J. J. Granizo[1]
M. J. Giménez[2]
J. Barberán[3]
P. Coronel[4]
M. Gimeno[4]
L. Aguilar[2]

Efficacy of cefditoren in the treatment of upper respiratory tract infections: a pooled analysis of six clinical trials

[1] Granadatos, S.L. Pozuelo de Alarcón (Madrid)
[2] Microbiology Department School of Medicine Universidad Complutense Madrid
[3] Infectious Diseases Department Hospital Central de la Defensa Gómez Ulla Madrid
[4] Scientific Department Tedec-Meiji Farma Madrid

Objective. A pooled analysis of all upper respiratory tract infection studies performed with cefditoren (CDN) was performed.

Methods. Studies were prospective, comparative, multicentre and randomised. Comparators were penicillin V (pharyngitis) and cefuroxime or amoxicillin/clavulanate (sinusitis). A total of 1,322 patients were randomized, 1,241 included in intention-to-treat (ITT) and 1,010 in per-protocol populations (PP) in pharyngotonsillitis studies, and 1,819 randomized, 1,726 included in ITT and 1,589 in PP in acute sinusitis studies.

Results. No significant differences in pharyngitis clinical response were found (success rates: 89.4% to 95.3%). *S. pyogenes* eradication was higher with cefditoren at end of therapy (EOT) (90.4% vs. 82.7%; p=0.002) and follow-up (84.7% vs. 76.7%; p=0.008), although no statistically significant (p<0.001). In both groups, clinical failures were significantly higher (p<0.001) in patients showing *S. pyogenes* persistence than in those showing eradication (≥98.5% vs. 51.4%). No differences in sinusitis clinical response were found between CDN and comparators both at EOT (80.2% vs. 84.8%) and at end of follow-up (71.2% vs. 77.4%).

Conclusion. Cefditoren had similar point estimates of clinical efficacy to comparators in pharyngotonsillitis and sinusitis, and a tendency to higher *S. pyogenes* eradication in pharyngotonsillitis.

Key words:
Cefditoren. *S. pyogenes*. Clinical trial. Pooled analysis. Sinusitis. Pharyngotonsillitis.

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Correspondencia:
Lorenzo Aguilar
Microbiology Department
School of Medicine
Universidad Complutense
Av. Complutense, s/n
28040 Madrid
e-mail: laguilar@med.ucm.es

Eficacia del cefditoren en el tratamiento de las infecciones del tracto respiratorio alto: análisis combinado de seis ensayos clínicos

Objetivo. Se realizó un análisis combinado de los datos de todos los ensayos clínicos llevados a cabo con cefditoren en el tratamiento de infecciones del tracto respiratorio alto.

Métodos. Los estudios eran prospectivos, multicéntricos, aleatorizados y comparativos con penicilina V en faringoamigdalitis y con cefuroxima o amoxicilina/clavulánico en sinusitis. Un total de 1.322 pacientes fueron aleatorizados, 1.221 incluidos en la población por intención de tratar (ITT) y 1.110 en la población por protocolo (PP) en los estudios de faringoamigdalitis. En los de sinusitis, 1.819 pacientes fueron aleatorizados, con 1.726 pacientes incluidos en la ITT y 1.589 en la PP.

Resultados. No se encontraron diferencias significativas en la respuesta clínica en faringoamigdalitis entre cefditoren y comparadores (curación del 89,4 al 95,3%). La erradicación de *S. pyogenes* fue superior para cefditoren al final del tratamiento (90,4 frente al 82,7%; p=0,002) y al final del seguimiento (84,7 frente al 76,7%; p=0,008), aunque sin alcanzar significación estadística (p<0,001). En ambos grupos de tratamiento los fracasos clínicos fueron significativamente superiores (p<0,001) en pacientes que presentaron persistencia de *S. pyogenes* que en aquellos en los que ocurrió la erradicación (≥98,5 frente al 51,4%). En sinusitis no se encontraron diferencias en la respuesta clínica a cefditoren frente a comparadores tanto al final del tratamiento (82,2 frente al 84,8%) como del seguimiento (71,2 frente al 77,4%).

Conclusión. Cefditoren presentó una eficacia clínica estimada similar a la de los comparadores en el tratamiento de sinusitis y faringoamigdalitis, con una tendencia a una mayor tasa de erradicación de *S. pyogenes* en esta última patología.

Palabras clave:
Cefditoren. *S. pyogenes*. Ensayo clínico. Análisis combinado de datos. Sinusitis. Faringoamigdalitis.

INTRODUCTION

Infection, particularly respiratory tract infections, is the major cause of physician visits in the ambulatory care setting[1,2]. Upper respiratory tract infections are responsible for 200 visits/1,000 population annually to physicians in the United States[3]. Pharyngitis, although more frequent in children, is responsible for an estimated 6.7 million visits to primary care physicians by adults complaining of sore throat[4], while the other common condition treated by these physicians, rhinosinusitis, accounts for 1 billion cases of viral etiology per year complicated by 20 million cases of acute bacterial sinusitis in the United States[5].

While etiological diagnosis of pharyngitis is not possible on clinical grounds alone, and is easy with the development of rapid antigen tests to detect *Streptococcus pyogenes,* diagnosis of acute bacterial sinusitis continues to be a challenge because paranasal sinuses are accessible only with invasive sampling that is not performed in daily practice and thus, physicians have to rely on clinical findings. When investigational puncture studies are performed in patients with acute sinusitis Streptococcus pneumoniae and *Haemophilus influenzae* are the most common pathogens, accounting together for 50% cases[6].

S. pyogenes, S. pneumoniae and *H. influenzae* are thus the most prevalent isolates in community-acquired upper respiratory tract infections, each of them with its own resistance problems: *a)* high resistance to macrolides (including the increasing MLSB phenotype implying a high resistance level) in *S. pyogenes*[7] and *S. pneumoniae*[8]; *b)* amoxicillin resistance among penicillin-resistant *S. pneumoniae* related to specific clones[9], and *c)* the recently increasing BLNAR β-lactamase negative ampicillin-resistant) and BLPACR (β-lactamase positive amoxicillin/clavulanic acid resistant) resistance phenotypes among *H. influenzae* isolates[10,11]. Lastly, it has been hypothesized that β-lactamase from β-lactamase producing isolates, as H. influenzae, may protect non-β-lactamase producing isolates as *S. pyogenes* or *S. pneumoniae*[12,13].

Cefditoren-pivoxil (CDN) is an oral 3rd generation cephalosporin, with minimum concentrations required to inhibit 90% (MIC90) of respiratory isolates lower than those of amoxicillin and cefuroxime[11,14]. Cefditoren has shown efficacy in the treatment of lower respiratory tract infections[15,16].

This paper presents the results of a pooled efficacy analysis of all studies carried out with CDN in patients with community-acquired upper respiratory tract infections.

MATERIAL AND METHODS

Study design and patients

Data from all clinical trials carried out with CDN in the treatment of community-acquired upper respiratory tract infections, consisting in six prospective, comparative, randomised, multicentre, parallel group Phase III trials were evaluated in this pooled efficacy analysis. Three were acute pharyngotonsillitis studies (ME 309, CEF 97008 and CEF 97010) and three were acute sinusitis studies (ME 305, CEF 97004 and CEF 97007) running from 1996 to 1999. All studies were double-blinded except study ME309 that was open and studies CEF 97004 and CEF 97007 that were investigator-blinded. A total of 275 centers were involved in USA (216 centers), Spain (43 centers), Germany (10 centers) and Romania (6 centers). Study CEF 97008 was published[17] and studies CEF 97008, CEF 97010, and CEF 97004 were presented at 40th ICAAC[18,19]. Details of the studies and treatment regimens are summarized in table 1.

Studies were conducted in accordance to Declaration of Helsinki (1996 revision for studies CEF 97004, CEF 97007, CEF 97008 and CEF 97010; Hong Kong 1989 revision for study ME 305 and ME 309), to Good Clinical Practice (GCP) regulations governing clinical study conduct and to all applicable local regulations. Independent institutional review boards approved the protocols. Each patient (parent or legal guardian in the case of minor patients) signed an informed consent prior to the performance of any study-related procedures.

Pharyngotonsillitis

Patients aged at least 12 years (studies CEF 97008 and CEF 97010) or 18 years (study ME 309) with clinical diagnosis of acute bacterial pharyngotonsillitis (based on clinical assessment of fever, odynophagia, exudate, lymphadenitis and leukocytosis) in the three studies, plus demonstrated streptococcal etiology by positive rapid immunoassay in studies CEF 97008 and CEF 97010, were eligible. Patients with known hypersensitivity to β-lactam compounds, tonsillectomy, female patients who were pregnant, lactating or using inadequate contraception, and patients with known significant liver impairment (aspartate aminotransferase, alanine aminotransferase, or total bilirubin >2 times the upper limit of normal) or renal insufficiency (serum creatinine >2.3 mg/dl) were excluded. Other exclusion criteria were evidence of cardiovascular disease or prosthesis, impaired immunological function, HIV-infection, antimicrobial therapy in the previous five days, concomitant infection requiring antibiotic therapy, and leukocyte count <4,000/mm^3 or >30,000/mm^3. Previous inclusion in the study was also considered an exclusion criterion.

Disposition of pharyngotonsillitis patients

A total of 311, 503 and 508 patients were randomized in studies ME 309, CEF 97008 and CEF 97010, respectively. The intention-to-treat population (ITT) consisted in diagnosed patients who received at least one dose of the study drug and had *S. pyogenes* isolated pretreatment in the case of studies CEF 97008 and CEF 97010. The per protocol (PP) po-

Table 1 Summary of Phase III studies with cefditoren in patients with community acquired upper respiratory tract infections

Infection/study	No. patients Randomized	ITT*	PP**	Treatment duration (days) Cefditoren 200 mg BID	Cefditoren 400 mg BID	Comparators
Acute pharyngotonsillitis						
ME 309	311	309	274	5	—	Penicillin V 400 mg tid 10 days
CEF 97008	503	397	368	10	—	Penicillin VK 250 mg qid 10 days
CEF 97010	508	508	368			
Total	1,322	1,214	1,010			Penicillin VK 250 mg qid 10 days
Acute sinusitis						
ME 305	205	201	172	10	—	Cefuroxime 250 mg bid 10 days
CEF 97004	777	700	635	10	10	Amoxicillin/clavulanate 875/125 mg bid 10 days
CEF 97007	837	825	782	10	10	Amoxicillin/clavulanate 500/125 mg tid 10 days
Total	1,819	1,726	1,589			

*ITT: intention-to-treat population; **PP: per-protocol population.

pulation included all patients of the ITT population without major protocol violations (intake ≤80% of study drug based on the number of tablets returned and on date and time of first and last intake of study medication, lost to follow-up, additional antibiotics, and no clinical response assessment within visit window). Treatment arms, randomized, ITT and PP populations per study are shown in table 1.

Pharyngotonsillitis clinical evaluation

Patients were assessed pre-therapy, on-therapy, at the end of therapy (EOT; within 48 h of last dose intake), and at the end of follow-up (28-35 days after randomization). Endpoint was clinical response at EOT and at the end of follow-up. Clinical response was considered as resolution of or improvement in all pre-treatment signs/symptoms without the need for additional antimicrobial therapy and no reasons for clinical failure. Clinical failure was considered when the pre-treatment signs/symptoms of the infection improved with the need for additional antimicrobial therapy or did not improve and/or worsened, or there was a recurrence (cure or improvement at EOT with reappearance during follow-up).

Pharyngotonsillitis microbiological evaluation

Samples for microbiological cultures were taken at all study visits in studies CEF 97008 and CEF 997010 and sent to Covance Central Laboratory Services inc. for culture, bacitracin and Lancefield testing. Microbiological response was eradication (absence of *S. pyogenes* in visits performed at EOT and at the end of follow-up), persistence (presence of *S. pyogenes* in visits performed at EOT and at the end of follow-up), or recurrence (absence of *S. pyogenes* in EOT visit with reappearance in the end of follow-up visit).

Sinusitis

Patients aged at least 12 years (studies CEF 97004 and CEF 97007) or 18 years (study ME 305) with clinical diagnosis of acute sinusitis based on clinical signs/symptoms (fever, sinus headache, facial pain/pressure/tightness over the maxillary sinuses, mucopurulent rhinorrhea, nasal obstruction and hyposmia) present for ≥ 7 days but ≤ 4 weeks, together with compatible sinus X-ray or CT scan were eligible. Patients with known hypersensitivity to β-lactam compounds, chronic maxillary sinusitis (symptoms present for ≥3 months and/or 3 or more episodes of sinusitis in the preceding 6 months), presence of nasal polyps, previous sinus surgery, female patients who were pregnant, lactating or using inadequate contraception, and patients with known significant liver impairment (aspartate aminotransferase, alanine aminotransferase, or total bilirubin >2 times the upper limit of normal) or renal insufficiency (serum creatinine >2.3 mg/dl) were excluded. Other exclusion criteria were evidence of cardiovascular disease or prosthesis, im-

paired immunological function, HIV-infection, antimicrobial therapy in the previous five days, concomitant infection requiring antibiotic therapy, and leukocyte count <4,000/mm^3 or >30,000/mm^3. Previous inclusion in the study was also considered an exclusion criterion.

Disposition of sinusitis patients

A total of 205, 777 and 837 patients were randomized in studies ME 305, CEF 97004, and CEF 97007, respectively. ITT population consisted in diagnosed patients who received at least one dose of the study drug. PP population included all patients of the ITT population without major protocol violations (diagnosis insufficiently supported by radiographic assessment, intake ≤80% of study drug based on the number of tablets returned and on date and time of first and last intake of study medication, lost to follow-up, additional antibiotics, and no clinical response assessment within visit window). Treatment arms, randomized, ITT and PP populations per study are shown in table 1.

Sinusitis clinical evaluation

Patients were assessed pre-therapy, on-therapy, at EOT (within 48 h of last dose intake), and at the end of follow-up (7-14 days after last dose intake in studies CEF 97004 and CEF 97007 and 34 ± 2 days after last dose intake for study ME 305). End-point was clinical response at EOT and at the end of follow-up. Clinical response was considered as resolution of or improvement in all pre-treatment signs/symptoms with at least no worsening in the radiographic appearance of the sinuses without the need for additional antimicrobial therapy. Clinical failure was considered when the pretreatment signs/symptoms of the infection did not improve or worsened, including the appearance of new symptoms, further antimicrobial therapy was required and/or worsening was observed in the radiographic appearance of the sinuses, or there was a clinical relapse (cure or improvement at EOT with worsening or reappearance during follow-up).

Statistical analysis

Pooled analysis was performed using absolute data from final study reports of patients included in the six clinical trials. Comparison of the response rates between different treatment pooled groups (CDN 200 mg, CDN 400 mg and comparators) was performed using the chi square test or Fisher exact test when necessary. A $p<0.001$ was considered statistically significant in order to reduce the probability of acceptance of false alternative hypotheses due to the multiple comparisons performed between treatment groups including small samples, or due to differences in study designs.

RESULTS

Study population

A total of 3,141 patients were randomized in the six studies. Table 2 shows demographic data of randomized pa-

Table 2 Demographic characteristics (age ± SD; sex: % males and race: % caucasian) of patients included in the different studies

Infection/study	Cefditoren						Comparators		
	200 mg BID			400 mg BID					
	Age	Sex	Race	Age	Sex	Race	Age	Sex	Race
Acute pharyngotonsillits									
ME 309	29.1±12.1	42.9	99.4				29.0±11.4	38.7	99.3
CEF 97/008	28.5±10.9	62.9	84.0				29.1±11.3	61.1	89.5
CEF 97/010	26.4±10.9	61.8	86.2				27.1±11.0	67.3	88.6
Total	27.3±11.3	57.8	88.4	–	–	–	28.3±11.3	58.2	91.5
Acute sinusitis									
ME 305	37.1±11.9	39.4	99.0	–	–	–	35.6±13.8	48.1	96.2
CEF 97/004	40.7±13.9	58.8	91.1	39.8±14.4	59.8	88.1	39.0±14.5	62.6	87.2
CEF 97/007	39.9±14.8	56.6	78.3	38.9±14.9	64.5	76.3	40.7±15.5	55.9	79.1
Total	39.8±14.3	54.8	86.7	39.3±14.7	62.2	82.0	39.2±14.8	57.3	85.2

tients included in each individual study and in total in pharyngotonsillitis and sinusitis studies. Globally, most patients were white race without differences in age or gender between treatment arms when considering individual pathologies (acute pharyngotonsillitis and acute sinusitis). As expected, patients included in sinusitis studies were older than patients in pharyngotonsillitis studies. Figures 1 and 2 show disposition of patients in acute pharyngotonsillitis and sinusitis studies, respectively.

Acute pharyngotonsillitis

When pooling data from the three studies of acute pharyngotonsillitis, no significant differences in clinical response rates were found between CDN and comparators both at EOT and at the end of follow-up, with success rates ranging from 89.4% to 95.3% (table 3). When analyzing microbiological outcomes, differences between CDN and comparators in response rates at EOT (90.4% vs. 82.7%; p=0.002) or at the end of follow-up (84.7% vs. 76.7%; p=0.008) did not reach statistical significance considering the significance value adequate for this pooled analysis (p<0.001) (table 3).

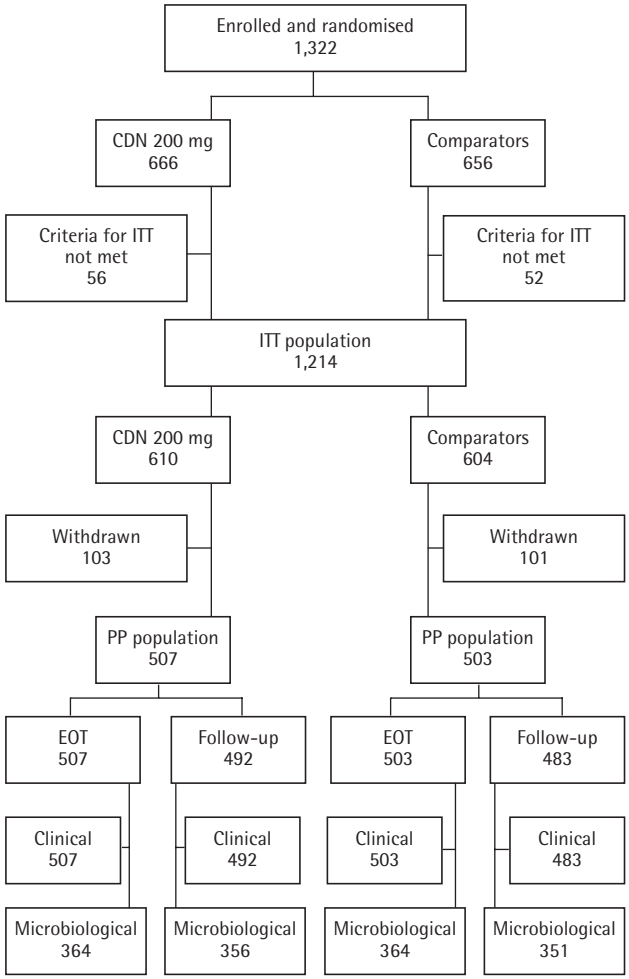

Figure 1 *Disposition of patients for clinical (three studies) and microbiological (two studies) evaluation in acute pharyngotonsillitis studies. CDN: cefditoren; ITT: intention-to-treat; PP: per-protocol population; EOT: end of therapy; Follow-up: end of follow-up.*

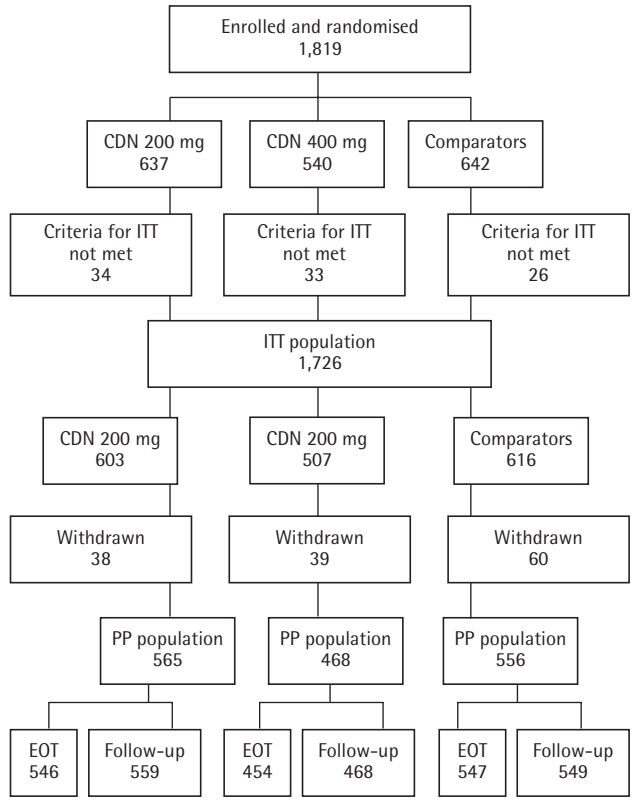

Figure 2 *Disposition of patients for clinical evaluation in acute sinusitis studies. CDN: cefditoren; ITT: intention-to-treat; PP: per-protocol population; EOT: end of therapy; Follow-up: end of follow-up.*

Table 4 shows the relationships between clinical and microbiological responses. Significant (p < 0.001) higher clinical response (≥ 98.5%) was found among patients showing *S. pyogenes* eradication than in those showing bacteriological persistence (≤ 51.4%). Or, from the other perspective, significant (p < 0.001) higher bacteriological response (*S. pyogenes* eradication) (≥ 88.7%) was found among patients showing clinical response than in those showing clinical failure (≤ 22.7%). Although higher *S. pyogenes* eradication rate was found among patients showing clinical failure with CDN than with comparators (22.7% vs. 5.9%), this difference was not statistically significant (p = 0.098).

Table 3 Clinical (% responders) and microbiological (% eradication) outcome at end of therapy (EOT), and at end of follow-up (Follow-up)

	Cefditoren				Comparators	
	200 mg BID		400 mg BID			
	EOT	Follow-up	EOT	Follow-up	EOT	Follow-up
Acute pharyngotonsillits						
Clinical	483/507 (95.3)	452/492 (91.9)	-	-	464/503 (92.2)	432/483 (89.4)
Microbiological	329/364 (90.4)*	301/356 (84.7)**	-	-	301/364 (82.7)	269/351 (76.7)
Acute sinusitis						
Clinical	443/546 (81.1)	403/559 (72.1)	364/454 (80.2)	333/468 (71.2)	464/547 (84.8)	425/549 (77.4)

*p=0.002 vs. comparators; **p=0.008 vs. comparators.

Acute sinusitis

When pooling data from the three studies of acute sinusitis, similar response rates were found in the three treatment arms, ranging from 80.2% to 84.8% at EOT and from 71.2% to 77.4% at the end of follow-up. No differences in EOT response rates were found between CDN 200 mg or 400 mg and comparators (p>0.05), as well as at the end of follow-up, between CDN 200 mg and comparators (p=0.041), or CDN 400 mg and comparators (p=0.022).

Tolerability

When pooling safety data of the 6 studies, treatment-related adverse events (AEs) were reported in 22.6% of the CDN 200 mg group, 26.1% of the CDN 400 mg group, and 20.9% of the comparator group. By body system, the incidence of AEs affecting the digestive system was 15.6%, 18.1%, and 10.8% in the respective treatment groups; urogenital AEs occurred in 1.7%, 3.5%, and 3.5%; skin AEs in 1.6%, 0.9%, and 1.9%; and central nervous system AEs in 1.7%, 1.7%, and 1.7%, respectively.

Table 4 Relationships between clinical and microbiological responses in acute pharyngotonsillitis at the end of therapy (EOT) and at the end of follow-up (Follow-up)

Clinical responder (%) among patients showing *S. pyogenes*							
Eradication				Persistence			
EOT		Follow-up		EOT		Follow-up	
CDN 200 mg	Comparators	CDN 200 mg	Comparators	CDN 200 mg	Comparators	CDN 200 mg	Comparators
324/329 (98.5)	299/301 (99.3)	298/301 (99.0)	266/269 (98.9)	18/35 (51.4)	31/63 (49.2)	18/55 (32.7)	34/82 (41.5)
***S. pyogenes* eradication (%) among patients showing**							
Clinical response				Clinical failure			
EOT		Follow-up		EOT		Follow-up	
CDN 200 mg	Comparators	CDN 200 mg	Comparators	CDN 200 mg	Comparators	CDN 200 mg	Comparators
324/342 (94.7)	299/331 (90.3)	298/316 (94.3)	266/300 (88.7)	5/22 (22.7)	2/34 (5.9)	3/40 (7.5)	3/51 (5.9)

CDN: cefditoren.

DISCUSSION

Previous publications suggest that orally administered third generation extended-spectrum cephems may offer therapeutic alternatives in the therapy for uncomplicated lower respiratory tract infections[20]. This was also reported for cefditoren in a previous pooled analysis[15], reinforced by the knowledge of increasing resistance in *S. pneumoniae* and *H. influenzae* to other agents[20]. In upper respiratory tract infections, the same target bacteria should be covered in acute bacterial sinusitis, the fifth most common diagnosis for which antibiotics are prescribed[21]. Since it is not possible to predict which cases will resolve spontaneously, the use of an antimicrobial is recommended[22]. Because of the high potential for treatment failure due to resistance, the choice of the agent has significant impact on the outcome, treatment costs and quality of life associated with the illness[22]. In the present pooled analysis, clinical outcome with CDN had similar point estimates of efficacy to that obtained with the comparators (standard oral treatments with cefuroxime or amoxicillin/clavulanate) in pooled sinusitis data. In this sense, cefditoren may offer an alternative based on the knowledge of local patterns of antimicrobial resistance, one of the factors to be considered in selecting therapy[23].

With respect to the other prevalent isolate of community-acquired upper respiratory tract infections, *S. pyogenes,* resistance problems come not only from the prevalence of resistance to macrolides[7], but also from copathogenicity (protection of *S. pyogenes* susceptible to penicillin by colocalized bacteria resistant to penicillin due to β-lactamase production)[12,24,25]. Copathogenicity has been hypothesised by some authors to be responsible of penicillin treatment failures in the treatment of group A β-hemolytic streptococci pharyngitis due to β-lactamase producing organisms in the pharynx as *H. influenzae* or *Moraxella catarrhalis*[12], but criticised by others[26,27]. A previous meta-analysis showed significantly higher bacteriological failures with penicillin vs. cephalosporins[28], as in a previous pooled analysis where bacteriological failures were also significantly higher with penicillin than with a 3rd generation cephem[29]. In this pooled analysis microbiological response was higher both at EOT (90.4% vs. 82.7%; p=0.002) and at the end of follow-up (84.7% vs. 76.7%; p=0.008) with cefditoren vs. comparators, but did not reach the statistical significance set at p<0.001. Logically, bacteriological response was associated with clinical response in both treatment arms, since clinical failures were significantly higher (p<0.001) among patients showing microbiological persistence vs. those showing eradication. Treatment failures are important in group A β-hemolytic pharyngitis since they increase the risk of suppurative[12] or inflammatory disorders associated with streptococcal infection[30].

In the present analysis, the oral 3rd generation cephalosporin cefditoren had similar point estimates of clinical efficacy to comparators in sinusitis, and of clinical and microbiological efficacy in pharyngotonsillitis, with a tendency to higher bacteriological response for *S. pyogenes*.

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