

Update on the clinical utility and optimal use of cefditoren

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Abstract: This article reviews and updates published data on cefditoren. The in vitro activity of cefditoren and its potential pharmacokinetic/pharmacodynamic adequacy to cover emerging resistance phenotypes in the present decade is reviewed. Cefditoren's in vitro activity against most prevalent bacterial respiratory pathogens in the community and its pharmacokinetic/pharmacodynamic profile suggests a significant role for cefditoren in the treatment of respiratory tract infections. Clinical trials (in acute exacerbations of chronic bronchitis, community-acquired pneumonia, pharyngotonsillitis, and sinusitis) performed during clinical development outside Japan, mainly in adults, are reviewed, together with new clinical studies in the treatment of pharyngotonsillitis, sinusitis, and otitis media in children, mainly in Japan, for efficacy and safety assessment. The results of these studies support the adequacy of cefditoren for the treatment of community-acquired respiratory tract infections with a safety profile similar to previous oral antibiotics. From the data reviewed, it is concluded that cefditoren is an adequate option for the treatment of mild-to-moderate community-acquired respiratory infections, especially in geographical areas with a reported prevalence of phenotypes exhibiting nonsusceptibility to common oral antibiotics.

Keywords: acute exacerbations of chronic bronchitis, community-acquired pneumonia, pharyngotonsillitis, sinusitis, otitis media

Introduction: resistance issues and the development of new antibiotics

Appropriate use of antimicrobials is defined by the World Health Organization as “the cost-effective use of antimicrobials which maximizes clinical and therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance.”¹ Antimicrobial resistance is one of the most urgent health threats people face all around the world² and is emerging to every class of existing antibiotics, affecting environments, hospitals, and the community.³

Increasing awareness of optimizing therapy not only involves maximizing therapeutic outcome but also minimizing the risk of resistance emerging during therapy, both in the infecting pathogen and in the normal flora.⁴ While optimizing outcome is directed at the individual patient level, emergence of resistance is an ecological issue and a trade-off between these two objectives is not easy to achieve.⁴ There is a dynamic situation in which the introduction of new antimicrobials necessitated by the emergence of resistance to existing compounds produces new selective pressure that selects new resistances, thus closing the circle. Therefore, resistance selection and diffusion in the community derived from antibiotic consumption requires, in turn,

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new antibiotics. However, a new antibiotic is only needed if it can counter existing resistances and if it possesses limited capability of resistance selection in human microbiota (“ecological effect”).

Around 85%–90% of antibiotic consumption occurs in the community, with 80% of this consumption for the treatment of respiratory tract infections.⁵ The most prevalent bacterial isolates causing respiratory infections in the community (*Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae*) are part of normal flora in humans, with the nasopharynx as the exclusive host. Antibiotic consumption can select resistant populations or subpopulations present in the nasopharynx that can be further transmitted to other individuals.

S. pneumoniae is a natural transformable bacterial pathogen showing rapid evolution in response to clinical interventions. Following the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) for immunization in children, the incidence of invasive pneumococcal disease has declined both in children and adults (reflecting “herd immunity”).⁶ The decrease in the incidence of invasive disease caused by serotypes included in PCV7 runs in parallel with decreases in nonsusceptibility to penicillin (oral) and erythromycin among invasive isolates, from both adults and children,^{7,8} but not among noninvasive isolates such as those from middle-ear fluid.⁹ However, emergence of serotypes not encompassed by the vaccine is worrisome and may be associated with heightened antimicrobial resistance and virulence.⁶ In Spain, recent published data show that nonsusceptibility rates to penicillin/erythromycin are around 20% among invasive isolates⁸ but around 45%–50% among middle-ear isolates.⁹ Worldwide, approximately 30% of isolates are resistant to macrolides¹⁰ and a similar percentage of *S. pneumoniae* are now considered multidrug resistant.¹¹ In contrast, rates of resistance to fluoroquinolones are still low.¹²

However, antibiotic pressure does not always result in the emergence of resistance. In the case of *S. pyogenes*, consumption of β -lactams has not resulted in the appearance of penicillin resistance, probably because of the absence of selectable variants carrying mechanisms of β -lactam resistance.¹³ In contrast, the rate of erythromycin resistance varies among countries, ranging from 6.9% in the USA¹⁴ to 25.6% in Hong Kong.¹⁵ In a recent study performed in Eastern Europe, the rate of erythromycin resistance in *S. pyogenes* was low (<10%) in Romania and Baltic countries, intermediate (10%–20%) in Poland and the Czech Republic, and high (>25%) in Hungary and Slovakia.¹⁶ In Spain, the erythromycin resistance rate was 19.0% in 2006–2007.¹⁷

In 2000, the first fluoroquinolone-resistant *S. pyogenes* isolate was reported;¹⁸ since then, reports of such isolates have occurred in the USA, Europe, and Japan.^{19–22}

Haemophilus influenzae resistance to fluoroquinolones continues to be exceptionally rare; however, this species is intrinsically resistant to macrolides, which is associated with the presence of efflux pumps in virtually all strains.²³ Ampicillin resistance varies on a geographical and temporal basis, from 8.7% in South Africa to approximately 30% in Asia²⁴ and the USA.²⁵ In Europe, mean ampicillin resistance has been reported as 16.4%, with resistance due to β -lactamase production ranging from 17.6% in France to 0% in Germany and The Netherlands.²⁶ With respect to strains showing mutations in the *ftsI* gene encoding PBP3 (β -lactamase-negative ampicillin-resistant [BLNAR] strains and β -lactamase positive amoxicillin/clavulanate-resistant [BLPACR] strains), one study carried out in Europe and Canada in 2006–2007 showed an 11.4% prevalence of genotypic BLNAR.²⁷ The country with the highest prevalence was Japan, with 42.9% BLNAR²⁸ and an increase in the prevalence of BLPACR from 1999 to 2008.²⁹

In vitro activity and pharmacokinetics/pharmacodynamics of cefditoren

The intrinsic activity of cefditoren against *S. pneumoniae* isolates has been explored in different studies.^{30–41} Cefditoren showed high intrinsic activity against penicillin-susceptible strains (minimum inhibitory concentration [MIC]₉₀ from ≤ 0.03 to 0.06 $\mu\text{g/mL}$), with MIC₉₀ ranging from 0.25 to 0.5 $\mu\text{g/mL}$ against penicillin-intermediate and from 0.5 to 1 $\mu\text{g/mL}$ against penicillin-resistant isolates. MIC values against penicillin-intermediate and -resistant strains were lower than those of amoxicillin, cefdinir, cefprozil, cefuroxime, cefixime, cefibuten, cefpodoxime, erythromycin, clarithromycin, and azithromycin,^{32–41} with the MIC₉₀ of cefditoren against penicillin nonsusceptible isolates one-dilution lower than that of cefotaxime. In the most recently published surveillance, the MIC₉₀ of cefditoren was similar to that of ceftriaxone.⁴²

Against *S. pyogenes* and *H. influenzae*, cefditoren has demonstrated markedly high intrinsic activity, with an MIC₉₀ of ≤ 0.06 $\mu\text{g/mL}$ in the studies performed.^{16,17,32,34,36,41,43–47} In the case of *H. influenzae*, the high intrinsic activity of cefditoren was maintained against strains exhibiting *ftsI* mutations in contrast to amoxicillin/clavulanate and cefuroxime.^{43,45,46}

Cefditoren is orally administered as cefditoren-pivoxil, which is further hydrolyzed during absorption and distributed in the blood as active cefditoren. In fasting patients, the oral

bioavailability of cefditoren-pivoxil is low (15%–20%), but when administered with high-fat meals, the mean maximum concentration (C_{\max}) and area under the concentration–time curve (AUC) values for cefditoren increase to 50% and 70%, respectively.⁴⁸ In a Phase I study administering a single 400 mg dose of cefditoren-pivoxil with a high-fat meal to Caucasian male subjects ≥ 18 years of age, values of the pharmacokinetic parameters determined were: $C_{\max} = 3.7 \pm 0.7 \mu\text{g/mL}$, time to achieve maximum concentration in serum (T_{\max}) = 2 h, $\text{AUC}_{0-\infty} = 12.5 \pm 1.6 \mu\text{g} \times \text{h/mL}$ and half-life time to achieve C_{\max} (T_{\max}) ($t_{1/2}$) = 1.54 ± 0.20 h.⁴⁹ Binding to plasma proteins (primarily human serum albumin) averages 88% for cefditoren.⁴⁸

As for all β -lactams, the pharmacokinetic/pharmacodynamic parameter predicting bacterial eradication and subsequent efficacy for cefditoren is the time (expressed as % dosing interval) that serum concentrations exceed the MIC of the infecting pathogen (% $t > \text{MIC}$). Values of 33% $t > \text{MIC}$ are considered bacteriostatic endpoints⁵⁰ and those of 40% $t > \text{MIC}$ as predictive values for clinical cure in humans.^{51,52} To investigate the pharmacodynamic coverage of cefditoren, a Monte Carlo simulation was performed⁵³ using data from the mentioned Phase I study in ten healthy male volunteers, where 400 mg of cefditoren-pivoxil was administered orally as single dose after a high-fat meal.⁴⁹ Cut-off values considered were 33% $t > \text{MIC}$ and 40% $t > \text{MIC}$. Target attainments $> 90\%$ were obtained for MICs of 0.5 $\mu\text{g/mL}$ for total drug (using both cut-off values) and 0.25 $\mu\text{g/mL}$ (33% $t > \text{MIC}$) and 0.12 $\mu\text{g/mL}$ (40% $t > \text{MIC}$) for the free drug.⁵³ This means that, using the strictest cut-off (40% $t > \text{MIC}$), concentrations obtained after administration of 400 mg cefditoren-pivoxil cover isolates with MICs up to 0.5 $\mu\text{g/mL}$ (total drug) and up to 0.12 $\mu\text{g/mL}$ (free drug), with a probability of $\geq 96\%$.⁵³ Taking advantage of the fact that cefditoren protein-binding rates in mice and humans are almost identical, study of a pneumococcal sepsis mouse model was undertaken. Animals were infected with penicillin-intermediate and -resistant isolates (MICs of 1 and 2 $\mu\text{g/mL}$ for penicillin and cefditoren, respectively) and 100% survival rates (vs 0% in untreated controls) were linked to cefditoren $t > \text{MIC} \approx 35\%$ (free $t > \text{MIC} \approx 20\%$),⁵⁴ values lower than those classically considered for therapeutic efficacy.

Clinical studies of efficacy

Pharyngotonsillitis

Several studies^{55–59} have been published on cefditoren in recent years, providing additional information to data obtained from clinical trials performed during the clinical development of cefditoren.^{60–62}

The most recently published study, by Tsumura et al compared cefditoren-pivoxil for 5 days versus amoxicillin for 10 days in children with group A beta-hemolytic streptococci acute tonsillopharyngitis in Japan.⁵⁵ No difference in clinical efficacy was found between both arms (100% for cefditoren vs 97.9% for amoxicillin), with 100% bacteriological efficacy in both groups.⁵⁵ Changes in oral microflora were also assessed, showing absence of flora disturbance with cefditoren in contrast with amoxicillin, which produced a clear decrease in oral microbial flora.⁵⁵

The same comparator was used in the study by Ozaki et al where children were randomized to receive either 3 mg/kg cefditoren-pivoxil three times daily (tid) for 5 days (103 patients; mean age: 5.5 ± 2.3 years) or amoxicillin 10 mg/kg tid for 10 days (155 patients; mean age: 5.2 ± 2.0 years).⁵⁶ The 258 isolates recovered showed MIC_{90} values of 0.06 $\mu\text{g/mL}$ for amoxicillin and $\leq 0.03 \mu\text{g/mL}$ for cefditoren.⁵⁶ Eradication was 100% with amoxicillin and 99% with cefditoren-pivoxil, without differences in recurrence rates during the 4-week follow-up period: 9.7% in the amoxicillin arm and 7.8% in the cefditoren-pivoxil arm.⁵⁶

In a different open prospective multicenter study by Sakata, cefditoren-pivoxil (3 mg/kg tid) was administered for 7 days to 90 enrolled children (age range: 8 months to 12 years).⁵⁷ A total of 79 patients complied with treatment intake and follow-up visits (at the end of therapy and 1 month after end of therapy) and were included in the efficacy analysis. Isolates of the same basal T type were found at the end of therapy in four patients and five patients presented with recurrence 1 month after the end of therapy (again with the same T type and pulsed field gel electrophoresis pattern).⁵⁷

Kawamata et al evaluated the efficacy of cefditoren in an open multicenter study (147 centers) including a large number of children presenting with *S. pyogenes* laryngopharyngitis (464 patients) or tonsillitis (254 patients).⁵⁸ Age range was 9 months to 14 years (median age: 5 years) and mean daily doses were $\geq 9 \text{ mg/kg}$ and $< 13.5 \text{ mg/kg}$.⁵⁸ The clinical response rate was 98.5% for laryngopharyngitis and 98.4% for tonsillitis.⁵⁸ In the subset of patients in which bacteriological response could be assessed (205 for laryngopharyngitis and 119 for tonsillitis), the *S. pyogenes* eradication rate was 94.6% and 92.4%, respectively.⁵⁸

In two of these three studies performed in Japan,^{56,57} the bacteriological recurrence rate ranged from 6.3% to 9.7% in the treatment of *S. pyogenes* pharyngotonsillitis with β -lactams. It has been reported that clinical isolates from recurrent streptococcal pharyngitis show emm type-specific features, with emm12 the most frequently detected

(expressing PrtF1 protein that allows higher invasive capability) followed by emm6 (more likely producing biofilm, thus allowing embedded *S. pyogenes* survival).⁵⁹ In the absence of specific resistance traits, localization of *S. pyogenes* in biofilms or inside tonsillar tissue can contribute to functional antibiotic resistance.^{63,64} In addition, with respect to β -lactams that can be hydrolyzed by β -lactamases, the presence of resident bacteria producing these inactivating enzymes (as with *H. influenzae* isolated from adeno-tonsil samples that also produces biofilms⁶⁵) and the specific resistance traits in these indirect pathogens have also been proposed as an explanation for treatment failures⁶⁶ and recurrences.⁶⁷

Cefditoren has been assessed in the treatment of pharyngotonsillitis episodes in children presenting recurrent pharyngotonsillitis. The study by Kikuta et al compared the efficacy obtained with 9 mg/kg tid cefditoren-pivoxil for 5 days versus 10 days in children (mean age: 6.77 ± 2.04 years) with a history of at least one previous episode of group A β -hemolytic streptococcal pharyngotonsillitis.⁶⁸ A total of 77 and 149 patients were included in the 5-day and 10-day treatment arms, respectively.⁶⁸ The frequency of previous episodes was 2.79 ± 1.35 .⁶⁸ Bacteriological failure was similar in the 5-day treatment arm (9.1%) and the 10-day treatment group (11.4%), but significantly higher recurrences were found in the 5-day treatment group (9.1% vs 0.7%; $P = 0.03$).⁶⁸ The interval between the preceding episode and the presently treated episode was lower ($P = 0.018$) in the treatment failure group (7.05 ± 7.31 months) than in the treatment success group (11.04 ± 14.57 months).⁶⁸ No differences in clinical failure were found between groups: 18.2% in the 5-day group versus 12.1% in the 10-day group.⁶⁸

Efficacy results of all these studies in children carried out in Japan support efficacy data obtained during the clinical development of cefditoren outside Japan in the treatment of pharyngotonsillitis, including that from 1322 randomized patients ≥ 12 years of age analyzed in an efficacy pooled analysis.⁶² No significant differences were found between the clinical response obtained with cefditoren-pivoxil and penicillin V (95.3% vs 92.2% at end of treatment and 91.9% vs 89.4% at late follow-up), but eradication of *S. pyogenes* was higher with cefditoren-pivoxil in the two studies with microbiological assessment:^{60,61} 90.4% versus 82.7% ($P = 0.002$) at the end of therapy and 84.7% versus 76.7% ($P = 0.008$) at the end of follow-up.⁶² Bacteriological efficacy was associated with higher clinical responses: 98.5%/99.0% at the end of treatment/follow-up for cefditoren-pivoxil and 99.3%/98.9% for penicillin V among patients showing

bacterial eradication, in contrast to clinical responses of 51.4%/32.7% at the end of treatment/follow-up for cefditoren-pivoxil and 49.2%/41.5% for penicillin V in patients showing *S. pyogenes* persistence.⁶²

Acute sinusitis

A recently published study of children in Thailand evaluated the efficacy of cefditoren in the treatment of bacterial rhinosinusitis.⁶⁹ This randomized, investigator-blinded controlled study in children aged 1–15 years compared the clinical efficacy provided by cefditoren-pivoxil 4–6 mg/kg twice per day (bid) (maximum dose 300 mg/day) versus 80–90 mg/kg/day amoxicillin amoxicillin/clavulanic acid (maximum dose 800 mg/day) administered bid for 14 days.⁶⁹ Changes in sinus symptoms were assessed daily by patients or parents using a quantitative symptom score. The primary outcome was rate of improvement 7 and 14 days after the initial visit and the secondary outcomes were relapse (defined as subjective rating of lack of improvement at day 21 or 28 in a patient rated as improved on day 14), recurrence (defined as sinus symptoms lasting for ≥ 10 days during the second month of follow-up in a patient rated as improved on day 28), and time to improvement.⁶⁹ A total of 66 patients were evaluated in the cefditoren-pivoxil group and 72 in the amoxicillin/clavulanic acid.⁶⁹ The median time to improvement was 3.0 days in both groups, without differences in rates of improvement between groups: 78.8% for cefditoren-pivoxil versus 84.7% for amoxicillin/clavulanic acid. The differences in rates of relapse at day 28 (9.1% for cefditoren-pivoxil vs 11.1% for amoxicillin/clavulanic acid) and recurrence rates (3.0% for cefditoren-pivoxil vs 5.6% for amoxicillin/clavulanic acid) were not statistically significant.⁶⁹

Efficacy results from children obtained in this study are in accordance with efficacy rates obtained in adults in the clinical trials performed during the clinical development of cefditoren outside Japan.^{62,70} Data from the three clinical trials were analyzed in a pooled analysis.⁶² Regimens compared were cefditoren-pivoxil 200 mg or 400 mg bid for 10 days, cefuroxime-axetil 250 mg bid for 10 days, and amoxicillin/clavulanic acid 875/125 mg bid for 10 days or 500/125 mg tid for 10 days. Clinical response was considered resolution or improvement in all pretreatment signs/symptoms with at least no worsening in the radiographic appearance of the sinus without the need for additional therapy. Patients were assessed pretherapy, at the end of treatment (within 48 hours of the last dose intake) and at the end of follow-up (7–14 days in one study and 34 ± 2 days after the last dose intake in the two remaining studies).⁶² A total of 1819 randomized patients

(mean age: 39.8 ± 14.3 years) were included: 1726 patients in the intention-to-treat and 1589 patients in the per-protocol populations.⁶² No differences ($P > 0.001$) in clinical response were found by comparing cefditoren-pivoxil 200 mg versus cefditoren-pivoxil 400 mg versus comparators both at the end of therapy (81.1% vs 80.2% vs 84.8%) and at the end of follow-up (72.1% vs 71.2% vs 77.4%).⁶²

Acute otitis media

No trials in the treatment of acute otitis media were performed during the clinical development of cefditoren outside Japan. A limited number of clinical studies have been published in Japan using cefditoren for the treatment of acute otitis media in children.^{71–74} The most recently published study corresponds to a huge postmarketing study in pediatric patients with acute otitis media performed in 305 medical institutions with 2006 patients.⁷¹ Age range was 1 month–14 years (median: 3 years) and up to 90% of patients presented with moderate/severe acute otitis media.⁷¹ The median daily dose of cefditoren was 10.0 mg/kg and median total treatment period was 7 days. A total of 1958 patients were eligible as efficacy analysis population, with a clinical response rate of 93.5%.⁷¹ In 832 patients, the causative organism was detected during the baseline microbiological examination, with 1217 isolates identified.⁷¹ *S. pneumoniae* (n = 397), *H. influenzae* (n = 393), and *Moraxella catarrhalis* (n = 166) together represented up to 78.6% of all isolates and 261 microorganisms were from other species.⁷¹ Among the 397 isolated *S. pneumoniae* strains, 58.9% were nonsusceptible to penicillin and among the 393 *H. influenzae* isolates, 28.0% were ampicillin nonsusceptible (mainly BLNAR strains: 27.2%).⁷¹ The per-pathogen clinical response rate was 89.7% for *S. pneumoniae*, 90.3% for *H. influenzae*, 92.2% for *M. catarrhalis*, and 92.7% for other microorganisms.⁷¹ In patients infected by isolates with specific resistance traits, clinical and bacteriological responses were 88% and 85.7%, respectively, for penicillin-intermediate pneumococci; 90.1% and 77.5%, respectively, for penicillin-resistant pneumococci; and 92.5% and 81.8%, respectively, for BLNAR *H. influenzae*.⁷¹

Lower respiratory tract infections

No further clinical studies have been published with cefditoren in the treatment of lower respiratory tract infections apart from those performed during the clinical development of cefditoren (four studies in community-acquired pneumonia [CAP] and three studies in acute exacerbations of chronic bronchitis [AECB]). Data from these clinical trials were pooled and analyzed by comparing cefditoren with

comparators (amoxicillin/clavulanic acid, cefuroxime-axetil, cefpodoxime, and clarithromycin) in a previous publication.⁷⁵ The per-pathogen bacteriological response was determined by pooling data from CAP and AECB studies. Response was defined as eradication or presumed eradication (absence of sputum for culture in a patient with clinical response).⁷⁵ A total of 406 *S. pneumoniae* isolates (56 of them nonsusceptible to oral penicillin) were recovered prior to treatment initiation, with similar bacteriological response rates for cefditoren and comparators (88.5% for cefditoren-pivoxil 200 mg, 92.0% for cefditoren-pivoxil 400 mg, and 89.9% for comparators).⁷⁵ Of the 56 penicillin nonsusceptible (MIC ≥ 0.12 $\mu\text{g/mL}$) *S. pneumoniae* isolates recovered, all those isolated from patients in the cefditoren-pivoxil 400 mg group (n = 20), 16/19 (84.2%) in the cefditoren-pivoxil 200 mg group, and 16/17 (94.1%) in the comparators group were eradicated or presumed eradicated.⁷⁵ Up to 29 of the 56 nonsusceptible isolates were penicillin resistant (MIC ≥ 2 $\mu\text{g/mL}$), 18 in the cefditoren-pivoxil arm and eleven in the comparators group. Eradication or presumed eradication rates among patients with penicillin-resistant initial isolates were 94.4% (17/18) for cefditoren (pooled 200 mg and 400 mg) and 90.9% (10/11) for comparators.⁷⁵ *H. influenzae* was isolated in baseline cultures of 595 patients: 224 patients in the cefditoren-pivoxil 200 mg arm, 175 in the cefditoren-pivoxil 400 mg arm, and 196 in the group of pooled comparators.⁷⁵ Bacteriological response rates were similar in all groups: 86.6% for cefditoren-pivoxil 200 mg versus 85.7% for cefditoren-pivoxil 400 mg versus 82.7% for comparators.⁷⁵

For the clinical response analysis, data from AECB and CAP studies were analyzed separately. Pooled analyses included 1379 patients with CAP and 1560 patients with AECB as the overall efficacy populations.⁷⁵ Similar clinical response rates were obtained for cefditoren-pivoxil 200 mg (91.8%), cefditoren-pivoxil 400 mg (89.2%), and comparators (91.5%) at the end of therapy and at the end of follow-up (87.8% vs. 85.9% vs. 90.4%, respectively) in CAP studies.⁷⁵ Similar response rates were found in AECB studies: cefditoren-pivoxil 200 mg (85.8%) versus cefditoren-pivoxil 400 mg (91.3%) versus comparators (87.1%) at the end of therapy and 81.3% versus 81.2% versus 83.3%, respectively, at the end of follow-up.⁷⁵ However, slightly higher efficacy was obtained with 400 mg cefditoren-pivoxil (vs 200 mg) by the end of therapy (91.3% vs 85.8%, $P = 0.014$).⁷⁵

Safety and tolerability issues

Safety data from 13 clinical trials carried out in adults during the clinical development of cefditoren outside Japan for the

treatment of community-acquired respiratory infections were analyzed in a pooled analysis and showed that the adverse event profiles of cefditoren-pivoxil and comparators are similar.⁷⁶ For both groups, diarrhea was the most frequent adverse event (9.9% for cefditoren vs 6.9% for comparators) followed by vaginosis among female populations (3.9% vs 4.6%), nausea (3.5% vs 3.6%), abdominal pain (1.8% vs 1.1%), and dyspepsia (1.1% vs 0.9%).⁷⁶

New data from recently published studies update the information mainly with data from children in Japan. In a postmarketing surveillance evaluating safety in 2006 children with acute otitis media treated with cefditoren-pivoxil (median daily dose: 10.0 mg/kg with a median total treatment period of 7 days), the incidence of adverse reactions was 1.79%, without unexpected or serious adverse drug reactions reported.⁷¹ The most frequent adverse drug reaction was diarrhea (1.30%) that resolved or subsided during cefditoren-pivoxil treatment or after discontinuation or completion of therapy in all cases.⁷¹ Data from the clinical studies carried out with cefditoren in the treatment of pharyngotonsillitis from 2007 to 2010 in Japan showed that the percentage of adverse events was very low and diarrhea was the most frequent event.^{56–58} In the largest study (734 children), the incidence of adverse reactions was 1.50% (eleven events in eleven patients), with three events of diarrhea and three of hematuria in urinalysis without clinical symptoms.⁵⁸ In a study carried out in children in Thailand comparing cefditoren-pivoxil (66 patients) with amoxicillin/clavulanic acid (72 patients) for 10 days in the treatment of acute bacterial rhinosinusitis, the most frequent adverse event was diarrhea, with significant ($P = 0.02$) differences in the percentages found for both compounds (4.5% with cefditoren-pivoxil vs 18.1% for amoxicillin/clavulanic acid).⁶⁹

Patients ingesting pivalic acid containing prodrugs may develop hypocarnitinemia.⁷⁷ However, it has been reported that net carnitine losses after cefditoren-pivoxil administration are <10% of body stores, thus it is not likely to result in adverse effects.⁷⁸ Carnitine metabolism was studied in 16 pediatric patients under treatment with cefditoren-pivoxil, with increased carnitine excretion and a decrease in free carnitine in serum that disappeared when dosing was terminated without carnitine-related side effects.⁷⁹ Nevertheless, two reports on clinical manifestations of hypocarnitinemia after cefditoren-pivoxil administration can be found in the literature: one reporting a carnitine-associated encephalopathy within hours of cefditoren-pivoxil administration for infection control after hysterectomy in a 47-years old woman⁸⁰ and the other in an 18-month child after 6 months of treatment for untreatable acute otitis media.⁸¹

Optimizing cefditoren use

The most prevalent respiratory infections in the community are pharyngotonsillitis, otitis media, sinusitis, AECB, and CAP, with *S. pyogenes* the most prevalent bacterial isolate from pharyngotonsillitis and *S. pneumoniae* and *H. influenzae* the most prevalent from the latter four infections. New antibiotics aiming to treat community respiratory infections should address the current issue of these bacterial species' resistance to common antibiotics.

As previously described, the main resistance issues in terms of *H. influenzae* is their resistance to macrolides in virtually all strains due to efflux pumps²³ and the increasing prevalence of BLNAR and BLPACR phenotypes in certain geographical areas.^{27–29} These phenotypes/genotypes should be considered resistant to oral β -lactams such as amoxicillin, amoxicillin/clavulanic acid, cefaclor, and cefuroxime.⁸² Nontypable *H. influenzae* is one of the most common bacterial causes of AECB.⁸³ It has been postulated that, with eradication, fewer viable pathogens remain in the bronchial tissue after antimicrobial treatment, requiring a longer period for the bacterial population to increase sufficiently to induce a new exacerbation,⁸⁴ although the acquisition of new strains has also been associated with an increased risk of new exacerbations.⁸⁵ Cefditoren may play an important therapeutic role in areas with significant rates of BLNAR/BLPACR phenotypes in the treatment of infections potentially caused by *H. influenzae* such as AECB.

During its clinical development, clinical trials of cefditoren in the treatment of lower respiratory tract infections showed its capability for eradication or presumed eradication of *S. pneumoniae*, including penicillin-intermediate and -resistant strains.⁷⁵ Introduction of conjugate vaccines has produced a shift in serotype distribution (with their associated nonsusceptibility). There has been a decrease in PCV7 serotypes (associated with a decrease in penicillin/erythromycin nonsusceptibility), with an increase in non-PCV7 serotypes (some of them, as serotype 19A, non susceptible to penicillin). Although cefditoren exhibited an intrinsic activity higher than that of other β -lactams against these serotypes,⁸⁶ there are no clinical studies showing the specific activity of cefditoren or other compounds against these emerging serotypes.

In addition, it has been pointed out that cefditoren may be the logical option for sequential therapy after intravenous treatment with cefotaxime or ceftriaxone for *S. pneumoniae* CAP.⁸⁷ This is based on cefditoren's spectrum and intrinsic in vitro activity, which is similar to that of intravenous third-generation cephalosporins (cefotaxime or ceftriaxone), together with its pharmacodynamic adequacy.⁸⁷

Macrolide resistance is the main resistance issue in *S. pyogenes*, but strains are uniformly susceptible to all β -lactams. However, clinical failures of penicillin/amoxicillin treatment derived from indirect protection of *S. pyogenes* by β -lactamases produced by *M. catarrhalis* or *H. influenzae* have been reported.⁸⁸ Indirect protection of *S. pyogenes* could also affect amoxicillin/clavulanic acid efficacy when BLPACR strains are present, as has occurred in vitro.⁶⁶ Oral β -lactams resistant to β -lactamases such as cefditoren could offer advantages by countering indirect pathogenicity, although clinical effects of indirect pathogenicity have been criticized by some authors.^{89,90}

Conclusion

Cefditoren is a third-generation cephalosporin active against the principal community-acquired respiratory tract pathogens (including resistance phenotypes) that has demonstrated efficacy and safety in comparative clinical trials in adults with AECB, CAP, sinusitis, or pharyngotonsillitis.

The results of new clinical studies of cefditoren in the treatment of pharyngotonsillitis, sinusitis, and otitis media in children, mainly in Japan, support the adequacy of cefditoren for the treatment of these community-acquired respiratory tract infections and demonstrate that cefditoren has a safety profile similar to that of previous oral β -lactams. Cefditoren may be an interesting option in the pediatric field where fluoroquinolones are not indicated. Nevertheless, additional clinical trials in pediatric otitis media are needed, since penetration to middle-ear fluid is unknown.

Cefditoren is thus indicated for the treatment of mild-to-moderate community-acquired respiratory tract infections (when it is feasible for medication to be taken with meals) particularly in geographical areas with a reported prevalence of phenotypes exhibiting nonsusceptibility to common oral antibiotics among community respiratory pathogens.

Disclosure

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