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Antimicrobial Treatment in Acute Maxillary Sinusitis: A Meta-Analysis

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ABSTRACT. *Objective.* The aims of this study were to assess which antibiotic is most effective in the treatment of acute maxillary sinusitis in otherwise healthy adults and adolescents, and which has the fewest side effects. *Design.* To assess the short-term effects of antimicrobial treatments, a meta-analysis was performed using Mantel-Haenszel procedures on 16 comparative, randomized studies with a total number of 3358 patients. No placebo-controlled studies were available. Antimicrobial treatments were categorized according to type, spectrum, β -lactamase inhibition, and bactericidal effect. Outcomes were clinical cure, clinical success, and adverse events. *Results.* When studies were analyzed separately, we found significant differences between cefpodoxim and cefaclor in relation to clinical cure, and between loracarbef and doxycycline in relation to clinical success. When data was pooled, sulphonamides were significantly more effective than penicillins in relation to clinical cure, and macrolids were more effective than penicillins in relation to clinical success, whereas cephalosporins caused significantly less adverse events than penicillins. When studies were stratified (standard classic meta-analysis), antibiotics with β -lactamase inhibition offered significantly more clinical cures than antibiotics without β -lactamase inhibition. However, this significant effect was only due to one study from Southern Europe, published before 1991. *Conclusion.* Differences in outcome between antimicrobial treatments of acute sinusitis in otherwise healthy adults and adolescents appear to be small. Therefore, the cheapest antimicrobial treatment can be selected. J CLIN EPIDEMIOL 50;8:881–890, 1997. © 1997 Elsevier Science Inc.

KEY WORDS. Acute maxillary sinusitis, drug therapy, antibiotics, pooled analysis, meta-analysis, heterogeneity

INTRODUCTION

There is still much debate in general practice as to whether antibiotics influence the outcome of acute upper respiratory tract infections. Recent randomized clinical trials on acute otitis media, acute tonsillitis, and acute bronchitis have failed to confirm treatment effectiveness, but antibiotics are routinely prescribed for these conditions and for acute maxillary sinusitis in most countries [1–3]. This was the reason for us to investigate the effectiveness of antibiotics in patients with acute maxillary sinusitis by means of a meta-analysis. We pooled data in order to evaluate which antimicrobial treatment is the most effective and which causes the fewest side effects. We selected 16 randomized, controlled trials in which the effects of antibiotics in acute maxillary sinusitis were studied.

SUBJECTS AND METHODS

Selection of Appropriate Studies

Studies were selected using a Medline literature search based on the key terms [sinusitis and drug therapy] or [maxillary sinusitis and drug therapy]. Mesh headings were exploded. Because bacterial resistance to antibiotics increased in recent years, we only looked back to the period 1984–August, 1995. The search was limited to studies published in English, French, German, Dutch, Danish, and Swedish. To detect studies missed by the Medline search, three other strategies were followed. First, all selected papers were cross-referenced, i.e., the references were used to detect previously published studies [4]. Second, we checked the reference list of a recent Dutch Ph.D. theses on acute maxillary sinusitis, as well as the reference list accompanying the Dutch general practitioners guideline on acute sinusitis [5–7]. Finally, *Excerpta Medica* was reviewed for any additional studies.

Studies were only used for analysis if they provided primary data on the effectiveness and side-effects of different antibiotics in the treatment of acute sinusitis in otherwise healthy adults (aged 13 years and over), and if the study design was blinded, comparative, and randomized.

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Evaluating the Selected Studies

The main questions for analysis were, "Which of the following type of antibiotics (penicillins, cephalosporins, tetracyclines, macrolids, and sulphonamides) is most effective and which is best tolerated?" We then further analyzed data to see if there were any differences related to specific properties of antibiotics: spectrum (broad/narrow), β -lactamase inhibition (no/yes), and bactericidal effect (no/yes).

The effectiveness of antibiotics was assessed by comparing outcomes. All included studies reported their data in a comparable way regarding the outcomes, clinical cure and clinical success, although not all studies assessed both outcomes. Clinical cure was defined as complete recovery with absence of all signs and symptoms. Clinical success was defined as either clinical cure or clinical improvement, i.e., there was no need for an additional follow-up treatment. Therefore, clinical success is a broader definition than clinical cure, i.e., a patient may have improved on the day of assessment but is not necessarily cured. We considered antibiotics to be "not tolerated" when adverse events which was severe enough to lead to cessation of the treatment, occurred. Minor adverse events were not included in this analysis.

In addition to type and properties of the antibiotics studied and the outcome, the following background characteristics were recorded for each study: setting (primary care/secondary care), prescription of local decongestants (no/yes), treatment dose (prescribed daily dose/antibiotic divided by daily dose [DDD] as defined by the WHO [8]) ($\leq 1/\geq 1$), duration of treatment (< 10 days/ ≥ 10 days), basis for the diagnosis sinusitis (clinical signs/clinical signs plus ultrasound/radiograph/aspiration plus culture), geographical area of population (Northern Europe/Southern Europe/United States), and year of publication ($\leq 1990/\geq 1990$). The background characteristic follow-up time was almost equivalent to duration of treatment because in most studies patients were assessed 1 or 2 days after completion of the antibiotic course. Therefore, separate results for this characteristic are not presented.

A pre-structured questionnaire was used to document the study characteristics of interest (the aforementioned type and properties of antibiotics, outcomes and background characteristics). All studies were assessed according to this questionnaire by the first and the second author separately. Any disagreements were subsequently solved by reviewing a paper together. Only data provided in the publications were considered. No attempts were made to contact authors for missing information. All calculations were made using the resulting data lists.

Analysis

The analysis consisted of four steps. In the first step, odds ratios and 95% confidence intervals (exact) were calculated with respect to the three outcomes: clinical cure, clinical success, and adverse events, for each study separately.

This analysis just repeated the analysis of the data in each study.

In the second step, we pooled data on antibiotic subgroups from the various studies to obtain more precise estimates. Contingency tables were constructed on the basis of type and properties of antibiotics on the one hand, and outcomes on the other hand. Associations were estimated from these tables by means of a Mantel-Haenszel procedure in which unstratified odds ratios were calculated [9]. Each study thus contributed to twelve contingency tables ($12 = 4 \times 3$: four for type and properties of antibiotics, and three for outcomes) in this step, but sometimes to only one category of a contingency table. For example, with regard to the property "spectrum," twelve studies compared two broad spectrum antibiotics and thus contributed to only one category in the contingency tables of the three respective outcomes. This second step was performed under the assumption that base rates were homogeneous, i.e., we assumed that base rates (such as percentage of clinical cure) did not differ between studies given a specific type or property of antibiotics.

In the third step of the analysis, we did not assume that base rates were necessarily homogeneous. In this step, we calculated stratified odds ratios by means of a Mantel-Haenszel procedure, again for type and properties of antibiotics on the one hand, and outcomes on the other hand. Odds ratios were calculated using stratification by study. The step can yield fewer statistically significant differences due to loss of power or due to heterogeneity of base rates. Loss of power happened because studies that compared two antibiotics from a similar type or with a similar property did not contribute to the respective odds ratio. For example, only one study contributed to this stratified analysis of the effects of β -lactamase inhibiting properties on clinical cure. The assumption of homogeneity of base rates in the second step of the analysis was considered to be justified if the odds ratio stratified by study did not differ from the unstratified odds ratio for more than 15% [10]. This third step is the most stringent way to correct for heterogeneity, and is comparable to a standard classic meta-analysis in which patients are stratified by study. The third step of the analysis could be considered as a check on the assumption of homogeneity of base rates in the previous step.

In the final, fourth step, we clustered studies with similar characteristics, to increase the power of the analyses as presented in step 3. For this purpose, background characteristics instead of studies, were considered as potential confounders. Again by means of a Mantel-Haenszel procedure, stratified odds ratios were calculated, now with stratification by background characteristics. All background characteristics (setting, prescription of local decongestants, treatment dose, duration of treatment, basis for the diagnosis sinusitis, geographic area, and year of publication) were considered separately. This procedure was applied only for clinically significant odds ratios as calculated in the third step. Instead of using *p*-values, we chose rather arbitrary a cut-off point

TABLE 1. Characteristics of the selected studies

Author	Country	Diagnosis ^a and setting	Antibiotics	Days	Dose	LD	n for effect	n for safety
Williams [12] (1995)	USA	2 SC	Co-trimoxazole	10	960 mg BID	Yes	40	40
			Co-trimoxazole	3	960 mg BID		40	40
Calhoun [13] (1993)	USA, Canada	2 PC	Amoxicillin	14	500 mg TID	Yes	61	72
			Clarithromycin	14	500 mg BID		55	70
Huck [14] (1993)	USA	2 SC	Amoxicillin	10	500 mg TID	No	28 ^b	28
			Cefaclor	10	500 mg TID		28	28
Dubois [15] (1993)	USA	3 SC	Amoxicillin + clav.	14	375 mg TID	Yes	128	251
			Clarithromycin	14	500 mg BID		132	246
Scand. Study Group [16] (1993)	Finland, Iceland, and Sweden	3 SC	Doxycycline	10	100 mg UID ^c	No	164	330
			Loracarbef	10	400 mg BID		168	332
De Abate [17] (1992)	USA	3 SC	Amoxicillin + clav.	10	500 mg TID	No	8	62
			Ceftibuten	10	400 mg UID		17	117
Camacho [18] (1992)	USA	2 SC	Amoxicillin + clav.	10	500 mg TID	No	124	160
			Cefuroxim-axetil	10	250 mg BID		115	157
Sydnor [19] (1992)	USA	3 SC	Amoxicillin + clav.	10	625 mg TID	No	21 ^b	54
			Loracarbef	10	400 mg BID		22	59
Casiano [20] (1991)	USA	3 SC	Amoxicillin	10	500 mg TID	No	15	37
			Azithromycin	5	250 mg UID ^c		23	41
Karma [21] (1991)	Finland and Sweden	3 SC	Amoxicillin	10	500 mg TID	Yes	35	50
			Clarithromycin	10	500 mg BID		32	50
Gehanno [22] (1990)	Belgium and France	2 SC	Cefaclor	10	500 mg TID	Yes	114	125
			Cefpodoxim-proxetil	10	200 mg BID		122	133
Brodie [23] (1989)	UK	1 PC	Amoxicillin	10	250 mg TID	No	52 ^b	80
			Cefuroxim-axetil	10	250 mg BID		45	80
Nord [24] (1988)	Europe	2 SC	Amoxicillin	10	500 mg TID	Yes	133	148
			Bacampicillin	10	800 mg BID		138	149
Ekedahl [25] (1987)	Sweden	3 SC	Cefaclor	10	Unknown	Yes	105 ^b	105
			Doxycycline	10	100 mg UID ^c		108	108
Scheld [26] (1986)	USA	3 SC	Amoxicillin	10	500 mg TID	Yes	27	40
			Cyclacillin	10	500 mg TID		26	40
Frühwald [27] (1984)	Germany	2 SC	Co-tetroxazin	7	350 mg BID	No	35	35
			Co-trimoxazole	7	960 mg BID		43	43

Abbreviations: LD = local decongestants, PC = primary care, SC = secondary care.

^aDiagnosis: 1 = clinical signs, 2 = ultrasound or radiograph, 3 = aspiration plus culture.

^bOnly evaluable for clinical cure or clinical success.

^cThe first day a double dose.

of greater than 1.50 or less than 0.67 as being clinically significant [11]. Clustering of studies was considered to be justified if the odds ratio adjusted for a background characteristic did not differ from the odds ratio stratified by study for more than 15% [10]. Moreover, the odds ratio should not vary across strata. This was considered to be true if the odds ratio per stratum did not differ from the odds ratio per combined stratum for more than 15% [10]. Otherwise, we considered confounding or effect modification by unmeasured background characteristics to be present.

RESULTS

Studies

In our search, 68 papers were selected; six papers were excluded because they did not examine the effectiveness and safety of antimicrobial treatment; three papers were excluded because only children were included; and one paper was excluded because no primary data were presented. Another 16 articles were excluded because there was no "ho-

mogeneous" study population (in 10, several ear, nose and throat infections were studied, results were not stratified by location; in 1, adults as well as children were studied, results were not stratified by age group; and in five, acute as well as chronic sinusitis was studied, results were not stratified by diagnosis); seven articles were excluded because they were not comparative; six were excluded because they were not randomized; eight were excluded because the assessment was not blinded. Of the remaining 21 papers, 16 studies were on acute maxillary sinusitis and five papers were on chronic sinusitis only. The 16 studies on acute sinusitis were included in this analysis [12–27]. Their characteristics are presented in Table 1. In Table 2, the characteristics of the antibiotics studied are shown.

Study Specific Effects (Step 1)

A total of 3310 subjects received antimicrobial treatment. The odds ratios and 95% confidence intervals for the 16 studies with respect to clinical cure, clinical success, and

TABLE 2. Classification of the antibiotics included

Antibiotic	Antibiotic type	Spectrum	β -lactamase inhibition	Bactericidal effect	Oral dose (mg/day)
Amoxicillin	Penicillins	Broad	No	Yes	1125 ^a
Amoxicillin + clav.	Penicillins	Broad	Yes	Yes	1500 + 375 ^a
Bacampicillin	Penicillins	Broad	No	Yes	1200 ^b
Cyclacillin	Penicillins	Broad	No	Yes	1500 ^c
Cefaclor	Cephalosporins	Broad	No	Yes	1500 ^a
Cefpodoxim-proxetil	Cephalosporins	Broad	Yes	Yes	400 ^a
Ceftibuten	Cephalosporins	Broad	Yes	Yes	400 ^b
Cefuroxim-axetil	Cephalosporins	Broad	Yes	Yes	1000 ^a
Loracarbef	Cephalosporins	Broad	Yes	Yes	600 ^d
Doxycyclin	Tetracyclines	Broad	Not applicable	No	100 ^a
Azithromycin	Macrolids	Narrow	Not applicable	No	300 ^a
Clarithromycin	Macrolids	Narrow	Not applicable	No	500 ^a
Co-tetroxazin	Sulphonamides	Broad	Not applicable	Yes	700 ^c
Co-trimoxazole	Sulphonamides	Broad	Not applicable	Yes	1920 ^a

^aFarmacotherapeutisch Kompas 1995. Amstelveen: Ziekenfondsraad, 1995.^bWHO, ATC-classification, Oslo.^cDDD not yet established.^dGeneesmiddel Informatie Centrum. Informatarium Medicamentorum's Gravenhage: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, 1995.

TABLE 3. Odds ratio and confidence intervals per study, exact; statistically significant odds ratios are boldface

Author	Treatment	Clinical cure	Clinical success	Adverse events
Williams [12] (1995)	Co-trimoxazole 10D	1	1	
	Co-trimoxazole 3D	1.29 (0.48–3.44)	0.63 (0.17–2.43)	^a
Calhoun [13] (1993)	Amoxicillin	1	1	1
	Clarithromycin	1.12 (0.50–2.51)	1.30 (0.39–4.35)	0.68 (0.11–4.18)
Huck [14] (1993)	Amoxicillin		1	
	Cefaclor	^b	1.00 (0.22–4.47)	^a
Dubois [15] (1993)	Amoxicillin + clav.	1	1	1
	Clarithromycin	0.88 (0.53–1.48)	2.42 (0.73–8.07)	1.02 (0.35–2.95)
Scand. Study Group [16] (1993)	Doxycyclin	1	1	1
	Loracarbef	1.28 (0.82–1.99)	3.95 (1.08–14.44)	1.11 (0.44–2.76)
De Abate [17] (1992)	Amoxicillin + clav.	1		1
	Ceftibuten	2.80 (0.42–18.69)	^c	0.97 (0.92–1.01)
Camacho [18] (1992)	Amoxicillin + clav.	1	1	1
	Cefuroxime – axetil	1.20 (0.70–2.04)	1.24 (0.62–2.48)	0.68 (0.11–4.10)
Sydnor [19] (1992)	Amoxicillin + clav.		1	1
	Loracarbef	^b	1.05 (0.13–8.24)	0.14 (0.02–1.19)
Casiano [20] (1991)	Amoxicillin	1		^a
	Azithromycin	1.03 (0.24–4.51)	^c	
Karma [21] (1991)	Amoxicillin	1	1	1
	Clarithromycin	0.51 (0.18–1.42)	0.91 (0.17–4.85)	0.98 (0.94–1.02)
Gehanno [22] (1990)	Cefaclor	1	1	1
	Cefpodoxim – proxetil	2.45 (1.32–4.55)	1.46 (0.49–4.34)	0.70 (0.15–3.18)
Brodie [23] (1989)	Amoxicillin		1	1
	Cefuroxim – axetil	^b	1.32 (0.21–8.25)	1.04 (0.99–1.08)
Nord [24] (1988)	Amoxicillin	1	1	1
	Bacampicillin	0.75 (0.46–1.24)	1.17 (0.49–2.81)	0.74 (0.25–2.20)
Ekedahl [25] (1987)	Cefaclor		1	
	Doxycyclin	^b	0.66 (0.31–1.43)	^a
Scheld [26] (1986)	Amoxicillin	1		1
	Cyclacillin	0.61 (0.09–4.01)	^c	1.00 (0.06–16.56)
Frühwald [27] (1984)	Co-tetroxazin	1	1	1
	Co-trimoxazole	0.45 (0.08–2.47)	1.24 (0.07–20.49)	1.05 (0.98–1.12)

^aThere were no reported side-effects in one or both treatment groups.^bThere were no assessments for clinical cure or clinical success.^cAll patients were cured in one or both treatment groups.

TABLE 4. Odds ratios and confidence intervals, unstratified, exact; statistically significant odds ratios are boldface

	Clinical cure		Clinical success		Adverse events	
	% (n)	Odds ratio (95% CI)	% (n)	Odds ratio (95% CI)	% (n)	Odds ratio (95% CI)
Type of antibiotic						
Penicillins	67 (695)	1	90 (743)	1	3.2 (1171)	1
Cephalosporins	71 (536)	1.16 (0.90–1.50)	93 (739)	1.33 (0.91–1.96)	2.0 (1139)	0.61 (0.35–1.07) ^a
Tetracyclines	59 (164)	0.70 (0.49–1.01) ^a	89 (269)	0.89 (0.55–1.45) ^a	2.1 (435)	0.63 (0.27–1.34) ^a
Macrolids	67 (242)	0.96 (0.70–1.33)	95 (242)	2.06 (1.08–4.24)^a	2.2 (407)	0.67 (0.28–1.44) ^a
Sulphonamides	82 (157)	2.13 (1.36–3.40)^b	93 (157)	1.42 (0.73–3.05) ^b	1.3 (158)	0.38 (0.04–1.51) ^b
Spectrum						
Broad	69 (1552)	1	91 (1908)	1	2.5 (2903)	1
Narrow	67 (242)	0.89 (0.66–1.20)	95 (242)	1.84 (1.00–3.69)	2.2 (407)	0.89 (0.39–1.80)
β -lactamase inhibition						
No	69 (549)	1	91 (712)	1	2.6 (905)	1
Yes	69 (682)	1.02 (0.79–1.31) ^a	92 (770)	1.11 (0.76–1.62) ^a	2.6 (1405)	0.99 (0.57–1.75) ^a
Bactericidal effect						
No	64 (242)	1	92 (511)	1	2.1 (842)	1
Yes	70 (1217)	1.36 (1.07–1.72)	92 (1639)	0.95 (0.64–1.38) ^a	2.5 (2468)	1.20 (0.70–2.17)

^aThe base-rate was heterogeneous.^bHomo/heterogeneity could not be determined because the studies including sulphonamides compared two modalities of sulphonamide treatment.

adverse events are presented in Table 3. Analyzing all studies separately, we found significant differences in only two studies. A significantly different effect on clinical cure was found between cefpodoxim and cefaclor [22]. A significantly different effect on clinical success was found between loracarbef and doxycycline [16]. Some odds ratios were substantial but very imprecise (confidence intervals were wide). The following reasons explain the empty cells in Table 3: there were no reported side-effects in one or both treatment groups; there were no assessments for clinical cure or clinical success; all patients were cured in one or both treatment groups.

Unstratified Odds Ratios (Step 2)

Not all outcomes were assessed for all patients, so the denominators differ. The overall clinical cure rate after microbial therapy was 69% (1234/1794), the overall clinical success rate was 92% (1971/2151). The overall adverse events rate was 2.4% (81/3310). Overall, sulphonamides had a significantly higher clinical cure rate than penicillins, and macrolids had a significant higher clinical success than penicillins (Table 4, row 1). Broad-spectrum antibiotics had a significantly higher clinical success rate than narrow-spectrum ones (Table 4, row 2). Overall, antibiotics without β -lactamase inhibition did not differ from those with β -lactamase inhibition (Table 4, row 3). Bactericidal antibiotics had a significant higher clinical success than bacteriostatic ones (Table 4, row 4).

Odds Ratios after Stratification by Study (Step 3)

When we did not assume that base rates were necessarily homogeneous, and analyzed the data by means of a Mantel-

Haenzel procedure stratified by study, nearly all statistically significant differences disappeared. One exception was that antibiotics with β -lactamase inhibition gave a higher clinical cure rate with statistical significance than those without with regard to clinical cure (Table 5, row 3).

The loss of statistical significant differences indicated that there was a considerable loss of power or that base-rates were heterogeneous. In all comparisons, there was a loss of power, as is shown by a comparison of the number of patients in Table 4 with the number of patients in Table 3. The assumption of homogeneity of base rates in the second step of the analysis was considered to be justified if the odds ratio stratified by study in Table 5 did not differ from the unstratified odds ratio in Table 4 for more than 15%. On the basis of this criterion, for 10 base rates, the assumption of homogeneity was not justified (these base rates are marked in Table 4) and, for three base rates, odds ratios stratified by study could not be calculated (also marked in Table 4).

Stratification by study yielded clinically significant odds ratios (<0.67 or >1.50) for five contingency tables: β -lactamase inhibition regarding clinical cure; type of antibiotic (penicillins, macrolids) regarding clinical success; spectrum regarding clinical success; type of antibiotic (penicillins, cephalosporins) regarding adverse events; and type of antibiotic (penicillins, tetracyclines) regarding adverse events.

Odds Ratios after Stratification by Background Characteristics (Step 4)

In this fourth step, we clustered studies with similar characteristics. This step was applied only for clinically significant odds ratios as calculated in the third step. For seven comparisons, no stratification was possible due to empty cells. In

TABLE 5. Odds ratios and confidence intervals, stratified by study, exact; statistically significant odds ratios are boldface

	Clinical cure		Clinical success		Adverse events	
	(N-R/N-T) ^a	Odds ratio (95% CI)	(N-R/N-T) ^a	Odds ratio (95% CI)	(N-R/N-T) ^a	Odds ratio (95% CI)
Type of antibiotic						
Penicillins		1		1		1
Cephalosporins	(132/132)	1.27 (0.74–2.19)	(225/210)	1.19 (0.65–2.21)	(384/330)	0.48 (0.14–1.44)
Tetracyclines	—	_b	—	_b	—	_b
Macrolids	(239/242)	0.87 (0.58–1.30)	(239/242)	1.56 (0.70–3.63)	(410/407)	0.83 (0.30–2.24)
Sulphonamides	—	_c	—	_c	—	_c
Spectrum						
Broad		1		1		1
Narrow	(239/242)	0.87 (0.58–1.30)	(239/242)	1.56 (0.70–3.63)	(410/407)	0.83 (0.30–2.24)
β -lactamase inhibition						
No		1		1		1
Yes	(114/122)	2.44 (1.27–4.81)	(188/167)	1.42 (0.50–4.18)	(205/213)	1.45 (0.34–7.07)
Bactericidal effect						
No		1		1		1
Yes	(406/407)	1.20 (0.89–1.62)	(511/515)	1.24 (0.75–2.05)	(842/850)	1.16 (0.58–2.32)

^aN-R indicates the number of patients in the reference group (penicillins, broad spectrum, no β -lactamase inhibition, and no bactericidal effect respectively).

N-T indicates the number of patients in the treatment group.

^bThere was no direct comparison between tetracyclines and penicillins.

^cNo study compared sulphanomides with any other type of antibiotic.

all other comparisons, there was an increase of power, as is shown by a comparison of the number of patients in Table 5 with the number of patients in Table 6. In all except four contingency tables, clustering of studies appeared to be not justified because the odds ratios adjusted for the background characteristics changed by 15% or over (Table 6) compared with the odds ratio stratified by study (Table 5). The four "stable" odds ratios are marked in Table 5. Additionally, in these four cases, odds ratios varied across strata (Table 7). These results indicate the existence of confounding or effect modification by unmeasured background characteristics.

Because in the third step antibiotics with β -lactamase inhibition performed statistically significantly better with regard to clinical cure than those without β -lactamase inhibition, while the base-rate was heterogeneous (Table 4) we studied this result in more detail. When comparing antibiotics with and without β -lactamase inhibition, the significant effect of antibiotics with β -lactamase inhibition on clinical cure was only found in a study from Southern Europe, published before 1991 (Table 8) [22].

DISCUSSION AND CONCLUSIONS

In this meta-analysis, we found hardly any differences between all antimicrobial treatments considered in the treatment of acute maxillary sinusitis. When all studies were analyzed separately, statistically significant differences were found between antibiotics in only two out of 16 studies. Our calculations were comparable to the original authors' conclusions. This analysis by study was in fact a re-analysis

of data as already performed in each separate study. Because the width of the confidence intervals in the first step could be due to small sample sizes, the data of all studies were pooled under the assumption of homogeneity of base-rates. However, there was heterogeneity between the base-rates of several studies, so this assumption appeared to be invalid. The next step was a standard classic meta-analysis in which we stratified patients by study. In this step, study was used to adjust for heterogeneities between studies. This left only one significant effect: antibiotics with β -lactamase inhibition offered a significantly better bacteriological cure than antibiotics without β -lactamase inhibition. The final step was to increase the power of the analysis by estimating effects adjusted for background characteristics instead of for separate studies. Background characteristics as measured appeared to explain heterogeneity of base rates of odds ratios in a minority of the included studies. Remarkable was that the statistically significant effect of antibiotics with β -lactamase inhibition on clinical cure was only found in a study from Southern Europe, published before 1991 [22]. Based on growing resistance patterns due to the increasing use of antibiotics, it seems reasonable to suppose that the effectiveness of antibiotics with β -lactamase inhibition has decreased over time.

The meta-analysis of step 3 can be considered as a fixed-effect meta-analysis of binary outcomes. Since the stratified odds ratios differed from the pooled odds ratios, homogeneity of base rates could not be assumed and simple pooling gave biased estimates of the odds ratios. In the analysis of step 3, there is a tremendous loss of statistical power. This loss of power could be repaired by considering a random-

TABLE 6. Odds ratios and confidence intervals, stratified by background characteristics, exact; stable odds ratios are **boldface**

	Clinical cure β -lactamase inhibition no; yes		Clinical success type of antibiotic penicillins; macrolids		Clinical success spectrum broad; narrow		Adverse events type of antibiotic penicillins; cephalosporins		Adverse events type of antibiotic penicillins; tetracyclines	
	N-R/N-T ^a	Odds ratio (95% CI)	N-R/N-T ^a	Odds ratio (95% CI)	N-R/N-T ^a	Odds ratio (95% CI)	N-R/N-T ^a	Odds ratio (95% CI)	N-R/N-T ^a	Odds ratio (95% CI)
Study	114/122		239/242		239/242		384/330		440/435	
[15% less/15% more]	2.44 (1.27–4.81)		1.56 (0.70–3.63)		1.56 (0.70–3.63)		0.48 (0.14–1.44)		0.43 (0.24–1.19)	
	[2.07; 2.81]		[1.33; 1.79]		[1.33; 1.79]		[0.41; 0.55]		[0.37; 0.49]	
Setting	549/682		743/242		1908/242		1171/1139		1171/435	
primary care/secondary care	1.03 (0.79–1.33)		2.07 (1.09–4.28)		1.85 (1.00–4.28)		0.61 (0.34–1.06)		0.59 (0.25–1.27)	
Geographical area	549/682		743/242		1672/242		1171/881			
N. Europe/S. Europe/USA	0.95 (0.73–1.25)		2.27 (1.17–4.78)		2.39 (1.27–4.88)		0.51 (0.26–0.95)			
Year of publication	549/682		743/242				1171/1139		1171/435	
$\leq 1990 / > 1990$	1.26 (0.92–1.75)		2.41 (1.23–5.10)				0.61 (0.35–1.07)		0.62 (0.26–1.33)	
Diagnosis sinusitis	549/682		691/242		1811/242		1171/1139			
1/2/3 ^b	0.98 (0.76–1.28)		1.57 (0.77–3.42)		1.69 (0.91–3.42)		0.62 (0.35–1.08)			
Duration of therapy			743/219		1908/242					
<10 days/ ≥ 10 days			1.85 (0.97–3.82)		1.81 (0.99–3.64)					
Local decongestants	549/682		743/242		1908/242		1171/1139		1171/435	
no/yes	1.31 (0.94–1.83)		1.87 (0.97–3.92)		1.97 (1.06–3.99)		0.65 (0.36–1.16)		0.64 (0.26–1.44)	
Treatment dose	549/682		743/242		1908/242		01171/1139			
DDD ≤ 1 / DDD > 1	0.91 (0.68–1.22)		1.95 (1.00–4.11)		1.51 (0.79–3.16)		0.71 (0.39–1.24)			

^aN-R indicates the number of patients in the reference group (no β -lactamase inhibition, penicillins, broad spectrum, penicillins, and penicillins, respectively).^b1 = clinical signs; 2 = ultrasound or radiograph; 3 = aspiration plus culture.^cNo stratification is possible due to empty cells.

TABLE 7. Odds ratios and confidence intervals for clinically significant odds ratios, stratified by background characteristics, exact

Outcome	Type of antibiotic	
	Penicillins	Macrolids
Clinical success		
Diagnosis		
Clinical signs	1	1.20 (0.54–2.61)
Ultrasound or radiograph	1	0.60 (0.29–1.21)
Aspiration plus culture	1	1.86 (0.68–5.58)
Strata combined	1	1.57 (0.77–3.42)
	Spectrum	
	Broad	Narrow
Clinical success		
Diagnosis		
Clinical signs	1	^a
Ultrasound or radiograph	1	1.10 (0.43–3.61)
Aspiration plus culture	1	2.15 (0.96–5.66)
Strata combined	1	1.69 (0.91–3.42)
Dose		
DD ≤ 1		Infinite
DD > 1	1	1.27 (0.64–2.70)
Strata combined	1	1.51 (0.79–3.16)
	Type of antibiotic	
	Penicillins	Cephalosporins
Geographical area		
Northern Europe	1	0.48 (0.14–1.44)
Southern Europe	1	0.70 (0.30–1.61)
United States of America	1	^b
Strata combined	1	0.26 (0.05–0.88)

^aAll studies with clinical signs as basis for the diagnosis sinusitis included only broad spectrum antibiotics.

^bNone of the studies performed in the United States of America included cephalosporins.

effect model with a random base-rate term per study. Instead of this complicated method, we tried to stratify on background characteristics. This increased the power of the analysis, because more studies could be included. However, we found in this analysis of step 4, a heterogeneity of the odds ratios, per background characteristic related stratum, suggesting that there is either heterogeneity of base-rates within such strata or heterogeneity of odds ratios (effect modification). Due to the very unbalanced design of this dataset, it is hard to infer which of these mechanisms caused this heterogeneity.

A meaningful interpretation of pooled results is only possible if studies concern sufficiently comparable patient groups [28]. Therefore, the analysis was restricted to prospective, comparative, randomized studies on otherwise healthy adults, with acute maxillary sinusitis. We excluded studies in which the results were not specified for adult or adolescent patients with acute maxillary sinusitis. Furthermore, we excluded all studies on patients with other dis-

eases like asthma, chronic obstructive pulmonary disease (COPD), or diabetes. Despite this, heterogeneity occurred.

Some authors claim that the main arguments to prescribe antibiotics are the long-term benefits of antibiotics, such as the reduction of the number of patients with chronic or recurrent sinusitis, and the prevention of serious complications (such as brain abscess) [29,30]. This could not be analyzed, because none of the studies had a long-term follow-up. Moreover, the long-term adverse effects of antibiotics, such as allergic reactions to penicillins that may begin more than two weeks after the start of therapy [31], could also not be analyzed.

In this analysis we could not assess whether antibiotics are more effective than placebos in the treatment of acute maxillary sinusitis. At the moment, there are five published placebo-controlled studies on antibiotics in acute maxillary sinusitis. All five studies are outside the time-frame of our meta-analysis. In a recently published placebo-controlled study [32], amoxycillin and penicillin V led to a significantly higher clinical success rate than placebo treatment (86% versus 57%). In another recently published placebo-controlled study [33], amoxycillin did not significantly influence the clinical course of maxillary sinusitis (clinical success rate 83% versus 77%). In the three other (old) placebo-controlled studies, the pooled clinical cure rate after placebo treatment or natural course was 60% and the pooled clinical success rate was 88% [34–36]. The results of the recently published *British Medical Journal* study [32], and those described in the current paper are hard to compare, because the firstly mentioned recently published study used a different diagnostic strategy (computed tomography). As far as we know, there are no published data to link the diagnostic computed tomography to the diagnostic strategies of the studies included in our meta-analysis. The pooled results of the three old studies indicate that acute maxillary sinusitis is often a self-limiting disease [34–36]. Because this outcome-rate resemble the results of our analysis, and because of the results of the recently published *Lancet* study [33], we

TABLE 8. Odds ratios and confidence intervals for clinical cure given a β -lactamase inhibition, stratified by geographical area and year of publication, exact

	β -lactamase inhibition	
	No	Yes
Geographical area		
Northern Europe	1	1.01 (0.67–1.53)
Southern Europe	1	2.44 (1.27–4.81)
United States of America	1	0.52 (0.31–0.85)
Strata combined	1	0.95 (0.73–1.25)
Year of publication		
≤1990	1	2.42 (1.42–4.30)
>1990	1	0.75 (0.46–1.19)
Strata combined	1	1.26 (0.92–1.75)

Statistically significant odds ratios are boldface.

expect only small differences between placebo and antimicrobial treatment in case of acute maxillary sinusitis. Moreover, recent randomized clinical trials on acute otitis media, acute tonsillitis, and acute bronchitis have failed to show an effectiveness of antimicrobial treatment [1–3].

A major source of bias in a meta-analysis is that studies, that were not published because their results were not statistically significant, are not included. Because of this so-called publication bias, the analysis will tend to overestimate the actual effect [37]. As our main result was a zero effect, nearly all antimicrobial treatments being of equal value, an adjustment for this bias would not change our conclusions.

In conclusion, nearly all antibiotics seem to be of comparable value in the treatment of acute maxillary sinusitis; only those with β -lactamase inhibition may be slightly more effective. This means that price alone could dictate the choice of an antibiotic in the treatment of acute maxillary sinusitis. Whether the prescription of antibiotics for this disease is actually justified remains to be seen. There is a strong need for placebo controlled, randomized studies on antimicrobial treatment (antibiotics with β -lactamase inhibition) with short-term outcomes and diagnostic strategies comparable with those in other trials. Moreover, the nearly total lack of knowledge on the long-term effects of antimicrobial treatment in acute maxillary sinusitis stresses the need for additional long-term studies.

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