

A Combination of Amoxicillin and Clavulanate Every 12 Hours vs Every 8 Hours for Treatment of Acute Bacterial Maxillary Sinusitis

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Objective: To compare the safety and efficacy of a combination of amoxicillin and clavulanate potassium given orally every 12 hours (amoxicillin, 875 mg; clavulanate, 125 mg) with that given every 8 hours (amoxicillin, 500 mg; clavulanate, 125 mg) for the treatment of patients with acute bacterial maxillary sinusitis.

Design: Multicenter double-blind randomized double-dummy controlled trial.

Setting: Physicians' offices and ambulatory care clinics.

Patients: One hundred seventy patients at least 18 years of age with acute bacterial maxillary sinusitis who could be treated with an oral antimicrobial agent were randomized, and data from 134 were suitable for evaluation. Four patients were withdrawn from this study because of adverse effects.

Interventions: Patients received a combination of amoxicillin and clavulanate orally every 12 hours (amoxi-

illin, 875 mg; clavulanate, 125 mg) or every 8 hours (amoxicillin, 500 mg; clavulanate, 125 mg) for 14 days.

Main Outcome Measure: Clinical success at the end of therapy.

Results: Clinical success at the end of therapy was similar for the 2 treatment groups, 93% and 88% of patients in the every 12-hour and every 8-hour groups, respectively ($P = .76$; 95% confidence interval, -4.0% to 15.6%). Clinical success rates at follow-up 2 to 4 weeks after the end of therapy were also similar in the 2 groups. Adverse events related to treatment were reported with similar frequency in the 2 groups.

Conclusion: Amoxicillin and clavulanate given every 12 hours is as effective and as safe as administration every 8 hours for the treatment of acute bacterial maxillary sinusitis.

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ACUTE BACTERIAL sinusitis is among the most common infections treated in the community. According to the National Ambulatory Medical Care Survey,^{1,2} there were more than 4 million patient visits for "sinus problems" and an estimated 2 million visits for presumed acute bacterial sinusitis in 1991. Proper treatment of acute bacterial sinusitis is necessary to reduce symptoms and prevent complications, such as intracranial and orbital infections or exacerbations of asthma or bronchitis.³

The most common bacterial pathogens of community-acquired acute sinusitis continue to be *Streptococcus pneumoniae* and *Haemophilus influenzae*, accounting for more than 50% of isolates.^{2,4} There is an increased frequency of β -lactamase production by *H influenzae* and *Moraxella (Branhamella) catarrhalis*, penicillin resistance of *Staphylococcus aureus*, and multiple-drug resistance of *S pneumoniae*. The problem of

antimicrobial resistance is complicated by bacterial pathogens not being identified in many patients treated for acute bacterial sinusitis. The frequency with which drug-resistant bacteria are isolated and the limited patient-specific identification and susceptibility information available have led to the use of antimicrobial regimens that are effective against a relatively resistant and broad spectrum of pathogens.^{4,5} Consideration must be given to the use of antimicrobial agents that are β -lactamase resistant.

Amoxicillin-clavulanate is a combination product containing the semisynthetic penicillin, amoxicillin, and the β -lactamase inhibitor, clavulanate potassium. The established oral dose regimen for acute bacterial sinusitis in adults is an equivalent of 500 mg of amoxicillin and 125 mg of clavulanate given every 8 hours.⁶ Since patient compliance is a major factor that determines outcome for outpatient treatment of many infections, it is necessary to

PATIENTS AND METHODS

STUDY DESIGN

This was a multicenter study with 11 participating centers in the United States and Canada. Treatment was randomized and administered in a double-blind, double-dummy manner (each patient received 1 of the 2 active treatments with a placebo of the alternative treatment) to 2 parallel treatment groups.

PATIENTS

Patients were 18 years of age or older and presented with acute bacterial maxillary sinusitis that could be treated with an oral antimicrobial agent. To be included in the assessment of clinical response, patients with acute bacterial maxillary sinusitis were required to have an infection of less than 4 weeks' duration as defined by at least 2 major (postnasal discharge, rhinorrhea, cough) or 1 major and 2 minor (headache, facial pain, tooth pain, earache, sore throat, halitosis, increased wheeze, fever) criteria and abnormal findings on review of their radiographs (opacification, an air fluid level, or ≥ 5.0 -mm swelling of the mucosa with Waters view) or coronal computed tomographic (CT) scans of affected sinuses.

To remain in the study, patients were required to have a baseline serum creatinine level of less than 200 $\mu\text{mol/L}$ (2.3 mg/dL). If the baseline sinus radiograph or coronal CT scan showed no abnormalities or was reported as unreadable or missing after therapy was initiated, the patient's data were considered unsuitable for evaluation for efficacy, but were considered suitable for safety evaluation.

Patients were excluded for any of the following reasons: (1) a previous hypersensitivity reaction to penicillin, cephalosporins, or other β -lactam antibiotics, (2) more than 24 hours of antibiotic treatment immediately before study entry, (3) treatment with any investigational agent in the prior month or during the study, (4) presence of a serious underlying disease

that was likely to preclude evaluation of study medication response, (5) presence of a concomitant infection that precluded evaluation of response, or (6) pregnancy or lactation. Patients were also excluded if they had (1) evidence of chronic sinusitis as defined by 2 or more episodes of acute sinusitis within the preceding 12 months or continuing symptoms for longer than 4 weeks, (2) intraorbital or intracranial complications that interfered with the interpretation of a radiograph or CT scan of the affected sinuses, or (3) been previously enrolled in this study.

ANTIMICROBIAL TREATMENT

Patients were randomly assigned to receive either oral amoxicillin-clavulanate every 12 hours (amoxicillin, 875 mg; clavulanate, 125 mg; equivalent to 1750 mg of amoxicillin daily) plus an oral placebo every 8 hours or oral amoxicillin-clavulanate every 8 hours (amoxicillin, 500 mg; clavulanate, 125 mg; equivalent to 1500 mg of amoxicillin daily) plus an oral placebo every 12 hours. The placebo was identical in appearance to the active treatment. Each regimen was administered for 14 days. Additional antimicrobial agents or probenecid were not permitted. Nasal corticosteroids and decongestants, as well as oral antihistamines and decongestants, were allowed at the investigator's discretion.

At the end of treatment, compliance was assessed using data from tablet counts done at each visit. Patients had to receive a minimum of 80% and a maximum of 120% of the prescribed medication doses.

EVALUATIONS

The patients' regimens were evaluated for clinical efficacy 5 to 7 days after the start of treatment by telephone interview and during a clinic visit 2 to 3 days after completion of therapy. Patients returned for clinical evaluation 2 to 4 weeks after the end of treatment. A sinus radiograph or a coronal CT scan was performed on all patients who received more than 3 days of therapy.

determine the most convenient dose regimen that is effective. The objective of this study was to compare the safety and efficacy of amoxicillin-clavulanate given every 12 hours (amoxicillin, 875 mg; clavulanate, 125 mg) with that given every 8 hours (amoxicillin, 500 mg; clavulanate, 125 mg) for the treatment of patients with acute bacterial maxillary sinusitis.

RESULTS

PATIENTS

One hundred seventy patients received study medication, 87 for amoxicillin-clavulanate every 12 hours (12-hour group) and 83 for every 8 hours (8-hour group). A total of 134 patients (78.8%) were evaluated at the end of therapy and completed the study according to protocol. Patient characteristics are given in **Table 1**. No significant differences were detected ($P > .05$) with respect to any of the baseline characteristics. Compliance with the antibiotic regimen ($\geq 80\%$ and $\leq 120\%$ of doses taken) was similar for the 12-hour and 8-hour groups (92% [80/87] and 96% [80/83],

respectively). Eighteen percent of the patients (16/87) in the 12-hour group and 27% (22/83) in the 8-hour group received concurrent nasal steroids.

CLINICAL RESPONSE

Clinical response at the end of therapy was similar for the 2 treatment groups with success rates of 93% (57/61) and 88% (64/73) in the 12-hour and 8-hour groups, respectively ($P = .76$; 95% CI, -4.0% to 15.6%) (**Table 2**). Clinical success was maintained at the time of follow-up visit in 82% (50/61) and 81% (59/73) of patients who were judged to be clinical successes at the end of treatment ($P = .81$; 95% CI, -15.5% to 11.0%) for the 12-hour and 8-hour groups, respectively. Recurrence of infection was observed in 7 patients (11.5%) and 4 patients (5.5%) in the 12-hour and 8-hour groups, respectively.

BACTERIOLOGIC RESPONSE

One hundred thirty-eight organisms were isolated from pre-therapy cultures in 86 patients. Organisms isolated from

Clinical response (cure, improvement, failure, or unable to evaluate) was determined 2 to 3 days after completion of treatment. Cure was defined as complete resolution of signs and symptoms of infection such that no additional antimicrobial therapy was required. Improvement was defined as incomplete resolution of the signs and symptoms of infection with no additional antimicrobial therapy required. Failure was defined as inability to improve the signs and symptoms of infection after 3 or more days of therapy such that additional antimicrobial therapy was required. Unable to evaluate was assigned when a valid assessment of clinical outcome could not be made (such as when a patient received concomitant antibiotics for an intercurrent illness). Cure or improvement was judged to be clinical success. Clinical response was again assessed 2 to 4 weeks after therapy and determined to be either persistent cure, failure, or recurrence. Persistent cure was defined as complete resolution of signs and symptoms of infection for patients who were cured or improved at the end of therapy such that no additional antibiotic therapy was administered. Failure was defined as lack of resolution of signs and symptoms of infection for patients neither cured nor improved at the end of therapy such that additional antibiotic therapy was required. Recurrence was defined as reappearance of signs and symptoms of infection for those patients who were cured or improved at the end of therapy such that additional antibiotic therapy was required.

Antral sinus puncture of the affected sinuses was performed within 48 hours immediately before initiation of treatment in the 26 consenting patients to obtain a sample for culture. The sinus exudate or pus sample was immediately inoculated onto 5% sheep blood and chocolate agar plates in 5% to 10% CO₂ atmosphere for 18 to 48 hours. All potential pathogens were tested for susceptibility to ampicillin and amoxicillin-clavulanic acid by a central laboratory (SmithKline Beecham Clinical Laboratory, Van Nuys, Calif) in accordance with standards approved by the National Committee for Clinical Laboratory Standards. Disk diffusion was performed for aerobic organisms; and agar dilution, for anaerobic organisms. Initially, patients were

allowed to undergo direct, rigid rhinoscopy with aspiration of pus directly from the orifice of the maxillary sinus. That procedure was discontinued when it was realized that normal nasal flora were cultured from many patients.

Safety was determined for all randomized patients by interview at each visit. Clinical chemical and hematologic screening tests were performed at the start of treatment and, if clinically indicated, at the end of treatment and 2 to 4 weeks after completion of treatment. Also, patients completed a diary describing changes in bowel habits.

DATA ANALYSIS

The primary efficacy end point was clinical response at the end-of-therapy visit. Outcome data were assessed on an "intention-to-treat" basis and for those patients who adhered to the protocol.

The study was designed to enroll at least 100 evaluable patients per treatment (200 patients total) to determine with 80% power ($\beta = .20$) that the lower confidence limit of the 2-sided 95% confidence interval (CI) ($\alpha = .05$) of the difference in the success rates between the 2 treatment groups was not greater than 15%, assuming that the clinical response rate in the 2 groups was 80% to 85%. Therefore, the study was designed to detect a 15% or greater difference in success rates.

Treatment groups were compared with respect to baseline characteristics before making efficacy comparisons. Continuous data (age and duration of therapy) were analyzed by Student *t* test, while categorical data were analyzed with the χ^2 test. The difference in the success rates between treatment groups was assessed by analyzing a linear model with effects caused by center and treatment (Statistical Analysis System, version 6.07, SAS Institute, Cary, NC). The equivalence of the 2 treatment groups was also assessed by determining the 2-tailed 95% CIs of the difference in the proportions of patients with clinical success. The treatment groups were considered equally effective if the lower 95% confidence limit was not below -15%.

patients in each study group are shown in **Table 3**. Specimens were collected by rigid rhinoscopy in 60 patients (70%) and by antral sinus puncture in 26 (30%). When only specimens collected by antral puncture were considered, the most commonly isolated organisms were *S pneumoniae* (8 isolates), viridans streptococci (7 isolates), coagulase-negative staphylococci (6 isolates), and *Propionibacterium acnes* (6 isolates). Since too few pathogens were isolated by antral puncture, the planned analysis of bacteriologic efficacy is not presented.

INTENTION-TO-TREAT ANALYSIS

The 2 regimens were similar when assessed by intention-to-treat analysis of all 170 patients who received study medication. Clinical success at the end of therapy was achieved in 72 (83%) of 87 patients who received the every 12-hour regimen and in 71 (86%) of 83 who received the every 8-hour regimen ($P = .24$; 95% CI, -13.7 to 8.2). Failures occurred in 7% (4/61) of the 12-hour group and 14% (10/73) of the 8-hour group (the remainder, 10% [9/87] and 2% [2/83], respectively, were indeterminate).

ADVERSE EVENTS

Twenty-seven (15.9%) of 170 patients reported 29 adverse events related or possibly related to the study medication. Adverse events related or possibly related to the study regimens were observed in 10% (9/87) and 20% (17/83) of patients in the 12-hour and the 8-hour groups, respectively ($P = .13$). The most common adverse event was genital moniliasis (4.7% [8/170] of patients) (**Table 4**) which was reported in 2.3% (2/87) and 7.2% (6/83) of patients in the 12-hour and 8-hour groups, respectively ($P = .05$). Nausea was reported in 1.1% (1/87) and 3.6% (3/83) of patients and diarrhea in 2.3% (2/87) and 1.2% (1/83) of patients in the 12-hour and 8-hour groups, respectively. Four patients reported adverse events that led to withdrawal from the study (1 patient with diarrhea and 1 with coughing in the 12-hour group and 1 patient with coughing and 1 with rash in the 8-hour group). The only adverse event requiring withdrawal that was judged to be severe was diarrhea.

From patient bowel habit diaries, diarrhea (defined as ≥ 3 watery stools in 1 day) was judged to have occurred in 14 patients (8 patients in the 12-hour group and 6 in the 8-

hour group). The mean pretherapy frequency of bowel movements was 1.2 (median, 1) per day in each group. This increased to 1.4 per day (median, 1) and 1.6 per day (median, 1) during therapy for the 12-hour and 8-hour groups, respectively. Mean pretherapy stool consistency (rated as 1,

hard; 2, well formed; 3, semiformal; 4, loose; and 5, watery) was 2.1 (median, 2) and 2.4 (median, 2) for the 12- and 8-hour groups, respectively. Mean stool consistency during therapy increased to 2.7 (median, 3) and 2.6 (median, 3) for the 12-hour and the 8-hour groups, respectively.

Table 1. Patient Characteristics

	Amoxicillin-Clavulanate Treatment*		P†
	12-Hour Group	8-Hour Group	
Patients randomized, No.	87	83	...
Patients withdrawn, No.			
Protocol deviations or violations	15	5	...
Adverse experience	2	2	...
Lack of efficacy	2	1	...
Unavailable for follow-up	6	2	...
Reason not given	1	0	...
Patients completing therapy, No.	61	73	...
Age, y			
Mean (± SD)	39.3 (± 11.0)	40.3 (± 13.3)	.64
Range	23.0-75.0	18.0-81.0	
Sex, No.			
Men	31	29	.23
Women	30	44	
Race, No.			
White	57	62	.17
Black	1	6	
Oriental	0	1	
Other	3	4	
Duration of therapy, d			
Mean (± SD)	14.4 (± 1.9)	14.6 (± 1.5)	.47
Range	2.0-17.0	3.0-15.0	

*The 12-hour group received 875 mg of amoxicillin and 125 mg of clavulanate sodium every 12 hours; the 8-hour group, 500 mg of amoxicillin and 125 mg of clavulanate sodium every 8 hours.

†Ellipses indicate data not calculated.

COMMENT

Patient compliance is encouraged when a regimen is simplified to less-frequent daily dosing, and this directly influences outcome from an antimicrobial regimen. Amoxicillin-clavulanate has traditionally been administered in a regimen of 500 mg of amoxicillin with 125 mg of clavulanate every 8 hours for adults. This regimen is as effective for treatment of acute bacterial sinusitis as other agents, such as loracarbef,^{7,8} cefuroxime axetil,⁹ cefitibuten dihydrate,¹⁰ and clarithromycin.¹¹ Amoxicillin-clavulanate has been recommended as one of the first-line antibiotics for

Table 2. Summary of Clinical Response for Evaluable Patients

Clinical Outcome	Patients Completing Amoxicillin-Clavulanate Treatment, No. (%)*	
	12-Hour Group (n = 61)	8-Hour Group (n = 73)
At end of therapy		
Cure	41 (67.2)	43 (58.9)
Improvement	16 (26.2)	21 (28.8)
Overall clinical success†	57 (93.4)	64 (87.7)
Failure	4 (6.6)	9 (12.3)
At follow-up		
Persistent cure	50 (82.0)	59 (80.8)
Recurrence	7 (11.5)	4 (5.5)
Failure	4 (6.6)	10 (13.7)

*See the first footnote to Table 1 for an explanation of the treatment groups.

†Overall clinical success is cure plus improvement.

Table 3. Bacteria Isolated by Rigid Rhinoscopy or Antral Sinus Puncture at Baseline From Patients Who Completed Therapy

Bacteria	12-Hour Group*		8-Hour Group*	
	Rigid Endoscopy	Sinus Puncture	Rigid Endoscopy	Sinus Puncture
Patients with pretherapy cultures, No.	35	15	25	11
Total No. of isolates	56	13	82	28
Coagulase-negative staphylococci	15 (27)	3 (23)	13 (16)	3 (11)
<i>Staphylococcus aureus</i>	7 (13)	0	15 (18)	2 (7)
<i>Streptococcus pneumoniae</i>	6 (11)	4 (31)	5 (6)	4 (14)
Viridans streptococci	3 (5)	1 (8)	7 (9)	6 (21)
<i>Propionibacterium acnes</i>	4 (7)	2 (15)	6 (7)	4 (14)
<i>Corynebacterium</i> species	4 (7)	0	3 (4)	1 (4)
<i>Bacillus</i> species	1 (2)	0	4 (5)	0
<i>Moraxella (Branhamella) catarrhalis</i>	1 (2)	0	2 (2)	0
<i>Haemophilus influenzae</i>	2 (4)	0	1 (1)	0
<i>Neisseria</i> species	3 (5)	1 (8)	0	0
Other gram-negative bacilli†	10 (18)	2 (15)	20 (24)	4 (14)
Other streptococci	0	0	1 (1)	1 (4)
Miscellaneous anaerobes	0	0	5 (6)	3 (11)

*See the first footnote to Table 1 for an explanation of the treatment groups. Data are given as number and number (percentage).

†Includes isolates of *Acinetobacter lwoffii*, *Citrobacter diversus*, *Enterobacter taylorae*, *Enterobacter aerogenes*, *Enterobacter agglomerans*, *Enterobacter cloacae*, *Escherichia coli*, *Flavobacterium odoratum*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Pseudomonas stutzeri*, *Pseudomonas acidovorans*, *Serratia marcescens*, and *Xanthomonas maltophilia*.

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Table 4. Adverse Events Related or Possibly Related to the Study Medication

Event	Patients Receiving Amoxicillin-Clavulanate Treatment, No. (%) [*]		
	12-Hour Group (n = 87)	8-Hour Group (n = 83)	Total (N = 170)
Genital moniliasis	2 (2.3)	6 (7.2)	8 (4.7)
Nausea	1 (1.1)	3 (3.6)	4 (2.3)
Diarrhea	2 (2.3)	1 (1.2)	3 (1.8)
Abdominal pain	1 (1.1)	2 (2.4)	3 (1.8)
Dyspepsia	1 (1.1)	2 (2.4)	3 (1.8)
Fungal infection	2 (2.3)	0	2 (1.2)
Dizziness	0	2 (2.4)	2 (1.2)
Vomiting	0	1 (1.2)	1 (0.6)
Headache	0	1 (1.2)	1 (0.6)
Rash	0	1 (1.2)	1 (0.6)
Hemorrhoid flare	1 (1.1)	0	1 (0.6)
Vaginitis	0	1 (1.2)	1 (0.6)
Flatulence	0	1 (1.2)	1 (0.6)

^{*} See the first footnote to Table 1 for an explanation of the treatment groups.

treatment of acute bacterial sinusitis (along with a combination of trimethoprim and sulfamethoxazole, loracarbef, and cefuroxime axetil).⁵

The equivalence of the 12-hour and 8-hour dosing regimens is supported by pharmacokinetic and pharmacodynamic data. Antibacterial efficacy of β -lactam antimicrobial regimens is related to the duration of time the plasma concentration of the antimicrobial remains greater than the minimal inhibitory concentration.^{12,13} A study in healthy volunteers demonstrated that amoxicillin-clavulanate (amoxicillin, 875 mg; clavulanate, 125 mg) given every 12 hours resulted in a minimal inhibitory concentration comparable to 500 mg of amoxicillin and 125 mg of clavulanate given every 8 hours (M. R. Hust, MD, written communication, April 1994). Equivalent minimal inhibitory concentration suggests that 2 regimens would result in a similar clinical outcome.

This trial documents the effectiveness of an every 12-hour regimen of amoxicillin-clavulanate in direct comparison with the traditional every 8-hour regimen in patients with acute bacterial maxillary sinusitis. Both regimens were well tolerated, with low frequencies of gastrointestinal tract complaints.

When only specimens collected by antral puncture were included, *S pneumoniae* was the most commonly isolated organism. The species of bacteria obtained by rigid rhinoscopy differ significantly from those reported by other studies.^{2-5,7-11} The large numbers of *S aureus* and coagulase-negative staphylococci probably represent contamination by skin-colonizing bacteria. Rigid rhinoscopy is clearly an inadequate method for obtaining uncontaminated sinus cultures.

A major difficulty in treating acute bacterial sinusitis is that pathogens are not identified in as many as 60% of patients,⁴ and therapy must be initiated before organism identification even when sinus puncture is performed. Antimicrobial agents effective against potentially resistant pathogens must therefore be used for empiric treatment. The most common pathogens identified in studies^{4,8-10,14} of patients with acute bacterial sinusitis were *S pneumoniae* and *H influenzae*, with *S aureus*, gram-negative bacilli, and anaerobes identified with varying frequency. β -Lactamase-producing bacteria (such as *H influenzae*) are resistant to penicillins alone and susceptible to the amoxicillin-clavulanate combination.

In conclusion, amoxicillin-clavulanate (amoxicillin, 875 mg; clavulanate, 125 mg) given every 12 hours is as effective and as safe as every 8-hour administration (amoxicillin, 500 mg; clavulanate, 125 mg) for the treatment of acute bacterial maxillary sinusitis. Reduced frequency of administration with the every 12-hour regimen should improve patient compliance with treatment.

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REFERENCES

- Schappert SM. National Ambulatory Medical Care Survey: 1991 summary. *Vital Health Stat* 13. 1994;1-79.
- Gwaltney JM. Acute community-acquired sinusitis. *Clin Infect Dis*. 1996;23:1209-1223.
- Friedman RA, Harris JP. Sinusitis. *Ann Rev Med*. 1991;42:471-489.
- Gwaltney JM, Scheld WM, Sande MA, Syndor A. The microbiologic etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. *J Allergy Clin Immunol*. 1992;90:457-462.
- Gwaltney JM, Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. *Ann Otol Rhinol Laryngol Suppl*. 1995;167:22-30.
- Augmentin [prescribing information]. Philadelphia, Pa: SmithKline Beecham Pharmaceuticals; 1996.
- Syndor TA, Scheld WM, Gwaltney JM, et al. Loracarbef (LY163892) vs amoxicillin/clavulanate in bacterial maxillary sinusitis. *Ear Nose Throat J*. 1992;71:225-232.
- Nielsen RW. Acute bacterial maxillary sinusitis: results of US and European comparative therapy trials. *Am J Med*. 1992;92(suppl 6A):70S-73S.
- Camacho AE, Cobo R, Otte J, et al. Clinical comparison of cefuroxime axetil and amoxicillin/clavulanate in the treatment of patients with acute bacterial maxillary sinusitis. *Am J Med*. 1992;93:271-276.
- DeAbate CA, Perrotta RJ, Dennington ML, Ziering RM. The efficacy and safety of once-daily cefibuten compared with co-amoxiclav in the treatment of acute bacterial sinusitis. *J Chemother*. 1992;4:358-363.
- Dubois J, Saint-Pierre C, Tremblay C. Efficacy of clarithromycin vs amoxicillin/clavulanate in the treatment of acute maxillary sinusitis. *Ear Nose Throat J*. 1993;72:804-810.
- Drusano GL. Role of pharmacokinetics on the outcome of infections. *Antimicrob Agents Chemother*. 1988;32:289-297.
- Vogelman B, Gudmundsson S, Leggett J, et al. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. *J Infect Dis*. 1988;158:831-847.
- Jousimies-Somer HR, Savolainen S, Ylikoski JS. Bacteriological findings in acute maxillary sinusitis in young adults. *J Clin Microbiol*. 1988;26:1919-1925.