

Correspondence

Carbapenems in febrile neutropenic patients

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Harold Gaya*

Department of Microbiology, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

*On behalf of the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer.

Sir,

Deaney & Tate¹ report a meta-analysis of trials conducted with imipenem/cilastatin in the treatment of fever in neutropenic cancer patients. We believe that this meta-analysis was statistically well-conducted and the authors acknowledge certain limitations inherent in this approach. In particular, the absence of an intention-to-treat analysis in this study is notable, since this is an important potential source of bias.

However, we make a number of additional observations regarding the conclusions drawn by the authors. It is important to consider the extent and duration of neutropenia when considering the treatment of neutropenic patients. Essentially there are two types of neutropenic episode. Short episodes, lasting less than 10 days, occur mostly in patients with solid tumours. These episodes are associated with a relatively low risk of life-threatening infection and studies have demonstrated that infections that occur during such episodes may be treated effectively using monotherapy with a broad-spectrum agent such as ceftazidime or a carbapenem.^{2,3} Periods of prolonged and profound neutropenia, which may last up to 3–4 weeks, occur more commonly in patients with haematological malignancies. These episodes are associated with a greater risk of life-threatening infection, the treatment of which has been investigated in relatively few studies. We suggest that because this analysis did not differentiate between these risk groups, its implications for their treatment are unclear.

Furthermore, the authors compared the various studies with imipenem–cilastatin according to the rates of clinical failure. Analysis of success rates was not considered feasible because the studies employed a number of different criteria for success. However, the studies also used a variety of criteria for failure, including death or failure to respond after 72 h of treatment, which are very different

endpoints. Again, this would seem to compromise the validity of the analysis.

It should be emphasized that imipenem–cilastatin cannot be considered superior to a β -lactam–aminoglycoside combination in this setting on the basis of this analysis alone. There is no substitute for statistically robust prospective randomized studies.⁴ We recently performed such a study comparing a new carbapenem, meropenem (1 g every 8 h), with an established combination regimen, ceftazidime (2 g every 8 h) plus amikacin (20 mg/kg once-daily).⁵ A total of 1034 patients were randomized in this trial; calculations based on experience from previous trials indicated that this number was sufficient to detect a 10% increase in the success rate in the meropenem group relative to the combination group with a type I error level of 5% and a power in excess of 90%. More than 75% of the patients recruited had leukaemia or lymphoma and the median duration of neutropenia was 16 days and 17 days in the meropenem and ceftazidime/amikacin groups, respectively. Treatment success was defined according to the stringent definitions of our group and the Immunocompromised Host Society.⁴ Intention-to-treat analysis showed that the rates of clinical success achieved by meropenem (270/483; 56%) and ceftazidime/amikacin (245/475; 56%) were equivalent.

Deaney & Tate¹ did not consider the tolerability of imipenem–cilastatin in their meta-analysis. Some trials in neutropenic patients have observed a relatively high incidence of seizures and nausea and vomiting with imipenem–cilastatin, used at a dosage of 1 g every 6 h.^{3,6,7} In our trial with meropenem, no drug-related seizures occurred and vomiting was reported in only one patient in each treatment group.

In conclusion, large prospective randomized trials provide the best indication of the usefulness of a drug in a given clinical situation. To date the largest such trial with a carbapenem in this setting has demonstrated that meropenem is as effective and well-tolerated as ceftazidime plus amikacin in persistently and profoundly neutropenic cancer patients.⁵

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Are TEM β -lactamases encoded by pBR322 and Bluescript plasmids enzymatically indistinguishable?

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E. B. Chaibi^{a*}, J. Peduzzi^a, M. Barthelemy^a and R. Labia^{a,b}

^aMuséum National Histoire Naturelle, CNRS URA 401, 63 rue Buffon, 75231 Paris Cedex 05; ^bUMR 175, CNRS-MNHN, 6 rue de l'Université, 29000 Quimper, France

Tel: +33-40 79 31 41; Fax: +33-40 79 31 47.

Sir,

Recently, Fonze *et al.*¹ published the three-dimensional structure of TEM-1 β -lactamase, an enzyme frequently encountered in clinical isolates of bacteria resistant to some β -lactams, particularly penicillins. Jelsch *et al.*² and Strynadka *et al.*³ have also reported the three-dimensional structure of a β -lactamase, which is referred to as TEM-1, although it has two amino acid substitutions, Ile-84 for Val and Val-184 for Ala, relative to the true TEM-1 sequence,⁴ using the ABL numbering scheme for class A β -lactamases.⁵ These amino acid substitutions are the result of two base changes which were introduced within the *bla* gene in order to remove the *Pst*I and *Hinc*II restriction sites.⁶

Sowek *et al.*⁷ claimed that these two enzymes were enzymatically indistinguishable. We have compared the kinetic parameters of natural TEM-1 β -lactamase, encoded by the plasmid pBR322,⁴ with those of TEM-Bluescript (TEM-Bs) encoded by the plasmid Bluescript.⁶ The TEM-Bs β -lactamase amino acid sequence is identical to that used by Jelsch *et al.*² and Strynadka *et al.*³ for crystallographic studies. We purified the β -lactamases to 95% homogeneity as previously described,⁸ and determined their substrate and inhibitor profiles according to Lenfant *et al.*⁹

The TEM-Bs β -lactamase had slightly higher K_m values

Table. Comparative kinetic parameters of TEM-1 and TEM-Bs β -lactamases

Antibiotics	TEM-1 ^a			TEM-Bs ^a			Ratio ^b (%)
	k_{cat} (s ⁻¹)	K_m (μ M)	k_{cat}/K_m (μ M ⁻¹ ·s ⁻¹)	k_{cat} (s ⁻¹)	K_m (μ M)	k_{cat}/K_m (μ M ⁻¹ ·s ⁻¹)	
Benzylpenicillin	1200	22	54.5	625	28	22.3	40.9
Amoxycillin	920	25	36.8	580	30	19.3	52.5
Ticarcillin	115	10	11.5	62	15	4.1	35.9
Carbenicillin	132	13.5	9.8	75	15	5.0	51.1
Piperacillin	990	45	22.0	655	60	10.9	49.6
Cephalothin	122	230	0.5	75	350	0.2	40.4
Cefoperazone	470	260	1.8	212	240	0.9	48.9
Cephaloridine	2045	950	2.2	1100	1000	1.1	51.1
Clavulanic acid		0.2 ^c			0.1 ^c		
Sulbactam		0.9 ^c			0.7 ^c		
Tazobactam		0.01 ^c			0.01 ^c		

^aThe standard deviation for analysis was $\pm 10\%$.

^b k_{cat}/K_m values of TEM-Bs relative to those of TEM-1.

^cMeasured as K_i by competition with benzylpenicillin.

than those of TEM-1 for all the β -lactams except cefoperazone (Table). K_i values of clavulanic acid, sulbactam and tazobactam were identical for both β -lactamases. Moreover, for all β -lactam antibiotics, k_{cat} values of TEM-Bs were approximately half those of TEM-1. Thus, the catalytic efficiencies (k_{cat}/K_m) of TEM-Bs were half to one-third those of TEM-1.

Most of the new extended-spectrum β -lactamases hydrolysing third-generation cephalosporins,¹⁰ and enzymes resistant to β -lactamase inhibitors such as clavulanic acid and sulbactam are derived from the TEM-1 β -lactamase.¹¹ The interaction between these enzymes and their substrates is usually investigated by molecular modelling, starting from the three-dimensional structure of TEM-type β -lactamase (TEM-1 or TEM-Bs). From the literature, the optimum crystallization conditions of the proteins are not the same. Moreover, superposition of their α -carbons shows a root-mean-square deviation close to 0.5 Å.

When comparing kinetic data and molecular modelling from different authors, great care needs to be exercised concerning the origin of the enzymes

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In-vitro activity of ketolides against mycoplasmas

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C. M. Bébéar^a, H. Renaudin^a, M. D. Aydin^a, J. F. Chantot^b and C. Bébéar^{a*}

^aLaboratoire de Bactériologie, Hôpital Pellegrin, Place Amélie Raba Léon, 33076 Bordeaux;

^bDépartement des Recherches en Anti-infectieux, Roussel-Uclaf, 102 route de Noisy, 93235 Romainville Cedex, France

*Corresponding author. Tel: +335-56-79-56-67; Fax: +335-56-79-60-42.

Sir,

Tetracyclines and macrolides are the two groups of antibiotics commonly used for the treatment of mycoplasmal infections. However, macrolides show differential activity according to the species. Ketolides, a new class of antibacterial macrolides synthesized by Roussel-Uclaf, are characterized by a 3-keto group instead of the cladinose moiety. They have been shown to display a high in-vitro activity against multi-resistant pneumococci, as well as a well-balanced spectrum against other relevant respiratory pathogens.¹ Therefore, it was of interest to test their activity against mycoplasma species. The in-vitro activity of four ketolides, RU 004, RU 306, RU 469 and RU 399, was tested against clinical isolates and reference strains of *Mycoplasma pneumoniae* (seven strains), *Mycoplasma hominis* (11 strains), *Mycoplasma genitalium* (three strains), *Mycoplasma fermentans* (four strains), *Mycoplasma penetrans* (two strains) and *Ureaplasma urealyticum* (thirteen strains), and compared with that of erythromycin, clarithromycin, josamycin and azithromycin.²

Susceptibility testing of *M. pneumoniae*, *M. hominis*, *M. fermentans*, *M. genitalium* and *M. penetrans* was performed by an agar dilution method on Hayflick modified medium,³ inoculated with 10⁴–10⁵ colour changing units (CCU) and incubated at 37°C. The final concentrations of

Table. Comparative MICs of ketolides, reference macrolides and azithromycin against mycoplasmas

Antibiotic	MIC range (mg/L)					
	<i>M. pneumoniae</i> (n = 7)	<i>M. genitalium</i> (n = 3)	<i>M. hominis</i> (n = 11)	<i>M. fermentans</i> (n = 4)	<i>M. penetrans</i> (n = 2)	<i>U. urealyticum</i> (n = 13)
RU 004	≤0.01	≤0.01	0.5–2	0.5–1	0.01–0.1	0.01–0.02
RU 306	≤0.01	≤0.01	0.5–2	0.5–4	0.1	0.02–0.05
RU 469	≤0.01	≤0.01	1–16	4–8	0.01–0.1	0.02–0.1
RU 399	≤0.01	≤0.01	2–16	4–8	0.05–0.1	0.05–0.2
Erythromycin	≤0.01	≤0.01	>64	>64	1–4	0.5–2
Clarithromycin	≤0.01	≤0.01	>64	32–>64	0.2	0.1–0.2
Josamycin	0.02	0.02	0.1–0.5	0.2–0.5	0.5–1	0.2–0.5
Azithromycin	≤0.01	≤0.01	16–32	32–>64	0.2–0.5	1–2

antibiotics tested were 0.01–64 mg/L. The MIC was read as the lowest concentration of each drug completely inhibiting growth, when visible growth could be seen on the control plate without antibiotic. For *U. urealyticum*, the MICs were determined by a broth dilution method performed in microplates. Shepard liquid medium³ containing antibiotic dilutions (0.01–64 mg/L), was inoculated with *U. urealyticum* to yield approximately 5×10^3 to 5×10^4 CCU in 0.2 mL and incubated at 37°C. The final MIC was the lowest antibiotic concentration without colour change that remained stable after 40 h incubation.

The results of the in-vitro tests are given in the Table. Ketolides showed very high activity against *M. pneumoniae* and *M. genitalium*, comparable to that of erythromycin, other macrolides and azithromycin. Against *M. hominis* and *M. fermentans*, RU 004 and RU 306 were active, whereas the MICs of RU 469 and RU 399 were higher, but still lower than those of erythromycin, clarithromycin and azithromycin. Josamycin remained the most active against these organisms. All four ketolides showed the highest activity against *M. penetrans*. Ketolides were very active against all *U. urealyticum* strains, with the same activity against strains susceptible or resistant to tetracycline. The MICs of ketolides were lower than those of all the other products tested.

The MBCs of RU 004, the most active ketolide, and of the comparative compounds were determined for a reference strain of each species in test tubes containing 2 mL of Shepard broth medium for *U. urealyticum*, or 2 mL of Hayflick modified broth medium for the other mycoplasma species. When the MIC was recorded, 100 µL were transferred from tubes without colour change to 5 mL of fresh antibiotic-free broth. The MBC was defined as the lowest antibiotic concentration inhibiting a colour change in this culture within 4–10 days, according to the species.

The MBCs of RU 004 were identical to the MICs for *M. pneumoniae* and *M. genitalium*, as were the MBCs of erythromycin, josamycin, clarithromycin and azithromycin. Against *M. hominis* and *M. fermentans*, the MBCs of RU 004 were 16 and 1 mg/L respectively, lower than those of josamycin (32 and 16 mg/L), the only macrolide that gave low MICs against these two species. Against *M. penetrans*, the MBC was 0.2 mg/L, as compared with 64 mg/L of erythromycin and 4 mg/L of clarithromycin, josamycin and azithromycin.

To summarize, of the ketolides, RU 004 was the most active against all the mycoplasma species. Furthermore, this antibiotic was bactericidal against most of the mycoplasma strains tested, except *M. hominis*. Thus, RU 004 showed good potential for the treatment of respiratory and genital tract mycoplasmal infections.

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Susceptibility of multi-resistant *Streptococcus pneumoniae* to ciprofloxacin, ofloxacin and levofloxacin

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Peter C. Fuchs*, Arthur L. Barry and Steven D. Brown

The Clinical Microbiology Institute, PO Box 947, Tualatin, OR 97062, USA

*Tel: + 1-(503) 692-4690; Fax: + 1-(503) 692-6184.

Sir,

Resistance of *Streptococcus pneumoniae* to penicillin is now recognized as a worldwide phenomenon.¹ Penicillin-resistant strains, particularly with low-level resistance (MICs of 0.12–1.0 mg/L), are often still susceptible to some of the newer β -lactams such as some third-generation cephalosporins and carbapenems, but even with these drugs their MICs are significantly higher than against penicillin-susceptible strains.^{2,3} Pneumococcal resistance to several non- β -lactam antimicrobial agents is also more common among penicillin-resistant strains than among penicillin-susceptible ones.³ We recently assessed the effect of multiple drug resistance on the susceptibility of pneumococci to three fluoroquinolones (ciprofloxacin, ofloxacin and levofloxacin) and report our findings here.

From our collection of recent clinical isolates of *S. pneumoniae* from multiple US medical centres, 209 strains were selected for this study based on known antibiotic resistance patterns. These included 97 penicillin-resistant strains (MIC \geq 2.0 mg/L), 60 penicillin-intermediate strains (MIC = 0.12–1.0 mg/L) and 52 penicillin-susceptible strains (MIC \leq 0.06 mg/L). The number of drugs tested to which each strain was resistant varied from none to 11. Forty strains were susceptible to all antimicrobial agents tested.

Three quinolones (ciprofloxacin, ofloxacin and levofloxacin) were tested in parallel with 12 other agents, including six β -lactam and six non- β -lactam antimicrobial agents, and these are listed in the Table.

Antimicrobial susceptibility tests were performed by broth microdilution, following the procedure outlined by the National Committee for Clinical Laboratory Standards (NCCLS).⁴ All (100%) isolates were susceptible to vancomycin and levofloxacin. Of the other quinolones, 99% were susceptible to ofloxacin and 90% to ciprofloxacin. For the remaining antimicrobials, the proportion susceptible ranged from 25% for penicillin to 87% for clindamycin.

Not unexpectedly, the susceptibility to other β -lactams correlated strongly with susceptibility to penicillin. There was also a correlation between penicillin susceptibility and susceptibility to non- β -lactam, non-quinolone antimi-

crobinals excluding vancomycin. This was most striking for co-trimoxazole, for which the proportion susceptible decreased from 82% of penicillin-susceptible strains to 13% of penicillin-resistant strains.

There was also considerable correlation between resistance to several non- β -lactam agents and resistance to others. The strongest correlation occurred between chloramphenicol and tetracycline, with 100% of the 39 chloramphenicol-resistant strains being resistant to tetracycline, and between clindamycin and erythromycin, with 100% of the 27 clindamycin-resistant strains being resistant to erythromycin.

The geometric mean MIC of each of the three quinolones showed no appreciable differences in relation to penicillin susceptibility (Table). Minimal variations in quinolone geometric mean MICs were observed in relation to susceptibility categories of other antibiotics singly and in combination, but there was no correlation with these categories.

It is important to remember that the pneumococcal population in this study was a highly selected one and that the antimicrobial resistance described here should not be compared with other published reports describing populations of consecutive or randomly selected isolates. Most of the correlations we observed support the observations of other investigators.^{2,3} We also confirm studies demonstrating no correlation between ciprofloxacin resistance and penicillin resistance.² Furthermore, we found no correlation between any of the quinolone MICs and MICs of clindamycin, erythromycin, chloramphenicol, tetracycline or co-trimoxazole. Thus, these three quinolone antimicrobial agents share one important characteristic that might be considered in selecting a therapeutic anti-pneumococcal agent, i.e. they are not affected by resistance to other antibiotics. The role of ciprofloxacin in pneumococcal disease is unsettled since significant rates of failure to eradicate the organism in pneumococcal lower respiratory tract infections have been reported,⁵ as have clinical failures.⁶ Levofloxacin, because of its better blood and tissue levels, may, at least theoretically, be a preferable drug in this setting.

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Correspondence

Table. Geometric mean MICs of three quinolones in relation to susceptibility or resistance to other antibiotics when testing *S. pneumoniae*

Organism characteristic ^a	Number ^b	Geometric mean MIC mg/L for:		
		levofloxacin	ofloxacin	ciprofloxacin
Penicillin-susceptible	52	0.84	1.49	0.75
Penicillin-intermediate	60	0.86	1.55	0.87
Penicillin-resistant	97	0.85	1.52	0.82
Amoxicillin-susceptible	109	0.83	1.50	0.81
Amoxicillin-intermediate	39	0.91	1.62	0.82
Amoxicillin-resistant	61	0.86	1.51	0.83
Cefuroxime-susceptible	178	0.87	1.59	0.83
Cefuroxime-resistant	122	0.86	1.51	0.82
Cefepime-susceptible	107	0.85	1.53	0.81
Cefepime-intermediate	75	0.88	1.54	0.82
Cefepime-resistant	27	0.79	1.43	0.81
Cefotaxime-susceptible	113	0.86	1.54	0.82
Cefotaxime-intermediate	64	0.87	1.59	0.84
Cefotaxime-resistant	32	0.81	1.35	0.75
Imipenem-susceptible	118	0.84	1.50	0.81
Imipenem-intermediate	82	0.90	1.59	0.83
Imipenem-resistant	9	0.68	1.26	0.79
Clindamycin-susceptible	180	0.86	1.54	0.82
Clindamycin-resistant	27	0.84	1.47	0.79
Erythromycin-susceptible	142	0.85	1.52	0.79
Erythromycin-resistant	67	0.86	1.53	0.87
Tetracycline-susceptible	142	0.86	1.54	0.81
Tetracycline-resistant	67	0.84	1.50	0.84
Chloramphenicol-susceptible	170	0.85	1.52	0.81
Chloramphenicol-resistant	39	0.85	1.56	0.85
Co-trimoxazole-susceptible	81	0.87	1.56	0.84
Co-trimoxazole-intermediate	37	0.80	1.38	0.70
Co-trimoxazole-resistant	91	0.86	1.56	0.85
Resistant to beta, cl, e, t ± c, cot	17	0.89	1.63	0.89
Resistant to beta, e, cot	16	0.92	1.61	1.00
Resistant to beta, t, c, cot	16	0.81	1.61	0.84
Resistant to beta, cot	33	0.85	1.49	0.79
Resistant to beta only	36	0.91	1.65	0.84
Sensitive to all antibiotics	40	0.85	1.52	0.79

^aAbbreviations: beta, one or more β -lactams; cl, clindamycin; e, erythromycin; t, tetracycline; c, chloramphenicol; cot, co-trimoxazole.

^bCombinations with eight or fewer organisms are not listed.

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