Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data

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Summary

Background **Primary-care physicians continue to overprescribe antibiotics for acute rhinosinusitis because distinction between viral and bacterial sinus infection is difficult. We undertook a meta-analysis of randomised trials based on individual patients' data to assess whether common signs and symptoms can be used to identify a subgroup of patients who benefit from antibiotics.**

Methods **We identified suitable trials—in which adult patients with rhinosinusitis-like complaints were randomly assigned to treatment with an antibiotic or a placebo—by searching the Cochrane Central Register of Controlled Trials, Medline, and Embase, and reference lists of reports describing such trials. Individual patients' data from 2547 adults in nine trials were checked and re-analysed. We assessed the overall effect of antibiotic treatment and the prognostic value of common signs and symptoms by the number needed to treat (NNT) with antibiotics to cure one additional patient.**

Findings **15 patients with rhinosinusitis-like complaints would have to be given antibiotics before an additional patient was cured (95% CI NNT[benefit] 7 to NNT[harm] 190). Patients with purulent discharge in the pharynx took longer to cure than those without this sign; the NNT was 8 patients with this sign before one additional patient was cured (95% CI NNT[benefit] 4 to NNT[harm] 47). Patients who were older, reported symptoms for longer, or reported more severe symptoms also took longer to cure but were no more likely to benefit from antibiotics than other patients.**

Interpretation **Common clinical signs and symptoms cannot identify patients with rhinosinusitis for whom treatment is clearly justified. Antibiotics are not justified even if a patient reports symptoms for longer than 7–10 days.**

Introduction

An upper-respiratory-tract infection is the third most common reason for a doctor's consultation in the USA.[1] About a third of these consultations are diagnosed as acute rhinosinusitis, and 80% of patients with this diagnosis are prescribed an antibiotic.[2] In Europe, antibiotic prescription rates in primary care range from 72% to 92% for patients with acute rhinosinusitis.[3–5]

Primary-care physicians continue to overprescribe antibiotics for acute rhinosinusitis because distinction between viral and bacterial sinus infections is difficult.[2,6] In a primary-care setting, no test, sign, or symptom, or combination of these can clearly identify patients who benefit from antibiotics.[7] Increased rates of antibiotic resistance are seen in countries where antibiotic use is highest and antimicrobial resistance has led to increased morbidity, mortality, and cost throughout the world.[8–12]

Guidelines therefore recommend deferral of antibiotic treatment until a patient has had symptoms for at least 7–10 days.[13,14] This recommendation was made on the basis of the time usually taken to progress from a viral to an established secondary bacterial infection, rather than on evidence from randomised trials. However, both discomfort and cost of additional office visits would be reduced if patients with a bacterial infection did not have to wait 7–10 days before starting treatment. We undertook an individual patient meta-analysis of randomised trials to assess whether common signs, symptoms, or specific patient characteristics can be used to identify a subgroup that would benefit from antibiotic treatment.

Methods

Trial selection

We requested individual patients' data from the investigators of all known trials in which adult patients with rhinosinusitis-like complaints were randomly assigned to treatment with an antibiotic or a placebo. Patients in these trials had to have clinical signs and symptoms of rhinosinusitis, such as a previous common cold or two stages of illness (symptoms initially improving then deteriorating), purulent nasal discharge, unilateral facial pain, toothache, pain when chewing, purulent discharge in the pharynx, or pain on bending. We identified suitable trials by a formal search of the Cochrane Central Register of Controlled Trials, Medline, and Embase, and reference lists of reports describing such trials. The process followed is described in a protocol registered with the Cochrane Collaboration.[15] Trials were excluded if patients were recruited partly on the basis of results of imaging or laboratory tests or bacterial culture because in a primary-care setting such methods are not routinely used or recommended.[13] We included trials in which concomitant medication was part of the trial design, provided the same medication was given to patients in both randomly assigned groups.

The suitability of each trial providing individual patients' data was checked by use of a protocol or case

	Country	Patients (n)	Antibiotic	Inclusion criteria	
				Age (years)	Clinical diagnosis
Norrelund (1978)[24]	Denmark	140	Pivampicillin	≥14	At least PND or blocked nose and nasal voice
Stalman (1997)[25]	Netherlands	192	Doxycycline	≥15	At least 2: PND, previous cold, pain on bending
Kaiser (2001)[26]	Switzerland	269	Azithromycin	≥18	URTI (common cold or acute sinusitis)
De Sutter (2002)[27]	Belgium	416*	Amoxicillin	≥12	URTI and PND
Bucher (2003)[28]	Switzerland	252*	Amoxicillin and clavulanic acid	≥18	PND and frontal or maxillary pain
Varonen (2003)[29]	Finland	150	Amoxicillin, phenoxymethylpenicillin, or doxycycline	≥18	Clinical diagnosis of acute maxillary sinusitis
Meltzer (2005)[30]	International	503†	Amoxicillin	≥12	Moderate symptom score (PND, postnasal drip, nasal congestion, sinus headache, facial pain)
Merenstein (2005)[31]	USA	135	Amoxicillin	≥18	Symptoms for least 7 days and PND or pus in nasal cavity or unilateral facial pain
Williamson (2007)[32]	UK	240	Amoxicillin	≥16	At least 2: PND, unilateral face pain, pus in nasal cavity
Schering-Plough (NP)[33]	International	485†	Amoxicillin	≥12	Moderate symptom score (PND, postnasal drip, nasal congestion, sinus headache, facial pain)

PND=purulent nasal discharge. URTI=upper-respiratory-tract infection. NP=not published. *One patient randomised but not treated. †Only those patients randomised to antibiotic or placebo.

Table 1: **Trials included**

report form, or both. Data from each trial were first checked against reported results, and queries were resolved with the principal investigator, trial data manager, or statistician. The cure rates for all trials included in this meta-analysis might differ slightly from previous reports because we treated data in a consistent manner across all trials.

Patients and outcome

Our intention-to-treat population consisted of all patients randomly assigned and receiving at least one dose of medication. Our outcome of interest was the proportion of patients cured at the time the primary outcome of the trial was assessed. We used the definition of cure as that defined in an individual trial or as defined by agreement with the primary investigator in advance of the analysis (in some trials, the primary outcome was continuous and not binary). Patients receiving a known antibiotic in addition to or as a replacement for randomised treatment were regarded as not cured. In four trials, the primary outcome was assessed solely from patients' diaries; however, patients did not always complete these diaries. Last diary entries were brought forward in these trials because sick patients might become disillusioned with an ineffective treatment and lose interest or because those that were cured might not continue to record information once they had recovered.

A range of clinical signs and symptoms were recorded at baseline in the various trials but with a large overlap between trials. In our analysis, we assessed the prognostic value of any sign or symptom recorded in at least four trials. Although point-of-care tests might have prognostic value, C-reactive protein concentrations were recorded in only one trial.[16]

Statistical analysis

We used random-effects models for the odds ratio (OR) for cure because of the close relation between such models and a proportional hazards model for time to cure (webappendix). However, we reported clinical risk as the number needed to treat (NNT).[17] As a precursor to individual patient analyses, we did a typical meta-analysis with aggregated data. We fitted a random-effects model to the OR in every trial, and used the method of DerSimonian and Laird to estimate the variance of the random treatment effects.[18]

See **Online** for webappendix

In our model for individual patient analyses, the probability of cure for a patient in a trial was a function of the average odds of cure if not treated, the average OR for cure if given antibiotics, and random trial and random treatment effects (webappendix). The distribution of the random trial and treatment effects was bivariate normal, which allowed for any correlation between the treatment effect and underlying risk.[19,20] The model implies that the effect of treatment can be expected to differ from trial to trial and that these trials are a sample of past and future trials. With this model we can predict the outcome for new patients in future trials.[21]

To assess the prognostic value of a sign or symptom, we added a further two parameters to this model (webappendix). These parameters show how the presence of a sign or symptom first multiplies the odds of cure if not treated and second multiplies the OR for cure if treated. If a sign or symptom has prognostic value, the first multiplier will probably have a numerical value less than 1 (because patients with this sign or symptom are probably sicker and take longer to cure than those without this sign or symptom) and the second multiplier should have a numerical value greater than 1 (because antibiotic treatment should provide

	Interval (days) to outcome assessment*	Number cured/total with known outcome (% cured)		Outcome not known	
		Placebo	Antibiotic	Placebo	Antibiotic
Norrelund (1978)[24]	8	33/64 (52%)	40/71 (56%)	3	2
Stalman (1997)[25]	10	59/93 (63%)	63/95 (66%)	1	3
Kaiser (2001)[26]	8	72/132 (55%)	76/133 (57%)	1	3
De Sutter (2002)[27]†	10	60/201 (30%)	79/198 (40%)	7	9
Bucher (2003)[28]†	14	83/126 (66%)	89/124 (72%)	1	0
Varonen (2003)[29]‡	14	39/57 (68%)	70/85 (82%)	3	3
Meltzer (2005)[30]	15	161/248 (65%)	185/251 (74%)	4	0
Merenstein (2005)[31]	14	25/60 (42%)	32/56 (57%)	8	11
Williamson (2007)[32]§	10	29/51 (57%)	36/54 (67%)	12	6
Williamson (2007)[32]¶	10	35/56 (63%)	30/46 (65%)	8	7
Schering-Plough (NP)[33]	15	161/245 (66%)	162/236 (69%)	0	4

NP=not published. *Interval between baseline and primary assessment of cure. †One patient randomised but not treated. ‡Two patients excluded because treatment was not known. §Without and ¶with concomitant nasal steroids in both randomised groups.

Table 2: **Outcomes of included trials**

additional benefit for patients with this sign or symptom).

We used R (version 2.5.1) for all analyses, the meta package (version 0.8–2) for aggregate data meta-analyses, and the R2WinBUGS package (version 2.1–4) and WinBUGS (version 1.4.1) for individual patient data meta-analyses (webappendix).

To fit a model in WinBUGS, we ran five Markov chains, burnt in every chain for 5000 iterations, and then sampled every chain during the next 10 000 iterations, taking every fifth value. We used the Markov chains to simulate 10 000 new patients and for every patient we calculated a risk difference—the difference between the probability of cure if treated and if not treated—and inverted the risk difference to give the NNT. We plotted the posterior distribution of these NNTs and summarised this distribution to give a mean and 95% credible interval (CI);[22]—ie, a Bayesian confidence interval.[23]

Role of the funding source

The sponsors had no role in the study design, data collection, data analysis, or data interpretation, or writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

We identified ten trials that met our inclusion criteria (table 1);[24–33] all trials were double-blind. No summary of final results was available for the unpublished trial.[33] Individual patients' data were available for all but the earliest trial.[24]

Our intention-to-treat population consisted of 2640 patients. Two patients had to be excluded from our analysis because their randomised treatment was not known.[29] One trial used a factorial design with four randomised groups.[32] To meet our inclusion criteria, data from this trial were split into two subtrials: patients randomly assigned to an antibiotic or placebo without concomitant nasal steroids in both randomised groups or patients randomly assigned to an antibiotic or placebo with concomitant nasal steroids in both randomised groups.

In two trials, the primary outcome was assessed on the basis of a mean symptom score.[30,33] For these trials, cure was defined as all five symptoms assessed by the patient as either not present or only mild—similar definitions were used in other trials.[25,27,32] The primary assessment of outcome was either after 8–10 or 14–15 days (table 2). Outcome was generally assessed in a telephone interview[28,29,31] or from a patient's diary.[25,30,32,33] In other trials, physicians assessed patients at a clinical examination[26] or patients filled out a questionnaire,[24] and in one trial outcome was assessed from three sources of information—a questionnaire given to patients, a patient diary, and a clinical examination.[27] In trials using patients' diaries, outcome was assessed by last diary entries being brought forward for 10 (5%) of 192, 66 (13%) of 503, and 43 (9%) of 485 patients in three trials, for a median of 1 (IQR 1–2), 1 (1–6), and 2 (1–7) days, respectively[25,30,33] and by subsequent telephone interview with 14 (6%) of 240 patients in one trial.[32] The outcome was unknown for 14% of the patients in two trials[31,32] and for not more than 4% of the patients in the other trials (table 2). In total, cure was assessed for 2547 patients (96% of our intention-to-treat population).

In a meta-analysis of aggregated data (figure 1), the estimated OR for the overall treatment effect of antibiotics relative to placebo was 1·35 (95% CI 1·15–1·59). The estimated variance of random treatment effects was 0 (and therefore I^2, a measure of heterogeneity,[34] was also 0). If we excluded the only trial for which individual patients' data were not available,[24] the estimate of the overall treatment effect was almost unchanged (OR 1·36, 1·15–1·61). If we excluded trials that used patients' diaries[25,30,32,33] or trials that potentially had a lower rate of bacterial infection,[26,30,33] the estimate of the overall treatment effect was similar but slightly less precise (1·43, 1·13–1·79 and 1·44, 1·15–1·79, respectively) than the analysis including all trials. In one trial, no attempt was made to exclude patients with a common cold;[26] in two trials, patients with signs or symptoms suggestive of a serious bacterial infection were excluded.[30,33]

In an analysis of individual patients' data (and therefore with the earliest trial excluded[24]), the estimated OR for the overall treatment effect was 1·37 (95% CI 1·13–1·66). The mean NNT for 10 000 simulated new patients was 15 (95% CI NNT[benefit] 7 to NNT[harm] 190; figure 2), which implied that 15 patients had to be given antibiotics before one additional patient was cured. However, the NNT could be as low as 7 or treatment might offer no benefit at all (NNT=∞); treatment might even have a

slightly harmful effect such that one fewer patient is cured for every 190 patients treated.[35] A meta-analysis of aggregate data risk differences for these trials gave a mean NNT of 14 (95% CI NNT[benefit] 9 to NNT[benefit] 30). The Bayesian credible interval for the NNT was wider than the CI for aggregate data because the Bayesian model took into account the uncertainty in the estimate of each parameter in the model and in the Monte Carlo simulation of new patients.[36]

In these nine trials the treatment effect was almost independent of the underlying risk. In our model, patients in the trial with the lowest cure rates[27] were estimated to have a 32% probability of a cure without treatment; new patients simulated with this degree of risk had a mean NNT of 13 (95% CI NNT[benefit] 5 to NNT[harm] 100). Patients in the trial with the highest cure rates[29] were estimated to have a 71% probability of a cure without treatment; new patients simulated with this degree of risk had a mean NNT of 18 (95% CI NNT[benefit] 8 to NNT[harm] 70). This near independence between cure rate and treatment effect suggested that trials did not have lower cure rates because investigators were more successful at recruiting patients with a bacterial infection in some trials than in others.

Table 3 shows the multiplicative effect of individual baseline signs or symptoms on the odds of cure if a patient remained untreated and on the OR for cure if treated. We used a continuous measure of a sign or symptom whenever possible because this led to improved precision in the estimates of prognostic value. However, for the duration of symptoms and for temperature, we also included a binary measure because this increased the number of trials that could be included in an analysis.

Duration of symptoms was recorded as a continuous variable in all but one trial in which it was recorded as the binary variable 6 days or more.[29] Patients reporting a longer duration of symptoms took longer to cure but were no more likely to benefit from treatment than other patients (table 3). Similar, though less precise, results were recorded for patients who had symptoms for 6 days or more (table 3) and for those with symptoms for 7 days or more, or for 10 days or more (data not shown).

We assessed symptom severity at baseline using symptom scores from five trials,[27,29,30,32,33] a mood score from one trial,[25] and a question on overall state of health from three trials.[26,28,31] Each measure of symptom severity was then converted to a ridit score for that trial—the midpoint of the percentages covered by a specific level of severity in the cumulative distribution of severity when ordered from lowest to highest.[37] Scores were between 0 and 100%; the lowest and highest scores in a trial corresponded to patients with least and most severe symptoms, respectively; patients with median symptom severity in their trial had a score of about 50%. Patients reporting severe symptoms took longer to cure, but they were no more likely to benefit from treatment than other patients (table 3).

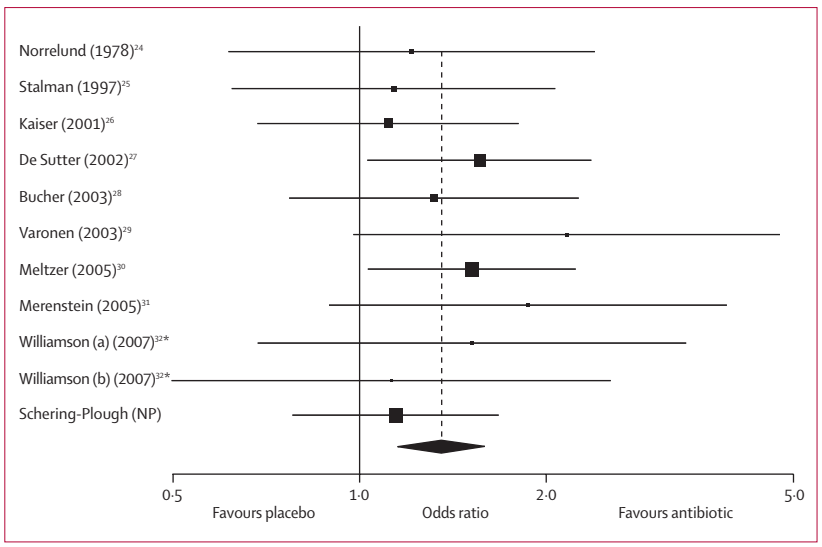

Figure 1: **A meta-analysis of the odds ratio (OR) for cure with aggregate data**
The squares show the estimated ORs and the horizontal lines through the squares show the 95% CIs. The size of the square is proportional to the precision of the estimated ORs. The vertical dotted line shows the estimated overall OR from a random-effects meta-analysis and the width of the diamond represents the 95% CIs for this overall estimate. NP=not published. *Trial split into two subtrials, without (a), and with (b) concomitant nasal steroids in both randomised groups.

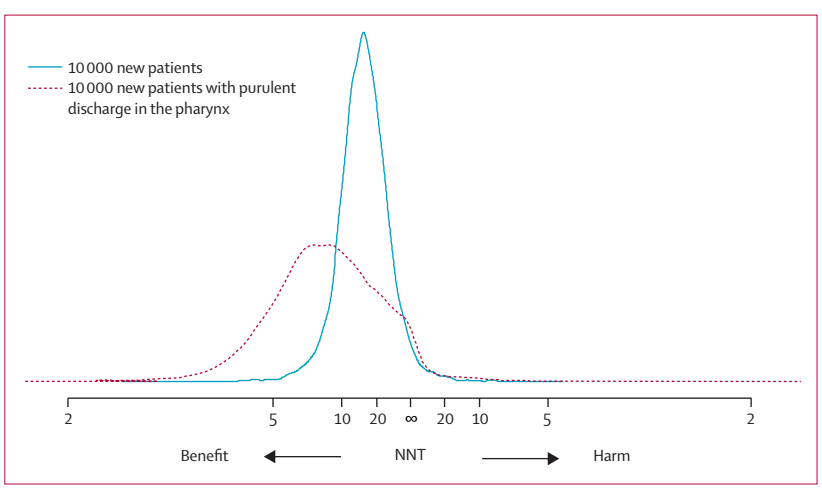

Figure 2: **Distribution of the number needed to treat (NNT) for 10 000 simulated new patients**

For other patient-reported symptoms—a previous common cold (or two stages of illness[29]), pain on bending, unilateral face pain, pain in the teeth, and purulent nasal discharge—estimates were not sufficiently precise to draw any conclusion about their prognostic value other than that these symptoms might not be reliable enough to be of any real use. We treated a previous common cold and two stages of illness as synonymous; however, one symptom could be more prognostic than the other.

In each trial, physicians were asked to do rhinoscopy with a rhinoscope or (in one trial) an otoscope.[31] Although no firm conclusion could be drawn about the prognostic value of purulent nasal discharge, patients with purulent discharge in the pharynx took longer to cure and were more

	Reference number of trials excluded	Mean (95% CI) effect on odds of cure if untreated*	Mean (95% CI) effect on OR for cure†
Signs or symptoms reported by patient‡			
Duration of symptoms (per week)	29	0·90 (0·81–0·99)	0·95 (0·82–1·10)
Duration of symptoms at least 6 days§	None	0·84 (0·63–1·11)	0·95 (0·64–1·36)
Symptom severity (per 10% of the trial ridit score)¶	None	0·93 (0·90–0·97)	0·99 (0·93–1·05)
Previous common cold	26,28,30,31,33	1·19 (0·80–1·87)	1·00 (0·54–1·84)
Pain on bending	26,29–31,33	1·30 (0·83–2·01)	0·69 (0·38–1·30)
Unilateral face pain	30,33	1·16 (0·85–1·58)	0·78 (0·51–1·20)
Pain in teeth	28,30,31,33	0·83 (0·58–1·20)	1·08 (0·65–1·81)
Purulent nasal discharge	None	1·02 (0·79–1·32)	1·09 (0·76–1·55)
Signs noted by physician			
Purulent nasal discharge	None	1·04 (0·81–1·33)	1·06 (0·75–1·50)
Purulent discharge in pharynx	30–33	0·65 (0·45–0·96)	1·60 (0·95–2·76)
Temperature (per °C)	25,26,29	0·93 (0·71–1·21)	1·28 (0·87–1·88)
Temperature above 37·5°C	25	0·72 (0·43–1·20)	1·05 (0·51–2·18)
Other			
Age (per 10 years)	None	0·88 (0·81–0·96)	1·04 (0·92–1·18)

*exp(γ) (webappendix equation [2]). †exp(δ) (webappendix equation [2]). ‡Continuous measures have units in parentheses. §24 patients excluded with symptoms for longer than 30 days. ¶Within each trial, the score was the midpoint of percentages covered by a specific level of severity in the cumulative distribution of severity when ordered from lowest to highest.[37]

Table 3: **Multiplicative effect of baseline signs and symptoms on the odds of cure if untreated and on the odds ratio (OR) for cure if given antibiotics**

likely to benefit from treatment than other patients (table 3). Our findings also suggested that treatment might offer additional benefit for patients with a higher temperature (table 3). The mean NNT for 10 000 simulated new patients with purulent discharge in the pharynx was 8 (95% CI NNT[benefit] 4 to NNT[harm] 47; figure 2). This result was obtained from an analysis of only 1269 patients in five trials (32% had purulent discharge in the pharynx). However, the multiplicative effect of purulent nasal discharge on the OR for cure was only slightly higher in these trials (1·18, 95% CI 0·73–1·92) than in all trials (table 3).

We included age in this list of signs and symptoms because risk factors often cluster in patients and older patients commonly have more risk factors than younger patients.[38] The median age for all patients was 35 years (IQR 26–45) and the median age in each trial varied from 30[26] to 42.[32] As with symptom duration and severity, older patients took longer to cure but they were no more likely to benefit from treatment than other patients (table 3).

Discussion

Our analysis of 2547 patients from nine trials showed that 15 patients with rhinosinusitis-like complaints need to be given antibiotics before one additional patient benefits from treatment. Common clinical signs and symptoms could not identify a subgroup of patients for whom treatment was clearly justified. Although purulent discharge in the pharynx had some prognostic value, eight patients with this sign still needed to be treated before one additional patient benefited.

Previous meta-analyses of aggregated data have included trials in which patients were recruited partly on the basis of results of imaging or laboratory tests or bacterial culture.[39–42] We did not include such trials because these diagnostic methods are either not practical in a primary-care setting or not cost effective.[43] Such trials are likely to recruit more patients with bacterial infection. As a result, previous meta-analyses have reported an increased overall treatment effect (with NNT of about 7) and have noted heterogeneity between trials in the effect of treatment.[13,42] We noted a lower overall treatment effect and no heterogeneity between trials in our meta-analysis. Our results are more realistic for a primary-care setting than those of previous meta-analyses and support guidelines that do not recommend antibiotic treatment for clinically diagnosed acute rhinosinusitis unless confirmed by imaging or bacterial culture.[44] In line with other meta-analyses, our analysis shows that 64% of patients were cured at 14 days even without antibiotic treatment (webappendix). One serious complication (a brain abscess) was reported among 1381 patients randomly assigned to placebo;[28] such complications are probably even rarer than this proportion suggests.[43]

Our results showed that most common signs and symptoms do not help distinguish a bacterial infection from a viral infection. In particular, patient-reported symptoms such as a previous common cold or facial pain do not seem as reliable as some guidelines suggest.[45,46] Although these symptoms are common in patients with acute bacterial rhinosinusitis, they are equally common in patients with viral upper-respiratory-tract infections.[47] Purulent nasal discharge is consistently associated with bacterial infection in diagnostic studies,[47] but our results suggest that its prognostic value is not sufficient to justify antibiotic treatment for patients with this sign.

Many guidelines recommend prescription of antibiotics if patients have had symptoms for longer than 7–10 days.[13,14] Patients reporting symptoms of an upper-respiratory-tract infection for at least 8 days are often diagnosed as having acute rhinosinusitis and given antibiotic treatment.[48] Our results suggest that antibiotics are not warranted when a patient reports symptoms for this duration. However our results are not evidence against a strategy of watchful waiting before prescription of an antibiotic.[14,43]

Although patients reporting more severe symptoms are not more likely to benefit from antibiotics than other patients, this result should be interpreted with caution. High fever, periorbital swelling, erythema, or intense facial pain suggests a serious complication and then prompt treatment with antibiotics is essential.[46,49] All trials had an exclusion criterion of this sort to ensure patient safety. However, our results suggest that moderate symptom severity does not distinguish a bacterial from a viral infection.

The main strength of our study is that we were able to include individual patients' data from all but one of ten eligible trials, and exclusion of this trial had no effect on estimates obtained from aggregate data. These trials were of high quality[42] and with logical and consistent treatment of missing values, the outcome of the trial was known for most of the patients in our intention-to-treat population. Rather than rely on the imperfect reference standards used in diagnostic studies, we were able to assess the prognostic value of signs and symptoms by the effect of treatment on patient outcome.[16,47]

The limitations of this study included diary entries in four trials being brought forward and variation between trials in the inclusion criteria, antibiotic used, when and how outcome was assessed, and the way in which signs and symptoms were assessed and recorded.[50] Nevertheless, no appreciable heterogeneity between trials in the treatment effect was noted, with a slightly higher cure rate among patients randomised to an antibiotic than to placebo in all trials (table 2). Despite variation between trials in the way signs and symptoms were assessed and recorded, consistent results were seen for three proxy measures of underlying risk—symptom duration, symptom severity, and age. As these measures increased, patients took longer to cure but were no more likely to benefit from treatment than other patients.

The implication for primary care is that antibiotics offer little benefit for patients with acute rhinosinusitis-like complaints. Common clinical signs and symptoms cannot identify a subgroup for which treatment is clearly justified, given the cost, adverse events, and bacterial resistance associated with antibiotic use. Antibiotics are not justified even if a patient reports symptoms for longer than 7–10 days, and symptom severity is important only in that signs suggestive of a serious complication are the sole reason for immediate antibiotic treatment. Although our results do not apply to children[51] or to patients with a suppressed immune system, they should reassure physicians that only watchful waiting and symptomatic relief are warranted for almost all adult patients with acute rhinosinusitis-like complaints.[14]

Contributors

HCB, JY, and ADS designed this study; ADS designed and was responsible for the formal search strategy. HCB, GAVE, LK, DM, ADS, IW, and HV were investigators on included trials, provided data for their respective trials, and resolved queries about their trial data. JY checked and analysed the data and all authors discussed the results. JY prepared the report and all authors saw and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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