DELAYED CLINICAL RESPONSE OF DEEP FACIAL INFECTIONS DUE TO PRIOR UNREGULATED ANTIBIOTICS USE ASSESSED BY CRP LEVELS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

OBJECTIVES

This study aimed to assess the efficacy of serum CRP levels as monitoring tools for patients with fascial space infections who had a delayed clinical response to initial treatment, as per guidelines, due to prior unregulated antibiotics.

METHODOLOGY

This case series study was conducted at Lady Reading Hospital's Department of Oral and Maxillofacial Surgery and Ophthalmology from January 2024 to March 2025, with ethics approval and informed consent obtained from 35 participants with fascial space infections requiring hospitalization and prior antibiotic use. Those with recurrent infections, trauma, or chronic conditions were excluded. Diagnosis involved a comprehensive history, clinical examination, and imaging studies (OPG for odontogenic infections and CT for non-odontogenic infections). Infection severity was tracked through C-reactive protein (CRP) levels measured at admission, day three, and discharge. Initial treatment followed clinical guidelines, utilizing first-line antibiotics and incision and drainage. If CRP levels did not decrease, the antibiotic regimen was adjusted, leading to improved outcomes. Data were analyzed using SPSS.

RESULTS

The most commonly involved space was the submandibular space (31%), followed by unilateral and bilateral submandibular, sublingual, and submental spaces (20%). Orbital cellulitis was observed in 17% of patients. When asked about the prior unregulated use of antibiotics, 65.7% of patients admitted to having used them. The Mean CRP on the day of admission was 15.46 mg/dl with a SD of 6.42. The follow-up means CRP on the 3rd day of admission was 15.17mg/dl with SD 9.77, showing a poor response to initial treatment in 54.3% of the patients. The mean CRP on the day of discharge and after the change of antibiotic was markedly reduced, with a mean of 3.2mg/dl and SD of 3.7, showing resolution of infection.

CONCLUSION

Delays in infection resolution lead to longer hospital stays and increased antibiotic resistance. Urgent action is needed to establish national antibiotic programs, implement public awareness campaigns, and enforce stricter regulations on antibiotic use to improve outcomes and reduce antibiotic resistance.

KEYWORDS: *Antibiotics, Infection, Facial Spaces, CRP, Clinical Response*

INTRODUCTION

Orofacial and neck infections, whether odontogenic or non-odontogenic, can spread in unpredictable ways because of the anatomical connectivity of potential spaces. Potential spaces act as areas of least resistance for the spread of infection.[1] Due to the anatomical relationships, these infections can range from minor, locally confined infections to serious, organ and life-threatening illnesses as they include the origin of the upper airway and may extend to possible spaces created by the lower head and upper cervical fascial planes, such as the buccal, sublingual, submandibular, temporal, masseteric, canine, and parapharyngeal, which further exhibit fatal complications like mediastinitis, cavernous sinus thrombosis, and brain abscess if left untreated.[2] Since these infections remain the primary cause of morbidity and mortality, maxillofacial surgeons continue to face significant challenges despite significant improvements in health services.[3] Fever, swelling, trismus, pain, and, at a later stage, dysphagia, dyspnea, and voice changes are part

of the classic clinical presentation. This infection quickly progresses from a localized to a deep neck-space infection that compromises the airway. Odontogenic infections can result in toxicity and potentially fatal conditions such as respiratory distress, reduced consciousness, meningitis, cavernous sinus thrombosis, and impaired vision.[1] Maxillofacial infections are now far more severe than they were in the past, necessitating early diagnosis and more aggressive treatment. For early diagnosis and monitoring of treatment response, we frequently use clinical laboratory tests. The most widely used traditional laboratory tests for identifying acute inflammation and tracking the response to treatment are C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell (WBC) counts.[4] Only trace amounts of C-reactive protein (CRP) are found in healthy, normal people. It plays a role in the innate immune system's processes of complement activation, antigen clearance, and activation-mediated phagocytosis. It is a good indicator of the degree of tissue damage and inflammation, and the most effective single screening test for an acute-phase reaction. Within 48 hours, the serum concentration peaks, first surpassing 5 mg/l in 6 hours. Regardless of health or illness, CRP has a plasma half-life of roughly 19 hours. Consequently, the intensity of the pathological process, which determines the plasma CRP concentration, is directly reflected in the stimulus that causes the secretion.[5] Empirical antibiotics use and incision and drainage are the main treatment options, but understanding the microorganisms involved and their sensitivity pattern is also crucial. Sometimes, despite incision and drainage, antibiotic use, and other treatments, the patient's condition remains unchanged. This could be because the bacterial strains are resistant, leading to the ineffective use of antibiotics. A broad range of facultative anaerobes, including the Streptococci viridians and Streptococcus anginosus groups, as well as strict anaerobes, particularly anaerobic cocci and species of Prevotella and Fusobacterium, are present in the pathological process of odontogenic infection. Gram-positive cocci and strictly anaerobic gram-negative rods are the primary isolates.[6] Antibiotic misuse-recognized globally as a major contributor to antimicrobial resistance-includes practices such as self-medication, obtaining antibiotics without a prescription, and poor adherence to treatment regimens, such as skipping doses or not completing the full course. Multiple factors contribute to these behaviors, but organizations like the WHO emphasize promoting responsible antibiotic use among patients as a critical strategy to combat antimicrobial resistance.[7] Deep facial infections are potentially life-threatening and require timely recognition and management. In many low- and middle-income countries, including Pakistan, over-the-counter and unregulated antibiotic use is common. Such indiscriminate exposure can mask clinical signs, alter the local microbiological profile, and delay the apparent clinical response to standard therapy. C-reactive protein (CRP) is a sensitive biomarker of inflammation and a valuable tool for monitoring treatment response. Evaluating the pattern of delayed clinical improvement in relation to prior unsupervised antibiotic use and correlating it with CRP levels can provide valuable insight into the impact of inappropriate antibiotic practices. This case series highlights the public health implications of antibiotic misuse and underscores the need for strengthened antibiotic stewardship and early, evidence-based management protocols for deep facial infections in resource-limited settings.

METHODOLOGY

This case series study was conducted in the Department of Oral and Maxillofacial Surgery and Ophthalmology at Lady Reading Hospital from January 2024 to March 2025. The study was initiated after obtaining approval from the institutional ethics committee, with reference number 219/LRH/MTI dated May 26, 2025, and written informed consent was obtained from all participants. A total of 35 patients, representing both genders and a wide range of ages, ethnicities, and geographical backgrounds, were included. All participants were admitted with fascial space infections requiring hospital management and had a history of prior antibiotic use before presentation. Patients with recurrent infections, infections secondary to trauma, or those with chronic medical conditions were excluded. Diagnosis of a fascial space infection was based on a detailed history, including documentation of any previous unregulated antibiotic use, and a comprehensive clinical examination to assess signs of infection. For odontogenic infections, the diagnosis was confirmed with an orthopantomogram (OPG), while non-odontogenic infections were evaluated using a CT scan. The severity of the acute-phase infection was monitored by serial measurements of C-reactive protein (CRP) taken at three time points: admission, the third day of hospitalization, and discharge. Initial treatment followed standard clinical guidelines, including the use of antibiotics and incision-and-drainage procedures when indicated. First-line antibiotics included amoxicillin with clavulanic acid or cephalosporins, in combination with metronidazole. The response to the initial antibiotic therapy was evaluated through serial CRP measurements and clinical indicators of infection. When CRP levels failed to decline and there was no clinical improvement, the antibiotic regimen was

modified. The alternative treatment proved effective, as evidenced by a reduction in CRP levels and improvement in clinical symptoms. All data were recorded on a predesigned proforma. Statistical analysis was carried out using SPSS software (version 25). To begin with, the data distribution was checked for normality by examining the skewness and kurtosis values. Descriptive statistics were then applied: categorical variables, such as patients' age groups and gender, were summarized as frequencies and percentages, while continuous (scale) variables were expressed as means with their corresponding standard deviations. To evaluate the effect of treatment, a paired sample t-test was used to compare serial CRP levels, specifically, the CRP measured on the third day after the initial antibiotic therapy and the CRP level after the antibiotic regimen was changed. A p-value of less than 0.05 was considered statistically significant. Additionally, a bivariate correlation analysis was conducted to investigate the relationship between the CRP level at admission and the CRP level on the third day of initial treatment. This analysis helped to assess how well the patients were responding to the first course of antibiotics given at admission.

RESULTS

A total of 35 patients with facial space infection were enrolled in this prospective cross-sectional study. The frequencies of females (51.4%) outnumber the males (48.6%) by almost 3%. The mean age is 25.71 years ± 18.8 years, with a minimum of 4 years and a maximum of 65 years, as the age bracket was open and not defined by a specific number. The most commonly involved space was the submandibular space (31%), followed by unilateral and bilateral submandibular, sublingual, and submental spaces (20%), as shown in Table 1. Orbital cellulitis was observed in 17% of patients (Figure 1). When asked about the prior unregulated use of antibiotics, 65.7% of patients admitted to having used them. The Mean CRP on the day of admission was 15.46 mg/dl with a SD of 6.42. After admission, the management guidelines were followed, which include initial antibiotics (Amoxicillin/cephalosporin and metronidazole) plus incisional drainage where indicated. The follow-up means CRP on the 3rd day of admission was 15.17mg/dl with SD 9.77, showing a poor response to initial treatment in 54.3% of the patients. Due to no response to the initial treatment decision, a change in antibiotic was made, as shown in Table No. 2. The mean CRP on the day of discharge and after the change of antibiotic was markedly reduced, with the mean of 3.2mg/dl and SD of 3.7, showing resolution of infection. Inferential statistical analysis using a paired sample t-test on serial CRPs reveals that, with a 95% confidence interval, the p-value is statistically significant ($p < 0.001$). On the correlation analysis, the correlation coefficient was ($r=0.722$). The p-value was statistically significant, indicating that patients with a high level of CRP on admission had a high CRP level after initial antibiotic use, suggesting a lack of response to treatment due to the unregulated use of antibiotics.

Figure: 1 Child presenting with severe left periorbital swelling and necrotic changes consistent with advanced orbital cellulitis.

Table 1: Distribution of Anatomical Spaces Involved in Deep Facial Infections

Space involved	Frequency (n)	%age
Orbital	06	17.1
Periorbital	03	8.6
Buccal	01	2.9
Submandibular	11	31.4
Unilateral	07	20.0
Bilateral	07	20.0

Percentages are based on the total sample of 35 patients.

Table 2: Frequency of Postoperative Complications

Complication	Frequency (n)	%age
Vancomycin and Metro	01	2.9
Meropenem and Metro	04	11.4
linezolid and Metro	11	31.4
Moxifloxacin and Metro	02	5.7
No change in the Antibiotic	17	48.6

Percentages are calculated from a total sample size of 35 patients.

Table 3: Comparing CRP on the Third Day of Admission with CRP at Discharge

Variable Compared	Mean Difference (mg/L)	95% CI of Difference (mg/L)	t (df =34)	P-Value
CRP (3rd day) vs. CRP (discharge)	11.89 ± 8.11	9.10 to 14.68	8.67	<0.001

Notes: Values are mean ± standard deviation unless otherwise indicated. Paired-samples t-test shows a significant reduction in CRP between the 3rd day and discharge.

Table 4: Pearson correlation between CRP on admission and CRP on the 3rd day of admission

Variables	Pearson Correlation (r)	P-value	n
CRP on admission vs. CRP on 3rd day	0.722	<0.001	35

Note: Pearson correlation shows a strong positive association between CRP levels on admission and on the 3rd day of admission. Correlation is significant at the 0.01 level (two-tailed).

DISCUSSION

Fascial space infections of the maxillofacial region can result in prolonged illness, leading to unpredictable results and serious complications, even death, despite the use of antibiotics.[8] Inappropriate and unregulated use of antibiotics is widespread in underdeveloped countries like Pakistan, creating adverse clinical and economic threats to the health of the patient.[9] In our study, 65.7% have used self-prescribed broad-spectrum antibiotics due to the easy availability of over-the-counter antibiotics, increasing antimicrobial resistance (AMR). Misuse of antibiotics is the primary factor contributing to antimicrobial resistance, according to a study. Approximately 50% of global antibiotics cannot be adequately justified.[10] The inappropriate use of antibiotics is evident through multiple factors, one of which is the critical condition of the patient when they present to the hospital. Similarly, in our study, 54.3% of patients did not respond to the initial treatment given according to the guidelines, and their markers of infection remained elevated despite antibiotic use. CRP is the primary indicator of an acute phase reaction, with a short lifespan of 5 to 6 hours, and can be used to diagnose and monitor the response to treatment.[11] According to a study, the serum concentration of CRP increases up to "000 fol" within a few hours of clinical presentation, and it continues to increase if the clinical response to treatment is poor.[12] In our study, similar results were observed, with a mean CRP level of 15.46 ± 6.42 on the day of admission. Notably, this level did not decline, as evidenced by the mean CRP on the 3rd day of admission, which was 15.17 ± 9.77, indicating a poor response in 54.3% of patients. A study conducted by G. Mahesh et al. concluded that serum C-reactive protein is an immediate effect of treatment in normal circumstances and can be used as a monitoring tool for deep fascial space infections.[13] Due to the poor clinical response to the first antibiotic in 54.3% of cases, as indicated by the CRP level, due to resistance to the recommended antibiotic, the decision was made to switch to non-resistant and undocumented medications. Another study reported that the rising rate of antibiotic resistance is alarming.[9] In our study, the most common space involved was the submandibular space (31%), followed by unilateral and bilateral submandibular, submental, and sublingual spaces, at 20% and 17%, respectively, with orbital cellulitis accounting for 20%. Similar findings were observed in a local study, with submandibular space involvement was 41.7% of the cases.[14] In another study, orbital cellulitis was found to occur in 15% of pediatric patients, a rate similar to that observed in your study.[15] This study reveals that fascial space infections are more prevalent in early childhood, particularly among children under 10 years old, and again in individuals in their fifth decade of life, a period often associated with a reduced immune response. Similar trends have been reported in other studies as well.[16,17,18] Antibiotic misuse-recognized globally as a major contributor to antimicrobial resistance encompasses practices such as self-medication, obtaining antibiotics without a prescription, and poor adherence to treatment regimens, including skipping doses or not completing the full course. Multiple factors contribute to these behaviors, but organizations like the WHO emphasize promoting responsible antibiotic use among patients as a critical strategy to combat antimicrobial resistance.

LIMITATIONS

Our study has some limitations, including the data being collected from a single tertiary care hospital, which limits the generalizability of the findings to other regions or healthcare settings. A small sample size of only 35 patients, the study may lack the statistical power to detect subtle associations or patterns. Information regarding prior unregulated antibiotic use was based on patient recall, which may introduce recall bias or underreporting.

CONCLUSIONS

This study demonstrates that patients with deep fascial space infections, as objectively determined by persistently elevated C-reactive protein levels after initial management, exhibit a delayed clinical response due to prior use of unregulated and uncontrolled antibiotics. In low- and middle-income countries like Pakistan, the results highlighted the adverse effects of self-medication and easy access and availability of over-the-counter antibiotics, unlike in the West. Delays in infection resolution not only result in more extended hospital stays but also exacerbate antibiotic resistance. To improve clinical outcomes and prevent the development of resistance patterns in these vulnerable settings, there is an urgent need for national antibiotic dispensing programs, public awareness campaigns, and robust regulations on antibiotic usage.

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The authors accept responsibility for all aspects of the work and will ensure that any concerns regarding the accuracy or integrity of any part are properly investigated and resolved.