Are amoxycillin and folate inhibitors as effective as other antibiotics for acute sinusitis? A meta-analysis

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Abstract

Objectives: To examine whether antibiotics are indicated in treating uncomplicated acute sinusitis and, if so, whether newer and more expensive antibiotics with broad spectra of antimicrobial activity are more effective than amoxycillin or folate inhibitors.
Design: Meta-analysis of randomised trials.
Setting: Outpatient clinics.
Subjects: 2717 patients with acute sinusitis or acute exacerbation of chronic sinusitis from 27 trials.
Interventions: Any antibiotic versus placebo; amoxycillin or folate inhibitors versus newer, more expensive antibiotics.
Main outcome measurements: Clinical failures and cures.
Results: Compared with placebo, antibiotics decreased the incidence of clinical failures by half (risk ratio 0.54 (95% confidence interval 0.37 to 0.79)). Risk of clinical failure among 1553 randomised patients was not meaningfully decreased with more expensive antibiotics as compared with amoxycillin (risk ratio 0.86 (0.62 to 1.19); risk difference 0.9 fewer failures per 100 patients (1.4 more failures to 3.1 fewer failures per 100 patients)). The results were similar for other antibiotics versus folate inhibitors (risk ratio 1.01 (0.52 to 1.97)), but data were sparse (n = 410) and of low quality.
Conclusions: Amoxycillin and folate inhibitors are essentially as effective as more expensive antibiotics for the initial treatment of uncomplicated acute sinusitis. Small differences in efficacy may exist, but are unlikely to be clinically important.

Introduction

Acute sinusitis is a common infection. It is usually treated with antibiotics, often in conjunction with decongestants. A wide variety of antibiotics are used, but there is little information to allow doctors to determine the best initial choice of antibiotic, in particular whether any of the newer broad spectrum drugs are significantly more effective than older, less expensive drugs such as amoxycillin or co-trimoxazole (trimethoprim plus sulfamethoxazole). The usual pathogens in this infection are *Streptococcus pneumoniae* and *Haemophilus influenzae*, with a lesser contribution of *Moraxella catarrhalis* and other species.[1] These species are generally but not uniformly susceptible to amoxycillin and co-trimoxazole. If newer, more expensive antibiotics are more effective then their use would be warranted, but, if not, they should be reserved for specific circumstances. Avoiding unnecessary use of newer, broad spectrum antibiotics is important because of costs but also because of concern about the rising rate of antimicrobial resistance.

A recent meta-analysis considered 12 randomised trials comparing antibiotics of different classes and four trials comparing similar class antibiotics and found no substantive differences among them in the treatment of acute sinusitis.[2] However, the analysis was limited to randomised studies of adults published from 1984 to 1995. No overall comparison with the older drugs amoxycillin and co-trimoxazole was carried out, and the effects of antibiotics compared with placebo were not formally addressed. Our study focuses on both of these issues.

Methods

Study selection

Using the terms of specific antibiotic classes and "sinusitis," we searched Medline up to May 1998 for randomised trials of acute sinusitis. We also manually searched *Excerpta Medica* and recent abstracts for the interscience conference on antimicrobial agents and chemotherapy (1993-7)[3] and inspected references of all trials, review articles, and special issues for additional studies. No language restrictions were applied. Trials were eligible for inclusion if three criteria were fulfilled: (*a*) the trial compared amoxycillin or a folate inhibitor with another antibiotic, generally one with a broad spectrum of activity, including cephalosporins, penicillins with β lactamase inhibitors, tetracyclines, quinolones, and macrolides; (*b*) patients were randomly assigned to treatment arms; and (*c*) the trial evaluated acute sinusitis or an acute exacerbation of chronic sinusitis. We excluded trials that compared doses of non-antimicrobial drugs and trials of subacute or chronic sinusitis (mean duration of symptoms > 3 weeks). We also examined placebo controlled studies to assess the effect of antibiotics on the natural course of acute sinusitis.

Data extraction

Data were extracted independently by two authors. Outcomes of interest were clinical cure, improvement,

Additional table available on our website

and failure as assessed within 48 hours of the end of treatment. Cures and failures were recorded as defined by the individual study: cure generally meant resolution of all signs and symptoms, and failure generally signified no change or worsening of signs and symptoms. We also extracted data on radiographic cure, improvement, or failure and bacteriological cure or failure as defined by each study. In our main analyses we used clinical outcomes as the end points most relevant to doctors because primary care practitioners do not routinely obtain sinus films for uncomplicated acute sinusitis and almost never perform sinus aspirates, and because there is no evidence of a correlation between radiographic or bacteriological failure and clinical outcomes. We separately assessed bacteriological and radiographic failures and patient withdrawals due to adverse drug effects.

Quality assessment

We assessed studies for the following characteristics: blinded versus unblinded design, criteria for diagnosis of sinusitis, clinical outcomes, loss of subjects to follow up, and use of decongestants. The diagnosis of sinusitis was considered "firm" if culture of sinus aspirations or radiographic evaluations (presence of air-fluid levels, mucosal thickening >6 mm, or sinus opacification) were confirmatory. Any other diagnostic criteria, including nasal swabs, were considered "subjective." We considered outcome criteria to be well specified when symptoms or signs were assessed by patients or physicians in a way that could be replicated; criteria were specified to some extent when the signs or symptoms used to evaluate outcome were noted but not how these were evaluated; and criteria were unclear when no mention was made of how clinical outcomes were determined.

In addition to this subject-specific assessment of quality, we used the scale developed by Jadad et al to assess the methodological quality of clinical trials.[4] This scale has a maximum score of 5 (highest quality) and focuses on randomisation, double blinding, and description of withdrawals.

Data synthesis and statistical analysis

We pooled the results from (*a*) placebo controlled studies to determine the effect of treatment with any antibiotic on the outcome of acute sinusitis, (*b*) studies in which amoxycillin was compared with various antibiotics except folate inhibitors to compare the outcomes of treatment, and (*c*) studies in which folate inhibitors were compared with other antibiotics except amoxycillin. We pooled risk ratios, risk differences, and event rates in the control group using both the Mantel-Haenszel fixed effects model[5] and the DerSimonian and Laird random effects model,[6] which takes into account the variability of the true treatment effect between studies. We assessed the heterogeneity between studies with χ^2 tests and deemed $P<0.1$ to indicate significance.[7]

Unless stated otherwise, we report the results calculated with the random effects model, but fixed effect calculations provided similar estimates. We also report rates weighted by the inverse of their variance with random effects[8] and results from a series of sensitivity analyses.

Results

Trial characteristics and quality assessment

We identified 80 randomised clinical trials of antibiotic treatment of acute sinusitis. Most were ineligible for our meta-analysis: 48 did not use the reference drugs pertinent to this analysis, three inextricably combined patients with sinusitis with those with other infections,[9–11] and two inextricably combined patients with acute, chronic, and recurrent sinusitis.[12 13] Of the 27 trials that qualified for our meta-analysis, six were placebo controlled (one study comparing amoxycillin also had a placebo arm),[14–19] 13 compared amoxycillin with other antibiotics,[16 20–31] and eight compared a folate inhibitor (co-trimoxazole, trimethoprim plus sulfametopyrazine, or brodimoprim) with other antibiotics.[32–39] (For details of these trials, see extra table on the *BMJ* website.) An additional large ($n=438$) and well done trial using penicillin V as the reference drug was excluded from our main analysis because penicillin V is less active in vitro than amoxycillin against *H influenzae* and *M catarrhalis* but was included in the sensitivity analysis.[40] Among the included trials, sample size ranged from 14 to 323 patients (2717 patients overall). The mean ages of patients ranged from 25 to 44 years, except for two trials that evaluated paediatric patients exclusively.[16 20]

Eleven of the 27 trials were double blind, and six were single blind (five investigator blind). Twelve trials used "firm" methods for diagnosing acute sinusitis, and the others used clinical criteria. Eight trials required the use of decongestants and two trials allowed it; 17 did not deal with this issue by protocol. The criteria for clinical outcomes were well specified in eight of the trials, specified to some extent in 12, and unclear in seven trials. Antral punctures were done in three trials,[20–30] and either antral puncture or nasal swabs in two trials,[21 24] both in the amoxycillin analysis.

Table 1 Meta-analysis of clinical outcomes recorded in six trials of 761 patients comparing antibiotics with placebo for treating uncomplicated acute sinusitis[14-19]

Outcome	Risk ratio (95% CI) for antibiotic treatment	Outcome (95% CI) with placebo
Clinical cure	1.33 (1.02 to 1.74)	34% (21% to 51%)
Clinical failure	0.54 (0.37 to 0.79)	31% (21% to 43%)

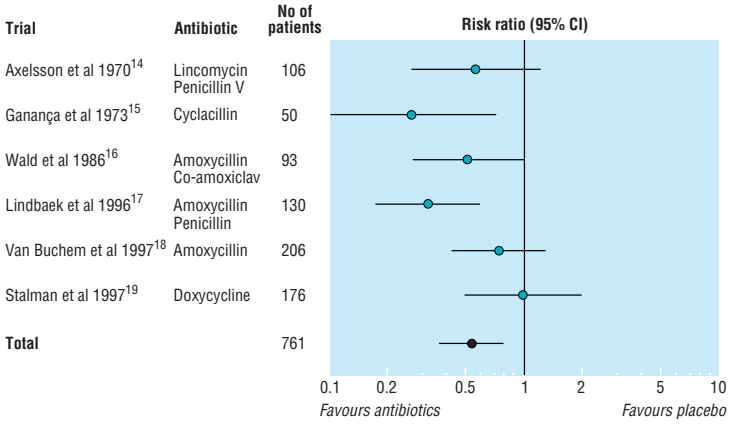

Fig 1 Random effects model of risk ratios (95% confidence intervals) of clinical failure associated with antibiotic treatment of acute sinusitis compared with placebo

Table 2 Meta-analysis of outcomes recorded in trials comparing newer, more expensive antibiotics with amoxycillin or folate inhibitors for treating uncomplicated acute sinusitis

Outcome	No of studies	No of patients	Risk ratio (95% CI)*	Outcome (95% CI) with reference drug†
Newer, more expensive antibiotics *v* amoxycillin[16 20-31]				
Clinical failure	13[16 20-31]	1553	0.86 (0.62 to 1.19)	11% (8% to 14%)
Clinical cure	11[16 20-29]	1172	1.04 (0.98 to 1.11)	72% (64% to 80%)
Radiographic failure	4[20 21 25 28]	270	0.89 (0.35 to 2.26)	17% (9% to 31%)
Bacteriological failure	7[16 20 21 25 28 30 31]	435	0.68 (0.41 to 1.14)	10% (5% to 19%)
Withdrawal	12[16 21-31]	1505	1.01 (0.56 to 1.81)	4% (3% to 6%)
Newer, more expensive antibiotics *v* folate inhibitors[32-39]				
Clinical failure	8[32-39]	410	1.01 (0.52 to 1.97)	11% (6% to 22%)
Clinical cure	7[32-38]	361	1.01 (0.88 to 1.17)	73% (58% to 84%)
Radiographic failure	3[32 37 38]	132	1.46 (0.79 to 2.71)	20% (7% to 44%)
Bacteriological failure	3[32 36 38]	122	1.70 (0.90 to 3.21)	19% (9% to 37%)
Withdrawal	5[32 35-38]	219	0.47 (0.10 to 2.20)	6% (3% to 13%)

*Risk ratio for treatment with other antibiotics. †Amoxycillin or folate inhibitor.

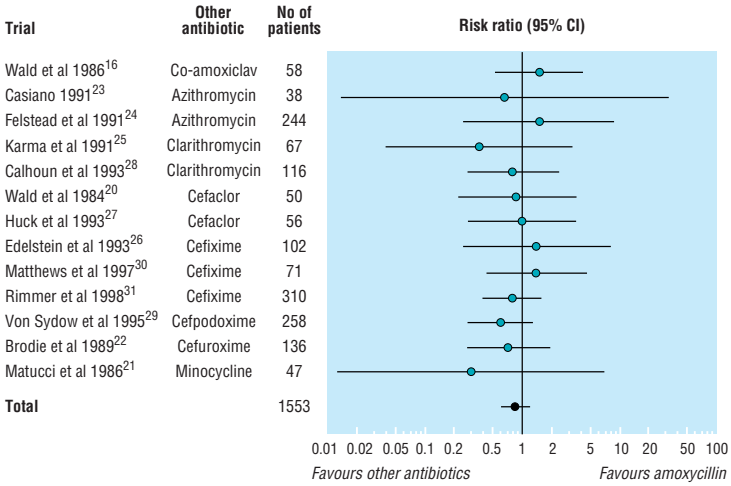

Fig 2 Random effects model of risk ratios (95% confidence intervals) of clinical failure associated with treatment of acute sinusitis with more expensive antibiotics compared with amoxycillin

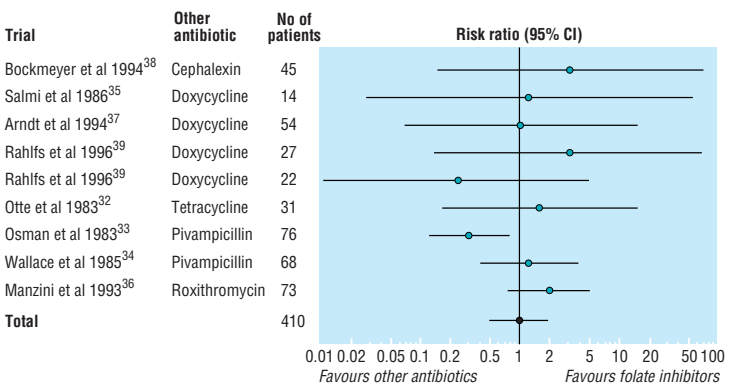

Fig 3 Random effects model of risk ratios (95% confidence intervals) of clinical failure associated with treatment of acute sinusitis with more expensive antibiotics compared with folate inhibitors

Antibiotics *v* placebo

In the six studies comparing any antibiotic with placebo, antibiotics were significantly more effective, reducing treatment failures by almost half (table 1, fig 1). However, symptoms improved or disappeared in 69% of patients without any antibiotic treatment (95% confidence interval 57% to 79%). Although the observed heterogeneity between trials did not reach significance, there was a suggestion that one trial that included patients simply on the basis of sinusitis-like symptoms without further diagnostic documentation had the highest rates of cure or improvement in the placebo group (85% at 10 days) and showed no benefit from antibiotics,[19] whereas trials with more tightly defined patient populations and lower spontaneous improvement rates showed a clear benefit from antibiotics.

Amoxycillin and folate inhibitors *v* other antibiotics

Clinical outcomes

There was no statistically significant or clinically meaningful difference in rate of failure or cure between amoxycillin and other antibiotics (table 2, fig 2). Compared with other antibiotics, treatment of 100 patients with amoxycillin would lead to only 0.85 more failures. The results were similar for folate inhibitors, but the data were more limited (table 2, fig 3). Compared with other drugs, the risk differences of clinical cure with amoxycillin were 3.2% (95% confidence interval −1.5% to 7.8%) and with folate inhibitors they were 1.2% (−10% to 12.4%). The results were similar when we added a trial comparing penicillin with azithromycin to the comparisons with amoxycillin.

There was no heterogeneity of treatment effects in the comparisons with amoxycillin. By contrast, there was some evidence of heterogeneity in the studies comparing folate inhibitors with other antibiotics ($P=0.09$ for clinical cure, $P=0.18$ for clinical failures), possibly because co-trimoxazole seemed less effective than pivampicillin plus pivmecillinam in one study.[34]

Sensitivity analyses showed similar results (table 3). In all of these analyses there was a tendency for an estimated 11-20% risk reduction in clinical failures with other antibiotics compared with amoxycillin that did not reach formal statistical significance. This tendency corresponded to a clinically negligible benefit (less than 1 failure averted per 100 patients). Because of sparse data, sensitivity analysis was less useful for folate inhibitors.

Radiographic and bacteriological outcomes and patient withdrawals

Radiographic and bacteriological data were not available for many trials (table 2). Rates of radiographic failures within 48 hours of the end of treatment were not significantly different among patients treated with other antibiotics compared with patients treated with amoxycillin or penicillin or folate inhibitors. Likewise, rates of bacteriological failure were not significantly different, although most samples were obtained with nasal swabs and the data are therefore not reliable. There was no significant difference between different treatments in the rate of patients withdrawal.

Discussion

This meta-analysis showed that in two thirds of the cases of sinusitis, there is spontaneous improvement or cure without antibiotic treatment. Among patients with

sinusitis defined by clinical criteria alone, the rate of spontaneous resolution may be even higher. Treatment with any antibiotic reduced the rate of clinical failures by half. Treatment with newer, generally more expensive, antibiotics did not seem to reduce the rate of treatment failure beyond what amoxycillin and co-trimoxazole could achieve.

Table 3 Sensitivity and subgroup analyses for clinical failures recorded in trials comparing newer, more expensive antibiotics with amoxycillin or folate inhibitors for treating uncomplicated acute sinusitis

	Other antibiotics *v* amoxycillin		Other antibiotics *v* folate inhibitors	
Subgroups of trials	**No of trials (patients)**	**Risk ratio (95% CI)***	**No of trials (patients)**	**Risk ratio (95% CI)***
Patients:				
Children	2 (108)	1.24 (0.54 to 2.84)	0	not applicable
Adults	11 (1445)	0.80 (0.56 to 1.14)	9 (410)	1.01 (0.52 to 1.97)
Antibiotics used in comparison:				
Tetracyclines	1 (47)	3.39 (0.15 to 79.2)	5 (148)	1.17 (0.32 to 4.23)
All others	12 (1506)	0.87 (0.63 to 1.20)	4 (262)	1.03 (0.35 to 3.00)
Resistant pathogens excluded:				
Yes	3 (176)	1.00 (0.37 to 2.72)	1 (45)	3.41 (0.15 to 79.5)
No	10 (1377)	0.84 (0.60 to 1.19)	8 (365)	0.96 (0.48 to 1.95)
Diagnosis of sinusitis:				
Subjective	4 (543)	0.89 (0.46 to 1.71)	8 (379)	0.99 (0.47 to 2.08)
Firm	9 (1010)	0.88 (0.60 to 1.28)	1 (31)	1.65 (0.17 to 16.3)
Assessment of outcomes:				
Unclear	3 (468)	0.88 (0.50 to 1.55)	4 (131)	1.18 (0.44 to 3.13)
Specified	10 (1085)	0.85 (0.57 to 1.26)	5 (279)	1.05 (0.35 to 3.10)
Blinding:				
Unblinded or single blind	8 (821)	0.89 (0.53 to 1.50)	7 (365)	0.99 (0.44 to 2.23)
Double blind	5 (732)	0.84 (0.55 to 1.27)	2 (45)	1.54 (0.22 to 11.0)
Publication date:				
1983-91	7 (640)	1.00 (0.57 to 1.75)	4 (189)	0.71 (0.28 to 1.81)
1993-8	6 (913)	0.82 (0.55 to 1.23)	5 (221)	1.77 (0.79 to 3.96)
Jadad quality score:				
<3	6 (539)	0.85 (0.49 to 1.48)	7(365)	0.99 (0.44 to 2.23)
⩾3	7 (1014)	0.86 (0.58 to 1.28)	2 (45)	1.54 (0.22 to 11.0)

*Risk ratios <1 mean that other antibiotics were better than the reference drugs (amoxycillin or folate inhibitors). There was no significant heterogeneity between subgroups for any of the sensitivity analyses (P>0.1).

Limitations of study

We compared the reference drugs amoxycillin and folate inhibitors with a heterogeneous array of antibiotics with differing antibacterial spectra. It is possible that, by grouping these drugs, we have obscured some important and systematic differences between the drug classes. There were too few studies in any single antibiotic group to allow a meaningful meta-analysis of each class. However, simple inspection of figures 2 and 3 suggests that there was no consistent superiority of any drug class over the reference drugs.

The total number of patients available for pooling in this meta-analysis was small. It is possible that a significant advantage of newer antibiotics might have been evident if more data were available. However, the chance of this advantage being large enough to be clinically important is small. Even with the most extreme values for the 95% confidence intervals, clinical failure would be averted in one of 32 patients treated with amoxycillin or one of 16 patients treated with a folate inhibitor, probably not enough to justify routine use of newer antibiotics as first line treatment. If the data were affected by publication bias, the effect presumably would be to reduce the amount of data unfavourable to the newer drugs. In that case, the advantages of the newer drugs would be even less than we found. Bias related to poor quality of the studies would also presumably act in favour of the newer drugs,[41] in which case their advantages would again be reduced. Sensitivity analysis showed that, when only trials with a Jadad quality score of at least 3 were considered, the estimates for all major end points of treatment effect were unchanged for the major comparisons.

Another concern is the comparability of patients included in these trials to current patient populations. Some of the studies were conducted when the rates of antimicrobial resistance of *H influenzae*, *M catarrhalis*, and *S pneumoniae* were much lower. Yet sensitivity analysis showed no evidence of a difference in results between recent and older studies, or between studies that included or excluded patients infected by drug resistant organisms. We were unable to find sufficient data based on sinus puncture to allow us to evaluate the effect of resistance to the antibiotic treatment on the outcome of sinusitis.

Implications of study

We found only two studies, with a total of 113 patients, that directly compared amoxycillin and folate inhibitors.[42 43] The small number of patients did not allow a meaningful comparison of the drugs: the risk ratio of failure with folate inhibitors versus amoxycillin was 0.5, but the 95% confidence interval was wide (0.08 to 3.01). Co-trimoxazole has a broader spectrum than amoxycillin, being active against amoxycillin resistant *H influenzae* and *M catarrhalis*. Its use should largely satisfy those concerned about antimicrobial resistance when prescribing treatment for community acquired acute sinusitis.

Complications of sinusitis can be serious, including brain abscess, orbital cellulitis, subdural empyema, and meningitis. We found no mention of such complications among more than 2700 patients in 27 trials. Large referral hospitals rarely report such complications.[44 45] To our knowledge, there are no data to suggest that the use of newer, more expensive antibiotics would reduce the rate of these rare complications. Nevertheless, it should be emphasised that our data apply to patients with uncomplicated, community acquired, acute sinusitis. Patients with complicated sinusitis and those severely ill with sinusitis or with important underlying diseases might merit initial treatment with drugs other than amoxycillin or a folate inhibitor.

Our meta-analysis highlights the need to improve the quality of studies in outpatient antibiotic management. Because of the subjective nature of the relevant end points, double blind design is extremely important in evaluating treatments for sinusitis. Study protocols should require either radiographic findings or antral puncture and aspiration as criteria for study entry. Nasal swabs have been shown to be inaccurate indicators of the pathogens in sinusitis.[46 47] Patients with chronic and subacute sinusitis should be studied separately from patients with acute sinusitis. The use of decongestants should be specified by protocol. Clinical outcomes should be defined with a detailed scoring system. Patients with infection caused by drug resistant organisms should not be excluded from the analysis; instead, particular attention should be paid to the

Key messages

- A major question in managing acute sinusitis is whether antibiotics should be used, and if so which drugs should be chosen
- In a comprehensive meta-analysis we evaluated evidence from randomised controlled trials comparing, firstly, antibiotics against placebo and, secondly, amoxycillin and folate inhibitors against newer, more expensive antibiotics
- Antibiotics were significantly more efficacious than placebo in achieving cure of clinical symptoms, but over two thirds of placebo patients showed spontaneous resolution or improvement of symptoms
- Amoxycillin and folate inhibitors had overall similar efficacy compared with newer antibiotics
- The current evidence does not justify the use of expensive, broad spectrum antibiotics in the community for treating uncomplicated acute sinusitis

outcome of these infections in order to determine if antibiotic resistance is an important predictor of treatment failure. Finally, the optimal duration of treatment should be addressed, as was done in one recent, well conducted study.[47]

Conclusions

Most clinical trials of new antibiotics compare the drugs with other newer drugs rather than with the inexpensive older drugs that we examined. There are obvious commercial reasons for this strategy: if the efficacy of a new drug were shown to be merely equivalent to that of an older drug the findings would hardly provide a useful marketing tool. There is societal value in decreasing the unnecessary use of newer, broad spectrum antibiotics to reduce the cost of care and possibly to reduce the rate of development of resistant microorganisms in the community.[48–50] Even more fundamental is the need for accurate, inexpensive, and non-invasive methods to diagnose acute bacterial sinusitis.[51 52] Such methods might sharply reduce the number of patients needing any antibiotic treatment given that most of the patients with acute sinusitis experienced spontaneous cure or improvement of symptoms.

Contributors: MB and JL had the original idea for the meta-analysis. All the authors took part in the design and implementation of the study protocol and data analysis. SDdeF wrote the initial draft of the manuscript, and all the authors participated in its revision. JL is guarantor for the study.

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Conflict of interest: None.

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Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats

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Abstract

Objectives: To better understand reasons for antibiotics being prescribed for sore throats despite well known evidence that they are generally of little help.
Design: Qualitative study with semi-structured interviews.
Setting: General practices in South Wales.
Subjects: 21 general practitioners and 17 of their patients who had recently consulted for a sore throat or upper respiratory tract infection.
Main outcome measures: Subjects' experience of management of the illness, patients' expectations, beliefs about antibiotic treatment for sore throats, and ideas for reducing prescribing.
Results: Doctors knew of the evidence for marginal effectiveness yet often prescribed for good relationships with patients. Possible patient benefit outweighed theoretical community risk from resistant bacteria. Most doctors found prescribing "against the evidence" uncomfortable and realised this probably increased workload. Explanations of the distinction between virus and bacterium often led to perceived confusion. Clinicians were divided on the value of leaflets and national campaigns, but several favoured patient empowerment for self care by other members of the primary care team. Patient expectations were seldom made explicit, and many were not met. A third of patients had a clear expectation for antibiotics, and mothers were more likely to accept non-antibiotic treatment for their children than for themselves. Satisfaction was not necessarily related to receiving antibiotics, with many seeking reassurance, further information, and pain relief.
Conclusions: This prescribing decision is greatly influenced by considerations of the doctor-patient relationship. Consulting strategies that make patient expectations explicit without damaging relationships might reduce unwanted antibiotics. Repeating evidence for lack of effectiveness is unlikely to change doctors' prescribing, but information about risk to individual patients might. Emphasising positive aspects of non-antibiotic treatment and lack of efficacy in general might be helpful.

Introduction

It has been known for many years that antibiotics modify the course of most sore throats only slightly if at all.[1 2] Nevertheless, they are often prescribed[3–6] despite accumulating evidence from trials.[7–12] When patients expect antibiotics they are more likely to be prescribed,[13] and when physicians perceive that patients expect antibiotics they are 10 times more likely to be prescribed.[14] General practitioners describe this as the most uncomfortable decision about prescribing that they make.[15] Antibiotic prescribing is rising in primary care, especially for respiratory tract conditions.[16] There are growing concerns about cost,[17] increasing workload for these usually self limiting conditions,[10 18 19] and the rising prevalence of antibiotic resistant bacteria.[20–23] The House of Lords Science and Technology Committee report on antibiotic resistance recommended prudent use of antibiotics, particularly in general practice.[24] Large scale change in prescribing practice is associated with reduced antibiotic resistance.[21]

Interventions for changing this complex behaviour need to be based on a deep understanding of patients' and doctors' perceptions and problems.[4 8 25] We started a programme of research to address overprescribing of antibiotics for sore throats in primary care: we report here the first phase, which aims to achieve a better

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