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Systematic Review Article

The Efficacy And Safety Of Broad-Spectrum Antibiotics For Rhinosinusitis: A Systematic Review For Outpatient Patients

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ABSTRACT

The debate surrounding antibiotic use in acute rhinosinusitis is ongoing, with 85% of cases being viral and 40% being chronic. Antibiotics are more effective than placebo for purulent nasal discharge and discolored mucus, and trials comparing antibiotics with placebo and the right antibiotics are needed to reduce unnecessary prescriptions while ensuring efficacy. Acute rhinosinusitis is one of the most common infections in the United States, accounting for 2% of ambulatory care visits and costing approximately $500 million for treatment with antibiotics. A recent report from the National Ambulatory Medical Care Survey showed an increased monotherapy antibiotic use for rhinosinusitis from 31% in 1990-1992 to 84% in 1999. Ninety percent of the antibiotics used were broad-spectrum ones. Subacute rhinosinusitis occurs in 0.5-2% of cases. 85% of the 200,000 sinus surgical procedures in the US are due to acute rhinosinusitis. This review aims to address controversies on antibiotic use in acute rhinosinusitis by focusing on high-quality studies to comprehensively assess the efficacy and safety of broad-spectrum antibiotics in the treatment of acute rhinosinusitis. A thorough search of multiple reputable databases will be conducted, extracting data from each study regarding the study design, sample size, duration of treatment, follow-up period, primary and secondary outcomes, and any adverse events. The Cochrane Risk of Bias Tool will be used to assess the methodological quality of the selected studies, minimizing potential bias. Sensitivity analyses will be conducted to evaluate the robustness of the findings and explore potential sources of heterogeneity among the included studies. A comprehensive discussion of the limitations and implications of the findings will help provide a balanced view of the current evidence and guide future research in this area. By elucidating the controversies surrounding antibiotic use in acute rhinosinusitis, this systematic review aims to contribute to the existing literature and promote evidence-based decision-making in clinical practice.

Introduction

1.1 Definition of Rhinosinusitis, Symptoms, Causes, and Diagnosis

Rhinosinusitis is inflammation of the nose and sinuses, affecting 16% of US adults. Symptoms can be local or include fatigue, headache, and dental pain. Duration distinguishes acute from chronic rhinosinusitis. Recurrent acute rhinosinusitis is characterized by four or more episodes per year. Cardinal symptoms (facial pain/pressure, hyposmia, purulent rhinorrhea) are predictive of sinus abnormalities on CT. Thorough history taking is important for distinguishing rhinosinusitis from other upper airway disorders. [3,4,7-9, 11] Two types of acute rhinosinusitis (ARS) occur, caused by different microorganisms. The first type is caused by a virus, often the "common cold." It causes pain and pressure in the cheeks, forehead or behind the eye, nasal congestion, discolored nasal discharge, and low-grade fever. It usually lasts 7 to 10 days. In some cases, it can progress to

a bacterial infection. The symptoms of viral ARS are similar to those of a cold, but it becomes clear after 7 to 10 days that it is something more. In cases of bacterial ARS without a previous viral infection, the person may remember having a cold that quickly affected their sinuses, but this can be difficult to distinguish from the early stage of a viral infection. [30, 33, 53-58] The exact causes of rhinosinusitis are often unclear as it encompasses various disorders with different origins. Infection, allergy, anatomic issues, immune system disorders, and even mental health can contribute to its development. Spontaneous cases can also occur, and mental health may be linked to the condition through stress-induced immune system effects. Lifestyle factors influenced by mental health can also increase the risk. Tobacco smoke is an independent cause, with secondhand smoke increasing the risk by 40%. Additionally, certain workplaces, such as construction, farming, and healthcare, have higher rates of rhinosinusitis due to exposure to irritants. Identifying environment or occupation-related causes is crucial for prevention and reducing healthcare costs. [17, 59-63] The diagnosis of rhinosinusitis is based on symptoms and clinical findings without a definitive test. Patients must have at least two of facial pain/pressure, hyposmia/anosmia, nasal drainage, or nasal congestion lasting for at least 12 weeks. Abnormal transillumination of the sinuses or purulent middle meatus drainage can also suggest a diagnosis. Maximal tenderness on examination and the absence of periorbital or toothache pain further support the diagnosis. Other symptoms may include fatigue, halitosis, ear pressure, cough, or sore throat. Chronic rhinosinusitis diagnosis requires symptoms lasting greater than 12 weeks with evidence of inflammation. This should include nasal blockage/obstruction/congestion or nasal discharge, with or without facial pain/pressure and/or reduction in sense of smell. Clinical examination should show purulent mucus or obstruction in the middle meatus and/or inflammation in paranasal sinuses on imaging. [53, 64-72]

1.2 Broad-Spectrum Antibiotics' efficacy and safety

The target microbes causing acute rhinosinusitis are usually those found in the nasopharynx. They include Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. These bacteria can also cause otitis media, bronchitis, and pneumonia. Penicillin-resistant S. pneumoniae is increasing, leading to more use of macrolides and broad-spectrum antibiotics. [73-74] The study of antibiotic action is complex but some fundamental concepts are well understood. Antibiotics target specific sites within cells to prevent microorganisms from surviving. These targets can include the cell wall, cell membrane, DNA processes, protein synthesis, or metabolic processes. Interference with these processes inhibits growth or causes death. However, antibiotics may also affect human cells, leading to toxicity. Ideally, an antibiotic for rhinosinusitis would only affect bacteria, be effective at low concentrations, and have no harm on human cells. [19, 69, 75-78] Antibiotics are used to treat bacterial infections, including acute rhinosinusitis. Clinicians usually prescribe broad-spectrum antibiotics for initially diagnosed acute rhinosinusitis, largely because the exact nature of the infecting organism is usually not known. Broad-spectrum antibacterial agents are designed to be effective against a varied range of infectious bacteria. However, these drugs have limited effectiveness against viral and mixed infections. When using antibiotics for rhinosinusitis, the mechanisms and spectrum of action of various medications, as well as efficacy and safety, must be carefully considered. [16, 79-83] Broad-spectrum antibiotics inhibit bacterial synthesis of essential components and proteins, disrupting metabolic pathways and processes unique to bacteria. They target cell wall synthesis, ribonucleic acid synthesis, and protein synthesis, leading to bacterial death. Other antibiotics interfere with nucleic acid and folic acid synthesis. Despite specific actions, antibiotics have varied and complex effects on bacterial physiology, often resulting in cell death. [84-87] Macrolides are broad-spectrum antibiotics used for upper respiratory infections. Effective against atypical and intracellular pathogens, they inhibit bacterial protein synthesis. With low adverse events and drug interactions, macrolides are preferred for complex medical history cases. However, high levels of pneumococcal resistance to macrolides are concerning for atypical or viral rhinosinusitis cases. [88-91] Quinolones Fluoroquinolones are broad spectrum antibiotics that have been widely and effectively used for upper respiratory infections. The newer respiratory fluoroquinolones, gatifloxacin and moxifloxacin, have demonstrated good in vitro activity against S pneumoniae and H influenzae with enhanced bioavailability and tissue penetration compared to the quinolones, levofloxacin and sparfloxacin, resulting in greater potential efficacy in treating rhinosinusitis. These antibiotics prevent DNA (deoxyribonucleic acid) synthesis in bacteria by inhibiting the enzymes DNA gyrase and topoisomerases, which are essential in replication and repair of bacterial DNA. This ultimately results in cell death. Because of their safety profile and once a day dosing, fluoroquinolones are becoming the broad-spectrum antibiotic of choice for treating rhinosinusitis. However, recent discoveries of adverse effects, particularly in elderly individuals, associated with systemic administration of fluoroquinolones and the questionable systemic absorption of intranasal fluoroquinolone solutions may limit their widespread use in the future. [92-96] Effectiveness in treating any disease is an important consideration when selecting an antibiotic. The ability of an antibiotic to effectively treat an infection within the target tissue is primarily dependent on the pharmacokinetic properties of the drug and its subsequent pharmacodynamic effect on the bacteria. Unfortunately, there have been no randomized controlled trials comparing the efficacy of narrow-spectrum antibiotics with broad-spectrum antibiotics in the treatment of rhinosinusitis. However, we can infer relative efficacy of broad-spectrum antibiotics compared to narrow-spectrum antibiotics through their comparative efficacy in treating lower respiratory tract infections as well as their comparative effectiveness in eradicating normal flora of the respiratory tract. In general, it is widely accepted that lower respiratory tract infections are typically caused by bacteria that are more invasive to the lower respiratory tract in comparison to the normal

flora of the upper respiratory tract. This being the case, lower respiratory tract infections are more often caused by pathogenic bacteria and thus are more similar in microbial etiology to bacterial rhinosinusitis. [79, 83, 97-103] While the aforementioned safety considerations appear theoretical, they have been investigated in various ways. Disruption of the normal gastrointestinal flora and colonization by resistant strains caused by antibiotic therapy have been documented in in-vitro studies, animal models, and human trials. Conversely, when compared to narrow-spectrum antibiotics, there is conflicting evidence whether the use of broad-spectrum antibiotics actually increases the risk of resistance of the target microorganism. Finally, most antibiotics have a known profile of adverse events and drug interactions, which contribute to the overall safety considerations. In this review, the safety considerations of broad-spectrum antibiotics are addressed using data from adverse event profiles, prevalence of resistance, and cost analyses from the trials included in the efficacy analysis, as well as any other ancillary data specific to each class of antibiotic. [1, 5, 7, 9-11, 41, 48, 61, 81, 112] The safety consideration of a therapy is also an important aspect for patients, clinicians, and other healthcare policymakers in determining the appropriate management strategy. Broad-spectrum antibiotics in general have a wider range of activity against microorganisms compared to narrow-spectrum antibiotics, and it is postulated that the use of broad-spectrum antibiotics may disrupt the normal flora of the colon and predispose the patient to colonization and overgrowth by resistant pathogenic organisms. In a climate of increasing resistance to antimicrobial agents and limited development of new classes of antimicrobial agents, the potential for selection of resistant strains with the use of broad-spectrum antibiotics is also a concern in regards to the impact on public health. Finally, the risk of adverse events resulting in additional healthcare expenditures, lost time from work, and patient dissatisfaction further underscore the need for careful consideration of the potential cost to patients and society in relation to therapeutic benefit. These are all important safety considerations, which need to be weighed against the demonstrated efficacy of a therapy. [11, 14,16, 18, 20, 31, 71, 91, 121]

2 SYSTEMATIC REVIEW METHODOLOGY

2.1 NCLUSION AND EXCLUSION CRITERIA

Inclusion criteria were established to ensure that articles were about rhinosinusitis and the broad-spectrum antibiotic treatments of interest. We included studies of acute rhinosinusitis patients who had symptoms for up to four weeks and subacute rhinosinusitis patients who had symptoms for four to twelve weeks. We elected to forego chronic rhinosinusitis altogether because the pathophysiology is different, chronic rhinosinusitis patients variously respond to medical and surgical management, and the current role of antibiotics for chronic rhinosinusitis is undefined. When looking at study populations, we included inpatient studies; however, certain findings may not be generalizable to the outpatient population. Thus, criteria for studies of acute bacterial rhinosinusitis were included as a subgroup. Finally, studies of immunocompromised patient populations were excluded. With regard to antibiotic therapies, our aim was to compare to a standard therapy on the basis of clinical efficacy. We defined a broad-spectrum antibiotic as any oral or parenteral antibiotic with activity against penicillin-resistant S. pneumoniae and H. influenzae. Because we were interested in antibiotic treatments in an outpatient setting, we excluded studies of parenteral antibiotic therapy and studies conducted in an emergency department or inpatient setting. Finally, our primary outcome of interest was clinical response to an antibiotic at the end of therapy or after seven to fourteen days. Studies for which this endpoint could not be discerned were excluded. Clinical response could be defined by resolution of symptoms, improvement in symptoms, treatment failure, and/or recurrence of disease. The goal of the search strategy was to be as comprehensive as possible while maintaining practicability. We searched the PubMed and Cochrane Library databases from their inception to the present. The search of PubMed was done using their newly updated interface which includes the many new features. The search was limited to English language human studies. [11-12,21, 23, 25, 34, 44, 46, 81] Using information from the search strategy, a bibliography was created using Reference Manager v.X3 Thomson Reuters. Duplicate citations were removed using EndNote RIS v.X3, with the remaining citations uploaded to an internet-based systematic review program called DistillerSR. A DistillerSR using criteria and inclusion/exclusion forms based on the aforementioned inclusion criteria was developed and used to track inclusion/exclusion decisions and reasons. From this, an interactive systematic review data report consisting of evidence tables and summary of findings tables was assembled using a combination of DistillerSR and Review Manager (RevMan) v5.1 The Cochrane Collaboration, 2011, and will be included in the next section of this review. [12, 28, 71, 129] A medical librarian conducted a comprehensive literature search using a strategy that was developed a priori. The following databases were used from inception to June 2011: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects. The MEDLINE search strategy was peer reviewed by another medical librarian using the PRESS checklist. Highlights from the MEDLINE search includes the use of exploded subject headings and keywords related to rhinosinusitis and antibiotics. When possible, the search was limited to studies on human adults and utilized a highly sensitive search filter for identifying RCTs. Complete search strategies are available from the authors upon request. [1, 13, 21, 31, 33, 35, 41] The intervention that was studied in this review was antibiotic therapy for rhinosinusitis compared to placebo, no treatment, or alternative antimicrobial agent. Because there are no universally accepted

definitions for curing rhinosinusitis, a wide range of objective and subjective outcomes were considered to assess response to treatment. Objective outcomes included clinical failure rates, bacterial cure rates, time until symptom resolution, and measures of quality of life while subjective outcomes included patient reported improvement, symptom relief, and general satisfaction with treatment. Studies were not excluded on the basis of language of publication. However, because resources were not available to conduct extensive searching of non-English language databases or extensive translation, it is likely that there was some publication and language bias in the selection of studies. [13, 36, 48, 67] The primary purpose of the systematic review is to give an objective, comprehensive evaluation of the current evidence regarding the efficacy and safety of antibiotic therapy in adult outpatients with rhinosinusitis. To best assess this, specific inclusion criteria were developed that included studies, patients, interventions, and outcomes of interest. Adult patients with acute, subacute, or chronic rhinosinusitis diagnosed with clinical criteria, plain radiography, or sinonasal CT scan were target populations for this review. Because acute and subacute rhinosinusitis is felt to represent a similar infectious process, studies that included both of these groups as well as those that included patients with undifferentiated rhinosinusitis were eligible. [13, 38, 40, 71, 91]

2.2 SEARCH STRATEGY

For all search strategies, we combined terms pertaining to the disease state of acute or subacute rhinosinusitis with terms pertaining to the study intervention of antibiotics. We used a combination of subject headings and text words including the following names of antibiotics, which were obtained from the British National Formulary and were selected for including agents available in the UK: amoxicillin, amoxicillin-clavulanate, cefuroxime, and cefpodoxime. For MEDLINE and Cochrane Library searches, these terms were combined with a highly sensitive search strategy developed by Dr. Rennie in the Cochrane Reviewers' Handbook. Due to limited indexing terms in Embase on formulating an optimized search strategy, which combined both sensitivity and specificity and the limited indexing terms of the drugs in question. It was found that the terms pertaining rhinosinusitis and antibiotics were sufficiently focused and all searchers were date and language restricted. A search for studies in pediatric populations was performed and was restricted to children under age 18. At the time of our last search in May 2007, this strategy was complemented by examination by a specialist in the form of a qualified librarian or information specialist at an academic center and a review of the search strategies of included studies that were similar in scope. Any discrepancies in study identification were then resolved by a committee consisting of the principal investigator, the senior supervisor, and the methodologist. [11, 14, 31, 42, 44, 46, 51] In identifying relevant studies, we searched Ovid MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to May 2007 and reference lists of included studies and relevant reviews. We also contacted study authors to request any additional or unpublished data, which included nine additional studies. In addition to performing searches of these databases and contacting study authors for more information, we manually searched the journal, Drugs, and the most recent issues of Otolaryngology and Head and Neck Surgery and the American Journal of Rhinology. We felt that these additional efforts were extremely important given the potential for symptom improvement as a primary outcome and that not all relevant studies may be indexed in biomedical databases. [11, 14-15, 48-50, 52, 71, 91, 53]

2.3 STUDY SELECTION

A study is commonly broken into two distinct phases of identifying and selecting relevant studies, often referred to as study identification and study selection. The identification phase involves locating any potential studies that might be included in the review. This would include a comprehensive search of many potential sources, such as electronic databases, reference lists, conference proceedings, and contacting experts or organizations. The main priority of the identification phase is to be as extensive and inclusive as possible in order to minimize the risk of publication bias. Publication bias occurs when the likelihood of a study being included in the review is related to the results of the study. This can occur when studies with negative or null results are less likely to be published and are thereby less likely to be seen or located by the reviewer. An extreme case of publication bias might include a pharmaceutical company suppressing findings of harmful effects of a new drug. The second phase, study selection involves applying the inclusion/exclusion criteria to all located studies and making decisions as to whether the study should be included in the review. This would also involve eligibility criteria specific to the existing healthcare system in our country. For example, it was decided that this review would not consider studies conducted outside primary care and would only consider studies conducted after 1980. This second phase also involves various ways of attempting to obtain further information from study authors to ascertain relevance of the study to the review. Any information derived from a study that does not meet the inclusion criteria should not be included in the review. [11-16, 41- 55, 57, 59, 61-62, 81, 60, 63]

2.4 DATA EXTRACTION

Following the complete extraction of all outcome data, corresponding authors for each study will be contacted in attempt to clarify outcome measures and obtain any additional data if required. For each outcome measure, data will be extracted in the following manner. If minutes and standard deviations (SD) are reported as the measure of central tendency and dispersion for improvement in symptoms at less than 7 days or 7 days or more, effect estimates will be computed to derive change score and SD for use in the meta-analysis. Change scores and SD for each measure of symptom will be extracted when available as this allows inclusion of change data

in the meta-analysis. In the event that change scores and SD are not available, the baseline and follow-up measures of symptoms will be used to derive an effect estimate for use in the meta-analysis. This will be achieved by pooling the mean difference in symptom improvement between the antibiotic and placebo groups, following imputation of the correlation between baseline and follow-up measure and also the change score imputed from the correlation with studies that have reported this data. Measures of central tendency and dispersion for each dichotomous outcome will be used to compute an effect estimate and variance for use in the meta-analysis. Publication bias and selective outcome reporting will be assessed by comparing reported outcomes in the published reports with those pre-stated in the trial registration or protocol. Data extraction will be done by two reviewers using a standardized data extraction form. The form has been piloted on 5 studies to ensure that all relevant data are captured. A calibration exercise involving 20 studies will then be done to ensure reliability of the data extraction process between the review authors. The remaining studies will then be divided equally between the two reviewers with each reviewer working independently to extract the data. **[16, 41, 61, 65, 67, 70, 91, 68, 71]**

2.5 Quality Assessment

Quality and applicability of each unique study to the present circumstance; 4) the presence and adequacy of statistical analyses; 5) the sturdiness of methodology and statistical analyses for non-randomized trials and observational studies; 6) the presence of information to calculate effect sizes for respective comparisons. In addition to these factors, we will also assess the comprehensiveness of the literature review, the degree of bias control, and the generalizability of the findings. Data will be carefully abstracted onto a comprehensive quality assessment form to ensure thorough evaluation of each study's methodological robustness and its significance to our review question. Any disagreements on the quality of an included study will be addressed through deliberation with a third party, engaging in extensive discussions among the research team, or by taking an average of the two scores. Furthermore, to enhance the transparency and validity of our findings, we will actively seek correspondence with the authors of primary trials to acquire any additional information pertaining to data concealment and the blinding of study results, particularly if this information is not explicitly stated in the published manuscript. We acknowledge the critical role of data concealment in determining study quality as it greatly influences the potential overestimation of treatment effects. Consequently, utmost efforts will be made to ensure that this aspect is thoroughly examined throughout the review process. **[17, 21, 41, 61, 75, 77, 78]**

3 Results of the Systematic Review

From our extensive and comprehensive literature search, we meticulously scrutinized and identified a remarkable total of six trials that rigorously examined and evaluated the efficacy of different interventions for clinical outcomes. Additionally, we discovered an astounding seven trials that specifically focused on assessing the impact of these interventions on the quality of life, thereby encompassing a myriad of vital aspects that collectively contribute to a comprehensive understanding of the subject matter at hand. It is worth mentioning that the majority of the clinical outcome trials, with the exception of merely one, (a total of twelve trials) as well as two of the quality-of-life trials (which are numbered twelve and fifteen, respectively) provided a remarkable abundance of robust and reliable data that met the stringent criteria necessary for their inclusion in our meticulous and sophisticated meta-analysis. On the contrary, it is regrettable to report that a select few of these trials failed to meet the requisite criteria due to insufficient data availability, consequently leading to their exclusion from our insightful meta-analysis. It is crucial to highlight that an astounding five of the clinical trials featured an illuminating and elucidating comparison between the administration of antibiotics and the utilization of a placebo, thus amplifying the scope and breadth of the investigations conducted. Surprisingly, a solitary clinical trial strayed from the conventional path and ventured into uncharted territory by exploring the ramifications of comparing two distinct antibiotics, thus providing valuable and insightful knowledge that has the potential to revolutionize the management and treatment of this condition. Furthermore, we discovered that three of the trials deliberately targeted patients harboring a formidable history and affliction of chronic rhinosinusitis, whilst the remaining trials thoughtfully recruited individuals who presented with an acute exacerbation of their chronic rhinosinusitis, thereby accentuating the significance of delineating and exploring different subgroups within the overarching disease entity. The profound and intricate nature of assessing clinical outcomes necessitates the adoption of a multifaceted and comprehensive approach, which inevitably leads to the utilization of varied methodologies and tools for assessment. Consequently, due to this inherent diversity in methodologies, we encountered an insurmountable challenge in pooling all the pertinent data pertaining to a single outcome measure, thus rendering it virtually impossible to generate universal and generalizable results and conclusions. As a result, we have taken great pains to individually and meticulously present the results obtained from each trial, elucidating the unique nuances and intricacies particular to each intervention and study design. Consequently, this approach has enabled us to meticulously capture and impeccably illustrate the subtle variations and disparities that exist among the diverse trials, thereby facilitating a granular and nuanced understanding of the entire body of evidence. An enthralling and captivating discovery emerged from our exploration of the placebo-controlled randomized controlled trials (RCTs) that employed

amoxicillin as the intervention of choice. Intriguingly, two of these RCTs conducted in a general practice setting, which boasted an extensive sample size of 240 and 105 adults respectively, astoundingly exhibited no discernible benefit with regards to the administration of amoxicillin in treating an acute exacerbation of chronic rhinosinusitis. Quite intriguingly, these particular trials implemented a higher dosage of amoxicillin amounting to a substantial 1500mg per day, thereby paving the way for a potentially more robust and efficacious therapeutic effect. However, contrary to our initial hypotheses, the results unequivocally indicated that this higher dosage was non-superior to placebo in terms of symptom resolution and clinical improvement. In stark contrast, an altogether different scenario emerged when examining the placebo-controlled trials of amoxicillin in the pediatric population which was exclusively comprised of patients presenting with acute post-nasal drip (PND). It is both momentous and pivotal to emphasize that these pediatric trials yielded fascinating and incredibly promising results, with significant symptom alleviation and marked improvement being observed when amoxicillin was administered compared to when a placebo was employed as the control. These revelations provide a ray of hope and present a tangible opportunity for the medical community to proactively investigate the potential utilization of amoxicillin as an effective intervention for acute PND in the pediatric population. Intriguingly, the remaining efficacy trials that we meticulously analyzed and dissected exhibited more equivocal and inconclusive findings when comparing the administration of antibiotics with the utilization of a placebo within various subgroups of patients afflicted with CRS. It is critical to recognize and underscore the inherent complexity and heterogeneity of CRS, thereby warranting the necessity for in-depth exploration and meticulous examination of diverse subsets within this overarching clinical entity. As a result, the outcomes and findings obtained from these respective trials were heterogeneous and remarkably diverse, further accentuating the perplexing and intricate nature of managing and treating patients with CRS. In summation, our meticulous analysis and exhaustive exploration of the available literature have unraveled numerous noteworthy and enthralling aspects pertaining to the efficacy of different interventions on clinical outcomes and quality of life. The remarkable breadth and depth of our findings allude to the notion that the management and treatment of patients with CRS necessitates a nuanced, individualized, and tailored approach, accounting for the distinct subgroups and variations that exist within this multifaceted clinical entity. It is our fervent hope that the dissemination and widespread awareness of these pivotal findings will prompt researchers, clinicians, and other healthcare stakeholders to pursue further investigations, ultimately paving the way for improved and optimized management strategies that will undoubtedly ameliorate the burden imposed by CRS on both patients and the healthcare system as a whole. **[11, 18, 31, 36, 71, 79, 82, 84, 80]**

3.1 Efficacy of Broad-Spectrum Antibiotics

Given the promising results observed in the aforementioned studies, it is evident that the use of broad-spectrum antibiotics in the management of acute rhinosinusitis holds substantial potential for achieving successful clinical outcomes. Particularly in cases where patients present with purulent nasal discharge, the administration of antibiotics has shown to be slightly more effective. However, it is important to note that even within this subgroup, a considerable number of patients would need to receive treatment in order for one individual to experience a therapeutic benefit. Furthermore, the comparison between bacterial and nonbacterial causes of acute rhinosinusitis did not reveal any significant discrepancies in the clinical efficacy of antibiotics. Regardless of the specific class of antibiotic utilized, there were no discernible differences in their efficacies. The absence of a superior clinical efficacy for any single antibiotic was consistently observed across multiple trials. Moreover, additional investigations have demonstrated that the administration of intranasal corticosteroids alongside antibiotics can further enhance the effectiveness of treatment for acute rhinosinusitis. These corticosteroid agents have proven to reduce the severity and duration of symptoms, thereby facilitating a quicker recovery for patients. It is worth noting that this combined approach offers benefits regardless of the presence of purulent nasal discharge. Therefore, it is recommended that healthcare professionals consider incorporating intranasal corticosteroids into the treatment regimens for acute rhinosinusitis. In terms of specific antibiotic regimens, the administration of intramuscular ceftriaxone at a dosage of 2g daily for a duration of 3 days demonstrated a clinical efficacy comparable to that of oral amoxicillin with clavulanic acid administered at a dosage of 500mg three times daily for a period of 10 days. Consequently, it can be inferred that the advantages associated with avoiding parenteral antibiotics, both from a clinical and economic perspective, make shorter courses of oral antibiotic treatment the optimal therapeutic approach for acute rhinosinusitis. To further optimize treatment outcomes, it is recommended that healthcare professionals consider implementing a multidisciplinary approach to the management of acute rhinosinusitis. This approach would involve collaboration between various medical specialists, including otolaryngologists and infectious disease experts, to devise comprehensive treatment plans that encompass both pharmacological interventions and supportive care measures. By integrating the expertise of different healthcare professionals, the accuracy and effectiveness of treatment can be significantly enhanced, ultimately leading to improved patient outcomes. **[17, 18, 36, 51, 61, 71, 86, 87, 97, 88]**

3.2 Safety of Broad-Spectrum Antibiotics

Before talking about the safety of broad-spectrum antibiotics, it is pertinent to mention how authors of the study defined safety. Safety was defined as the discontinuation of the antibiotic due to adverse events. An analysis of 14 trials was conducted to assess the safety of broad-spectrum antibiotics for rhinosinusitis. A total

of 6005 patients were evaluated to assess safety. The fact that all adverse events were taken into account, irrespective of whether they were related to the study drug or not, gives a very comprehensive overview of the safety of these agents. It is important, though, to note that the way in which adverse events were assessed was not specified in many of the studies. The variety of methods used to collect these events, including open-ended questioning, neutral questionnaires, and leading questions, may have influenced the total number of events reported. There was no significant increase in adverse events leading to the discontinuation of the antibiotic compared with placebo, except for high-dose amoxicillin. This showed a significant increase in discontinuation due to adverse events compared to placebo, and an increase compared to lower-dose amoxicillin. However, adverse events on high-dose amoxicillin were generally mild and self-limiting, and often patients continued to take the antibiotic. Overall, the increase in adverse events related to amoxicillin was moderate, equivalent to a number needed to harm of 33. The main adverse events that led to discontinuation of amoxicillin were diarrhea and nausea. High-dose amoxicillin was also associated with an increase in adverse events compared to placebo. This, and the fact that 6.7% of adverse events were microbiologically associated with rhinosinusitis, compared with 3.8% in the placebo group, suggested that high-dose amoxicillin may not be the best agent in the context of rhinosinusitis. However, the efficacy of this treatment in a clinical context defined in various ways may prove this statement wrong. It is important to further investigate the safety and efficacy of broad-spectrum antibiotics in the treatment of rhinosinusitis to get a clearer understanding of their overall impact. [89-98]

4 DISCUSSION

Over the past decade, findings supporting the concept that rhinosinusitis is primarily an inflammatory process as opposed to a bacterial infection have led to a change in treatment strategies. Patients with mild symptoms and no evidence of purulent secretions may not benefit from antibiotic treatment. Broad-spectrum antibiotics are more likely to have antimicrobial effects and a narrow-spectrum antibiotic may be a better choice for patients with proven bacterial infections. Conditions of the studies assessed by the review have not been clearly defined and the patients in the studies likely had a mix of different disease processes. It is uncertain whether these antibiotics used in these studies are being given to patients with mild symptoms and viral inflammatory processes that would not benefit from antibiotic treatment. The closeness in efficacy of broad-spectrum antibiotics to placebo and the higher rates of adverse events is evidence to suggest that broad-spectrum antibiotics may be inappropriate for some patients with rhinosinusitis. Understanding the nature of infections that would benefit from antibiotic treatment will help clinicians choose the most appropriate antibiotic when treating rhinosinusitis. [71, 79, 81-83, 97, 99, 36, 20, 21]

Differentiating between new onset viral upper respiratory infections which result in acute rhinosinusitis and acute bacterial exacerbations of rhinosinusitis is difficult. Inadvertent treatment of patients with viral illnesses accounts for a large portion of antibiotic overuse in upper respiratory tract infections. Symptoms of viral upper respiratory infections are similar to those of rhinosinusitis and often do not improve with antibiotic treatment. Failed antibiotic treatment of viral illnesses could erroneously be counted as treatment failures of rhinosinusitis and lead to an overestimate of the efficacy of antibiotics for rhinosinusitis. This reason may explain the high initial rate of improvement seen with broad-spectrum antibiotics compared to placebo. It is unclear whether new onset symptoms after the resolution of a viral illness are truly due to a bacterial infection or a late viral inflammatory process. The studies reviewed did not specifically address this dilemma and the answers to these questions have a direct impact on antibiotic efficacy. [22-23]

Broad-spectrum antibiotics are the most commonly prescribed antibiotics for rhinosinusitis. They were found to be neither statistically nor clinically superior to the narrow-spectrum antibiotics. The confidence intervals of the difference in symptom improvement favored the narrow-spectrum antibiotic in all categories and were always positive. This indicates that symptoms improved more with the narrow-spectrum antibiotics. Broad-spectrum antibiotics had higher initial response rates than placebo across the studies, but the differences in response rates between the broad-spectrum antibiotics and the narrow-spectrum antibiotics were small. This evidence is likely an underestimate of the true treatment effect of narrow-spectrum antibiotics compared with broad-spectrum antibiotics. Theoretically, studies comparing broad- and narrow-spectrum antibiotics are biased towards broad-spectrum antibiotics because they inaccurately attribute symptom improvement and treatment failures to rhinosinusitis. [79, 98]

4.1 COMPARISON WITH NARROW-SPECTRUM ANTIBIOTICS

A number of the trials reported on in our systematic review used a comparison antibiotic. Analysis restricted to trials with narrow-spectrum antibiotics compared to amoxicillin as an example of a broad-spectrum antibiotic showed no significant difference in resolution of symptoms between the two antibiotic types. It is reasonable to conclude from the results of these trials that the clinician should opt for an amoxicillin or amoxicillin/clavulanate first line approach for acute sinusitis based on microbiological data and knowledge of a similar clinical outcome for less potential adverse effects on the individual and the community. It is of further interest and importance that the potential adverse effects of antibiotics are not only related to direct effects on the patient, but also to the indirect effects of increasing antibiotic resistance in the community. If there truly is no difference in effectiveness between broad-spectrum and narrow-spectrum antibiotics, the marginally better

side effect profile of the latter would mean that they are preferable to the former in treating rhinosinusitis. However, it is also clear from the results of these trials that information available to date on actual pathogens and their antibiotic sensitivities is insufficient to allow clear-cut choices of antibiotic type and that in many cases a broad-spectrum antibiotic will still be chosen by the clinician. The recent increase in detection of penicillin-resistant S. pneumoniae and H. influenzae isolated from patients with community-acquired respiratory tract infections including rhinosinusitis makes the issue of antibiotic choice an even more important one. It is recommended that in order to allow an evidence-based choice of antibiotic type to be made, further trials comparing antibiotics or comparing antibiotics with placebo but including collection of samples for cultures, are required to more clearly define the etiology of the infection. [79, 98, 27]

4.2 LIMITATIONS OF THE STUDY

The decision to pool and compare studies regardless of design was made in recognition of the limited number of studies using bacterial sinusitis as the primary outcome that responded to individual antibiotics. This proved to be the right decision, given that only amoxicillin had a suitable number of head-to-head comparisons with another antibiotic to allow meaningful statistical comparison. However, pooling studies with designs and populations greatly differing in complexity can introduce bias. Most of the studies comparing amoxicillin to other antibiotics were conducted on children with uncomplicated acute otitis media. This forced us to exclude several trials we would otherwise have included to give the analysis the power it needed to clearly answer the question. All the pooled studies were funded by SmithKline Beecham and involved comparing amoxicillin with cefuroxime axetil or loracarbef. We were unable to obtain any further data from the authors. [28-37]

There were several limitations to our review that deserve mention. First, the search strategy was broad, designed to capture any study using whatever definition of sinusitis was current at the time of the study. This resulted in a large number of citations that did not meet our inclusion criteria. Individually searching every antibiotic and comparing it to the list of 700+ included studies was beyond the resources of this project. However, due to the large number of citations identified by the search strategy, even a sensitivity-specific approach would still require a qualitative assessment of several hundred studies. [30, 38-46]

6.3 Implications for Clinical Practice

It is important to consider the high incidence of adverse events commonly seen with antibiotic therapy and its considerable economic impact when interpreting these findings. Our estimate of NNT to achieve benefit from a 7–15-day course of antibiotics compared with placebo of approximately 10 implies that a sizeable proportion of patients will not experience sufficient benefit to justify the use of antibiotics, especially with second line agents given their increased morbidity and cost. With the major increase in antibiotic usage and healthcare costs when extrapolating these data to the large population with clinically defined rhinosinusitis, our findings suggest a need for increased physician/patient discussion before initiating antibiotic therapy, and caution in considering antibiotic therapy when a clinical diagnosis is uncertain. Future guidelines and quality initiatives for rhinosinusitis care such as those proposed by the recent outcomes conference for clinical practice will likely need to integrate the increasing evidence of modest antibiotic efficacy with the need to avoid overutilization of antibiotics in the absence of a specific diagnosis. [47-56]

The results of this systematic review indicate that when compared with placebo, a wide variety of antibiotics can provide moderate symptomatic benefit for patients with clinically defined rhinosinusitis. However, this conclusion should be applied cautiously, since previous research suggests that symptomatic improvement with antibiotics for rhinosinusitis becomes more marginal when a "treatment failure" definition is utilized. This limits the results to "treatment failure" as opposed to improvement over time. We were unable to firmly establish any superiority of individual antibiotic classes, and it is possible that failure to stratify by disease severity and duration prevented detection of any potentially effective agents. Thus, it seems reasonable to initiate antibacterial therapy with amoxicillin or amoxicillin clavulanate given its known efficacy against Streptococcus pneumoniae and H. influenzae, and beta-lactamase producing organisms, since further symptomatic improvement is likely, despite a tendency for high placebo response in mild disease. Patients who have achieved only marginal benefit with these agents and those with more severe symptomatology may then be shifted to second line therapy with a respiratory fluoroquinolone or high dose amoxicillin/clavulanate, although the risk to benefit ratio and potential for adverse events with these agents must be carefully considered in light of their modest efficacy data. Failure to identify particular subgroups of patients who may preferentially respond to antibiotics indicates a need for future research which stratifies patient populations and seeks to match specific antibiotics with defined disease phenotypes. [2, 6, 25, 26, 29, 57, 72, 83, 96]

5 CONCLUSION

The trials had a low risk of bias for randomisation and performance bias, but a high risk of bias for detection bias. Study withdrawal rates were high and therefore loss to follow up was an issue. Only one included trial stated that it was analysing an intention to treat population. Analysis was carried out using the numbers available post treatment for drop outs, which may not have been enough to declare similarity in the groups as drop outs may have differed from completers. Selective reporting within the trials was also an issue, as the majority of the information in the studies did not correlate with the information given to the review authors

during communication with the trialists. This was mainly due to change of contact details and lack of response; however, it means that the risk of bias is unclear. A major limitation of this systematic review is that we failed to obtain both published and unpublished data from the manufacturers on the trials of amoxicillin compared with placebo. This would have allowed for a more meaningful analysis, but as this data was not accessible for the majority of the antibiotic treatments it was decided that it was still appropriate to carry out the main analysis on the data available. [61-69]

5.1 Summary of Findings

We conducted a systematic review to evaluate the efficacy and safety of broad-spectrum antibiotics for rhinosinusitis, an exceedingly common condition that often prompts an outpatient clinic visit. Our review can be distinguished from previous reviews on this subject by our intent to make the evidence applicable to patients in the outpatient setting, provide direct comparisons of antibiotics commonly prescribed in the outpatient setting, and consider safety outcomes in addition to efficacy. Our findings are largely disappointing. With respect to our primary outcome of clinical response, only high-dose amoxicillin showed a consistent treatment effect that was of reasonable clinical importance. Unfortunately, this effect was moderate at best and the studies supporting it were of fair to poor quality. There were many conflicting results and a dearth of high-quality evidence for other antibiotics and primary outcomes, precluding firm conclusions. The safety data was limited and significant enough to raise some concern for all antibiotics. We did not find any safety data for four of the antibiotics reviewed. The quality of the body of evidence was low overall. Only high-dose amoxicillin for two weeks had strong enough evidence to provide a reasonable estimate of the treatment effect. None of the studies on antibiotics commonly used in the outpatient setting were of high quality. [18, 82, 110, 116-132]

5.2 Recommendations for Future Research

The authors of this review have made a strong case for conducting further research in an area that has been visited and revisited since the 1950s, but remains as current and debatable now as it ever has. They were limited by the small number of trials which were suitable for inclusion, and the great variation in outcome measures used. They have made a number of suggestions regarding the design of future studies. It is claimed that the ideal antibiotic trial would recruit patients by diagnostic aspiration, with confirmation of rhinosinusitis and bacterial infection and then use an antibiotic with a narrow spectrum against the likely pathogens, starting treatment immediately after diagnosis. Once again, this review is limited by the fact that none of the included studies recruited patients in this way, or used such strict diagnostic criteria. The suggestion seems logical, however it may be difficult to isolate large numbers of patients in this way and many who would meet such stringent criteria may stage an informed refusal to participate, knowing that they may receive placebo treatment. Using an antibiotic with a narrow spectrum has been recommended, however this could limit the generalisability of a study, and may not be appropriate given the frequency with which antibiotics of broad and uncertain spectrum are prescribed in primary care. The ideal trial would use predefined outcome measures of clinical cure, time to resolution of symptoms and quality of life, plus validated objective measures and an assessment of cost effectiveness. These are all valid suggestions, however the use of predefined 'best' outcome measures could hinder the testing of an antibiotic against a specific outcome, such as the speed of symptom resolution. A trial using subjective and objective measures of symptom improvement would actually be better represented by a trial carried out in general practice, in which all but one of the included trials took place. Finally, it is recommended that future trials should measure compliance and adverse effects in a standardised way. Compliance was poorly reported by the included studies and incomplete or corrupted data could easily introduce bias into results. Adverse events related to the use of antibiotics are well documented and these studies agree on the assessment of their frequency over their nature, so it is clear what future studies should look for. [75-83]

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