In vitro antibacterial activity of ceftobiprole against clinical isolates from French teaching hospitals: proposition of zone diameter breakpoints

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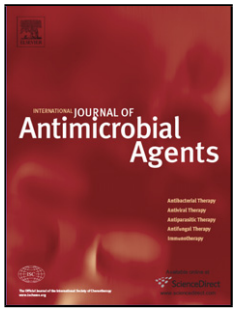

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In vitro antibacterial activity of ceftobiprole against clinical isolates from French teaching hospitals: proposition of zone diameter breakpoints

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ABSTRACT

The aims of this study were to determine the in vitro activity profile of ceftobiprole, a pyrrolidinone cephalosporin, against a large number of bacterial pathogens and to propose zone diameter breakpoints for clinical categorisation according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) minimum inhibitory concentration (MIC) breakpoints. MICs of ceftobiprole were determined by broth microdilution against 1548 clinical isolates collected in eight French hospitals. Disk diffusion testing was performed using 30 μg disks according to the method of the Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM). The in vitro activity of ceftobiprole, expressed by $MIC_{50/90}$ (MICs for 50% and 90% of the organisms, respectively) (mg/L), was as follows: meticillin-susceptible *Staphylococcus aureus*, 0.25/0.5; meticillin-resistant *S. aureus* (MRSA), 1/2; meticillin-susceptible coagulase-negative staphylococci (CoNS), 0.12/0.5; meticillin-resistant CoNS, 1/2; penicillin-susceptible *Streptococcus pneumoniae*, ≤0.008/0.03; penicillin-resistant *S. pneumoniae*, 0.12/0.5; viridans group streptococci, 0.03/0.12; β-haemolytic streptococci, ≤0.008/0.016; *Enterococcus faecalis*, 0.25/1; *Enterococcus faecium*, 64/128; Enterobacteriaceae, 0.06/32; *Pseudomonas aeruginosa*, 4/16; *Acinetobacter baumannii*, 0.5/64; *Haemophilus influenzae*, 0.03/0.12; and *Moraxella catarrhalis*, 0.25/0.5. According to the regression curve, zone diameter breakpoints could be 28, 26, 24 and 22 mm for MICs of 0.5, 1, 2 and 4 mg/L respectively. In conclusion, this study confirms the potent in vitro activity of ceftobiprole against many Gram-positive bacteria, including MRSA but not *E. faecium*, whilst maintaining a Gram-negative spectrum similar to the advanced-generation cephalosporins such as cefepime. Thus ceftobiprole appears to be well suited for the empirical treatment of a variety of healthcare-associated infections.

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1. Introduction

Ceftobiprole is a pyrrolidinone-3-ylidenemethyl cephalosporin [1,2] with demonstrated in vitro activity against meticillin-resistant *Staphylococcus aureus* (MRSA) [2–4], Enterobacteriaceae [1,4] and *Pseudomonas aeruginosa* [4]. Ceftobiprole was also found to be effective against ceftriaxone-resistant *Streptococcus pneumoniae* in a murine model of pneumonia [5], against MRSA both in rat and rabbit endocarditis [6,7] and against multiple Gram-negative and Gram-positive bacteria in a murine model of septicaemia [1] as well as in a mouse skin infection model with *P. aeruginosa* [5]. Consequently, ceftobiprole was selected for clinical development for treatment of hospital-acquired pneumonia and complicated skin and skin-structure infections [8].

2. Materials and methods

2.1. Bacterial strains

Over a 3-month period (October–December 2008), a total of 1548 non-consecutive, single-patient isolates were collected from eight French hospitals from the main types of pathological specimens from inpatients in hospital wards representing different medical and surgical specialties.

Isolates tested included 173 *S. aureus* (90 meticillin-susceptible and 83 meticillin-resistant), 104 coagulase-negative staphylococci (CoNS) (50 meticillin-susceptible and 54 meticillin-resistant), 63 *Enterococcus faecalis*, 40 *Enterococcus faecium*, 83 *S. pneumoniae*, 60 β-haemolytic streptococci, 19 viridans group streptococci, 129

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Escherichia coli, 114 *Klebsiella pneumoniae*, 36 *Klebsiella oxytoca*, 90 *Enterobacter cloacae*, 49 *Enterobacter aerogenes*, 32 *Citrobacter* spp., 114 *Proteus mirabilis*, 45 *Morganella morganii*, 39 *Proteus vulgaris*, 10 *Providencia rettgeri*, 15 *Providencia stuartii*, 98 *P. aeruginosa*, 71 *Acinetobacter* spp., 31 *Stenotrophomonas maltophilia*, 7 *Burkholderia cepacia*, 71 *Haemophilus influenzae*, 19 *Haemophilus parainfluenzae* and 36 *Moraxella catarrhalis.* These included 30% urinary tract isolates, 19.9% respiratory tract isolates, 22.8% bloodstream isolates, 11.9% wound skin isolates and 15.4% isolates of other origin.

2.2. Antimicrobial susceptibility testing

Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) [9] and the Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM) method [10]. The disk diffusion test was also performed according to the CA-SFM method [10].

Zone diameter breakpoints were supported by charts relating MIC to zone diameter distributions according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints [11,12] approved by CA-SFM [10].

Quality control was performed by testing the following strains: MRSA U2A 1593; meticillin-susceptible *S. aureus* (MSSA) U2A 1825; *E. coli* U2A 1278; and *E. coli* U2A1764 (provided by the French National Reference Centre of Antibiotics, Institut Pasteur, Paris). Intercentre variabilities were similar to those usually observed for

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these techniques. All centres provided results not significantly different from those of the reference centre (with a 5% risk of error) (data not shown).

Results were examined to ensure that reported MICs were within acceptable standards set by the CLSI based on the following American Type Culture Collection (ATCC) quality control strains: *S. aureus* ATCC 29213; *E. faecalis* ATCC 29212; *E. coli* ATCC 25922; and *P. aeruginosa* ATCC 27853.

3. Results

Ceftobiprole MIC values were ≤4 mg/L for all strains of *S. aureus*, with MIC_{50} and MIC_{90} values (MICs for 50% and 90% of the organisms, respectively) of 0.25 mg/L and 0.5 mg/L for MSSA and 1 mg/L and 2 mg/L for MRSA.

Meticillin-susceptible CoNS were more susceptible ($MIC_{50/90}$ = 0.12/0.5 mg/L) to ceftobiprole than meticillin-resistant CoNS (MR-CoNS) isolates ($MIC_{50/90}$ = 1/2 mg/L). Thus, according to the proposed EUCAST breakpoints (≤4 mg/L), all staphylococci were susceptible to ceftobiprole.

MIC_{50} and MIC_{90} values of ceftobiprole against *E. faecalis* were 0.25 mg/L and 1 mg/L, respectively, and at a concentration of ≤2 mg/L all strains were inhibited. MIC_{50} and MIC_{90} values of ceftobiprole against *E. faecium* were 64 mg/L and 128 mg/L, respectively, and only 12.5% of strains had a MIC value of ≤2 mg/L.

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The activity of ceftobiprole against *S. pneumoniae* correlated well according to penicillin susceptibility. MICs varied from 0.03 mg/L for penicillin-susceptible isolates to 0.5 mg/L for penicillin-intermediate or -resistant isolates.

β-Haemolytic streptococci were very susceptible to ceftobiprole ($MIC_{50/90}$ = ≤0.008/0.016 mg/L). MICs of ceftobiprole for viridans group streptococci ranged from 0.06 mg/L to 2 mg/L.

Among cefotaxime-susceptible Enterobacteriaceae, MIC_{50} and MIC_{90} values were 0.06 mg/L and 1 mg/L, respectively. However, against cefotaxime-non-susceptible Enterobacteriaceae overall, MICs of ceftobiprole were notably increased, as the MIC_{50} and MIC_{90} values were 4 mg/L and 128 mg/L, respectively.

Using the proposed EUCAST breakpoints of ≤1 mg/L, a susceptibility rate of >90% was noted for *P. mirabilis*, *Providencia* spp., *Morganella* spp., *E. coli* and *K. pneumoniae*. *Proteus vulgaris* was refractory to ceftobiprole, with $MIC_{50/90}$ values of 32/64 mg/L and a susceptibility rate of only 23.1%.

Against ceftazidime-susceptible *P. aeruginosa* isolates, ceftobiprole MICs ranged from 0.5 mg/L to 32 mg/L, with an MIC_{50} of 4 mg/L and an MIC_{90} of 16 mg/L. Against ceftazidime-non-susceptible *P. aeruginosa*, ceftobiprole MICs were slightly higher, ranging from 1 mg/L to 128 mg/L ($MIC_{50/90}$ = 8/32 mg/L).

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Among ceftazidime-susceptible *A. baumannii* isolates, MIC_{50} and MIC_{90} values were 0.25 mg/L and 4 mg/L, respectively, but they increased to 0.5 mg/L and 64 mg/L among ceftazidime-non-susceptible isolates.

Most of the *B. cepacia* and *S. maltophilia* isolates tested were resistant to ceftobiprole, with $MIC_{50/90}$ values of 16/128 mg/L and 64/128 mg/L, respectively. Thus, percentage susceptibilities using the proposed breakpoint of ≤4 mg/L were 73.2% for *Acinetobacter* spp., 64.3% for *P. aeruginosa*, 42.9% for *B. cepacia* and 3.2% for *S. maltophilia*.

The MIC range of ceftobiprole against *H. influenzae* was ≤0.008–0.5 mg/L; MIC_{50} and MIC_{90} values were similar for ampicillin-susceptible isolates (0.03/0.12 mg/L) and ampicillin-non-susceptible isolates (0.06/0.12 mg/L). None of the isolates were β-lactamase-negative ampicillin-resistant (BLNAR) isolates.

The MIC range of ceftobiprole against the 36 *M. catarrhalis* isolates tested was ≤0.008 to 2 mg/L, with MIC_{50} and MIC_{90} values of 0.25 mg/L and 0.5 mg/L, respectively.

According to EUCAST MIC breakpoints of 1/4 mg/L for Enterobacteriaceae, 4/4 mg/L for *Pseudomonas* and staphylococci, 0.5/0.5 mg/L for streptococci and 2/4 mg/L for other species, zone diameter breakpoints with a 30 μg ceftobiprole disk content are supported by charts relating MIC to zone diameter distributions. They could be 26 mm and 22 mm (≥26 mm, susceptible; 22–25 mm, intermediate; and <22 mm, resistant) for Enterobacteriaceae (Fig. 1), 22 mm (≥22 mm, susceptible; and <22 mm,

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resistant) for *Pseudomonas* (Fig. 2) and staphylococci (Fig. 3), 28 mm (≥28 mm, susceptible; and <28 mm, resistant) for streptococci (data not shown), and 24 mm and 22 mm (≥24 mm, susceptible; 22–23 mm, intermediate; and <22 mm, resistant) for other species (data not shown).

4. Discussion

This study confirms the potency of ceftobiprole against MRSA. Both against MRSA and MR-CoNS, ceftobiprole had MIC_{50} and MIC_{90} values of 1 mg/L and 2 mg/L, respectively [13,14]. As an agent to combat MRSA, ceftobiprole is intended for use in hospitals, an environment where antibiotic resistance is well established.

Regardless of penicillin susceptibility status, ceftobiprole shows potent activity against *S. pneumoniae*, although ceftobiprole MIC_{90} values increased with growing resistance to penicillin.

The activity of ceftobiprole against Enterobacteriaceae depended largely on the β-lactam resistance phenotype of the tested isolates. Ceftobiprole was highly active against cefotaxime-susceptible and non-extended-spectrum β-lactamase (ESBL)-producing isolates. Some isolates of *P. vulgaris*, *Enterobacter* spp., *C. freundii* and *K. oxytoca* appeared to be more resistant to ceftobiprole. The cefotaxime-susceptible isolates that are resistant to ceftobiprole (7.76%) were especially *P. vulgaris* and *K. oxytoca*.

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A large proportion of the cefotaxime-intermediate isolates (77.8%) were susceptible to ceftobiprole and, interestingly, approximately one-quarter of the cefotaxime-resistant isolates (25.4%) were susceptible to ceftobiprole.

The antibacterial spectrum of ceftobiprole against Enterobacteriaceae is most close to that of cefepime [13], although this new cephalosporin was more unstable than cefepime to some ESBLs and some class C or A cephalosporinases [3]. As with other cephalosporins, the in vitro activity of ceftobiprole against ESBL-positive isolates of *E. coli*, *K. pneumoniae* and *E. cloacae* was notably diminished [6].

Ceftobiprole demonstrated variable activity against the non-fermentative Gram-negative bacilli tested, as shown by 73.2% susceptibility at ≤4 mg/L and MIC_{50} values of 0.5 mg/L for *A. baumannii* and no activity against *B. cepacia* (MIC_{50} = 16 mg/L) and *S. maltophilia* (MIC_{50} = 64 mg/L). Numerous ceftazidime-susceptible isolates of *P. aeruginosa* were susceptible to ceftobiprole (77.5%). At a susceptible breakpoint equal to 4 mg/L, 64.3% of *P. aeruginosa* isolated tested in this study would be judged as being treatable with ceftobiprole. Mutants selected with cefepime had increased AmpC activity, whereas mutants selected with ceftobiprole did not overexpress AmpC. However, increased efflux and not AmpC derepression is the predominant response to ceftobiprole for first-step mutations in *P. aeruginosa* [15].

Like many third- and fourth-generation cephalosporins, ceftobiprole was very active against respiratory pathogens such as *H. influenzae*, *H. parainfluenzae* and *M. catarrhalis*, regardless of ampicillin resistance.

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Finally, the MIC breakpoints that could be adopted in Europe were 1/4, 4/4, 0.5/0.5 and 2/4 mg/L for Enterobacteriaceae, *Pseudomonas* and staphylococci, streptococci and other species, respectively.

According to the graphs relating MIC to zone diameter distributions (Figs 1–3), zone diameter breakpoints could be 28, 26, 24 and 22 mm for MICs of 0.5, 1, 2 and 4 mg/L, respectively, by using the CA-SFM disk diffusion method.

The current study confirms the potent activity of ceftobiprole against a broad range of Gram-positive and Gram-negative pathogens. This activity, together with the known advantages of β-lactams (cidality, diffusion, pharmacokinetics, etc.), may allow ceftobiprole to be used as monotherapy for serious hospital-acquired infections where combination therapy would otherwise be required. The clinical availability of ceftobiprole will present the option for the treatment of MRSA, including those strains possessing reduced susceptibility to vancomycin, with a therapeutic broad-spectrum cephalosporin coupled with environmental (patient or hospital) suppression of MRSA. In addition, given the broad-spectrum activity against species involved in nosocomial infections (MRSA, Enterobacteriaceae and *P. aeruginosa*), ceftobiprole appears well suited for use in the empirical treatment of a variety of healthcare-associated infections.

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5. Conclusion

This study performed on a large number of isolates (*n* = 1548) confirms the potent in vitro activity of ceftobiprole against clinically relevant Gram-positive and Gram-negative pathogens.

Ceftobiprole demonstrated excellent activity against wild-type isolates with very low MICs. Notably, ceftobiprole displayed potent activity against MRSA and also against Enterobacteriaceae, *P. aeruginosa* and *A. baumannii.* The in vitro profiles of ceftobiprole observed against cephalosporinase- or ESBL-producing isolates and towards some species with special β-lactamases (e.g. *P. vulgaris*, *K. oxytoca* etc.) illustrate the necessity for widespread geographical surveillance.

Moreover, this study allowed us to determine zone diameter breakpoints, which are 28, 26, 24 and 22 mm for MICs of 0.5, 1, 2 and 4 mg/L, respectively, used for clinical categorisation according to the EUCAST MIC breakpoints.

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Competing interests

None declared.

Ethical approval

Not required.

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Fig. 1. Distribution of ceftobiprole minimum inhibitory concentrations (MICs) and zone diameters against 673 Enterobacteriaceae isolates. S, susceptible, R, resistant.

Fig. 2. Distribution of ceftobiprole minimum inhibitory concentrations (MICs) and zone diameters against 98 *Pseudomonas aeruginosa* isolates. S, susceptible, R, resistant.

Fig. 3. Distribution of ceftobiprole minimum inhibitory concentrations (MICs) and zone diameters against 277 staphylococcal isolates. S, susceptible, R, resistant.

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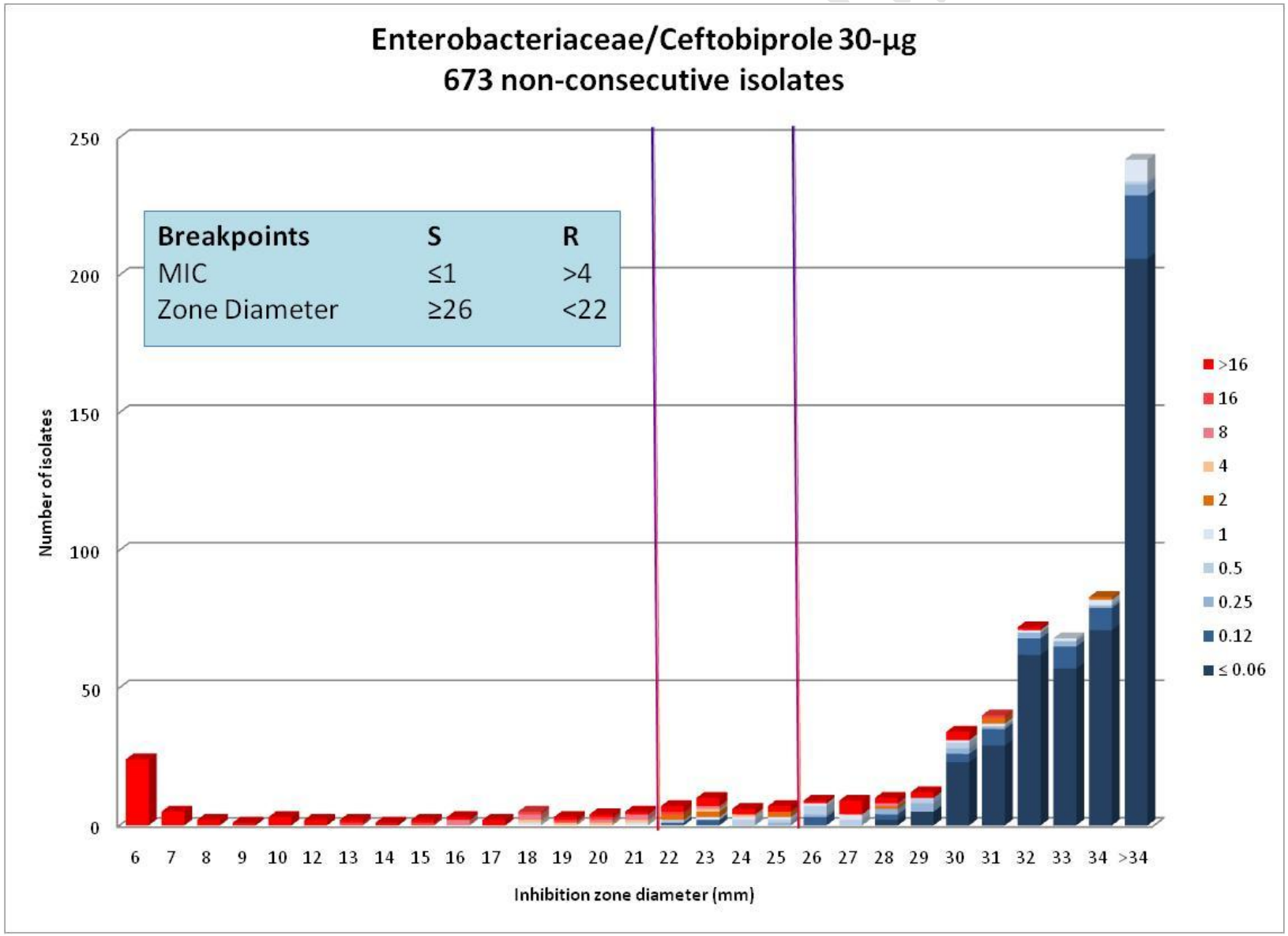

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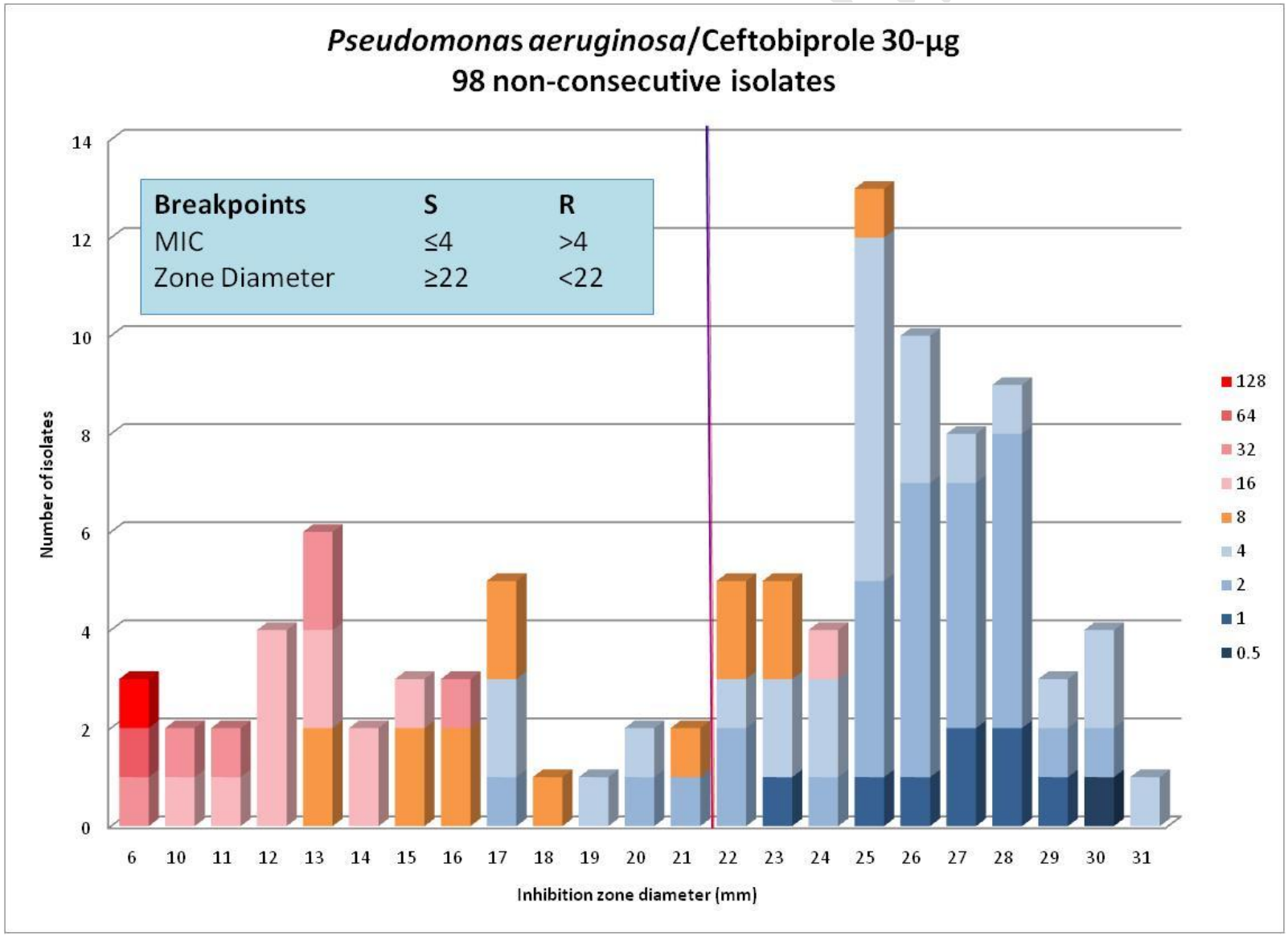

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