Evidence Report/Technology Assessment

Number 124

Update on Acute Bacterial Rhinosinusitis

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public-and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and on new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of the evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality and improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc.ahrq.gov**.

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Structured Abstract

Context. Our last report on the treatment of acute bacterial sinusitis was published in 1999. Since then, many more trials were published comparing different antibiotics not found in the previous report. In addition, universal pneumococcal vaccination was introduced in the pediatric population. It is of interest to examine the effects of these new developments on the treatment of acute bacterial rhinosinusitis.

Objectives. To perform a systematic review of the literature published since 1997 on comparisons of antibiotics in the treatment of acute bacterial rhinosinusitis, to summarize the adverse events and note any reported impact of pneumococcal vaccine on the treatment of acute bacterial rhinosinusitis.

Data Sources. We searched the MEDLINE® database and bibliographies of selected reviews. Additional studies were provided by technical experts.

Study Selection. English-language, comparative trials of antibiotics for the treatment of acute bacterial rhinosinusitis in both adult and pediatric populations were included. Studies of sinusitis with complications or that included both subjects with sinusitis and subjects with other respiratory tract infections were excluded.

Data Extraction. We extracted information about the study design, demographics, eligibility criteria, antibiotic dosing regimens, outcome measures, including dropouts, and adverse events. Based on these data, studies were graded for quality.

Data Synthesis. Thirty-nine randomized controlled trials from 1997 to 2004 met the inclusion criteria for this report. With the exception of 5 studies that did not provide the information, all studies were either funded by pharmaceutical companies or had authors associated with the pharmaceutical industry. Only one study exclusively evaluated pediatric population. The trials evaluated pencillins, cephalosporins, macrolides, azalides, ketolides, quinolones, carbapenems and tetracyclines. In 5 placebo-controlled trials, antibiotics were more effective than placebo, reducing the risk of clinical failure by about 25-30 percent 7 to 14 days after treament initiation. Compared to amoxicillin/clavulanate, treatment with cephalosporins result in about 3.5 more clinical failures per 100 patients at 10-25 days after treatment initiation. There was no consistent difference observed when comparing amoxcillin-clavulanate, cephalosporins and quinolones to the group encompassing macrolides, azalides and ketolide.

Eight studies that evaluated different treatment durations generally found no differences in efficacy outcomes between the shorter and longer duration therapies.

Thirty-four of the comparative trials and five additional non-comparative studies reported adverse events. Descriptions of adverse events were diverse among studies. It was not possible to make meaningful comparisons of adverse event rates across different antibiotic classes given the large variation in the adverse event rates within the same antibiotic class. Overall, the most common adverse events involved the gastrointestinal and the nervous system (such as headache). We did not identify any article in our literature search that directly addressed the impact of pneumococcal vaccine on the treatment of acute bacterial rhinosinusitis.

Conclusions. About two-thirds of the patients with acute rhinosinusitis receiving placebos recovered without antibiotics. Antibiotics are superior to placebo in the treatment of rhinosinusitis. Amoxicillin/clavulanate is more effective than the cephalosporin class of antibiotics in the treatment of sinusitis only in the short-term follow up, with an absolute risk difference of about 3.5 percent.

There are only a few studies that specifically examined the effect of different treatment duration on outcome efficacy; they generally found no difference between shorter and longer duration of treatment. It is not possible to compare the rates of adverse events across different antibiotic classes. Severe adverse events in general are uncommon; they occurred in up to about 3.5 percent of patients in all classes of antibiotics.

As of September 2004, there have not been any published studies examining the effect of the pneumococcal vaccine on the treatment of acute sinusitis.

A minority of studies were placebo controlled. In addition, from a health care cost standpoint, there were very few comparative studies between newer antibiotics and older inexpensive ones (like amoxicillin and trimethoprim/sulfamethoxazole).

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Evidence Report/Technology Assessment

Number 124

Update on Acute Bacterial Rhinosinusitis

Summary

Authors: Ip S, Fu L, Balk E, Chew P, DeVine D, Lau J

Introduction

This is an update of the original evidence report, *Diagnosis and Treatment of Acute Bacterial Rhinosinusitis,* published in March 1999 by the Agency for Health Care Policy and Research.[1] Our objective is to summarize and analyze comparative studies on the antibiotic efficacies in the treatment of acute bacterial sinusitis. The research questions in this evidence report are:

1. Given a clinical diagnosis of acute bacterial rhinosinusitis, what are the comparative efficacies of the antibiotics in resolving symptoms and preventing complications or recurrence?
   - 1a. Is there evidence that duration of antibiotic treatment in acute bacterial rhinosinusitis affects efficacy?
2. What adverse effects are reported for antibiotics used for acute bacterial rhinosinusitis?
3. How does the introduction of the pneumococcal vaccine affect the resistance patterns of pneumococcus and the treatment decisions in acute bacterial rhinosinusitis?

Methods

Acute bacterial rhinosinusitis is defined by clinical signs and symptoms of inflammation of sinuses and nasal passages of less than 30 days. Cure, improvement, and treatment failure definitions are based on the original reports. Studies of subjects with either acute sinusitis or acute exacerbation of chronic sinusitis were included. Studies of sinusitis with complications, those that exclusively evaluated chronic sinusitis and studies of acute sinusitis along with other respiratory infections were excluded.

Inclusion Criteria

- Pertinent to the research questions.
- Included subjects with acute rhinosinusitis or acute exacerbation of chronic sinusitis.
- Any age group.
- Included at least 10 subjects in each arm.
- Comparative studies for the evaluation of antibiotic efficacy. (Non-comparative studies were included in the review of adverse events only.)
- Reported clinical and/or radiological and/or microbiological failures.

Exclusion criteria

- Studies that included only patients with chronic sinusitis.
- Studies that included other upper respiratory infections in addition to acute sinusitis.

Search Strategy and Retrievals

We searched MEDLINE® using a broad search strategy covering the period from 1997 to September 2004. The search terms were: "sinusitis," "rhinosinusitis," "anti-bacterial agents," "anti-infective agents" and other relevant terms. We limited the search results to human studies and English-language studies. We conducted a separate search using terms such as "vaccines" and "pneumococcal vaccine" to look for studies to address the question of pneumococcal vaccine and sinusitis. This separate search identified a total of 273 abstracts for screening. None of these qualified for inclusion in this update. We also sought additional articles by reviewing reference lists of selected review articles and meta-analyses and contacting members of the Technical Expert Panel. We did not seek unpublished studies.

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Evidence-Based Practice

Meta-analysis

We constructed an antibiotic comparative matrix to assess the feasibility of performing meta-analyses of clinical failure. We determined that it would be feasible to compare the efficacy of antibiotics with placebo, as well as four different antibiotic classes with each other. Comparisons were made between amoxicillin-clavulanate, cephalosporins, quinolones and the combined category of macrolides, azalides and ketolide. We calculated the risk ratios and risk differences for clinical failure. All meta-analyses were performed using a random effects model.

Adverse Events Data Extraction

Adverse event data were extracted from the antibiotic comparison studies that met the inclusion criteria. In addition, adverse event data were also taken from non-comparative antibiotic studies that reported this data. We abstracted for each study the percentage of subjects who experienced at least one adverse event, the percentage who withdrew from a study due to adverse events, the percentage with severe adverse events and the percentage who experienced gastrointestinal, central nervous system, skin/extremity and/or cardiovascular events.

Results

The MEDLINE® search identified 704 abstracts. After screening the abstracts, 87 articles were retrieved for further evaluation. A total of 39 studies ultimately qualified for inclusion in this update. These trials enrolled 15,739 subjects from 1997 to 2004 and studied antibiotic comparisons in treatment of acute bacterial rhinosinusitis. With the exception of five studies that did not provide the information, all the studies were either funded by pharmaceutical companies or had authors associated with the pharmaceutical industries. No study exclusively evaluated a pediatric population. The classes of antibiotics studied consist of penicillins, cephalosporins, macrolides, azalides, ketolides, quinolones, carbapenems and tetracyclines. There were 22 comparisons with amoxicillin/clavulanate and only five comparisons with amoxicillin.

Overall, antibiotics were more effective than placebo, reducing the risk of clinical failure by about 25 to 30 percent within 7 to 14 days after treatment initiation ($p<0.01$). However, symptoms improved or were resolved in 65 percent of patients without any antibiotic treatment at all (95% CI, 40-91%). Amoxicillin-clavulanate, compared to antibiotics in the cephalosporin class, was 41 percent more effective in reducing clinical failure within 10 to 25 days after treatment initiation ($p=0.01$). In absolute terms, this means treating 100 patients with antibiotics in the cephalosporin class will lead to 3.5 more failures (95% CI, 0.86 to 6) as compared to amoxicillin-clavulanate. The results 24 to 45 days after treatment initiation, however, did not show significant difference ($p=0.5$). There was no consistent trend observed when comparing amoxicillin-clavulanate, cephalosporins and quinolones to the group encompassing macrolides, azalides and ketolides.

There are eight studies that reported data on comparison of treatment duration with outcome efficacy. One study showed that 10 days vs. 5 days of amoxicillin-clavulanate 500 mg three times a day showed a non-significant 28 percent reduction in clinical failure rate.[2] Two studies on 10 days vs. 5 days of telithromycin showed that the clinical failure rate between the two treatment durations was comparable.[3,4] The studies on gemifloxacin (5 days vs. 7 days),[5] azithromycin (3 days vs. 6 days),[6] and gatifloxacin (5 days vs. 10 days)[7] showed therapeutic equivalence of the two durations.

Thirty-four comparative trials and five non-comparative trials reported adverse events. Descriptions of adverse events were diverse among studies. It was not possible to make meaningful comparisons of adverse event rates across different antibiotic classes given the enormous variation in the reported rate of adverse events within the same antibiotic class. For example, the reported rate of diarrhea with amoxicillin-clavulanate across different studies ranged from under 2 percent to more than 30 percent. Overall, the most common adverse events involved the gastrointestinal and the central nervous system. Severe adverse events were rare, occurring in less than 10 percent of any given study population. We did not identify any article in our literature search that directly addressed the effect of pneumococcal vaccine in the treatment of acute bacterial sinusitis.

Discussion

- About two-thirds of the patients receiving placebos recovered without antibiotics.
- Antibiotic is more effective than placebo.
- Amoxicillin-clavulanate is more effective than cephalosporin in the short-term followup.
- There are no significant differences between other classes of antibiotics.
- There is a lack of studies that compare newer antibiotics with inexpensive ones like amoxicillin and trimethoprim/sulfamethoxazole.

Limitations

Heterogeneous study population and definitions of clinical success/failure across studies, studies powered primarily for non-inferiority rather than superiority, few studies within each comparison grouping, and the possibility of publication bias all

lend limitations to our meta-analyses. Sinus aspirations and cultures, the gold standard for diagnosing and assessing bacterial sinusitis were performed in a minority of trials. Almost all the studies that were sponsored by pharmaceutical companies concluded that the sponsored drug was either superior or therapeutically equivalent to the comparator. In actuality, virtually all the studies demonstrate non-inferiority only. It is possible that there may be unpublished trials with negative results. This could be a continual limitation if mandatory registration of drug trials is not implemented. A notable omission compared to our previous report is the lack of comparative studies between newer expensive antibiotics and older inexpensive ones (like amoxicillin and trimethoprim/sulfamethoxazole). This is an important issue to be addressed for health care cost containment.

Future Research

Future trials should incorporate bacteriologic data to help characterize the changing epidemiology of acute bacterial rhinosinusitis. In order to make meaningful comparisons across studies, there should be general agreement in defining inclusion/exclusion criteria, clinical success/failure, and the appropriate time of outcome assessment. To reduce the possibility of bias, the intent-to-treat population should be uniformly defined across studies and data should be collected and reported in addition to per-protocol results. Also, results from all drug trials should be duly reported. Prevalence of different pneumococcal serotypes and their resistance patterns will have to be continually monitored to help guide the optimal treatment of acute bacterial rhinosinusitis.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022. It is expected to be available in summer 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 124, *Update on Acute Bacterial Rhinosinusitis.* In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Chapter 1. Introduction

The Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC), under a contract from the Agency for Healthcare Research and Quality (AHRQ), produced the original evidence report on the *Diagnosis and Treatment of Acute Bacterial Rhinosinusitis* (March 1999).[1] Key points from the report relevant to this review are:

- About two-thirds of the patients receiving placebos recovered without antibiotics.
- Antibiotics are significantly more effective than placebo for treating acute bacterial sinusitis, reducing the clinical failure rate by one-half (risk ratio [RR], 0.54; 95 percent confidence interval [CI], 0.37 to 0.79). Patients are cured more quickly and more often when treated with antibiotics compared with no treatment.
- Amoxicillin and folate inhibitors were as efficacious as the newer and more expensive antibiotics.
- About 4 percent of the patients in the amoxicillin arms of the clinical trials withdrew as a result of side effects, but this percent did not differ statistically from that in patients treated with other antibiotics.

The EPC Program periodically seeks updates of evidence reports when justified by current scientific evidence. In the intervening 6 years since the original report, newer antibiotics have been introduced and universal pneumococcal vaccination implemented in care of the pediatric population. To examine the effects of these developments on the treatment of acute bacterial sinusitis, the Tufts-NEMC EPC reviewed the literature published since the last report for the research questions listed below. Our objective was to identify and analyze evidence from comparative studies on the antibiotic efficacies in the treatment of acute bacterial sinusitis.

Research Questions

In 2004, after consultation with our panel of technical experts, we developed the following research questions for this report:

1. Given a clinical diagnosis of acute bacterial rhinosinusitis, what are the comparative efficacies of the antibiotics in resolving symptoms and preventing complications or recurrence?

   1a. Is there evidence that duration of antibiotic treatment in acute bacterial rhinosinusitis affects efficacy?

2. What adverse effects are reported for antibiotics used for acute bacterial rhinosinusitis?

3. How does the introduction of the pneumococcal vaccine affect the resistance patterns of pneumococcus and the treatment decisions in acute bacterial rhinosinusitis?

Chapter 2. Methodology

The Tufts-NEMC EPC conducted a systematic review of the literature published since 1997 to summarize the evidence and we performed meta-analysis on comparative drug trials if there were 3 or more studies in the same grouping. We held meetings and teleconferences with technical expert representatives from three science partners (the American Academy of Family Physicians, American Academy of Otolaryngology-Head and Neck Surgery, and American Academy of Pediatrics) to refine the three research questions addressed in this evidence report. To answer the question on comparative efficacies of the antibiotics and the effect of different treatment durations on acute bacterial sinusitis, we sought only published results from randomized controlled trials. For the question on adverse events, we examined the reported adverse event data in these trials. For the question on pneumococcal vaccine's effect on treatment decision in acute sinusitis, we looked for published articles that directly addressed this question.

Definitions

As in the original evidence report, we have focused this update on acute uncomplicated bacterial sinusitis. Sinusitis is defined as clinical signs and symptoms of inflammation of the paranasal sinuses and nasal passages (including: nasal congestion/discharge, nasal mucosa hyperemia, cough, fever, craniofacial pain/tenderness, periorbital edema, headache, toothache, earache, hyposmia/anosmia, halitosis, malaise, opacities/mucosal thickening/air-fluid level of the sinuses on standard films and/or CT scan, and positive sinus culture). Rhinosinusitis is included in this grouping. Acute duration is defined as having signs and symptoms of less than 30 days' duration. Uncomplicated sinusitis is defined as the lack of clinically evident neurological, soft tissue or other complications present prior to treatment initiation. Treatment failure is defined as the lack of improvement or worsening in signs and symptoms by the end of therapy. Recurrence includes persistent or relapsed disease assessed after a period of at least one week following the end of therapy. Some studies reported clinical success rate rather than clinical failure rate. In such instances, the clinical failure rate is calculated as: 100 percent clinical success rate.

Search Strategy and Retrieval

We searched MEDLINE® using a broad search strategy covering the period from January 1997 to September 2004. The search terms were: "sinusitis," "rhinosinusitis," "anti-bacterial agents" and other relevant terms. See Appendix A. We limited search results to human and English-language studies. Studies of any age group were included.

For the question on pneumococcal vaccine and sinusitis, the search terms were: "vaccines", "pneumococcal vaccine", "sinusitis" and "rhinosinusitis".

Additional sources of published articles were provided by members of the Technical Expert Panel (TEP), and also sought from reference lists of selected review articles and meta-analyses.

Inclusion Criteria

Studies that

- included subjects with acute rhinosinusitis
- included subjects with acute exacerbation of chronic sinusitis
- included any age group, in any country
- were based in primary care and/or specialty clinics
- included at least 10 subjects in each treatment arm
- addressed component(s) of the Research Questions: efficacy of antibiotics, antibiotic treatment duration, antibiotic adverse effects, pneumococcal vaccine effect on resistance patterns
- were randomized, comparative trials (5 non-comparative studies were included in the review of adverse events only)

Exclusion Criteria

Studies that

- included only patients with chronic sinusitis without acute exacerbation
- included other respiratory infections in addition to acute rhinosinusitis

Adverse Events Data Extraction

Adverse event data were extracted from the antibiotic comparison studies obtained via the defined search strategy. In addition, we abstracted data from non-comparative antibiotic studies that included safety analyses. We did not seek out the adverse event data collected by the pharmaceutical companies. For each study we recorded the percentage of subjects who experienced at least one adverse event, the percentage who withdrew from a study due to adverse events, the percentage with severe adverse events and the percentage who experienced gastrointestinal, central nervous system, skin/extremity and/or cardiovascular events. In addition, any other adverse events occurring in at least 2% of study subjects were also extracted. For antibiotics with two or more studies, we calculated a median and weighted mean percentage of study subjects experiencing at least one adverse event.

Methodological Quality Grading

We used a 3-category grading system (A, B, C) to denote the methodological quality of each study. This grading system has been used in most of the previous evidence reports from the Tufts-NEMC EPC as well as in evidence-based clinical practice guidelines.[2] For this report, we have slightly modified the grading system to take into account the percentage of dropout in the study. This system defines a generic grading system that is applicable to varying study designs including randomized controlled trials, cohort, and case-control studies:

A Category A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized study; clear description of the population, setting, interventions and comparison groups; sufficient power (arbitrarily defined as minimum sample size of 30 subjects per treatment arm); clear description of the intervention used; appropriate comparator; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; double-blinding; no reporting errors; less than 10% dropout; clear reporting of dropouts; and no obvious bias.

B Category B studies are susceptible to some bias, but not sufficiently so as to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis or reporting, have large amounts of missing information, or discrepancies in reporting. Specific criteria included large (>20%) or unequal dropout rate, large discrepancy in baseline and final numbers of subjects, unclear duration or numbers of subjects, missing baseline data, or irreconcilable apparent differences between data in figures, tables, and text.

Two investigators independently reviewed each primary study for methodological quality according to this grading system. Discrepancies in assigned grade between investigators were resolved via discussion and consensus. In addition to applying this grading system to each study, additional comments relating to potential sources of bias and other study limitations were noted and recorded during data extraction. Such comments are included in the evidence tables.

Meta-Analysis

Based on the available data, meta-analysis of primary studies was possible only for Research Question 1 regarding the comparative efficacies of antibiotics in the treatment of acute bacterial rhinosinusitis. Table 4 in chapter 3 shows the number of comparisons between the various antibiotics that were obtained by our search strategy. Meta-analysis was possible for the following comparisons:

1. antibiotics with placebo for treatment failure
2. cephalosporins with amoxicillin/clavulanate for treatment failure and recurrence
3. the combined category of macrolides/azalides/ketolides with amoxicillin/clavulanate for treatment failure and recurrence
4. quinolones with amoxicillin/clavulanate for treatment failure and recurrence
5. macrolides/azalides/ketolides with cephalosporins for treatment failure and recurrence
6. quinolones with cephalosporins for treatment failure and recurrence
7. quinolones with macrolides for treatment failure and recurrence

We calculated risk ratios and risk differences for each of these comparisons. All meta-analyses were performed using a random effects model. Similar to our previous report,

cumulative meta-analyses ordered by methodological quality of the studies were used to explore possible treatment effect trends as studies with lower quality scores were added to studies with higher quality scores. We used a three level quality score (from A to C) in this meta-analysis.

Several studies reported intention-to-treat data in addition to per-protocol data. However, because intention-to-treat data were not uniformly defined and less common, all meta-analyses were reported using per-protocol data. Some studies included multiple study arms comparing different doses of the same antibiotic. Chi-square analyses were used to determine the presence of heterogeneity in treatment outcome between different doses of the same antibiotic. To avoid arbitrarily selecting one treatment dose, multiple study arms evaluating the same antibiotic were combined for meta-analyses.

A few studies reported rates of microbiological treatment failure. However, because no more than 2 to 3 such studies were available for each comparison, we did not perform meta-analysis on microbiological treatment results.

Peer Review Process

The EPC requested nominations for potential external reviewers from the members of the Technical Expert Panel, which included the original individuals appointed to the first Panel in 1998 by the American Academy of Family Physicians, American Academy of Otolaryngology-Head and Neck Surgery, and American Academy of Pediatrics. The EPC also directly contacted researchers in the field inviting them to peer review. We provided material to reviewers, including the draft evidence report, guidance on the review process, and a structured evaluation form for collecting feedback from reviewers. We collated responses received from reviewers and made these available the EPC evidence review team. We then produced a structured summary report of the reviewers' comments and the responses made by the EPC review team for review by the AHRQ Task Order Officer.

Chapter 3. Results

From MEDLINE® we identified 704 citations for potential inclusion. Upon screening the abstracts, 87 articles were retrieved for full-text screening. A total of 39 studies ultimately qualified for inclusion in this update.

1. Given a clinical diagnosis of acute bacterial rhinosinusitis, what are the comparative efficacies of the antibiotics in resolving symptoms and preventing complications or recurrence?

We identified a total of 39 randomized controlled trials including 15,739 patients from 1997 to 2004 that studied antibiotic comparisons in treatment of acute bacterial sinusitis (Tables 1 & 2). With the exception of 5 studies that did not provide the information, all the studies were either funded by pharmaceutical companies or had authors associated with the pharmaceutical industry. Twelve of the studies consisted of subjects from the United States. Ten out of 39 studies included subjects less than 18 years old. No study was explicitly restricted to the pediatric population, although one study consisted only of subjects whose age ranged from 6 months to 17 years. Sample size of the studies ranged from 40 to 1,798. Of 13,220 patients whose per-protocol results were reported in the studies, less than 3 percent received placebo. All studies stated explicit requirements of clinical signs and symptoms of acute sinusitis for entry into the studies. In addition, 33 studies included results from either radiography or computed tomography (CT) scan of the sinuses as part of their eligibility criteria. Four studies are considered to be superior in methodological, reporting and data quality (A). Twenty-two studies are considered moderate (B) and nineteen studies low quality (C). The low quality studies often had limitations due to high dropout rate and incomplete reporting of data.

The antibiotics studied are listed in Tables 1 & 2. The classes of antibiotics studied consist of penicillins, cephalosporins, macrolides, azalides, ketolides, quinolones, carbapenems and tetracyclines. There are a total of 112 comparisons reported in the 39 trials (Table 4); 7 compare antibiotics to placebos; 5 compare various antibiotics (including 2 placebos) to amoxicillin, 22 compare various antibiotics (including 1 placebo) to amoxicillin/ clavulanate; 10 compare various antibiotics to cefuroxime. In contrast to the previous evidence report, there was no comparison against trimethoprim/sulfamethoxazole.

Duration of treatment varied between 3 days and 4 weeks. Twenty-six of the studies included at least one antibiotic that was prescribed for 10 days. Primary outcome assessment took place anywhere from 3 days to more than 4 weeks after the initiation of treatment.

Results of Meta-analyses

We performed 13 different meta-analyses to answer Research Question 1 regarding the comparative efficacy of different antibiotics on treatment failure and recurrence rates (Table 5). All meta-analyses were reported using per-protocol data from the primary studies. Meta-analyses were also performed substituting per-protocol data with modified intention-to-treat data available in 5 studies; results were similar and are not reported here. None of the cumulative meta-analyses ordered by study methodological quality demonstrated any alteration of treatment effect trend by the addition of studies with lower quality scores to those with higher quality scores. As a result, studies of all methodological quality are included in these meta-analyses.

Placebo-controlled trials. There were 5 trials (7 comparisons, total of 780 enrolled patients) comparing antibiotics to placebo. All of these trials recruited patients from a primary care setting. Four of the 5 trials used an antibiotic in the penicillin class, while the fifth trial compared azithromycin to placebo. Overall, antibiotics were more effective than placebo, reducing the risk of clinical failure by about 25% to 30% 7 to 14 days after treatment initiation (risk ratio [RR] 0.69, 95% confidence interval [CI] 0.53-0.89, Table 5). Nevertheless, symptoms improved or were cured in 65% of patients without any antibiotic treatment at all (95% CI 40-91%).

Antibiotic comparison trials. Five studies, involving a total of 3033 patients, compared various quinolones to cefuroxime. Except for one study, all antibiotics were given for 10 days. In the four studies that reported data for outcome assessment between 11 to 26 days after initiation of treatment, there was a non-statistically significant trend suggesting that quinolones were superior to cefuroxime in reducing clinical failure (RR 0.68, 95% CI 0.44 to 1.04).

There were four studies involving a total of 2765 patients, which showed that amoxicillin/clavulanate, when compared to antibiotics in the cephalosporin class, was 41% more effective in reducing clinical failure 10 to 25 days after treatment initiation (RR 1.41, 95% CI 1.08 to 1.82). In absolute terms, this means treating 100 patients with antibiotics in the cephalosporin class will lead to 3.5 more failures (95% CI 0.9 to 6.0) as compared to amoxicillin/clavulanate. However, data from four studies involving a total of 2797 patients did not show a significant difference in recurrence rates between amoxicillin-clavulanate and cephalosporins (RR 1.10, 95% CI 0.83 to 1.45) 24-45 days after treatment initiation.

There was no consistent trend observed when comparing amoxicillin/clavulanate, cephalosporins or quinolones to the group encompassing macrolides, azalides and ketolides.

Table 1. Placebo-controlled antibiotic trials for the treatment of acute bacterial rhinosinusitis from 7/1997 to 8/2004

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Bucher 2003	Switzerland	Pharm	252	124	Amox/Clav	875/125 mg bid	6 days	14	23.4%	1° outcome was "time to cure." X-ray not required for inclusion. Eligibility criteria changed midway	C
				127	Placebo	bid			26%		
Hansen 2000	Denmark	Pharm	139	71	Penicillin V	1333 mg bid	7 days	7	28%*	*calculated rates, differ from rates in abstract (29% for penicillin, 63% for placebo); X-ray not required for inclusion	C
				62	Placebo	2 tabs bid			51.5%*		
Haye 1998	Norway	ND	87	84	Azithromycin	500 mg qd	3 days	3-5 *	6%	*Paper did not define this as the timing for 1° outcome. Subjects should have no empyema on X-ray; 1 author associated with Pharm.	B
			82	81	Placebo	qd			12.3%		
Lindbaek 1998	Norway	Norwegian Research Council	70	20	Penicillin V	1320 mg tid	10 days	10	10%	Subjects > 15 y/o; CT showed thickening without air-fluid levels or total opacification	C
				22	Amoxicillin	500 mg tid			13.6%		
				21	Placebo	tid			14.3%		
Varonen 2003	Finland	Government & industry	150	88	Amoxicillin 750 mg x2 or Penicillin V 1500 IU x2 or Doxycyclin 100 mg x2		7 days	14	20.5%	Subgroup data for each abx was not reported; X-ray not required for inclusion	A
				59	Placebo				32.2%		

Abx: antibiotics; Amox/clav: amoxicillin/clavulanate; bid: twice a day; Pharm: pharmaceutical industry; qd: once a day; qid:, four times a day; Rx: prescription; tid: three times a day; X-ray: sinus radiography; y/o, years old

Table 2. Antibiotic-comparison trials for the treatment of acute bacterial rhinosinusitis from 7/1997 to 8/2004

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Adelglass 1998 a	ND	Pharm	140	108	Cefprozil	500 mg bid	10 days	11-15	13.9%	Subjects ≥ 13 y/o	C
			138	111	Amox/Clav	500/125 mg tid			8.1%		
Adelglass 1998 b	ND	Pharm	108	101	Levofloxacin	500 mg qd	14 days	16-19	4.0%		B
			108	89	Clarithromycin	500 mg bid			6.7%		
Adelglass 1999	US	Pharm	307	267	Levofloxacin	500 mg qd*	10-14 days	12-19	11.6%	*adjusted down if there is kidney impairment	B
			308	268	Amox/Clav	500/125mg q8h*			12.7%		
Buchanan 2003	Argentina France S. Africa US	Pharm	240	189	Telithromycin	800 mg qd	5 days	16-24	14.8%	Subjects ≥13 y/o in non-US sites; ≥18 y/o in US	C
			116	89	Cefuroxime	250 mg bid	10 days		18%		
Bucher 2003	Switzerland	Pharm	252	124	Amox/Clav	875/125 mg bid	6 days	14	23.4%	1° outcome was "time to cure." X-ray not required for inclusion. Eligibility criteria changed midway	C
				127	Placebo	bid			26%		
Burke 1999	North America	Pharm	542	223	Moxifloxacin	400 mg qd	10 days	17-31	10.3%		B
				234	Cefuroxime	250 mg bid			10.7%		
Chatzimanolis 1998	Greece	Pharm	60	29	Roxithromycin	150 mg bid	10 days minimum	~10-12	6.9%		C
				27	Amox/clav	500/125 mg tid			11.1%		
Clement 1998	ND	Pharm	254	136	Azithromycin	500 mg qd	3 days	21-28	12.5%	133 pts used vasoconstrictors, mucolytics & steroids.	B
				74	Amox/clav	500/125 mg tid	10 days		16.2%		
Clifford 1999	ND	Pharm	560	236	Ciprofloxacin	500 mg bid	10 days	16-19	15.7%		B
				221	Clarithromycin	500 mg bid	14 days		8.6%		
Ferguson 2002	Canada & 8 countries in Europe	Pharm	423	181	Gemifloxacin	320 mg qd	5 days	18-25	12.7%		B
				175			7 days		13.1%		

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Gehanno 2000	France	Pharm	433	181	Amox/clav	500 mg tid	5 days	14	21.6%	Some pts received steroids.	B
				179			10 days		15.6%		
Gwaltney 1997	US Europe	ND	585	474	Cefdinir	600 mg qd	10 days	17-24	10.3%	Subjects ≥13 y/o; X-ray not required for inclusion; 2 authors associated with Pharm.	B
			610	481		300 mg bid			12.7%		
			603	491	Amox/clav	500 mg tid			9%		
Steurer 2000 (subgroup of Gwaltney) 1997	Europe	Pharm	569	93	Cefdinir	600 mg qd	10 days	17-25	5.4%	Subjects ≥13 y/o; X-ray not required for inclusion.	C
				96		300 mg bid			10.4%		
				106	Amox/clav	500/125 mg tid			3.8%		
Hansen 2000	Denmark	Pharm	139	71	Penicillin V	1333 mg bid	7 days	7	28%*	*calculated rates, differ from rates in abstract (29% for penicillin, 63% for placebo); X-ray not required for inclusion	C
				62	Placebo	2 tabs bid			51.5%*		
Haye 1998	Norway	ND	87	84	Azithromycin	500 mg qd	3 days	3-5 *	6%	*Paper did not define this as the timing for 1° outcome. Subjects should have no empyema on X-ray; 1 author associated with Pharm.	B
			82	81	Placebo	qd			12.3%		
Henry 1999 a	US	Pharm	132	193 clinically assessable	Cefuroxime	250 mg bid	10 days	36-40	50%*	*Calculated from reported satisfactory rate.	C
			131		Amox/clav	500 mg tid			59%*		

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Henry 1999 b	US	Pharm	252	219	Sparfloxacin	400 mg qd Day 1; 200 mg qd Days 2-10	10 days	20±3	16.9%**	**calculated from reported success rate which is based on a denominator of total population minus the indeterminate cases	B
			252	211	Clarithromycin	500 mg q12h	14 days		16.6%**		
Henry 2003	US	Pharm	941	272	azithromycin	500 mg qd	3 days	22-36	28.3%		B
				271			6 days		26.6%		
				251	Amox/clav	500/125 mg tid	10 days		28.7%		
Jareoncharsri 2004	Thailand	Pharm	ND	34	Levofloxacin	300 mg qd	14 days	21	8.8%	Subjects ≥16y/o	C
				26	Amox/clav	500/125 mg tid			15.4%		
Johnson 1999	ND	Pharm	501	228	Ciprofloxacin	500 mg bid	10 days	11-18	13%		A
				225	Cefuroxime	250 mg bid			17%		
Klapan 1999	ND	ND	100	47	Azithromycin	500 mg qd	3 days	10-12	0%	Subjects ≥15 y/o; authors from Pharm.	B
				47	Amox/clav	500/125 mg tid	10 days		0%		
Klein 1998	ND	Pharm	83	13	Ciprofloxacin	500 mg bid	≥ 10 days	≥11-17	0%	Included subjects with acute exacerbation of chronic sinusitis	C
				19	Cefuroxime	250 mg bid			26.3%		
Klossek 2003	8 countries in Europe	ND	503	223	Moxifloxacin	400 mg qd	7 days	17-20	3.1%	2 authors associated with Pharm.	A
				229	Trovafloxacin	200 mg qd	10 days		7.9%		

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Kultluhan 2002	Turkey	ND	10	ND	Amox/clav 1 g bid or Ciprofloxacin 500 mg or Clarithromycin 500 mg bid or Cefuroxime 250 mg bid; Choice of antibiotics depended on maxillary sinus puncture and C&S results.		1 week	Day 28	50%*	*calculated relapse rate at day 28 assuming all patients completed the study; age range of subjects 16-45 y/o	C
			10				2 week		20%*		
			10				3 week		20%*		
			10				4 week		30%*		
Lasko 1998	ND	Pharm	119	98	Levofloxacin	500 mg qd	10-14 days	12-19	6.1%		B
			117	93	Clarithromycin	500 mg bid			6.5%		
Lindbaek 1998	Norway	Norwegian Research Council	70	20	Penicillin V	1320 mg tid	10 days	10	10%	Subjects > 15 y/o; CT showed thickening without air-fluid levels or total opacification	C
				22	Amoxicillin	500 mg tid			13.6%		
				21	Placebo	tid			14.3%		
Luterman 2003	US Canada S. Africa Argentina Chile	Pharm	754	146	Telithromycin	800 mg qd	5 days	17-24	24.7%	Stability problem with amox/clav, 100 pts from that group were excluded & replaced; data from excluded pts were not reported.	C
				140			10 days		27.1%		
				137	Amox/clav	500/125 mg tid	10 days		25.5%		
Murray 2000	US Canada	Pharm	284	122	Clarithromycin Extended release	1000 mg qd	14 days	24-31	14.8%	Subjects ≥ 12 y/o	B
				123	Clarithromycin immediate release	500 mg bid			21.1%		

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Namyslowski 2002	Poland	ND	231	104	Amox/clav	875/125 mg bid	14 days	15-18	2.9%	Included only subjects with chronic sinusitis & acute exacerbation of chronic sinusitis	B
				102	Cefuroxime	500 mg bid			7.8%		
Rakkar 2001	US	Pharm	475	170	Moxifloxacin	400 mg qd	10 days	24-31	14%	X-ray not required for inclusion	B
				171	Amox/clav	875 mg bid			16%		
Roos 2002	9 countries in Europe	ND	341	123	Telithromycin	800 mg qd	5 days	17-21	8.9%	Patients with pathogens known to be resistant to telithromycin before Rx were excluded. 3 authors associated with Pharm.	C
				133			10 days		9%		
Seggev 1998	US Canada	Pharm	170	61	Amox/clav	875/125 mg q12h	14 days	16-17	6.6%	Some pts received concurrent nasal steroids	C
				73		500/125 mg q8h			12.3%		
Sher 2002	ND	ND	445	137	Gatifloxacin	400 mg qd	5 days	17-24	25.6%	2 authors associated with Pharm.	B
				127			10 days		20.5%		
				141	Amox/clav	875 mg bid	10 days		28.4%		
Siegert 2000	7 countries in Europe	ND	493	211	Moxifloxacin	400 mg am	7 days	14	3.3%	2 authors associated with Pharm.	B
				225	Cefuroxime	250 mg bid	10 days		9.3%		
Siegert 2003	7 countries in Europe	Pharm	558	228	Faropenem daloxate	300 mg bid	7 days	14-23	11%		B
				224	Cefuroxime	250 mg bid			11.6%		

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Simon 1999	US	ND	50	ND	Erythromycin-sulfisoxazole	Erythromycin component 10 mg/kg/ dose qid	14 days	17-27 (1 week after end of Rx)	4%*	*reported failure rate, denominators not stated; age range of subjects: 6 months to 17 years; sinus films not obtained	C
			50		Ceftibuten	9 mg/kg/day, maximum 400 mg/day	10 days		8%*		
			50				15 days		8%*		
			50				20 days		0%*		
Stefansson 1998	S. Africa and 7 countries in Europe	ND	185	171	Cefuroxime	250 mg bid	10 days	11-14 and 38-45	9%**	**ITT, included failure & unevaluable patients; per protocol results similar but actual data not shown; 2 authors associated with Pharm.	C
			185	175	Clarithromycin	250 mg bid			7%**		
Sterkers 1997	France	ND	458	134	Ceftibuten	400 mg qd	8 days	10	17.2%	Subjects ≥15 y/o	B
				138		200 mg bid			13%		
				128	Amox/clav	500/125 mg tid			10.9%		
Varonen 2003	Finland	Government & industry	150	88	Amoxicillin 750 mg x2 or Penicillin V 1500 IU x2 or Doxycyclin 100 mg x2		7 days	14	20.5%	Subgroup data for each abx was not reported; X-ray not required for inclusion	A
				59	Placebo				32.2%		
Weis 1998	US	Pharm	1414	613	Ciprofloxacin	500 mg bid	10 days	14-26	8.8%	X-ray not required for inclusion.	B
				606	Cefuroxime	250 mg bid			9.9%		

Abx: antibiotics; Amox/clav: amoxicillin/clavulanate; bid: twice a day; C&S: culture and sensitivities; ITT: intention-to-treat analysis; ND: no data or not explicitly stated; Pharm: pharmaceutical industry; qd: once a day; qid: four times a day; Rx: prescription; tid: three times a day; X-ray: sinus radiography; y/o: years old.

Table 3. Randomized controlled trials of antibiotics in treatment of sinusitis from 7/1997 to 8/2004

Author Study ID	Penicillins			Cephalosporins				Macrolides/ Azalides/Ketolides					Others		Quinolones							Placebo
	Amoxicillin	Amox/clav	Penicillin	Cefprozil	Cefdinir	Cefti-buten	Cefuro-xime	Azithro-mycin	Clarithro-mycin	Erythro-mycin	Roxithro-mycin	Telithro-mycin	Doxy-cycline	Faro-penem	Gati-floxacin	Gemi-floxacin	Cipro-floxacin	Moxi-floxacin	Levo-floxacin	Spar-floxacin	Trova-floxacin	
Adelglass ID 534		x		x																		
Adelglass ID 540									x										x			
Adelglass ID 490		x																	x			
Buchanan ID 95931							x					x										
Bucher ID 9		x																				x
Burke ID 524							x											x				
Chatzimanolis ID 585		x									x											
Clement ID 583		x						x														
Clifford ID 480									x								x					
Ferguson ID 225																xx						
Gehanno ID 373		xx																				
Gwaltney ID 648		x			xx																	
Hansen ID 97079			x																			x
Haye 1998								x														x
Henry ID 10		x						xx														
Henry ID 482									x											x		
Henry ID 462		x					x															
Jareoncharsri ID 34		x																	x			
Johnson ID 491							x										x					
Klapan ID 500		x						x														
Klein ID 599							x										x					
Klossek ID 164																		x			x	
Lasko ID 530									x										x			
Lindbaek 1998	x		x																			x
Luterman ID 97041		x										xx										
Murray ID 375									xx													
Namyslowski ID 189		x					x															
Rakkar ID 97064		x																x				
Roos ID 240												xx										
Seggev ID 563		xx																				
Sher ID 257		x													xx							
Siegert ID 143							x							x								
Siegert ID 415							x											x				
Simon ID 475 Pedi						xxx				x												
Stefansson ID 97076							x		x													
Sterkers ID 633		x				xx																
Varonen ID 97080	x		x										x									x
Weis ID 545							x										x					

Amox/clav: amoxicillin/clavulanate

Table 4. Comparison of antibiotics/placebo in the randomized controlled trials: each trial contributes 1 or more comparisons to the table

		Penicillins			Cephalsporins				Macrolides / Azalides / Ketolides					Quinolones							Others			Number of Comparisons for Each Drug
		Amoxicillin	Amoxicillin clavulanate	Penicillin	Cefprozil	Cefdinir	Ceftibuten	Cefuroxime axetil	Azithromycin	Clarithromycin	Erythromycin	Roxithromycin	Telithromycin	Gatifloxacin	Gemifloxacin	Ciprofloxacin	Moxifloxacin	Levofloxacin	Sparfloxacin	Trovafloxacin	Faropenem	Doxycycline	Placebo	
Penicillins	Amoxicillin			2																		1	2	5
	Amoxicillin clavulanate		2		1	2	2	2	4			1	2	2			1	2					1	22
	Penicillin																					1	3	6
Cephalosporins	Cefprozil																							1
	Cefdinir					2																		4
	Ceftibuten						4				3													9
	Cefuroxime axetil									1			1			3	2				1			10
Macrolides / Azalides/ Ketolides	Azithromycin								1														1	6
	Clarithromycin									1						1		2	1					6
	Erythromycin																							3
	Roxithromycin																							1
	Telithromycin												2											7
Quinolones	Gatifloxacin													1										6
	Gemifloxacin														1									1
	Ciprofloxacin																							4
	Moxifloxacin																		1					4
	Levofloxacin																							4
	Sparfloxacin																							1
	Trovafloxacin																							1
Others	Faropenem																							1
	Doxycycline																						1	3
Placebo	Placebo																							7

Table 5. Per-protocol meta-analyses of treatment failure & recurrence with different antibiotics

Antibiotics Compared	Studies Included	Study Day of Assessment	Outcome Assessed	Risk Ratio (95%CI)	Risk Difference [per 100 people treated] (95% CI)
Antibiotics vs. Placebo	Bucher 2003* Hansen 2000 Haye 1998 Lindbaek 1998† Varonen 2003	14 7 10-12 10 14	Treatment Failure	0.69 (0.53-0.89)	-7.47 (-14.26 - -0.68)
Cephalosporins vs. Amoxicillin/clavulanate	Adelglass 1998 a Gwaltney 1997‡ Namyslowski 2002‡ Sterkers 1997‡	11-15 11-14 15-18 10	Treatment Failure	1.41 (1.08-1.82)	3.62 (1.03-6.22)
	Adelglass 1998 a Gwaltney 1997† Henry 1999 a Sterkers 1997†	24 31-45 36-40 40	Recurrence	1.10 (0.83-1.45)	2.37 (-0.75-5.49)
Macrolides, Azalides and Ketolides vs. Amoxicillin/clavulanate	Chatzimanolis 1998 Henry 2003 Klapan 1999	10-17 8-15 10-12	Treatment Failure	0.76 (0.54-1.08)	-1.56 (-4.59-1.48)
	Clement 1998 Henry 2003 Klapan 1999 Luterman 2003†	21-28 22-36 28 31-45	Recurrence	0.95 (0.79-1.14)	-2.34 (-6.45-1.78)
Quinolones vs. Amoxicillin/clavulanate	Adelglass 1999 Jareoncharsri 2004 Sher 2002†	12-19 21 12-24	Treatment Failure	0.35 (.06-1.9)	-11.45 (-29.92-7.02)
	Adelglass 1999 Rakkar 2001	38-46 36-56	Recurrence	0.74 (0.34-1.6)	-1.06 (-3.5-1.37)
Macrolides, Azalides and Ketolides vs. Cephalosporins	Buchanan 2003 Simon1999§ Stefansson 1998	16-24 17-25 11-13	Treatment Failure	0.81 (0.53-1.24)	-1.78 (-5.61-2.06)
	Buchanan 2003 Simon 1999§ Stefansson 1998	31-45 40-50 38-45	Recurrence	1.11 (0.82-1.51)	1.68 (-3.68-7.05)
Quinolones vs. Cephalosporins (Cefuroxime)	Johnson 1999 Klein 1998 Siegert 2000‡ Weis 1998	11-17 14-25 14 14-26	Treatment Failure	0.68 (0.44-1.04)	-4.51 (-9.15-0.14)
	Burke 1999 Johnson 1999 Klein 1998 Siegert 2000	37-41 24-38 27-46 34-41	Recurrence	0.85 (0.57-1.27)	-1.07 (-3.44-1.29)
Quinolones vs. Macrolides (Clarithromycin)	Adelglass 1998 b Clifford 1999‡ Henry 1999 b Lasko 1998	16-19 16-17 20-23 12-19	Treatment Failure	1.01 (0.59-1.73)	0.15 (-5.89-6.19)
	Adelglass 1998 b Clifford 1999‡ Henry 1999 b	42-46 29-42 31-45	Recurrence	0.70 (0.42-1.15)	-4.44 (-8.18 - -0.69)

* No significant difference was found between combined study arms evaluating antibiotics in the same class ($P \geq .05$).
‡ Per-protocol results for this study were significantly different than intent-to-treat results ($P < .05$).
‡ Treatment results were significantly different between combined study arms evaluating the same antibiotic class ($P < .05$).
§ Only studies with days of assessment entirely contained by the specified interval were included.
‖ Results recorded 14 (vs. 7) days after treatment initiation were used.

1a. Is there evidence that duration of antibiotic treatment in acute bacterial rhinosinusitis affects efficacy?

There are eight studies that reported data on comparisons of the effect of treatment duration on outcomes (Table 6). One study that compared 10 days with 5 days of amoxicillin/clavulanate 500 mg tid reported a statistically non-significant 27% reduction in clinical failure rate[3]. Another study of ceftibuten concluded that 20 days of treatment may be more effective than either 10 days or 15 days regimen (0% failure rate vs. 8% vs. 8%, respectively)[4]; however, the study did not report the actual number of patients who completed the study. Two studies of 10 days vs. 5 days of telithromycin reported that the clinical failure rate between the two treatment durations were comparable.[5,6] The studies on gemifloxacin (5 days vs. 7 days)[7], azithromycin (3 days vs. 6 days)[8] and gatifloxacin (5 days vs. 10 days)[9] showed therapeutic equivalence of the 2 durations. One study compared nasal smear findings for certain periods after different durations of antibiotic treatment and concluded that at least 2 weeks of antibiotics would be an appropriate treatment duration for acute maxillary sinusitis because the average nasal smear score (derived from number of neutrophils) was significantly different beginning from study day 21 between the 7-day-antibiotic group and the other groups. [10]

Table 6. Comparing different durations of treatment in sinusitis

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Ferguson 2002	Canada & 8 countries in Europe	Pharm	423	181	Gemifloxacin	320 mg qd	5 days	18-25	12.7%		B
				175			7 days		13.1%		
Gehanno 2000	France	Pharm	433	181	Amox/clav	500 mg tid	5 days	14	21.6%	Some pts received steroids.	B
				179			10 days		15.6%		
Henry 2003	US	Pharm	941	272	Azithromycin	500 mg qd	3 days	22-36	28.3%		B
				271			6 days		26.6%		
				251	Amox/clav	500/125 mg tid	10 days		28.7%		
Kultluhan 2002	Turkey	ND	10	ND	Amox/clav 1 g bid or Ciprofloxacin 500 mg or Clarithromycin 500 mg bid or Cefuroxime 250 mg bid; Choice of abx depending on maxillary sinus puncture C&S results.		1 week	28	50%*	*calculated relapse rate at day 28 assuming all patients completed the study; age range of subjects 16-45 y/o; conclusion of study based on nasal smear results, not clinical failure rate	C
			10				2 week		20%*		
			10				3 week		20%*		
			10				4 week		30%*		
Luterman 2003	US Canada S. Africa Argentina Chile	Pharm	754	146	Telithromycin	800 mg qd	5 days	17-24	24.7%	Stability problem with amox/clav, 100 patients from that group were excluded & replaced; data from excluded pts were not reported.	C
				140			10 days		27.1%		
				137	Amox/clav	500/125 mg tid	10 days		25.5%		
Roos 2002	9 countries in Europe	ND	341	123	Telithromycin	800 mg qd	5 days	17-21	8.9%	Pts with pathogens known to be resistant to telithromycin before Rx were excluded. 3 authors associated with Pharm.	C
				133			10 days		9%		
Sher 2002	ND	ND	445	137	Gatifloxacin	400 mg qd	5 days	17-24	25.6%	2 authors associated with Pharm.	A
				127			10 days		20.5%		
				141	Amox/clav	875 mg bid	10 days		28.4%		

Author Year	Country	Funding	# Randomized or Enrolled	# per Protocol	Antibiotic	Dose	Duration	Time of evaluation of 1° outcome (days after start of Rx)	Clinical failure rate per protocol	Comments	Quality
Simon 1999	US	ND	50	ND	Erythromycin-sulfisoxazole	Erythromycin component 10 mg/kg/dose qid	14 days	17-27 (1 week after end of Rx)	4%*	*reported failure rate, denominators not stated; age range of subjects: 6 month to 17 years; sinus films not obtained	C
			50		Ceftibuten	9 mg/kg/day, maximum 400 mg/day	10 days		8%*		
			50				15 days		8%*		
			50				20 days		0%*		

Abx: antibiotics; Amox/clav: amoxicillin/clavulanate; bid: twice a day; C&S: culture and sensitivities; ND: no data or not explicitly stated; Pharm: pharmaceutical industry; qd: once a day; qid: four times a day; Rx: prescription; tid: three times a day; y/o: years old.

2. What adverse effects are reported for antibiotics used for acute bacterial rhinosinusitis?

Thirty-four of the comparative trials and five additional non-comparative trials reported adverse events. Descriptions of adverse events were diverse among studies. Almost all reported probable treatment-related adverse events, but many of them did not state the criteria for determining whether an event was considered likely treatment-related or not. Several studies also graded the severity of events; however, no study gave clear criteria for the grading scale. Other studies reported serious adverse events only. Few studies differentiated between severe (a description of degree) and serious (life-threatening, disabling or requiring prolonged hospitalization) events. Virtually all studies examined only short-term adverse events with assessment ending at the conclusion of patient follow-up 2 months or less after treatment initiation.

The overall percentage of subjects who reported at least one adverse event varied from 3% to 88% (Table 7). In general, an average adverse event rate of 15% to 40% of subjects was observed for the different classes of antibiotic. The adverse event rate for placebo was in this range, as well. Severe adverse events were rare, occurring in 0 to 7.7% of subjects. Severe adverse events included diarrhea, abdominal pain and nausea on amoxicillin/clavulanate; abdominal pain, diarrhea, constipation, urticaria, headache/dizziness, loss of appetite/disorientation/insomnia and vaginitis/monilia on levofloxacin; headache, asthenia, diarrhea, vomiting, dizziness and agitation on moxifloxacin; vaginitis, headache, nausea, diarrhea, arthralgia, increased cough and dyspnea on cefuroxime; diaphoresis/rash and loss of appetite/disorientation/insomnia on clarithromycin; and increased coagulation test on faropenem. Very few specific serious adverse events were reported by studies. Reported serious adverse events included diplopia on amoxicillin/clavulanate; myocardial infarction, lumbar disk lesion and neuropathy on levofloxacin; asthma on sparfloxacin; allergic reaction, facial/tongue edema, hepatitis, asthma and convulsion on gatifloxacin; maxillary antral abscess, convulsions, and collapse during local anesthesia on clarithromycin; facial edema on ciprofloxacin; amblyopia, ischemic heart disease and maxillary sinus surgery on cefuroxime; and tachycardia on moxifloxacin. Discontinuation due to adverse events was uncommon with fewer than 10% of subjects removed from any trial due to adverse events.

It is difficult to compare the rates of occurrence of particular adverse events by antibiotic class given the heterogeneity among studies. Overall, the most common events involved the gastrointestinal system, specifically reports of nausea or vomiting, diarrhea and abdominal pain. Central nervous system adverse events, mostly complaints of headaches, were also common. Some subjects in each antibiotic class reported skin disorders, such as rash and photosensitivity. Taste perversion seemed to be a problem specific to clarithromycin administration with anywhere between 8% and 21% of study subjects reporting this complaint.

Cardiovascular problems were a particular concern to investigators of quinolones given their association with prolongation of the QT_c interval on electrocardiogram. Nevertheless, cardiac-related adverse event rates were low with quinolones, as well as for all classes of antibiotics. In the study conducted on 10,822 subjects with sinusitis by Faich et al. [11], an independent safety committee was convened to search for a link between moxifloxacin and cardiac-related events. Investigators asked patients specifically about symptoms suggestive of a possible cardiac event such as chest pain or tachycardia; however, electrocardiograms were not routinely collected. The

committee concluded that there was no evidence of increased mortality or detectable treatment-associated ventricular tachyarrhythmias in that trial. In a study of 253 patients treated with sparfloxacin conducted by Garrison et al.[12] which did collect electrocardiograms on all patients, there was a mean increase in the QT_c interval from baseline to day 4 of 0.010±0.024 sec., but no cardiovascular adverse events related to this increase.

Some women in each antibiotic class experienced vaginal moniliasis. Comparison of the rates of moniliasis between classes is problematic as the incidence reported by some studies may be under-estimated. Some reports are unclear as to whether they excluded men from the denominator in their calculations. Other studies did not specifically report the incidence of vaginal moniliasis but the incidence of vaginitis or urogenital complaints.

Tables 8 to 11 present the specific adverse events reported in each antibiotic class.

Table 7: Summary ranges of percent of patients experiencing adverse events with placebo and each antibiotic

	# of Studies	Subjects with Adverse Events, Overall %	Gastrointestinal			CNS	Skin/ Extr.	CV	Other†	Study Withdrawal Due to Adverse Events	Severe Adverse Events
			Nausea/ Vomiting	Diarrhea	Abdominal Pain						
PLACEBO											
Placebo	3	3.2-27.1 (18.3,15.6)*	1.2	6.1-6.3	1.2-12.5					0-2.1	0
CEPHALOSPORINS											
Cefdinir	1	33.6	2	21	2.3	1.7				2.3	ND
Ceftibuten	1	11.8		9.2						2.3	ND
Cefprozil	1	16.4	5	7.1			0.7			2.1	ND
Cefuroxime	10	9.2-45 (17.7, 22.5)*	1.7-6.6	2-6.2	1.1-2.8	0.8-5.5	2.9	1.7	Urogenital: 2.3-2.9	0.7-7.8	0-3.6
CARBAPENEMS											
Faropenem	1	16.8								2.6	0.4
PENICILLINS											
Amoxicillin/clavulanate	17	7-51.1 (25.6, 30.2)*	1.1-12.1	1.8-32.3	0.8-11.1	0-2.7	2.5-5.1		Vaginal moniliasis: 3-5.3	0-8.9	0-3.4
Penicillin	1	18.3		15.5						ND	ND
MACROLIDES, AZALIDES AND KETOLIDES											
Azithromycin	4	4-34.3 (22.6, 29.1)*	4-8	4.2-19.1	3.4-4.2	3		1		0-2.9	0-3
Clarithromycin	6	9.7-82.4 (43.9, 42.3)*	4.8-7	5.6-27	3.6-3.7	0-9	0.5		Taste perversion: 7.7-20.9	3.2-5.7	7.7
Roxithromycin	1	3.4		3.4						ND	ND
Telithromycin	3	22.2-42.4 (34.5, 35.3)*	3.6-10.6	6-19.9	3.3-4.2	1.5-5.2			Vaginal moniliasis: 2.4	2-6	≥3
QUINOLONES											
Ciprofloxacin	4	11.3-46 (38.3, 25.6)*	2.5	1-6		1.5-6.7				0.4-3.8	ND
Gatifloxacin	2	14	4.4-11.4	1.4-8		2.8		0.4		2.4	0.1-2.7
Gemifloxacin	1	37	≥3	≥3						0.7	ND
Levofloxacin	5	8.8-87.9 (22.7, 30.1)*	0-5.6	0.9-2.7	1-1.9	2.8-6.7		0.3		1.8-3.7	0-6.7
Moxifloxacin	6	12.2-58.1 (36.6, 18.8)*	1.2-14.1	1.2-9.5	1.9-4.1	1.6-9.5	1.2-3.8	1.2	Nervousness: 2.7-3.8 Whole body: 3.8-9.5	5.1-5.8	1.6-2.7
Sparfloxacin	2	45.6-54.9 (50.3, 50.3)*	4.3-4.8	7.5-23.8	1.6-2	4.3	7.9-9.5	0		3.6-4.4	0.4
Trovafloxacin	1	32.7	4	1.2	1.6	11.6				Unclear	0.8

Abd: abdominal; CNS: central nervous system (headache or dizziness/vertigo); CV: cardiovascular (palpitations, syncope, arrhythmia, cardiac insufficiency, etc.); ND: no data; Skin/Extr: skin (photosensitivity, rash, urticaria, eczema flare, etc.) or extremities;
*Median and weighted mean percentages reported if ≥2 studies for each antibiotic.
†Other adverse events occurring in ≥ 2% of patients in at least 2 studies.

Table 8: Adverse events for placebo and penicillins, N (%)

Study	Subjects with Adverse Events	Gastrointestinal			CNS	Skin/ Extr.	CV	Other[†]	Study Withdrawal Due to Adverse Events	Severe Adverse Events
		Nausea/ Vomiting	Diarrhea	Abd. Pain						
PLACEBO										
Hansen 2000	2/62 (3.2)			1 (1.6)					ND	ND
Haye 1998	15/82 (18.3)	1 (1.2)	5 (6.1)	1 (1.2)					0 (0)	0 (0)
Varonen 2003	13/48 (27.1)		3 (6.3)	6 (12.5)		0(0)		Fatigue 3 (6.3)	1 (2.1)	ND
AMOXICILLIN/CLAVULANATE										
Adelglass 1998 a	53/138 (38.4)	14 (10.1)	35 (25.4)			7 (5.1)			9 (6.5)	ND
Adelglass 1999	146/302 (48.3)	5 (1.7)	35 (11.6)	5 (1.7)					16 (5.3)	0 (0)
Chatzimanolis 1998	7/27 (25.9)		5 (18.5)	3 (11.1)					Unclear	ND
Clement 1998	23/89 (25.8)	1 (1.1)	13 (14.6)	7 (7.9)	0 (0)				2 (2.2)	3 (3.4)
Gehanno 2000 (Non-comparison study)	46/433 (10.6)	X	X	X		X			8 (1.8)	ND
Gwaltney 1997	234/603 (38.8)	9 (1.5)	133 (22.1)	25 (4.1)	16 (2.7)			Vaginal moniliasis: 18 (3.0)	30 (5.0)	ND
Henry 2003 [‖]	160/313 (51.1)	38 (12.1)	101 (32.3)						28 (8.9)	0 (0)
Henry 1999 a [‖]	38/131 (29.0)	6 (4.6)	25 (19.1)					Vaginitis: 5 (3.8)	8 (6.1)	ND
Jareoncharsri 2004	2/26 (7.7)	X					X		ND	0 (0)
Klapan 1999	5/50 (10)	5 (10.0)	1 (2.0)						0 (0)	0 (0)
Luterman 2003[§]	101/245 (41.2)	19 (7.8)	58 (23.7)	6 (2.4)	5 (2.0)			Vaginal moniliasis: 13 (5.3)	11 (4.5)	ND
Namyslowski 2002	8/115 (7)		3 (2.6)						4 (3.5)	0 (0)
Rakkar 2001	60/237 (25.3)	13 (5.5)	24 (10.1)	2 (0.8)	5 (2.1)	6 (2.5)		Whole body: 20 (8.4) Moniliasis: 15 (6.3) Asthenia: 5 (2.1) Urogenital: 9 (3.8) Elevated LFTs: 11 (4.6)	8 (3.4)	ND
Seggev 1998	26/170 (15.3)	4 (2.4)	3 (1.8)	6 (3.5)	2 (1.2)			Fungal infection: 10 (5.6)	4 (2.4)	1 (0.6)
Sher 2002	not reported	(4)	(14)					Vaginitis: (9% of women)	3 (1.9)*	4 (3)*
Sterkers 1997	16/146 (11)	15 (10.3)							5 (3.4)	ND
PENICILLIN										
Hansen 2000	13/71 (18.3)	11 (15.5)							ND	ND

Numbers reported are for all adverse events, unless only likely drug-related adverse events were reported by a study.
Abd: abdominal; CNS: central nervous system (headache or dizziness/vertigo); Skin/Extr: skin (photosensitivity, rash, urticaria, eczema flare, etc.) or extremities; CV: cardiovascular (palpitations, syncope, arrhythmia, cardiac insufficiency, etc.); X: actual percent not reported

* Denominator not specified, so based on number enrolled, or percentage stated by authors
† Only reported for adverse events that occurred in ≥ 2%; see study summaries for less common adverse events.
‡ Estimated from stated odds ratio
§ Study only reported adverse events that occurred on at least 2 occasions. ‖Study only reported adverse events that occurred in more than 5% of subjects

Table 9: Adverse events for cephalosporins and faropenem, N (%)

Study	Subjects with Adverse Events	Gastrointestinal			CNS	Skin/ Extr.	CV	Other†	Study Withdrawal Due to Adverse Events	Severe Adverse Events
		Nausea/ Vomiting	Diarrhea	Abd. Pain						
CEFDINIR										
Gwaltney 1997	400/1189 (33.6)	24 (2.0)	250 (21.0)	27 (2.3)	20 (1.7)				27 (2.3)	ND
CEFIBUTEN										
Sterkers 1997	36/304 (11.8)	28 (9.2)							7 (2.3)	ND
CEFPROZIL										
Adelglass 1998 a	23/140 (16.4)	7 (5.0)	10 (7.1)			1 (0.7)			3 (2.1)	ND
CEFUROXIME										
Buchanan 2003	20/121 (16.5)	8 (6.6)	6 (5)				2 (1.7)	Abnormally low creatinine clearance	2 (1.7)	ND
Burke 1999	112/274 (40.9)	11 (5.1)	17 (6.2)	3 (1.1)	15 (5.5)	8 (2.9)		Whole body: 15 (5.5) Special senses: 9 (3.3) Urogenital: 8 (2.9)	6 (2.2)	10 (3.6)
Henry 1999 b	23/132 (17.4)		8 (6.1)					Vaginitis 3 (2.3)	2 (1.5)	ND
Johnson 1999	113/251 (45)*	X	X		X				6 (2.4)*	ND
Klein 1998	10/28 (34)*	X	X						1 (2.9)*	ND
Namyslowski 2002	11/116 (9.5)		3 (2.6)						9 (7.8)	1 (0.9)
Siegert 2003	49/273 (17.9)	X				X			2 (0.7)	0 (0)
Siegert 2000	88/252 (35.1)	9 (3.6)	15 (6.0)	7 (2.8)	2 (0.8)				11 (4.4)	ND
Stefansson 1998	17/185 (9.2)	13 (7.0)							ND	ND
Weis 1998	81/700 (11.6)	12 (1.7)	14 (2.0)		12 (1.7)				26 (3.7)	ND
FAROPENEM										
Siegert 2003	46/274 (16.8)	X				X			7 (2.6)	1 (0.4)

Numbers reported are for all adverse events, unless only likely drug-related adverse events were reported by a study.
Abd: abdominal; CNS: central nervous system (headache or dizziness/vertigo); Skin/Extr: skin (photosensitivity, rash, urticaria, eczema flare, etc.) or extremities; CV: cardiovascular (palpitations, syncope, arrhythmia, cardiac insufficiency, etc.); X: actual percent not reported.

* Denominator not specified, so based on number enrolled, or percentage stated by authors.
† Only reported for adverse events that occurred in ≥ 2%; see study summaries for less common adverse events.
‡ Estimated from stated odds ratio
§ Study only reported adverse events that occurred on at least 2 occasions
‖ Study only reported adverse events that occurred in more than 5% of subjects

Table 10: Adverse events for macrolides, azalides and ketolide, N (%)

Study	Subjects with Adverse Events	Gastrointestinal			CNS	Skin/ Extr.	CV	Other†	Study Withdrawal Due to Adverse Events	Severe Adverse Events
		Nausea/ Vomiting	Diarrhea	Abd. Pain						
AZITHROMYCIN										
Clement 1998	29/165 (17.6)	8 (4.8)	7 (4.2)	7 (4.2)	5 (3)		2 (1)		0 (0)	5 (3)
Haye 1998	24/87 (27.6)	7 (8)	11 (12.6)	3 (3.4)					0 (0)	1 (1.1)
Henry 2003 ‖	214/623 (34.3)	50 (8)	119 (19.1)						18 (2.9)	0 (0)
Klapan 1999	2/50 (4)	2 (4)							0 (0)	0 (0)
CLARITHROMYCIN										
Adelglass 1998 b	88/108 (82.4)	7 (6.5)	6 (5.6)	4 (3.7)	0 (0)			Taste perversion: 13 (12.0) Fungal infection: 3 (2.8) Insomnia: 3 (2.8)	ND	ND
Clifford 1999	158/278 (56.8)	Overall GI: 81 (29.1) Diarrhea: 36 (13.0)			25 (9)			Taste perversion: 58 (20.9) Special senses: 60 (21.6)	9 (3.2)	ND
Henry 1999 b	122/252 (48.4)	12 (4.8)	68 (27)	9 (3.6)		1 (0.5)		Taste perversion: 22 (8.7) Elevated LFT's or blood glucose: 6 (2.4)	14 (5.6)	ND
Lasko 1998	46/117 (39.3)	39 (33.3)			5 (4.3)			Taste perversion: 9 (7.7)	ND	9 (7.7)
Murray 2000	85/283 (30)	(7)	(7)					Taste perversion: (10)	16 (5.7)	ND
Stefansson 1998	18/185 (9.7)	8 (4.3)							ND	≥3
ROXITHROMYCIN										
Chatzimanolis 1998	1/29 (3.4)	1 (3.4)							Unclear	ND
TELITHROMYCIN										
Buchanan 2003	56/252 (22.2)	22 (8.7)	15 (6)		7 (2.8)			Abnormally low creatinine clearance	5 (2.0)	ND
Luterman 2003‖	211/498 (42.4)	53 (10.6)	99 (19.9)	21 (4.2)	26 (5.2)			Vaginal moniliasis: 12 (2.4)	30 (6.0)	≥1
Roos 2002	115/333 (34.5)	12 (3.6)	38 (11.4)	11 (3.3)	5 (1.5)			Vaginal moniliasis: 8 (2.4)	7 (2.1)	ND

Numbers reported are for all adverse events, unless only likely drug-related adverse events were reported by a study.
Abd: abdominal; CNS: central nervous system (headache or dizziness/vertigo); Skin/Extr: skin (photosensitivity, rash, urticaria, eczema flare, etc.) or extremities; CV: cardiovascular (palpitations, syncope, arrhythmia, cardiac insufficiency, etc.); X: actual percent not reported
***** Denominator not specified, so based on number enrolled, or percentage stated by authors
† Only reported for adverse events that occurred in ≥ 2%; see study summaries for less common adverse events.
‡ Estimated from stated odds ratio

§ Study only reported adverse events that occurred on at least 2 occasions
‖ Study only reported adverse events that occurred in more than 5% of subjects

Table 11: Adverse events for quinolones, N (%)

Study	Subjects with Adverse Events	Gastrointestinal			CNS	Skin/ Extr.	CV	Other†	Study Withdrawal Due to Adverse Events	Severe Adverse Events
		Nausea/ Vomiting	Diarrhea	Abd. Pain						
CIPROFLOXACIN										
Clifford 1999	120/282 (42.6)	Overall GI: 58 (20.6) Diarrhea: 17 (6.0)			19 (6.7)			Taste Perversion: 7 (2.5) Special senses: 14 (5)	9 (3.2)	ND
Johnson 1999	115/250 (46)*	X	X		X				1 (0.4)*	ND
Klein 1998	10/28 (34)*	X	X						1 (3.6)*	ND
Weis 1998	80/711 (11.3)	18 (2.5)	7 (1)		11 (1.5)				27 (3.8)	ND
GATIFLOXACIN										
Sher 2002	ND	(11.4)	(8)					Vaginitis in women: (9)	7 (2.7)*	7 (2.7)*
Sher 2002 (non-comparison)	1605/11,476(14)	505 (4.4)	161 (1.4)		321 (2.8)		41 (0.4)		ND	14 (0.1)
GEMIFLOXACIN										
Ferguson 2002	(37)	(≥3)	(≥3)						3 (0.7)	ND
LEVOFLOXACIN										
Adelglass 1998 b	94/107 (87.9)	6 (5.6)	1 (0.9)	2 (1.9)	3 (2.8)				ND	2 (1.9)
Adelglass 1999	114/297 (38.4)	0 (0)	4 (1.3)	3 (1)					11 (3.7)	0 (0)
Jareoncharsri 2004	3/34 (8.8)	X	X	X	X				ND	0 (0)
Lasko 1998	27/119 (22.7)	20 (16.8)			8 (6.7)				ND	8 (6.7)
Sydnor 1998	29/329 (9)	4 (1.2)	9 (2.7)				1 (0.3)		6 (1.8)	8 (2.4)
MOXIFLOXACIN										
Burke 1999	126/263 (47.9)	37 (14.1)	18 (6.8)	5 (1.9)	25 (9.5)	9 (3.4)		Whole body: 25 (9.5) Nervousness: 7 (2.7)	15 (5.7)	7 (2.7)
Gehanno 2003[§]	31/255 (12.2)	6 (2.4)	3 (1.2)	6 (2.4)	4 (1.6)	3 (1.2)	3 (1.2)		ND	ND
Faich 2004	1793/10,822 (16.6)	827 (8.1)	259 (2.4)		378 (3.5)			Whole body: 371 (3.4)	ND	ND
Klossek 2003	74/248 (29.8)	3 (1.2)	14 (5.6)	5 (2)	5 (2)			Asthenia: 5 (2.0)	≥2	4 (1.6)
Rakkar 2001	136/234 (58.1)	33 (14.1)	7 (3)	5 (2.1)	9 (3.8)	9 (3.8)		Moniliasis 8 (3.4) Nervousness: 9 (3.8) Special senses 7 (3.0)	12 (5.1)	ND
Siegert 2000	105/242 (43.3)	17 (7)	23 (9.5)	10 (4.1)	7 (2.9)				14 (5.8)	ND
SPARFLOXACIN										
Henry 1999 b	115/252 (45.6)	12 (4.8)	60 (23.8)	4 (1.6)		24 (9.5)		Elevated LFT's or blood glucose: 8 (3.2)	11 (4.4)	ND
Garrison 2000	139/253 (54.9)	11 (4.3)	19 (7.5)	5 (2)	11 (4.3)	20 (7.9)	0 (0)	Insomnia: 7 (2.8)	9 (3.6)	1 (0.4)
TROVAFLOXACIN										
Klossek 2003	82/251 (32.7)	10 (4)	3 (1.2)	4 (1.6)	29 (11.6)			Asthenia: 6 (2.4)	≥6	2 (0.8)

Numbers reported are for all adverse events, unless only likely drug-related adverse events were reported by a study.
Abd: abdominal; CNS: central nervous system (headache or dizziness/vertigo); Skin/Extr: skin (photosensitivity, rash, urticaria, eczema flare, etc.) or extremities; CV: cardiovascular (palpitations, syncope, arrhythmia, cardiac insufficiency, etc.); X: actual percent not reported
* Denominator not specified, so based on number enrolled, or percentage stated by authors
† Only reported for adverse events that occurred in ≥ 2%; see study summaries for less common adverse events.
‡ Estimated from stated odds ratio
§ Study only reported adverse events that occurred on at least 2 occasions
‖ Study only reported adverse events that occurred in more than 5% of subjects

3. How does the introduction of the pneumococcal vaccine affect the resistance patterns of pneumococcus and the treatment decisions in acute bacterial rhinosinusitis?

We did not identify any article in our literature search that directly addressed this question. Streptococcus pneumoniae is one of the most common pathogens identified in acute bacterial sinusitis. In the early 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was approved for routine administration to infants and children in United States. In the same year, the American Academy of Pediatrics (AAP) recommended routine administration of PCV7 to all children 23 months and younger.[13] It is therefore, important to monitor the changes in serotypes and antibiotic susceptibility of S. pneumoniae as a result of the introduction of PCV7 to the population. Furthermore, recommendations for treatment of acute bacterial sinusitis may well have to be modified depending on the results of the surveillance. Surveillance data are already appearing demonstrating the changing epidemiology of S. pneumoniae serogroups after the introduction of PCV7. Data collected from the US Pediatric Multicenter Pneumococcal Surveillance Group reported that before the licensure, nonvaccine serogroups accounted for 6% of the isolates recovered from children ≤ 24 months old; in 2002, nonvaccine-serogroup isolates were 37.6% of the total isolates in this age group. Also, among the isolates of S. Pneumoniae belonging to the serogroups contained in PCV7, the proportion that were nonsusceptible to penicillin decreased from 54% in 2001 to 43% in 2002.[14] Another report reported that rate of invasive pneumococcal disease decreased from an average of 24.3 cases per 100,000 persons in 1998 and 1999 to 17.3 per 100,000 in 2001. The largest decline was in children under two years of age. Disease rates also fell for adults. This observation suggests that the use of pneumococcal vaccine in children may be reducing the rate of disease in adults as well.[15] A randomized controlled trial between 1995 and 1999 involving 1,662 infants reported that the heptavalent pneumococcal vaccine reduced the number of episodes of acute otitis media by 6% (95% CI -4 to 16%) and also reduced the number of episodes due to the serotypes contained in the vaccine by 57% (95% CI 44 to 67%), whereas the number of episodes due to all other serotypes increased by 33%.[16] This suggests that the impact of pneumococcal immunization on acute sinusitis in adults will also depend on the virulence and resistance patterns of the serotypes that replace those contained in the vaccine.

Chapter 4. Conclusions and Discussion

This report examined the available evidence from randomized trials on the efficacy of antibiotics in patients with acute bacterial rhinosinusitis published since our original report in 1999. Overall, as in our previous report, antibiotics were found to be superior to placebo in the treatment of sinusitis, reducing the risk of clinical failure by almost 30%. Judging from the prevalence of comparisons involving amoxicillin/clavulanate, it appears that most investigators view this antibiotic as the preferred agent in a comparative drug trial. It is also more effective than the cephalosporin class of antibiotics in the treatment of sinusitis, reducing clinical failure rate by approximately 40% within 10-25 days after treatment initiation. However, in absolute terms, this implies that for every 100 patients treated with a cephalosporin, only about 3.5 more clinical failures would occur than in patients treated with amoxicillin/clavulanate. The superiority in clinical efficacy of amoxicillin/clavulanate over cephalosporins disappears when patients are examined for recurrence 24-45 days after treatment initiation.

There are only a few studies that specifically examined the effect of different treatment durations on outcome efficacy. In the one study of 10 vs. 5 days of amoxicillin/clavulanate, the 10-day regimen showed a statistically non-significant reduction of clinical failure by 27% (22% of patients failed on 5 days of treatment compared to 16% on 10 days of treatment). Studies on telithromycin (10 vs. 5 days), gemifloxacin (7 vs. 5 days), gatifloxacin (10 vs. 5 days) and azithromycin (6 vs. 3 days) all showed therapeutic equivalence between the 2 durations. In conclusion, most of the studies generally found no difference between shorter and longer duration of treatment.

It is difficult to compare the rates of adverse events across different antibiotic classes given the enormous variation in the reported rate of adverse events within the same antibiotic class. For example, the reported rate of diarrhea with amoxicillin/clavulanate across different studies ranged from under 2% to more than 30%. This may be due to a lack of an agreed definition of diarrhea, different study populations, and different reporting criteria. In all classes of antibiotics, gastrointestinal disturbances were most common, followed by headaches and skin rashes, as well as vaginal moniliasis. Cardiovascular complaints were rare. Severe adverse events in general occurred in up to about 3.5% of patients in all classes.

As of September 2004, there had not been any published studies examining the effect of the pneumococcal vaccine on the treatment of acute sinusitis. Preliminary surveillance data suggests a changing epidemiology of Streptococcus pneumoniae as a result of the introduction of the 7-valent pneumococcal vaccine in the pediatric population. Prevalence of different pneumococcal serotypes and their resistance patterns will have to be continually monitored to help guide the optimal treatment of acute sinusitis.

Limitations

Heterogeneous study population across studies, different definitions of clinical success/failure, studies powered primarily for non-inferiority rather than superiority, relatively few studies within each comparison grouping, and the possibility of publication bias all lend limitations to our meta-analyses. Different inclusion criteria may also affect the comparability of the populations across studies. In some studies, patients were recruited from general practices and in others, from otolaryngology practices. In addition to requiring an abnormal sinus

radiograph for study entry, some trials also included C-reactive protein and erythrocyte sedimentation rate cut-offs in their inclusion criteria. Definitions of cure ranged from symptomatic relief to radiographic resolution to no days with restricted activities at home or work. Sinus aspirations and cultures, the gold standard for diagnosing and assessing bacterial sinusitis were performed in a minority of trials.

Fifteen of 39 studies included in this review explicitly stated the power calculation used to determine sample size a priori. Virtually all of these studies were powered to demonstrate non-inferiority rather than superiority of one treatment over another. Given that the rate of spontaneous clinical resolution of acute bacterial sinusitis is approximately 65% and even higher with antibiotics, demonstration of superiority of one treatment over another requires extremely large sample sizes.

A notable omission compared to our previous report is the lack of comparative studies between newer expensive antibiotics and older inexpensive ones (like amoxicillin and trimethoprim-sulfamethoxazole). This has important implications for healthcare cost containment. We are unaware of any sound reasons in 2005 why amoxicillin and trimethoprim-sulfamethoxazole should not be used in comparative trials in treatment of bacterial sinusitis; although, our update did not specifically examine the resistance patterns of various pathogens in the last few years to amoxicillin and folate inhibitors.

Future Research

In the future, more studies that incorporate bacteriological data will help characterize the changing epidemiology of acute sinusitis. We used per-protocol results for our meta-analyses, as these are more consistently reported than intention-to-treat results. To reduce the possibility of bias, intention-to-treat population should be uniformly defined across studies and data should be collected and reported in addition to per-protocol results.

Almost all the trials sponsored by pharmaceutical companies concluded that the sponsored drug was either superior or therapeutically equivalent to the comparator, thus raising the concern that there may be unpublished trials with negative results. This concern can only be resolved if results from all drug trials are duly reported. In addition, the pharmaceutical companies' research agenda appears to be driven by the desire to compare their products against those of their competitors. Such an agenda does not necessarily address clinically important issues that are relevant to the management of acute bacterial rhinosinusitis. Such potential bias can be addressed if there is funding from government and other independent entities to support research, which has as its primary objective the improvement of care of patients with acute bacterial rhinosinusitis.

Compared to our previous report in 1999, the quality of studies in this field has improved. All the studies stated explicit inclusion and exclusion criteria, method of analyses and primary outcome measurements. However, in order to make meaningful comparisons across studies; there should be general agreement in defining eligibility criteria, clinical success and failure, appropriate time of outcome assessment and precise criteria for numerators and denominators in the calculation of clinical success or failure rates.

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Mixed population

Kakish KS, Mahafza T, Batieha A, et al. Clinical sinusitis in children attending primary care centers. Pediatric Infectious Disease Journal 2000;19(11):1071-4.
Observational cohort study

Kroslak M. Efficacy and acceptability of fusafungine, a local treatment for both nose and throat infections, in adult patients with upper respiratory tract infections. Curr Med Res Opin 2002;18(4):194-200.
Mixed population

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Not sinusitis

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Non-comparative study

Appendix A: Search Strategies

Ovid: Search from MEDLINE ®
< 1966 to September Week 2 2004>

Sinusitis Update

#	Search History	Results
1	rhinosinus$.tw.	1103
2	sinusitis.tw.	6979
3	exp Sinusitis/	9502
4	or/1-3	11736
5	(upper adj6 respirat$).tw.	9698
6	Infect$.tw.	643403
7	sinus$.tw.	74358
8	6 and (5 or 7)	9665
9	4 or 8	19042
10	limit 9 to human	17756
11	limit 10 to english language	12205
12	In Vitro/	327623
13	11 not 12	12162
14	196$.yr.	888556
15	197$.yr.	2410634
16	198$.yr.	3208775
17	(1991$ or 1992$ or 1993$ or 1994$ or 1995$ or 1996$).yr.	2480047
18	13 not (or/14-17)	5737
19	exp ANTIMICROBIAL CATIONIC PEPTIDES/	2756
20	exp Anti-Infective Agents/	815121
21	exp Anti-Bacterial Agents/	324676
22	trimethoprim.mp.	11682
23	Amdinocillin.mp.	523
24	alamethicin.mp.	490
25	amikacin.mp.	4730
26	amphotericin.mp.	12324

#	Search History	Results
27	ampicillin.mp.	17897
28	amoxicillin.mp.	8189
29	anisomycin.mp.	1232
30	ANTIMYCIN.mp.	3401
31	aurodox.mp.	31
32	azithromycin.mp.	2513
33	azlocillin.mp.	724
34	aztreonam.mp.	1982
35	bacitracin.mp.	2443
36	bambermycin$.mp.	92
37	Bongkrekic.mp.	302
38	brefeldin.mp.	2693
39	butirosin sulfate.mp.	61
40	calcimycin.mp.	11117
41	candicidin.mp.	241
42	capreomycin sulfate.mp.	137
43	carbenicillin.mp.	2899
44	carfecillin.mp.	37
45	cefaclor.mp.	1398
46	exp Cefadroxil/	394
47	Cefadroxil.mp.	529
48	exp Cefamandole/	1907
49	Cefamandole.mp.	1544
50	cefazolin.mp.	2933
51	cefixime.mp.	883
52	cefmenoxime.mp.	480
53	cefmetazole.mp.	542
54	cefonicid.mp.	234
55	cefoperazone.mp.	1774
56	cefotaxime.mp.	6872
57	cefotetan.mp.	652

#	Search History	Results
58	cefotiam.mp.	592
59	cefoxitin.mp.	2981
60	cefsulodin.mp.	554
61	ceftazidime.mp.	4564
62	ceftizoxime.mp.	1325
63	ceftriaxone.mp.	4735
64	cefuroxime.mp.	2722
65	Cephacetrile.mp.	156
66	Cephalexin.mp.	2489
67	cephaloglycin.mp.	119
68	Cephaloridine.mp.	1967
69	exp Cephalosporins/	29060
70	cephalothin.mp.	3513
71	Cephamycins.mp.	1391
72	cephapirin.mp.	306
73	cephradine.mp.	721
74	Chloramphenicol.mp.	28895
75	chlortetracycline.mp.	2203
76	citrinin.mp.	318
77	clarithromycin.mp.	4329
78	Clavulanic Acid$.mp.	3306
79	clindamycin.mp.	5827
80	Cloxacillin.mp.	1869
81	colistin.mp.	1648
82	cyclacillin.mp.	103
83	dactinomycin.mp.	16697
84	daptomycin.mp.	286
85	demeclocycline.mp.	653
86	dibekacin.mp.	518
87	dicloxacillin.mp.	690
88	dihydrostreptomycin sulfate.mp.	639

#	Search History	Results
89	distamycins.mp.	672
90	doxycycline.mp.	5949
91	echinomycin.mp.	178
92	edeine.mp.	116
93	enviomycin.mp.	69
94	Erythromycin.mp.	15895
95	Erythromycin Estolate.mp.	190
96	Erythromycin Ethylsuccinate.mp.	505
97	filipin.mp.	808
98	floxacillin.mp.	421
99	fosfomycin.mp.	1341
100	framycetin.mp.	268
101	fusidic acid.mp.	1464
102	Gentamicin$.mp.	18514
103	gramicidin.mp.	2713
104	hygromycin b.mp.	901
105	imipenem.mp.	4800
106	josamycin.mp.	550
107	Kanamycin.mp.	8823
108	kitasamycin.mp.	45
109	exp Lactams/	78059
110	Lactams.mp.	7122
111	lasalocid.mp.	728
112	Leucomycins.mp.	1703
113	Lincomycin.mp.	2387
114	lymecycline.mp.	105
115	mepartricin.mp.	92
116	methacycline.mp.	360
117	methicillin.mp.	8925
118	mezlocillin.mp.	990
119	mikamycin.mp.	23

#	Search History	Results
120	minocycline.mp.	2908
121	miocamycin.mp.	291
122	moxalactam.mp.	1455
123	mupirocin.mp.	679
124	mycobacillin.mp.	49
125	nafcillin.mp.	680
126	natamycin.mp.	502
127	nebramycin.mp.	101
128	Neomycin.mp.	8741
129	netilmicin.mp.	1578
130	netropsin.mp.	557
131	nigericin.mp.	1575
132	nisin.mp.	771
133	novobiocin.mp.	2049
134	nystatin.mp.	3316
135	Oleandomycin.mp.	794
136	Oligomycins.mp.	2565
137	oxacillin.mp.	2863
138	oxytetracycline.mp.	3880
139	paromomycin.mp.	979
140	penicillanic acid.mp.	1524
141	penicillic acid.mp.	153
142	exp Penicillins/	48539
143	penicillin.mp.	29069
144	piperacillin.mp.	3081
145	pivampicillin.mp.	308
146	polymyxin$.mp.	5058
147	pristinamycin.mp.	291
148	prodigiosin.mp.	315
149	ribostamycin.mp.	131
150	Rifabutin.mp.	806

#	Search History	Results
151	rifamycin$.mp.	1518
152	ristocetin.mp.	2162
153	rolitetracycline.mp.	262
154	roxarsone.mp.	78
155	roxithromycin.mp.	955
156	rutamycin.mp.	73
157	sirolimus.mp.	3153
158	Sisomicin.mp.	678
159	spectinomycin.mp.	1697
160	spiramycin.mp.	915
161	exp Streptogramins/	1072
162	Streptogramin$.mp.	742
163	Streptomycin.mp.	13591
164	Streptovaricin.mp.	123
165	sulbactam.mp.	1677
166	sulbenicillin.mp.	165
167	talampicillin.mp.	103
168	teicoplanin.mp.	1915
169	tetracycline.mp.	22308
170	thiamphenicol.mp.	609
171	thiostrepton.mp.	311
172	ticarcillin.mp.	1650
173	tobramycin.mp.	4593
174	troleandomycin.mp.	648
175	tunicamycin.mp.	3618
176	tylosin.mp.	887
177	tyrocidine.mp.	170
178	Tyrothricin.mp.	507
179	valinomycin.mp.	3665
180	vancomycin.mp.	10205
181	vernamycin.mp.	19

#	Search History	Results
182	Virginiamycin.mp.	1099
183	cycloserine.mp.	1546
184	rifampin.mp.	12623
185	viomycin.mp.	441
186	Amoxicillin-Potassium Clavulanate Combination.mp.	1184
187	antitreponemal.mp.	89
188	ethambutol.mp.	3654
189	ethionamide.mp.	989
190	iproniazid.mp.	938
191	isoniazid.mp.	11012
192	prothionamide.mp.	223
193	pyrazinamide.mp.	2312
194	thioacetazone.mp.	391
195	p-aminosalicylic acid.mp.	470
196	Thalidomide.mp.	3133
197	Acedapsone.mp.	42
198	Clofazimine.mp.	985
199	Dapsone.mp.	4057
200	Ethionamide.mp.	989
201	Sulfameter.mp.	50
202	telithromycin.mp.	366
203	exp ciprofloxacin/	6711
204	ciprofloxacin.mp.	10454
205	exp fluroquinolones/	0
206	fluroquino$.mp.	24
207	Trimethoprim-Sulfamethoxazole.mp.	6168
208	or/19-207	873109
209	18 and 208	1391
210	limit 209 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or guideline or interview or lectures or legal cases or	687

#	Search History	Results
	legislation or letter or meta analysis or news or newspaper article or patient education handout or periodical index or practice guideline or "review" or review, academic or "review literature" or review, multicase or "review of reported cases" or review, tutorial)	
211	209 not 210	704
212	from 211 keep 1	1

Ovid MEDLINE(R)
<1966 to September Week 3 2004>

Pneumococcal Vaccine

#	Search History	Results
1	exp vaccines/	97637
2	vaccin$.mp.	139243
3	1 or 2	142925
4	exp Pneumonia/	46421
5	pneumo$.tw.	108436
6	4 or 5	126474
7	3 and 6	5881
8	exp pneumococcal vaccines/	1599
9	7 or 8	6054
10	limit 9 to human	4797
11	limit 10 to "all child (0 to 18 years)"	2297
12	10 not 11	2500
13	limit 12 to "all adult (19 plus years)"	1220
14	10 not 13	3577
15	limit 14 to english language	3055
16	limit 15 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or guideline or interview or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or patient education handout or periodical index or practice guideline or "review" or review, academic or "review literature" or review, multicase or "review of reported cases" or review, tutorial)	1125
17	15 not 16	1930
18	limit 17 to yr=1996-2004	1129
19	exp ANTIMICROBIAL CATIONIC PEPTIDES/	2763
20	exp Anti-Infective Agents/	815813
21	exp Anti-Bacterial Agents/	324881
22	trimethoprim.mp.	11684
23	Amdinocillin.mp.	523

#	Search History	Results
24	alamethicin.mp.	490
25	amikacin.mp.	4731
26	amphotericin.mp.	12332
27	ampicillin.mp.	17907
28	amoxicillin.mp.	8194
29	anisomycin.mp.	1232
30	ANTIMYCIN.mp.	3405
31	aurodox.mp.	31
32	azithromycin.mp.	2519
33	azlocillin.mp.	724
34	aztreonam.mp.	1982
35	bacitracin.mp.	2445
36	bambermycin$.mp.	92
37	Bongkrekic.mp.	302
38	brefeldin.mp.	2695
39	butirosin sulfate.mp.	61
40	calcimycin.mp.	11122
41	candicidin.mp.	242
42	capreomycin sulfate.mp.	137
43	carbenicillin.mp.	2899
44	carfecillin.mp.	37
45	cefaclor.mp.	1399
46	exp Cefadroxil/	394
47	Cefadroxil.mp.	529
48	exp Cefamandole/	1907
49	Cefamandole.mp.	1544
50	cefazolin.mp.	2933
51	cefixime.mp.	883
52	cefmenoxime.mp.	480
53	cefmetazole.mp.	542
54	cefonicid.mp.	234

#	Search History	Results
55	cefoperazone.mp.	1774
56	cefotaxime.mp.	6872
57	cefotetan.mp.	652
58	cefotiam.mp.	592
59	cefoxitin.mp.	2981
60	cefsulodin.mp.	554
61	ceftazidime.mp.	4566
62	ceftizoxime.mp.	1325
63	ceftriaxone.mp.	4740
64	cefuroxime.mp.	2724
65	Cephacetrile.mp.	156
66	Cephalexin.mp.	2491
67	cephaloglycin.mp.	119
68	Cephaloridine.mp.	1967
69	exp Cephalosporins/	29070
70	cephalothin.mp.	3513
71	Cephamycins.mp.	1391
72	cephapirin.mp.	306
73	cephradine.mp.	721
74	Chloramphenicol.mp.	28903
75	chlortetracycline.mp.	2204
76	citrinin.mp.	318
77	clarithromycin.mp.	4333
78	Clavulanic Acid$.mp.	3306
79	clindamycin.mp.	5828
80	Cloxacillin.mp.	1869
81	colistin.mp.	1648
82	cyclacillin.mp.	103
83	dactinomycin.mp.	16699
84	daptomycin.mp.	286
85	demeclocycline.mp.	653

#	Search History	Results
86	dibekacin.mp.	518
87	dicloxacillin.mp.	690
88	dihydrostreptomycin sulfate.mp.	639
89	distamycins.mp.	672
90	doxycycline.mp.	5954
91	echinomycin.mp.	178
92	edeine.mp.	116
93	enviomycin.mp.	69
94	Erythromycin.mp.	15904
95	Erythromycin Estolate.mp.	190
96	Erythromycin Ethylsuccinate.mp.	505
97	filipin.mp.	809
98	floxacillin.mp.	421
99	fosfomycin.mp.	1341
100	framycetin.mp.	268
101	fusidic acid.mp.	1464
102	Gentamicin$.mp.	18524
103	gramicidin.mp.	2717
104	hygromycin b.mp.	901
105	imipenem.mp.	4800
106	josamycin.mp.	550
107	Kanamycin.mp.	8824
108	kitasamycin.mp.	45
109	exp Lactams/	78094
110	Lactams.mp.	7130
111	lasalocid.mp.	729
112	Leucomycins.mp.	1703
113	Lincomycin.mp.	2388
114	lymecycline.mp.	106
115	mepartricin.mp.	92
116	methacycline.mp.	360

#	Search History	Results
117	methicillin.mp.	8933
118	mezlocillin.mp.	990
119	mikamycin.mp.	23
120	minocycline.mp.	2908
121	miocamycin.mp.	291
122	moxalactam.mp.	1455
123	mupirocin.mp.	679
124	mycobacillin.mp.	49
125	nafcillin.mp.	680
126	natamycin.mp.	502
127	nebramycin.mp.	101
128	Neomycin.mp.	8747
129	netilmicin.mp.	1578
130	netropsin.mp.	558
131	nigericin.mp.	1575
132	nisin.mp.	771
133	novobiocin.mp.	2050
134	nystatin.mp.	3316
135	Oleandomycin.mp.	794
136	Oligomycins.mp.	2567
137	oxacillin.mp.	2864
138	oxytetracycline.mp.	3882
139	paromomycin.mp.	981
140	penicillanic acid.mp.	1526
141	penicillic acid.mp.	153
142	exp Penicillins/	48564
143	penicillin.mp.	29083
144	piperacillin.mp.	3082
145	pivampicillin.mp.	308
146	polymyxin$.mp.	5059
147	pristinamycin.mp.	292

#	Search History	Results
148	prodigiosin.mp.	316
149	ribostamycin.mp.	131
150	Rifabutin.mp.	807
151	rifamycin$.mp.	1519
152	ristocetin.mp.	2162
153	rolitetracycline.mp.	262
154	roxarsone.mp.	79
155	roxithromycin.mp.	956
156	rutamycin.mp.	73
157	sirolimus.mp.	3173
158	Sisomicin.mp.	678
159	spectinomycin.mp.	1697
160	spiramycin.mp.	915
161	exp Streptogramins/	1074
162	Streptogramin$.mp.	742
163	Streptomycin.mp.	13593
164	Streptovaricin.mp.	123
165	sulbactam.mp.	1678
166	sulbenicillin.mp.	165
167	talampicillin.mp.	103
168	teicoplanin.mp.	1916
169	tetracycline.mp.	22315
170	thiamphenicol.mp.	609
171	thiostrepton.mp.	311
172	ticarcillin.mp.	1650
173	tobramycin.mp.	4594
174	troleandomycin.mp.	650
175	tunicamycin.mp.	3618
176	tylosin.mp.	889
177	tyrocidine.mp.	170
178	Tyrothricin.mp.	507

#	Search History	Results
179	valinomycin.mp.	3666
180	vancomycin.mp.	10208
181	vernamycin.mp.	19
182	Virginiamycin.mp.	1101
183	cycloserine.mp.	1547
184	rifampin.mp.	12633
185	viomycin.mp.	441
186	Amoxicillin-Potassium Clavulanate Combination.mp.	1184
187	antitreponemal.mp.	89
188	ethambutol.mp.	3655
189	ethionamide.mp.	989
190	iproniazid.mp.	938
191	isoniazid.mp.	11017
192	prothionamide.mp.	223
193	pyrazinamide.mp.	2313
194	thioacetazone.mp.	391
195	p-aminosalicylic acid.mp.	471
196	Thalidomide.mp.	3140
197	Acedapsone.mp.	42
198	Clofazimine.mp.	987
199	Dapsone.mp.	4058
200	Ethionamide.mp.	989
201	Sulfameter.mp.	50
202	telithromycin.mp.	368
203	exp ciprofloxacin/	6719
204	ciprofloxacin.mp.	10462
205	exp fluroquinolones/	0
206	fluroquino$.mp.	24
207	Trimethoprim-Sulfamethoxazole.mp.	6169
208	or/19-207	873848
209	18 and 208	273

#	Search History	Results
210	rhinosinus$.tw.	1103
211	sinusitis.tw.	6984
212	exp Sinusitis/	9506
213	or/210-212	11742
214	(upper adj6 respirat$).tw.	9703
215	Infect$.tw.	644056
216	sinus$.tw.	74408
217	215 and (214 or 216)	9675
218	213 or 217	19055
219	limit 218 to human	17767
220	limit 219 to english language	12215
221	In Vitro/	327772
222	220 not 221	12172
223	196$.yr.	888556
224	197$.yr.	2410634
225	198$.yr.	3208776
226	(1991$ or 1992$ or 1993$ or 1994$ or 1995$ or 1996$).yr.	2480055
227	222 not (or/223-226)	5747
228	exp ANTIMICROBIAL CATIONIC PEPTIDES/	2763
229	exp Anti-Infective Agents/	815813
230	exp Anti-Bacterial Agents/	324881
231	trimethoprim.mp.	11684
232	Amdinocillin.mp.	523
233	alamethicin.mp.	490
234	amikacin.mp.	4731
235	amphotericin.mp.	12332
236	ampicillin.mp.	17907
237	amoxicillin.mp.	8194
238	anisomycin.mp.	1232
239	ANTIMYCIN.mp.	3405
240	aurodox.mp.	31

#	Search History	Results
241	azithromycin.mp.	2519
242	azlocillin.mp.	724
243	aztreonam.mp.	1982
244	bacitracin.mp.	2445
245	bambermycin$.mp.	92
246	Bongkrekic.mp.	302
247	brefeldin.mp.	2695
248	butirosin sulfate.mp.	61
249	calcimycin.mp.	11122
250	candicidin.mp.	242
251	capreomycin sulfate.mp.	137
252	carbenicillin.mp.	2899
253	carfecillin.mp.	37
254	cefaclor.mp.	1399
255	exp Cefadroxil/	394
256	Cefadroxil.mp.	529
257	exp Cefamandole/	1907
258	Cefamandole.mp.	1544
259	cefazolin.mp.	2933
260	cefixime.mp.	883
261	cefmenoxime.mp.	480
262	cefmetazole.mp.	542
263	cefonicid.mp.	234
264	cefoperazone.mp.	1774
265	cefotaxime.mp.	6872
266	cefotetan.mp.	652
267	cefotiam.mp.	592
268	cefoxitin.mp.	2981
269	cefsulodin.mp.	554
270	ceftazidime.mp.	4566
271	ceftizoxime.mp.	1325

#	Search History	Results
272	ceftriaxone.mp.	4740
273	cefuroxime.mp.	2724
274	Cephacetrile.mp.	156
275	Cephalexin.mp.	2491
276	cephaloglycin.mp.	119
277	Cephaloridine.mp.	1967
278	exp Cephalosporins/	29070
279	cephalothin.mp.	3513
280	Cephamycins.mp.	1391
281	cephapirin.mp.	306
282	cephradine.mp.	721
283	Chloramphenicol.mp.	28903
284	chlortetracycline.mp.	2204
285	citrinin.mp.	318
286	clarithromycin.mp.	4333
287	Clavulanic Acid$.mp.	3306
288	clindamycin.mp.	5828
289	Cloxacillin.mp.	1869
290	colistin.mp.	1648
291	cyclacillin.mp.	103
292	dactinomycin.mp.	16699
293	daptomycin.mp.	286
294	demeclocycline.mp.	653
295	dibekacin.mp.	518
296	dicloxacillin.mp.	690
297	dihydrostreptomycin sulfate.mp.	639
298	distamycins.mp.	672
299	doxycycline.mp.	5954
300	echinomycin.mp.	178
301	edeine.mp.	116
302	enviomycin.mp.	69

#	Search History	Results
303	Erythromycin.mp.	15904
304	Erythromycin Estolate.mp.	190
305	Erythromycin Ethylsuccinate.mp.	505
306	filipin.mp.	809
307	floxacillin.mp.	421
308	fosfomycin.mp.	1341
309	framycetin.mp.	268
310	fusidic acid.mp.	1464
311	Gentamicin$.mp.	18524
312	gramicidin.mp.	2717
313	hygromycin b.mp.	901
314	imipenem.mp.	4800
315	josamycin.mp.	550
316	Kanamycin.mp.	8824
317	kitasamycin.mp.	45
318	exp Lactams/	78094
319	Lactams.mp.	7130
320	lasalocid.mp.	729
321	Leucomycins.mp.	1703
322	Lincomycin.mp.	2388
323	lymecycline.mp.	106
324	mepartricin.mp.	92
325	methacycline.mp.	360
326	methicillin.mp.	8933
327	mezlocillin.mp.	990
328	mikamycin.mp.	23
329	minocycline.mp.	2908
330	miocamycin.mp.	291
331	moxalactam.mp.	1455
332	mupirocin.mp.	679
333	mycobacillin.mp.	49

#	Search History	Results
334	nafcillin.mp.	680
335	natamycin.mp.	502
336	nebramycin.mp.	101
337	Neomycin.mp.	8747
338	netilmicin.mp.	1578
339	netropsin.mp.	558
340	nigericin.mp.	1575
341	nisin.mp.	771
342	novobiocin.mp.	2050
343	nystatin.mp.	3316
344	Oleandomycin.mp.	794
345	Oligomycins.mp.	2567
346	oxacillin.mp.	2864
347	oxytetracycline.mp.	3882
348	paromomycin.mp.	981
349	penicillanic acid.mp.	1526
350	penicillic acid.mp.	153
351	exp Penicillins/	48564
352	penicillin.mp.	29083
353	piperacillin.mp.	3082
354	pivampicillin.mp.	308
355	polymyxin$.mp.	5059
356	pristinamycin.mp.	292
357	prodigiosin.mp.	316
358	ribostamycin.mp.	131
359	Rifabutin.mp.	807
360	rifamycin$.mp.	1519
361	ristocetin.mp.	2162
362	rolitetracycline.mp.	262
363	roxarsone.mp.	79
364	roxithromycin.mp.	956

#	Search History	Results
365	rutamycin.mp.	73
366	sirolimus.mp.	3173
367	Sisomicin.mp.	678
368	spectinomycin.mp.	1697
369	spiramycin.mp.	915
370	exp Streptogramins/	1074
371	Streptogramin$.mp.	742
372	Streptomycin.mp.	13593
373	Streptovaricin.mp.	123
374	sulbactam.mp.	1678
375	sulbenicillin.mp.	165
376	talampicillin.mp.	103
377	teicoplanin.mp.	1916
378	tetracycline.mp.	22315
379	thiamphenicol.mp.	609
380	thiostrepton.mp.	311
381	ticarcillin.mp.	1650
382	tobramycin.mp.	4594
383	troleandomycin.mp.	650
384	tunicamycin.mp.	3618
385	tylosin.mp.	889
386	tyrocidine.mp.	170
387	Tyrothricin.mp.	507
388	valinomycin.mp.	3666
389	vancomycin.mp.	10208
390	vernamycin.mp.	19
391	Virginiamycin.mp.	1101
392	cycloserine.mp.	1547
393	rifampin.mp.	12633
394	viomycin.mp.	441
395	Amoxicillin-Potassium Clavulanate Combination.mp.	1184

#	Search History	Results
396	antitreponemal.mp.	89
397	ethambutol.mp.	3655
398	ethionamide.mp.	989
399	iproniazid.mp.	938
400	isoniazid.mp.	11017
401	prothionamide.mp.	223
402	pyrazinamide.mp.	2313
403	thioacetazone.mp.	391
404	p-aminosalicylic acid.mp.	471
405	Thalidomide.mp.	3140
406	Acedapsone.mp.	42
407	Clofazimine.mp.	987
408	Dapsone.mp.	4058
409	Ethionamide.mp.	989
410	Sulfameter.mp.	50
411	telithromycin.mp.	368
412	exp ciprofloxacin/	6719
413	ciprofloxacin.mp.	10462
414	exp fluroquinolones/	0
415	fluroquino$.mp.	24
416	Trimethoprim-Sulfamethoxazole.mp.	6169
417	or/228-416	873848
418	227 and 417	1394
419	limit 418 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or guideline or interview or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or patient education handout or periodical index or practice guideline or "review" or review, academic or "review literature" or review, multicase or "review of reported cases" or review, tutorial)	689
420	418 not 419	705
421	209 not 420	262

#	Search History	Results
422	from 421 keep 1	1

Appendix B: Data Extraction Form

Extraction Form

Name Year ID#

Stated Purpose of the Study:

Population & Setting:
X patients from? # of (ENT?, Primary care?) centers in ? country from ? study years.
Drug1 group (n=): Mean age (range)= N yrs (J-K) Males= N (M%)
Drug2 group (n=): Mean age (range)= N yrs (J-K) Males= N (M%)

Inclusion Criteria:
≥X y.o. in outpatient? setting with Si/Sx of acute sinusitis/acute exacerbation of chronic sinusitis (based on ?) of X duration AND radiologic signs (air-fluid levels?, opacification? or mucosal thickening≥6mm?)

Exclusion Criteria: ?

Study Design: Randomized (? method of randomization and concealment), double / not blinded (list method of masking), multi-center? trial. ? if pre-stratified by center.

Treatments: Drug 1 X mg D for X days
Drug 2 X mg D for Y days

Outcome: (Primary) End of study? (X weeks after enrollment)
(Secondary) End of therapy? (Y weeks after enrollment)

Stated definitions of success and failure…

Results: ? enrolled and randomized. X/Y in Drug1group and A/B in Drug2 group were evaluated for clinical efficacy (*intent to treat analysis / per protocol analysis*). X/Y in Drug1 group and A/B in Drug2 group were excluded for reasons including: ?

1. Clinical Failure: (Primary) X/Y in Drug1 group and A/B in Drug2 group failed. **(Secondary)** X/Y in Drug1 group and A/B in Drug2 group failed.

2. Microbiological Failure: Most common pathogens isolated at baseline: A, B, C. Determined by sinus aspiration? at baseline and X weeks after treatment. X/Y in Drug1 group and A/B in Drug2 group failed.

Adverse Events: Adverse events occurred in X/Y in Drug1 group (*nausea*=#, *diarrhea*=#, *other*=#), and A/B in Drug2 goup (*nausea*=#, *diarrhea*=#, *other*=#). Discontinuation due to major adverse events occurred in X/Y in Drug1 group (symptoms causing d/c) and A/B in Drug2 group (symptoms).

Funding: ?

Comments: Use of adjuvant therapy? Compliance with study medications is?

Appendix C: Evidence Tables

Adelglass et al. 1998 ID 534

Stated Purpose of the Study: To compare the efficacy and tolerability of cefprozil with amoxicillin/clavulanate in the treatment of adults with severe acute bacterial sinusitis

Population & Setting: 278 patients from multi-center enrolled in the study, study years not specified. Patients were stratified according to the severity of disease before randomization.
Baseline statistics:

Cefprozil	140	Mean age 36.9	Males 42%
Amox/Clav	138	Mean age 37	Males 50%

Inclusion criteria: ≥ 13 y/o; signs and symptoms of acute sinusitis; abnormal sinus x-ray, women of childbearing potential were required to have a negative pregnancy test on enrollment, be using an acceptable method of contraception, and not be lactating

Exclusion criteria: hx of hypersensitivity to beta-lactam abx; abx within 24 h of study entry, long-acting parenteral PCN within 2 weeks of enrollment; see paper for others

Study design: Multicenter, open-label study. To achieve balance in the severity of signs and symptoms, the eligible patients were stratified according to the severity of disease before randomization. Method of randomization not explicitly stated.

Treatments:
Cefprozil 500 mg twice a day for 10 days
Amox/Clav 500/125 mg three times a day for 10 days

Outcome:
Primary – clinical response satisfactory (either cure or improvement, based on a clinical score) or unsatisfactory, assessed on days 11 – 15 (after the initiation of treatment)
Secondary – assessment for relapse 2 weeks after the end of therapy
Sinus cultures were not performed as part of the study.
See paper for subgroup analysis for "severe sinusitis."

Results:
278 patients randomized into 2 groups (cefprozil 140; amox/clav 138)
219 assessable for efficacy (cefprozil 108; amox/clav 111)
Clinical failure – Cefprozil 15/108 (13.9%); Amox/Clav 9/111 (8.1%)
2-week post treatment follow up Failure – Cefprozil 18/100 (18%); Amox/Clav 16/99 (16.2%)

Adverse events:

At least one event	cefprozil	23/140 (16.4%)	amox/clav	53/138 (38.4%)
Diarrhea		10/140 (7.1%)		35/138 (25.4%)
Nausea		4/140 (2.9%)		12/138 (8.7%)
Rash		1/140 (0.7%)		7/138 (5.1%)

See table VII in paper for others.
3 patients treated with cefprozil and 9 patients treated with amox/clav discontinued treatment because of adverse events, most commonly diarrhea (cefprozil 2; amox/clav 7).

Funding: Bristol-Myers Squibb
Comments:

Adelglass et al. 1998 ID 540

Stated Purpose of the Study: To compare the clinical efficacy and safety of oral levofloxacin once daily for 14 days with those of oral clarithromycin twice daily for 14 days in patients with acute bacterial sinusitis

Population & Setting:

216 patients from 20 sites were randomized into 2 groups (108 in each group).

Levofloxacin	101	mean age (range) 41.1 (18-83)	males 58.4%
Clarithromycin	89	mean age (range) 38.8 (19-68)	males 70.8%

Inclusion criteria: ≥ 18 y/o; radiograph supported dx of acute bacterial sinusitis (see paper for details regarding clinical criteria); x-ray showed opacification, air-fluid level, and/or mucosal thickening of ≥ 5 mm; see paper for others

Exclusion criteria: chronic sinusitis (presence of current signs/symptoms for > 4 weeks or > 2 episodes of acute sinusitis within the past 12 months); calculated creatinine clearance ≤ 50 ml/min; nasal steroids and others (see paper)

Study design: randomized, single (investigator) – blinded, parallel group study; subject randomization list was computer-generated and stratified by site; equal numbers of subjects were assigned to each treatment group;

Treatments:

Levofloxacin oral	500 mg once daily in AM for 14 days
Clarithromycin oral	500 mg twice a day for 14 days

Outcome:

Primary: clinical response 2-5 days post treatment; clinical success was defined as cure or improvement
Secondary: relapse rate assessed one month after therapy

Results:

216 patients were randomized; 190 evaluable. 4/101 in Levofloxacin group withdrew due to symptomatic failure; 5/89 in Clarithromycin group withdrew (4 due to symptomatic failure; 1 for other reasons)

Reported clinical failure rate:	Levofloxacin	4/101 (4%)	Clarithromycin	6/89 (6.7%)
ITT analysis:	Levofloxacin	8/108 (7.4%)	Clarithromycin	17/108 (15.7%)

One month after therapy relapse rate: Levofloxacin 4/97 (4.1%) Clarithromycin 6/83 (7.2%)

Adverse events:

2 serious events in Levofloxacin group, lumbar disk lesion and neuropathy, not felt to be treatment related by investigator

	Levofloxacin (n=107)	Clarithromycin (n=108)
At least one adverse event	94 (87.9%)	89 (82.4%)
Drug-related adverse event	15 (14%)	25 (23.1%)
Abdominal pain	2 (1.9%)	4 (3.7%)
Dizziness	3 (2.8%)	0
Nausea	6 (5.6%)	7 (6.5%)
Diarrhea	1 (0.9%)	6 (5.6%)

Insomnia	1 (0.9%)	3 (2.8%)
Taste perversion	1 (0.9%)	13 (12%)
Fungal infection	2 (1.9%)	3 (2.8%)

See table 3 in paper for rest.

Funding: Ortho-McNeil Pharmaceutical
Comments:

Adelglass et al. 1999 ID 490

Stated Purpose of the Study: To compare the efficacy and safety of levofloxacin 500 mg orally once daily for 10-14 days with those of amox/clav 500/125 mg orally 3 times daily for 10-14 days in treating acute sinusitis in adult outpatients.

Population & Setting: 615 patients from 28 centers in US enrolled in the study. 307 randomly assigned to levofloxacin and 308 to amox/clav. Patients were enrolled by both office-based primary care physicians and otolaryngologists, study years not specified.
Baseline statistics:

Levofloxacin 306	Mean age (range) 39.2 (18-85)	Males 37.6%
Amox/Clav 309	Mean age (range) 38.6 (18-84)	Males 35.6%

Inclusion criteria: ≥ 18 y/o; female and male outpatients with 2/5 typical signs and symptoms of acute sinusitis (see paper for details); radiographic evidence including air-fluid level, opacification, or ≥ 4 mm mucosal thickening of at least 1 sinus on sinus x-ray, CT, or sinus scope

Exclusion criteria: hx of hypersensitivity to beta-lactam abx levofloxacin or any quinolone; chronic sinusitis > 4 weeks, pregnancy (or inability to r/o pregnancy), breast feeding, calculated creatinine clearance of ≤ 20 mL/min, see paper for others

Study design: Multicenter, open-label study. Method of randomization not explicitly stated.

Treatments:
for patients with normal renal function, Levofloxacin 500 mg once daily for 10 – 14 days;
for patients with creatinine clearance of 50 mL/min, an initial loading dose of levofloxacin 500 mg followed by 500 mg every 48 hours;
Amox/Clav 500/125 mg every 8 hours for 10 – 14 days, dosage was adjusted in accordance with package insert instructions for patients with renal impairment.
Duration of therapy could extend beyond 14 days if medically justified; the decision to extend therapy was made between days 10 and 14 of therapy.

Outcome:
Primary – clinical response satisfactory (either cure or improvement, based on a clinical score) or failure, assessed on 2-5 days post therapy; clinical success rate was calculated based on the number of evaluable patients
Secondary – assessment for relapse 28 - 32 days after the end of therapy
Sinus cultures were not performed as part of the study.

Results:
615 patients randomized into 2 groups (levofloxacin 307; amox/clav 308)
535 evaluable for efficacy (levofloxacin 267; amox/clav 268)

Reported Clinical failure – Levofloxacin 31/267 (11.6%);
Amox/Clav 34/268 (12.7%)

4 week post treatment follow up Relapse – Levofloxacin 5/233 (2.1%)
Amox/Clav 9/231 (3.9%)

Adverse events:	Levofloxacin	Amox/Clav
Adverse event	114/297 (38.4%)	146/302 (48.3%)
Diarrhea	4/297 (1.3%)	35/302 (11.6%)
Abdominal Pain	3/297 (1%)	5/302 (1.7%)
Flatulence	1/297 (0.3%)	4/302 (1.3%)

Vomiting	0	5/302 (1.7%)
Vaginitis	2 (1.1% of women)	8 (4.1% of women)
Genital moniliasis	2 (0.7% of women)	10 (3.3% of women)

11/297 (3.7%) patients treated with levofloxacin and 16/302 (5.3%) patients treated with amox/clav discontinued treatment because of adverse events.
In the levofloxacin group, those who discontinued because of adverse events included 4 patients with urticaria, rash or pruritus; 4 patients with GI adverse events; and 1 patient with asthenia-dizziness and symptoms of influenze. In the amo/clav group, all discontinued for GI adverse events except for one instance of fatigue.
No serious drug-related events or deaths occurred during the study

Funding: R. W. Johnson Pharmaceutical Research Institute
Comments:

Buchanan et al. 2003 ID 91698

Stated Purpose of the Study: To establish the clinical equivalence of 800 mg of telithromycin once daily for 5 days with 250 mg of cefuroxime axetil twice daily for 10 days in the treatment of patients with acute bacterial maxillary sinusitis (ABMS)

Populaton and Setting: 385 subjects were randomized in 73 sites in 4 countries: Argentina (3), France (6), South Africa (9), and the United States (55). Study took place from 4/2000 to 11/2000.
Telithromycin group = 240 Median age = 40 Males= 42%
Cefuroxime group= 116 Median age = 40.5 Males= 41%

Inclusion criteria: ≥ 18 y/o and consent for sinus puncture (US only); ≥ 13 y/o and consent for sinus endoscopy (at non-US sites); for females, postmenopausal for at least one year or surgically unable to bear children or a normal menses within 1 month of study entry, plus a negative pregnancy test and agreement to use contraceptive; ABMS as evidenced by clinical and radiological findings (see paper for details); gram stain or microbiological results of sinus specimens

Exclusion criteria: > 3 episodes of sinusitis requiring abx within the previous 12 months; hx of sinusitis > 28 days; suspicion of sphenoidal sinusitis requiring treatment other than oral abx; nosocomial sinusitis and others (see paper)

Study design: multicenter, multinational, randomized, double-blind, active-controlled trial; method of randomization, not stated.

Treatments: Patients were randomized in a 2:1 ratio
Telithromycin - 2 x 400 mg capsules in am for 5 days and 2 matched placebo capsules in evening from days 1-5 and 2 matched placebo capsules in am and pm from days 6-10.
Cefuroxime Axetil - 2 x 125 mg capsules in am and pm for 10 days.

Outcome:
Primary Outcome: Clinical cure is assessed by study investigators, it is defined by return to preinfection state, with no ABMS-related signs and symptoms present, as determined on a scale of 0-3 in which 0=absent, 1=mild, and 3= severe, supplemented by a sinus x-ray/CT scan confirming no worsening or the presence of only those residual symptoms indicative of a normal course of clearance in the infection process, with no requirement for additional abx. Test of Cure visit took place at days 16-24 after the 1st day of abx.
Secondary Outcome: Late post therapy visit (days 31-45 after the 1st day of abx)

Results:
Clinical failure: Telithromycin 28/189 (14.8%); Cefuroxime 16/89 (18%)
Microbiological failure: Telithromycin 20/132 pathogens (15.2%);
Cefuroxime 11/61 pathogens (18%)
Secondary Outcome at late post therapy visit: Clinical Failure: Telithromycin 35/174 (20.1%);
Cefuroxime 18/82 (22%)

Adverse events:
Adverse events possibly related to study medications: telithromycin 56/252; cefuroxime 20/121;
Most frequent in telithromycin: nausea 6.7%, diarrhea 6%, dizziness 2.8%, vomiting 2%
Most frequent in cefuroxime: nausea 4.1%, diarrhea 5%, vomiting 2.5%
Most common “clinically noteworthy abnormal lab value” was abnormally low creatinine clearance in both groups.

2 cefuroxime patients experienced one or more adverse event known to have a potential for association with prolonged QTc (palpitations, arrhythmia, syncope, vertigo and cardiac insufficiency)
Discontinuation rates due to adverse events were 2% for telithromycin and 1.7% for cefuroxime.

Funding: Aventis Pharmaceuticals
Comments:

Bucher et al. 2003 ID 9

Stated Purpose of the Study: To evaluate the effect of a amox/clav on adults with clinically diagnosed acute rhinosinusitis in a general practice setting

Population & Setting: 252 patients from 24 general practices in Switzerland over 4 winter seasons (November to April, 1997-2001) were randomized.

Amox/clav	124	mean age 37	males 46%
Placebo	127	mean age 37	males 45.7%

Inclusion criteria: hx of repeated purulent nasal d/c and maxillary or frontal unilateral or bilateral pain for at least 48 hours but < 1 month and presence or absence (see paper) of pus under rhinoscopy

Exclusion criteria: < 18 y/o; URI or abx within the previous 4 weeks; after year 2000, pts with CRP > 100 mg/L; pts with CRP between 50 and 99 mg/L were reassessed at day 3 (3 pts) and excluded if clinical worsening was noted or the CRP level had increased to > 100 mg/L (none); see paper for rest of details

Study design: randomized, placebo-controlled, double-blind trial; stratified randomization, with the general practice or outpatient clinic as the stratification unit and patients randomized in blocks of 6; a computer random-number generator was used, and the allocation sequence was performed by a statistician who was not involved in the final analysis; patients were consecutively enrolled; study physicians were required to record the reason why eligible patients were not recruited

Treatments:

Amox/Clav	875/125 mg twice daily for 6 days
Placebo	matching tablets for 6 days

All patients received decongestant therapy with xylometazolin hydrochloride spray and acetaminophen 500 mg tablet, with a maximal dose of 3 g/day

Outcome:

Primary outcome was time to cure.
Definition of cure = zero days (since the previous visit or interview) during which rhinosinusitis restricted activities at home or work

Results: 252 randomized, 1 randomized but never took any medication, 249 completed the trial (see Figure 1 in paper for details)

Calculated Failure rate (100% - reported cure rate) at 1 week:	amox/clav	70.2%
	Placebo	69.3%
Calculated Failure rate (100% - reported cure rate) at 2 weeks:	amox/clav	23.4%
	Placebo	26%

In Cox proportional analysis, with adjustment for severity of restrictions at baseline, modification of the inclusion criteria, open treatment, and concomitant medication with steam inhalation, the hazard ratio for the effect of antibiotic treatment on time to cure was 0.99 (95% CI, 0.68-1.45)

Reported Relapse rate at 28 days	amox/clav	2/124 (1.6%)
	Placebo	5/125 (4%)

Adverse events:
At 7 and 14 days was significantly more likely in the amon/clav group than in the placebo group, with odds ratio of 3.89 (95% CI, 2.09 – 7.25) and 1.71 (95% CI, 0.91 – 3.23) at 7 and 14 days, respectively.

4 adverse events of moderate or severe intensity that were thought to be drug related: 2 in the amox/clav group (diarrhea) and 2 in the placebo group (diarrhea and vomiting)(?)
In the placebo group, there was 1 serious disease-related adverse event; after 2 weeks of symptomatic treatment, the patient was then treated for 1 week with amox/clav (1 g twice daily) but experienced a brain abscess caused by an amox/clav sensitive strain of Streptococcus milleri. The patient was operated on and recovered but has a frontal syndrome.
There were 2 additional serious adverse events in the placebo group, 1 myocardial infarction and 1 severe depressive episode; both were thought to be neither disease nor drug related.

Funding: GlaxoSmithKline, Swiss Academy of the Medical Sciences, Astra Klinik Fonds University Hospital Basel, and Forum fur interdisziplinare Hausarztmedizin, University of Basel.

Comments:

Burke et al. 1999 ID 524

Stated Purpose of the study: To compare the efficacy and safety of Moxifloxacin with those of Cefuroxime axetil for the treatment of community-acquired acute sinusitis.

Population & Setting:
542 patients from 48 clinical sites (primary care, allergists, infectious disease) in North America. Unknown study years.
Moxifloxacin group (n=223): Mean Age (range) = 40 yrs (18-76) Males= 84 (38%)
Cefuroxime axetil group (n=234): Mean age (range) = 39 yrs (18-78) Males=94 (40%)

Inclusion Criteria:
≥18 y/o with acute sinusitis (based on having at least 2 of the following: nasal congestion, post-nasal drainage, frequent coughing/throat clearing, frontal headache, malar tenderness/pain and purulent nasal discharge) of 1-4 weeks duration AND radiologic signs of sinusitis (air-fluid levels, opacification or mucosal thickening≥6mm).

Exclusion Criteria:
More than 2 episodes of acute sinusitis within the previous 12 months despite therapy; allergy to carboxyquinolones or ß-lactams; history of carboxyqinolone therapy or of sinus surgery; pregnancy, nursing or not using contraception; inability to take oral medications; bacteremia or meningitis; received investigational drugs during the preceding 30 days; requiring concomitant systemic antimicrobial therapy with non-study drugs; hepatic or renal insufficiency; immunocompromise; prolonged QT_c interval or taking medications that prolong QT_c; received an antimicrobial agent within 24 hours of enrollment, unless treatment failure.

Study Design: Randomized (by block-design random code, with unknown concealment method), double-blinded (medications encapsulated in gelatin), multi-center trial. Unknown if prestratified by center.

Treatment: 1) Moxifloxacin 400 mg QD + matched placebo QD for 10 days
2) Cefuroxime axetil 250 mg PO BID for 10 days

Outcome: **(Primary)** End of therapy (7-21 days after therapy)
(Secondary) Follow up (27-31 days after therapy)
Resolution: Resolution or improvement of clinical Si/Sx and radiographic findings and no additional antibiotics required.
Failure: No change, worsening or reappearance of infection and need for additional antibiotics.
Indeterminate: Clinical response could not be determined.

Results: 542 enrolled and randomized. 223 in the moxifloxacin group and 234 in the cefuroxime axetil group were evaluated for clinical efficacy (*per protocol* analysis). 44 in the moxifloxacin group and 41 in the cefuroxime axetil group were excluded (for reasons including insufficient duration of therapy and entry criteria violation). Rates of and reasons for ineligibility stated to be similar between treatment arms.

Clinical Failure: (Primary) 23/223 (10.3%) in the moxifloxacin group and 25/234 (10.7%) in the cefuroxime axetil group failed. **(Secondary)** 3/184 in the moxifloxacin group and 5/202 in the cefuroxime axetil group relapsed.

Adverse Events: Adverse events were experience by 126/263 in the moxifloxacin group and 112/274 in the cefuroxime axetil group. Discontinuation due to adverse events occurred in 15/263 in the moxifloxacin group and 6/274 in the cefuroxime axetil group (*P*=.04). Severe drug-related adverse events occurred in 7 (3%) of patients taking moxifloxacin (2 headache, 1

asthenia, 1 diarrhea, 1 vomiting, 1 dizziness and 1 agitation) and 10 (4%) of patients taking cefuroxime (5 headache, 2 nausea 1 diarrhea, 1 arthralgia, 1 increased cough, 1 dyspnea).

	Moxifloxacin (n=263)	Cefuroxime (n=274)
Any drug-related AE	96 (37%)	70 (26%)
Nervousness	7	2
Asthenia	5	4
Dizziness	13	7
Headache	12	8
Nausea	28	11
Diarrhea	18	17
Vomiting	9	3
Abdominal pain	5	3
Skin and Appendages	9	8
Special senses	3	9
Urogenital	3	8

Funding: Bayer

Comments: Use of decongestants and antihistamines were "standardized by each study center." Steroid use was prohibited unless the patient had already been receiving treatment prior to study entry. Compliance of ≥80% of study medication administered required for inclusion in analysis.

Chatzimanolis et al. 1998 ID 585

Stated Purpose of the Study: To compare the clinical efficacy and tolerability of roxithromycin and amox/clav, given in the conventional doses used in respiratory tract infections, in acute or recurrent sinusitis

Population & Setting: 60 patients with acute or recurrent sinusitis were enrolled in Greece.

Roxithromycin	31	mean age (range) 39 (18-70)	males 54.8%
Amox/clav	29	mean age (range) 37 (18-70)	males 58.6%

Inclusion criteria: recurrent or acute sinusitis; diagnosis of sinusitis was mainly documented by clinical and endoscopy findings, bacteriology and x-ray; > 18 y/o of either sex;

Exclusion criteria: not stated

Study design: open, randomized study

Treatments:
Roxithromycin 150 mg oral twice a day for at least 10 days
Amox/Clav 500/125 mg oral thrice a day for at least 10 days

Outcome: Clinical response was assessed within 48 hours after the end of treatment.

Results: 60 patients enrolled, 56 patients evaluated for efficacy and safety
For roxithromycin, treatment lasted 10 -14 days (mean 11 days)
For amox/clav, treatment lasted 10 – 15 days (mean 12 days)
Calculated Clinical Failure Rate post-treatment (100% - reported satisfactory case rate in clinically assessable population): 2/29 (6.9%) in roxithromycin; 3/27 (11.1%) in amox/clav

Microbiological failure: 2 in roxithromycin and 3 in amox/clav out of a total of 48 patients (combined roxithromycin and amox/clav) Unable to calculate actual rate as denominators for antibiotics were not reported.

Adverse events:

	Roxithromycin n=29	Amox/Clav n=27
GI	1 (3.4%)	7 (25.9%)

3 patients from Amox/Clav had discontinuation of medication 2° to adverse event?)

Funding: Hoechst Marion Roussel
Comments:

Clement & de Gandt 1998 ID 583

Stated Purpose of the Study: To compare azithromycin with amox/clav in the treatment of acute sinusitis

Population & Setting:
254 patients from 38 ENT clinics in unknown country (authors are from Belgium), Unknown study years.
Azithromycin group (n=158): Mean age (range) = 42.1 yrs (unknown range) Males=61 (37%)
Co-amoxiclav group (n=82): Mean age (range) = 38.7 yrs (unknown range) Males= 38 (47.2%)

Inclusion Criteria:
Adults of any age with acute ethmoidal or maxillary sinusitis (based on a scoring system described in the study) for an unspecified duration AND endoscopic evidence of pus from a sinus ostium AND unspecified CT scan evidence.

Exclusion Criteria:
Chronic sinusitis; suspected fungal sinusitis; allergy to macrolides or ß-lactams; infection requiring IV antibiotics; immunocompromise; pregnancy/nursing; receiving ergot derivatives, digoxin, cyclosporine or phenytoin; received investigational drugs during the preceding month

Study Design: Randomized (unknown method of randomization or concealment), not blinded, multi-center trial. Unknown if prestratified by center.

Treatment: 1) Azithromycin 500 mg PO qd for 3 days
2) Co-amoxiclav 500/125 mg PO TID for 10 days

Outcome (Primary): Follow up (21-28 days after enrollment)
Response rate was based on clinical scoring system 0-21.
Cure: score=0, *Improvement:* score=1-20, *Failure:* score=21

Results: 254 enrolled and randomized. 136 in azithromycin group and 74 in co-amoxiclav group were evaluated for clinical efficacy (*per protocol analysis*). 7 in azithromycin group (lost to follow up) and 7 in co-amoxiclav group (lost to follow up, premature discontinuation of treatment due to lack of efficacy or adverse event) were excluded.

1. Clinical Failure: 17/136(12.5%) in azithromycin group and 12/74(16.2%) in co-amoxiclav group had *no response* (includes failure and relapse). 17/136 in azithromycin group and 10/74 in co-amoxiclav group had *improvement* but not *cure.*

2. Microbiological Failure: Most common pathogens isolated at baseline: *S. pneumoniae, H. influenzae* and *S. aureus. Presumed persistence* determined by presence of purulent discharge at day 21-28 only for those patients from whom pathogens were isolated at baseline by endoscopy of the ostia. 5/52 in azithromycin group and 5/31 in co-amoxiclav group had *presumed persistence* of infection.

Adverse Events: Discontinuation due to adverse events occurred in 0/165 in azithromycin group and 2/89 in co-amoxiclav group.

	Azithromycin (n=165)	Co-amoxiclav (n=89)
# reporting drug-related AE	29	23
Drug related AE	24	19
Abdominal pain	7	7

Diarrhea	7	13
Nausea	8	1
CNS (headache/vertigo)	5	0
Severe AE	5	3
Study withdrawal due to AE	0	2

Funding: Pfizer, Belgium

Comments: 133 patients used adjuvant therapy (vasoconstrictors, mucolytics and corticosteroids). Compliance with study medications is unknown.

Clifford et al. 1999 ID 480

Stated Purpose of the Study: To compare the efficacy and safety of a 10-day oral treatment course of ciprofloxacin to those of 14-day therapy with clarithromycin for the management of adults with acute maxillary sinusitis or acute exacerbations of chronic sinusitis

Population & Setting: 560 patients enrolled at 19 clinical sites

Ciprofloxacin	236 (efficacy-valid population)	mean age (range) 40.4 (18-74)	males 38%
Clarithromycin	221 (efficacy-valid population)	mean age (range) 41 (18-76)	males 44%

Inclusion criteria: ≥ 18 y/o; primary dx of clinically (see paper for details) and radiologically documented acute sinusitis of ≤ 4 weeks duration; x-ray: opacification, or ≥ 6 mm of mucosal thickening or air-fluid level;

Exclusion criteria: inability to take oral medications; symptoms > 4 weeks (chronic sinusitis); unwillingness to undergo a sinus aspiration; need for concomitant anti-bacterial agents during the study period; baseline creatinine ≥ 3 mg/dL; terfenadine or astemizole during the study period; nasal or oral steroids; abx within 5 days of enrollment unless the patient was a treatment failure or had received only 1 or 2 doses of the abx; see paper for rest

Study design: prospective, randomized, double-blind, multicenter comparative trial; patients were randomly assigned to 1 of 2 treatment groups by means of a block design random code computer-generated at Bayer; study drugs were encapsulated in opaque gelatin capsules for blinding purposes.

Treatments:
Ciprofloxacin 2x250 mg twice a day for 10 days; placebo for days 11 to 14
Clarithromycin 2x250 mg twice a day for 14 days

Outcome:
Primary: clinical response 2-3 days post-treatment
Secondary: follow up at 28 day

Results: 560 enrolled; 559* included in Intent to treat analysis; 457 valid for efficacy analysis

Clinical failure rate in efficacy-valid group: ciprofloxacin 37/236 (15.7%)
Clarithromycin 19/221 (8.6%)
Clinical failure rate in Intent to treat group: ciprofloxacin 45/272* (16.5%)
Clarithromycin 25/267* (9.4%)

28-day follow up relapse rate in efficacy-valid group: ciprofloxacin 7/175 (4%)
Clarithromycin 18/187 (9.6%)
28-day follow up relapse rate in Intent to treat group: ciprofloxacin 9/196 (4.6%)
Clarithromycin 20/223 (9%)

Adverse events: 559 valid for safety analysis, 1 was excluded because no study drug (the paper did not specify which one) was administered; therefore, calculated rates are based on 560

	Ciprofloxacin (282)	Clarithromycin (278)
At least 1 adverse event	120 (42.6%)	158 (56.8%)
At least 1 drug-related event	93 (33%)	133 (48%)
GI	58 (20.6%)	81 (29.1%)

Nervous system	19 (6.7%)	25 (9%)
Special-senses related	14 (5%)	60 (21.6%)
Diarrhea	17 (6%)	36 (13%)
Taste perversion	7 (2.5%)	58 (20.9%)
Discontinuation 2° to adverse event	9 (3.2%)	9 (3.2%)

One episode each of arthralgia and tinnitus in the ciprofloxacin group, and 1 episode each of peripheral edema, hyperuricemia, and pleural pain in the clarithromycin group were reported as unchanged at the final evaluation.

Funding: Bayer Corporation

Comments: *Unclear why the denominators in ITT (272+267=539) do not add up to the reported 559?

Faich 2004 ID 20

REJECTED STUDIES: Adverse Events extraction only

Stated Purpose of the Study:

Population and Setting:
18,409 patients from 3,377 family practice and general internist sites in the US and Puerto Rico between 4/00-6/00.

Diagnoses included in the study:
Acute maxillary sinusitis, community acquired pneumonia, acute bacterial exacerbation of chronic bronchitis

Treatment: Moxifloxacin 400 mg QD x 5-10 days (10 days for sinusitis indication)

Study Design: multicenter, open-label noncomparative surveillance study

Adverse Events Included in Analyses: Those contactable by phone (70%, 12,854) or office visit (27%, 4,908) within 48 hours of treatment completion. 3% (n=645) were lost to follow-up.

Funding: Bayer Pharmaceuticals Corp.

Comments: Use of adjuvant therapy is unknown

Adverse Events: Of the 18,374 safety-validated patients, 3257 (17.7%) had one or more AE. No difference in AE rate by gender, race or age.

Most common reasons for early discontinuation due to AE:

Reason	Number
Nausea	396
Dizziness	202
Vomiting	161
Diarrhea	124
Headache	81
Abdominal pain	66
Rash	64
Palpitation	48

Serious adverse events were reported in 168 (0.9%). And 131 (0.7%) were hospitalized. 843 had possible cardiac-related events. An independent safety committee concluded there was no evidence of increased mortality or treatment-associated ventricular tachyarrhythmias. 6 deaths occurred, 5 were deemed not related to study drug and 1 was unlikely related.

Most common AE deemed probably or possibly drug related by the investigator ***only in those with sinusitis indication***: (SEE TABLE 2)

Reason	Number
Any	1793/ 10,822 (16.6%)
Nausea	729 (6.7%)
Body as a whole	371 (3.4%)
Diarrhea	259 (2.4%)
Dizziness	245 (2.3%)
Vomiting	143 (1.3%)
Headache	133 (1.2%)

Ferguson et al. 2002 ID 225

Stated Purpose of the Study: To compare clinical and radiologic efficacy of 2 treatment regimens, 5 days vs. 7 days of gemifloxacin therapy, in adults with acute bacterial rhinosinusitis

Population & Setting: 423 patients from 59 centers in 9 countries (Belgium, Canada, Estonia, Finland, Germany, Ireland, Italy, Lithuania, and the Netherlands) were randomized.
In ITT analysis

5-day Gemifloxacin	218	mean age 41.4	males 42.7%
7-day Gemifloxacin	203	mean age 39.7	males 41.9%

Inclusion criteria: > 18 y/o; signs and symptoms of acute bacterial rhinosinusitis for at least 7 but not more than 28 days (see paper for details); radiologic confirmation was required within 72 hours of randomization (sinus opacification and/or air-fluid level); patients in Germany and Lithuania were required to consent to an initial sinus endoscopy/rhinoscopy at study entry

Exclusion criteria: abx within 7 days before enrollment; signs and symptoms of disseminated infection requiring hospitalization or parenteral abx; hypersensitivity to fluoroquinolone abx; receipt of an investigational drug in the 30 days before the first dose of study medication; see paper for others

Study design: prospective, double-blind, multicenter, parallel-group study; method of randomization not stated

Treatments:
Gemifloxacin oral 320 mg once daily for 5 days; matching placebo once daily for study day 6 & 7
Gemifloxacin oral 320 mg once daily for 7 days

Outcome:
Primary: clinical response at follow-up (study days 18-25); success was defined as sustained improvement or resolution in signs and symptoms of acute bacterial rhinosinusitis so that no additional abx was required
Secondary: clinical response at end of therapy (study days 9 to 11)

Results: 423 randomized, 421 received at least 1 dose of study medication and were included in the Intent-to-treat (ITT) analysis; 356 were in the completed per-protocol-analysis (181 in 5-day group and 175 in 7-day group).

Calculated clinical failure (100% - reported clinical success rate in per-protocol patients):
5-day group 12.7%
7-day group 13.1%

Calculated clinical failure (100% - reported clinical success rate in ITT population):
5-day group 16.5%
7-day group 15.8%

Data on secondary clinical response at end of therapy (study days 9 to 11) were not reported.

Adverse events: diarrhea, nausea, and rash were the only reported events that occurred in 3% of patients or more in either group.

	5-day group	7-day group
adverse events while on therapy + 30 days post-therapy	33.5%	40.4%

Rash	1.4%	5.9%
Patients withdrawn 2° to adverse events	2/218 (0.9%)*	1/203 (0.5%)**

*one broken leg injury and one maculopapular rash
**vertigo

Funding: GlaxoSmithKline
Comments:

Garrison 2000 ID 438

REJECTED STUDIES: Adverse events extraction only

Stated Purpose of the Study: Determine the efficacy and safety of sparfloxacin in the treatment of AMS, microbiologically documented by maxillary sinus puncture, aspiration and culture.

Population and Setting:
253 patients in the outpatient setting of unknown specialty type by 21 investigators in the US

Diagnoses included in the study: Acute maxillary sinusitis

Treatment: Sparfloxacin 400 mg X1 (loading dose) followed by 200 mg QD for a total Rx of 10 days PLUS nasal decongestant therapy for the first 3 days of antibiotic treatment

Study Design: Open, non-comparative multicenter trial

Adverse events included in analysis: All 253 patients

Funding: Rhône-Poulenc Rorer Pharmaceuticals Inc.

Comments: Nasal decongestant administered for the first 3 days of antibiotic treatment

Adverse Events: One or more adverse events were reported by 139/253 (54.9%).

Most common AE	**N, % (of 253 total)**
Headache	33, 13.0%
Photosensitivity reaction	20, 7.9%
Diarrhea	19, 7.5%

Many others with frequency over 2%--see original paper.

62/253 (24.5%) reported AE “considered by investigator to be possibly or probably related to the study medication” (not specified by what criteria considered related).

AE related to study drug	**N, %**
Photosensitivity reaction	16 (6.3%)
Diarrhea	14 (5.5%)
Headache	11 (4.3%)
Nausea	11 (4.3%)
Insomnia	7 (2.8%)
Dyspepsia	5 (2.0%)
Pruritis	4 (1.6%)
Nervousness	3 (1.2%)

9/253 (3.6%) discontinued study due to AE, 6 were considered related to study medication(4 with photosensitivity reaction, 1 with headache and 1 with 1 urticaria). One patient discontinued the study prematurely due to a serious adverse event (asthma) that was considered by the investigator to be remotely related to study medication. No other patients experienced serious adverse events. No cardiovascular AE related to increase in QTc interval. No deaths occurred. 1 elevated creatinine.

Gehanno 2003 ID 41

REJECTED STUDIES: Adverse events extraction only

Stated Purpose of the Study: Evaluate the efficacy of moxifloxacin for treating acute maxillary sinusitis after confirmed failure of empirical antimicrobial therapy and acute sinusitis with a higher risk of complications, such as frontal or sphenoidal sinusitis and pansinusitis.

Population and Setting:
258 patients from 52 ENT centers throughout France between 1/01 to 7/01

Diagnoses included in the study: Acute maxillary sinusitis after confirmed failure of empirical antimicrobial therapy and acute sinusitis with a higher risk of complications such as frontal or sphenoidal sinusitis and pansinusitis

Treatment: Moxifloxacin 400 mg QD x7 days

Study Design: multi-center, non-comparative study

Adverse events included in analysis: Events that occurred at least 2 times and that occurred after the first dose of moxifloxacin until 7-10 days after the last dose were reported. Only 255/258 received the study medication. Serious adverse events were followed until 4-5 weeks after the last dose.

Adverse Events: 31/255 patients (12.2%) experienced at least 1 adverse event.
No data on number of patients with serious adverse events, or the number of patients who discontinued treatment due to adverse events.

Events deemed by investigators to be possibly or probably related to moxifloxacin treatment

Event	Number
Abdominal pain	6 (2.4%)
Nausea	6 (2.4%)
Neurosensorial	4 (1.6%)
Cardiovascular (includes tachycardia)	3 (1.2%)
Diarrhea	3 (1.2%)
Musculoskeletal complaints (includes arthralgia)	3 (1.2%)
Skin/Mucous membrane (includes rash)	3 (1.2%)

Funding: unknown

Comments: Use of adjuvant therapy is unknown. Corticosteroids were not permitted.

Gehanno et al. 2000 ID 373

Stated Purpose of the Study: The efficacy and tolerance of amoxicillin-clavulanate, with and without associated short steroid therapy, was evaluated in adults with acute sinusitis.

Population & Setting: 433 patients recruited from 51 private ENT specialists in France were randomized. The study was carried out from 11/1991 to 7/1994.
In ITT population:

5-day amox/clav (with or without steroids)	205	mean age 39.1	male 82/205 (40%)
10-day amox/clav (with or without steroids)	212	mean age 30.5	male 82/212 (39%)

Inclusion criteria: outpatients ≥ 18 y/o with acute sinusitis (see paper for details) < 10 days; opacities with or without air-fluid levels on standard films or computed tomography

Exclusion criteria: acute sinusitis requiring immediate surgical drainage and acute exacerbations of chronic sinusitis; abx or steroids in the 15 days preceding recruitment; see paper for others

Study design: muticenter, randomized, double-blind, placebo-controlled, parallel
2x2 factorial arrangement

Treatments:

A: Amox/Clav 500 mg three times a day for 5 days, then matching placebo for 5 more days
B: Amox/Clav 500 mg three times a day for 10 days
Also, for both group A and B, patients were randomized to receive 8 mg of methylprednisiolone three times daily or a matching placebo for study days 1 to 5

Outcome:

Primary: primary efficacy was assessed on day 14; success was defined as clinical recovery on day 14, with or without radiological normalization

Results:

433 randomized, 417 in Intent to treat (ITT) analysis, 360 in per-protocol analysis

Reported clinical failure rate on day 14, in ITT population:
5-day group 41/205 (20%)
10-day group 32/212 (15%)

Reported clinical failure rate on day 14, in per-protocol population:
5-day group 39/181 (21.6%)
10-day group 28/179 (15.6%)

Reported recurrence rate on day 30 follow up:
5-day group 11/162 (6.8%)
10-day group 7/175 (4%)

Absence of interaction between the duration of treatment by the antibiotic and the adjunctive use of methlyprednisolone was verified, permitting separate analysis of each treatment.
Evaluation at day 14 showed no evidence of a higher rate of recovery in the group treated by methylpredinsolone than in the placebo group (actual data not provided).

Adverse events:

433 in safety analysis; recorded adverse events were nausea, vomiting, diarrhea, gastric pain, skin reactions and Candida superinfection.

	5-day (213)	10-day (220)
patients with adverse events	20 (9.4%)	26 (11.8%)
discontinuation 2° to adverse events	1 (0.4%)	7(3.2%)

	steroids (219)	no steroids (214)
patients with adverse events	24 (11%)	22 (10.3%)
discontinuation 2° to adverse events	5 (2.3%)	3(1.4%)

Funding: SmithKline Beehcam

Comments: some patients received both amox/clav and methylprednisolone (see explanation in paper), actual data not provided.

Gwaltney et al. 1997 ID 648

Stated Purpose of the Study: To evaluate cefdinir for the treatment of acute community-acquired bacterial sinusitis.

Population & Setting: 1798 patients in US (1229) and Europe (569) participated

Cefdinir 600 mg once a day = 585	Median age (range) = 35 (12-83)	Males= 44%
Cefdinir 300 mg twice a day = 610	Median age (range) = 35 (13-88)	Males= 43%
Amox/Clav 500mg thrice a day=603	Median age (range) = 34 (13-79)	Males= 45%

Inclusion criteria: ≥13 y/o; males and females; signs and symptoms of acute sinusitis; had to include facial pain and purulent nasal discharge; dx confirmed by x-ray showing disease of the maxillary sinus; duration of illness ≤ 4 weeks; see paper for details

Exclusion criteria: hx of sensitivity to beta lactams, treatment with systemic abx within prior 48 hours;, significant renal or hepatic disease; requirement of Fe therapy; pregnant or lactating

Study design: Two (one in US, one in Europe) randomized, Investigator-blinded,multi-center trials were conducted. The studies were identical in design, with the exception that admission sinus aspiration was optional in US and mandatory in Europe. Patients were randomly assigned at each site to one of 3 treatment groups. Medications were dispensed by a third party, and all records regarding study medications were kept at a separate site. Patients were instructed to withhold details of study medication appearance and dosing schedule.

Treatments:

Cefdinir 600 mg once a day for 10 days
Cefdinir 300 mg twice a day for 10 days
Amoxicillin/Clavulanate 500 mg three time a day for 10 days

Outcome:

Primary: Satisfactory clinical response is defined by cure or improvement, assessed by absence or presence of clinical signs and symptoms. Test of cure visit took place 7-14 days post therapy.
Secondary: rate for continued clinical response with initial success was determined 3 to 5 weeks post therapy

Results: Evaluable patients were defined as those who took ≥ 80% of prescribed medications, returned for the test of cure visit (except for failures prior to scheduled visits), and did not take non-study systemic abx for other infections.

Calculated Clinical Failure Rate at 1-3 days post-treatment (100% - reported satisfactory cases in clinically evaluable population):

Cefdinir 600 mg once a day	49/474 (10.3%)
Cefdinir 300 mg twice a day	61/481 (12.7%)
Amox/Clav thrice a day	44/491 (9%)

Calculated Clinical Failure Rate at 3-5 wks post-treatment (100% - reported satisfactory cases in clinically evaluable population):

Cefdinir 600 mg once a day	37/379 (9.8%)
Cefdinir 300 mg twice a day	39//370(10.5%)
Amox/Clav thrice a day	30/389 (7.7%)

Calculated Microbiological failure at 7-14 days post therapy (evaluable patients):

Cefdinir 600 mg once a day	25/215
Cefdinir 300 mg twice a day	31/225 (1

Amox/Clav thrice a day	28/256 (10.9%)

Calculated Microbiological failure at 3-5 wks post therapy (evaluable patients):

Cefdinir 600 mg once a day	10/169 (5.9%)
Cefdinir 300 mg twice a day	20/167 (12%)
Amox/Clav thrice a day	14/203 (6.9%)

Adverse events:
Cefdinir once a day 188/582 (32%); Cefdinir twice a day 212/607 (35%); Amox/Clav 234/603 (39%) experienced at least one side effect (see table 6 in paper). The most frequent adverse event is GI related; mild diarrhea occurred in approximately 20% of each group. Diarrhea was the most common reason for discontinuation of treatment.
8/582 (1.4%) patients of the cefdinir OD group and 19/607 (3.1%) patients of the cefdinir BD and 30/603 (5%) patients of amox/clav groups discontinued treatment because of an adverse event. No clinically important alterations in laboratory values were observed for any of the groups.

Funding:
Comments: authors Leigh and Tack associated with Parke-Davis

Hansen et al. 2000 ID 97079

Stated Purpose of the Study: To compare the effectiveness of penicillin V and placebo given to patients with a dx of acute maxillary sinusitis based on pain in the maxillofacial area combined with either raised CRP or ESR.

Population & Setting: 139 patients from 26 general practices in town and rural areas from Denmark. Study took place from 11/1995 to 4/1997. 71 were given PCN and 62 placebo. Median age was 37 (quartiles 30 to 46). 33 (25%) were males. Consecutively included only once if they fulfilled the inclusion criteria.

Inclusion criteria: 18-65 years; pain in the maxillofacial area and values of CRP > 10 mg/L or ESR > 10 mm/h in males and > 20 mm/h in females.

Exclusion criteria: known allergy to PCN; pregnancy; breastfeeding; previous maxillary sinus surgery; ENT malignancy; DM; rheumatic arthritis; collagen vascular diseases; facial trauma; Rx with steroids, probenecid or immunotherapy; abx treatment previous 2 weeks or ongoing Rx; Symptoms > 4 weeks. After randomization, excluded if severe side effects, unwilling to continue or did not show up for control visit.

Study design: Randomized (a block randomization was used with 10 dark colored glasses in each block containing 5 glasses of PCN and 5 glasses of placebo; each glass contained 28 tablets; the general practitioner received one block each), double-blind, placebo-controlled.

Treatments: Penicillin V 1333 mg (2 million IE) twice daily for 7 days.
Placebo: 2 tablets twice daily for 7 days.

Outcome: Pain score after 7 day of treatment (from patient kept diary). Pain score of zero is considered a cure.

Results: After randomization, 2 in placebo and 4 in PCN group were withdrawn because of non-compliance. Another 6, 3 in each group, stopped treatment before day 7, due to lack of effect in 4 and side effects in 2 treated with PCN. They were included in analyses and registration of side effects until they dropped out. 133 patients in final analysis, 71 in PCN group, 62 in placebo.

Calculated Clinical Failure Rate of PCN at 7 days post initiation of treatment (100% - reported percentage of patients with pain score of zero at 7 days multiply by number of patients at 7 days divided by number of patients at day zero): 100% - 75%x68/71= 28%

Calculated Clinical Failure Rate of placebo at 7 days post initiation of treatment (100% - reported percentage of patients with pain score of zero at 7 days multiply by number of patients at 7 days divided by number of patients at day zero): 100% - 51%x59/62= 51.5%

See table 1 for original reported data.

Adverse events: 13 (18%) patients treated with PCN claimed to have side effects – 11 due to GI symptoms and 2 with unspecified symptoms – in contradiction to two (3%) patients treated with placebo – one with abdominal pain and one with unspecified symptoms (p=0.009).

Funding: PCN and placebo tablets from Nycomed Amersham, Denmark; financial support from Danish Practitioners' Foundation.

Comments: calculated results differ from reported results in the abstract (PCN failure 29%, placebo failure 63%)?

Haye et al. 1998 ID 562

Stated Purpose of the Study: To compare the efficacy of azithromycin to placebo in the treatment of patients with clinical symptoms and signs of acute maxillary sinusitis but without radiological evidence of empyema

Population & Setting: 169 patients recruited from general practices in Norway in the winter season were randomized.

Azithromycin group	87	mean age (range)= 40.2 (21-84)	males 20.7%
Placebo	82	mean age (range)= 43.2 (18-68)	males 31.7%

Inclusion criteria: ≥ 18 y/o; hx of URI; signs and symptoms of acute maxillary sinusitis: presence of nasal secretion (purulent at the time of examination) for > 10 days and < 30 days, and maxillary sinus tenderness and/or pain of < 30 days' duration; radiograph should not show complete opacity or an air-fluid level, and the mucosal thickness must be < 6 mm, should not show frontal or sphenoidal sinusitis

Exclusion criteria: hx of intolerance to macrolides, azalides, PCN, or lactose; >2 episodes of sinusitis in the past 12 months; abx within the preceding 2 weeks; see paper for rest

Study design: double-blind, double-dummy, parallel-group, multicenter study; computer randomized in blocks of six to either of the two treatment groups

Treatments:
Azithromycin one 500 mg tablet daily for 3 days
Matching Placebo one tablet daily for 3 days

Outcome: Primary outcome not defined.

Results: 169 patients enrolled in the study; all patients had at least one follow up visit after treatment; in patients who did not return for visits on study day 10-12 or study day 23-27, the results from the previous visit were carried forward.

	Azithromycin	Placebo
Reported Failure rate at 3-5 days:	5/84 (6%)	10/81 (12.3%)
Reported combined failure + relapse rate at 10-12 days (counted some patients who were not present at this visit but were present at the previous visit):	6/86 (7%)	9/81 (11.1%)
Reported combined failure + relapse rate at 23-27 days (counted some patients who were not present at this visit but were present at the previous visits):	9/87 (7%)	10/82 (12.2%)

Adverse events:

	Azithromycin (n=87)	Placebo (n=82)
Patients with adverse events	24 (27.6%)	15 (18.3%)
GI (diarrhea, nausea, abdominal pain)	22 (25.3%)	12 (14.6%)

One azithromycin related adverse event was considered severe (details not provided).
No patient in either treatment group discontinued therapy due to an adverse event.

Funding:
Comments: author Odegard associated with Pfizer

Henry et al. 1999 ID 482

Stated Purpose of the Study: To compare the efficacy and tolerability of a 10-day regimen of sparfloxacin with a 14-day regimen of clarithromycin in patients with well-defined acute maxillary sinusitis

Population & Setting: 504 patients from 61 centers in US participated.
Sparfloxacin 252
Clarithromycin 252

Inclusion criteria: ≥ 18 y/o; dx of acute maxillary sinusitis (AMS) within the previous 2 weeks; at least one symptom of AMS and sinus x-ray abnormalities (see paper for details)

Exclusion criteria: Symptoms of AMS within the previous 4 weeks; chronic sinusitis; systemic abx within 7 days before start of study; pregnancy, baseline QTc > 500 msec and others (see paper)

Study design: randomized, double-masked, comparative, multicenter trial. Randomized in a 1:1 ratio. To preserve masking, patients were provided with cards containing encapsulated study medications and placebos.

Treatments:
Sparfloxacin arm - 2x 200 mg tablets on day one, followed by 1x 200 mg tablet each am from days 2 through 10, plus appropriate am and pm placebos for 14 days
Clarithromycin arm - 2x 250 mg tablets every 12 hours for 14 days.

Outcome: Primary: Test of cure occurs on study day 20±3; clinical success is defined by number of patients with clinical outcomes of cure plus improvement divided by the total population minus the indeterminate cases.
Secondary: recurrence of infection was assessed on day 38± 7

Results: 504 enrolled, 430 clinically assessable; primary reasons for exclusion were incorrect dx of AMS, normal x-ray at baseline, and non-compliance

Calculated Clinical Failure Rate (100% - reported clinical success rate* in clinically assessable population):
Sparfloxacin 37/219 (16.9%)
Clarithromycin 35/211 (16.6%)

Calculated Clinical Failure Rate in all-treated population (100% - reported clinical success rate in all-treated population):
Sparfloxacin 40/230 (17.4%)
Clarithromycin 40/224 (17.9%)

Secondary follow up at 3- 4 weeks after therapy
Calculated Clinical Relapse Rate (100% - reported sustained clinical success rate in clinically assessable population):

Sparfloxacin 52/191 (27.2%)
Clarithromycin 56/185 (30.3%)
Calculated Clinical Relapse Rate in all-treated population (100% - reported sustained clinical success rate in all-treated population):
Sparfloxacin 56/197 (28.4%)
Clarithromycin 61/194 (31.4%)

Adverse events:

	Sparfloxacin n=252	Clarithromycin n=252
diarrhea	60 (23.8%)	68 (27%)
photosensitivity	24 (9.5%)	1 (0.45)
taste perversion	2 (0.8%)	22 (8.7%)
nausea	12 (4.8%)	12 (4.8%)
abdominal pain	4 (1.6%)	9 (3.6%)
flatulence	5 (2%)	4 (1.6%)
discontinuation 2° to med	11 (4.4%)	14 (5.6%)
adverse lab values**	8 (3.2%)	6 (2.4%)

**elevations in lipase, aspartate aminotransferase, alanine aminotransferase or blood glucose

5 patients in the clarithromycin group experienced serious adverse events, 1 of which (rash) was considered to be drug related; 4 of these patients were discontinued from the study.

Funding: Rhone-Poulenc Rorer

Comments: ***clinical success rate is defined by number of patients with clinical outcomes of cure plus improvement divided by the total population minus the indeterminate cases

Henry et al. 2003 ID 10

Population & Setting:
941 patients from multiple (unknown number) of centers in the U.S. Unknown study years.

Azithromycin for 3 days group (n=312):
Mean age (range) = 40.2 yrs (18-76) Males=123 (39.4%)

Azithromycin for 6 days group (n=311):
Mean age (range) = 41.3 yrs (18-80) Males=124 (39.9%)

Amoxicillin-clavulanate group (n=313):
Mean age (range) = 42.4 yrs (18-84) Males=134 (42.8%)

Inclusion Criteria:
≥18 y.o. in outpatient setting with acute sinusitis (based on: purulent nasal discharge or facial pain and/or pressure and/or tightness) for 8-27 days duration AND radiologic signs of sinusitis (air-fluid levels, opacification or mucosal thickening≥6mm).

Exclusion Criteria:
History of chronic sinusitis; allergy to penicillins or macrolides; history of sinus surgery; systemic anti-histamine treatment; systemic antibiotic treatment for over 24 hours within 2 weeks of enrollment.

Study Design: Randomized (unknown method of randomization or concealment), double-blinded (amoxicillin-clavulanate given as a suspension to facilitate masking), multicenter trial. Unknown if prestratified by center.

Treatment:
1) Azithromycin 500 mg QD for day 1-3 + matched placebo tab QD day 4-6 + matched placebo suspension TID for 10 days
2) Azithromycin 500 mg QD for 6 days+ matched placebo suspension TID for 10 days
3) Amoxicillin-clavulanate 250/62.5 mg TID for 10 days + matched placebo QD for 6 days

Outcome:
(Primary) End of study (22-36 days after enrollment)
(Secondary) End of therapy (8-15 days after enrollment)

Cure: Resolution of Si/Sx, no worsening in radiographic findings and no additional antibiotics required.
Improvement: Partial resolution of Si/Sx and no additional antibiotics required.
Failure: Persistence of Si/Sx or emergence of new Si/Sx and/or the need for additional antibiotics or a change in antimicrobial therapy.

Results: 941 enrolled and randomized; 298 in azithromycin for 3 days group, 294 in azithromycin for 6 days group, and 288 in the amoxicillin-clavulanate group were included in the *intent to treat analysis* for clinical efficacy. 5 in azithromycin for 3 days group, 5 in azithromycin for 6 days group, and 6 in the amoxicillin-clavulanate group were excluded due to enrollment by an ineligible center. Others excluded for not meeting entry criteria, visits outside the protocol-specified windows or unknown/missing data.

Clinical Failure: (**Primary)** 85/298 in azithromycin for 3 days group, 76/294 in azithromycin for 6 days group, and 82/288 in the amoxicillin-clavulanate group failed. **(Secondary)** 35/303 in azithromycin for 3 days group, 33/298 in azithromycin for 6 days group, and 43/291 in the amoxicillin-clavulanate group failed.

Adverse Events: (**Primary)** Adverse events were experience by 97/312 in azithromycin for 3 days group (*nausea*=23 *diarrhea*=53, *flatulence*=17), 117/311 in azithromycin for 6 days group (*nausea*=27, *diarrhea*=66, *flatulence*=11) and 160/313 in the amoxicillin-clavulanate group (*nausea*=38, *diarrhea*=101, *flatulence*=6). Discontinuation due to adverse events occurred in 7 in azithromycin for 3 days group, 11 in azithromycin for 6 days group and 28 in the amoxicillin-clavulanate group. No treatment-related serious adverse events occurred in any treatment arm.

Funding: Pfizer

Comments: Compliance is stated as being recorded by investigators (amount taken, reasons for missed doses and amount of study medication returned at the end of therapy), but data is not shown. Sinus films at the end of therapy compared to baseline showed improvement/resolution in 71.7% in azithromycin for 3 days group, 74.2% in azithromycin for 6 days group and 66.2% in the amoxicillin-clavulanate group.

Henry et al. 1999 ID 462

Stated Purpose of the Study: To compare the efficacy and tolerability of a 10-day regimen of cefuroxime axetil 250 mg twice daily with a 10-day regimen of amoxicillin/clavulanate 500 mg/125 mg three times daily in adult patients with acute bacterial maxillary sinusitis

Population & Setting: 263 patients from 9 centers in US participated.

cefuroxime	132	mean age (range) 40.5 (19-70)	males 52%
amox/clav	131	mean age (range) 39.4 (18-82)	males 38%

Inclusion criteria: men and women ≥ 18 y/o; clinical dx of acute maxillary sinusitis (AMS) within the previous 30 days; ≥ 2 of the following symptoms with at least moderate severity: rhiniorrhea, nasal congestion, or cough, sinus x-ray: opacification, ≥ 4 mm membrane thickening, and/or air-fluid level in 1 or both maxillary sinuses; and others (see paper)

Exclusion criteria: dx or hx of chronic sinusitis; sinus washout or systemic abx in the previous 7 days; sinus surgery in the past month, pregnancy, see paper for others

Study design: randomized, double-masked, multicenter trial. Method of randomization not explicitly stated.

Treatments:
Cefuroxime 250 mg twice a day plus matched placebo once daily for 10 days
Amox/Clav 500 mg three times a day for 10 days

Outcome:
Primary: Post treatment response and follow-up assessment 26 –30 days after cessation of treatment. Satisfactory response comprised of both "cure" and "improvement". For the outcome to be judged satisfactory, no residual opacification or air-fluid level was allowed on sinus x-ray (see paper for details). Data on post treatment 1-3 days not shown.

Results: 263 enrolled, 193 clinically assessable; primary reasons for exclusion were violation of selection criteria, failure to complete all required study visits, absence of urine compliance assay, and loss to follow-up

Actual result reads: "A satisfactory clinical response (cure or improvement) in the per-protocol analysis at the follow-up assessment was present in 50% and 41% of clinically assessable patients treated with cefuroxime axetil and amoxicillin/clavulanate, respectively (P=0.19). Fifty-one cefuroxime axetil patients and 54 amoxicillin/clavulanate patients were judged to be clinical failures or had clinical recurrences."

Calculated Clinical Failure Rate at follow-up assessment (100% - reported satisfactory case rate in clinically assessable population):

Cefurxoime	100%-50%=50%
Amox/Clav	100%-41%=59%

Adverse events:

	Cefuroxime n=132	Amox/Clav n=131
patients with ≥ 1 drug-related event	23 (17.4%)	38 (29%)
patients with ≥ 1 GI events	15 (11.4%)	30 (22.9%)
diarrhea	8 (6.1%)	25 (19.1%)

nausea	0	6 (4.6%)
vaginitis	3 (2.3%)	5 (3.8%)
patients withdrew 2° adverse event	2 (1.5%)	8 (6.1%)

Funding: Glaxo Wellcome

Comments: Table IV heading should specify the data is from a retrospective analyses using an overall symptom scoring system for the subset of symptoms published by the IDSA and not from the per-protocol analyses.

Jareoncharsri et al. 2004 ID 34

Stated Purpose of the study: To compare the efficacy, safety and antimicrobial activity of Levofloxacin with amoxicillin/clavulanic acid in the treatment of purulent sinusitis in adult Thai patients.

Population & Setting:
60 patients from 2 ENT centers in Thailand from 6/98-12/99.
Overall mean age (range) =35.5 yrs (17-68) Overall Males= 23 (38%)
Levofloxacin group (n=34) Co-amoxiclav group (n=26)
Unknown age range and number of males for each group, but demographic characteristics stated to be statistically comparable.

Inclusion Criteria:
≥16 y.o. in outpatient setting with acute sinusitis/acute exacerbation of chronic sinusitis (based on nasal obstruction, purulent nasal discharge or postnasal drip, impairment of sense of smell, foul smell and headache) of ≤4 weeks duration AND purulent discharge in the middle meatus or maxillary ostium by endoscopy AND abnormal radiologic signs (undefined).

Exclusion Criteria:
None listed

Study Design: Randomized (unknown method of randomization or concealment), not blinded, multi-center trial. Unknown if prestratified by center.

Treatment: Levofloxacin 300 mg QD for 14 days
Co-amoxiclav 500/125 mgTID for 14 days

Outcome: (Primary) End of study (day 21 after enrollment)*Cure:* Resolution of Si/Sx and no radiologic evidence of remaining disease
Improvement: Incomplete resolution of Si/Sx and improvement of radiologic findings
Relapse: Initial improvement/cure followed by recurrence of Si/Sx
Failure: Neither clinical nor radiologic improvement is seen

Results: Unknown number enrolled and randomized. 34 in levofloxacin group and 26 in co-amoxiclav group evaluated for clinical efficacy (unknown if *intent to treat analysis*). Unknown number excluded.

1. Clinical Failure: (Primary) 3/34 in levofloxacin group and 4/26 in co-amoxiclav group failed, relapsed or withdrew from therapy.

2. Microbiological Failure: Most common pathogens isolated at baseline: *Streptococcus species, H. influenzae* and *Staphylococcus species. Persistence* determined by repeated isolation of baseline pathogens at day 14 after enrollment. 6/28 in levofloxacin group and 6/20 had persistence of infection.

Adverse Events: Adverse events were experience by 3/34 in levofloxacin group (nausea, dizziness, abdominal pain and diarrhea) and 2/26 in co-amoxiclav group (nausea, palpitation, acute urticaria and bronchospam). All adverse events in both groups were mild and resolved spontaneously.

Funding: Daiichi Pharmaceutical Co.

Comments: Use of adjuvant therapy is unknown. Compliance with study medications is unknown. 14 days after enrollment, 62% in levofloxacin group and 62% in co-amoxiclav group showed radiological improvement.

Johnson et al. 1999 ID 491

Stated Purpose of the Study: To compare the efficacy and safety of a 10-day oral treatment of ciprofloxacin to cefuroxime axetil for the management of adults with acute bacterial sinusitis or acute exacerbations of chronic sinusitis

Population and Setting: 501 (ITT) adults in 17 otolaryngology offices, study years not specificed

Ciprofloxacin 228	mean age (range) 40 (18-72)	males 40%
Cefuroxime 225	mean age (range) 43 (18-85)	males 43%

Inclusion criteria: Primary dx of acute presumed or documented bacterial sinusitis or acute exacerbation of chronic bacterial sinusitis of up to 4 weeks' duration; > 18 y/o; clinical signs and symptoms of sinusitis and x-ray confirming maxillary sinusitis; for additional criteria, see paper; antral puncture procedure was performed on all patients

Exclusion criteria: inability to take oral medications, allergy to carboxyquinolones or beta-lactams; symptom duration > 4 weeks, administration of an antimicrobial agent within 5 days of study enrollment was also a reason for exclusion, unless the patient was a treatment failure or had received only 1 or 2 doses of the antibiotic, see paper for rest of criteria

Study design: Prospective, randomized (one of two treatment groups using a block-design random code), double-blind, two-arm comparative study

Treatments:
Ciprofloxacin 500 mg twice a day for 10 days
Cefuroxime 250 mg twice a day for 10 days

Outcome:
Primary - Clinical resolution – resolution based on the resolution or improvement of both clinical symptoms and radiography, as well as the physician's clinical judgment of whether or not additional antimicrobial treatment was necessary. Test-of-cure took place 1 – 7 days post-therapy.
Secondary – follow-up at 2 - 4 week

Results:
501 enrolled; 48 disqualified (22 cipro; 26 cefuroxime); 453 were valid for efficacy analysis (228 cipro; 225 cefuroxime);
Clinical failure = ciprofloxacin 29/228 (13%); cefuroxime 38/225 (17%)
Microbiological response; 99 (43%) ciprofloxacin and 90 (40%) cefuroxime had one or more causative organisms isolated pre-therapy.
Microbiological failure = ciprofloxacin 3/92 (3.3%); cefuroxime 5/100 (5%)
2-4 week follow up: clinical relapse = cipro 16/168 (9.5%) cefuroxime 20/165 (12.1%)

Adverse events:
115 (46%) cipro and 113 (45%) cefuroxime treated patients reported at least one treatment-emergent event.
87 (35%) cipro and 83 (33%) cefuroxime experienced at least one drug-related adverse event. Diarrhea, nausea, headache and dizziness were the most common events reported. Premature discontinuation of a study drug due to an adverse event was reported in one cipro patient (vasodilatation, facial edema and rash) and 6 cefuroxime patients (3 rash, 2 diarrhea, 1 dizziness and amblyopia).

Funding: Bayer

Klapan et al. 1999 ID 500

Stated Purpose of the study: To compare the efficacy and tolerability of a 3-day course of azithromycin and a 10-day course of amox/clav in the treatment of acute sinusitis in adults

Population & Setting:
100 patients from unknown number or type of centers possibly in Croatia. Unknown study years.
Azithromycin group (n=50): Mean age (range) = 33yrs (unknown range)
Males=40 (80%)
Amoxicillin/clavulanic acid group (n=50): Mean age (range) = 40yrs (unknown range)
Males=37 (74%)

Inclusion Criteria:
≥15 y/o with Si/Sx of acute sinusitis (undefined) of ≤4 weeks duration AND radiologic signs (air-fluid levels, opacification or mucosal thickening≥4mm or opacities) AND nasal endoscopy (complete obstruction of ostiomeatal complex or partial obstruction with purulent drainage).

Exclusion Criteria:
Chronic sinusitis; allergy to azithromycin or amoxicillin/clavulanic acid; pregnancy or nursing; viral infection; severe hepatic or renal impairment; GI disorder; immunodeficiency; received more than 1 dose of antibiotic within 7 days of enrollment.

Study Design: Randomized (unknown method of randomization or concealment), not blinded trial.

Treatment: Azithromycin 500 mg PO qd for 3 days
Amoxicilllin-clavulanic acid 500/125 mg PO TID for 10 days

Outcome: **(Primary)** End of treatment (10-12 days after initiation of treatment)
(Secondary) Follow up (4 weeks after initiation of treatment)
Response rate was based on clinical scoring system 0-3 (based on fever, headache, facial tenderness, nasal congestion/discharge, nasal mucosa hyperemia and post-nasal secretions)
Cured: complete disappearance of signs and symptoms, score≤1
Improvement: partial disappearance of signs and symptoms without need for further therapy
Failure: persistence or progression of signs or symptoms requiring further therapy
Relapse: reappearance of signs or symptoms at 4 weeks

Results: 100 enrolled and randomized. 47 in azithromycin group and 47 in amoxicillin/clavulanic acid group were evaluated for clinical efficacy (*per protocol analysis*). 3 in azithromycin group and 3 in amoxicillin/clavulanic acid group were excluded for reasons including: violation of inclusion criteria.

1. Clinical Failure:

- **(Primary)** 0/47 in azithromycin group and 0/47 in amoxicillin/ clavulanic acid group had *failure* or *relapse.* 3/47 in azithromycin group and 12/47 in amoxicillin/clavulanic acid group had *improvement.*
- **(Secondary)** 1/43 in azithromycin group and 4/46 in amoxicillin/clavulanic acid group had *failure* or *relapse.*

2. Microbiological Failure: Ostiomeatal sinus aspiration was performed in 70 patients at baseline (unknown reason not performed on all patients). Most common pathogens isolated at baseline: *H. influenzae, S. aureus* and *S. pneumoniae.* No pathogens cultured in 33%. Aspiration was repeated after 72 hours from treatment initiation if clinical failure. 0/23 in azithromycin group and 3/24 in amoxicillin/clavulanic acid group failed (includes *persistence* and *relapse*).

Adverse Events: Adverse events occurred in 2/50 in azithromycin group (*nausea*=2, *diarrhea*=0, *other*=0), and 5/50 in amoxicillin-clavulanic acid group (*nausea*=5, *diarrhea*=1, *other*=0). Discontinuation due to adverse events did not occur in either group.

Funding: Not disclosed

Comments: Some of the authors are from Pliva d.d. Pharmaceuticals Division, Zagreb, Croatia. Compliance with study medications is unknown.

Klein et al. 1998 ID 599

Stated Purpose of the Study: To compare the efficacy and safety of ciprofloxacin to cefuroxime in the treatment of adult outpatients with acute bacterial sinusitis or acute exacerbation of chronic sinusitis.

Population & Setting:

83 patients from a single (unknown type) center in unknown country. Unknown study years.

Ciprofloxacin group (n=13):	Mean age (range) = 46.8yrs (30-75)	Males= 6 (46%)
Cefuroxime axetil group (n=19):	Mean age (range) = 44.3yrs (25-71)	Males= 4 (21%)

Inclusion Criteria:

≥18 y.o. with acute sinusitis/acute exacerbation of chronic sinusitis (based on having at least 2 of the following: fever, leukocytosis, typical symptoms or physical findings) of ≤4 weeks duration AND radiologic signs (air-fluid levels, opacification or mucosal thickening≥6mm).

Exclusion Criteria:

Frequent, recurrent acute sinusitis; allergy to carboxyquinolones or ß-lactams; pregnancy or nursing; inability to undergo sinus aspiration or to take oral medications; bacteremia or meningitis; received investigational drugs during the preceding 30 days, or more than 2 doses of an antibiotic within 5 days of enrollment unless the patient was a treatment failure; baseline serum creatinine≥3.0 mg/dL.

Study Design: Randomized (computer-generated block-design random code with unknown concealment method), double-blinded (study drugs encapsulated in opaque capsules for masking), single-center trial

Treatment: Ciprofloxacin 500 mg PO BID for 10 or more days (range=14-18 days)
Cefuroxime axetil 250 mg PO BID for 10 or more days (range=13-18 days)

Outcome (Primary): End of therapy (1-7 days after treatment)
(Secondary): Follow up (2 to 4 week after treatment)
Resolution: complete resolution of Si/Sx, negative radiography and no further therapy required
Improvement: decrease in Si/Sx, decreased mucosal thickening and no further therapy required
Failure: no change, worsening or reappearance of Si/Sx requiring alternative therapy
Relapse: reappearance of any Si/Sx AND positive sinus x-rays

Results: 83 enrolled and randomized. 13 in ciprofloxacin group and 19 in cefuroxime axetil group were evaluated for clinical efficacy (*per protocol analysis)*. 51 (unknown number in ciprofloxacin vs. cefuroxime axetil group) were excluded for reasons including: no pathogen isolated and inadequate treatment length.

1. Clinical Failure:

- **(Primary)** 0/13 in ciprofloxacin group and 5/19 in cefuroxime axetil group were *failed.* 8/13 in ciprofloxacin group and 11/19 in cefuroxime axetil group had *improvement.*
- **(Secondary)** 3/9 in ciprofloxacin group and 1/9 in cefuroxime axetil group had *relapse.*

2. Microbiological Failure: Most common pathogens isolated at baseline: *H. influenzae* and *Streptococcus species.* By sinus aspiration if clinical failure at end of therapy.

- **(Primary)** 0 (of unknown number re-cultured) in ciprofloxacin group and 5 (of unknown number re-cultured) in cefuroxime axetil group failed. All 5 failures were due to super-infection, not persistence of pathogen originally cultured.
- **(Secondary)** 0 (of unknown number re-cultured) in ciprofloxacin group and 0 (of unknown number re-cultured) in cefuroxime axetil group failed.

Adverse Events: Drug-related adverse events were experienced by 10 (45%) of ciprofloxacin group and 10 (34%) or cefuroxime axetil group. Most events in both groups were GI related (diarrhea, nausea/vomiting and flatulence). Discontinuation due to adverse events occurred in 1 (rash) in the ciprofloxacin group and 1 (eczema flare) in the cefuroxime axetil group.

Funding: Bayer

Comments: Use of decongestants and antihistamines were permitted but not recorded. One-sided 95% CI were calculated for clinical and microbiological efficacy. More subjects in the cefuroxime axetil group had multiple organisms cultured at baseline than in the ciprofloxacin group. An unknown number of patients were removed from analysis for clinical failure with resistant pathogens cultured at end of study. Compliance with study drugs is unknown.

Klossek et al. 2003 ID 164

Stated Purpose of the Study: To compare the efficacy and safety of oral moxifloxacin 400 mg once daily for 7 days with those of oral trovalfloxacin 200 mg once daily for 10 days in treating adult out-patients with acute bacterial rhinosinusitis

Population & Setting: 503 patients with acute bacterial maxillary sinusitis were randomized. Patients were enrolled in 60 centers in 8 countries: Belgium, France, Germany, Great Britain, Greece, Lithuania, Spain and Sweden, by both office-based primary care physicians (UK) and otolaryngologists (other countries).

Moxifloxacin	223	mean age 38.8	males 43.9%
Trovafloxacin	229	mean age 41.9	males 49.3%

Inclusion criteria: male and female patients ≥ 18 y/o with acute sinusitis (see paper for details) and x-ray evidence of air-fluid level, opacification or ≥ 6 mm mucosal thickening.

Exclusion criteria: chronic sinusitis (symptomatic > 4 weeks), recurrence of > 2 episodes of acute sinusitis within the preceding 6 months, patients with hypersensitivity to any quinolone, receiving concomitant medication reported to increase the QT interval, and others (see paper)

Study design: This was a prospective, multinational, multicenter, randomized, double-blind, comparative study. Patients were randomly assigned 1:1 to one of two treatment groups using a block design computer-generated random code. As randomization was performed by the center, each patient within each center was assigned a sequential ascending random number to complete a pre-defined block size of four. Matching placebos were used.

Treatments:
Moxifloxacin 400 mg once daily for 7 days, matching placebo once daily for days 8-10
Trovafloxacin 200 mg once daily for 10 days

Outcome:
Primary – clinical response 7-10 days after the end of therapy, "clinical resolution" is defined by disappearance of signs and symptoms or improvement and no further therapy required
Secondary – final follow up 3 to 4 weeks after the end of therapy

Results: Primary efficacy analysis was performed on clinically evaluable patients: confirmed clinical and x-ray dx of acute sinusitis, received at least 5 days of therapy (with no other abx administered concomitantly), followed the protocol and received post-therapy clinical evaluation within 3 to 14 days after ending the study drug therapy
503 enrolled, 452 valid for efficacy analysis; most common reasons fro exclusion were violation of the time schedule for evaluation and insufficient duration of therapy

Reported clinical failure rate 7-10 days post –therapy:

Moxifloxacin	7/223 (3.1%)
Trovafloxacin	18/229 (7.9%)

Microbiological failure rate:

Moxifloxacin	5/90 (5.6%)
Trovafloxacin	10/101 (9.9%)

Adverse events:
Drug-related adverse events occurring in ≥ 2% of patients

	Moxifloxacin N=248	Trovafloxacin N= 251
Dizziness	3 (1.2%)	21 (8.4%)
Diarrhea	14 (5.6%)	3 (1.2%)
Nausea	3 (1.2%)	10 (4%)
Asthenia	5 (2%)	6 (2.4%)
Vertigo	2 (0.8%)	8 (3.2%)
Abdominal Pain	5 (2%)	4 (1.6%)

One or more serious events were reported for 4 moxifloxacin and 2 trovafloxacin-treated patients. However, only 2, in one patient of the moxifloxacin group, were considered to be drug-related (pruritus and tachycardia) necessitating study drug discontinuation. 5 patients (2%) receiving moxifloxacin and 12 (4.8%) of trovafloxacin treated patients discontinued therapy prematurely. Early discontinuation was at least in part due to dizziness/vertigo in 6/12 patients who received trovafloxacin compared to 1/5 of those in the moxifloxacin group.
Of the 499 patients evaluated for safety, treatment-emergent adverse events were reported by 74 (29.8%) of moxifloxacin group and 82 (32.7%) of the trovafloxacin group.

Funding: not stated

Comments: authors Arvis & Leberre associated with Bayer Pharma, France

Kutluhan et al. 2002 ID 97073

Stated Purpose of the Study: To determine the most appropriate duration of treatment in adult patients with bacterial acute maxillary sinusitis and to investigate whether a linear correlation is present between nasal smear findings and symptoms of acute maxillary sinusitis at the time of diagnosis and the follow-up period

Population & Setting:
Selected group of 40 clinic patients in Turkey enrolled in the study between 1998 and 2001.
Mean age (range): 29 (16-45)

Inclusion criteria: bacterial acute maxillary sinusitis diagnosed by maxillary sinus puncture; also clinical signs and symptoms (major and minor, see table 1 in paper); x-ray opacification and air-fluid level;

Exclusion criteria: x-ray findings of mucosal thickening or cysts…etc.; acute sinusitis within the last 6 months; chronic sinusitis

Study design: prospective, randomized; method of randomization not stated

Treatments:

Group 1 = 10 patients	1 week antibiotic
Group 2 = 10 patients	2 week antibiotic
Group 3 = 10 patients	3 week antibiotic
Group 4 = 10 patients	4 week antibiotic

Antibiotic choice was made depended on culture and sensitivity results from maxillary sinus puncture.
Amox/Clav 1 g twice a day
Ciprofloxacin 500 mg (dosing frequency not specified)
Clarithromycin 500 mg twice a day
Cefuroxime 250 mg twice a day

Patients were allowed Paracetamol if needed.

Outcome: Presence or absence of symptoms at study day 7, 14, 21, 28 and 56

Results: Total number of patients completed the study was not explicitly stated in the paper.
At day 7 and 14, no reported relapse in any patients.
At day 28, relapse of the symptoms was noted in 5, 2, 2 and 3 patients in groups 1, 2, 3, and 4.

Assuming all patients completed the study, the following **relapse rate at day 28** can be calculated:

1 week antibiotic	5/10 (50%)
2 week antibiotic	2/10 (20%)
3 week antibiotic	2/10 (20%)
4 week antibiotic	3/10 (30%)

Adverse events: data not presented

Funding:

Comments: Total number of patients completed the study was not explicitly stated in the paper. Number of patients with relapse on other study days was not reported.

Lasko et al. 1998 ID 530

Stated Purpose of the Study: This report presents the findings of the first multicenter, randomized, double-blind trial in acute sinusitis evaluating the efficacy of levofloxacin compared with clarithromycin in the management of acute sinusitis.

Population & Setting: 236 patients were randomized into 2 groups.

Levofloxacin	119	Mean age (range)	40.4 (18-83)	Males	44.4%
Clarithromycin	117	Mean age (range)	39.9 (18-78)	Males	41.9%

Inclusion criteria: male and female patients > 18 y/o with clinical symptoms of acute sinusitis and positive x-ray of opacification, air fluid level or mucosal thickening ≥ 5 mm, not pregnant, see paper for details.

Exclusion criteria: symptoms > 4 weeks or hx of > 2 episodes of sinusitis within the previous year, reaction to quinolone or macrolide abx and others (see paper)

Study design: multicenter, randomized, double-blind trial; randomization based on a computer-generated randomization schedule; double-blinding was accomplished by encapsulation of 250 mg tablets of levofloxacin or clarithromycin.

Treatments:

Levofloxacin	2x 250 mg capsules in am and matching placebos in pm for 10-14 days
Clarithromycin	2x 250 mg capsules twice a day for 10-14 days

Outcome: Primary: Clinical success is defined by “cured” or “improved”. The assessment took place 2-5 days after completing therapy.
Secondary: Patients were assessed for relapse or worsening of symptoms and had a repeat sinus x-ray at days 28-32 after completing therapy.

Results: 236 randomized; 191 evaluable for clinical efficacy; 21 (17.6%) unevaluable in Levofloxacin arm, 24 (20.5%) unevaluable in clarithromycin arm; majority of patient were excluded either because the admission x-ray was negative or they were lost to follow-up.

Reported clinical failure rate in evaluable patients:

Levofloxacin	6/98 (6.1%)
Clarithromycin	6/93 (6.5%)

Adverse events:

	Levofloxacin (n=119)	Clarithromycin (n=117)
All Body Systems	27 (22.7%)	46 (39.3%)
GI	20 (16.8%)	39 (33.3%)
CNS (dizziness,headache)	8 (6.7%)	5 (4.3%)
Taste Perversion	1 (0.8%)	9 (7.7%)
Loss of appetite, disorientation and insomnia	5 (4.2%)	4 (3.4%)

See table 6 for rest.
Comparison of laboratory data collected at admission and post therapy demonstrated no significant changes in laboratory values.

Funding: Janssen-Ortho Inc.
Comments:

Lindbæk et al. 1998 ID 586

Stated Purpose of the Study: To compare the efficacy of penicillin V, amoxicillin and placebo given to patients with mucosal thickening on CT without fluid level or total opacification

Population & Setting:
244 patients from 29 family practice centers in Norway. Unknown study years.

Penicillin V group (n=20):	Mean age (range)= 41.2 yrs (unknown range)	Males= 8 (40%)
Amoxicillin group (n=22):	Mean age (range)= 37.1 yrs (unknown range)	Males= 11 (50%)
Placebo (n=21)	Mean age (range)= 32.5 yrs (unknown range)	Males= 6 (29%)

Inclusion Criteria:
Patients with clinical Si/Sx of acute sinusitis (based on scoring system including: hyposmia/anosmia, unilateral facial pain, pain in upper teeth, pain worsening at bending forward, "double sickening," nasal obstruction, rhinorrhea, sinus pain, malaise, fever and purulent secretion) of ≥7 days duration AND paranasal sinus mucosal thickening ≥5mm without air-fluid levels or total opacification on CT scan.

Exclusion Criteria:
Age≤ 15 years; pregnancy; ongoing antibiotic treatment; immunosuppressive treatment, previous sinus/nose surgery; alcohol or drug abuse; rheumatic disease; penicillin allergy; chronic sinusitis; high fever; high degree of pain.

Study Design: Randomized (unknown method of randomization and concealment), double blinded to clinician, patient and radiologist (study drugs were all similar-appearing tablets), multi-center trial. Unknown if prestratified by center.

Treatment:
1) Penicillin V 1320 mg TID for 10 days
2) Amoxicillin 500 mg TID for 10 days
3) Matched Placebo TID for 10 days

Outcome: Subjects kept a diary and after 10 days of treatment answered if they thought they still had sinusitis. If the answer was *no,* the diary was stopped (*day of cure*). The daily diary continued until the answer was *no* until a maximum of 30 days.
(Primary) *Subjective status:* After 10 days of treatment, subjects ranked their own condition as *restored, much better, somewhat better, unimproved* or *worse.*
(Secondary) *Clinical score:* Assessed after 10 days of treatment. Maximum value of 4. Summed from four visual analogue scales based on subjects' ranking their own degree of nasal obstruction, rhinorrhea, sinus pain and malaise.

Results: 244 enrolled and 70 randomized. 20 in penicillin V group, 22 in amoxicillin group and 21 in placebo group were evaluated for clinical efficacy (*intent to treat analysis*). 7 subjects were excluded (unknown from which groups) for reasons including: poor quality CT scans and failure to return a diary.
Clinical Failure: (Primary) 2/20 in penicillin V group, 3/22 in amoxicillin group and 3/21 in placebo group failed (includes *unimproved* and *worse*). **(Secondary)** Mean reduction in clinical score was 1.1 (95%CI 0.8,1.5) in penicillin V group, 1.1 (0.6-1.6) in amoxicillin group, and 1.0 (0.7-1.3) in placebo group.

Adverse Events: not reported
Funding: Norwegian Research Council

Comments: Use of nasal decongestants and paracetamol was allowed but not recorded. Compliance with study medications is unknown. If a patient asked for another antibiotic after 10 days because subjective symptoms persisted, (s)he was given amoxicillin 500 mg TID for 10 days. The median number of days before a patient was no longer feeling ill (Kaplan-Meier plot) was 13.5 days in penicillin V group and 10 days in both the amoxicillin and placebo groups.

Luterman et al. 2003 ID 97041

Stated Purpose of the Study: To compare the efficacy and safety of 5- and 10-day courses of telithromycin with that of a standard 10-day regimen of amoxicillin/clavulanic acid in the treatment of acute maxillary sinusitis (AMS).

Population and Setting: 7/17/98-6/16/99 in 69 centers in US, Canada, S. Africa, Argentina & Chile
Median age (range):
Group 1: 800 mg telithromycin qd for 5 days : 38 y/o (18-69)
Group 2: 800 mg telithromycin for 10 days: 39 y/o (18-84)
Group 3: 500/125 mg amoxicillin/clavulanic tid for 10 days: 38.5 (16-79)

Inclusion criteria: ≥ 18 y/o with presumed acute maxillary sinusitis (purulent nasal discharge, maxillary tenderness…etc.); <28 days Symptoms; sinus x-ray: presence of air-fluid level and/or total sinus opacity and/or ≥6 mm mucosal thickening within 48 hours of enrollment.

Exclusion criteria: History of chronic or recurrent sinusitis, sphenoid or nosocomially acquired sinusitis, suspected nonbacterial infection, obstructive anatomic lesions in nasopharynx, documented resistant organisms, immotile cilia syndrome, CF or odontogenic infection; immune-compromised, hypersensitivity to macrolide or beta-lactam abx; on steroids or any drug that interferes with efficacy and safety assessments of study medication; progressively fatal illness, long Q-T syndrome, severe hypokalemia, hx of drug or ETOH abuse, renal or hepatic impairment, and lactation or pregnancy

Study Design: Randomized (1:1:1) Controlled Trial, double-blind, 3-arm, parallel-group design

Treatments: Group 1: 800 mg telithromycin qd for 5 days
Group 2: 800 mg telithromycin for 10 days
Group 3: 500/125 mg amoxicillin/clavulanic tid for 10 days

Outcome: (Primary) Test of Cure Outcome visit between days 17 and 24. **(Secondary)** Late post-therapy visit between days 31 and 45; cure: no infection, clinical improvement or to preinfection state without need for further abx; normal, improved or not worse sinus x-rays; pts whose signs or symptoms were unchanged or worse and who needed more abx were treatment failures.

Results: 754 enrolled, 753 received at least 1 abx, 146 excluded because x-ray was not consistent,
modified ITT: 607
Clinically evaluable at end of study: 423, Group 1: 146; Group 2: 140; Group 3: 137
184 excluded because of major protocol violation
Clinical Failure:
Group 1: 36/146 (24.7%); Group 2: 38/140 (27.1%); Group 3: 35/137 (25.5%)

Microbiological Failure: 29 patients had sinus punctures. Most common organisms isolated were S. pneumoniae and H. influenzae.

- **Primary:** Group 1: 1/7; Group 2: 1/7; Group 3: 2/10
- **Secondary:** Group1: 2/7; Group 2: 2/7; Group 3: 2/7

Adverse events: 327 patients (44%) experienced one or more treatment-emergent adverse events that were considered to be possibly related to a study med during the study. Diarrhea and nausea were the most common adverse events in each treatment group. 41 patients (5.5%) withdrew because of adverse events (group 1: 16 [6.6%], group 2: 14 [5.5%], group 3: 11 [4.5%]).

7 patients (1%) experienced at least one serious adverse event – 3 in the 10-day telithromycin group (allergy, gastroenteritis, and pseudomembranous colitis [one patient each]) and one in the amox/clav group (pseudomembranous colitis) were considered drug related. No deaths occurred during the study. No patient had QTc interval of 500 msec. or more.

Funding: Aventis Pharmaceutical

Comments: Stability problem with amox/clav; 100 patients from that group were excluded, new population were recruited. Data from the excluded patients were not reported.

Murray et al. 2000 ID 375

Stated Purpose of the Study: To compare the clinical efficacy and tolerability of clarithromycin extended-release(ER) (1000 mg once daily) and clarithromycin immediate-release (IR) (500 mg twice daily) over a 14-day treatment course in patients with acute maxillary sinusitis

Population & Setting: 284 patients from 37 investigative sites throughout the US and Canada between 3/1998 and 10/1998 were studied.

Clarithromycin ER	142	mean age (range)	41.9 (13-78)	males 35%
Clarithromycin IR	141	mean age (range)	41 (15-73)	males 38%

Inclusion criteria: ≥ 12 y/o; presumptive dx of acute maxillary sinusitis supported by confirmatory sinus radiographs obtained within 72 hours before treatment; signs and symptoms for at least 7 days before and not longer than 28 days before the pretreatment visit (see paper for details)

Exclusion criteria: chronic maxillary sinusitis; frontal, ethmoid or sphenoid sinusitis, systemic abx within 3 weeks; significant renal or hepatic impairment; pregnant or likely to become pregnant; see paper for others

Study design: Phase III, randomized, controlled, double-blind, parallel-group, multicenter study. Randomly assigned in a 1:1 ratio at each investigative site.

Treatments:
Clarithromycin extended-release (ER) two 500 mg tablets once daily plus placebo for clarithromycin IR for 14 days
Clarithromycin immediate-release (IR) one 500 mg tablet twice daily plus placebo for clarithromycin ER for 14 days
All patients were dispensed 0.05% oxymetazoline nasal spray to be used as a decongestant twice daily in conjunction with clarithromycin during the 1st 3 days of study drug administration.

Outcome: Test of cure was determined on 10 to 17 days after completion of therapy. Clinical cure was defined by resolution or improvement of symptoms, no worsening of x-ray appearance of sinuses and no further abx needed.

Results: 284 enrolled; 283 received treatment; 38 (20 ER; 18 IR) were deemed non-assessable
Calculated Clinical Failure Rate (100% - reported clinical cure rate):
Clarithromycin extended release 18/122 (14.8%)
Clarithromycin immediate release 26/123 (21.1%)
Clinical response rates were similar in the intent-to-treat analysis per study authors.

Adverse events:
Adverse events were reported by 45/142 (32%) in the clarithromycin ER group and 40/141 (28%) in the IR group. Most commonly reported drug-related adverse events were

	ER	IR
Abnormal taste	10%	10%
Diarrhea	6%	8%
Nausea	5%	9%

No patient in this study experienced a serious adverse event.
Premature discontinuation from treatment due to a drug-related adverse event occurred in 5/142 (4%) of patients in the ER group and 11/141 (8%) in the IR group.

2/142 (1%) in the ER group and 10/141 (7%) in the IR group prematurely discontinued treatment because of a drug-related GI or abnormal taste adverse event.

Funding: Abbott Laboratories
Comments:

Namyslowski et al. 2002 ID 189

Stated Purpose of the Study: To compare the clinical efficacy and safety of oral amox/clav with that of cefuroxime axetil in the treatment of chronic bacterial sinusitis and acute exacerbation of chronic sinusitis in adults

Population & Setting: 231 (outpatients or inpatients) in 4 centers in Poland were enrolled.

	Intent to treat population		
Amox/Clav	115	mean age 37	males 57%
Cefuroxime	116	mean age 41	males 47%

Inclusion criteria: ≥ 18 y/o; hospitalized and non-hospitalized; chronic sinusitis > 3 months; abnormal x-ray; acute exacerbation of chronic sinusitis confirmed by x-ray, symptoms ≤ 4 weeks with a history of at least 2 acute sinusitis requiring abx the previous 12 months; antral sinus puncture within 48 hours prior to starting therapy and evidence of the presence of an infection for which oral antibiotic therapy with either amox/clav or cefuroxime was appropriate (no further explanation given, see paper for details regarding inclusion criteria)

Exclusion criteria: history of hypersensitivity reaction to beta-lactam abx or received abx within 2 weeks prior to enrollment; confirmed or suspected allergic sinusitis; see paper for rest

Study design: prospective, randomized, parallel, open, multicenter

Treatments:

Amox/Clav	875/125 mg oral twice a day for 14 days
Cefuroxime axetil	500 mg oral twice a day for 14 days

Outcome:
Primary: clinical response at the end of therapy (study day 15-18)

Results: 231 in intention-to-treat population; 206 evaluable

Intent to treat population

Reported failure rate:	amox/clav 3/115 (2.6%)	cefuroxime 8/116 (6.9%)
Reported Indeterminate rate:	amox/clav 6/115 (5.2%)	cefuroxime 8/116 (6.9%)
Calculated failure rate (100% - reported clinical cure rate):		
	amox/clav 9/115 (7.8%)	cefuroxime 16/116 (13.8%)

Clinically evaluable population

Reported failure rate:	amox/clav 3/104 (2.9%)	cefuroxime 8/102 (7.8%)
Reported Indeterminate rate:	amox/clav 2/104 (1.9%)	cefuroxime 4/102 (3.9%)
Calculated failure rate (100% - reported clinical cure rate):		
	amox/clav 5/104 (4.8%)	cefuroxime 12/102 (11.8%)

Microbiological failure in evaluable population:
Amox/clav 22/65 (33.8%)
Cefuroxime 20/62 (32.3%)

Adverse events:

	Amox/Clav (n=115)	Cefuroxime (n=116)
Patients with at least 1 adverse event	8 (7%)	11 (9.5%)
Patients with serious adverse event*	1 (0.9%)	3 (2.6%)
Patients with drug related adverse event	5 (4.3%)	5 (4.3%)

Diarrhea	2.6%)	3 (2.6%)
Urticaria	0	2 (1.7%)
Facial edema	0	1 (0.9%)
Discontinuation of med 2° to adverse event	4 (3.5%)	9 (7.8%)

*amox/clav group: 1 experienced an eye disorder the day after starting treatment
cefuroxime group: 1 urticaria related to study drug; 1 underwent maxillary sinus surgery 7 days after starting treatment; 1 experienced a cardiovascular disorder and was hospitalized

Funding:
Comments:

Rakkar et al. 2001 ID 97064

Stated Purpose of the Study: To compare the efficacy and safety of a 10-day oral treatment of moxifloxacin with amoxicillin/clavulanate for the outpatient management of uncomplicated acute sinusitis of suspected bacterial origin

Population & Setting: 475 patients in 85 primary care practice sites in US, study years not specified

Moxifloxacin = 234 (Intent To Treat)	Mean age (range)= 43 (19-78)	males= 31%
Amox/Clav = 237	Mean age (range)= 42 (18-87)	males= 35%

Inclusion criteria: ≥ 18 y/o; outpatient men and non-pregnant women, clinical dx of acute suspected bacterial sinusitis ≥ 7 days but < 30 days duration (nasal congestion, post-nasal drainage, frequent coughing or throat clearing, frontal headache, malar tenderness/pain and purulent nasal discharge)

Exclusion criteria: symptoms > 4 weeks (chronic sinusitis) or frequent recurrent acute sinusitis (> 2 episodes within the past 12 months despite appropriate therapy; history of sinus surgery and others (see paper)

Study design: Prospective, multicenter, non-blinded, two-arm comparative study. Patients were randomly assigned to one of two treatment groups using a block design random code. A pill count was used to assess patient compliance at completion of the study.

Treatments:
Moxifloxacin 400 mg once a day for 10 days
Amox/Clav 875 mg twice a day for 10 days

Outcome:
Primary: Clinical response at the test-of-cure visit (14-21 days post treatment) was the primary efficacy variable.
Secondary: Clinical response at day 26-46 post treatment

Results on Intent to Treat (ITT) population:
475 patients randomized into 2 groups moxifloxacin (238) and amox/clav (237). 4 patients in the moxifloxacin group never received the study medication and were excluded from the ITT population in the study. 85% (199/234) of moxifloxacin and 82% (194/237) of amox/clav reported clinical resolution.

Clinical Failure (ITT): **Primary:** moxifloxacin 35/234 (15%) and amox/clav 43/237 (18.1%)
Secondary (denominator assumed): moxifloxacin 6/234 (2.6%) and amox/clav 4/237 (1.7%)
134 patients were excluded from per protocol (efficacy) analysis (see table 1 in paper).

The per protocol (efficacy) population included 170 moxifloxacin and 171 amox/clav treated patients. 86% of moxifloxain and 84% for amox/clav reported clinical resolution.
Clinical Failure (patients who actually received study medications): **Primary:** Moxifloxacin 24/170 (14%) and Amox/clav 27/171 (16%)
Secondary (denominator assumed): moxifloxacin 6/170 (3.5%) and amox/clav 6/171 (3.5%)

Adverse events: 471 patients were evaluated for safety, treatment emergent adverse events were reported for 136 (58%) moxifloxacin and 124 (52%) amox/clav treated patients. Premature discontinuation due to any adverse event was required in 5% (12) and 3% (8) of patients, respectively. Drug-related adverse events were reported in 30% of moxifloxacin and 25% of amox/clav treated patients and were primarily GI-related: nausea (11% moxifloxacin, 5%

amox/clav) and diarrhea (3% moxifloxacin, 10% amox/clav). An elevation in hepatic enzymes (100% above baseline for ALT/AST) was noted 0-6 days post-treatment in a small number of patients. Specifically, enzyme elevations were observed in 1.7% of moxifloxacin-treated patients (n=4) compared with 4.6% of amox/clav treated patients (n=11).

Funding: Bayer

Comments: Use of oral or nasal decongestants or antihistamines was permitted during the study period, including phenylephrine nose drops as needed. Systemic or topical corticosteroids were not allowed unless the patient had been on long-term therapy before study entry.

Roos et al. 2002 ID 240

Stated Purpose of the Study: To compare the efficacy and tolerability of a 5 and 10 day course of oral treatment with telithromycin 800 mg once daily in patients with community acquired acute maxillary sinusitis

Population & Setting: 343 from 37 centers in 9 countries (Austria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece and Sweden) enrolled. The study was conducted between 4/1998 and 4/1999.

5-day telithromycin	167	median age (range) 34 (18-65)	male 49.7%
10-day telithromycin	168	median age (range) 39 (18-66)	male 48.2%

Inclusion criteria: 18-65 y/o with a dx of acute maxillary sinusitis; x-ray showing total sinus opacity or air-fluid level and at least 1 clinical criterion (see paper for details)

Exclusion criteria: chronic sinusitis (> 1 month); recurrent sinusitis (> 3 episodes that required abx in the previous 12 months); concomitant sphenoidal sinusitis; patients were suspected non-bacterial infections or microbiologically documented infection with pathogens known to be resistant to telithromycin before treatment were also excluded; known long QT syndrome; pregnancy; lactation; other abx 7 days prior to study entry

Study design: randomized, double-blind study; patients were pre-screened by sinus puncture; susceptibility testing was performed using disk diffusion methods at each individual center; disk zone inhibition and MIC testing were also carried out by a central laboratory;
Method of randomization not stated;
Blinding was maintained by matching placebos.

Treatments:
Telithromycin 800 mg once daily for 5 days, matching placebo once daily on study day 6-10
Telithromycin 800 mg once daily for 10 days

Outcome:
Primary – Primary efficacy variable was the rate of clinical cure at the post-therapy/test of cure visit (days 17-21) in the clinical per-protocol population. Clinical cure was defined as the improvement or return to preinfection state, or improvement with persistence of residual symptoms but with no need for subsequent abx, with a sinus x-ray or CT scan that was either normal or improved.
Secondary – Secondary efficacy variables were clinical outcome at the late post-therapy visit (days 31-36) along with bacteriologic outcome at the post-therapy/test of cure and late post-therapy visits.

Results: 343 enrolled, 341 randomized; 336 received at least 1 dose of medication; of the 336, one was excluded because x-ray was not consistent with acute maxillary sinusitis; 335 in the modified intent-to-treat population; 79 excluded for major protocol violations, leaving 256 in the clinical per-protocol population

	Telithromycin 5-day	10-day
Post-therapy, TOC days 17-21		
Calculated Clinical Failure Per-protocol	11/123 (8.9%)	12/133 (9%)
Calculated Failure mod ITT	29/167 (17.4%)	21/168 (12.5%)
Late post-therapy, days 31-36		
Calculated Clinical Failure Per-protocol	12/108 (11.1%)	12/120 (10.8%)

Calculated Failure mod ITT	32/167 (19.2%)	23/168 (13.7%)

Microbiological Failure

	Telithromycin 5-day	10-day
Post-therapy, TOC days 17-21		
Calculated Bacteriological Failure Per-protocol	5/70 (7.1%)	7/69(10.1%)
Calculated Failure mod ITT	17/97 (17.5%)	11/104 (10.6%)
Late post-therapy, days 31-36		
Calculated Bacteriological Failure Per-protocol	6/60 (10%)	8/61 (13.1%)
Calculated Failure modITT	20/97 (20.6%)	13/104 (12.5%)

Adverse events:

166 in 5-day group and 167 in 10-day group were included in the safety analysis.
50/166 (30.1%) in 5-day group and 64/167 (38.3%) in 10-day group experienced at least 1 treatment-emergent adverse event.
6/166 (3.6%) in 5-day group and 1/167(0.6%) in 10-day group discontinued the study because of adverse events. The events in the 5-day group were diarrhea, nausea, vomiting, cholelithiasis, facial edema, infection, and increased alkaline phosphatase levels (1 each). GI pain was the reason for discontinuation of the one patient in the 10-day group.
1 patient in the 5-day group had increased aspartate transaminase that was considered to be clinically noteworthy abnormal laboratory value (CNALV, defined as >3 upper limit of normal)
1 patient in the 10-day group had increased ALT that was considered to be CNALV.
The patients recovered without sequelae.

Adverse event ≥ 2% in either Rx group	5-day (166)	10-day (167)
Diarrhea	16 (9.6%)	22 (13.2%)
Nausea	8 (4.8%)	4 (2.4%)
GI pain	3 (1.8%)	8 (4.8%)
Vaginal Moniliasis	5 (3%)	3 (1.8%)
Increased ALT	4 (2.4%)	1 (0.6%)
Vertigo	1 (0.6%)	4 (2.4%)

Funding:

Comments: Patients with pathogens known to be resistant to telithromycin before treatment were excluded; authors Leroy, Rangaraju and Boutalkb associated with Aventis Pharma

Seggev et al. 1998 ID 563

Stated Purpose of the Study: To compare the safety and efficacy of amox/clav given orally every 12 hours with that given every 8 hours in patients with acute bacterial maxillary sinusitis

Population & Setting: 170 patients from 11 centers in US and Canada participated.

12-hour group	61 (pts completed study)	mean age (range)= 39.3 (23 – 75)	male= 50.8%
8-hour group	73 (pts completed study)	mean age (range)= 40.3 (18 - 81)	male= 39.7%

Inclusion criteria: ≥ 18 y/o; acute bacterial maxillary sinusitis < 4 weeks duration (see paper for clinical criteria) and abnormal x-ray (opacification, air fluid level, or ≥ 5 mm swelling of the mucosa) or abnormal CT scan; baseline serum creatinine < 2.3 mg/dL

Exclusion criteria: hx of hypersensitivity to PCN, cephalosporins, or other beta-lactams; pregnancy or lactation; chronic sinusitis as defined by 2 or more episodes within the previous 12 months or continuing symptoms for longer than 4 weeks; intraorbital or intracranial complications that interfered with the interpretation of a radiograph or CT scan of the affected sinuses; see paper for others

Study design: multi-center, randomized, double-blind, double-dummy (each patient received 1 of the 2 active treatments with a placebo of the alternative treatment, parallel; method of randomization not stated

Treatments:

Amox/Clav 875/125 mg every 12 hours plus an oral placebo every 8 hours for 14 days
Amox/Clav 500/125 mg every 8 hours plus an oral placebo every 12 hours for 14 days

Nasal steroids and decongestants, oral antihistamines and decongestants were allowed at the investigator's discretion.

Outcome:

Primary: Clinical response was assessed 2 to 3 days after completion of treatment. Clinical success was defined as either cure or improvement.
Secondary: Clinical response was assessed 2 – 4 weeks after the end of treatment.

Results:

Reported end of therapy Clinical Failure Rate (100% - reported clinical success rate in evaluable population):
12-hour group = 4/61 (6.6%) 8-hour group = 9/73 (12.3%)
Calculated Intent to treat failure rate (100% - reported ITT clinical success rate):
12-hour group = 15/87 (17.2%) 8-hour group = 12/83 (14.5%)
Reported 2-4 wk follow up Failure Rate (100% - reported persistent cure plus recurrence rate in evaluable population):
12-hour group = 4/61 (6.6%) 8-hour group = 10/73 (13.7%)

Adverse events: 2 patients in the 12-hour group and 2 patients in the 8-hour group reported adverse events (12-hour group, 1 with diarrhea and 1 with coughing; 8-hour group, 1 with coughing and 1 with rash) that led to withdrawal from the study.

	Amox/clav 12-hour n=87	8-hour n=83
possible drug related adverse	9 (10.3%)	17 (20.5%)

genital moniliasis	2 (2.3%)	6 (7.2%)
nausea	1 (1.1%)	3 (3.6%)
diarrhea	2 (2.3%)	1 (1.2%)
abdominal pain	1 (1.1%)	2 (2.4%)
dyspepsia	1 (1.1%)	2 (2.4%)
fungal infection	2 (2.3%)	0
dizziness	0	2 (2.4%)

see table 4 in paper for others.

Funding: SmithKline Beecham

Comments: 16/87 (18.4%) in the 12-hour group and 22/83 (26.5%) in the 8-hour group received concurrent nasal steroids.

Sher 2002 ID 209

REJECTED STUDIES: Adverse events extraction only

Stated Purpose of the Study: Evaluate the efficacy and safety of gatifloxacin 400 mg once daily in adults with acute uncomplicated bacterial sinusitis, community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis. **Note: only the diagnosis of acute uncomplicated rhinosinusitis is included in this study*

Population and Setting: 11,564 adult patients enrolled by 2,795 investigators in the US over an unknown time period.

Diagnoses included in the study:
Acute uncomplicated bacterial rhinosinusitis

Treatment: Gatifloxacin 400 mg QD x 10 days

Study Design: open-label, multicenter, noncomparative study.

Adverse Events Included in Analyses: All patients who received at least one dose of gatifloxacin (N=11,476) were evaluated for safety from the first day of study drug therapy to 7-14 days after the last dose of gatifloxacin by office visit or telephone. Adverse events were monitored until resolution or stabilization. The definition of serious adverse events included cancer, death or persistent or significant disability; were life-threatening; required prolonged hospitalization; resulted in drug dependence, abuse or overdose; jeopardized the patient; or required intervention to prevent a serious outcome.

Adverse Events: 1605/11,476 subjects (14.0%) experience drug-related adverse events.

Most common adverse events deemed drug-related:

Symptom	% (N=11,476)
Nausea	4.4%
Dizziness	1.8%
Diarrhea	1.4%
Headache	1.0%

41/11,476 (0.4%) experienced adverse events related to the cardiovascular system. No patients displayed abnormal electrocardiograms. 14 serious adverse events occurred in 11,476 patients (0.1%) and included: allergic reaction, facial/tongue edema, bacterial infection, migraine, diarrhea, hepatitis, hyperglycemia, hypoglycemia, confusion, asthma, increased cough and convulsion.

Funding: Bristol-Myers Squibb Co.

Comments: Use of intranasal corticosteroids, oral or topical decongestants and antihistamines was permitted.

Sher et al. 2002 ID 257

Stated Purpose of the Study: To compare the clinical efficacy of 5-day course of gatifloxacin, 10-day course of gatifloxacin and 10-day course of amoxicillin/clavulanate in patients with acute, uncomplicated maxillary sinusitis

Population & Setting: 445 patients from 30 study centers were enrolled. Study years not specified.

5-day Gatifloxacin	149	mean age (range) 41.13 (18-74)	males 36%
10-day Gatifloxacin	141	mean age (range) 42.38 (18-72)	males 35%
Amox/Clav	155	mean age (range) 41.88 (18-89)	males 36%

Inclusion criteria: >18 y/o; clinical dx of acute uncomplicated maxillary sinusitis for at least 7 days and radiographic findings, opacification, air/fluid level, or mucosal thickening of ≥ 5 mm in 1 or both maxillary sinuses (see paper for details)

Exclusion criteria: sinusitis > 28 days, complicated sinusitis, anatomic abnormalities, >1 dose of systemic antibiotic within 7 days of enrollment and others (see paper).

Study design: Multicenter, investigator-blinded, randomized. Patients were randomized to treatment by means of a centralized telephone system. A permuted block design was used to minimize imbalance in treatment arms at each site and in the study overall. Patients in each treatment group received blister cards containing the appropriate combination of active drug and matching placebo tablets to provide 10 days of twice-daily therapy.

Treatments:
Gatifloxacin 400 mg once daily for 5 days
Gatifloxacin 400 mg once daily for 10 days
Amox/Clav 875 mg twice daily for 10 days

Outcome: Primary: clinical response was determined by the investigator at each site and was classified as cure, failure, or unable to determine. Clinical cure was defined as improvement in or resolution of all acute signs and symptoms. Test of cure visit took place 7 to 14 days after the completion of study treatment.

Results: 405/445 patients were classified as clinically evaluable. 40 unevaluable patients were distributed evenly between groups (see paper for details)

Calculated Clinical Failure Rate (100% - reported clinical cure rate):

5-day Gatifloxacin	35/137 (25.6%)
10-day Gatifloxacin	26/127 (20.5%)
Amox/Clav	40/141 (28.4%)

Adverse events:

	5-day Gatifloxacin	10-day Gatifloxacin	Amox/Clav
vaginitis	9% of women	9% of women	14% of women
diarrhea	9% of subjects	7% of subjects	14% of subjects
nausea	9%	14%	4% (p=0.007)

Ten patients discontinued therapy due to ≥ 1 drug-related adverse event (2, 5 and 3 patients in 5-day gatifloxacin, 10-day gatifloxacin and amox/clav, respectively).
One patient in the amox/clav group discontinued therapy due to elevated liver enzymes.

Three patients in the 10-day gatifloxacin group had abnormal baseline laboratory values (2 elevated aspartate aminotransferase level; 1 elevated bilirubin level) that had worsened 7 to 23 days after the completion of therapy.

Funding:
Comments: Authors Li & Pierce associated with Bristol-Myers Squibb

Siegert et al. 2000 ID 415

Stated Purpose of the Study: To compare the efficacy and safety of moxifloxacin with that of cefuroxime axetil for the treatment of acute bacterial sinusitis in adults.

Population & Setting:
498 patients in 60 centers in 7 countries: Finland, France, Germany, Greece, Israel, Spain and Sweden
Moxifloxacin group (n=242) mean age= 40.4 y/o 109 males (45%)
Cefuroxime group (n=251) mean age= 40.3 y/o 111 males (44.2%)

Inclusion Criteria: ≥ 18 y/o outpatients; acute bacterial sinusitis; sinusitis diagnosed either bacteriologically or clinically on the basis of sinus x-ray together with 2 or more symptoms: purulent nasal d/c or nasal congestion, post-nasal drainage, frequent coughing or throat clearing, malar tenderness or pain, frontal headache

Exclusion Criteria: hx of hypersensitivity to study or related drug, chronic sinusitis, received systemic abx within 48 hours of enrollment; pregnancy, lactation and others (see original paper)

Study Design: Prospective, randomized, multicenter, double-blind phase III clinical trial; method of randomization not stated

Treatment: Moxifloxacin 400 mg in AM, placebo in PM for 7 days; placebo twice a day on study days 8-10
Cefuroxime Axetil 250 mg twice a day for 10 days

Outcome (Primary): End of treatment examination on study day 14 (4 days after the end of Rx); Clinical response was the primary efficacy evaluation.
Secondary: follow up evaluation 27-31 days after the end of treatment

Results: 498 enrolled; 493 randomized; 436 evaluable
On study day 14:

In ITT population, reported Failure: 11/242 in Moxifloxacin; 22/251 in Cefuroxime
reported Indeterminate: 9/242 in Moxifloxacin; 7/251 in Cefuroxime
reported Missing: 6/242 in Moxifloxacin; 3/251 in Cefuroxime

Calculated Clinical Failure Rate in ITT population (100% - (number of clinical resolution/total ITT population) x100%): 26/242 (10.7%) in Moxifloxain; 32/251 (12.7%) in Cefuroxime
In evaluable population, reported Failure rate: 7/211 (3.3%) in Moxifloxacin; 21/225 (9.3%) in Cefuroxime

At follow up 27-31 days after the end of treatment:
Calculated Cinical Failure Rate in follow up population (100% - (number of clinical success/total follow up population) x100%): 19/204 (9.3%) in Moxifloxacin; 22/204 (10.8%) in Cefuroxime

Reported Microbiological failure rate at end of treatment (day 10): 6/109 (5.5%) in Moxifloxacin group; 19/115 (16.5%) in the Cefuroxime group.

Adverse events:

	Moxifloxacin (n=242)	Cefuroxime (n=252)
Any adverse event	105 (43.4%)	88(35.1%)
Drug-related adverse event	74 (30.6%)	56 (22.3%)
Serious adverse event*	3 (1.2%)	8 (3.2%)
Discontinuation 2° to adverse event	14 (5.8%)	11 (4.4%)
Diarrhea	23 (9.5%)	15 (6%)
Abdominal pain	10 (4.1%)	7 (2.8%)
Nausea	9 (3.7%)	5 (2%)
Vomiting	8 (3.3%)	4 (1.6%)
Vertigo	7 (2.9%)	2 (0.8%)

*details not provided in paper

Funding:
Comments: authors Hampel and Sommerauer associated with Bayer

Siegert et al. 2003 ID 143

Stated Purpose of the Study: To compare the efficacy and safety of 7-day courses of faropenem daloxate (300 mg twice daily) and cefuroxime axetil (250 mg twice daily) in adult patients with acute bacterial sinusitis.

Population & Setting:
10/200-6/2001
561 patients in 43 centers: France, Germany, Greece, Israel, Lithuania, Spain and Sweden
Faropenem group (n=228) mean age= 41.4 y/o 90 males (39.5%)
Cefuroxime group (n=224) mean age= 42.5 y/o 103 males (46%)

Inclusion Criteria: ≥ 18 y/o; acute sinusitis based on at least purulent ant/post nasal d/c or nasal congestion, and at least 2 minor symptoms like frequent throat clearing, facial/malar tenderness or pressure, halitosis, ear discomfort or fever AND x-ray with air-fluid level, opacification or ≥ 6 mm mucosal thickening of at least one sinus

Exclusion Criteria: hx of hypersensitivity to study or related drug, chronic or recurrent sinusitis, received systemic abx > 24 hours within 7 days of enrollment; and others (see original paper)

Study Design: Prospective, multicenter, double-blind comparative study; randomly assigned 1:1 to one of two treatment groups using a block design computer-generated random code

Treatment: Faropenem daloxate 300 mg bid for 7 days
Cefuroxime Axetil 250 mg bid for 7 days

Outcome (Primary): Post-therapy (7 to 16 days after the end of Rx);
Clinical cure: disappearance of signs and symptoms or significant improvement and no further therapy required
Clinical Failure: no change, insufficient improvement or reappearance of Si/Sx's
Bacteriological Response: Cultures were collected pre and post Rx, eradication: causative organism was not present at the post Rx. If no sample was obtained in patient who improved, eradication was presumed

Results: 561 enrolled; 558 randomized;
Drop Outs: 51 in Faropenem group and 55 in Cefuroxime group were excluded (reasons include violation of time schedule for eval and concomitant intake of steroids)
228 in Faropenem and 224 in Cefuroxime were analyzed for clinical efficacy;
Clinical failure: 25/228 in Faropenem; 26/224 in Cefuroxime
Microbiological failure: Out of 136 patients with pathogenic organisms, most common organisms isolated at baseline were S. pneumoniae (64), H. influenzae (41), S. aureus (20) and M. catarrhalis (12).
Failure: 6/71 (8.5%) in the Faropenem group; 6/65 (9.2%) in the Cefuroxime group.

Adverse events: Faropenem, 46/274 (16.8%); cefuroxime, 49/273 (17.9%); most were in digestive and skin and appendages systems.
Drug related event: faropenem 26/274 (9.5%); cefuroxime 28/273 10.3%); 3 patients in cefuroxime group had abnormal liver function tests, 0 in faropenem group; 1 patient in faropenem group experienced a drug-related adverse event of severe intensity, i.e., the coagulation test increased. Treatment was discontinued as a result of an adverse event in 7 patients (2.6%) of the faropenem group and 2 patients (0.7%) who received cefuroxime.

Funding: Bayer

Simon 1999 ID 475

Stated Purpose of the Study: To compare the effectiveness of 10, 15, and 20 days of ceftibuten therapy versus 14 days of erythromycin-sulfisoxazole therapy in treating acute sinusitis in childhood

Population & Setting: 200 patients from a single private practice in US were enrolled in the study. Enrollment period from 4/1996 to 7/1997.

Erythromycin-sulfisoxazole	50	age range = 8 mos to 11 years	males 58%
Ceftibuten 10 days	50	age range = 9 mos to 12 years	males 52%
Ceftibuten 15 days	50	age range = 6 mos to 17 years	males 44%
Ceftibuten 20 days	50	age range = 6 mos to 16 years	males 44%

Inclusion criteria: persistent purulent nasal drainage for at least 10 days plus day and nighttime cough

Exclusion criteria: none stated

Study design: randomized, single-blinded (patient's family), parallel study; method of randomization not stated

Treatments:
Erythromycin-sulfisoxazole (erythromycin component: 40 mg/kg/day) divided into 4 doses for 14 days
Ceftibuten 9mg/kg/day (maximum dose 400 mg/day) for 10 days
Ceftibuten 9mg/kg/day (maximum dose 400 mg/day) for 15 days
Ceftibuten 9mg/kg/day (maximum dose 400 mg/day) for 20 days

Outcome:
Primary: Effectiveness of the therapy was confirmed by the phone interview during the treatment course and confirmed by evaluation for clinical response 1 week after the treatment was completed. Success was determined by resolution of purulent nasal drainage and cough. Failure constituted persistence of the manifestations or more intense symptoms during the treatment. **Secondary:** Children were followed up for recurrence 40-50days after treatment imitation.

Results: Reported failure rate, denominators not stated
Primary:

Erythromycin-sulfisoxazole	4%
Ceftibuten 10 days	8%
Ceftibuten 15 days	8%
Ceftibuten 20 days	0%

Secondary:

Erythromycin-sulfisoxazole	10%
Ceftibuten 10 days	12%
Ceftibuten 15 days	8%
Ceftibuten 20 days	8%

Adverse events: no information

Funding:
Comments: sinus films not obtained; no placebo comparison

Stefansson et al. 1998 ID 97076

Stated Purpose of the Study: Phase IV study to compare the efficacy and safety of cefuroxime axetil and clairthromycin administered twice daily in the treatment of acute sinusitis.

Population & Setting: 370 patients with clinical dx of sinusitis from 22 centers in Czech Republic, Finland, Iceland, Israel, Jordan, Poland, South Africa & Sweden
185 in cefuroxime group mean age = 36.5 yrs males= 46%
185 in clarithromycin group mean age = 37.2 yrs males= 39%

Inclusion criteria: ≥ 18 y/o; clinical dx of sinusitis; initial onset of symptoms within 30 days of study entry; opacification and/or air fluid level in the maxillary sinus; 2 of the following symptoms: rhinorrhea, nasal congestion, facial pain

Exclusion criteria: received systemic abx within previous 7 days; a dx of chronic sinusitis (>30 days' duration) or received abx for recurrent sinusitis during the previous 30 days; received nasal steroid preparations or nasal washout; undergone or required sinus surgery; known hypersensitivity to cephalosporins or macrolides; reduced renal function or marked hepatic impairment; immune deficiency or participated in a clinical trial within 1 month prior to enrollment

Study design: randomized, double-blind, parallel-group, multicenter study; no further details provided

Treatments: Cefuroxime Axetil oral 250 mg twice a day for 10 days
Clarithromycin oral 250 mg twice a day for 10 days
Placebo twice daily (?)

Outcome: **Primary** – Cure defined by improved or resolved clinical signs and symptoms assessed 1-3 days after completion of treatment and absent at follow up 28-35 days post-treatment, confirmed by x-ray. Improvement defined by improvement but incomplete resolution of clinical signs and symptoms, confirmed by x-ray at follow up.
Secondary – follow-up 28-35 days post-treatment

Results: 370 patients were recruited; 185 randomized into each group; 357/370 (96%) had x-ray showing air fluid level and/or opacification. 22 from cefuroxime and 17 from clarithromycin group were discontinued. Principal reasons were failure to return (11 cefuroxime, 8 clairthromycin), lack of efficacy (7 in each group) and adverse events (2 clairthromycin). 24 excluded from clinically-evaluable population as a result of protocol violations

Calculated Clinical failure rate in ITT (100%-reported rate of cured or improved):
9% in cefuroxime group
7% in clarithromycin group

At follow up 28-35 days post treatment, relapse, failure or unevaluable:
32/185 in cefuroxime group
42/185 in clarithromycin group

Adverse events: 17/185 in cefuroxime and 18/185 in clarithromycin reported drug-related adverse event. These were mainly GI (13 cefuroxime and 8 clarithromycin). 3 clarithromycin had infection or inflammation of the reproductive tract. Serious adverse events recorded in clarithromycin group: maxillary antral abscess, convulsions and collapse during local anesthesia.

Funding:

Comments: x-ray results obtained after randomization (even though it is one of the inclusion criteria); overlapping definitions of “Cure” and “Improvement”; unclear why placebo is mentioned in the methods section; 39 patients were discontinued from the study but 354 patients had results reported (39+354=393>370 sample size)???
Authors Sedani & Staley associated with GlaxoWellcome Research & Development, UK.

Sterkers 1997 ID 633

Stated Purpose of the Study: To compare the efficacy and tolerability of 8 days of ceftibuten 400 mg once a day, ceftibuten 200 mg twice a day, and amox/clav 500/125 mg three times a day in the treatment of acute sinusitis in adults

Population & Setting:
458 patients enrolled from 58 centers in France, study years not specified.

Ceftibuten 400 mg once a day	152	mean age 38.4	males 32%
Ceftibuten 200 mg twice a day	157	mean age 41.8	males 41%
Amox/clav 500/125 mg thrice a day	149	mean age 43.1	males 44%

Inclusion criteria: sinusitis with purulent nasal discharge, confirmed by rhinoscopy; presence of fluid or opacification of the maxillary sinus on a plain radiograph

Exclusion criteria: age < 15 y/o; chronic sinusitis; abx treatment within 8 days of enrollment; allergy to beta lactam or lidocaine; renal insufficiency and others (see paper)

Study design: Multi-center, comparative, randomized, open-label, parallel-group design; method of randomization not stated

Treatments:
Ceftibuten 400 mg once a day for 8 days
Ceftibuten 200 mg twice a day for 8 days
Amox/clav 500/125 mg thrice a day for 8 days

Outcome:
Primary – clinical and radiological outcome 2 days after the end of treatment
Secondary – follow up on study day 40

Results:

Reported Clinical failure rate on day 10:	Ceftibuten 400 mg once a day	23/134 (17.2%)
	Ceftibuten 200 mg twice a day	18/138 (13%)
	Amox/clav 500/125 thrice a day	14/128 (10.9%)
Reported Clinical failure rate on day 40:	Ceftibuten 400 mg once a day	25/134 (18.7%)
	Ceftibuten 200 mg twice a day	24/138 (17.4%)
	Amox/clav 500/125 thrice a day	16/128 (12.5%)

Bacteriological Failure according to pathogen (Date of assessment not specified)

	Ceftibuten 400 once a day	200 twice a day	Amox/Clav thrice a day
H. Flu	2/19 (10.5%)	4/33 (12.1%)	2/26 (7.7%)
S. Pneumoniae	6/23 (26.1%)	2/23 (8.7%)	4/25 (16%)
M. Catarrhalis	2/7 (28.6%)	1/5 (20%)	1/10 (10%)

Adverse events:

	Ceftibuten 400 once a day	200 twice a day	Amox/Clav thrice a day
At least 1 adverse event	20/150 (13.3%)	16/154 (10.4%)	16/146(11%)
Drug related adverse event	13/150 (8.7%)	6/154 (3.9%)	7/146 (4.8%)
GI adverse event	17/150 (11.3%)	11/154 (7.1%))	15/146 (10.3%)

# withdrawn 2° adverse	3/150 (2%)	4/154 (2.6%)	5/146 (3.4%)

Funding:
Comments:

Steurer & Schenk 2000 ID 417

Stated Purpose of the Study: To compare the efficacy and safety of cefdinir and amox/clav in patients with acute maxillary sinusitis.

Population & Setting: 569 (Intent-to-treat) patients in 16 medical centers in Europe participated

Cefdinir 600 mg once a day = 182	Median age= 30	Males= 58.8%
Cefdinir 300 mg twice a day = 198	Median age= 32	Males= 58.1%
Amox/Clav 500/125 thrice a day=189	Median age= 29	Males= 60.3%

Inclusion criteria: ≥13 y/o; males and non-lactating females unlikely to be pregnant during Rx; all patients had maxillary sinus aspirations

Exclusion criteria: subacute or chronic maxillary sinusitis (> 3 weeks); frontal and ethmoid sinusitis, diseases that precluded evaluation of response to study medication (i.e., chronic dental disease, foreign bodies, local traumas) and others (see paper)

Study design: Investigator-blinded, randomized, comparative, multicenter phase III study with 3 parallel treatment groups. For each study center an independent randomized schedule was prepared that was consistent with the planned ratio of 1:1:1 for the 3 treatment groups. Patients were given consecutive patient numbers after screening. Medication was dispensed by a third person; the patients were instructed not to reveal the type of medication to the investigator.

Treatments:

Cefdinir 600 mg once a day for 10 days
Cefdinir 300 mg twice a day for 10 days
Amoxicillin 500 mg/Clavulanate 125 mg three time a day for 10 days

Outcome:

Primary: Clinical cure based on professional opinion and microbiological response at test of cure visit on days 7-15 post therapy
Secondary: Long-term follow up on days 21-25 post therapy

Results:

Clinical failure (evaluable patients):	Cefdinir 600 mg once a day	5/93 (5.4%)
	Cefdinir 300 mg twice a day	10/96 (10.4%)
	Amox/Clav thrice a day	4/106 (3.8%)
Microbiological failure (evaluable patients):		
	Cefdinir 600 mg once a day	2/123 (1.6%)
	Cefdinir 300 mg twice a day	13/131 (9.9%)
	Amox/Clav thrice a day	10/138 (7.2%)
Long term follow up microbiological failure (evaluable patients):		
	Cefdinir 600 mg twice a day	3/109 (2.8%)
	Cefdinir 300 mg twice a day	11/103 (10.7%)
	Amox/Clav thrice a day	6/116 (5.2%)

Adverse events:

Cefdinir once a day 75/181 (41%); Cefdinir twice a day 88/197 (45%); Amox/Clav 94/189 (50%) experienced at least one adverse event (see table 7 in paper). The most frequent adverse event is GI related. Diarrhea was the most common reason for discontinuation of treatment.
3 patients of the cefdinir OD group and 12 patients of the cefdinir BD and amox/clav groups discontinued treatment because of an adverse event.

Funding: Parke-Davis
Comments: This data reported previously in Gwaltney 1997 ID 648 article?

Sydnor 1998 ID 590

REJECTED STUDIES: Adverse Events extraction only

Stated Purpose of the Study: Evaluate the efficacy and safety of levofloxacin in treating adult outpatients with acute bacterial sinusitis

Population and Setting: 329 patients at 24 centers in unknown countries over an unknown time period.

Diagnoses included in the study:
Acute, bacterial maxillary sinusitis

Treatment: Levofloxacin 500 mg QD x 10-21 days

Study Design: multicenter, noncomparative prospective study. Tablets were film coated possibly for masking purposes.

Adverse Events Included in Analyses: Safety evaluations were performed from the first dose of the study drug until the first post-therapy visit (2-5 days after completion of therapy or upon early withdrawal for subjects discontinuing the study). Evaluation included assessment of adverse events, results of laboratory tests, physical examination findings and vital sign measurements.

Funding: R W Johnson Pharmaceutical Research Institute

Comments: Use of intranasal or systemic corticosteroids was permitted and use of decongestants was encouraged.

Adverse Events: 29/329 (9%) subjects reported at least one adverse event considered to definitely or probably related to levofloxacin. Most adverse events were mild to moderate in severity.

Most common adverse events:

Symptom	% (N=329)
Diarrhea	2.7%
Flatulence	1.5%
Nausea	1.2%

8 subjects (2.4%) reported serious adverse events were reported, two of which were considered related to levofloxacin administration (genital moniliasis and rash). 6 subjects (1.8%) discontinued the study due to adverse events (including rash, pruritus, edema, diarrhea, nausea and abdominal pain) all of which were considered related to levofloxacin administration. One subject had a myocardial infarction while on levofloxacin, although the episode was not considered related to study drug. There were no significant changes in lab tests, vital signs or physical exam findings.

Varonen et al. 2003 ID 97080

Stated Purpose of Study: Compare the effects of antibiotics to that of placebo in clinically diagnosed acute maxillary sinusitis (AMS) in adults and to study whether sinus ultrasound would help to detect patients who would benefit from antibiotic therapy.

Population & Setting: 150 patients from 9 primary care centers in Finland were randomized. Study took place from 11/1998 to 10/1999. 148 analyzed (2/150 had missing data).
Antibiotic group (n=88) Mean age= 40.6 yrs Males= 24 (27%)
Placebo group (n=60) Mean age= 38.1 yrs Males= 20 (33%)

Inclusion Criteria: >18 y.o.; clinical diagnosis of acute maxillary sinusitis (minimum 3 symptoms and one sign; symptoms: nasal obstruction, discharge, headache, postnasal drip, cough, sinus pain, unilateral facial pain, maxillary toothache, hyposmia, anosmia, malaise and fever; signs: purulent secretion in nasal cavity, discharge in pharynx and tenderness in sinus tapping).

Exclusion Criteria: AMS symptoms > 30 days, abx the previous month, allergy to study meds, pregnancy or breast feeding, exacerbation of chronic sinusitis, previous paranasal sinus or sinus surgery, clinical suspicion of dental or frontal sinusitis or pan-sinusitis or suspicion of a severe complication.

Study Design: a double-blind, randomized (treatments were previously randomized in blocks of 20 consecutive patients at the Military Pharmacy in Helsinki and distributed in identical sealed bottles; the study medications were coded with six-number individual codes and physicians, patients and the main researcher remained blind until the recruitment ended), placebo-controlled multicenter trial.

Treatments: 4 treatment groups, all for 7 days: amoxicillin 750 mg x2, penicillin V 1500 IU x2, doxycline 100 mg x2 or placebo x2. Placebo group was doubled: 2/5 received placebo.

Outcome: **(Primary)** Recovery at the 2- week (after initial consultation) follow up by telephone survey of patients own reported symptoms. (**Secondary)** subjective symptom scores on days 3 and 10 in patient diaries, frequency of side effects, duration of sinusitis, use of additional meds and the frequency of chronic or recurrent sinusitis and number of physician consultations during the 1-year follow up.

Results:

Clinical Failure: 18/88 in antibiotic group; 19/59 in placebo (chi square 3.33, df=1, p=0.068)
Drop outs: Out of 60 in the placebo group, one was excluded for pregnancy, one was not reached by phone.
Other outcome: On day 3, the difference in symptom scores was 2.1 (p=0.048). Patients receiving abx recovered faster than those receiving placebo. By day 10, the difference had disappeared.

Adverse events:
Out of 82 in abx group (stomach pain 18 (22%), diarrhea 6 (7%), fatigue 5 (6%), rash 2 (2%), headache 3 (6%), vaginal discharge 3 (4%))
Out of 48 in placebo group (stomach pain 6 (12%), diarrhea 3 (6%), fatigue 3 (6%), headache 3 (4%).

Funding: Government and industry
Comments: subgroup data for each antibiotic was not reported

Weis et al. 1998 ID 545

Stated Purpose of the study: To compare the efficacy and safety of 10-day oral regimens of ciprofloxacin and cefuroxime axetil in the treatment of clinical acute rhinosinusitis in adult in primary care settings

Population & Setting: 1414 patients were enrolled by 127 physicians in US between 2/17/98 and 5/29/98

Ciprofloxacin	712	mean age	43.5	males	31.5%
Cefuroxime	702	mean age	43.5	males	34.3%

Inclusion criteria: ≥ 18 y/o; < 4 weeks duration of acute rhinosinusitis; at least 2 major or 1 major and 2 minor factors (Major: facial congestion/fullness, nasal drainage/purulence/discoloration, hyposmia/anosmia, facial pain/pressure, fever, nasal obstruction/blockage; Minor: headache, halitosis, fatigue, dental pain, cough, ear pain/pressure/fullness)

Exclusion criteria: hypersensitivity to carboxyquinolones or beta-lactam agents or anaphylaxis to PCN or its derivatives; hx of chronic sinusitis; pregnancy or lactation; baseline serum creatinine > 3 mg/dL; see paper for rest

Study design: open-label, prospective, randomized, nationwide, multicenter, outpatient comparative trial; randomly assigned to one of two treatment groups through the use of a block-design random code computer-generated at Bayer Corporation

Treatments:

Ciprofloxacin	500 mg tablet twice a day for 10 days
Cefuroxime	250 mg tablet twice a day for 10 days

Outcome: Primary efficacy: clinical response 4-16 days post therapy

Results: 1414 randomized; 1223 were efficacy valid; 1219 clinically evaluable

Clinical Failure rate (100% - reported clinical resolution rate):

Ciprofloxacin	54/613 (8.8%)
Cefuroxime	60/606 (9.9%)

Adverse events:

	Ciprofloxacin (n=711)	Cefuroxime (n=700)
Drug-related adverse event:	80 (11.3)	81 (11.6)
Nausea	18 (2.5%)	12 (1.7%)
Diarrhea	7 (1.0%)	14 (2.0%)
Headache	4 (0.6%)	7 (1.0%)
Vaginitis	4 (0.6%)	7 (1.0%)
Discontinuation 2° to adverse events	27/712 (3.8%)	26/702 (3.7%)

Funding: Bayer

Comments:

APPENDIX D. Peer Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with constructive feedback. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

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