In vitro activity of ceftobiprole against clinical isolates collected from blood and respiratory specimen of hospitalized patients: results of the PEG study

Michael Kresken,[1,2] Barbara Körber-Irrgang,[1] Dieter Hafner[3]

[1]Antiinfectives Intelligence GmbH, Rheinbach, Germany; [2]Rhine University of Applied Sciences, Cologne, Germany;
[3]Institute of Pharmacology and Clinical Pharmacology, Heinrich-Heine-University, Düsseldorf, Germany

Poster P0831

Professor Michael Kresken
Antiinfectives Intelligence GmbH
Von-Liebig-Straße 20
DE-53359 Rheinbach, Germany
Tel: +49 2226 908 912
e-mail: michael.kresken@antiinfectives-intelligence.de

Introduction and purpose

- The selection of initial empirical antibiotic therapy for patients with community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP) is based on local antimicrobial profiles and sensitivity patterns and on risk factors for multidrug-resistant pathogens (e.g. previous antibiotic use and recent hospitalization).[1,2]
- The empirical treatment of HAP has become increasingly complicated by the emergence and spread of methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant Gram-negative pathogens, while the treatment of CAP is compromised by antibiotic-resistant pneumococci.[3]
- Ceftobiprole medocaril, a new-generation cephalosporin, was recently approved in Europe for the treatment of CAP and HAP (excluding ventilator-associated pneumonia [VAP]) in adults. Ceftobiprole, the active moiety of ceftobiprole medocaril, has broad-spectrum *in vitro* activity against Gram-positive and Gram-negative pathogens, including MRSA, *Enterobacteriaceae* and *Pseudomonas aeruginosa*.[4]
- In a double-blind, randomized study involving 781 patients, ceftobiprole medocaril (500 mg i.v. every 8 hours) was non-inferior to ceftazidime (2 g i.v. every 8 hours) plus linezolid (600 mg i.v. every 12 hours) for clinical cure rates at the test-of-cure visit (77.8% vs 76.2%, excluding VAP, for the clinically evaluable set).[5]
- The objective of this study was to evaluate the *in vitro* activity of ceftobiprole against key pathogens associated with HAP and CAP, namely *S. aureus*, *Streptococcus pneumoniae*, *Enterobacteriaceae* and *P. aeruginosa*, collected during a resistance surveillance study conducted by the Paul Ehrlich Society (PEG) in 2010.

Methods

- Isolates from the respiratory tract and blood of hospitalized patients were prospectively collected from 25 laboratories in Germany (n = 21), Switzerland (n = 3) and Austria (n = 1).
  - For each isolate, the patient's age and sex, details of the hospital department and ward (intensive care unit or general ward), specimen type and collection date were recorded.
  - Isolates were shipped to a central laboratory (Antiinfectives Intelligence, Rheinbach, Germany) for re-identification and susceptibility testing.
- Isolates were identified using standard laboratory methods and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.
- Minimum inhibitory concentrations (MICs) of ceftobiprole and comparators were determined for each isolate by the broth microdilution method according to the international standard ISO 20776-1.[6] The resulting MICs were interpreted (when possible) using the species-related clinical breakpoints defined by the European Committee on Antimicrobial Susceptibility Testing (Table 1).[7,8]
- The Clinical and Laboratory Standards Institute MIC method was used to screen for and confirm isolates with an extended-spectrum β-lactamase (ESBL)-producing phenotype.
- Statistically significant differences in resistance rates were determined by comparing 95% confidence intervals (CIs). Intervals were constructed using the Newcombe–Wilson method without continuity correction.

Results

- Of the 1246 isolates tested, 813 (65.2%) were recovered from respiratory tract specimens and 433 (34.8%) from blood. There were 544 (43.7%) isolates from patients in intensive care units and 702 (56.3%) from patients in general wards.
  - In total, 588 (47.2%) isolates were recovered from patients with HAP and 283 (22.7%) from patients with CAP (unknown source for the remaining 375 [30.1%] patients).

Table 1. Minimum inhibitory concentration breakpoints for ceftobiprole.[7,8]

Organism	EUCAST breakpoint (mg/L)[a]	
	Susceptible ≤	Resistant >
PK/PD breakpoint	4	4
Enterobacteriaceae	0.25	0.25
Pseudomonas aeruginosa	–[b]	–[b]
Staphylococcus aureus	2	2
Streptococcus pneumoniae	0.5	0.5
All other organisms	–[b]	–[b]

[a]Species-related breakpoint not defined.
EUCAST, The European Committee on Antimicrobial Susceptibility Testing; PD, pharmacodynamics; PK, pharmacokinetics.

Table 2. Distribution of MICs of ceftobiprole for isolates collected from the respiratory tract or blood of hospitalized patients.

Organism/phenotype (n)	Number (cumulative %) of isolates inhibited by ceftobiprole at a concentration (mg/L) of:									S (%)
	≤ 0.25	0.5	1	2	4	8	16	32	> 32	
***Staphylococcus aureus* (188)**	41 (21.8)	115 (83.0)	3 (84.6)	26 (98.4)	3[a] (100)					98.4
Methicillin-susceptible (158)	41 (25.9)	115 (98.7)	1 (99.4)	1 (100)						100.0
Methicillin-resistant (30)			2 (6.7)	25 (90.0)	3[a] (100)					90.0
***Streptococcus pneumoniae* (254)**	241 (94.9)	10 (98.8)	3 (100)							98.8
Penicillin-susceptible (207)	207 (100)									100.0
Penicillin-nonsusceptible (47)	34 (72.3)	10 (93.6)	3 (100)							93.6
***Escherichia coli* (179)**	143 (79.9)	3 (81.6)	2 (82.7)				2 (83.8)	2 (84.9)	27 (100)	79.9
ESBL-negative (146)	141 (96.6)	3 (98.6)	2 (100)							96.6
ESBL-positive (33)	2 (6.1)						2 (12.1)	2 (18.2)	27 (100)	6.1
***Klebsiella pneumoniae* (108)**	86 (79.6)	3 (82.4)		2 (84.3)				1 (85.2)	16 (100)	79.6
ESBL-negative (90)	86 (95.6)	3 (98.9)		1 (100)						95.6
ESBL-positive (18)				1 (5.6)				1 (11.1)	16 (100)	0
***Klebsiella oxytoca* (44)**	19 (43.2)	11 (68.2)	4 (77.3)						10 (100)	43.2
***Enterobacter* spp. (89)[b]**	66 (74.2)	3 (77.5)	1 (78.7)	3 (82.0)	7 (89.9)	3 (93.3)	1 (94.4)	1 (95.5)	4 (100)	74.2
***Serratia* spp. (74)[c]**	63 (85.1)	5 (91.9)	3 (95.9)	1 (97.3)		1 (98.6)		1 (100)		85.1
***Citrobacter* spp. (26)[d]**	22 (84.6)	2 (92.3)							2 (100)	84.6
***Proteeae* (43)[e]**	33 (76.7)		1 (79.1)		1 (81.4)	1 (83.7)		2 (88.4)	5 (100)	76.7
***Pseudomonas aeruginosa* (241)**		2 (0.8)	10 (5.0)	58 (29.0)	69 (57.7)	48 (77.6)	23 (87.1)	7 (90.0)	24 (100)	NE
Ceftazidime-susceptible (191)		2 (1.0)	9 (5.8)	58 (36.1)	61 (68.1)	39 (88.5)	15 (96.3)	3 (97.9)	4 (100)	NE
Ceftazidime-resistant (50)			1 (2.0)		8 (18.0)	9 (36.0)	8 (52.0)	4 (60.0)	20 (100)	NE

[a]Etest® MICs were 3 mg/L for one isolate and 1–1.5 mg/L for two isolates. [b]Includes *Enterobacter cloacae* (n = 65), *E. aerogenes* (n = 19) and *E. asburiae* (n = 5). [c]Includes *Serratia marcescens* (n = 71), *S. liquefaciens* (n = 2) and *S. ureilytica* (n = 1). [d]Includes *Citrobacter freundii* (n = 13), *C. koseri* (n = 11), *C. braakii* (n = 1) and *C. farmeri* (n = 1). [e]Includes *Proteus mirabilis* (n = 29), *Morganella morganii* (n = 9) and *P. vulgaris* (n = 5).
ESBL, extended-spectrum β-lactamase; EUCAST, The European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; NE, not evaluable because EUCAST has not defined a species-related breakpoint; S, susceptible.

- Almost two-thirds of isolates (n = 793 [63.6%]) were recovered from male patients, and the median age of patients was 66 years (range, < 1–100 years).

Table 3. *In vitro* activity of ceftobiprole and comparators against Gram-positive isolates collected from the respiratory tract or blood of hospitalized patients.

Organism/phenotype (n)	Antibiotic concentration (mg/L)			Proportion of isolates that are S/I/R (%)[a]
	MIC_{50}	MIC_{90}	MIC range	
***Staphylococcus aureus* (188)**				
Ceftobiprole	0.5	2	≤ 0.25–4	98.4/–/1.6
Daptomycin	0.5	0.5	0.125–1	100/–/0
Levofloxacin	≤ 0.25	> 8	≤ 0.25–> 8	77.7/0/22.3
Erythromycin	0.5	> 32	≤ 0.25–> 32	75.5/0.5/23.9
Linezolid	1	1	≤ 0.25–2	100/–/0
Vancomycin	0.5	1	≤ 0.25–2	100/–/0
Methicillin-susceptible (158)				
Ceftobiprole	0.5	0.5	≤ 0.25–2	100/–/0
Daptomycin	0.5	0.5	0.125–1	100/–/0
Levofloxacin	≤ 0.25	0.5	≤ 0.25–> 8	92.4/0/7.6
Erythromycin	0.5	32	≤ 0.25–> 32	86.7/0/13.3
Linezolid	1	1	≤ 0.25–2	100/–/0
Vancomycin	0.5	1	≤ 0.25–2	100/–/0
Methicillin-resistant (30)				
Ceftobiprole	2	2	1–4	90.0/–/10.0
Daptomycin	0.5	1	0.25–1	100/–/0
Levofloxacin	> 8	> 8	4–> 8	0/0/100
Erythromycin	> 32	> 32	0.5–> 32	16.7/3.3/80.0
Linezolid	1	1	≤ 0.25–2	100/–/0
Vancomycin	0.5	1	0.5–1	100/–/0
***Streptococcus pneumoniae* (254)**				
Ceftobiprole	≤ 0.25	≤ 0.25	≤ 0.25–1	98.8/–/1.2
Ceftriaxone	≤ 0.125	≤ 0.125	≤ 0.125–1	97.2/2.8/0
Erythromycin	≤ 0.25	32	≤ 0.25–> 32	79.9/0/20.1
Levofloxacin	1	1	≤ 0.25–> 8	98.0/–/2.0
Penicillin	≤ 0.063	0.25	≤ 0.063–2	81.5/18.5/0
Penicillin-susceptible (207)				
Ceftobiprole	≤ 0.25	≤ 0.25	≤ 0.25	100/–/0
Ceftriaxone	≤ 0.125	≤ 0.125	≤ 0.125–0.5	100/0/0
Erythromycin	≤ 0.25	4	≤ 0.25–> 32	88.9/0/11.1
Levofloxacin	1	1	≤ 0.25–2	100/–/0
Penicillin-nonsusceptible (47)				
Ceftobiprole	≤ 0.25	0.5	≤ 0.25–1	93.6/–/6.4
Ceftriaxone	0.25	1	≤ 0.125–1	85.1/14.9/0
Erythromycin	8	> 32	≤ 0.25–> 32	40.4/0/59.6
Levofloxacin	1	8	≤ 0.25–> 8	89.4/–/10.6

[a]Sensitivity categories defined by species-related breakpoints according to EUCAST.
EUCAST, The European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; MIC_{50}, minimum concentration required to inhibit 50% of isolates; MIC_{90}, minimum concentration required to inhibit 90% of isolates; S, susceptible; I, intermediate; R, resistant.

In vitro activity of ceftobiprole and comparators against Gram-positive isolates

- Of the *S. aureus* isolates (n = 188), 158 (84%) were methicillin-susceptible (MSSA) and 30 (16%) were MRSA(Table 2).
- Ceftobiprole demonstrated potent activity against *S. aureus* (Table 2). MIC_{50} and MIC_{90} ($MIC_{50/90}$) values were 0.5/0.5 mg/L for MSSA isolates and 2/2 mg/L for MRSA isolates (Table 3). Overall, 98.4% of *S. aureus* isolates were susceptible to ceftobiprole.
  - All MSSA isolates and 27/30 (90.0%) of the MRSA isolates were susceptible to ceftobiprole (Table 3).
  - The MICs of the three ceftobiprole-resistant MRSA isolates were 4 mg/L (Table 2). When these isolates were retested by Etest®, MICs were 3 mg/L (resistant) for one isolate and 1–1.5 mg/L (susceptible) for two isolates, leaving only one truly resistant isolate.
- Rates of resistance to levofloxacin and erythromycin were 7.6% and 13.3%, respectively, for MSSA isolates and 100% and 80%, respectively, for MRSA isolates. All *S. aureus* isolates were susceptible to daptomycin, linezolid and vancomycin (Table 3).
- Of the *S. pneumoniae* isolates (n = 254), 47 (18.5%) showed reduced susceptibility to penicillin, but none was resistant to penicillin (Table 2).
- Ceftobiprole inhibited all *S. pneumoniae* isolates at 1 mg/L, although 3 (1.2%) of these isolates (from blood, with penicillin MICs of 1–2 mg/L) were categorized as ceftobiprole-resistant (Table 2).
- Resistance to erythromycin and levofloxacin was observed in 20.1% and 2.0% of *S. pneumoniae* isolates, respectively (Table 3).

In vitro activity of ceftobiprole and comparators against Gram-negative isolates

- Of the *Enterobacteriaceae* isolates (n = 563), 59 (10.5%) showed an ESBL-positive phenotype, including 33/179 (18.4%) *Escherichia coli* isolates and 18/108 (16.7%) *Klebsiella pneumoniae* isolates.
- In total, 432 (76.7%) *Enterobacteriaceae* isolates were susceptible to ceftobiprole (Table 2). $MIC_{50/90}$ values for ceftobiprole against *E. coli* and *K. pneumoniae* were similar to those for ceftriaxone (Table 4), but ceftobiprole showed greater activity against *Enterobacteriaceae* species that produce chromosomally encoded AmpC-lactamases (*Serratia marcescens* and *Enterobacter cloacae*; data not shown).
- For *E. coli* and *K. pneumoniae*, susceptibility rates to ceftobiprole were slightly lower than those for ceftriaxone (differences not significant; Table 4).
- Similarly to other broad-spectrum cephalosporins, ceftobiprole showed weak activity against isolates with an ESBL-positive phenotype; however, two *E. coli* isolates with an ESBL-positive phenotype were susceptible to ceftobiprole (Table 2).
- For *P. aeruginosa*, the $MIC_{50/90}$ values for ceftobiprole (4/32 mg/L) were similar to those for ceftazidime and cefepime (2/32 mg/L and 4/32 mg/L, respectively; Table 4).

Table 4. *In vitro* activity of ceftobiprole and comparators against isolates of the most frequent Gram-negative species collected from the respiratory tract or blood of hospitalized patients.

Organism/phenotype (n)	Antibiotic concentration (mg/L)			Proportion of isolates that are S/I/R (%)[a]
	MIC_{50}	MIC_{90}	MIC range	
***Escherichia coli* (179)**				
Ceftobiprole	≤ 0.25	> 32	≤ 0.25–> 32	79.9/–/20.1
Ceftriaxone	≤ 0.125	> 16	≤ 0.125–> 16	81.0/1.7/17.3
Meropenem	≤ 0.5	≤ 0.5	≤ 0.5	100/0/0
Piperacillin–tazobactam	2	64	≤ 1–> 64	85.5/3.4/11.2
Ciprofloxacin	0.125	> 8	≤ 0.063–> 8	57.0/2.2/40.8
Gentamicin	1	> 16	≤ 0.25–> 16	87.7/0/12.3
ESBL-negative (146)				
Ceftobiprole	≤ 0.25	≤ 0.25	≤ 0.25–1	96.6/–/3.4
Ceftriaxone	≤ 0.125	≤ 0.125	≤ 0.125–2	97.9/2.1/0
Meropenem	≤ 0.5	≤ 0.5	≤ 0.5	100/0/0
Piperacillin–tazobactam	2	16	≤ 1–> 64	89.7/2.7/7.5
Ciprofloxacin	≤ 0.063	> 8	≤ 0.063–> 8	65.8/2.7/31.5
Gentamicin	1	2	≤ 0.25–> 16	93.2/0/6.8
ESBL-positive (33)				
Ceftobiprole	> 32	> 32	≤ 0.25–> 32	6.1/–/93.9
Ceftriaxone	> 16	> 16	0.5–> 16	6.1/0/93.9
Meropenem	≤ 0.5	≤ 0.5	≤ 0.5	100/0/0
Piperacillin–tazobactam	2	64	≤ 1–> 64	66.7/6.1/27.3
Ciprofloxacin	> 8	> 8	≤ 0.063–> 8	18.2/0/81.8
Gentamicin	1	> 16	0.5–> 16	63.6/0/36.4
***Klebsiella pneumoniae* (108)**				
Ceftobiprole	≤ 0.25	> 32	≤ 0.25–> 32	79.6/–/20.4
Ceftriaxone	≤ 0.125	> 16	≤ 0.125–> 16	84.3/0/15.7
Meropenem	≤ 0.5	≤ 0.5	≤ 0.5–1	100/0/0
Piperacillin–tazobactam	4	32	≤ 1–> 64	81.5/6.5/12.0
Ciprofloxacin	≤ 0.063	> 8	≤ 0.063–> 8	78.7/1.9/19.4
Gentamicin	0.5	8	≤ 0.25–> 16	88.9/0/11.1
ESBL-negative (90)				
Ceftobiprole	≤ 0.25	≤ 0.25	≤ 0.25–2	95.6/–/4.4
Ceftriaxone	≤ 0.125	0.25	≤ 0.125–0.5	100/0/0
Meropenem	≤ 0.5	≤ 0.5	≤ 0.5	100/0/0
Piperacillin–tazobactam	2	8	≤ 1–> 64	91.1/3.3/5.6
Ciprofloxacin	≤ 0.063	0.5	≤ 0.063–> 8	91.1/2.2/6.7
Gentamicin	0.5	0.5	≤ 0.25–16	96.7/0/3.3
ESBL-positive (18)				
Ceftobiprole	> 32	> 32	2–> 32	0/–/100
Ceftriaxone	> 16	> 16	0.5–> 16	5.6/0/94.4
Meropenem	≤ 0.5	1	≤ 0.5–1	100/0/0
Piperacillin–tazobactam	16	> 64	4–> 64	33.3/22.2/44.4
Ciprofloxacin	> 8	> 8	≤ 0.063–> 8	16.7/0/83.3
Gentamicin	1	> 16	≤ 0.25–> 16	50.0/0/50.0
***Pseudomonas aeruginosa* (241)**				
Ceftobiprole	4	32	0.5–> 32	–[b]/–/–
Ceftazidime	2	32	0.5–> 32	79.3/–/20.7
Cefepime	4	32	0.5–> 32	74.7/–/25.3
Meropenem	1	16	≤ 0.5–> 32	71.0/14.9/14.1
Piperacillin–tazobactam	8	64	≤ 1–> 64	77.2/–/22.8
Ciprofloxacin	0.25	> 8	≤ 0.063–> 8	68.0/4.1/27.8
Gentamicin	2	16	≤ 0.25–> 16	86.7/–/13.3
Ceftazidime-susceptible (191)				
Ceftobiprole	4	16	0.5–> 32	–[b]/–/–
Ceftazidime	2	4	0.5–8	100/–/0
Cefepime	4	8	0.5–32	92.1/–/7.9
Meropenem	≤ 0.5	4	≤ 0.5–32	84.3/9.9/5.8
Piperacillin–tazobactam	8	16	≤ 1–64	90.1/–/9.9
Ciprofloxacin	0.25	4	≤ 0.063–> 8	78.5/4.2/17.3
Gentamicin	1	4	≤ 0.25–> 16	94.8/–/5.2
Ceftazidime-resistant (50)				
Ceftobiprole	16	> 32	1–> 32	–[b]/–/–
Ceftazidime	32	> 32	16–> 32	0/–/100
Cefepime	32	> 32	2–> 32	8.0/–/92.0
Meropenem	8	> 32	≤ 0.5–> 32	20.0/34.0/46.0
Piperacillin–tazobactam	64	> 64	8–> 64	28.0/–/72.0
Ciprofloxacin	8	> 8	0.125–> 8	28.0/4.0/68.0
Gentamicin	4	> 16	≤ 0.25–> 16	56.0/–/44.0

[a]Sensitivity categories defined by species-related breakpoints according to EUCAST. [b]Species-related breakpoint not defined.
ESBL, extended-spectrum β-lactamase; EUCAST, The European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; MIC_{50}, minimum concentration required to inhibit 50% of isolates; MIC_{90}, minimum concentration required to inhibit 90% of isolates; S, susceptible; I, intermediate; R, resistant.

Table 5. Projection of the proportion of ceftobiprole-susceptible isolates among microbiological aetiologies associated with HAP (excluding VAP).

Organism	Isolates recovered, n (%)[a]	PEG study		Projected susceptible isolates (%)
		Breakpoint (mg/L)	Susceptible isolates (%)	
Staphylococcus aureus	88 (33)	2[a]	99[b]	33
Streptococcus pneumoniae	21 (8)	0.5[a]	99	8
Enterobacteriaceae	91 (34)	0.25[a]	77	26
Pseudomonas aeruginosa	36 (13)	4[c]	58	8
Acinetobacter baumannii	20 (7)	–	0	0
Haemophilus influenzae	14 (5)	0.5[d]	100[e]	5
Total	**270 (100)**			**80**

[a]Species-related clinical breakpoint set by EUCAST. [b]Two out of three isolates with a MIC of 4 mg/L were considered susceptible to ceftobiprole (see text). [c]Pharmacokinetic/pharmacodynamic breakpoint set by EUCAST. [d]Presumed epidemiological cut-off value (ECOFF). [e]*H. influenzae* was not tested in the current study, but clinical isolates are usually fully susceptible to ceftobiprole.[4]
EUCAST, The European Committee on Antimicrobial Susceptibility Testing; HAP, hospital-acquired pneumonia; PEG, Paul Ehrlich Society; VAP, ventilator-associated pneumonia; –, breakpoint not defined.

Projected ceftobiprole susceptibility

- On the basis of the data reported here and the range of pathogens isolated during a phase 3 study in patients with HAP (Table 5),[5] it is estimated that 80% of the microbiological aetiologies associated with HAP (excluding VAP) would be susceptible to ceftobiprole.

Conclusions

- This analysis shows that ceftobiprole has potent *in vitro* antimicrobial activity against key pathogens associated with HAP and CAP.
- Ceftobiprole susceptibility was observed in:
  - 98.4% of all *S. aureus* isolates, including 90% of MRSA isolates
  - 98.8% of *S. pneumoniae* isolates.
- In addition, ceftobiprole demonstrated good activity against *Enterobacteriaceae*, with MIC_{50} and MIC_{90} values similar to those for ceftriaxone.
- Ceftobiprole was also effective against *P. aeruginosa*, with MIC_{50} and MIC_{90} values similar to those for ceftazidime and cefepime.
- Ceftobiprole may be a suitable option for the empirical treatment of HAP and CAP, especially when MRSA and Gram-negative infections are suspected.

References

1. Masterton RG *et al. J Antimicrob Chemother* 2009;62:5–34.
2. American Thoracic Society. *Am J Respir Crit Care Med* 2005;171:388–416.
3. Jones RN. *Clin Infect Dis* 2010;51(Suppl 1):S81–7.
4. Farrell DJ *et al. Antimicrob Agents Chemother* 2014;58:3882–8.
5. Awad SS *et al. Clin Infect Dis* 2014;59:51–61.
6. ISO 20776-1: 2006. Clinical laboratory testing and *in vitro* diagnostic test systems – susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test device. German version. Beuth-Verlag, Berlin.
7. EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. Version 4.0, 1 January 2014.
8. EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. Ceftobiprole Addendum 2014-07-16.

Disclosures

MK is a partner in and CEO of Antiinfectives Intelligence GmbH; BK-I is an employee of Antiinfectives Intelligence GmbH; D Hafner declares no competing interests.

Acknowledgements

The authors are grateful to the following members of the study group (in alphabetical order) who also contributed to the study: T Adam (Berlin), A Becker (Karlsruhe), K Becker (Münster), M Donat (Rostock), U Eigner (Heidelberg), H Fankhauser (Aarau), M Fille (Innsbruck), P Finzer (Moers, now Meerbusch), U Frank (Freiburg, now Heidelberg), R Frei (Basle), G Funke (Ravensburg), U Göbel (Berlin), A Haas (Fulda), A Hörauf (Bonn), M Holfelder (Heidelberg), D Jonas (Freiburg), E Kniehl (Karlsruhe), C Lass-Flörl (Innsbruck), S Lukas (Regensburg), C MacKenzie (Düsseldorf), R Mutters (Marburg), G Peters (Münster), S Petersdorf (Bonn, now Düsseldorf), W Pfister (Jena), A Podbielski (Rostock), H Rüssmann (Berlin), W Schneider (Regensburg), S Schubert (Kiel), S Schubert (Munich), H Seifert (Cologne), E Siegel (Mainz), HH Siegrist (La Chaux-de-Fonds), E Straube (Jena), H Weißer (Fulda), TA Wichelhaus (Frankfurt am Main), B Würstl (Munich), S Ziesing (Hannover).

This work was funded by Basilea Pharmaceutica International Ltd, and editorial support was provided by Oxford PharmaGenesis, Oxford, UK.

Presented at the 25th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, 25–28 April 2015.

Paul-Ehrlich-Gesellschaft für Chemotherapie e. V.
www.p-e-g.org