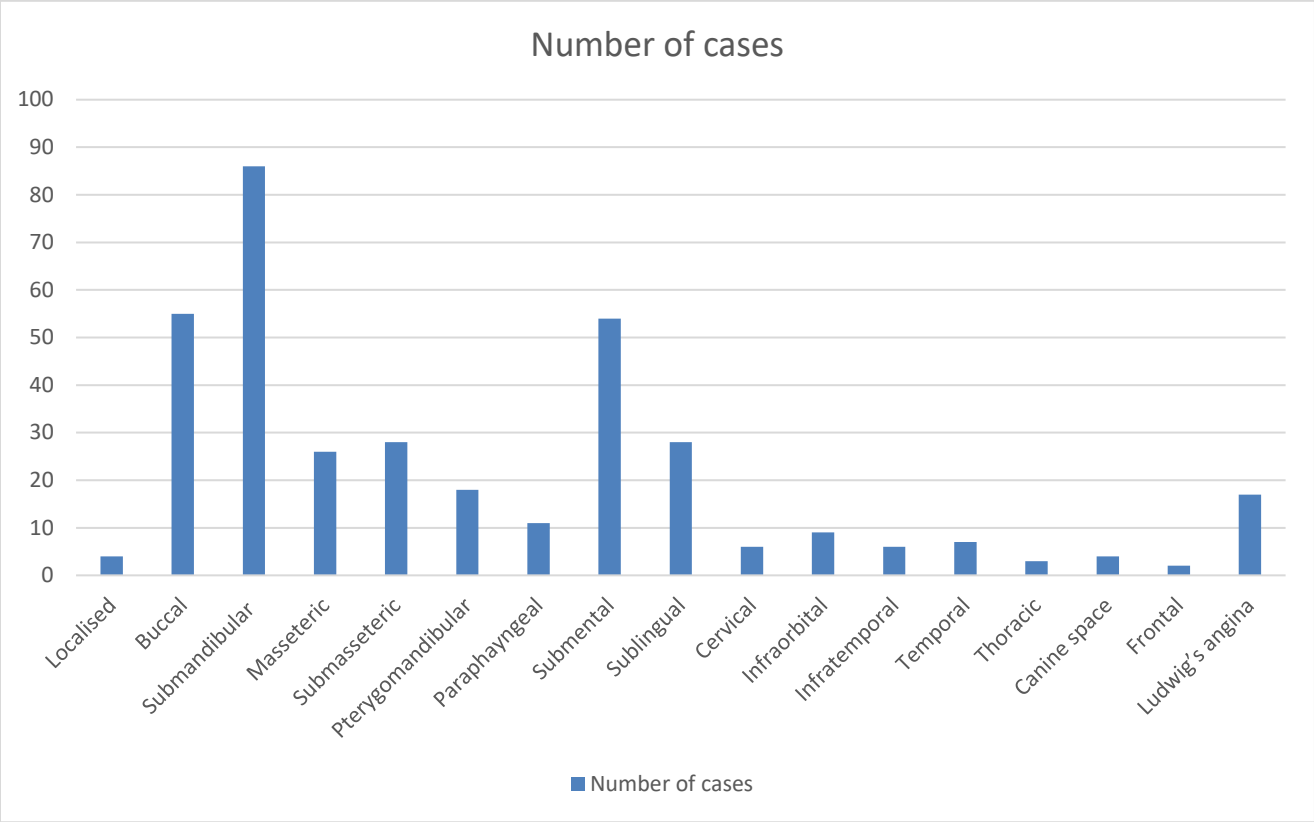


Figure 4.6: Number of cases per anatomical space.

4.5. Biological markers

The mean pulse and respiratory rates at admission were 90 +/- 14.66 and 20+/- 4.37respectively. While 5.3% (8 patients) presented to the hospital with a body temperature greater than 37.5°C, none developed a fever during the hospital stay. At admission the WBC and CRP were determined for the majority of patients 19 (12.5%) patients however did not have blood drawn for investigation at admission. The mean CRP and WBC upon admission were 142.63 ±101mg/dL and 14.01 ± 6.5x103/µL. Both CRP (p=0.0298, S=253850, R2=0.21169) and WBC (p=0.0328, S=350462), were identified as possible predictor variables for LOS (Spearman's rank correlation ratio).

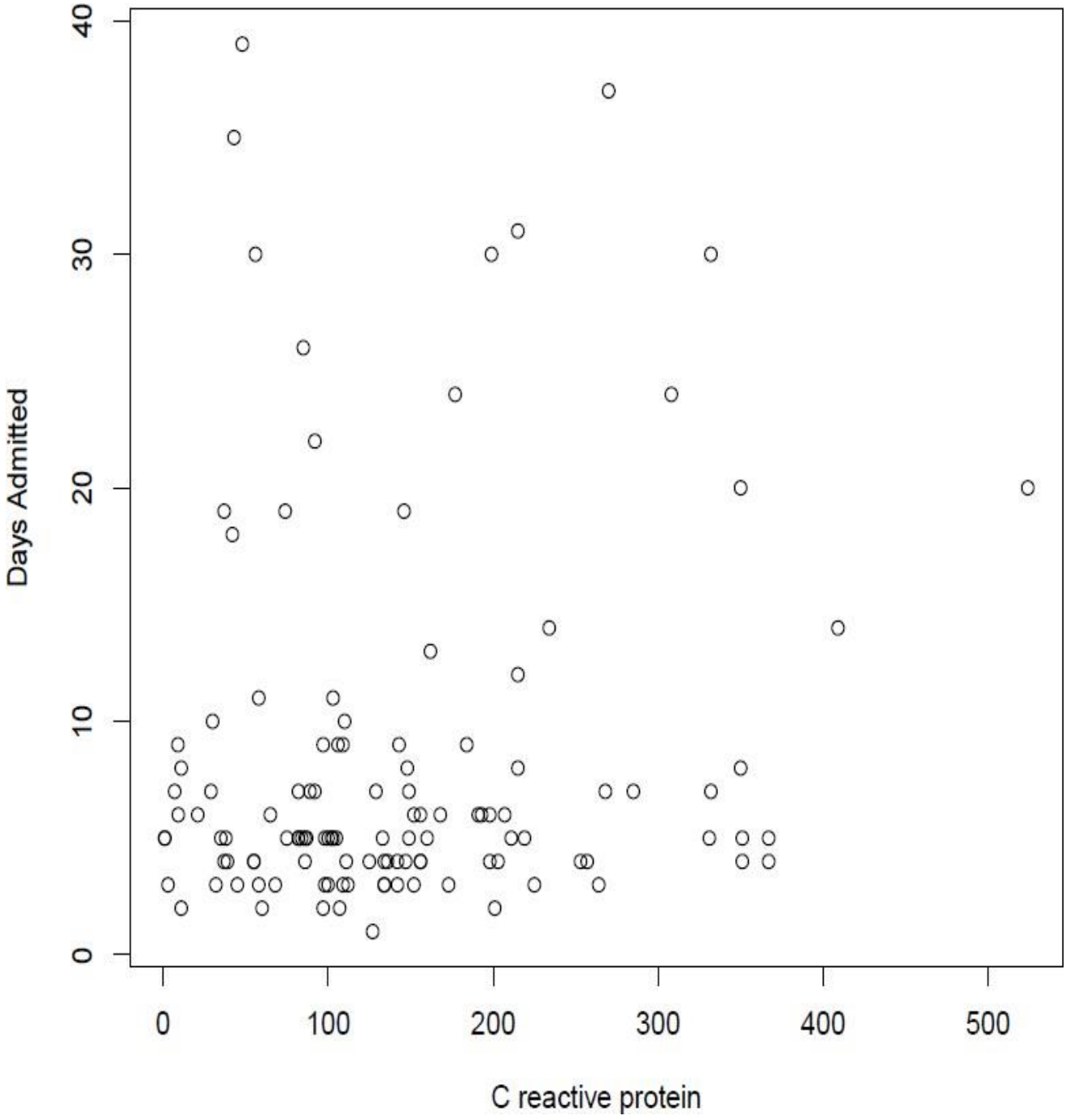


Figure 4.7: Length of hospital stay *versus* C-reactive protein count

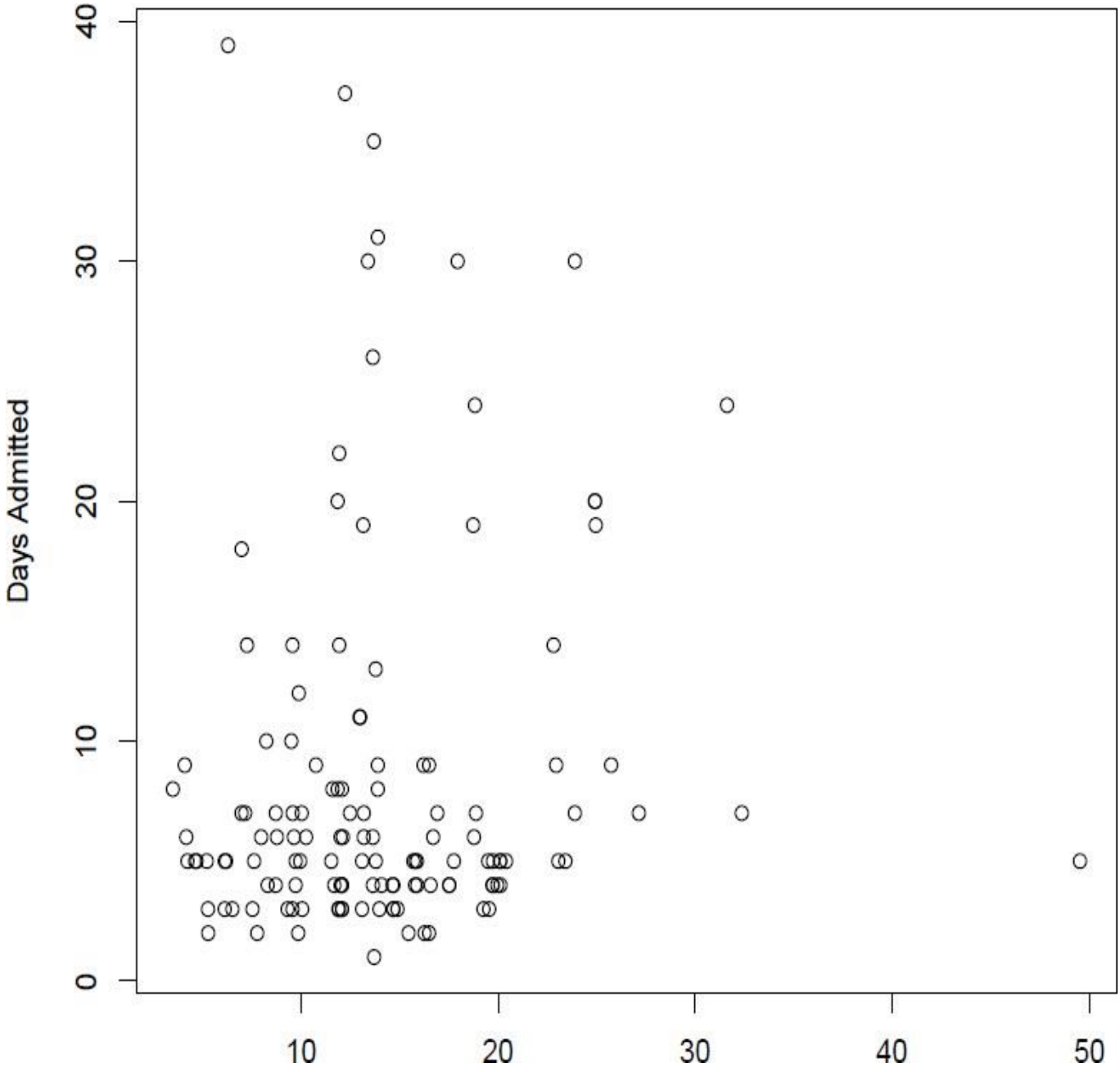


Figure 4.8: Length of hospital stay *versus* white blood cell count

4.6. Treatment

The majority of patients underwent I&D (142 patients, 93.4%) after admission. Eight (5.3%) patients received debridement and I&D, 120 (78.9%) had extraction with I&D, 18 (11.8%) I&D with fracture repair and 8 (5.3%) I&D with removal of hardware. Of the 152 patients, 10 (6.6%) did not receive any surgical treatment but were treated conservatively on an antibiotic regimen. The most common antibiotic regimen used was Augmentin® 1.2g IVI (134 patients, 88.2%). Only 16 (10.5%) patients required a second, alternative antibiotic to be administered. All patients were given chlorhexidine digluconate mouth rinse during the hospital stay. All patients treated surgically (142), were treated in the operating theatre under general anaesthesia. Four patients out of the total sample were treated under local anaesthesia after the initial I&D. None of the patients were treated under local anaesthesia before presenting to the hospital for treatment.

Table 4.6: Antimicrobial management of patients admitted with orofacial sepsis, primary and secondary regimen with predictor value.

Antibiotic prescribed		Number of patients	Percentage	p-value	t-value
1st regime	2nd regimen				
Augmentin®1.2g IVI	none	134	88.2	0.3087	10.53458
Augmentin®1.2g IVI	Flagyl IV	3	2.0	0.0377	5
Augmentin®1.2g IVI	Kefzol	2	1.3	0.2422	2.5
Clindamycin	none	5	3.3	0.07	2.4

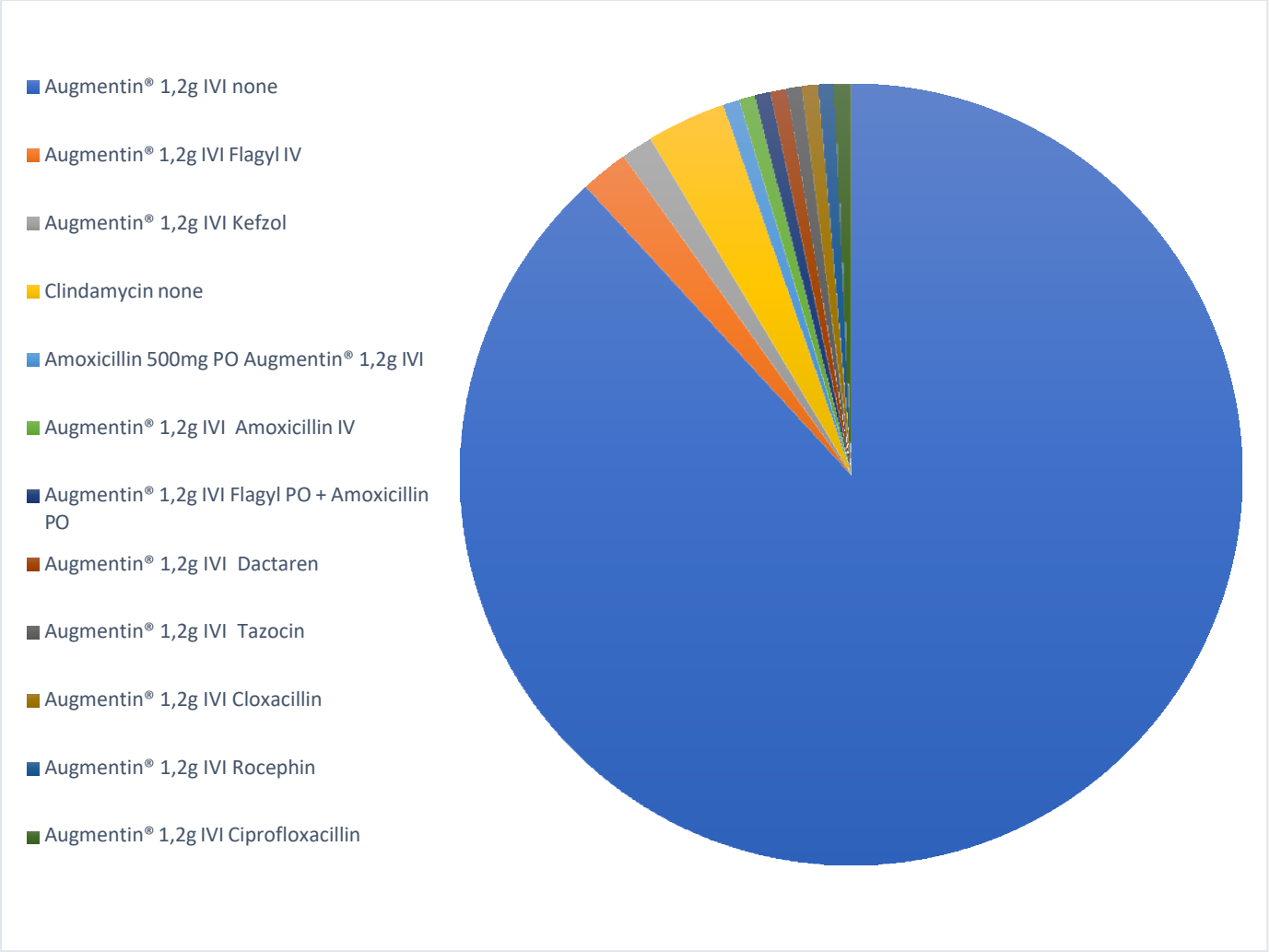


Figure 4.9: Prevalence of antimicrobial used in management of orofacial sepsis

4.7. Bacteria

A pus swab was sent for culture and analysis in 96 (63.1%) cases of which 22 (22..9%) patients received an inconclusive result. Out of the results obtained, 56 were tested for antibiotic sensitivity. The results were divided into three antibiotic groups: Penicillin sensitive (26. 46.4%), clavulanic acid sensitive (24 patients, 42.8%) and multi drug resistant (6 patients, 10.8%).

Eight patients were admitted for a LOS greater than the average LOS observed in the study, two cases of multi-drug resistant bacterial species, both had a LOS of nine days, both presented with only trismus at admission. The one patient presented with three spaces involved and a comorbid burden of five and the other only with one space involved and no medical comorbidities.

The most prevalent bacteria cultured was *Staphylococcus aureus* (9.5%, p=0.051). *Streptococcus* species (8.1% cases, p=0. 002), S*trep. viridans* (8.1%, 0.04), S*treptococcus Group* C (6.8%, p=0.03), *Streptococcus thoraltensis* (4.1%, p=0.01), *Klebsiella* species (4.1%, p=0.044) and *Steptococcus sanguinis* (4.1%, p=0.02).

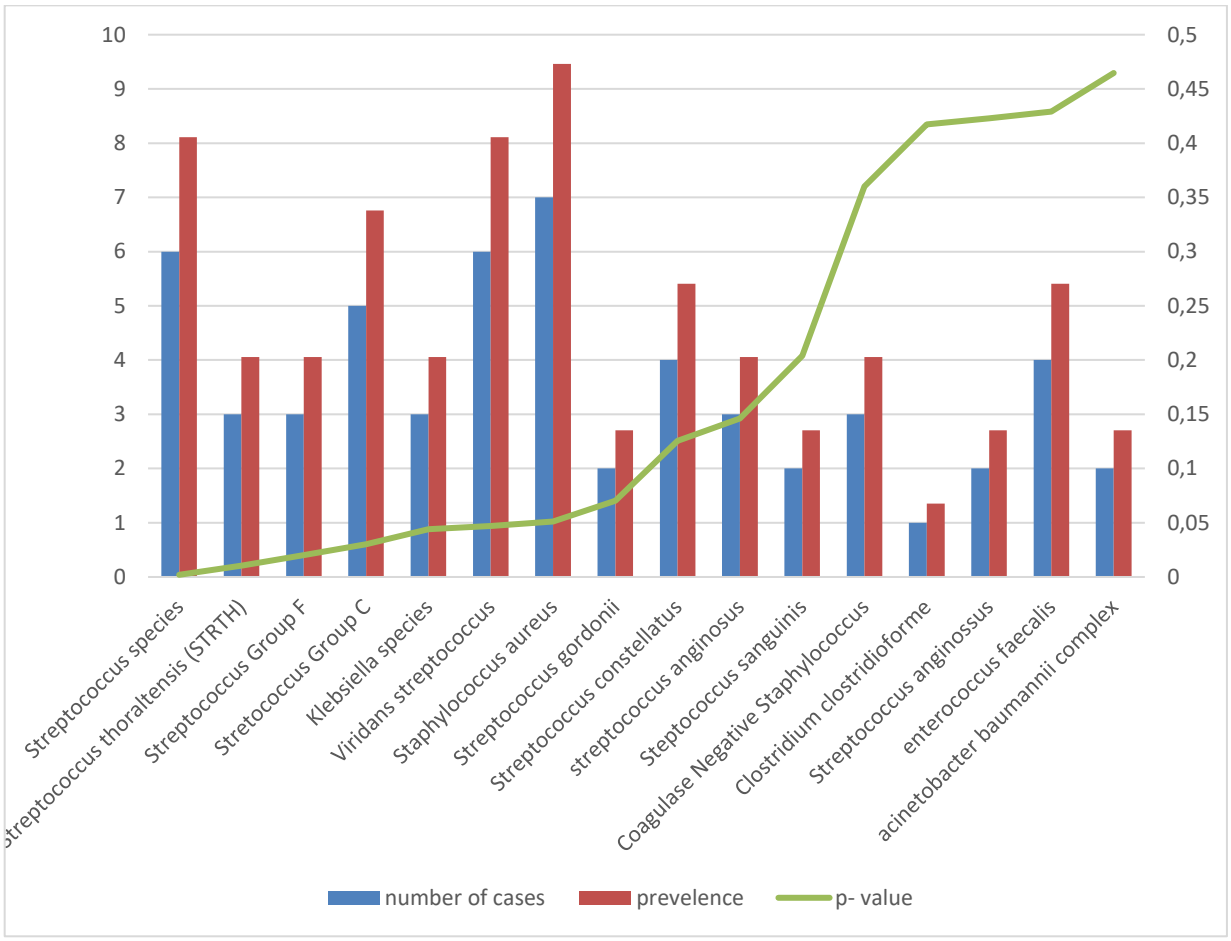


Figure 4.10: Prevalence of bacteria cultured in orofacial sepsis.

Table 4.7: Predictive value of bacteria cultured in orofacial infections.

Bacteria cultured:	**Number of cases**	**Prevalence**	**p-value**
Streptococcus species	6	8.1	0.002
Streptococcus thoraltensis (STRTH)	3	4.1	0.0104
Streptococcus Group F	3	4.1	0.0202
Streptococcus Group C	5	6.8	0.0303
Klebsiella species	3	4.1	0.044
Streptococcus viridans	6	8.1	0.0471
Staphylococcus aureus	7	9.5	0.051
Streptococcus gordonii	2	2.7	0.0704
Streptococcus constellatus	4	5.4	0.1255
Streptococcus anginosus	3	4.1	0.146
Steptococcus sanguinis	2	2.7	0.204
Coagulase Negative *Staphylococcus*	3	4.1	0.36
Clastridium clostridioforme	1	1.4	0.4174
Streptococcus anginossus	2	2.7	0.423
Enterococcus faecalis	4	5.4	0.429
Acinetobacter baumannii complex	2	2.7	0.464669

Chapter 5: Discussion

In this prospective study we sought to evaluate factors associated with hospitalisation outcomes in patients admitted with orofacial sepsis. The influence of delay in presentation, aetiology and location of sepsis, clinical presentation and comorbid status of the patients on the LOS in the hospital were also assessed. We found in this study that infection arising from mandibular 3rd molars, dysphagia, multiple fascial space involvement, biological markers for CRP and increased WCC, were all significant predictors for hospital outcomes and LOS in patients admitted for treatment of orofacial infections. In addition, there was a positive correlation between LOS and patients' comorbidity burden. The number of involved spaces function as a marker of disease severity and spread of infection. Dysphagia was accompanied by other factors such as multiple facial space involvement, higher comorbidity load and 3rd molar involvement.

5.1. Patient and demographic data

The mean age of the participants was 35 years, with 60..5% of all participants younger than 35 years old. This is younger than comparative studies done in South Korea, Nigeria and South Asia, that reported the mean age in the fourth and fifth decades (Ugboko, Ndukwe and Oginni, 2010; Park *et al.*, 2019a; Kim and Kim, 2021). Malaysia, Italy and Germany presented with a similar age distribution (Bertossi *et al.*, 2017; Heim *et al.*, 2019; Yew *et al.*, 2022). The younger age distribution can be attributed to South Africa being a developing country and to the young South African population according to the 2019 census, which reported that 35.1% of the population was between 15 and 34 years of age, with almost a third residing in Gauteng. We found no statistically significant relationship between age and LOS, in contrast to other studies (Christensen *et al.*, 2021; Schütz and Anous, 2021).

There was almost an equal distribution between males (57.2%) and females (42.8%). This concurs with the report by Heim *et al*., (2019) who found a nearly gender balance. In contrast to our findings, other studies have presented a higher male prevalence, reported as high as 65.7% (Flynn *et al.*, 2006; Kim, *et al.*, 2012; Bertossi *et al.*, 2017). Of the patients in our study, 51.9% were admitted to CHBAH with a mean LOS of 8.5±8.2 and 48.1% to CMJAH with a mean LOS of 7±6 days.

5.2. Health status

Many patients (55.3%) presented with no medical comorbidities, in contrast to similar studies in Korea and the USA, where they demonstrated the majority of patients presenting with at least one comorbid condition (Abramowicz *et al.*, 2017; Park *et al.*, 2019a; Kim and Kim, 2021). This finding makes sense as the majority of the participants in the present study were younger patients, who are generally healthy. In the current study 20.4% of participants presented with a single comorbid condition, more than half of which was due to cigarette use. The remaining patients (24.3%) presented with multiple comorbidities. Comorbid conditions such as DM, hypertension and metastatic cancer had a statistically significant predictive value on LOS. In light of these findings, it has been suggested that medically compromised patients, presenting with orofacial infections, should be treated promptly, commence antibiotic and supportive treatment as soon as possible, to reduce the adverse outcomes and shorten LOS (Abramowicz *et al.*, 2017; Kim and Kim, 2021).

Most cases in the current study (77%) were due to odontogenic causes, as described in previously documented studies 61.8% and 71% respectively (Park *et al.,* 2019; Kim *et al.,* 2021). However, this is lower than the results reported in Korean studies, which reported greater than 90% of cases caused by odontogenic infections (Yew *et al.,* 2021). Comparatively this may be attributed to the higher occurrence of maxillofacial trauma seen in the South African setting. Where we recorded 11.2% septic fracture cases and 4.6% septic hardware cases (Botha *et al.*, 2015).

Diabetes had a significant correlation with the LOS of patients admitted for orofacial infections. This correlates with previous studies, which assessed the relationship between DM and orofacial infections. Diabetes is known to predispose the oral cavity to infections, contributing towards the prevalence of orofacial odontogenic infections. The association between DM and periodontal disease has been well established, indeed, according to a recent study by Juncar *et al*., (2020) apical periodontal infections are more common independent of the amount of type 2 DM compensation (the threshold for decompensation was defined at a haemoglobin A1c value of 7%). Patients suffering from DM also have other factors that increase the risk of dental caries. These include hyposalivation, salivary glucose and changes to the oral microbiome. The higher caries risk and susceptibility to periodontitis result in a higher risk of odontogenic infections.

Furthermore, DM has been shown to alter neutrophil function (Stegenga *et al.*, 2008), cellular immunity, complement activation, and also T-lymphocyte responses to infection, thus aggravating the infection and supporting the spread of infection. Diabetes has been associated with unfavourable outcomes in orofacial infections. Some of these studies used LOS as measure (Christensen *et al*., 2021; Zheng *et al*., 2012), onset of severe complications (Yew *et al.*, 2021) or involvement of secondary spaces (Chang *et al.*, 2013).

We found that cigarette smoking did not demonstrate an association with prolonged LOS, which is in agreement with the findings by (Yew *et al.*, 2021). Yet in similar studies, cigarette smoking was shown to have an association with increased LOS (OR 3.694, 95% 1.314-10.389) (Yew *et al.*, 2022). Cigarette smoking compromises the oral health and increase the risk of caries, periodontal disease, and sepsis. Active smokers have been shown to have a higher risk of multiple facial space involvement and earlier spread of infection, than non-smokers (Eshghpour *et al*., 2021; Yew *et al*., 2022).

5.3. Hospital course

Local clinics and hospitals were the major source of patients' referral for treatment of orofacial sepsis, followed by walk-in patients. The majority of patients were referred by medical doctors (28.3%), followed by referrals by dental practitioners. A small number of patients were referred by professional nurses. A large number of patients were referred from a facility with a functioning or an active dental department. This may be attributed to the fact that dental clinics generally don't have after hour emergency care. It was also suggested that medical doctors are not familiar with the scope of dentists and would rather refer cases directly to MFOS departments than consulting with a dental department first (Giddon, 2006).

A fair number (25%) of patients arrived on antibiotic treatment received from the referring facility. Medical doctors tended to prescribe Co-amoxiclav 2g whilst dental practitioners mostly prescribed Amoxicillin 500mg combined with Metronidazole 400mg (56.2%) or Co-amoxiclav 2g. Patients referred on treatment did not provide a statistically significant predictor value ($p=0.475$) for LOS. This underscores the fact that successful treatment of orofacial sepsis depends heavily on source control and changing the environment through debridement and or incision and drainage, rather than reliance on antibiotics.

In the update published on management of odontogenic infections (Jevon *et al.*, 2020), the current guidelines identified Amoxicillin 500mg TDS as the first-line antibiotic for odontogenic abscesses. This may be coupled with Metronidazole 400mg BD in spreading infections. The haphazard and indiscriminate use of preoperative antibiotics in the present study points to the fact that more needs to be done to remind clinicians of the pathogenesis and pathogens responsible for odontogenic infections. Penicillin remain the antibiotic of choice for treating odontogenic infections. In the same review article, it was advised that patients be placed on early

supportive antibiotic management, when the decision was made that surgical intervention was needed.

The association between delay in seeking treatment and severe outcome of orofacial infections is well known (Ugboko *et al.,* 2010; Park *et al.*, 2019; Yew *et al.*, 2021). Due to the COVID-19 pandemic, we observed that more patients presented to the hospitals during relieved lock-down periods. The patients tended to wait for longer periods before seeking help, possibly fearing the risk of exposure to SARS-Covid. Similarly, in Yorkshire, they demonstrated a decrease in dental emergencies presenting for treatment, but an 80% increase in admissions of orofacial infections (Long and Corsar, 2020). It appears that fear of exposure and the subsequent delay in seeking treatment contributed to this rise in admissions. It was also reported that patients with comorbidities sought dental treatment less frequently both during and after the lockdown at a Swiss university centre. When these patients' dental care-seeking behaviours alter, there may be risks for significant consequences (Eggmann *et al.*, 2021). These may include the development of odontogenic infection, spread of infection and, if left untreated, life-threatening conditions, such as Ludwig's angina and Mediastinitis may ensue (Burnham *et al.,* 2011). As in all other countries, the pandemic had a great effect on health-seeking habits, with patients displaying a delay in seeking health care, avoidance of care or increased usage of telehealth (Moore *et al.*, 2022). In the current study there was a significant difference in the LOS between immediate and delayed treatment (p=0,003). Thus supporting the results obtained by Poeschi *et al.,* (2011) and Afwerke-Lynch *et al.,* (2020).

5.4. Clinical presentation, aetiology, and location of infection

Severe orofacial infections may be caused by multiple aetiological agents. Dental caries has been reported as the most common cause of orofacial infections, responsible for 65-69.7% of the cases of orofacial infections (Flynn *et al.*, 2006; Bertossi *et al.*, 2017; Jevon *et al.,* 2020). Other possible

causes include periodontal disease, pericoronitis, open fractures and postoperative infections (Eisler *et al.*, 2013; Botha *et al.*, 2015; Bertossi *et al.*, 2017; Eshghpour *et al.*, 2021). An increase in LOS was observed in patients whose orofacial sepsis was related to mandibular 3rd molars.

We found that trismus was the most prevalent symptom. Dysphagia had a statistically significant predictor value for LOS, as patients who presented with dysphagia had a longer LOS. Dysphagia has been reported to increase LOS by 2.99 days (Attrill *et al.*, 2018), and this is corroborated by studies conducted in Europe and North America (Taheri, Butz and Greenfield, 2000; Bradley *et al.*, 2011; Arnold *et al.*, 2016; Attrill *et al.*, 2018). Dysphagia was accompanied by other factors such as multiple facial space involvement, higher comorbidity load and 3rd molar involvement. Botha *et al*., (2015) addressed this in their retrospective analysis of Ludwig's angina.

Odontogenic infections follow a predictable pattern of spread to spaces anatomically related to the origin of the infection. The number of involved spaces function as a marker of disease severity and spread of infection. This complicates the recovery process leading to increased LOS (Zheng *et al.*, 2012; Bowe *et al.*, 2019; Christensen *et al.*, 2021; Schütz and Anous, 2021). The association between multi-space infections and LOS has been well documented (Zheng *et al.*, 2012; Yew *et al.*, 2021, 2022; Nhongo *et al.*, 2022). Additional findings that may correlate with infection severity include bilateral spread and mediastinal involvement, which are significant on the univariable analysis. The most appropriate and unbiased way to assess the severity of an odontogenic infection is by assessing the number of involved spaces. The most concerning odontogenic infection consequence is a compromised airway, which may necessitate a tracheostomy. The use of additional screening procedures (for SARS covid-19), the preoperative fasting strategy, the need for re-drainage, and admission to intensive care units, are some probable causes for the prolonged LOS, caused by multiple spaces involvement (Agbara *et al*., 2018; Kim *et al*., 2012; Zheng *et al*., 2012). Moreover, anatomical position of

infection plays a vital role in management. Involvement of masticatory spaces may lead to trismus, which may lead to difficult intubation and airway management in emergencies. Anticipated airway difficulty should be discussed with the anaesthetist prior to induction of anaesthesia (Chang *et al.*, 2013; Bowe *et al.*, 2019)

Life-threatening soft tissue cellulitis affecting the floor of the mouth and neck is known as Ludwig's angina. It involves three compartments of the floor of the mouth, the sublingual, submental, and submandibular. The infection spreads quickly, which may cause an obstruction of the airway (An, Singhal, and Madeo, 2022). In the present study, there was a statistically significant correlation between longer LOS and patients diagnosed with Ludwig's angina. Similar findings were reported by Botha *et al*., (2015), Dowdy *et al.,* (2019 b), Bridwell *et al.,* (2021) and Ugboko *et al.,* (2010).

5.5. Biological markers

The present investigation showed that longer LOS was reported at higher CRP concentrations. CRP is a liver-produced inflammatory protein typically with only trace quantities (10mg/L) in healthy individuals. Infections or severe inflammatory reactions may lead to a rise in CRP. There is a significant increase within the initial six hour period, peaking in the 24−48 hour period, followed by a rapid decrease after resolution of the infectious episode. It has been shown to display the highest sensitivity for bacterial sepsis (Ljungström *et al.*, 2017) and a moderate to strong correlation was found between LOS and CRP (Bègue *et al.*, 2021; Muna and ALhameed, 2022). Additionally, CRP is not influenced by anti-inflammatory drugs. The model by Bègue *et al.*, demonstrated that an increase of 1mg/L, results in an increase in LOS by 0.03 days.

Many studies looked at the correlation between LOS and CRP, with the majority of which found that CRP was an effective parameter for predicting LOS (Ljungström *et al.*, 2017; Heim *et al.*, 2019; Muna and ALhameed, 2022). In contrast, Mirochnik *et al*., (2017) did not find a significant correlation between CRP and LOS. An undisclosed number of patients included in their study had a surgical procedure before presenting to the emergency department, possibly leading to interpretation bias. Surgical interventions can be responsible for a rise in the CRP levels (Ljungström *et al.*, 2017). Other articles highlighted the role of the CRP level in predicting the severity of odontogenic cellulitis (Bègue *et al.*, 2021). Heim *et al*., (2019) showed that the CRP level and the WBC were significantly higher in patients with multiple-space infections. In addition, Christensen *et al*., (2021) found a higher CRP level in a reoperation group.

An elevated WBC is a known biological response to cellulitis is. However, we found a significant, though weak correlation between postoperative LOS and presurgical WBC. This correlation was weaker than the correlation between postoperative LOS and presurgical CRP level (Bègue *et al.*, 2021; Muna and ALhameed, 2022). A significant relationship between WBC and LOS was confirmed by Stathopoulos *et al.,* (2017). WBC on the day of admission, were greater when sepsis was concentrated on the mandible or when patients had numerous space infections (Heim *et al.*, 2019), suggesting that this parameter may serve as a severity signal in addition to the CRP level.

5.6. Treatment

In our study, surgical intervention was not performed in 6.6% of cases. In such circumstances, patients were admitted for intravenous antibiotic administration and strict observation of vital signs. The average LOS was 8.3 days. Burnham *et al.,* (2011) highlighted the over-prescription and inappropriate use of antibiotics, especially by non-dental trained healthcare providers. Dental abscesses should be managed early in primary dental clinics with appropriate medication and

removal of the causative agent, either by root canal treatment or extraction. Continuous monitoring and timeous review are mandatory to ensure that the infection has not progressed. Most of the patients in our study (93.4%) required surgical intervention. Surgical treatment comprised of solely I&D (n=9), with an average LOS of 8.2 days. I&D with extraction of affected teeth (n=120) resulted in an average LOS of 8.3 days. Similarly, Bowe *et al.,* (2019) found that I&D combined with extraction lead to faster clinical resolution of the infection. I&D with ORIF (n=18), presented with an average LOS of 5.3 days.

5.7. Bacteria

Maxillofacial infections are multi-microbial in origin, with some strains isolated from a site exerting an active pathogenic role on the body, and others providing support to the organisms by providing nutrients, growth factors and creating a favourable environment (Khemaleelakul, Baumgartner and Pruksakorn, 2002; Tent *et al.*, 2019). Aerobic flora dominate in the preliminary stages of suppuration, whereas anaerobic flora dominates in more established infections.

In most of the cases, pus swabs were sent for culture (n=96) and antibiotic sensitivity tests. The foremost pathogens cultured were *Staphylococcus aureus (*9.5%, p=0.051) and *Streptococcus species (*8.1%, p=0.002). Many previous studies obtained similar results (Chunduri *et al.*, 2012; Fating *et al.*, 2014; Tent *et al.*, 2019). A multilinear regression model was used to investigate the correlation between bacterial species cultured and LOS. The bacterial species cultured with statistically significant results include Streptococcus *thoraltensis* (4.1%, p=0.01), *Streptococcus* Group F (4.1%, p=0.02); *Streptococcus* Group C (6.8%, p=0.03) and *Klebsiella* species (4.1%, p=0.044).

All patients responded well to Amoxicillin-clavulanic acid (88.2%) and Clindamycin (3.3%). Bacteria were divided in 3 groups Penicillin sensitive (46.4%), Clavulanic acid sensitive (42.8%) and multidrug resistant (10.7%). This is in agreement with the incidence reported by previous studies (Kim, Chuang and August, 2017; Liau *et al.*, 2018). The average LOS in cases where the bacteria were sensitive to Penicillin was 7.88 days, Clavulanic acid sensitive 10.75 and multidrug resistant was 11.33 days. Multidrug resistant cases had a 437% longer LOS than Penicillin sensitive cases. This trend was also observed in previous studies (Kim, Chuang and August, 2017; Liau *et al.*, 2018; Tent *et al.*, 2019). Currently over 1000 genetic traits have been identified, granting β-lactamase expression (Liau *et al.*, 2018). Inappropriate antibiotic use contributes to antibiotic resistance. Patients with antibiotic-resistant infections demonstrate higher rates of morbidity and mortality as reported by the WHO (World Health Organization, 2021; Mendelson, National Department of Health, 2020). This concept is supported by the findings of the present study as evidenced by longer LOS.

Most patients (96%) were initiated on Amoxicillin-clavulanic acid at admission. Two percent of patients were given Metronidazole IVI postsurgery and 1.3% received Kefzol. The present study presented with a lower rate of non-response to initial therapy, confirming that Amoxicillin possesses a powerful antimicrobial activity against common orofacial pathogens, in contrast to the results of Chunduri *et al.,* (2012), which showed a dwindling susceptibility of common pathogens, isolated in orofacial infections, to Amoxicillin. Similarly, Kim *et al.,* (2017) reported a 32.5% resistance to Amoxicillin and a 40% resistance to Amoxicillin and Clavulanate.

5.8. Treatment outcomes

The study showed an overall average LOS of 8±7.4, with CHBAH an average LOS of 8.5 and CMJAH 7.6 days. These results are slightly higher than the Gauteng average LOS of 6.9 days as published in the South African Health Review of 2020 (Kula, 2020). This can be explained by the admission

processes followed during the COVID-19 pandemic. Patients were first admitted in a person-under-investigation (PUI) ward, until a negative COVID test result was obtained, and then admitted to a MFOS ward. Our study results are comparable to studies conducted in Eastern countries, but higher than results in the USA of 3.9 days (Agarwal *et al.*, 2007; Zheng *et al.*, 2012; Abramowicz *et al.*, 2017; Park *et al.*, 2019a) and other European countries ranging from 2.96 to 5.46 (Jundt and Gutta, 2012; Christensen *et al.,* 2013; Eisler *et al.*, 2013; Gams *et al.*, 2017).

Most of our study patients recovered uneventfully, with a mortality rate of 0.006%. One case of facial cellulitis succumbed to multi organ failure. This patient arrived at the hospital in septic shock and was severely immunocompromised, being HIV-positive and a known diabetic diagnosed with chronic nephritis. Death from isolated dental infections is rare, with a 10% increased risk of mortality with the progression to Ludwig's angina (Bowe *et al.*, 2019; Bridwell *et al.*, 2021).

Finally, there are several benefits and drawbacks of using LOS as the research's measurement instrument. Undoubtedly, LOS can be a principal factor in determining severity of orofacial odontogenic infections. LOS enables us to more accurately forecast how resources will be used, because LOS is a key factor in treatment outcomes. LOS is a easily recorded parameter, used worldwide as a data point for statistical analysis. However, other factors, such as hospital policy and national health care, may have an impact on LOS.

5.9. Limitations

The present study has a number of limitations. Firstly, as the study started during the COVID-19 pandemic, access of patients to treatment was limited, and often delayed, possibility affecting the outcome of this study.

Secondly, due to hospital COVID protocols, patients were delayed in admission, as patients required a negative PCR test for the novel COVID-19 virus before admission to the ward, resulting in delay in treatment and possibly affecting the outcome of this study. This also limited the access of the investigator to patient details. Thirdly, the number of surgeries patients received over the course of the treatment, were not recorded and correlated with the comorbidity burden and LOS.

Finally, the use of LOS as the measure of hospital outcome: LOS is a crucial variable for the quality of life of a patient, and a longer hospital stay predisposes a patient to nosocomial infections. Additionally, it aids in assessment of use of hospital resources (Gams *et al.*, 2017). Variables such as complications, improved speech and discharge status of the patient must be considered in determining hospital outcome, over and above LOS.

Notwithstanding these limitations, this study offers useful insight into the relationships between several parameters and hospital outcomes for patients with orofacial sepsis.

Chapter 6: Conclusion and recommendations

The present study evaluated parameters associated with hospitalisation outcomes in patients admitted with orofacial infections. The influence of factors such as delay in presentation, aetiology and location of sepsis, clinical presentation and comorbid status of the patients on the LOS in the hospital, were also assessed. We hypothesised that it is not possible to predict the outcome and length of in-hospital stay of a patient with orofacial sepsis by considering comorbid factors and clinical investigations at admission.

The study population comprised a younger population age, with the majority of patients falling within the 26-30 age group. We found that infection arising from mandibular 3rd molars, dysphagia, multiple facial space involvement and biological markers such as CRP and WCC were significant predictors for LOS in patients admitted for treatment of orofacial infections. In addition, there was a positive correlation between LOS and patients' comorbidity burden such as DM. Diagnosis of Ludwig's angina and the presence of multidrug resistant bacteria have significant effects on LOS. Dysphagia was accompanied by factors such as multiple facial space involvement, higher comorbidity load and 3rd molar involvement.

For patients hospitalized with orofacial sepsis, the following should be considered:

1. Careful consideration must be given to the timing, length, and presenting clinical signs to reduce LOS.

2. Orofacial infections involving 3rd molars and numerous fascial spaces should be treated aggressively to enhance outcomes, in particular those presenting with comorbidities such as diabetes, hypertension and/or metastatic cancer.

3. The use of biological factors such as WBC and CRP, aid in predicting severity of infections. CRP showed a strong predictor value and aid in decision making regarding an aggressive treatment regime.

4. Bacterial culture and antibiotic sensitivity tests aid in identifying and early initiation of an adequate antimicrobial regime.

Previous research has demonstrated that such parameters may be utilized to predict the clinical outcomes of patients, shorten treatment times, and simplify clinical procedures.

Future prospective studies, involving larger sample sizes in a non-Covid environment, are recommended to further substantiate and give statistical support for the role of cost-effective biological factors such as CRP and comorbidities, in predicting clinical outcomes and LOS for patients admitted with orofacial sepsis.

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Appendix A: Data collection sheet

Department of Maxillofacial and Oral Surgery

School of Oral Health Sciences

Faculty of Health Sciences

Factors associated with length of stay for patients hospitalized with Orofacial Sepsis

Demographic data:

Age: _____ Gender: M / F

Type of admission: elective / emergency

Referred from: Hospital / Clinic

Referred by: Medical Doctor / Dentist / Professional nurse

Patient referred on Active treatment? Yes / No

If on treatment, what treatment was given: _____

Days lapsed after initial presentation and treatment: _____/ immediate / unknown

Resident dentist in hospital: Yes / No

Active surgical department: Yes / No (general surgery / MFOS)

Diagnosis: _____

Type of infection: _____ (possible cause's skin / teeth)

Date of admission: _____

Temperature: _____ Respiratory rate: _____

Clinical complications at admission: _____(dyspnoea, dysphagia, trismus).

Comorbid burden:

- ☐ Acquired immunodeficiency syndrome
- ☐ Alcohol abuse
- ☐ Cigarette use
- ☐ Rheumatoid arthritis
- ☐ Collagen vascular diseases
- ☐ Chronic blood loss anaemia
- ☐ Congestive heart failure
- ☐ Chronic pulmonary disease
- ☐ Coagulopathy
- ☐ Depression
- ☐ Diabetes Mellitus
- ☐ Drug abuse
- ☐ Hypertension
- ☐ Hypothyroidism
- ☐ Liver disease
- ☐ Lymphoma
- ☐ Metastatic cancer
- ☐ Neurologic disorders
- ☐ Obesity
- ☐ Paralysis
- ☐ Peripheral vascular disorders
- ☐ Psychoses
- ☐ Pulmonary circulatory disorders
- ☐ Penal failure
- ☐ Solid tumour without metastasis
- ☐ Peptic ulcer disease
- ☐ Valvular disease

Anatomical consideration:

Submandibular / Masseteric / Pterygomandibular / Buccal / Paraphayngeal / Submental / Sublingual / Cervical / Infraorbital / Ludwig's angina / Infratemporal / Temporal / Thoracic

Treatment received in Hospital:

Surgical: Yes / No

Extraction / I&D / Other: _____

Time between admission and surgery _____

Non surgical: **Yes / No**

Antibiotics: _____ _____mg IV / PO / other _____

_____ _____ mg IV / PO / Other _____

Blood and Blood products: _____

Analgesics: **Yes / No**_____ _____ mg IV / PO / other

Disposition status:

- ☐ discharged routinely
- ☐ discharged against medical advice *versus* discharged routinely (refusal of treatment)

Length of stay: _____number of days

The infectious complications: Yes / No (If yes, Type of complication)

_____

_____

Special investigation:

Pus swab done: Yes / No

If so results obtained: _____

_____

Organism cultured: _____

_____

Blood tests done on admission: **YES / No**

- ☐ C reactive protein: _____
- ☐ White blood cell count: _____
- ☐ Other: _____

Appendix B: Informed consent form

Informed Consent Form for patients admitted to the Maxillofacial and Surgery department of Chris Hani Baragwanath Academic and Charlotte Maxeke Johannesburg Academic Hospitals for Orofacial sepsis and we are inviting to participate in research, "Factors associated with outcomes and length of stay for patients hospitalized with orofacial sepsis".

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

I am Dr R Scheepers, a MSc student from the University of the Witwatersrand. I am doing research on factors that influence the length of stay in hospital of patients with Orofacial sepsis. I am going invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

This consent form may contain words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain.

We have many patients admitted with sepsis and some people stay in hospital longer than others. With this research we aim to identify the factors that lengthen the stay of patients so that we can identify it early and minimize the length of stay in hospital for patients admitted with orofacial sepsis.

The research will involve extracting data from your file eg. date of admission, type and area of infection, medical comorbidities, treatment received. All patients will be anonymous as no personal detail will we recorded on the data collection sheet.

The choice that you make will have no bearing on your treatment.

Your participation is likely to help us identify factors affecting the length of stay of patients and help us improve treatment of patients in the future.

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact Dr R Scheepers, Wits Oral Health Centre, Ward 385 office 1, A0059004@wits.ac.za.

Appendix C: Certificate of Consent

Example: I have been invited to participate in research factors affecting length of stay of patients treated with Orofacial sepsis.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate [1]

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ **Thumb print of participant**

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of

[1] A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to

the research team). Participants who are illiterate should include their thumb print as well.

my ability made sure that the participant understands what the research entail.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

Appendix D: Maxillofacial and oral surgery department's standard antibiotic protocol

1. **MINOR ORAL SURGERY** (includ. impacted wisdom teeth)

   a) LOCALS: At booking appointment, give patient TTO for 2g Amoxyl. Patient to take antibiotics on date of extraction, 1hour before procedure. Allergic patient: Erythromycin 2g

   b) THEATRE: patient to be given 1MU Pen G IV. No further antibiotics

2. **OROFACIAL SEPSIS** (includ. Septic fractured mandibles)

   a) CELLULITIS: Amoxyl 500mg, 8 hourly, 5days

   b) SINGLE SPACE INFECTIONS (includ. submandibular, buccal, or submental)

      - Pen G 2MU 6hourly, can increase dose to 24MU in 24 hours.
      - Allergic patient: Clindamycin 600mg, 6hourly IV Can change to oral amoxyl or oral clindamycin while admitted in ward.

        Total of 5 days antibiotic treatment only.

        Relook at 72 hours and add Flagyl 500mg 6hourly, if no improvement.

   c) LUDWIGS ANGINA and CO-MORBIDITIES: # Pen G 4MU 6hourly + Flagyl 500mg 6hourly IV. Relook at 72 hours and stop all previous antibiotics and change to Rocephin (ceftriaxone) 1g IV daily. {Allergic patient: Clindamycin 600mg, 6 hourly IVI Relook at 72 hours and stop previous antibiotic and change to gentamycin, 1g IV daily (check kidney function)}

3. **TRAUMA**:

- CRFM: 2g Amoxyl 1hour before procedure.
- ORIF:

= healthy patient; intra-op: Kefzol 1g IV and Pen G 2MU 6hourly IV x 2doses only. No TTO's

= Immunocompromised pt; intra-op: Kefzol 1g IV, Pen G 2MU 6 hourly while admitted and TTO Amoxyl 500mg 8hourly for 5days.

- EXTRA-ORAL APPROACH: intra-op, Kefzol 1g IV and Augmentin® 1,2g 8hourly IV post- op in ward. TTO's, Amoxyl 500mg 8hourly for 5 days for immunocompromised pts only.

NB! Panfacial fractures should be treated as for extraoral approach, with or without immunocompromise.

4. **ORTHOGNATHICS/ SKELETAL /TMJ**:

- Intra-op: Kefzol 1g IV; post-op Pen G 2MU 6hourly IV for 2 days only.
- TTO's: Mouthwash and analgesics only.

5. **IMPLANTS**:

- Healthy patients: intra-op, Kefzol 1g IV only.
- Immunocompromised patient: Intra-op, Kefzol 1g IV, post-op: Pen G 2MU 6 hourly while admitted. TTO's: Amoxyl 500mg 8hourly for 2days only.
- Sinus Lifts: as for immunocompromised patient.

6. **RESECTIONS**:

- Intra-op, Kefzol 1g IV, post-op, Augmentin® 1,2g IV 8hourly for 5 days only. No TTO's.

Appendix E: Ethics certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Postgraduate Affairs

TO:	Dr R Scheepers School of Oral Health Sciences Department of Maxillofacial and Oral Surgery Medical School University E-mail: A0059004@students.wits.ac.za
CC:	Supervisor: Professor R Rikhotso <Risimati.Rikhotso@wits.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2021/01/27
REF:	R14/49
PROTOCOL NO:	**M201039** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Factors associated with hospitalization outcomes in patients with orofacial sepsis*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr R Scheepers

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201039

NAME: **(Principal Investigator)**	Dr R Scheepers
DEPARTMENT:	School of Oral Health Sciences Department of Maxillofacial and Oral Surgery Medical School University
PROJECT TITLE:	*Factors associated with hospitalization outcomes in patients with orofacial sepsis*
DATE CONSIDERED:	2020/10/30
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor R Rikhotso
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/01/27

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **October** and therefore reports and re-certification will be due in the month of **October** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

27 Jan 2021

Date

Appendix F: Faculty protocol approval

UNIVERSITY OF THE
WITWATERSRAND,
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Private Bag 3 Wits, 2050

Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

21 October 2020
Person No: 363836
PAA

Dr R Scheepers
Po Box 10290
Fonteinriet
1464
South Africa

Dear Dr Ruan Scheepers

Master of Science in Dentistry: Acknowledgement of receipt of research proposal

I am pleased to acknowledge receipt of your research proposal entitled *Factors associated with hospitalization outcomes in patients with orofacial sepsis* under the supervision of Mbulaheni Nemutandani (Principal Supervisor), Risimati Rikhotso (Principal Supervisor).

You will hear from us in due course.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix G: Turnitin Report

