A 2001 Multi-Center, Multi-Country Surveillance Study Identifying Antibiotic Resistance To Extended Spectrum Beta-Lactamase Producing Enterobacteriaceae, Vancomycin Resistant Enterococcus Faecium and Methicillin Resistant Staphylococcus Aureus Isolates: The PEARLS Study

S.K. Bouchillon[1], B.M. Johnson[1], D.J. Hoban[1], J.L. Johnson[1], M.J. Dowzicky[2], D.H. Wu[2], K. Focht[2], P.A. Bradford[3]

[1]Laboratories International for Microbiology Studies, Rolling Meadows, IL;
[2]Wyeth-Ayerst Pharmaceuticals, St. Davids, PA;

[3]Wyeth-Ayerst Research, Pearl River, NY

Revised Abstract

Background: The increase of extended spectrum beta-lactamase (ESBL), vancomycin resistant *Enterococcus faecium* (VREF) and methicillin resistant *Staphylococcus aureus* (MRSA) isolates worldwide has been reported in recent studies. The impact of high cephalosporin use may significantly affect the increased incidence of these organisms. The Pan-European Antimicrobial Resistance Using Local Surveillance (PEARLS) Study compares susceptibility results of various antimicrobials in Europe, the Middle East and South Africa. **Methods:** 8,617 isolates were evaluated from 30 investigative sites in: Austria; Belgium; France; Germany; Greece; Italy; Lebanon; Portugal; South Africa; Spain; Switzerland; The Netherlands and Turkey. Each investigator was required to collect the following selected species: 50 *Enterococcus faecium* (EF); 50 *Enterobacter cloacae* (EC); 50 *Enterobacter aerogenes* (EA); 75 *Escherichia coli* (EsC); 75 *Klebsiella pneumoniae* (KP); 25 *Acinetobacter* spp. (As); 25 *Pseudomonas aeruginosa* (PA); 25 *Serratia marcescens* (SM); 25 *Staphylococcus aureus* (SA). The following antimicrobials: amoxicillin/clavulanic acid (A/C); cefepime (Cfp); cefotaxime (Cft); ceftazidime (Cfz); ceftriaxone (Ctx); gentamicin (Gtm); imipenem (Imp); ciprofloxacin (Cip); levofloxacin (Lev); piperacillin/tazobactam (P/T) and vancomycin (Vcm) were evaluated following manufacturer's instructions and NCCLS guidelines. **Results:** ESBL Enterobacteriaceae isolates, including EsC, showed the lowest level of resistance to Imp at 1.2%. Cephalosporin resistant rates for ESBL Enterobacteriaceae (*K. pneumoniae* and *E. coli*) ranged from 18.6% to 62.9%. A/C and P/T resistant rates for ESBL producers (*K. pneumoniae* and *E. coli*) were 26.3% and 28.6%, respectively. Of the study drugs, only Vcm was effective against EF with an overall resistant rate of 9.1%. All the study drugs were effective against MSSA but only Vcm demonstrated good activity against both MSSA with 99.4% susceptible, and MRSA with 99.6% susceptible. **Conclusions:** All study drugs showed good activity against non-ESBL producing Enterobacteriaceae and MSSA. Only imipenem had good activity against the ESBL producing Enterobacteriaceae. None of the antimicrobials tested did well against VREF. Only vancomycin had good activity against MRSA. More studies are needed in order to monitor the impact specific antimicrobials may have in the hospital environment.

Introduction

The increasing occurrence of infections with antibiotic-resistant microorganisms has required the development of flexible and timely surveillance systems for monitoring these problems. This study is an ongoing surveillance to examine the resistance determinants and susceptibility patterns of common pathogens. This study attempts to set a baseline of activity for 11 antimicrobial agents against ESBL producers in selected Enterobacteriaceae, VREF and MRSA in 13 countries. These data will be used to identify selective pressures and determinants affecting the incidence of drug resistance.

Materials and Methods

- Isolates were collected between Jan 2001 and March 2002 from 30 study centers in 13 countries.
- All isolates were derived from blood, respiratory tract, urine (no more than 30% of all isolates), skin, wound, fluids and other defined sources. Only one isolate per patient was accepted.
- Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing and ESBL determination, as well as construction and management of a centralized database, was coordinated by International Health Management Associates, Inc. (IHMA, Rolling Meadows, IL).

Antimicrobial Susceptibility Testing

- MICs were determined by the NCCLS recommended broth microdilution testing method.[1] The microbroth dilution panels used in this study were purchased from Microscan® (Dade Behring Inc. Sacramento, CA. USA.).
- Quality Control of Microscan® panels included the following ATCC strains: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212.
- *Escherichia coli* and *Klebsiella pneumoniae* were tested for ESBL activity according to NCCLS guideliness[2] (table 2A, M100-S11).
- Preliminary ESBL activity was determined by screening cefotaxime, ceftazidime and ceftriaxone with MICs $\geq$ 1 using microbroth dilution panels.
- ESBL activity was confirmed by testing the following antibiotic disks: cefotaxime (30 mg), cefotaxime/clavulanic acid (30/10mg), and ceftazidime (30mg), ceftazidime/clavulanic acid (30/10mg). Antibiotic disks were manufactured by Oxoid Inc. Ogdensburg, New York. Mueller-Hinton agar used in testing was manufactured by Remel Inc. Lenexa, Kansas.
- An organism is interpreted as containing an ESBL if there is an increase of $\geq$ 5mm in the inhibition zone of the combination disc when compared to that of the cephalosporin alone: cefotaxime/clavulanic acid - cefotaxime $\geq$ 5 mm or ceftazidime/clavulanic acid - ceftazidime $\geq$ 5 mm.
- Quality control of antibiotic disks followed the manufacture's guidelines (Oxoid) using the following ATCC strains: *Klebsiella pneumoniae* ATCC 700603 and *Escherichia coli* ATCC 25922.

Results

Results are shown in the following Tables and Graphs.

Table 1. *In Vitro* Activity (mg/mL) and Susceptibilities (%) of 11 Antimicrobial Agents Against 8,617 Gram-negative and Gram-positive Isolates Collected in 30 Centers from 13 Countries

Organism	Drug	MIC_{50} / MIC_{90}	%Sus	%Int	%Res
Acinetobacter spp (n=536)	Amox/Clav	>16 / >16	na	na	na
	Cefepime	8 / >16	52.8	12.1	35.1
	Cefotaxime	16 / >32	34.9	22.9	42.2
	Ceftazidime	8 / >16	53.4	6.1	40.5
	Ceftriaxone	32 / >32	26.3	31.9	41.8
	Gentamicin	2 / >8	55.2	4.9	39.9
	Imipenem	0.5 / >8	78.2	1.8	20.0
	Ciprofloxacin	0.5 / >2	54.7	2.2	43.1
	Levofloxacin	0.5 / >4	60.8	3.6	35.6
	Pip/Tazo	8 / >64	54.7	10.0	35.3
	Vancomycin	>32 / >32	na	na	na
Enterobacter aerogenes (n=655)	Amox/Clav	>16 / >16	5.0	2.5	92.5
	Cefepime	0.25 / 2	96.5	1.1	2.4
	Cefotaxime	4 / 32	65.2	27.5	7.3
	Ceftazidime	8 / >16	52.4	8.8	38.8
	Ceftriaxone	4 / 32	75.1	19.7	5.2
	Gentamicin	0.5 / 2	96.2	1.2	2.6
	Imipenem	1 / 2	97.3	1.0	1.7
	Ciprofloxacin	0.03 / >2	68.7	1.8	29.5
	Levofloxacin	0.12 / >4	69.5	3.0	27.5
	Pip/Tazo	8 / 64	70.1	22.6	7.3
	Vancomycin	>32 / >32	na	na	na
Enterobacter cloacae (n=1164)	Amox/Clav	>16 / >16	3.9	0.9	95.2
	Cefepime	0.12 / 8	94.8	2.5	2.7
	Cefotaxime	0.5 / >32	66.8	5.7	27.5
	Ceftazidime	0.5 / >16	69.2	4.0	26.8
	Ceftriaxone	0.5 / >32	70.7	7.5	21.8
	Gentamicin	0.5 / 2	92.2	1.5	6.3
	Imipenem	0.5 / 1	97.7	0.2	2.1
	Ciprofloxacin	0.015 / 1	90.9	1.4	7.7
	Levofloxacin	0.06 / 2	91.2	1.7	7.1
	Pip/Tazo	2 / >64	72.3	9.6	18.1
	Vancomycin	>32 / >32	na	na	na
Enterococcus faecium (n=717)	Amox/Clav	16 / >16	na	na	na
	Cefepime	>16 / >16	na	na	na
	Cefotaxime	>32 / >32	na	na	na
	Ceftazidime	>16 / >16	na	na	na
	Ceftriaxone	>32 / >32	na	na	na
	Gentamicin	8 / >8	na	na	na
	Imipenem	>8 / >8	na	na	na
	Ciprofloxacin	>2 / >2	13.2	25.9	60.9
	Levofloxacin	>4 / >4	37.9	6.3	55.8
	Pip/Tazo	>64 / >64	na	na	na
	Vancomycin	1 / 16	89.5	1.4	9.1
Escherichia coli (n-2022)	Amox/Clav	8 / >16	69.8	18.9	11.3
	Cefepime	0.06 / 0.5	97.1	0.9	2.0
	Cefotaxime	0.06 / 0.5	95.4	1.5	3.1
	Ceftazidime	0.25 / 1	95.7	1.0	3.3
	Ceftriaxone	0.06 / 0.25	94.9	1.8	3.3
	Gentamicin	1 / 2	91.5	1.5	7.0
	Imipenem	0.5 / 0.5	98.6	0.2	1.2
	Ciprofloxacin	0.015 / >2	83.5	0.3	16.2
	Levofloxacin	0.03 / >4	83.8	2.2	14.0
	Pip/Tazo	1 / 8	94.3	2.7	3.0
	Vancomycin	>32 / >32	na	na	na
Klebsiella pneumoniae (n=1603)	Amox/Clav	4 / >16	75.4	11.5	13.1
	Cefepime	0.06 / 4	95.4	1.5	3.1
	Cefotaxime	0.06 / 32	86.7	7.2	6.1
	Ceftazidime	0.25 / >16	83.7	2.3	14.0
	Ceftriaxone	0.06 / 16	86.5	8.3	5.2
	Gentamicin	0.5 / >8	88.1	1.7	10.2
	Imipenem	0.5 / 1	98.3	0.2	1.5
	Ciprofloxacin	0.03 / 1	91.8	2.5	5.7
	Levofloxacin	0.06 / 1	92.8	3.2	4.0
	Pip/Tazo	2 / >64	84.5	4.5	11.0
	Vancomycin	>32 / >32	na	na	na
Pseudomonas aeruginosa (n=667)	Amox/Clav	>16 / >16	na	na	na
	Cefepime	4 / >16	75.1	12.8	12.1
	Cefotaxime	32 / >32	7.5	59.4	33.1
	Ceftazidime	2 / >16	79.2	7.0	13.8
	Ceftriaxone	32 / >32	11.4	48.6	40.0
	Gentamicin	2 / >8	81.4	2.6	16.0
	Imipenem	1 / >8	76.6	10.2	13.2
	Ciprofloxacin	0.25 / >2	74.7	4.2	21.1
	Levofloxacin	1 / >4	70.2	6.0	23.8
	Pip/Tazo	4 / >64	88.6	0.0	11.4
	Vancomycin	>32 / >32	na	na	na

Table 1. continued

Organism	Drug	MIC_{50} / MIC_{90}	%Sus	%Int	%Res
Serratia marcescens (n=527)	Amox/Clav	>16 / >16	4.2	4.5	91.3
	Cefepime	0.12 / 2	97.2	1.1	1.7
	Cefotaxime	0.5 / 16	87.5	7.0	5.5
	Ceftazidime	0.25 / 8	90.7	2.7	6.6
	Ceftriaxone	0.25 / 16	88.2	7.1	4.7
	Gentamicin	0.5 / 4	90.3	2.5	7.2
	Imipenem	1 / 1	96.4	0.8	2.8
	Ciprofloxacin	0.06 / 2	89.6	5.1	5.3
	Levofloxacin	0.12 / 2	93.2	4.1	2.7
	Pip/Tazo	37272	91.5	4.9	3.6
	Vancomycin	>32 / >32	na	na	na
Staphylococcus aureus (n=726)	Amox/Clav	2 / >16	65.0	0.0	35.0
	Cefepime	2 / >16	64.5	2.2	33.3
	Cefotaxime	2 / >32	66.3	2.6	31.1
	Ceftazidime	8 / >16	58.7	4.2	37.1
	Ceftriaxone	4 / >32	62.1	5.3	32.6
	Gentamicin	0.5 / >8	69.6	1.5	28.9
	Imipenem	0.5 / >8	73.8	0.7	25.5
	Ciprofloxacin	0.25 / >2	63.2	0.6	36.2
	Levofloxacin	0.25 / >4	64.7	15.7	19.6
	Pip/Tazo	1 / >64	66.3	0.0	33.7
	Vancomycin	1 / 1	99.4	0.2	0.4

Table 2. *In Vitro* Activity (mg/mL) and Susceptibilities (%) of 11 Antimicrobial Agents Against 3,253 Non-Extended Spectrum Beta-Lactamase (Non-ESBL) Producing Enterobacteriaceae and 350 Extended Spectrum Beta-Lactamase (ESBL) Producing Enterobacteriaceae Collected in 30 Centers from 13 Countries

Organism	Drug	MIC_{50}/MIC_{90}	%Sus	%Int	%Res
Enterobacteriaceae, Non-ESBL[1] (n=3253)	Amox/Clav	4 / >16	76.1	13.5	10.4
	Cefepime	0.06 / 0.25	99.2	0.2	0.6
	Cefotaxime	0.06 / 0.25	98.0	0.7	1.3
	Ceftazidime	0.25 / 0.5	97.5	0.5	2.0
	Ceftriaxone	0.06 / 0.12	98.0	1.1	0.9
	Gentamicin	0.5 / 2	94.4	0.7	4.9
	Imipenem	0.5 / 1	98.6	0.1	1.3
	Ciprofloxacin	0.015 / 2	89.5	0.7	9.8
	Levofloxacin	0.06 / 4	89.8	2.1	8.1
	Pip/Tazo	1 / 8	92.9	2.9	4.2
	Vancomycin	>32 / >32	na	na	na
Escherichia coli, non-ESBL (n=1914)	Amox/Clav	8 / >16	71.4	17.8	10.8
	Cefepime	0.06 / 0.25	99.3	0.2	0.5
	Cefotaxime	0.06 / 0.25	98.9	0.3	0.8
	Ceftazidime	0.12 / 0.5	98.7	0.3	1.0
	Ceftriaxone	0.06 / 0.12	98.9	0.3	0.8
	Gentamicin	1 / 2	93.2	0.8	6.0
	Imipenem	0.5 / 0.5	98.6	0.2	1.2
	Ciprofloxacin	0.015 / >2	85.6	0.3	14.1
	Levofloxacin	0.03 / >4	85.9	2.1	12.0
	Pip/Tazo	1 / 4	94.7	2.5	2.8
	Vancomycin	>32 / >32	na	na	na
Klebsiella pneumoniae, non-ESBL (n=1339)	Amox/Clav	2 / 16	83.0	7.1	9.9
	Cefepime	0.06 / 0.5	99.0	0.3	0.7
	Cefotaxime	0.06 / 0.25	96.7	1.4	1.9
	Ceftazidime	0.25 / 1	95.7	0.9	3.4
	Ceftriaxone	0.06 / 0.25	96.8	2.2	1.0
	Gentamicin	0.5 / 1	96.0	0.7	3.3
	Imipenem	0.5 / 1	98.5	0.0	1.5
	Ciprofloxacin	0.03 / 0.25	95.1	1.3	3.6
	Levofloxacin	0.06 / 0.5	95.3	2.2	2.5
	Pip/Tazo	2 / 16	90.4	3.5	6.1
	Vancomycin	>32 / >32	na	na	na
Enterobacteriaceae, ESBL[1] (n=350)	Amox/Clav	16 / >16	38.3	35.4	26.3
	Cefepime	4 / >16	71.4	10.0	18.6
	Cefotaxime	16 / >32	33.4	34.6	32.0
	Ceftazidime	>16 / >16	26.3	10.8	62.9
	Ceftriaxone	32 / >32	29.1	38.3	32.6
	Gentamicin	4 / >8	52.3	9.1	38.6
	Imipenem	0.5 / 1	97.1	1.2	1.7
	Ciprofloxacin	0.25 / >2	67.4	6.3	26.3
	Levofloxacin	0.5 / >4	71.4	7.5	21.1
	Pip/Tazo	8 / >64	62.3	9.1	28.6
	Vancomycin	>32 / >32	na	na	na
Escherichia coli, ESBL (n=94)	Amox/Clav	16 / >16	44.7	37.2	18.1
	Cefepime	8 / >16	56.4	15.9	27.7
	Cefotaxime	32 / >32	29.8	25.5	44.7
	Ceftazidime	16 / >16	39.4	12.7	47.9
	Ceftriaxone	32 / >32	19.1	33.0	47.9
	Gentamicin	2 / >8	64.9	16.0	19.1
	Imipenem	0.5 / 0.5	97.9	0.0	2.1
	Ciprofloxacin	>2 / >2	47.9	0.0	52.1
	Levofloxacin	4 / >4	47.9	4.2	47.9
	Pip/Tazo	2 / 64	86.2	6.4	7.4
	Vancomycin	>32 / >32	na	na	na
Klebsiella pneumoniae, ESBL (n=256)	Amox/Clav	16 / >16	35.9	34.8	29.3
	Cefepime	4 / >16	77.0	7.8	15.2
	Cefotaxime	16 / >32	34.8	37.9	27.3
	Ceftazidime	>16 / >16	21.5	10.3	68.4
	Ceftriaxone	16 / >32	32.8	40.2	27.0
	Gentamicin	8 / >8	47.7	6.6	45.7
	Imipenem	0.5 / 1	96.9	1.5	1.6
	Ciprofloxacin	0.25 / >2	74.6	8.6	16.8
	Levofloxacin	0.5 / >4	80.1	8.6	11.3
	Pip/Tazo	16 / >64	53.5	10.2	36.3
	Vancomycin	>32 / >32	na	na	na

[1] *Escherichia coli* and *Klebsiella pneumoniae* combined.

Table 3. *In Vitro* Activity (mg/mL) and Susceptibilities of 11 Antimicrobial Agents Against 652 Vancomycin Sensitive (VSE) and 65 Vancomycin-Resistant *Enterococcus faecium* (VRE) Collected in 30 Centers from 13 Countries

Organism	Drug	MIC_{50}/MIC_{90}	%Sus	%Int	%Res
Enterococcus faecium, non-VRE (n=652)	Amox/Clav	16 / >16	na	na	na
	Cefepime	>16 / >16	na	na	na
	Cefotaxime	>32 / >32	na	na	na
	Ceftazidime	>16 / >16	na	na	na
	Ceftriaxone	>32 / >32	na	na	na
	Gentamicin	8 / >8	na	na	na
	Imipenem	>8 / >8	na	na	na
	Ciprofloxacin	>2 / >2	13.8	27.8	58.3
	Levofloxacin	>4 / >4	40.5	6.8	52.8
	Pip/Tazo	>64 / >64	na	na	na
	Vancomycin	1 / 1	98.5	1.5	0.0
Enterococcus faecium, VRE (n=65)	Amox/Clav	>16 / >16	na	na	na
	Cefepime	>16 / >16	na	na	na
	Cefotaxime	>32 / >32	na	na	na
	Ceftazidime	>16 / >16	na	na	na
	Ceftriaxone	>32 / >32	na	na	na
	Gentamicin	8 / >8	na	na	na
	Imipenem	>8 / >8	na	na	na
	Ciprofloxacin	>2 / >2	7.7	3.1	89.2
	Levofloxacin	>4 / >4	10.8	1.5	87.7
	Pip/Tazo	>64 / >64	na	na	na
	Vancomycin	>32 / >32	0.0	0.0	100.0

Table 4. *In Vitro* Activity (mg/mL) and Susceptibilities of 11 Antimicrobial Agents Against 488 Methicillin-Sensitive *Staphylococcus aureus* (MSSA) and 238 Methicillin-Resistant *Staphylococcus aureus* (MRSA) Collected in 30 Centers from 13 Countries

Organism	Drug	MIC_{50}/MIC_{90}	%Sus	%Int	%Res
Staphylococcus aureus, MSSA (n=488)	Amox/Clav	1 / 4	91.1	0.0	8.9
	Cefepime	2 / 8	90.9	0.6	8.5
	Cefotaxime	2 / 4	91.3	0.2	8.5
	Ceftazidime	8 / 16	86.2	3.9	9.9
	Ceftriaxone	2 / 8	90.3	1.4	8.3
	Gentamicin	0.5 / >8	89.0	0.4	10.5
	Imipenem	0.5 / 1	93.3	0.2	6.5
	Ciprofloxacin	0.25 / >2	89.0	0.6	10.3
	Levofloxacin	0.12 / 4	89.7	2.8	7.5
	Pip/Tazo	1 / 4	91.3	0.0	8.7
	Vancomycin	1 / 1	99.4	0.0	0.6
Staphylococcus aureus, MRSA (n=238)	Amox/Clav	>16 / >16	11.6	0.0	88.4
	Cefepime	>16 / >16	10.3	5.4	84.3
	Cefotaxime	>32 / >32	14.9	7.4	77.7
	Ceftazidime	>16 / >16	2.5	5.0	92.6
	Ceftriaxone	>32 / >32	4.5	12.8	82.6
	Gentamicin	>8 / >8	29.3	3.7	66.9
	Imipenem	>8 / >8	33.5	1.7	64.9
	Ciprofloxacin	>2 / >2	10.3	0.4	89.3
	Levofloxacin	4 / >4	13.6	41.3	45.0
	Pip/Tazo	>64 / >64	14.9	0.0	85.1
	Vancomycin	1 / 1	99.6	0.4	0.0

Discussion

Outbreaks of ESBL producing Enterobacteriaceae, VREF and MRSA bacterial infections are now common problems for hospitals. The emphasis placed on antimicrobial drug resistance can be see in the 33,000-plus citations on Medline in the last 20 years. The objectives of this study are to set a baseline of *in vitro* activity of several antimicrobial agents and take a prospective longitudinal look at various determinants and risk factors affecting resistance in selected institutions. For example, one common factor leading to increased incidence of ESBL producing gram-negative organisms is the indiscriminate use of expanded-spectrum cephalosporins [3,4]. Further it has been shown that formulary changes that switch empiric treatment from ceftazidime to piperacillin/tazobactam can lower the incidence of *Klebsiella pneumoniae* strains that are resistant to both ceftazidime and piperacillin/tazobactam [4, 5].

Non-ESBL Enterobacteriaceae showed high susceptibility rates for most of the antimicrobial agents in this study. However, the ESBL Enterobacteriaceae exhibited high resistance rates among most the study drugs, especially the cephalosporins, piperacillin/tazobactam and amoxicillin/clavulanic acid. With a 97.1% susceptibility rate, imipenem was the only drug that inhibited more than 75% of the ESBL producing isolates.

Since the late 1980's when the first reports of vancomycin-resistant *enterococci* (VRE) appeared, geographic distribution and the importance of VRE as a nosocomial pathogen have increased worldwide. While colonization rates of VRE vary widely, this study found the actual overall incidence of VREF infections in this study to be 9.1% (65/717) [6]. Of all the antimicrobial agents in this study, only three, ciprofloxacin, levofloxacin, and vancomycin, have breakpoints assigned to *Enterococcus faecium* by the NCCLS. Of these three, only vancomycin was effective. Resistance rates for ciprofloxacin and levofloxacin against vancomycin-sensitive *Enterococcus faecium* (VSEF) were 58.3% and 52.8%, respectively.

Because methicillin-resistance in *Staphylococcus aureus* results from the expression of an acquired penicillin-binding protein, most *Staphylococcus aureus* resistance is not transferable *in vitro*. Measures that rely on limiting person to person contact are effective infection control measures against MRSA when strictly enforced. Vancomycin was the only effective agent against MRSA isolates in this study with an overall susceptibility rate of 89.5%.

Conclusions

- All study drugs were active against non-ESBL producing Enterobacteriaceae and methicillin-susceptible *Staphylococcus aureus*.
- Only imipenem had good activity against ESBL producing Enterobacteriaceae.
- Only vancomycin exhibited good activity against VSEF.
- Follow-up surveillance will aid in determining the impact formulary changes may have on antimicrobial susceptibilities.

References

1 National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*. Villanova, PA, USA: NCCLS, 1997: approved standard M7-A4.
2 National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*. Villanova, PA, USA: NCCLS, 2000: approved standard M100-S11.
3 Rice LB, Eckstein EC, DeVente J, Shlaes DM. Ceftazidime-resistant *Klebsiella pneumoniae* isolates recovered at the Cleveland Department of Veterans Affairs Medical Center. Clin Infect Dis 1996. 23(1):118-24.
4 Rice LB. Successful interventions for gram-negative resistance to extended-spectrum beta-lactam antibiotics. Pharmacotherapy, 1999. 19(8 pt 2):S120-S128.
5 Patterson JE, Hardin TC, Kelly CA, Garcia RC, Jorgensen JH. Association of antibiotic utilization measures and control of multiple-drug resistance in *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol, 2000. 21(7):455-8.
6 Barisic Z, Punda-Polic V. Antibiotic resistance among enterococcal strains isolated from clinical specimens. Int J Antimicrob Agents 2000. 16(1):65-68.

Acknowledgements

We acknowledge our appreciation for the contributions of the following investigators: Prof. Jan Verhoef; Prof. Marc Struelens; Dr. Jacqueline Nguyen; Dr. Rogelio Martin; Dr. Miguel Gobernado; Prof. Dr. J.A.A. Hoogkamp-Korstanje; Prof. Herman Goossens; Dr. George Araj; Prof. Gian Carlo Schito; Prof. Lynne Liebowitz; Prof. Dr. Serhat Unal; Dra. Emilia Cercenado; Prof. DDr. Apostolos Georgopoulos; Prof. Helen Giamarellou; Prof. Pavlos Nikolaidis; Prof. H. Crewe-Brown; Dr. Jose Correia da Fonseca; Dr. Volkan Korten; Dr. Daniel Talon; Prof. Franz Allerberger; Dr. Javier Aznar; Prof. Giovanni Fadda; Dr. Francesco Luzzaro; Prof. Daniela Cirillo; Dr. Dario Costa; Prof. Dr. Heinrich K Geiss; Dr. Marianne Horn; Dr. Stefan Ziesing; Prof. Dr. Harald Seifert; Prof. Jorge Garbino. Sponsored by Wyeth-Ayerst Pharmaceuticals.