ORIGINAL CONTRIBUTION

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The microbiology and the efficacy of antibiotic-based medical treatment of chronic rhinosinusitis in Singapore*

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SUMMARY

Background: *Medical therapy including appropriate antibiotic treatment is advocated for the management of chronic rhinosinusitis (CRS), with sinus surgery reserved for treatment failures. This study investigates the microbiology of CRS and their response to culture-directed antibiotic treatment.*

Methods: *Sinus aspirates of mucopus from 172 consecutive CRS patients, with (n = 89) and without (n = 83) previous antibiotic treatment, were obtained for bacterial culture at their first visit. Medical treatment which included initial empirical and subsequent culture-directed antibiotics was instituted. Endoscopic sinus surgery (FESS) was performed for patients with persistent CRS and/or complications of CRS. A follow-up of 12 months was scheduled for all patients.*

Results: *One hundred and twenty patients were treated successfully with antibiotic-based medical therapy. Thirty-eight patients did not respond to medical treatment and eventually underwent FESS. The incidence of CRS with nasal polyps (CRSwNP) was higher in FESS group than patients with medical treatment only. Staphylococcus aureus was the most common pathogen and amongst patients with no prior antibiotic treatment, the incidence was higher in patients with CRSwNP than CRS without NP (CRSwoNP). The rate of sensitivity of the cultured microbes to amoxicillin with clavulanate and cephalosporins was 78% and 70%, respectively.*

Conclusion: *The microbiology of CRS in Singapore is described. Staphylococcus aureus appears to be the most common bacterial isolates in both CRS with and without nasal polyps. Medical treatment with CRS using culture-directed antibiotics is effective in the majority of patients, especially in patients without nasal polyps.*

Key words: rhinosinusitis, microbiology, bacteriology, antibiotics, nasal polyps

INTRODUCTION

Since the development of functional endoscopic sinus surgery (FESS), it has been widely recognized for its role in the management of chronic rhinosinusitis (CRS). At the same time, awareness of the complications associated with FESS and a better understanding of the changes in sinus physiology after FESS have prompted a reconsideration of the role of non-surgical options in the management of this disabling condition [(1)]. An adequate duration of appropriate antibiotic treatment is an integral component of this strategy. However, the choice of antibiotic depends on a number of factors, such as the spectrum of microbes among patients in the local population and a history of antibiotic hypersensitivity reaction.

Numerous microbial culture studies of CRS using different techniques for sinus sampling have been reported. In addition, the widespread use of empirical antibiotic treatment for CRS may alter the microbiological spectrum, with up to one-fifth of bacterial pathogens resistant to commonly-used antibiotics [(2)]. This study was designed to investigate the microbiology of CRS patients (with or without nasal polyps) and their response to culture-directed antibiotic treatment. Clinical data was prospectively collected and the management of these patients was based on guidelines published in the Joint Task Force on Practice Parameters for Allergy and Immunology in 1998 [(3)]. This included an initial culture of sinus aspirate and culture-directed antibiotics for a duration of four to six weeks. The aims of this study were to characterise the microbial spectrum in sinus aspirates of CRS patients, and to determine the proportion of patients who responded successfully to medical management.

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MATERIALS AND METHODS

Study patients

The study subjects consisted of 172 consecutive patients who presented with symptoms and signs of CRS to the otolaryngology clinic at Tan Tock Seng Hospital (TTSH), Singapore from 2001 to 2002. The process and concept of the study were approved by the Domain-Specific Review Board (DSRB) of the National Healthcare Group (NHG) to which the hospital belongs. There were 115 males and 57 females, aged from 9 to 87 years old (mean of 41 years). There were 138 of Chinese ethnicity (80%), 10 Malays (6%), 18 of South Asian origin (10%) and 6 of other ethnic origins. The inclusion criteria were based on the concepts developed by the Task Force on Rhinosinusitis (1996) and were subsequently reviewed in an article by Lanza and Kennedy in 1997 [4]. All patients were assessed by otolaryngologists at the department and, by default, had mucopurulent sinus discharge, as this was required for the acquisition of sinus aspirates for culture. This was deemed to constitute one major factor for the diagnosis of CRS. In addition, patients had to have at least one major symptom of CRS (i.e. facial pain/pressure, facial congestion/fullness, nasal obstruction/blockage, nasal discharge/purulence/postnasal discharge, hyposmia/anosmia) for at least 12 weeks or more. Thus, each study patient would have had at least 2 major factors associated with CRS and this was considered sufficient to make a diagnosis of CRS. Details of their medical history, such as onset and duration of CRS symptoms, type and duration of prior medical treatment (e.g. antibiotics) or surgical procedures were carefully recorded.

Sinus sampling and microbiological examinations

Specimens for culture were obtained from affected sinuses using the Xomed sinus secretion aspirator under endoscopic visualization. A previous evaluation of this method reported 85.7% correlation with surgically-obtained maxillary sinus samples [5].

The sinus aspirates were placed in a sterile specimen bottle and sent directly to the hospital microbiology laboratory for culture and investigation. Standard laboratory protocols for the specimen handling, culture process and sensitivity testing were followed. Samples were cultured in both aerobic and anaerobic media. Culture plates were observed daily and monitored for microbial growth. Antibiotic sensitivity testing was based on the type of bacteria identified.

Management and follow-up treatments

Patients were managed conservatively for at least four weeks. The treatment regimen included culture-directed antibiotics, sinonasal decongestants, short course oral corticosteroids, nasal douching and antral puncture and washout for those with primarily maxillary sinus involvement. A common broad spectrum antibiotic was prescribed. The patients were instructed to return to the clinic one week later for a follow-up clinical assessment. If there was significant improvement or resolution of CRS and the antibiotic used was found to be effective against the bacterial species found by the culture-based sensitivity testing, this treatment was continued for a further 1-2 weeks. Otherwise, a new antibiotic was prescribed according to culture-based sensitivity testing.

Conservative medical management was deemed successful if there was symptomatic relief of CRS symptoms, resolution of endoscopic signs of CRS, and no recurrent episode of CRS requiring recourse to FESS within a one year follow-up period. A proportion of patients were deemed to have failed conservative therapy if there was no symptomatic improvement after the designated period of medical therapy or if there was progression of disease resulting in systemic inflammation or local complications. FESS was thus recommended to these patients. Based on the standard management protocol that was practiced in the department, patients with significant improvement or resolution of symptoms after either medical or surgical treatment were followed up with sinonasal examination at three-monthly intervals for at least 12 months. Patients were instructed to return to the clinic for re-evaluation.

RESULTS

A total of 7 patients (4%) dropped out during the follow-up. Among them, there were 3 patients who had failed medical treatment and for whom FESS had been recommended; 2 did not consent for FESS and another one had contra-indications for surgery. A further 4 patients in the medical treatment group were not available for assessment at the 12th month follow-up with no specific explanation. Figure 1 shows the schematic description of the treatment received by patients in

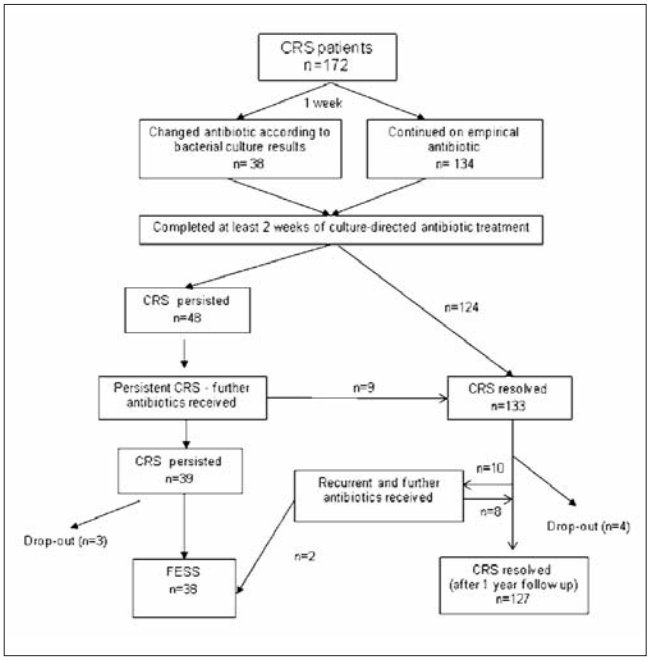

Figure 1. Flow diagram of treatment received and outcomes.

*The three most common empiric antibiotics

1. Amoxicillin with clavulanate	625 mg bd	43%
2. Trimethoprim – sulfamethoxazole	960 mg bd	13%
3. Cefuroxime	500 mg bd	12%

Table 1. The presence of pathogens versus pre-culture antibiotics.

Presence of pathogens in cultures	History of antibiotic therapy		p value for chi-square test
	No n=89 (100%)	Yes n=83 (100%)	
No pathogens*	16 (18)	24 (29)	0.025
Single pathogens	40 (45)	43 (52)	
Multiple pathogens	33 (37)	16 (19)	

* Note: cultures with coagulase negative Staphylococci (CNS) & normal flora were considered negative for pathogens. In recent years, CNS has been identified to be a common organism from sinonasal cultures of both patients with inflamed and normal sinuses. However, the role of CNS in CRS is not clearly established and most contemporary reports do not consider them pathogens [6,7]. In this study cohort, the hospital laboratory did not report antibiotic sensitivity when CNS was identified. Since the finding of CNS in culture did not result in a change in patient management, it seemed appropriate to classify cultures of CNS as negative for pathogens.

this study. For initial treatment, amoxicillin with clavulanate (43%), trimethoprim-sulfamethoxazole (13%), and cefuroxime (12%) were most commonly prescribed antibiotics.

According to medical history, 83 patients (48%) had received antibiotics within the 4 weeks prior to the baseline visit. Table 1 shows the frequency of positive cultures in relation to whether patients had been previously treated with antibiotics. Bacterial isolates (n = 156) were obtained from 132 patients with positive cultures. The microbial spectrum is listed in Table 2. Overall, there were significantly ($p < 0.025$) more bacterial isolates in the antibiotic free group. In particular, the incidence of *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and anaerobes was higher in the antibiotic-free group. However, there were more cases of Gram-negative cocci in the antibiotic treated group. The incidence of *Staphylococcus aureus* in the group of patients who were antibiotic-free (n = 29, 32%) was significantly higher than for those who had recent antibiotic treatment (n = 11, 13%) ($p = 0.004$). No racial differences were found among the study patients.

Table 2. Spectrum of microbial isolates.

Bacterial culture	No antibiotic treatment in the 7 days before samplin n=95	On antibiotic treatment at time of sampling n=61
Gram Positive Bacteria		
Staphylococcus aureus (MRSA)	28 (2)	11 (3)
Coagulase-negative Staphylococcus	8	7
Streptococcus pneumonia	2	5
Viridans group Streptococci	5	3
Beta-hemolytic Streptococci	3	–
Gram Negative Bacteria		
Haemophilus influenza	10	3
Pseudomonas aeruginosa	7	3
Enterobacter sp	3	1
Klebsiella pneumonia	2	3
Serratia marcescens	2	–
Proteus mirabilis	–	1
Citrobacter koseri	–	1
Eikenella corredens	1	–
Moraxella catarrhalis	1	4
Acinetobacter baumannii	–	2
Anaerobes	7	2
Fungi	4	4
Normal Flora	12	11

The difference in the incidence of *Staphylococcus aureus* between CRS patients with concurrent nasal polyposis (n = 8, 36%) and those without (n = 31, 21%) was not statistically significant ($p = 0.089$) (Table 2). However, within the antibiotic-free subgroup, the incidence of *Staphylococcus aureus* amongst patients with polyps (n = 8, 53%) was significantly higher than that of the polyp-free group (n = 20, 27%) ($p = 0.048$).

There were 22 patients (13%) who had concurrent nasal polyposis i.e. CRS with NP. This was a small proportion of the total number of patients. Thus it was not surprising that statistical comparison of the results of microbial culture in patients with and without nasal polyposis did not reveal any significant differences, except in the antibiotic-naïve subgroup as described above.

In the local community, amoxicillin with clavulanate, cefuroxime and cephalexin are often prescribed empirically for the treatment of upper respiratory tract infection. Table 3 shows the pattern of antibiotic sensitivities to these antibiotics from the bacterial isolates in our study.

Table 3. Antibiotic sensitivity and resistance patterns of the isolated bacteria (n = 125[1]).

Antibiotic	Sensitive	Resistant	Uncertain	Remarks
Amoxycillin	58 (46%)	67 (54%)	–	Resistant bacteria: *S. aureus* n = 26 *P. aeruginosa* n = 10
Amoxycillin with clavulanate	98 (78%)	27 (22%)	–	Resistant bacteria: *P. aeruginosa* n = 10 *Enterobacter* sp n = 4
Cefuroxime/ Cephalexin	87 (70%)	29 (22%)	9 (7%)[2]	*MRSA* n = 4
Erythromycin[3]	69 (55%)	56 (45%)	–	Sensitive bacteria: *H. influenzae* *Moraxella catarrhalis* *S. aureus*

Notes:

1. The number of isolates included in this analysis excluded 23 isolates of normal flora and 8 isolates of fungi.
2. Anaerobic bacteria were not routinely tested for sensitivity to cefuroxime and cephalexin; hence their susceptibility to these agents was classified as uncertain.
3. Erythromycin was not an antibiotic of choice, but was used for patients with a history of hypersensitivity to penicillins.

Table 4. Microbial spectrum in FESS patients.

Organism	Number of cases
Gram Positive Bacteria	
Staphylococcus aureus (MRSA)	9 (2)
Coagulase-negative Staphylococcus	2
Streptococcus milleri	1
Gram Negative Bacteria	
Haemophilus influenzae	4
Pseudomonas aeruginosa	4
Enterobacter sp	1
Moraxella catarrhalis	1
Anaerobes	1
Fungi	2
Normal Flora	2

Overall, CRS resolved in 127 patients (74%) with antibiotics alone and 131 patients (76%) were able to avoid formal sinus surgery (Figure 1). The organisms isolated from patients who eventually had FESS are listed in Table 4. There is a predominance of *Staphylococcus aureus*, *Haemophilus influenzae* and *Pseudomonas aeruginosa* in this group of patients.

DISCUSSION

The microbiology of chronic rhinosinusitis (CRS) has been reported in numerous studies using different sampling methods and from different subsites within the paranasal sinus complex. When compared with acute rhinosinusitis (ARS), a broader spectrum of microbial culture has been a consistent finding in CRS. However, in the literature, the results have been variable. While *Staphylococcus aureus* is the predominant organism [8] in CRS, other microbial species have been implicated as well. In particular, *Staphylococcus aureus* [9], anaerobes [9] and gram-negative bacteria [10] are found more frequently in CRS than in ARS [8], implying that these may be important aetiological factors in the persistence of sinus inflammation in CRS patients.

There has been much variability in reports on the incidence and role of anaerobic bacteria in CRS. The rate of recovery of anaerobes in our study patients was low, which is in agreement with other studies [11,12]. One possible reason could be that anaerobes are fastidious organisms and even processes considered standard in our institution during the period of study may not have been sufficiently sensitive to detect anaerobic infection [13]. Indeed, improvements in the acquisition and transport and processing of specimens for anaerobic culture are reported to result in higher rate of anaerobic recovery [14]. Another hypothesis for the low percentage of anaerobes in our series is that the aspiration technique may in itself result in conditions which are not favourable for the recovery of anaerobes by inadvertent exposure of the specimen to an oxygen-rich environment [15].

Recent research on the inflammatory mechanisms and the role of bacteria in CRS may provide an improved understanding of the disease. The role of staphylococcal exotoxins as superantigens with the ability to incite an exaggerated inflammatory reaction [16] provides a possible explanation for the predominance of *Staphylococcus aureus* in CRS, especially in CRS patients with nasal polyposis [17,18]. Likewise, the ability of certain bacterial species to organize biofilms, in particular *Staphylococcus aureus* and *Haemophilus influenzae* [19], may contribute towards the high incidence of both bacteria in CRS cultures.

Although the microbiology identified by sinus culture may not necessarily reflect the underlying aetiology of this multifactorial disease, the usefulness of antibiotic-based medical treatment of CRS is supported by its impact on the management of CRS patients in our cohort. Firstly, the results of bacterial culture influenced a change in antibiotic choice in a significant group of our patients (n = 38, 22%). In those who had persistent CRS after the initial course of antibiotics (n = 48), almost one-fifth (n = 9, 19%) were successfully treated with further courses of culture-directed antibiotics. Only a minority of patients in our study required sinus surgery. Overall, clinical and endoscopic resolution was achieved in 131 (76%) patients.

Knowledge of the microbiology of CRS and antibiotic resistance patterns is important both at the community and individual level. In patients who have already been treated with antibiotics, the rate of single pathogen cultures is higher compared to those who have not, with fewer negative and multiple-pathogen cultures. Another encouraging observation is that antibiotics seem to have the greatest impact on *Staphylococcus aureus* and *Haemophilus influenzae* which were the two most common species isolated from culture. These observations suggest that appropriate antibiotic treatment helps to eradicate bacteria in chronically-infected sinuses and may justify the use of empirical antibiotics by physicians in the primary healthcare setting.

The limited empirical use of quinolones amongst the study patients during the period of the study may be due a prevailing view that gram negative bacteria were not the predominant pathogens in CRS. In prescribing empirical therapy, many clinicians preferred to prescribe a single broad-spectrum antibiotic while awaiting the results of microbial culture and sensitivity testing. In up to half of these patients, only one pathogen is identified on culture facilitating subsequent culture-directed antibiotic therapy.

As elegant as this approach may appear, it is a fact that a percentage of cultures of obviously purulent sinus discharge will not grow any microbes. Furthermore, there are patients in whom CRS persists despite multiple-courses of culture-directed antibiotics. The apparent of failure of antibiotic therapy in these cases challenges a simplistic explanation for the mechanism by which bacteria cause inflammation. The finding of

intraepithelial *Staphylococcus aureus* and biofilm-producing bacteria may provide a possible method by which bacteria can evade normal host defense mechanisms and antibiotic treatment. In fact, both appear to be risk factors for recurrent CRS after sinus surgery [20,21].

CONCLUSION

This study describes the microbiology of CRS in patients at the time of their first presentation and the subsequent course of disease in response to medical treatment including culture-directed antibiotics. There was a predominance of *Staphyloccus aureus* and *Haemophilus influenza*, with the majority of species isolated sensitive to the empirical antibiotics which are most commonly used in our local practice. Satisfactory clinical resolution and avoidance of sinus surgery is achievable in three-quarters of patients. Persistent CRS refractory to antibiotic treatment in some patients suggest that more complex pathogen-host interactions exist in CRS need to be confirmed by further studies.

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