Article:
Miah, MS, Nix, P, Koukkoullis, A et al. (1 more author) (2016) The microbial causes of complicated Acute Bacterial Rhinosinusitis and implications for empirical antimicrobial therapy. The Journal of Laryngology & Otology, 130 (2). pp. 169-175. ISSN 0022-2151

https://doi.org/10.1017/S0022215115003369

Title Page

Title of the manuscript:

The microbial causes of complicated Acute Bacterial Rhinosinusitis and implications for empirical antimicrobial therapy

Authors:
Mr. Mohammed S. Miah[¶] FRCS (ORL-HNS), Mr. Paul Nix[¶] FRCS (ORL-HNS), Mr. Alexandros Koukkoullis[¶] MRCS, Professor Jonathan Sandoe[§] FRCP

Department of Otorhinolaryngology-Head & Neck Surgery[¶],

Department of Microbiology[§],

Leeds General Infirmary, Leeds, UK

Correspondence: Mr. Paul Nix MA, MD, FRCS (ORL-HNS)
Reprint requests Consultant ENT/Skull-Base Surgeon
Leeds General Infirmary
Great George Street, Leeds, UK, LS1 3EX
Email : paulnix@nhs.net
Tel: (+44) 0113 243 2799
Fax: (+44) 0113 245 5965

Brief running title: Microbiology of acute bacterial rhinosinusitis

Abstract page

Background: Microbiology of complicated acute bacterial rhinosinusitis is historic and not widely described. Reliable microbiology is necessary to inform current empirical antimicrobial treatments. This study was conducted in response to recent American guidelines on antimicrobial treatment of acute bacterial rhinosinusitis.

Objectives: Describe the micro-organisms in complicated acute bacterial rhinosinusitis and their antimicrobial susceptibility in the UK.

Methods: Retrospective data collection from 2007-2012. Complicated acute bacterial rhinosinusitis cases with sinogenic orbital/intracranial infections were studied. Bacteria from paranasal sinus pus were compared with organisms from orbital/intracranial infections.

Results: Streptococcus anginosus group bacteria were isolated from paranasal sinus pus samples in 61.3%, 83.3% of orbital and 77.8% of intracranial cases. All isolates of Streptococcus anginosus were sensitive to penicillin. No resistant organisms were isolated.

Conclusions: Streptococcus anginosus was the predominant organism isolated from cases of complicated acute bacterial rhinosinusitis in our UK center. Streptococcus anginosus is sensitive to penicillin and thus suggest the use of penicillin as an appropriate first-line empiric antibiotic for uncomplicated acute bacterial rhinosinusitis.

Key words:
Paranasal Sinus, Pus, Streptococcus Anginosus

Main Text

Introduction

Acute rhinosinusitis is predominantly caused by upper airway viral infections which are self limiting and management is symptomatic relief and patient reassurance[1]. Routine use of antimicrobial therapy is not indicated in such cases. A small number of patients develop secondary acute bacterial rhinosinusitis (ABRS), whose management necessitates the use of antimicrobials[1]. Accurate diagnosis depends on thorough clinical assessment of patients, most often by General Practitioners in the United Kingdom, as ABRS is generally treated in the community in various primary care settings. National bodies and local hospitals have produced guidelines in the form of algorithms in order to improve diagnosis and optimize use of antimicrobials.

Demonstrating bacterial infection in the paranasal sinuses is the gold standard for diagnosing of ABRS and paranasal sinus pus obtained from a sinus wash out is a far superior sample than a nasal swab. Cultures of nasal or throat swabs do not accurately reflect the clinical condition as there is a great difficulty in differentiating commensal from pathogen. Unfortunately, sinus washouts are not routinely done in the clinic setting or in the community. Imaging is also used to diagnose acute rhinosinusitis but is unable to differentiate between viral and bacterial infection[2]. A combination of clinical assessment, imaging and microbiology findings is considered the optimum method of diagnosis of ABRS. However, such an approach is not practical in the primary care settings for obvious reasons and also not always available immediately to hand even in the hospital settings. Therefore appropriate empirical antimicrobial therapy is often

given, based on local guidelines and experience.

The Infectious Diseases Society of America recently published guidelines for the treatment of ABRS, which highlighted the difficulties of microbiological sampling and limitations to the microbiology findings in many clinical trials of sinusitis treatment. However, they recommended the use of broad spectrum antimicrobials, such as co-amoxiclav, for first line therapy[3], partly in response to studies that showed an increase in resistance to penicillins in Streptococcus pneumoniae[4].

We were concerned that the microbiology of complicated ABRS is not current and aimed to review our empirical treatment regimens based on more accurate microbiology for the UK. We therefore conducted a retrospective evaluation of our recent complicated ABRS cases with the principal aim of describing the bacterial pathogens, their susceptibility to the antimicrobials commonly used in this setting, any corresponding sinogenic complications such as orbital or intracranial abscess, and extrapolate the results for treatment of uncomplicated ABRS in the community.

Materials and methods

Study design and case selection

This was a retrospective service evaluation of complicated **acute bacterial rhinosinusitis (ABRS)** cases referred to the Leeds Teaching Hospitals NHS Trust (Leeds, United Kingdom) during the period 1st January 2007-31st December 2012. For the purpose of this study, complicated ABRS was defined as acute bacterial rhinosinusitis plus orbital and/or intracranial infection. Cases were included according to specific inclusion and exclusion criteria:

Inclusion criteria

- Documented clinical evidence of ABRS**:**

  Suggested by the presence of at least 3 symptoms/signs of:

  Discoloured nasal discharge (with unilateral predominance)

  Severe local pain (with unilateral predominance)

  Fever (>38ºC)

  'Double sickening' (i.e. deterioration after an initial milder phase)

  AND

- Surgically obtained paranasal sinus pus culture and sensitivity +/- pus cultures from orbital and/or intracranial abscesses AND
- CT scan evidence of ABRS +/- orbital and/or intracranial abscess according to criteria previously defined by Manning et al[5]

Exclusion criteria

- Patients only with nasal Swabs; OR

- Patients with swabs taken during elective surgery for chronic rhinosinusitis; OR
- Patients without CT Scans; OR
- Post Traumatic sinusitis; OR
- Patients with swabs from non paranasal sinuses

Data gathering

Initially a database of all patients who had paranasal sinus pus cultures and cultures of orbital and intracranial abscess samples (positive for bacterial infection) between January 2007 and December 2012 was established. Data were collected retrospectively from medical notes and the hospital electronic and radiology databases and results stored on an excel file. Pre-hospital antibiotic therapy was determined from cases notes, electronic discharge system and GP referral letters where traceable. All CT scans were reviewed and correlated with the reports provided by the radiologists. Microbiology database of paranasal sinus pus cultures, orbital, frontal sinus and intracranial abscess cultures were cross referenced with documented clinical features and CT scans. This process allowed accurate identification of cases of complicated ABRS.

Antimicrobial therapy

Generally, once admitted to our hospital, all cases of complicated ABRS patients with orbital and/or intracranial infection were initially treated with empiric doses of intravenous Cefotaxime, Metronidazole and Flucloxacillin. Subsequently the antibiotic regime was altered based on patients' response and subsequent microbiological results

and susceptibility. Duration of treatment was guided by extent of infection, clinical response, radiological monitoring and organisms isolated.

Microbiological specimens

Paranasal sinus pus samples were obtained surgically using an endoscopic approach to the maxillary or ethmoid sinuses and via frontal sinus trephine. Pus samples and bacteriology swabs from orbital abscess cases were obtained through external-approach drainage procedures and from intracranial abscesses through burr-hole or craniotomy as appropriate. All specimens were promptly sent to the Microbiology laboratory for microscopy, culture and susceptibility studies.

Microbiological processing

Wound swabs were cultured on: horse blood agar, incubated in 5-10% CO_2; cysteine lysine electrolyte deficient ager, incubated in air; and, neomycin horse blood agar in anaerobic conditions all for 2 days at 37°C. Pus samples were cultured on horse blood agar and chocolate agar, incubated in 5-10% CO_2, for 2 days; cysteine Lysine electrolyte deficient ager, incubated in air for 2 days; neomycin horse blood agar in anaerobic conditions for 3 days; and fastidious anaerobic broth for 1 day, all at 37°C. Tissue specimens were cultured on horse blood agar and chocolate agar, incubated in 5-10% CO_2, for 3 days; fastidious anaerobic agar in anaerobic conditions for 5 days; and, Sabouraud's agar in air for 7 days all at 37° C. Brain heart infusion broth for tissue specimens was incubated for 5 days. Anaerobic conditions were achieved using MACS-MG-1000 anaerobic workstation (DW Scientific). Identification was carried out using standard techniques and susceptibility-testing by a disk diffusion method, latterly

according to Eucast criteria. No molecular techniques were employed direct on samples.

Ethical considerations

Local departmental approval was obtained formally. No ethics approval was sought as the project was categorized as a service evaluation, which did not affect the patient care at any level. All data were recorded and kept in accordance with Caldicott Guardianship protocols.

Results

In total 31 cases met the strict inclusion criteria and therefore were included in the study (figure 1). There was some duplication of cases due to the patient identification strategies and thus excluded (n=13). Patient demographic details are shown in table 1. Twenty nine cases were primary acute bacterial rhinosinusitis **(**ABRS) and two cases were secondary to odontogenic pathology. There were 16 cases of ABRS + periorbital cellulitis, 15 ABRS with suspected intracranial abscess on imaging criteria, nine intracranial and six orbital abscesses (table 1). Past history of sinus disease was present in four (12.9%) cases. Twenty-one (67%) cases were on oral antibiotics prior to hospital admission and of these five were on broad-spectrum antibiotics.

Streptococcus anginosus group (S. anginosus) bacteria were isolated from paranasal sinus pus samples in 61.3% (19/31) of all cases, 83.3% (5/6) of orbital abscesses and 77.8% (7/9) of intracranial abscess cases (table 2). In all cases where S. anginosus was found in orbital and intracranial abscesses, the corresponding paranasal sinus pus samples also

yielded S. anginosus. Beta-haemolytic streptococci were the next common streptococcal organisms isolated (16.1% of paranasal sinus pus samples). However, Beta-haemolytic streptococci were not isolated in the cases of orbital or intracranial abscesses.

Staphylococcus aureus (S. aureus) was the second most common pathogen isolated in 12 cases of paranasal sinus pus (38.7%). S. aureus was always isolated with another organism most notably a Streptococcus spp. In particular 66% of orbital abscess and 44% of intracranial abscess cases had a S. aureus isolated.

Multiple organisms (S. anginosus with other organisms) were isolated in 41.9% of all paranasal sinus pus samples. Stenotrophomonas maltophilia was isolated from the paranasal sinus pus sample in one case. This patient was immunocompromised but did not develop an orbital or intracranial abscess (only periorbital cellulitis). S. anginosus and Gram-negative anaerobic bacteria were isolated in one case each of an orbital and an intracranial abscess. One case of an orbital abscess also cultured Haemophilus influenzae.

All cases of S. anginosus, whether isolated from paranasal sinuses or abscess samples, and all Beta-haemolytic streptococci were susceptible to penicillin. The Haemophilus influenzae isolate was also susceptible to amoxicillin. The S. aureus isolates were resistant to penicillin but susceptible to methicillin (flucloxacillin).

Discussion

The bacteria responsible for acute bacterial rhinosinusitis ABRS are similar to those found in cases of community-acquired pneumonia, such as Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis and occasionally Staphylococcus aureus[3]. ABRS generally follows a viral respiratory tract infection and in some cases can be secondary to odontogenic infection, surgery or trauma. Most cases can be managed in the primary care setting with oral antimicrobials and only a small minority may require hospital care due to a lack of resolution, or when complicated ABRS develops. The microbiology of complicated ABRS is not well described, being historic and country specific, but does appear to differ from uncomplicated ABRS [6]

In this evaluation of complicated ABRS from a United Kingdom population, S. anginosus group bacteria were the predominant cause of ABRS (61%), as well as the corresponding orbital (83%) and/or intracranial abscesses (78%). These organisms were susceptible to penicillin in all cases. Interestingly this high incidence of S. anginosus is much more than previous reports in the literature regarding S. anginosus. Mortimore et al in 1998 described the microbiology of complicated sinusitis in a developing population quoting S. anginosus isolates in 50% of abscess[6] and Gwaltney in 1981 reported S. aureus was the second most common pathogen (38%) and no methicillin-resistant strains were identified[7]. A substantial number (42%) of cases had a mixed infection. Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis were uncommon in these patients. The microbiology of complicated ABRS appears to be markedly different from that of uncomplicated infection.

Prior treatment with antibiotics before the patient is admitted to hospital with a complication of ABRS does not appear to have an impact on the complication, Table 3. Twenty one of these patients received a pre-hospital course of oral antibiotics. Why such patients, despite an oral course of antibiotics, developed a sinogenic complication of their ABRS may relate to the microbial cause; S. aureus and S. anginosus are well known to cause abscesses and these pathogens may have a greater risk of complications. However, the reason why some patients develop complications of ABRS is likely to be multi-factorial involving smoking history, genetics, and host immune systems including anatomical barriers and biofilms but detailed discussion is beyond the scope of this article[8]. It is noteworthy that the microbiology of the eight patients presenting directly to the emergency department, and thus having no prior antibiotic treatment, was not markedly different from the patients presenting with prior antibiotic treatment.

Although it is assumed that the organisms responsible for ABRS occasionally also lead to the sinogenic complications necessitating admission to hospital, this is rarely described[6,9-10]. We have shown 100% agreement between paranasal sinus and abscess samples.

It is important to recognize features suggestive of ABRS as opposed to virally induced acute rhinosinusitis (approximately 90% of cases). The following features are suggestive of ABRS[3]: (1) onset with persistent symptoms or signs compatible with acute rhinosinusitis, lasting for =10 days without any evidence of clinical improvement; (2)

onset with severe symptoms or signs of high fever (=39ºC) and purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days at the beginning of illness; or (3) onset with worsening symptoms or signs characterized by the new onset of fever, headache, or increase in nasal discharge following a typical viral upper respiratory infection that lasted 5–6 days and were initially improving (‘‘doublesickening’’). Although the triad of headache, facial pain, and fever is considered a classic presentation of ABRS in adults, it is uncommon. Onset with persistent symptoms is far more frequent[1]. In children, the most common manifestations of ABRS are cough followed by nasal discharge and fever.

In recent years, a number of studies have demonstrated Streptococcus pneumoniae as the most common organism responsible for ABRS associated with high resistance rate to first line antibiotics in America[4]. Studies have also demonstrated methicillin-resistant Staphylococcus aureus in cases of complicated and uncomplicated ABRS with prevalence from 0% to 15.9%[11]. Both of these phenomena are contrary to the findings of this current study from a UK population, which indicates S. anginosus and methicillin sensitive S aureus as the most common pathogens of complicated ABRS and with no resistant organisms. In an era of increasing antibiotic resistance this is a very important finding. It highlights the importance of obtaining local / national microbiology sensitivities for pathogens before adopting international guidelines such as those proposed by the Infectious Diseases Society of America for the treatment of ABRS.

This study also highlights that in immunosuppressed patients, the role of broad-spectrum

antibiotic cover and ENT consultation may need to be considered from the outset, due to the possibility of unusual organisms which may not be sensitive to first-line antibiotics as recommended by most guidelines. It is also interesting to note that of the two cases presenting with sinogenic complication secondary to dental infections, Gram-negative organisms were also isolated.

Limitations of this Study

This was a retrospective study and as such may be criticized on methodology alone. This study examined complicated cases of ABRS only. The reason for this was to obtain disease specific microbiology cultures that are not usually available with uncomplicated cases of rhinosinusitis; however the results observed we feel are paramount to antibiotic treatment of acute rhinosinusitis in an era of increasing antibiotic resistance. The sample size was small and considering the rare incidence of complicated ABRS overall, it is reasonable to take account of the findings of this study as essential with some degree of caution. It is important to note that the high microbiology culture rates in this study are due to invasive sampling from a specific site was an inclusion criterion. The results from this study data has been extrapolated to make recommendation for treatment of uncomplicated ABRS in the community. This should be taken with a degree of caution for the treatment of cases in regions outside of the UK in particular.

Conclusion

This study describes the current microbiology causing acute bacterial rhinosinusitis ABRS in a UK population. Infectious Diseases Society of America's recent Clinical

Practice Guideline for ABRS in Children and Adults (2012) recommend co-amoxiclav rather than amoxicillin alone as initial empirical therapy. The most common organism involved in complicated ABRS in our region was S. anginosus which showed no resistance to simple penicillins like amoxicillin and penicillin (V). S. aureus was an important pathogen isolated in complicated patients. There do not appear to be the same epidemiological changes in the UK to drive more broad-spectrum empirical regimens but in complicated cases, empirical cover for Streptococci and S. aureus would appear to be appropriate. We would recommend the use of simple narrow spectrum penicillins as first line antibiotic therapy in cases of uncomplicated ABRS in our community and would not advocate any change to our current guidelines for uncomplicated ABRS. In the management of complicated ABRS however we would recommend an antibiotic regimen that covers both S. anginosus and S. aureus.

Funding:
No external sources of funding.

Conflict of interests:
None to declare.

References

1. Fokkens WJ, Lund VJ, Mullol J, Bachert C. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinology 2012; 23:1-298
2. Gwaltney JM, Jr., Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. The New England journal of medicine 1994; 330:25-30
3. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJC, Hicks LA. IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults. Clin Infect Dis 2012; 54:e72-e112
4. Brook I. Amoxicillin-clavulanate as the gold standard empirical therapy of acute bacteria rhinosinusitis. Expert Rev Anti Infect Ther 2012; 10:1367-9
5. Manning SC, Biavati MJ, Phillips DL. Correlation of clinical sinusitis signs and symptoms to imaging findings in paediatric patients. Int J Pediatr Otorhinolaryngol 1996; 37:65–74
6. Mortimore S, Wormald PJ, Oliver S. Antibiotic choice in acute and complicated sinusitis. The Journal of Laryngology and Otology 1998; 112:264-268
7. Gwaltney JM Jr, Sydnor A Jr, Sande MA. Etiology and antimicrobial treatment of acute sinusitis. Ann Otol Rhinol Laryngol Suppl 1981; 90:68-71
8. Brook I, Hausfeld JN. Microbiology of acute and chronic maxillary sinusitis in smokers and nonsmokers. Ann Otol Rhinol Laryngol 2011; 120:707-12
9. Brook I, Frazier EH. Microbiology of subperiosteal orbital abscess and associated maxillary sinusitis. Laryngoscope 1996; 106:1010-3
10. Brook I. Microbiology of intracranial abscesses and their associated sinusitis.

Arch Otolaryngol Head Neck Surg 2005; 131:1017-9

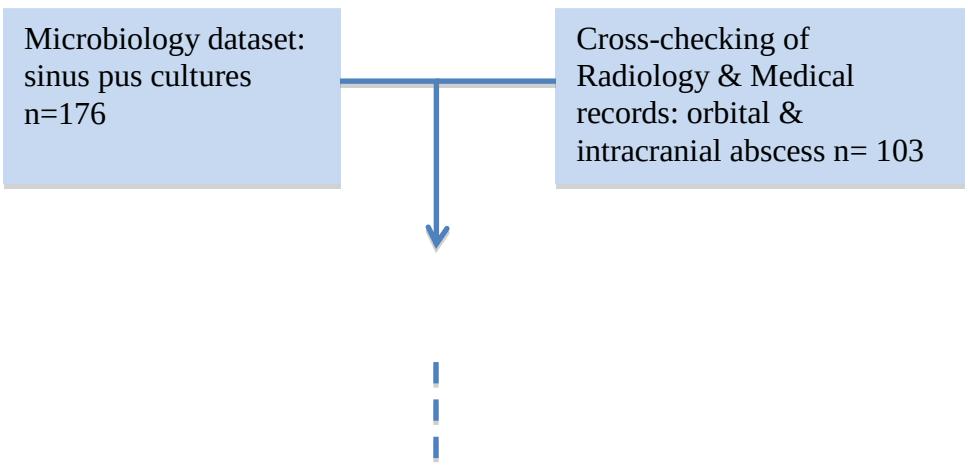
11. McCoul ED, Jourdy DN, Schaberg MR, Anand VK. Methicillin-resistant Staphylococcus aureus sinusitis in nonhospitalized patients: A systematic review of prevalence and treatment outcomes. Laryngoscope 2012; 122:2125-31

Summary

- There was 100% agreement between microbiology of directed sinus and abscess samples.
- Streptococcus anginosus was frequently isolated from paranasal sinus, orbital and intracranial abscess samples in the UK.
- Streptococcus anginosus is sensitive to penicillin and is an appropriate first-line empiric antibiotic in cases of **uncomplicated** acute bacterial rhinosinusitis.

FIGURES & TABLES

Figure 1: Flowchart of included cases.



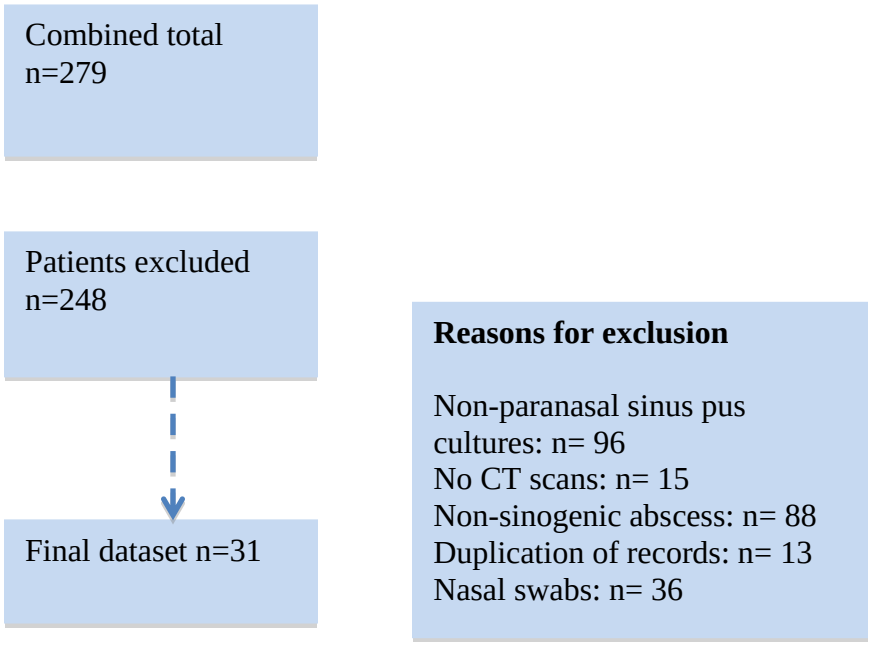

Combined total
n=279
Patients excluded
n=248
Final dataset n=31
Reasons for exclusion
Non-paranasal sinus pus cultures: n= 96
No CT scans: n= 15
Non-sinogenic abscess: n= 88
Duplication of records: n= 13
Nasal swabs: n= 36

Table 1: Patient demographic details and clinical characteristics.

Patients (n=31)	
Males: females ratio	19: 12
Mean age (range)	43 yrs (3-70)
Paediatric: adult ratio	6: 25
Previous sinus disease	4 (13%)
Abscess on CT scans Orbital abscess Intracranial abscess	 6 (19%) 9 (29%)
*Pre-hospital antibiotic amoxicillin-clavulanate penicillin amoxicillin flucloxacillin cephalexin **None	 4 1 9 6 1 8

*In 2 cases pre-hospital antibiotic could not be traced due to lack of documentations.
**Patients presented directly to hospital Emergency Department.

Table 2: Microbiology of various culture specimens are summarised here with most commonly isolated organisms.

Specimens	Bacterial organisms	Antibiotic sensitivities
Paranasal sinus pus: n=31	S. anginosus: 19 (61.3%)	Penicillin Erythromycin Cefotaxime
	Beta-haemolytic Streptococcus: 5 (16.1%)	Penicillin Erythromycin Clarithromycin
	H.influenzae: 3 (9.7%)	amoxicillin Erythromycin Clarithromycin
	S. aureus 12 (38.7)	Flucloxacillin
	*Gram negative anaerobes: 2 (6.5%)	Metronidazole
Orbital abscess: n=6	S. anginosus: 5 (83.3%)	Penicillin Erythromycin Cefotaxime
	S. aureus: 4 (66%)	Flucloxacillin
Intracranial abscess: n=9	S. anginosus: 7 (77.8%)	Penicillin Erythromycin Cefotaxime
	S. aureus: 4 (44.4%)	Flucloxacillin

Table 3: Pre-hospital antibiotic therapy by cases and complications.

Age	Complication	Organism 1	Organism 2	Pre-hospital Antibiotics
42	Pre-septal cellulitis	S. anginosus		Amoxicillin
70	Frontal Abscess	S. anginosus, S. aureus	S. anginosus	None
67	Pre-septal cellulitis	S. anginosus, S. aureus		None
65	Intracranial abscess	Stenotrophomonas maltophilia		Augmentin
57	Intracranial abscess	Beta-haemolytic Streptococcus-B		None
61	Pre-septal cellulitis	S. anginosus		No data available
48	Orbital Abscess	S. anginosus	S. anginosus	Flucloxacillin
20	Frontal Sub Empyema	Coliforms, S. aureus	Coliforms	Cephalexin
50	Orbital Abscess	H.influenzae, S. aureus	H.influenzae	Flucloxacillin
12	Frontal Subdural Empyema	S. anginosus	S. anginosus	Amoxicillin
9	Extradural Abscess	S. anginosus	S. anginosus	Flucloxacillin
22	Frontal Subdural Empyema/Potts	S. anginosus	S. anginosus	Amoxicillin
39	Frontal Subdural Empyema/Potts	S. anginosus	S. anginosus	Amoxicillin
60	Pre-septal cellulitis	S. anginosus		No data available
29	Pre-septal cellulitis	S. anginosus S. aureus		Flucloxacillin
54	Intracranial abscess	H.influenzae, S. aureus		Amoxicillin
48	Intracranial abscess	Strep Pneumoniae		none
66	Intracranial abscess	H.influenzae		none
52	Temporal lobe Abscess	S. aureus	S. aureus	Amoxicillin
63	Pre-septal cellulitis	Beta-haemolytic Streptococcus-A, S. aureus		Penicillin V
13	Orbital abscess	S. anginosus	S. anginosus	Flucloxacillin
54	Orbital Abscess	S. anginosus	S. anginosus	none
3	Pre-septal cellulitis	Beta-haemolytic Streptococcus-A, S. aureus		Amoxicillin
31	Intracranial abscess	Beta-haemolytic Streptococcus-A, S. aureus		none
57	Intracranial abscess	Beta-haemolytic Streptococcus-A, S. aureus		Amoxicillin
15	Frontal Subdural Empyema/Potts	S. anginosus, S. aureus	S. anginosus	None
52	Orbital Abscess	S. anginosus, Gram-negatives	S. anginosus,	Augmentin

			Gram-negatives	
6	Bilateral Orbital Cellulitis	S. anginosus		Augmentin
41	Orbital Abscess	S. anginosus	S. anginosus	Amoxicillin
49	Pre-septal cellulitis	S. anginosus		Augmentin
17	Subdural Abscess	S. anginosus	S. anginosus	Flucloxacillin