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Oral β-lactams in the treatment of acute bacterial rhinosinusitis

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Abstract

Acute bacterial rhinosinusitis (ABRS) is a well-known complication of viral upper respiratory tract infection and is associated with a significant socioeconomic burden. Difficulties in diagnosis, a substantial spontaneous resolution rate, and growing concerns regarding antimicrobial resistance make the proper management of ABRS quite challenging. Treatment guidelines have been developed, taking into account the major bacterial pathogens, rates of antimicrobial resistance, spontaneous resolution rates, and pharmacokinetic and pharmacodynamic considerations. Optimal choices for initial treatment of ABRS in patients without prior antibacterial exposure include the oral β-lactam agents amoxicillin/clavulanate, cefdinir, cefpodoxime, and cefuroxime. Clinicians are encouraged to consider the local pathogen distribution and rates of antibacterial resistance in selecting therapy for ABRS.

Keywords: Rhinosinusitis; β-Lactams

1. Introduction

Acute bacterial rhinosinusitis (ABRS) is among the most prevalent infectious diseases of adults and children for which antibacterial therapy is prescribed (Anon, 2005; Gwaltney et al., 2004; Sande and Gwaltney, 2004; Sinus and Allergy Health Partnership, 2004). As a complication of the common cold (0.5–10%), it is estimated that approximately 20 to 30 million cases of ABRS occur annually in the United States alone (Gwaltney et al., 2004), with expenses in excess of $3 billion each year for diagnosis and treatment (Ray et al., 1999; Sinus and Allergy Health Partnership, 2004). The management of ABRS is complicated by difficulties in differentiating viral from bacterial causes of rhinosinusitis, a high rate of spontaneous resolution, and an ever increasing rate of antimicrobial resistance among the major bacterial pathogens (Anon, 2005; Gwaltney et al., 2004; Sande and Gwaltney, 2004; Sinus and Allergy Health Partnership, 2004). Although complications of ABRS are rare (Gwaltney et al., 2004; Marple et al., 2006), they may be quite serious and include meningitis, brain abscess, orbital cellulitis, and abscesses (Clayman et al., 1991; Hytonen et al., 2000). It is clear that antibacterial therapy may shorten the course of ABRS (Ip et al., 2005; Marple et al., 2006); however, given the high rate of spontaneous resolution (~60%) and a growing concern regarding the overuse of antibacterial agents and the concomitant development of resistance among both commensal and pathogenic bacteria (Anon, 2005; Felmingham et al., 2005; Granizo et al., 2000; Johnson et al., 2006; Karchmer, 2004; Wu et al., 2004), a policy of "watchful waiting" has been encouraged (Marple et al., 2006; Sinus and Allergy Health Partnership, 2004).

In this summary, we provide an overview of the diagnosis, the microbiology and antimicrobial resistance issues, the clinical evidence supporting the efficacy of antibacterial therapy with an emphasis on the indicated oral β-lactam agents, and the importance of pathogen distribution, rates of resistance, and spontaneous resolution and pharmacokinetic (PK)/pharmacodynamic (PD) considerations in formulating treatment recommendations for this common infectious disease.

1.1. Diagnosis

Although various treatment guidelines and position articles stress the importance of distinguishing between viral and bacterial rhinosinusitis (Gwaltney et al., 2004; Marple et al., 2006; Sande and Gwaltney, 2004; Sinus and

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Table 1
Microbiology of ABRS: occurrence and rate of spontaneous resolution

Pathogen	% Occurrence		% Spontaneous resolution
	Adults	Children	
S. pneumoniae	20–43	25–30	30
H. influenzae	22–35	15–20	60
M. catarrhalis	2–10	15–20	80
Anaerobes	0–9	2–5	50
Streptococcus spp.	3–9		50
S. pyogenes		2–5	50
S. aureus	0–8		50
Other	4		50
Sterile		20–35	NA

Data compiled from Sinus and Allergy Health Partnership (2004). NA = data not available.

Allergy Health Partnership, 2004), in clinical practice, it is frequently difficult to differentiate between the 2 causalities due to similarities in clinical presentation (Gwaltney et al., 2004; Marple et al., 2006). Furthermore, the common imaging modalities are both insensitive and nonspecific in their abilities to differentiate a viral versus bacterial process (Sande and Gwaltney, 2004). As a result, uncomplicated rhinosinusitis is often overtreated by the administration of antibacterial agents (85–98% of patients presenting with headache, facial pain, nasal congestion, and rhinorrhea) for a process that is largely self-limited (Dosh et al., 2000; Gonzales et al., 1999).

The "gold standard" for establishing the diagnosis of ABRS and obtaining evidence for bacteriologic cure is maxillary sinus puncture and culture of the sinus aspirate (Gwaltney et al., 2004). Unfortunately, this approach is not often used outside the research setting and, at present, is only recommended in cases of treatment failure or more complicated recurrent disease (Marple et al., 2006; Sinus and Allergy Health Partnership, 2004). A less invasive means of establishing a bacterial etiology in cases of rhinosinusitis is by nasal endoscopy with sinus aspirate and culture (Talbot et al., 2001), although this approach is considered by some to be suboptimal (Sande and Gwaltney, 2004). Ambrose et al. (2004) described another alternative method of injecting a catheter through the medial wall of the maxillary sinus, leaving in place for 5 days, and monitoring continuous outcome parameters including bacterial eradication, cytokine levels, and antimicrobial levels.

The diagnosis of ABRS in a primary care setting is currently made from the history and clinical findings (Gwaltney et al., 2004; Marple et al., 2006). Given the fact that viral rhinosinusitis predominates by a wide margin over ABRS (90–98% versus 2–10% of patients presenting with symptoms), the predictive value of any single clinical criterion will be quite low (Gwaltney et al., 2004). Among the symptoms associated with ABRS, purulent nasal discharge, unilateral maxillary sinus tenderness, maxillary tooth or facial pain (especially unilateral), and/or a "double sickening" history (worsening of symptoms after an initial improvement) have been identified as useful predictors of bacterial infection (Berg and Carenfelt, 1988; Hansen et al., 1995; Lindbaek et al., 1996; Marple et al., 2006). Importantly, these signs and symptoms are most indicative of ABRS when they have *not* improved or have worsened after 7 to 10 days (Lindbaek et al., 1996; Sande and Gwaltney, 2004].

2. Microbiology

The microbiology of ABRS has been well established by studies using sinus puncture, aspiration, and culture (Berg and Carenfelt, 1988; Brook, 1996; Gwaltney et al., 1992; Gwaltney et al., 1981; Sinus and Allergy Health Partnership, 2004). The predominant pathogens are very similar to that of acute otitis media (AOM) (see Block et al., this supplement) and include *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, and miscellaneous bacteria including *Staphylococcus aureus*, *Streptococcus pyogenes*, and anaerobes (Table 1). It is important to note that spontaneous resolution of microbiologically documented infections due to each of these pathogens occurs at high rate (Table 1).

Given the issues complicating the diagnosis of ABRS, it is recommended that physicians be aware of the pathogens that predominate in their geographic area, along with their associated resistance rates, when selecting empiric antibacterial therapy for ABRS (Marple et al., 2006). As with AOM (Block et al., this supplement), antibacterial resistance surveillance programs have attempted to provide information regarding resistance among ABRS pathogens to key classes of antibacterial agents (Table 2) (Doern and Brown, 2004; Dohar et al., 2004; Felmingham et al., 2005; Hoban and Felmingham, 2002; Johnson et al., 2006; Mason et al., 2000; Pfaller et al., 2001; Pfaller and Jones, 2002; Sader

Table 2
In vitro activity of penicillins and macrolides (azalides) against ABRS isolates from 3 surveillance programs: TeqCES (1999–2000), RESP (1999–2000), and PROTEKT (2000–2002)

Organism	Antimicrobial agent	% Resistant (no. tested) by surveillance program[a]		
		TeqCES	RESP[b]	PROTEKT
S. pneumoniae	Penicillin	12.8 (448)	16.0 (618)	20.0 (640)
	Erythromycin	22.3	32.0	44.1
H. influenzae	Ampicillin	26.9 (649)	30.0 (1189)	11.8 (329)
	Azithromycin	2.0	0.6	0.0
M. catarrhalis	Penicillin	91.8 (783)	91.5 (1588)	97.6 (212)
	Erythromycin	2.6	2.0	NA
S. aureus	Penicillin	NA	89.2 (983)	NA
	Methicillin	NA	NA	9.5 (116)
	Erythromycin	NA	29.0	31.0

Data compiled from Pfaller et al. (2001), Pfaller and Jones (2002), Sokol (2001), and Dohar et al. (2004). TeqCES = Tequin (gatifloxacin) Clinical Experience Study (Pfaller and Jones, 2002); PROTEKT = Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (Dohar et al., 2004); NA = data not available.

[a] % Resistant according to interpretive criteria of CLSI (2006).

[b] The Respiratory Surveillance Program (Pfaller et al., 2001).

Table 3
Effect of geography on the spectrum of penicillin and erythromycin tested against *S. pneumoniae*: comparison of results from the RESP (1999–2000) and TeqCES (1999–2000) Programs

Antimicrobial agents	Surveillance Program	No. tested	% Resistant by region[a,b]								
			1	2	3	4	5	6	7	8	9
Penicillin	RESP	881	10	12	13	16	13	23	19	13	19
	TeqCES	682	13	5	11	23	6	14	0	9	15
Erythromycin	RESP	881	26	26	28	42	26	42	24	34	38
	TeqCES	682	25	5	27	37	45	45	20	25	29

Data compiled from Pfaller et al. (2001) and Pfaller and Jones (2002). TeqCES = Tequin (gatifloxacin) Clinical Experience Study (Pfaller and Jones, 2002).

[a] % Resistant according to CLSI (2006) interpretive criteria.

[b] Regions 1–9 are US census regions (Pfaller et al., 2001): region 1, Pacific; region 2, Mountain; region 3, West North Central; region 4, West South Central; region 5, East North Central; region 6, East South Central; region 7, New England; region 8, Mid-Atlantic; region 9, South Atlantic.

et al., 2003). Three such studies conducted in physician office practice settings in the United States between 1999 and 2002 provide information regarding resistance to penicillin and macrolides (azalides) among the major ABRS pathogens (Table 2) (Dohar et al., 2004; Pfaller et al., 2001; Pfaller and Jones, 2002). Overall, it is evident that high-level resistance to penicillin (MIC, >2 μg/mL) and ampicillin is prevalent among all of the major pathogens. Likewise, macrolide resistance is considerable (~30%) among ABRS isolates of *S. pneumoniae* and *S. aureus*, and is increasing among *H. influenzae* (Doern and Brown, 2004; Hoban and Felmingham, 2002; Leibovitz et al., 2004). These studies have also demonstrated variation in resistance profiles by geographic region throughout the United States (Table 3). Such information is highly desirable and useful to consider as one chooses empiric therapy for ABRS.

In addition to geographic variation in pathogen distribution and antimicrobial resistance, other factors known to influence resistance among ABRS pathogens include patient age, day-care setting, and prior antimicrobial exposure (Marple et al., 2006). The effect of prior drug exposure on the susceptibility of ABRS isolates of *S. pneumoniae* to penicillin and erythromycin was demonstrated in the Respiratory Surveillance Program (RESP) study where prior exposure to either a β-lactam or a macrolide was associated with decreased susceptibility to both agents (Table 4) (Pfaller et al., 2001; Sokol, 2001). Additional published data emphasize the important effect of long-acting macrolides/azalides exposure in promoting resistance to both β-lactams and macrolides/azalides among *S. pneumoniae* (Baquero, 1999; Doern and Brown, 2004). These exposures play a major role in the selection of empiric therapy (Marple et al., 2006; Sinus and Allergy Health Partnership, 2004).

Table 4
Influence of prior antimicrobial exposure (previous 3-months) on the in vitro susceptibility of ABRS isolates of *S. pneumoniae* to penicillin and erythromycin

Antibiotic exposure	No. tested	% Susceptibility by interpretive category[a]					
		Penicillin			Erythromycin		
		S	I	R	S	I	R
None	505	67	19	13	72	0.4	27
Prior β-lactam	55	45	20	35	49	0	51
Prior macrolide	29	48	31	21	45	0	55

Data compiled from Pfaller et al. (2001) and Sokol (2001). S = susceptible; I = intermediate; R = resistant.

[a] CLSI (2006) interpretive criteria.

Table 5
In vitro susceptibility of major ABRS pathogens to oral β-lactam antimicrobial agents

Organism	Antimicrobial agent	No. tested	MIC (μg/mL)[a]		
			50%	90%	% S[b]
S. pneumoniae	Amoxicillin/clavulanate	640	0.03	2	95.5
	Cefuroxime	640	0.12	8	66.1
	Cefpodoxime	640	0.12	2	65.0
	Cefdinir	1098[c]	0.12	4	78.5
H. influenzae	Amoxicillin/clavulanate	329	0.5	1	100.0
	Cefuroxime	329	1	2	99.4
	Cefpodoxime	329	0.06	0.25	99.4
	Cefdinir	329	0.25	0.5	97.3
M. catarrhalis	Amoxicillin/clavulanate	212	0.12	0.25	100.0
	Cefuroxime	212	1	4	>99.0
	Cefpodoxime	212	0.5	1	100.0
	Cefdinir	212	0.12	0.25	100.0

Data compiled from Dohar et al. (2004) and Sader et al. (2003).

[a] MIC 50% and 90%: MIC encompassing 50% and 90% of isolates tested, respectively.

[b] Percentage susceptible according to CLSI (2006) criteria.

[c] Data from Sader et al. (2003).

Although older inexpensive β-lactam agents such as ampicillin and amoxicillin continue to play an important role as familiar well-tolerated and effective agents for primary therapy for ABRS (Marple et al., 2006; Snow et al., 2001), resistance issues, as listed in Table 2, especially regarding *H. influenzae* and *M. catarrhalis*, have compromised efficacy (Leibovitz et al., 2004). Currently, amoxicillin/clavulanate offers excellent activity against *H. influenzae* and *M. catarrhalis* (β-lactamase positive and β-lactamase negative) as well as penicillin-susceptible *S. pneumoniae* and most penicillin-nonsusceptible *S. pneumoniae* (Table 5). Other oral β-lactams with similar activity include cefdinir, cefpodoxime, and cefuroxime (Table 5) (Chatterjee et al., 2005; Cohen, 2002; Dohar et al., 2004; Fulton and Perry, 2001; Gwaltney, 2002; Perry and Scott, 2004; Sader et al., 2003), although these agents are not active versus penicillin-resistant strains of pneumococci.

3. Therapy

In the absence of definitive culture and susceptibility data, most therapeutic choices in ABRS are made empirically, taking into account disease severity, pathogen occurrence

Table 6
Summary of clinical trials to determine the clinical and bacteriologic efficacy of oral β-lactams in the treatment of ABRS

Study (year)	No. of patients enrolled	Treatment regimen	Bacteriologic response (%)	Clinical efficacy
Adelglass et al. (1999)	615	Amoxicillin/clavulanate (500 mg tid × 10–14 days)	NA	87
		Levofloxacin (500 mg qid × 10–14 days)	NA	88
Clement and de Gandt (1998)	254	Amoxicillin/clavulanate (500 mg tid × 10 days)	84	84
		Azithromycin (500 mg qid × 3 days)	90	88
Gehanno et al. (2000)	433	Amoxicillin/clavulanate (500 mg tid × 5 days)	NA	80
		Amoxicillin/clavulanate (500 mg tid × 10 days)	NA	85
Henry et al. (2004)	941	Amoxicillin/clavulanate (250 mg tid × 10 days)	NA	72
		Azithromycin (500 mg qid × 3 days)	NA	71
		Azithromycin (500 mg qid × 6 days)	NA	74
Klapan et al. (1999)	100	Amoxicillin/clavulanate (500 mg tid × 10 days)	88	100
		Azithromycin (500 mg qid × 3 days)	100	100
Namyslowski et al. (2002)	231	Amoxicillin/clavulanate (875 mg bid × 14 days)	66	95
		Cefuroxime (500 mg bid × 14 days)	68	88
Rakkar et al. (2001)	475	Amoxicillin/clavulanate (875 mg bid × 10 days)	NA	84
		Moxifloxacin (400 mg qid × 10 days)	NA	86
Sher et al. (2002)	445	Amoxicillin/clavulanate (875 mg bid × 10 days)	NA	72
		Gatifloxacin (400 mg qid × 5 days)	NA	74
		Gatifloxacin (400 mg qid × 10 days)	NA	79
Sterkers (1997)	458	Amoxicillin/clavulanate (500 mg tid × 8 days)	89	89
		Ceftibuten (400 mg qid × 8 days)	80	83
		Ceftibuten (200 mg bid × 8 days)	89	87
Henry et al. (2004)	271	Cefdinir (600 mg qid × 10 days)	NA	83
		Levofloxacin (500 mg qid × 10 days)	NA	86
Gwaltney et al. (1997)	1798	Cefdinir (600 mg qid × 10 days)	88	90
		Cefdinir (300 mg bid × 10 days)	86	87
		Amoxicillin/clavulanate (500 mg tid × 10 days)	89	91
Steurer and Schenk (2000)	509	Cefdinir (600 mg qid × 10 days)	98	95
		Cefdinir (300 mg bid × 10 days)	90	90
		Amoxicillin/clavulanate (500 mg tid × 10 days)	93	96
Autret et al. (1994)	116	Cefpodoxime (8 mg/kg per day × 10 days)	NA	95
		Amoxicillin/clavulanate (40 mg/kg per day × 10 days)	NA	82
Gehanno et al. (1990)	267	Cefpodoxime (400 mg/day × 10 days)	NA	95
		Cefaclor (1500 mg/day × 10 days)	NA	84
Sabater et al. (1995)	66	Cefpodoxime (400 mg/day × 5 days)	NA	100
		Amoxicillin/clavulanate (1500 mg/day × 8 days)	NA	91
von Sydow et al. (1995)	286	Cefpodoxime (400 mg/day × 10 days)	NA	96
		Amoxicillin (1500 mg/day × 10 days)	NA	91
Burke et al. (1999)	542	Cefuroxime (250 mg bid × 10 days)	NA	89
		Moxifloxacin (400 mg qid × 10 days)	NA	90
Johnson et al. (1999)	501	Cefuroxime (250 mg bid × 10 days)	95	83
		Ciprofloxacin (500 mg bid × 10 days)	97	87
Siegert et al. (2000)	498	Cefuroxime (250 mg bid × 10 days)	83	91
		Moxifloxacin (400 mg qid × 7 days)	94	97
Siegert et al. (2003)	561	Cefuroxime (250 mg bid × 7 days)	91	88
		Faropenem (300 mg bid × 7 days)	91	89
Weis et al. (1998)	1414	Cefuroxime (250 mg bid × 10 days)	NA	90
		Ciprofloxacin (500 mg bid × 10 days)	NA	91

rates, and local resistance patterns, as well as the results of therapeutic efficacy trials. Although the spontaneous resolution rate of proven ABRS can be quite high (~60%, Table 1), placebo-controlled efficacy trials have demonstrated a positive effect of antibacterial therapy when the infecting organism is susceptible to the agent administered and the drug is present in adequate concentrations (time above the MIC, $T >$ MIC) at the site of infection (Anon, 2005; Gwaltney et al., 2004; Ip et al., 2005; Marple et al., 2006; Mason et al., 2000; Sande and Gwaltney, 2004; Sinus and Allergy Health Partnership, 2004).

Comparative efficacy trials of various oral agents in the treatment of ABRS abound (Table 6) (Ip et al., 2005). Unfortunately, most of these studies are merely noninferiority studies and are not powered sufficiently to provide information regarding superiority or inferiority among the various studied agents (Gwaltney et al., 2004; Ip et al., 2005). Furthermore, most of the studies suffer from inadequate outcome criteria for evaluating efficacy (Gwaltney et al., 2004). The fact that most of the trials use clinical criteria for study entry means that they will include a mixture of bacterial and nonbacterial rhinosinusitis

Table 7
Rank order of predicted therapeutic efficacy of antimicrobial agents according to the Poole (2004) therapeutic outcomes

Predicted efficacy	Relative rank order	
	Adults	Children
90–92%	Respiratory fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin), ceftriaxone, and amoxicillin/clavulanate	Ceftriaxone, amoxicillin/clavulanate
83–88%	Amoxicillin, cefpodoxime, cefdinir, cefuroxime, TMP/SMX, and cefixime (*H. influenzae* and *M. catarrhalis* only)	Amoxicillin, cefpodoxime, cefuroxime, TMP/SMX, and cefixime (*H. influenzae* and *M. catarrhalis* only)
77–81%	Doxycycline, clindamycin (based on Gram-positive coverage only), cefprozil, azithromycin, clarithromycin, erythromycin, and telithromycin	Clindamycin (based on Gram-positive coverage only), cefprozil, azithromycin, clarithromycin, and erythromycin
65–66%	Cefaclor, loracarbef	Cefaclor, loracarbef
62–63%	Spontaneous resolution rate in untreated adults with ABRS	Spontaneous resolution rate in untreated children with ABRS

Data compiled from Sinus and Allergy Health Partnership (2004). TMP/SMX = trimethoprim/sulfamethoxazole.

cases (Gwaltney et al., 2004). This potentially varying mixture, coupled with a substantial rate of spontaneous resolution, markedly reduces the value of such clinical trials and provides little guidance in selecting the best therapy (Sinus and Allergy Health Partnership, 2004).

In response to a need for guidance in selecting therapy for ABRS in the face of imperfect means of diagnosis and suboptimal clinical trials data, Poole (2004) and Sinus and Allergy Health Partnership (2004) have devised a mathematical prediction model that takes into account diagnostic uncertainty, pathogen distribution, spontaneous resolution rates, resistance trends, and PK/PD parameters, and arrives at a calculated predicted efficacy rate for the available antibacterial agents in the treatment of ABRS (Table 7). Among the oral β-lactams, it is clear that amoxicillin/clavulanate has the highest predicted efficacy (>90%), followed by the newer-generation cephalosporins (>80%; cefdinir, cefpodoxime, and cefuroxime). The macrolides/azalides and the older orally administered cephalosporins (cefaclor and loracarbef) are considerably less efficacious and *do not* offer much more than that anticipated by the spontaneous resolution rate (placebo).

Among the published guidelines (Marple et al., 2006), those of the Sinus and Allergy Health Partnership (2004) have taken into account the rank order of the Poole (2004) model regarding efficacy and further stratified patients according to severity of disease and prior patient exposure to antibacterial agents (Table 8). As shown previously (Table 4), prior antibacterial exposure markedly increases rates of resistance to β-lactams and macrolides among major ABRS pathogens such as *S. pneumoniae* and, therefore, must be considered in selecting appropriate therapy. Thus, initial therapy among patients with mild disease and no prior antibacterial exposure may include amoxicillin/clavulanate

Table 8
Recommended antimicrobial therapy for adults and children with ABRS

Disease state	Initial therapy[a]	Calculated % efficacy	
		Clinical (adult/child)	Bacteriologic (adult/child)
Mild, no recent antimicrobial use (past 4–6 weeks)	Amoxicillin/clavulanate	90–91/91–92	97–99/97–99
	Amoxicillin	87–88/86–87	91–92/90–92
	Cefpodoxime	87/87	91/92
	Cefuroxime	85/85	87/88
	Cefdinir	83/84	85/86
	β-Lactam allergic		
	TMP/SMX	83/83	84/84
	Macrolides	77/78	73/76
	Doxycycline	81/NR	80/NR
Mild, recent antimicrobial use (past 4–6 weeks) or moderate disease	Respiratory fluoroquinolones	92/NR	100/NR
	Amoxicillin/clavulanate	91/92	99/99
	Ceftriaxone	91/91	99/99
	β-Lactam allergic		
	Respiratory fluoroquinolones	92/NR	100/NR
	Macrolides	NR/78	100/NR
	TMP/SMX	NR/83	NR/84
	Clindamycin	79	78

Data compiled from Sinus and Allergy Health Partnership (2004). Telithromycin has been removed from this list because of reported serious hepatic toxicity (calculated efficacy at 73–77% before removal). Macrolides include erythromycin, clarithromycin, and azithromycin. TMP/SMX = trimethoprim/sulfamethoxazole; NR = not recommended.

[a] If no improvement or worsening after 72 h, initial therapy reevaluates and considers switch to respiratory fluoroquinolone (adults), high-dose amoxicillin/clavulanate, ceftriaxone, or combination therapy (e.g., clindamycin or TMP/SMX plus rifampin).

Table 9
Microbiologic eradication and clinical efficacy of cefdinir and amoxicillin/clavulanate in the treatment of ABRS

Pathogen	Microbiologic eradication						Clinical efficacy					
	Cefdinir				Amoxicillin/clavulanate		Cefdinir				Amoxicillin/clavulanate	
	600 mg qid		300 mg bid				600 mg qid		300 mg bid			
	n/*n*	%	*n*/*n*	%	*n*/*n*	%	*n*/*n*	%	*n*/*n*	%	*n*/*n*	%
S. pneumoniae	18/18	100.0	19/20	95.5	18/18	100.0	18/18	100.0	18/20	90.0	18/18	100.0
H. influenzae	16/17	94.1	14/19	73.7	25/25	100.0	15/17	88.2	14/19	73.7	24/25	96.0
M. catarrhalis	8/9	99.9	8/8	100.0	9/9	100.0	7/9	77.8	8/8	100.0	9/9	100.0
S. aureus	10/10	100.0	10/12	83.3	4/7	57.1	10/10	100.0	11/12	91.7	7/7	100.0
S. pyogenes	5/5	100.0	2/2	100.0	3/3	100.0	5/5	100.0	2/2	100.0	3/3	100.0

Data compiled from Steurer and Schenk (2000). Sinus aspirate and culture performed on entry into study and at test of cure visit on days 7 to 15 posttherapy.

or one of several oral cephalosporins (Table 8). The latter agents may be considered as effective (>80% predicted efficacy) substitutes for amoxicillin/clavulanate with the advantage of improved compliance due to greater palatability, tolerance, and a less frequent dosing schedule (Fulton and Perry, 2001; Perry and Scott, 2004; Powers et al., 2000; Steele et al., 2001).

As noted previously (Table 6), very few clinical efficacy trials have emphasized maxillary sinus puncture and culture in documenting the efficacy of treatment (Gwaltney et al., 2004). One notable exception is the study of Steurer and Schenk (2000) (Steurer and Schenk, 2000), where 2 different dosing regimens of cefdinir were compared with amoxicillin/clavulanate in the treatment of ABRS (Table 9). Both the diagnosis and efficacy of treatment were determined by using the results of maxillary sinus puncture and culture. This type of study not only provides rigorous criteria for the diagnosis of ABRS but also allows for specific assessment of bacteriologic eradication and clinical efficacy for infection due to specific bacteria (Table 9). In Table 9, cefdinir was highly effective not only in eradicating the major bacterial pathogens (microbiologic eradication) but also in alleviating the clinical signs and symptoms of ABRS (clinical efficacy), for example, comparable with amoxicillin/clavulanate. Given all of the problems inherent in the diagnosis and treatment of ABRS, it is only through rigorous studies such as this (Steurer and Schenk, 2000) that we will gain true understanding of the clinical and bacterial efficacy of the various choices for ABRS.

4. Conclusions

ABRS is an important and costly infectious disease of adults and children. Antimicrobial treatment is effective in eradicating infection and shortening illness. To avoid overtreatment of nonbacterial causes of rhinosinusitis, specific antibacterial therapy should only be instituted in those patients where typical signs and symptoms have persisted or become worse after 7 to 10 days of "watchful waiting". Antibacterial agents selected for treatment should be effective against the major causes of ABRS, including antimicrobial-resistant *S. pneumoniae* and β-lactamase–positive *H. influenzae* and *M. catarrhalis*. Among the most efficacious agents, with an appropriately narrow spectrum, are the β-lactams amoxicillin/clavulanate, cefdinir, cefpodoxime, and cefuroxime. Knowledge of prior antimicrobial therapy should alert the clinician to the increased potential of infection with a resistant pathogen that may require alternative therapy and/or more aggressive efforts to obtain an etiologic diagnosis.

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