A Multi-National *In Vitro* Surveillance of ESBL Producers, VREF and MRSA. Results of the Pan-European Antimicrobial Resistance Using Local Surveillance (PEARLS) Study: 2001 – 2002

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Revised Abstract

Background: The Pan-European Antimicrobial Resistance Using Local Surveillance (PEARLS) study investigates what effect antibiotic usage, particularly the relationship of cephalosporins and pip/tazo, has upon the incidence of ESBL, VREF and MRSA organisms in hospital isolates. Baseline *in vitro* data are recorded in this initial phase. **Methods**: During an 18 month period from 2001 – 2002, a total of 10,627 isolates were evaluated by broth microdilution. Isolates were collected from 36 investigative sites in 16 countries in Europe. 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**: Imp was the most active agent tested against ESBL producing Enterobacteriaceae (*E.coli* plus *K.pneumoniae*) with and overall 97.7 susceptibility rate and 1.5% resistance rate. Cephalosporin resistant rates for ESBL producing Enterobacteriaceae ranged from 22.0% in Cfp to 65.6% in Cfz. A-C and P-T resistant rates for ESBL producers were 30.0% and 29.0%, respectively. *Acinetobacter* resistance rates were >35% resistant to all drugs but Imp at 17.6%. *P. aeruginosa* resistance rates ranges from 11.0% (P-T) to 39.5% (Ctx). Of the study drugs, only Vcm was effective against *E.faecium* with an overall resistant rate (VRE) of 8.7%. All the study drugs were effective against MSSA but only Vcm demonstrated good activity against MRSA with 100% susceptible and no Vcm resistance detected. **Conclusions**: All study drugs showed good activity against non-ESBL producing Enterobacteriaceae and MSSA. Only Imipenem had good activity against the ESBL producing Enterobacteriaceae and *Acinetobacter* species. None of the antimicrobials tested well against VREF. Only vancomycin had good activity against MRSA. Piperacillin-tazobactam was the most active antimicrobial against *P. aeruginosa*.

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 16 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 December 2002 from 36 study centers in 16 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, Schaumburg, 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 guidelines[2] (table 2A, M100-S11)
- Preliminary ESBL activity was determined by screening cefotaxime, ceftazidime, and ceftriaxone with MICs ≥ 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 ≥ 5mm in the inhibition zone of the combination disc when compared to that of the cephalosporin alone: cefotaxime/clavulanic acid – cefotaxime ≥ 5 mm or ceftazidime/clavulanic acid – ceftazidime ≥ 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 10,571 Gram-negative and Gram-positive Isolates collected in 36 Centers from 16 Countries.

Organism	Drug	MIC50 / MIC90	%Sus	%Int	%Res
Acinetobacter spp (n=699)	Amox/Clav	>16 / >16	na	na	na
	Cefepime	8 / >16	50.4	11.6	38.0
	Cefotaxime	32 / >32	31.6	22.8	45.6
	Ceftazidime	16 / >16	49.5	6.4	44.1
	Ceftriaxone	32 / >32	23.8	30.9	45.3
	Gentamicin	4 / >8	53.5	4.2	42.3
	Imipenem	1 / >8	80.4	2.0	17.6
	Ciprofloxacin	1 / >2	51.5	2.3	46.2
	Levofloxacin	0.5 / >4	57.6	4.9	37.5
	Pip/Tazo	16 / >64	61.4	0.0	38.6
	Vancomycin	>32 / >32	na	na	na
Enterobacter aerogenes (n=824)	Amox/Clav	>16 / >16	4.7	2.7	92.6
	Cefepime	0.25 / 2	96.4	1.1	2.5
	Cefotaxime	4 / 32	65.5	26.7	7.8
	Ceftazidime	8 / >16	53.2	7.6	39.2
	Ceftriaxone	4 / 32	74.5	20.4	5.1
	Gentamicin	<0.5 / 2	94.9	1.6	3.5
	Imipenem	1 / 2	97.0	1.0	2.0
	Ciprofloxacin	0.03 / >2	67.7	1.9	30.4
	Levofloxacin	0.12 / >4	68.4	3.3	28.3
	Pip/Tazo	8 / 64	71.0	21.6	7.4
	Vancomycin	>32 / >32	na	na	na
Enterobacter cloacae (n=1388)	Amox/Clav	>16 / >16	3.7	0.9	95.4
	Cefepime	0.12 / 8	94.7	2.6	2.7
	Cefotaxime	0.5 / >32	67.4	6.0	26.6
	Ceftazidime	0.5 / >16	69.6	3.8	26.6
	Ceftriaxone	0.5 / >32	71.4	7.6	21.0
	Gentamicin	<0.5 / 2	92.0	1.4	6.6
	Imipenem	<0.5 / 1	97.9	0.2	1.9
	Ciprofloxacin	0.015 / 1	90.7	1.6	7.7
	Levofloxacin	0.06 / 2	91.3	1.7	7.0
	Pip/Tazo	2 / >64	73.0	9.6	17.4
	Vancomycin	>32 / >32	na	na	na
Enterococcus faecium (n=909)	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	13.9	25.3	60.8
	Levofloxacin	>4 / >4	37.8	6.4	55.8
	Pip/Tazo	>64 / >64	na	na	na
	Vancomycin	1 / 4	90.2	1.1	8.7
Escherichia coli (n-2423)	Amox/Clav	8 / >16	68.7	19.1	12.2
	Cefepime	0.06 / 0.5	96.6	1.0	2.4
	Cefotaxime	0.06 / 0.5	94.7	1.6	3.7
	Ceftazidime	0.25 / 1	95.1	1.3	3.6
	Ceftriaxone	0.06 / 0.25	94.2	2.0	3.8
	Gentamicin	1 / 4	91.0	1.5	7.5
	Imipenem	<0.5 / <0.5	98.6	0.2	1.2
	Ciprofloxacin	0.015 / >2	82.5	0.3	17.2
	Levofloxacin	0.03 / >4	82.7	2.4	14.9
	Pip/Tazo	1 / 8	93.9	2.9	3.2
	Vancomycin	>32 / >32	na	na	na
Klebsiella pneumoniae (n=2059)	Amox/Clav	4 / >16	73.2	12.5	14.3
	Cefepime	0.06 / 4	94.3	1.8	3.9
	Cefotaxime	0.06 / 32	85.2	7.7	7.1
	Ceftazidime	0.25 / >16	82.0	2.1	15.9
	Ceftriaxone	0.06 / 32	84.7	9.0	6.3
	Gentamicin	<0.5 / >8	85.9	2.6	11.5
	Imipenem	<0.5 / 1	98.4	0.2	1.4
	Ciprofloxacin	0.03 / 1	90.9	3.1	6.0
	Levofloxacin	0.06 / 2	92.5	3.3	4.2
	Pip/Tazo	2 / >64	83.2	5.1	11.7
	Vancomycin	>32 / >32	na	na	na
Pseudomonas aeruginosa (n=792)	Amox/Clav	>16 / >16	na	na	na
	Cefepime	4 / >16	74.4	13.5	12.1
	Cefotaxime	32 / >32	7.0	59.3	33.7
	Ceftazidime	2 / >16	79.3	6.7	14.0
	Ceftriaxone	32 / >32	10.1	50.4	39.5
	Gentamicin	2 / >8	80.4	2.5	17.1
	Imipenem	1 / >8	77.8	9.3	12.9
	Ciprofloxacin	0.25 / >2	74.4	4.0	21.6
	Levofloxacin	1 / >4	68.9	6.7	24.4
	Pip/Tazo	4 / >64	89.0	0.0	11.0
	Vancomycin	>32 / >32	na	na	na
Serratia marcescens (n=637)	Amox/Clav	>16 / >16	4.6	6.3	89.1
	Cefepime	0.12 / 1	97.5	0.9	1.6
	Cefotaxime	0.5 / 16	88.5	6.8	4.7
	Ceftazidime	0.25 / 8	91.4	2.5	6.1
	Ceftriaxone	0.25 / 16	89.1	6.8	4.1
	Gentamicin	<0.5 / 4	90.7	2.7	6.6
	Imipenem	37623	96.2	0.6	3.2
	Ciprofloxacin	0.06 / 1	90.6	4.5	4.9
	Levofloxacin	0.12 / 2	93.6	1.1	2.3
	Pip/Tazo	1 / 16	92.6	4.2	3.2
	Vancomycin	>32 / >32	na	na	na
Staphylococcus aureus (n=840)	Amox/Clav	2 / >16	67.1	0.0	32.9
	Cefepime	2 / >16	66.0	2.6	31.4
	Cefotaxime	2 / >32	68.1	2.5	29.4
	Ceftazidime	8 / >16	60.6	4.4	35.0
	Ceftriaxone	4 / >32	63.9	5.3	30.8
	Gentamicin	<0.5 / >8	70.7	1.3	28.0
	Imipenem	<0.5 / >8	74.8	0.6	24.6
	Ciprofloxacin	0.25 / >2	64.6	0.7	34.7
	Levofloxacin	0.25 / >4	66.7	14.7	18.6
	Pip/Tazo	1 / >64	68.3	0.0	31.7
	Vancomycin	1 / 1	100.0	0.0	0.0

Table 2. *In Vitro* Activity (mg/mL) and Susceptibilities (%) of 11 Antimicrobial Agents Against 3,999 Non-Extended Spectrum Beta-Lactamase (Non-ESBL) Producing Enterobacteriaceae and 483 Extended Spectrum Beta-Lactamase (ESBL) Producing Enterobacteriaceae collected in 36 Centers from 16 Countries.

Organism	Drug	MIC50/MIC90	%Sus	%Int	%Res
Enterobacteriaceae, Non-ESBL[1] (n=3999)	Amox/Clav	4 / >16	75.3	13.6	11.1
	Cefepime	0.06 / 0.25	98.9	0.3	0.8
	Cefotaxime	0.06 / 0.25	97.4	1.0	1.6
	Ceftazidime	0.25 / 0.5	97.0	0.5	2.5
	Ceftriaxone	0.06 / 0.12	97.4	1.3	1.3
	Gentamicin	<0.5 / 2	93.9	0.8	5.3
	Imipenem	<0.5 / 1	98.6	0.1	1.3
	Ciprofloxacin	0.015 / >2	89.0	0.8	10.2
	Levofloxacin	0.06 / 4	89.3	2.2	8.5
	Pip/Tazo	1 / 8	92.6	3.0	4.4
	Vancomycin	>32 / >32	na	na	na
Escherichia coli, non-ESBL (n=2293)	Amox/Clav	8 / >16	70.6	17.8	11.6
	Cefepime	0.06 / 0.25	70.6	17.8	11.6
	Cefotaxime	0.06 / 0.25	98.6	0.3	1.1
	Ceftazidime	0.12 / 0.5	98.6	0.3	1.1
	Ceftriaxone	0.06 / 0.12	98.5	0.5	1.0
	Gentamicin	1 / 2	92.9	0.8	6.3
	Imipenem	<0.5 / <0.5	98.6	0.2	1.2
	Ciprofloxacin	0.015 / >2	84.7	0.3	15.0
	Levofloxacin	0.03 / >4	84.9	2.3	12.8
	Pip/Tazo	1 / 8	94.5	2.5	3.0
	Vancomycin	>32 / >32	na	na	na
Klebsiella pneumoniae, non-ESBL (n=1706)	Amox/Clav	4 / >16	81.7	7.9	10.4
	Cefepime	0.06 / 0.5	98.6	0.3	1.1
	Cefotaxime	0.06 / 0.25	95.9	1.8	2.3
	Ceftazidime	0.25 / 2	94.8	0.9	4.3
	Ceftriaxone	0.06 / 0.25	96.0	2.5	1.5
	Gentamicin	<0.5 / 1	95.2	0.8	4.0
	Imipenem	<0.5 / 1	98.5	0.0	1.5
	Ciprofloxacin	0.03 / 0.25	94.8	1.4	3.8
	Levofloxacin	0.06 / 0.5	95.3	2.0	2.7
	Pip/Tazo	2 / 32	90.0	3.6	6.4
	Vancomycin	>32 / >32	na	na	na
Enterobacteriaceae, ESBL[1] (n=483)	Amox/Clav	16 / >16	33.1	36.9	30.0
	Cefepime	4 / >16	67.9	10.1	22.0
	Cefotaxime	32 / >32	31.7	32.9	35.4
	Ceftazidime	>16 / >16	23.8	10.6	65.6
	Ceftriaxone	32 / >32	26.9	37.5	35.6
	Gentamicin	8 / >8	45.1	12.0	42.9
	Imipenem	<0.5 / 1	97.7	0.8	1.5
	Ciprofloxacin	0.25 / >2	64.6	8.3	27.1
	Levofloxacin	0.5 / >4	69.8	7.9	22.3
	Pip/Tazo	8 / >64	59.8	11.2	29.0
	Vancomycin	>32 / >32	na	na	na
Escherichia coli, ESBL (n=130)	Amox/Clav	16 / >16	35.4	43.1	21.5
	Cefepime	8 / >16	53.1	14.6	32.3
	Cefotaxime	32 / >32	26.9	23.1	50.0
	Ceftazidime	16 / >16	33.8	18.5	47.7
	Ceftriaxone	>32 / >32	18.4	29.3	52.3
	Gentamicin	2 / >8	56.9	13.1	30.0
	Imipenem	<0.5 / <0.5	98.5	0.0	1.5
	Ciprofloxacin	>2 / >2	44.6	0.0	55.4
	Levofloxacin	>4 / >4	44.6	3.9	51.5
	Pip/Tazo	2 / 64	84.6	8.5	6.9
	Vancomycin	>32 / >32	na	na	na
Klebsiella pneumoniae, ESBL (n=353)	Amox/Clav	16 / >16	32.3	34.6	33.1
	Cefepime	4 / >16	73.4	8.5	18.1
	Cefotaxime	16 / >32	33.4	36.6	30.0
	Ceftazidime	>16 / >16	20.1	7.7	72.2
	Ceftriaxone	32 / >32	30.0	40.5	29.5
	Gentamicin	8 / >8	40.8	11.6	47.6
	Imipenem	<0.5 / 1	97.5	1.1	1.4
	Ciprofloxacin	0.25 / >2	72.0	11.3	16.7
	Levofloxacin	0.5 / >4	79.0	9.4	11.6
	Pip/Tazo	16 / >64	50.7	12.2	37.1
	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 830 Vancomycin Sensitive (VSE) and 79 Vancomycin-Resistant *Enterococcus faecium* (VRE) collected in 36 Centers from 16 Countries.

Organism	Drug	MIC50/MIC90	%Sus	%Int	%Res
Enterococcus faecium, non-VRE (n=830)	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	14.6	27.2	58.2
	Levofloxacin	>4 / >4	40.3	6.9	52.8
	Pip/Tazo	>64 / >64	na	na	na
	Vancomycin	1 / 1	98.8	1.2	0
Enterococcus faecium, VRE (n=79)	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	6.3	5.1	88.6
	Levofloxacin	>4 / >4	11.4	1.3	87.3
	Pip/Tazo	>64 / >64	na	na	na
	Vancomycin	>32 / >32	0	0	100

Table 4. *In Vitro* Activity (mg/mL) and Susceptibilities of 11 Antimicrobial Agents Against 570 Methicillin-Sensitive *Staphylococcus aureus* (MSSA) and 270 Methicillin-Resistant *Staphylococcus aureus* (MRSA) collected in 36 Centers from 16 Countries.

Organism	Drug	MIC50/MIC90	%Sus	%Int	%Res
Staphylococcus aureus, MSSA (n=570)	Amox/Clav	1 / 2	92.3	0	7.7
	Cefepime	2 / 8	91.9	0.5	7.6
	Cefotaxime	2 / 4	92.4	0.2	7.4
	Ceftazidime	8 / 16	87.5	3.9	8.6
	Ceftriaxone	2 / 8	91.6	1	7.4
	Gentamicin	<0.5 / 2	90.4	0.3	9.3
	Imipenem	<0.5 / <0.5	94	0.2	5.8
	Ciprofloxacin	0.25 / 1	90.2	0.7	9.1
	Levofloxacin	0.12 / 0.5	90.9	2.6	6.5
	Pip/Tazo	1 / 2	92.5	0	7.5
	Vancomycin	1 / 1	100	0	0
Staphylococcus aureus, MRSA (n=270)	Amox/Clav	>16 / >16	14.1	0	85.9
	Cefepime	>16 / >16	11.1	7	81.9
	Cefotaxime	>32 / >32	16.7	7.4	75.9
	Ceftazidime	>16 / >16	3.7	5.6	90.7
	Ceftriaxone	>32 / >32	5.5	14.1	80.4
	Gentamicin	>8 / >8	29.3	3.3	67.4
	Imipenem	>8 / >8	34.2	1.5	64.3
	Ciprofloxacin	>2 / >2	10.7	0.8	88.5
	Levofloxacin	4 / >4	15.6	40.4	44.1
	Pip/Tazo	>64 / >64	17.4	0	82.6
	Vancomycin	1 / 1	100	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 97.7% 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 VRE infections in this study to be 8.6% (79/918) [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 against VSE. Resistance rates for ciprofloxacin and levofloxacin against vancomycin-sensitive *Enterococcus faecium* (VSE) were 58.2% and 52.8%, respectively.

Because methicillin-resistance in *S. aureus* results from the expression of an acquired penicillin-binding protein, most *S. 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 100%.

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 VSE.
- Follow-up surveillance will aid in determining the impact formulary changes may have on antimicrobial susceptibilities.

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