

Efficacy and side effects of antibiotics in the treatment of acute rhinosinusitis: a systematic review*

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Abstract

Background: Acute rhinosinusitis (ARS) is one of the most common diagnoses for which an antibiotic is prescribed. Although the usage of antibiotics in the treatment of mild, moderate or uncomplicated ARS is not recommended by most international guidelines, overuse of antibiotics is still an alarming problem among patients and healthcare practitioners. We thus sought to review the evidence available through a systematic review of the existing literature on antibiotic usage in ARS.

Methodology: A search of the PubMed database was conducted for studies on antibiotic and placebo usage in the treatment of ARS.

Results: A total of 31 random control trials (RCT) reporting the clinical efficacy of treating ARS and side effects of using cefuroxime axetil, telithromycin, amoxicillin/potassium clavulanate, levofloxacin, moxifloxacin and clarithromycin were included in the review. Among them, 9 studies were performed double-blinded with placebo controls. The results showed that while antibiotics are more efficacious than placebos in the treatment of ARS, the risks of potential side effects need to be weighed against the potential benefit that antibiotics give to the patient. This is especially pertinent as usage of the placebo has shown to be almost as efficacious as using the antibiotic therapy, and also much safer.

Conclusion: The usage of antibiotics in ARS is widespread and there seems to be only slight added benefit in the usage of antibiotics over placebo in the treatment of ARS. Hence, larger scale studies should be done in the future to confirm the results of these studies.

Key words: systemic review, acute rhinosinusitis, efficacy, side effect, antibiotics, placebo effect

Introduction

Acute rhinosinusitis (ARS) is defined as a sudden onset of two or more symptoms, including one of either two key symptoms of nasal blockage/obstruction/congestion or nasal discharge, and facial pain/pressure and reduction or loss of smell for less than 12 weeks ⁽¹⁾. In the European Position Paper on Rhinosinusitis and Nasal polyps ⁽²⁾, ARS has been further classified into viral ARS (common cold) and post-viral ARS, where a small percentage of the patients with post-viral ARS will have bacterial ARS ⁽²⁾. It is a common and significant health problem worldwide, with prevalence rates varying from 6-15% depending on the study parameters, and is one of the top reasons for a visit to the

primary care physician ⁽²⁾.

Antibiotic therapy has long been used in the treatment of ARS, and ARS accounted for 9% and 21% of all paediatric and adult antibiotic prescriptions, respectively, in the USA in 2002 ⁽³⁾. According to the National Ambulatory Medical Care Survey (NAMCS) data, rhinosinusitis is the fifth most common diagnosis for which an antibiotic is prescribed ⁽²⁾. On the other hand, the global threat posed by emerging resistant microorganisms has become an international health issue, directly resulting from the careless abuse of antibiotics. The overuse of antibiotics has been reported in some European countries ⁽⁴⁾ to have directly resulted

in an increased prevalence of antimicrobial resistance in Europe ⁽⁵⁾. This phenomenon has also been confirmed by a recent survey on the management of ARS among Asian physicians ⁽⁶⁾. Hence, appropriate physician education promoting better understanding of the nature of ARS and evidenced-based treatment options will not only improve treatment outcomes, but also play an important role in combating the emerging healthcare issue resulting from the rising global antimicrobial resistance.

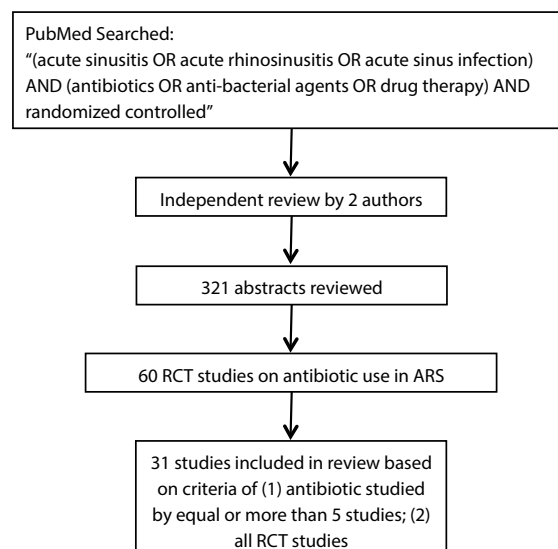
It has been stated clearly in a position paper (2001) and other studies that ARS resolves without antibiotic treatment in most cases ⁽⁷⁻⁹⁾. Symptomatic treatment and reassurance is the preferred initial management strategy for patients with mild symptoms. Antibiotic therapy should be reserved for patients with high fever or severe (unilateral) facial pain ⁽²⁾. Consensus in the management of ARS among GPs and different specialties who commonly treat ARS is very important. In the literature, multiple studies have been done to demonstrate the efficacy and safety profile of the various antibiotics used in the treatment of ARS, but there has been no systematic review done comparing the efficacy and safety of the different antibiotics. We thus sought to review the evidence available through a systematic review of the existing literature on antibiotic usage in ARS.

The aim of the study was to study the usage of common antibiotics used in the treatment of ARS, thus providing practitioners an idea of the efficacy and safety profile of these commonly used antibiotics.

Materials and methods

We performed a literature search of randomised controlled trials (RCT) to compare the efficacy and safety profile of commonly used antibiotics in the treatment of ARS (Scheme 1). To find the relevant studies, we searched the PubMed database. The following search terms were used "(acute sinusitis OR acute rhinosinusitis OR acute sinus infection) AND (antibiotics OR anti-bacterial agents OR drug therapy) AND randomized controlled". No limits were set for the performed search.

All retrieved articles were screened based on the title as well as the abstract. Full-text papers of relevant studies were then obtained for further evaluation. Only RCT studies that were published in English were evaluated and included. The diagnosis and evaluation of cure of ARS was required to be by clinical and/or radiological ($n = 8$) criteria and/or bacteriological criteria ($n = 4$) in patients with symptoms of ARS, and only antibiotics with at least 5 independent studies or more were included in our study. Clinical symptoms used by these studies to diagnose ARS included major criteria such as frontal or maxillary pain/tightness, purulent nasal discharge, or pus seen on nasoendoscopy and minor criteria such as sore throat, cough, fever, change in



Scheme 1. Flow chart.

perception of smell, halitosis or earache. These studies also incorporated these clinical symptoms into a written questionnaire, a verbal questionnaire or a phone questionnaire at the test-of-cure visits, which, together with physical and/or endoscopic examination looking for signs such as postnasal drip, facial tenderness over the sinuses, and pus seen on rhinoendoscopy was used as clinical outcome measures to determine cure. Data from these selected articles were then extracted and tabulated, focusing on the inclusion and exclusion criteria, number of patients, efficacy of the antibiotic treatment regimen (outcomes), side effects reported, and the antibiotic treatment regimen itself (dose and duration). Studies that looked at chronic rhinosinusitis or other lower respiratory tract infections, or other modalities of treatment other than antibiotics were excluded from our study.

Results

A total of 321 abstracts were found using the above search criteria. Of these 321 abstracts, a total of 31 studies satisfied the criteria for this review, and the antibiotics reviewed in this paper include cefuroxime axetil, telithromycin, amoxicillin/potassium clavulanate, levofloxacin, moxifloxacin and clarithromycin. Among them, nine studies were performed double-blinded with placebo controls. All studies used clinical outcomes to evaluate efficacy of treatment, and a small number of studies had secondary endpoints using radiological or bacteriological measures. Studies which had secondary endpoints have been indicated in Figures 1–8. The majority of studies had study endpoints at 10–14 days as well as 28–42 days post-treatment to look for cure.

Cefuroxime axetil (Figure 1)

Studies focusing on cefuroxime axetil found that the efficacy of cefuroxime axetil at 250 mg twice daily has an efficacy above

Table 1. Combined table of Antibiotics (n = 41).

Number of Studies	No. of study patients	Drug	Dose/Duration	Primary Outcomes	Efficacy % Median (range)	Side-Effects % (minor)	Level of Evidence
10	1888	Cefuroxime axetil	125-250 mg BD/5-10 days	Clinical cure rates at test-of-cure visit	85 (63-91.1)	8.1-34.2	1B
7	1563	Telithromycin	800 mg OD/5-10 days	Clinical cure rates at test-of-cure visit	80.9 (72.9-91.1)	21.3-46.9	1B
7	973	Amoxicillin/potassium clavulanate	500-875 g/125 mg for 6-14 days	Clinical cure rates at test-of-cure visit	77.4 (50-93)	17-51.1	1B
6	1050	Levofloxacin	500 – 750 mg OD, 5-10 days	Clinical success, resolution of > or = 3 ARS symptoms	91.4 (23.4-93.9)	15.3-39.8	1B
5	937	Moxifloxacin	400 mg OD, 5-10 days	Clinical cure rates at test-of-cure visit	86	16.9 - 38.2	1B
5	835	Clarithromycin	500 mg BD/10-14 days	Clinical cure rates at test-of-cure visit	85 (79-93.5)	28-48.4	1B

BD: Twice daily, OD: Once daily.

75% (n = 9)⁽¹⁰⁻¹⁸⁾, which is higher than the efficacy at 125 mg twice daily with an efficacy of 63% (n = 1)⁽¹⁹⁾. The occurrence of side effects in the dosing regimen of 125 mg twice daily was also significantly lower, with only 5.4% of patients reporting side effects, while patients using a dosing regimen of 250 mg twice daily reported adverse effects ranging from 8.1% to 34.2%, with the median percentage of adverse effects being reported at 22.6%. The most commonly reported side effects included diarrhoea, nausea, dizziness and vomiting.

Telithromycin (Figure 2)

The efficacy of telithromycin in treating ARS ranged from 72.9%

to 91.1%. All studies reviewed used a dose of 800 mg OD. Most studies had a dosing regimen that lasted for 5 days (n = 5)^(11-13, 20-22) while the rest had a dosing regimen that lasted for 10 days (n = 2)^(21, 22). There was no significant difference in the efficacy of using telithromycin 800 mg OD for 10 days over 5 days (10 days: 75.3% - 91%; 5 days: 72.9% - 91.1%). The objective benchmark for evaluating efficacy of telithromycin treatment was clinical cure rates at test-of-cure visit. Minor side effects were reported anywhere from 21.3% to 46.9% for the 10 days treatment regimen, and 30.1% to 42.2% for the 5 days treatment (not significant). There were no major side effects observed.

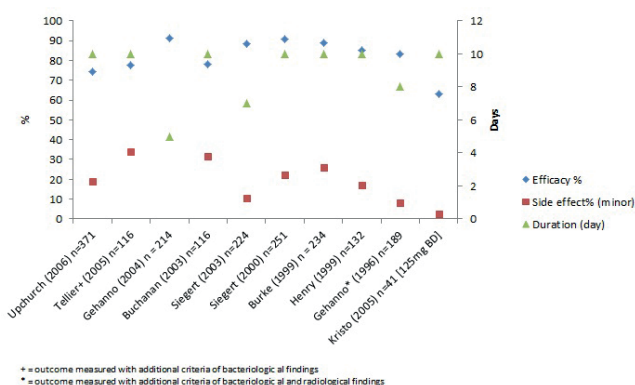


Figure 1. Comparing the dose and duration versus the clinical efficacy-side effects of cefuroxime axetil (without title).

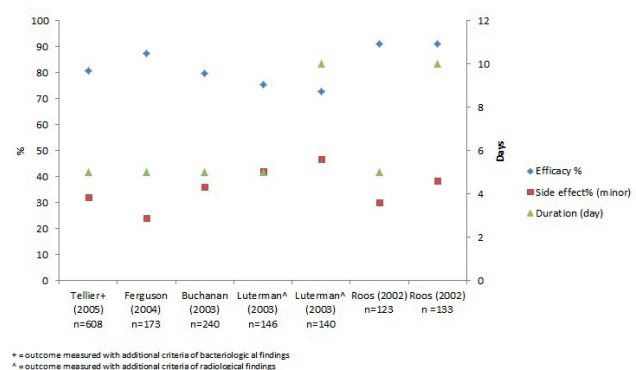


Figure 2. Comparing the dose and duration versus the clinical efficacy-side effects of telithromycin (without title).



Figure 3. Comparing the dose and duration versus the clinical efficacy-side effects of amoxicillin and potassium clavulanate (without title).

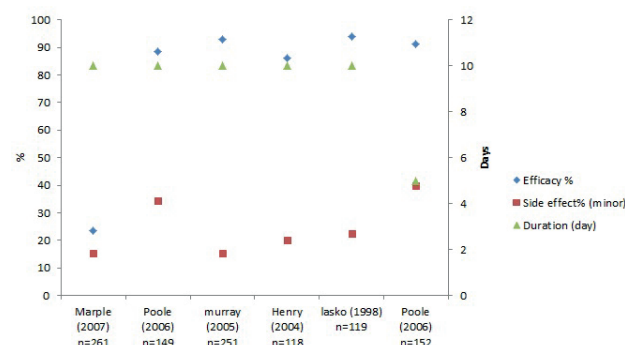


Figure 4. Comparing the dose and duration versus the clinical efficacy-side effects of levofloxacin (without title).

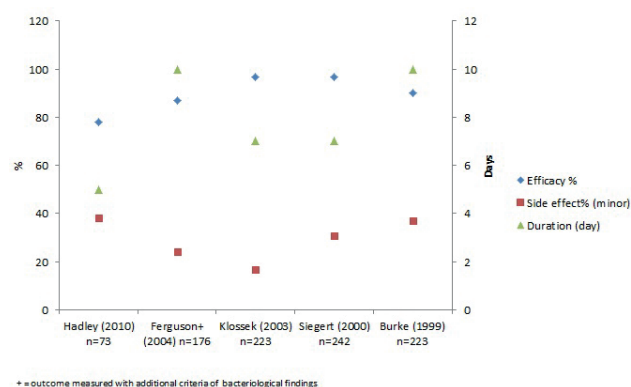


Figure 5. Comparing the dose and duration versus the clinical efficacy-side effects of moxifloxacin (without title).

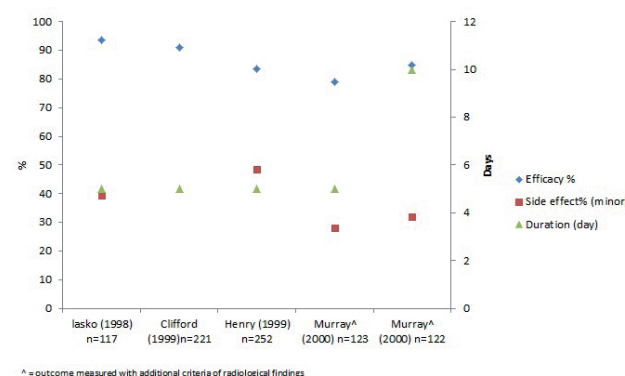


Figure 6. Comparing the dose and duration versus the clinical efficacy-side effects of clarithromycin (without title).

Amoxicillin/potassium clavulanate (Figure 3)

The efficacy of amoxicillin/potassium clavulanate ranged from 50% to 93%. All studies^(11,17,21,23-25) used a dosing regimen of 500/125 mg thrice a day for 10 to 14 days. Most studies reported quite a high incidence of minor adverse effects, with 3 studies reporting a side effect rate of more than 40%^(21,23,24).

Levofloxacin (Figure 4)

With regards to levofloxacin, 5 studies reported efficacies over 86%, but another 1 study reported an efficacy of only 23.4%⁽²⁶⁾. Most studies were made on a dosing regimen of 500 mg once daily for 10 days (n = 5)⁽²⁶⁻³⁰⁾, but 1 study used a dosing regimen of 500 mg once daily for 5 days⁽²⁷⁾. There was no apparent difference in efficacy between a 5 days and 10 days dosing regimen. Most studies on levofloxacin showed minor side effect occurrences to be less than 22.5% (n = 4)^(26,28-30), although 2 studies showed it to be around 40%⁽²⁷⁾. No major side effects were otherwise observed.

Moxifloxacin (Figure 5)

The majority of studies performed on moxifloxacin showed an efficacy close to or above 90%^(14,16,20,31). All studies were carried out using a dosing regimen of 400 mg one daily, given from a period of 5 to 10 days. The minor side effect profile of moxifloxacin ranged from 24.3% to 38.2% and no major side effects were observed.

Clarithromycin (Figure 6)

The efficacy of clarithromycin was relatively high, with a range from 79% to 93.5%^(17,30,32,33). All studies were performed with a total of 1000 mg given per day, for either 5 or 10 days, and no significant increase in efficacy or duration was noted with the 10 days regimen compared to the 5 days one.

Placebo effects (Figure 7 and 8)

The efficacy and side effect profile of placebos were generally lower than that of compared antibiotics, and the antibiotics studied in the 9 studies comparing efficacy and side effects

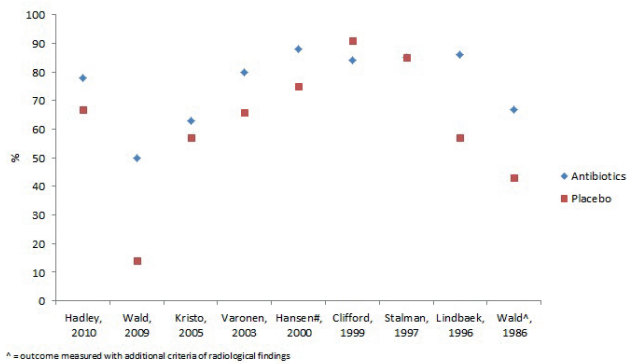


Figure 7. Comparing the clinical efficacy between antibiotics and placebo (without title).

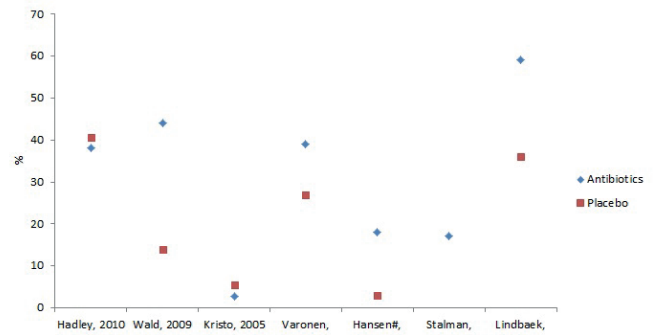


Figure 8. Comparing the side effects between antibiotics and placebo (without title).

of antibiotics had an efficacy ranging from 50-88%^(19,24,32,34-39), as compared to an efficacy of 14-91%^(19,24,32,34-39) for placebos compared in the studies. A similar comparison of the side effects showed that 2.7-59%^(1,9,24,35-39) of patients on antibiotics reported side effects, while 0-40.7%^(19,24,35-39) of patients on placebos showed adverse effects.

Discussion

In general, studies carried out to determine the efficacy of antibiotics in treating ARS have shown that they are effective treatments, with most antibiotics having an efficacy well above 80%. However, many of these studies also reported a high degree of minor side effects, with some antibiotics having up to a 40% incidence of side effects⁽³⁹⁾. The most common side effects reported were gastrointestinal related and included nausea, vomiting, diarrhoea and abdominal pain.

With the exception of 1 study, the efficacy of levofloxacin seems to be the highest. The study that showed an efficacy of only 23%⁽²⁶⁾ assessed resolution of symptoms at the on-treatment visit (day 3-5), which was significantly earlier than the other studies that assessed test-of-cure at a later date. Resolution of symptoms at day 3-5 would thus be significantly lower than assessment at day 21 or later due to various factors such as the natural course of ARS. Within the same antibiotic, studies which showed a lower incidence of side effects generally only included side effects that were possibly related to the treatment, while studies which reported higher incidences (> 40%) tended to include all side effects, regardless of the relation to the antibiotic treatment. Poole et al.⁽²⁷⁾ found a significantly higher side effect profile of levofloxacin 500 mg and 750 mg as compared to results from other studies (34.5% and 39.8%, respectively). This was because of the inclusion of treatment-emergent adverse events from the beginning of therapy on day 1 till the end of the study on day 24, whether related to the treatment or not,

and could have included a significant percentage of treatment unrelated adverse events.

Levofloxacin has been shown to have a high efficacy in the treatment of ARS with a high safety profile, and side effects being minor and predominantly gastrointestinal in nature. More research should be done to assess its viability as a first line antibiotic of choice in the treatment of ARS. Conversely, while the efficacy of clarithromycin (79% - 91%) and telithromycin (72.9% - 91.9%) is high, the incidence of side effects reported in the various studies done has also been shown to be high, with an incidence of 28% - 48.4%^(17,28,30) and 24.1% - 46.9%^(11,13,20-22), respectively. Clarithromycin and telithromycin should be used judiciously and their efficacy needs to be balanced against the common side effects. An interesting point to note is that studies on telithromycin reported no significant difference between efficacy and side effects in the use of telithromycin 800 mg OD for 5 days or 10 days, suggesting that there is no added benefit for a 10 day regimen over a 5 day one.

For amoxicillin/potassium clavulanate, the efficacy ranges from 50% to 93%^(11,21,23-25,34). One reason for the large range could be due to the 2 studies by Wald et al.^(24,34), which had small sample sizes of 28 patients in each study. The low efficacy of amoxicillin/potassium clavulanate found in these studies could possibly be thus in part due to random error, and not an accurate measure of the efficacy of the antibiotic used. The efficacy of amoxicillin/potassium clavulanate found in the other 5 studies ranged from 74.5% - 93%^(11,17,21,23,25), suggesting that the true efficacy of amoxicillin/potassium clavulanate is probably closer to 80%. In general, between studies, we note that there is a big variation of efficacy and side effects even just within the same drug, and in the future we need more standardized studies to be able to have better evidence on the efficacy and side effects of various drugs used in the treatment of ARS.

With reference to Figure 7 and 8, the antibiotics studied in the 9 studies comparing efficacy and side effects of antibiotics versus placebo showed that antibiotics are generally effective in treating ARS. This is true across the different antibiotics used in the treatment of ARS, most of which are commonly used in general practice for the treatment of ARS. However, the efficacy of placebos was found to be high in the studies as well, suggesting that there is a significant placebo effect present in the use of antibiotics to treat ARS. Some authors⁽³⁶⁾ have suggested that this is due in large part to the natural course of ARS, which tends to resolve clinically a few days after onset of symptoms. Studies also found that the usage of placebos generally causes fewer side effects than that of antibiotics (which is to be expected), although Hadley et al.⁽³⁹⁾ and Kristo et al.⁽¹⁹⁾ reported that the placebo group of patients actually experienced slightly more side effects (2-3%) than the antibiotic group of patients.

It can thus be seen that while antibiotics are more efficacious than placebos in the treatment of ARS, the risks of potential side effects need to be weighed against the potential benefit that antibiotics give to the patient. This is especially pertinent as usage of the placebo has shown to be almost as efficacious as using the antibiotic therapy, and also much safer. As there are only 9 studies performed thus far to compare antibiotics with placebos, and antibiotics used in the different studies are not the same, larger scale studies should be done in the future to confirm the results of these studies. In addition, it is important to note that both the Dutch study⁽⁴⁰⁾ and the study by Babar-Craig⁽⁴¹⁾, which was based on returned questionnaires by members of the British Rhinology Society and probably underestimated the incidence of complications, showed that prescription of antibiotics for ARS does not prevent the occurrence of complications. These facts, together with the risk of antibiotic resistance and of masking intracranial complications argue strongly against the

routine use of antibiotics in ARS⁽²⁾.

There are some limitations of this review that the diagnosis of ARS is difficult to standardize, and a good number of papers (n = 22) reviewed were studied before the 2005 European position paper on rhinosinusitis and nasal polyps⁽⁴²⁾ was published, suggesting that the diagnosis of ARS should be made based on duration of symptoms. We note, however, that the majority of these 22 studies done before 2005 used similar criteria as the one suggested in the 2005 EPOS guidelines⁽⁴²⁾. We also recognize that due to the stringent inclusion criteria we have used, there are potentially other antibiotics that are used in the treatment of ARS and have been studied, which may have been omitted in this paper.

Conclusion

The use of antibiotics in the treatment of ARS is widespread. However, clinical studies have found that while antibiotics are efficacious in treating ARS, there is a large placebo effect present as well, which may be due in part to the natural course of the disease. The side effects of antibiotics to treat ARS must be balanced against the therapeutic effect of antibiotics. Larger double-blind placebo controlled studies should be performed to effectively evaluate the true efficacy of antibiotics in the treatment of ARS.

Authorship contribution

Both authors have contributed to the study design, data search and analysis, and writing of the manuscript.

Conflicts of Interest

No conflicts of interest exists for each author involved in this manuscript.

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