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REVIEW ARTICLE

Antibiotic efficacy in patients with a moderate probability of acute rhinosinusitis: a systematic review

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Abstract The aim of this systematic review was to synthesize the results of original studies assessing antibiotic efficacy at different time points after initiating treatment in patients with a moderate probability of acute bacterial rhinosinusitis. We searched the Cochrane library for systematic reviews on the efficacy of antibiotic treatment in patients with acute rhinosinusitis (ARS). Only randomized controlled trials (RCTs) that compared treatment of any antibiotic with placebo were included. The synthesis of the results of six RCTs showed a benefit of antibiotic treatment compared to placebo for the rate of improvement after 3 [pooled odds ratio (OR) 2.78 (95 % confidence interval (CI) 1.39–5.58)] and 7 [OR 2.29 (95 % CI 1.19–4.41)] days after initiation in patients with symptoms and signs of ARS lasting for 7 or more days. After 10 days [pooled OR 1.36 (95 % CI 0.66–2.90)], improvement rates did not differ significantly between patients treated with or without antibiotics. Compared to placebo, antibiotic treatment relieves symptoms in a significantly higher proportion of patients within the first days of treatment. Reporting an overall average treatment efficacy may underestimate treatment benefits in patients with a self-limiting illness.

Keywords Acute rhinosinusitis · Acute sinusitis · Antibiotics · Antimicrobial treatment · Randomized controlled trial

Introduction

Antibiotics are effective in patients with acute rhinosinusitis (ARS) only in cases involving bacterial origin. Viruses cause most ARS, but discriminating between viral and bacterial rhinosinusitis is challenging and impossible in daily practice. In consequence, too many patients with ARS receive antibiotics [1–3]. Expert consensus guidelines recommend antibiotics only for patients with severe symptoms persisting for 10 days or more or for worsening of symptoms after initial improvement [1, 4, 5]. Authors who have synthesized the results from original studies on the efficacy of antibiotics did not address this specific patient population explicitly in their reviews, and their conclusions about the use of antibiotics in patients with ARS do not reflect agreement. One group of authors concluded that ARS resolves without antibiotic treatment [6], another group found that the overall efficacy of antibiotics is moderate [7], and a third group recommended prescribing the cheapest antibiotic [8].

The goal of systematic reviews is to support physicians and guideline developers in formulating their recommendations, but physicians sometimes have reservations about the results of these reviews, including a concern that some study results are synthesized that should not be [9]. Reasons for concern about synthesizing results from original studies include relevant differences among original studies in patient baseline characteristics or even unknown distributions of patient characteristics (e.g., duration of symptoms, fever present or not), differences in

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how (e.g., cure or improvement) and when (3, 10, or more days after treatment started) outcome was assessed, and inclusion of results from original studies with a moderate or even high risk of bias. A particular challenge is the synthesis of results from studies assessing treatment efficacy in patients with an illness such as ARS, for which even the presence or absence of the illness is difficult to establish.

The aim of this review was to synthesize results from a set of original studies assessing the efficacy of antibiotics compared to placebo in patients with a presumably moderate probability of ARS based on patient symptoms and signs.

Materials and methods

Literature search

We searched the Cochrane library for the terms "acute rhinosinusitis", "acute sinusitis", "antibiotic", and "antimicrobial" in the title, abstract, or key words to identify systematic reviews on the efficacy of antibiotic treatment in patients with ARS. From the identified reviews, only randomized controlled trials (RCTs) that compared treatment of any antibiotic with placebo were eligible for further analysis. Non-randomized trials and observational studies were excluded. Our reporting is based on the recommendations of the PRISMA statement [10].

Eligibility criteria

All RCTs included in the identified systematic reviews that met the following criterion were considered eligible: original studies that compared treatment of any antibiotic with placebo in patients with symptoms and signs of ARS lasting for 7 or more days with or without fever, i.e., a minimal duration of 7 or more days of symptoms and signs. The rationale to include only studies including patients with a duration of symptoms and signs (e.g., nasal discharge, purulent secretion, facial pain) lasting more than 7 days is based on the recommendation published in the "European Position Paper on Rhinosinusitis and Nasal Polyps" [1]. Those authors recommend antibiotic treatment only in patients with a duration of symptoms of more than 10 days. Because no original study was available that included only patients with this duration of symptoms, we modified the inclusion criteria for this review to 7 or more days. No limits for the study setting or language of the publication were applied. We excluded RCTs comparing treatment with any antibiotic versus any antibiotic.

Study selection, data extraction, and data synthesis

The bibliographic details of all retrieved original studies were stored in an endnote file. The full texts of the RCTs were reviewed by two reviewers independently (GG and JB). Researchers with specific language proficiencies were used for non-English language references. For each RCT included in this systematic review, both reviewers independently extracted data on study design, demographic characteristics, inclusion and exclusion criteria, duration of symptoms, treatment regimens including dosage and duration, use of concomitant drugs, clinical outcomes by group including number of patients and withdrawals, and time points of measurement. When the results of one original study were included in several publications, the most recent publication was chosen for this review, and missing information was added from previous publications. Disagreements were discussed and resolved by consensus or by third-party arbitration (JS).

Outcomes

The primary outcome of this systematic review focused on cure or improvement at different days of assessment. Cure was defined as complete resolution of signs and symptoms from rhinosinusitis, and improvement was defined as a reduction of signs and symptoms. Therefore, we categorized the following outcomes as cure: "restored" [11, 12] and "entirely improved" [13]. "Much better" and "somewhat better" [11, 12] were categorized as improvement.

All patients who were categorized as cured are by definition improved; thus, we counted the number of improved and cured patients for the primary outcome of improvement.

Assessment of risk of bias

Two reviewers (JB and JS) independently assessed the risk of bias of all included RCTs using the Cochrane Collaboration's tool for risk-of-bias assessment [14]. Disagreements were resolved by consensus.

Adverse events

We collected data about adverse events following the addendum of the CONSORT statement for better reporting of harms in randomized trials [15].

Statistical analysis

For the statistical analysis, we used R statistical software for Windows [16] and the package 'metaphor' [17]. We

classified the studies into two groups: The first group consisted of studies for which outcome was assessed at pre-specified time points (e.g., 3 days after randomization); in the second group, outcome was assessed at different days during a specific time frame (e.g., 7–12 days after randomization). We used a random effects model for pooling when I-squared was more than 50 %.

Results

Study selection

Figure 1 summarizes the selection process for inclusion and exclusion. We identified seven systematic reviews assessing efficacy of antibiotics in patients with ARS [6, 7, 18–22]. In the seven systematic reviews, 21 RCTs were included comparing treatment of any antibiotic with placebo in patients with ARS. All were reviewed in full text, and six RCTs were eligible for our analysis, resulting in exclusion of 15 RCTs. Eleven of the excluded RCTs did not mention duration of symptoms in the set of inclusion criteria [23–33], two RCTs investigated rhinosinusitis only in children [34, 35], the results of one RCT were not published [36], and one RCT did not report data on efficacy of antibiotic treatment compared to placebo at specified days after randomization [37].

Study characteristics

Table 1 presents the study characteristics of all RCTs included in this systematic review and meta-analysis

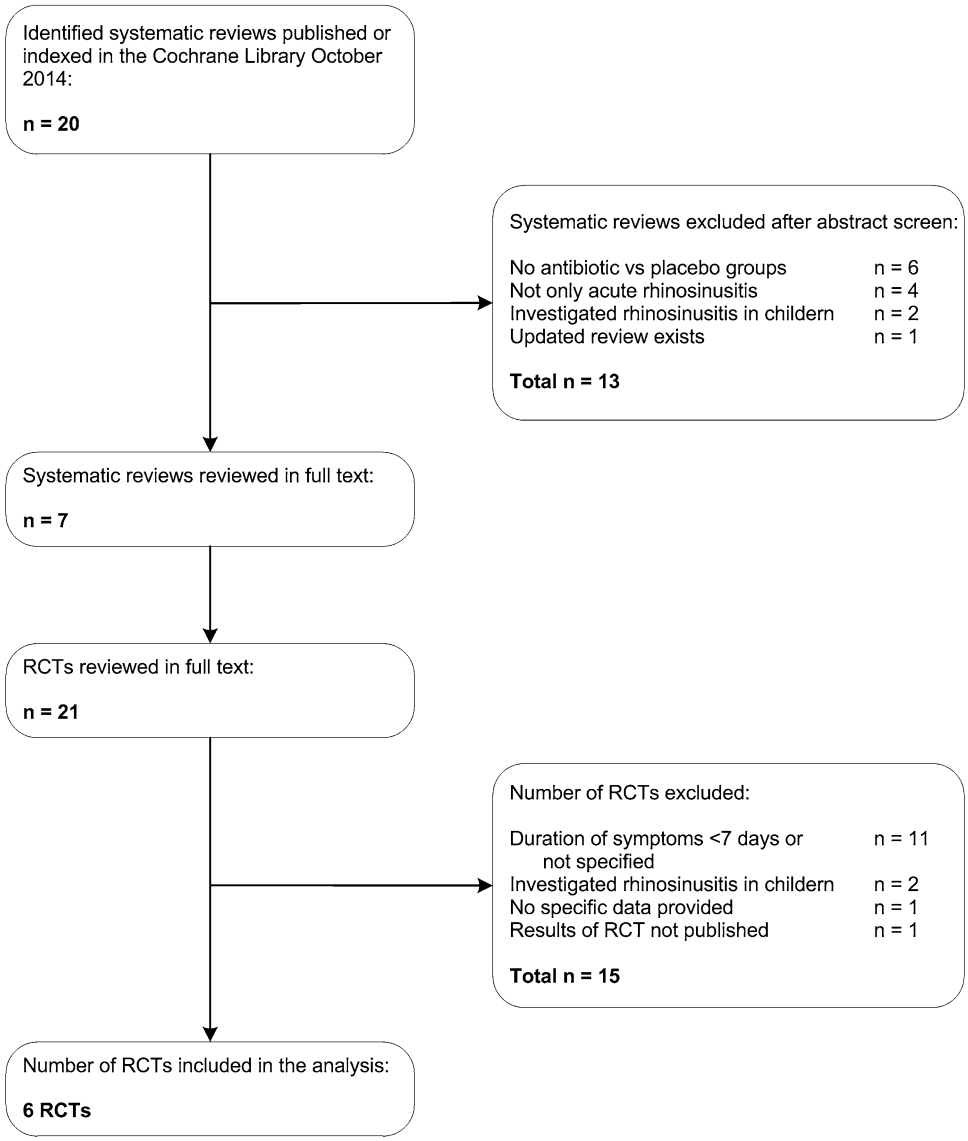

Fig. 1 Study flow

Table 1 Baseline characteristics of the six included RCTs

References	Number of patients (women)	Age mean: years (SD or range)	Duration of symptoms: days (SD)	Concomitant drugs allowed	Intervention	Control intervention	Outcome classification
Garbutt 2012 [38]	166 (106)	31.5 (18–69)	7–28 (11.1)	Yes	Amoxicillin 500 mg 3 × daily for 10 days	Placebo	Significant improvement, relapse, recurrence
Hadley 2010 [39]	118 (73)	38.5 (13.4)	7–27 (12.7)	Yes	Moxifloxacin 400 mg 1 × daily for 5 days	Placebo	Cure, improvement
Haye 1998 [40]	169 (125)	41.7 (18–70)	11–29 (nr)	nr	Azithromycin 500 mg 1 × daily for 3 days	Placebo	Cure, improvement, failure, relapse
Lindbaek 1996 [11]	130 (85)	38.6 (16–74)	8–29 (nr)	Yes	Group 1: Penicillin V 1,320 mg Group 2: Amoxicillin 500 mg 3 × daily for 10 days	Placebo Placebo	Restored, much better, somewhat better, unimproved, worse
Lindbaek 1998 [12]	63 (38)	40.2 (15.9)	8–29 (nr)	Yes	Group 1: Penicillin V 1,320 mg Group 2: Amoxicillin 500 mg 3 × daily for 10 days	Placebo Placebo	Restored, much better, somewhat better, unimproved, worse
Merenstein 2005 [13]	135 (93)	33.8 (9.8)	≥7 (11.2)	Yes	Amoxicillin 500 mg 3 × daily for 10 days	Placebo	Improved, not improved

nr not reported

(detailed information about inclusion/exclusion criteria and outcome definitions are summarized in Supplementary Table 1). Two RCTs compared amoxicillin [13, 38], one RCT moxifloxacin (fourth-generation fluoroquinolone) [39], and one RCT azithromycin (macrolide antibiotic) [40] with placebo. Two RCTs compared two antibiotics in separated groups (penicillin V and amoxicillin) versus placebo [11, 12].

The most recent RCT was conducted in 2012 [38], and the years of publication were between 1996 and 2012. Five RCTs had a double-blind design [11–13, 39, 40], and one RCT was triple-blinded [38].

In total, 781 patients were included in the six RCTs, and 520 (67 %) were females. Sample size ranged from 63 to 169 patients, and mean patient age was 37 years. No RCT reported the number of patients with fever at baseline. In four RCTs, the authors mentioned the presence of fever in the set of inclusion criteria [11, 12, 38, 39]; in one RCT, authors reported that the average body temperature was 36.7 °C ± 0.5 [13]; and in the remaining study, the authors did not document the presence of fever [40]. Only Hadley et al. [39] mentioned fever as a compulsory inclusion criterion. Concomitant drugs were explicitly allowed in all RCTs except for Haye et al. [40], who did not report information about concomitant drug use.

For the confirmation of bacterial origin of the ARS, only Hadley et al. [39] used sinus puncture and included only patients with positive cultures. Two RCTs took a sample either of nasal secretions [40] or from the nasopharynx [11], but verification of bacteria was not a mandatory inclusion criterion. Three RCTs did not report on sampling from the sinus or nasal secretions [12, 13, 38].

Risk of bias

Table 2 shows the risk of bias of all included RCTs. Four RCTs were found to have a low risk of bias [11–13, 40], and one RCT was found to have an uncertain risk of bias in one of the six domains [38]. The remaining RCT was found to have an uncertain risk in four of the six domains [39].

Efficacy of antibiotics

Figure 2 shows the odds ratios for the efficacy of antibiotics compared to placebo assessed at specific time points. Most RCTs showed a positive effect of antibiotic treatment over different observation periods (3–14 days). However, in many studies, the difference between antibiotics and placebo was not statistically significant. Lindbaek et al. [11] showed that treating patients with penicillin V or amoxicillin was significantly effective for the outcome 'improvement' at day 3 and for the outcome 'cure' at day 10. The pooled odds ratio for improvement on day 3 was 2.78 [95 % confidence interval (CI) 1.39–5.58]. The mean rate of improvement after 3 days was 66.4 % (range 36.5–84.9 %) in patients treated with antibiotics, and the mean rate in the placebo group was 44.4 % (range 34.6–73.3 %). In contrast, the pooled odds ratio for improvement on day 10 was 1.38 [95 % CI 0.66–2.90]; for cure on day 10, it was 1.92 (95 % CI 0.63–5.80). The mean rate of improvement on day 10 was 87.6 % (range 77.6–97.7 %) in patients treated with antibiotics, and the mean rate in the placebo group was 84.8 % (range 80.2–88.6 %).

Figure 3 shows the odds ratios for the efficacy of antibiotics versus placebo assessed at different days during a specific time frame. Haye et al. [40] found a significant benefit for placebo treatment for the outcome 'cure' on days 10–12 but not on days 3–5 or 23–27. For the endpoint 'improvement', no significant differences were shown. The treatment with moxifloxacin in Hadley et al. [39] for the endpoint cure showed no significant effect. Because both studies assessed their outcomes at different time points (e.g., 3–5, 6–8, 10–12 days), we refrained from pooling the results.

Table 2 Risk-of-bias assessment of all included RCTs

References	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective outcome reporting?	Free of other bias?
Garbutt 2012 [38]	+	+	+	?	+	+
Hadley 2010 [39]	?	?	?	+	+	?
Haye 1998 [40]	+	+	+	+	+	+
Lindbaek 1996 [11]	+	+	+	+	+	+
Lindbaek 1998 [12]	+	+	+	+	+	+
Merenstein 2005 [13]	+	+	+	+	+	+

+ Low risk, ? uncertain risk, – high risk

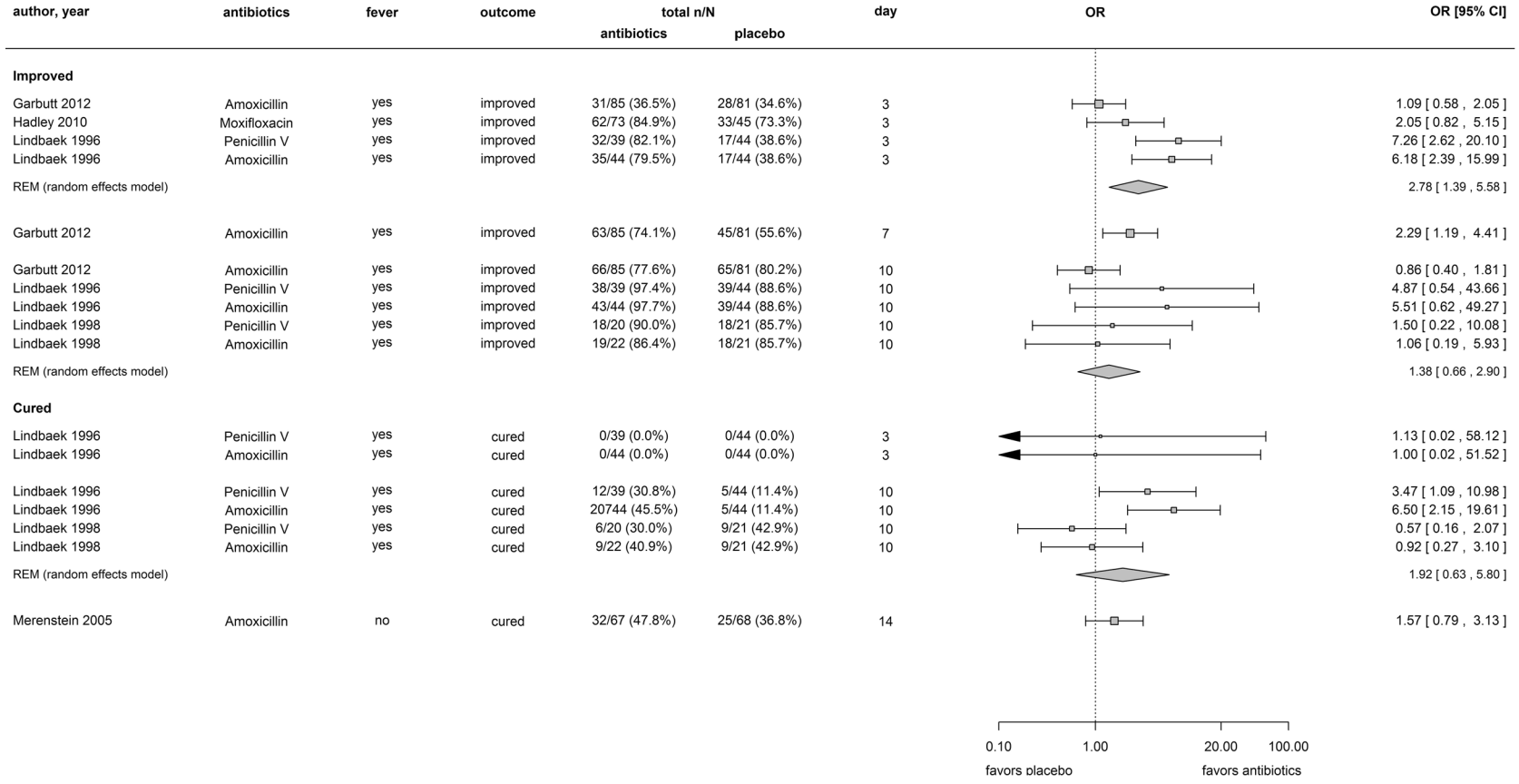

Fig. 2 Efficacy of antibiotics assessed at specific time points

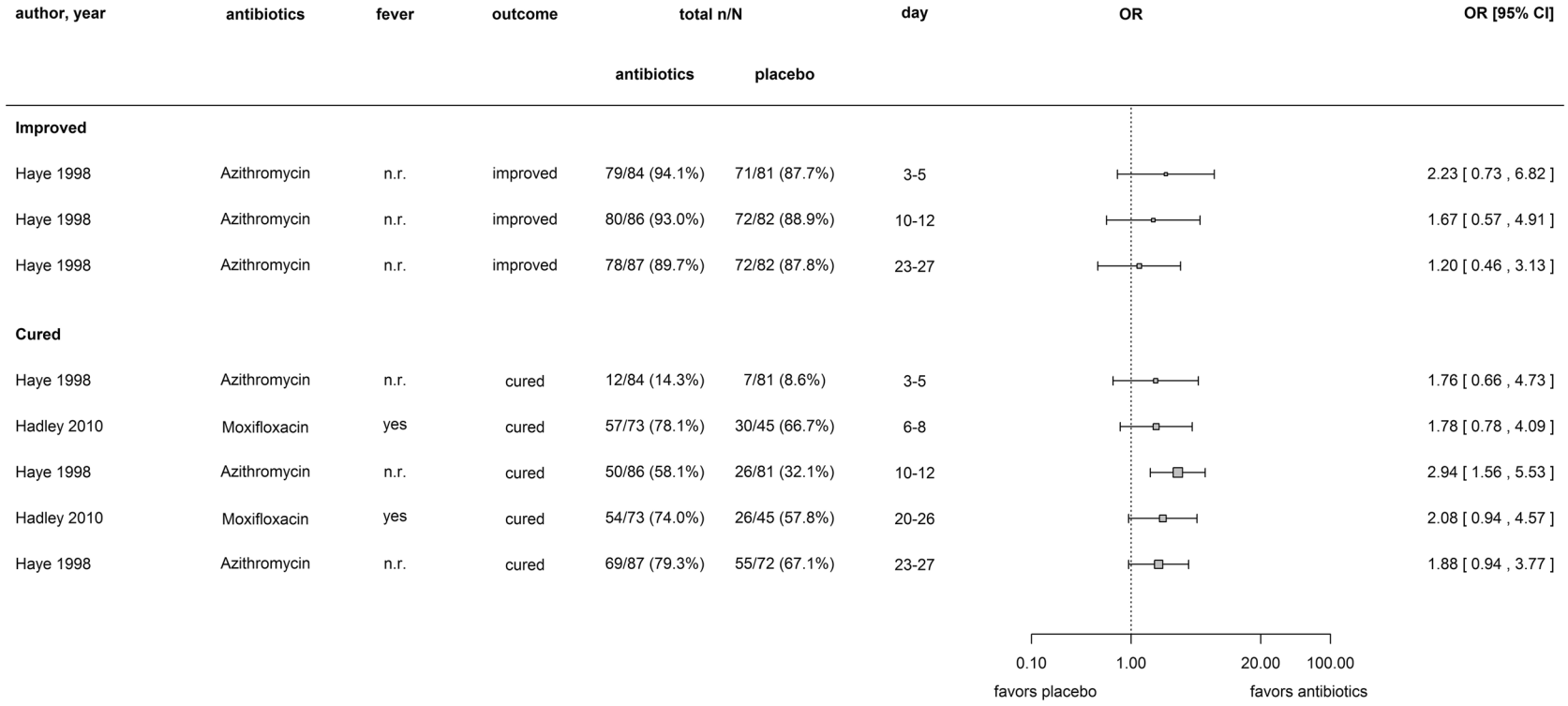

Fig. 3 Efficacy of antibiotics assessed at different days during a specific time frame

Table 3 Recording and reporting of adverse events

References	Drug therapy	Number of patients with AEs, *n* (%)	Number of patients with treatment related AEs, *n* (%)	Number of patients with AEs in placebo group, *n* (%)	Withdrawal because of AEs (due to harm), *n*	Seriousness or severity of AEs	Evaluation of attribution: event related to antibiotic	Data collection by personal interview	Data collection by telephone interview	Data collection by structured questionnaire	Data collection by patient diary	Timeframe of surveillance (at day)
Garbutt 2012 [38]	Amoxicillin	14/85 (16)	Not specified	11/81 (14)	1	nr	nr	Yes	No	nr	nr	10
Hadley 2010 [39]	Moxifloxacin	96/251 (38.2)	34/251 (13.5)	50/123 (40.7)	3	nr	Yes	Yes	No	nr	nr	3–4, 6–8, 14–18
Haye 1998 [40]	Azithromycin	nr	24/87 (27.6)	15/82 (18.3)	0	nr	Yes	Yes	No	nr	nr	3–5, 10–12, 23–27
Lindbaek 1996 [11]	Penicillin V	24/41 (58.5)	Not specified	16/44 (36.4)	2	Reported	nr	Yes	No	nr	nr	3, 10
Lindbaek 1996 [11]	Amoxicillin	25/45 (55.6)	Not specified	16/44 (36.4)	1	Reported	nr	Yes	No	nr	nr	3, 10
Lindbaek 1998 [12]	Penicillin V	1 (5)*	Not specified	nr	1	nr	nr	Yes	No	nr	nr	10
Lindbaek 1998 [12]	Amoxicillin	2 (9,1)*	Not specified	nr	2	nr	nr	Yes	No	nr	nr	10
Merenstein 2005 [13]	Amoxicillin	13/57 (22.8)	Not specified	7/59 (11.9)	0	nr	nr	No	Yes	nr	nr	3, 7, 14

Relapse/recurrence

In Garbutt et al. [38], eight patients (9 %) treated with amoxicillin had a relapse (see definition in Supplementary Table 1), and five patients (6 %) treated with amoxicillin had recurrent symptoms (see definition in Supplementary Table 1). In the placebo group, five patients (6 %) had a relapse, and two patients (2 %) reported recurrent symptoms. In Haye et al. [40], four patients (5 %) in the antibiotic group had a relapse between days 10–12 and seven patients (8 %) between days 23–27. By contrast, only three patients (4 %) treated with placebo had a relapse between days 10–12 and four patients (5 %) between days 23–27.

Adverse events

The recording and reporting of the adverse effects are summarized in Table 3. Data about adverse events were collected personally ($n = 5$) or by telephone ($n = 1$) [13] interviews. None of the six studies reported using a structured questionnaire or a patient diary to collect any adverse event. The evaluations (time frame of surveillance) were carried out between days 3–27. All studies reported frequencies of adverse events, but only one study reported on severity of adverse events [11]. Between zero [13] and three patients [39] per study withdrew from the study because of an adverse event in the treatment group. The most frequent adverse events were headache, nausea/vomiting, and diarrhea. Supplementary Table 2 shows the number of all adverse events for the treatment and placebo group per study.

Discussion

The synthesis of the results of the six RCTs shows a benefit of antibiotic treatment compared to placebo in patients with ARS symptoms and clinical signs for more than 7 days. Three and seven days after the initiation of an antimicrobial treatment, the rate of improvement in patients with antibiotics was significantly higher than that in controls. After 10 days, there was no significant difference in the improvement rates between patients treated with or without antibiotics. ARS, with a few exemptions, is a self-limiting illness; therefore, the only small and non-significant difference after 10 days is not entirely unexpected. The number of adverse events reported in the original studies varied widely, from 5 % to over 50 %. The most frequently reported adverse effects were diarrea and nausea/vomiting, and only a small number of patients withdrew from the studies because of adverse events of antibiotic treatment.

To our knowledge, this meta-analysis is the first to assess the outcome of improvement at specific time points (at days 3, 7, and 10). ARS is in general a self-limiting illness, and an effect of antibiotic treatment, if any, is expected after 2 to 3 days of treatment [38]. Six previous meta-analyses assessed clinical outcomes within different time frames (e.g., 3–5, 7–11 days) [7, 18–22], and in only one were results pooled for the endpoint 'cure'—indicating patients are free of any symptoms—at specific time points [6]. In four reviews, authors concluded that antibiotics exert a small benefit [7, 18–20], whereas other authors concluded that antibiotics have no positive effect [6, 21, 22].

According to a guideline [5] and a position paper [1], antibiotic treatment is recommended for patients with a duration of symptoms, including fever, of 10 or more days or worsening of symptoms after initial improvement. The results of our review support the recommendations in the guidelines that antibiotics are effective for these patients. The proportion of patients with improvement of symptoms 3 and 7 days after starting treatment was significantly higher in the group treated with antibiotics, and there seemed to be no relevant difference in the rate of improvement or cure rate after 10 days. For clinicians, the judgment to recommend antibiotics or not to patients with suspected ARS is challenging. Although the average efficacy of antibiotics measured 10 or more days after initiation of treatment seems to be insignificant, treatment with antibiotics is an option for patients who want to have a faster improvement of symptoms.

Prevention of complications of bacterial rhinosinusitis, such as meningitis or orbital or brain abscess, is sometimes mentioned as a reason for antibiotic treatment [19]. These complications are rare but serious. In all six RCTs, patients with severe symptoms, e.g., high fever, were excluded. These patients might carry the highest risk for severe complications, and for clinicians, it may be important to know that these patients were not included in the original studies.

In further clinical trials assessing the efficacy of antibiotic treatment in patients with ARS, methodological quality could be improved in two respects: precise reporting about the presence or absence of fever and recording and reporting of adverse effects. According to the guidelines, fever should be present in patients treated with antibiotics. In the published studies, we could not analyze patients with or without fever separately and compare the efficacy of antibiotic treatment between the two groups. Furthermore, an improvement in the recording and reporting of adverse effects would be very helpful for clinicians. The efficacy of antibiotic treatment in patients with ARS, even when present, is not very large. Therefore, knowledge about the frequency, severity, and duration of

adverse effects is essential for advising patients about treatment.

One strength of our study is that we pooled outcome results assessed at different, specific time points. Measurements within a time frame are more inaccurate because symptoms and signs can change quickly for illnesses such as ARS with a high rate of spontaneous resolution. Furthermore, we included only RCTs that compared antibiotic treatment with placebo. We followed the general principle that head-to-head trials comparing the treatment effect of two or more antibiotics should be conducted when placebo-controlled trials have shown that treatment is better than placebo [41].

The main limitation of this study is the small number of RCTs available that compared antibiotic treatment with placebo in patients with ARS. Furthermore, inclusion criteria and definitions of outcomes as well as their assessment varied among the included RCTs.

Our meta-analysis shows that antibiotic treatment compared to placebo relieves symptoms in a significantly higher proportion of ARS patients within the first days of treatment. However, the potential for adverse effects must be considered. In addition, in terms of the method of synthesizing results from original studies, reporting an overall average treatment efficacy in patients with an illness that has a high probability of spontaneous cure may underestimate treatment benefits.

Conflict of interest The authors declare that they have no conflict of interest.

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