Assessment of Antibiotic Resistance of Clinical Isolates of *Pseudomonas aeruginosa* (PA) Collected from Intensive Care Units (ICU) Patients with Nosocomial Pneumonia in 5 Belgian Hospitals during the 2004 – 2008 Period using EUCAST and CLSI breakpoints.

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M. Riou,[1] S. Carbonnelle,[1] L. Avrain,[1,2] J.P. Pirnay,[3] D. De Vos,[3,4] A. Simon,[5] D. Piérard,[6] F. Jacobs,[7] A. Dediste,[8] F. Van Bambeke,[1] P.M. Tulkens[1]

[1] Université catholique de Louvain, Unité de pharmacologie cellulaire et moléculaire, Brussels; [2] Coris BioConcept, Science Park Crealys, Gembloux; [3] Queen Astrid Military Hospital, Brussels; [4] Vrije Universiteit Brussel, Brussels; [5] Cliniques universitaires St-Luc, Brussels; [6] Universitair Ziekenhuis Brussel, Brussels; [7] Hôpital Erasme, Brussels; [8] Centre hospitalo-universitaire St Pierre, Brussels; Belgium.

Mailing address:
P.M. Tulkens
UCL 73.70 av. Mounier 73,
1200 Brussels – Belgium,
tulkens@facm.ucl.ac.be

Abstract (revised)

Background and Objective: *Pseudomonas aeruginosa* (PA) is a major opportunistic pathogen usually resistant to several antimicrobials, with one of its preferential niches being the respiratory tract of patients in ICU. Our objective was to evaluate the level of resistance of PA isolated from low respiratory tract of patients with nosocomial pneumonia towards commonly recommended antibiotics in this setting using bith CLSI and EUCAST breakpoints (the latter are based largely on [PK/PD] considerations). The aim was to help in setting optimized empirical therapies and/or assessing the necessity of an early determination of the resistance pattern of the offending organism.

Methods: 138 first, non-duplicate isolates were collected from 5 hospitals between 2004 and 2008 from ICU patients with a suspicion of nosocomial pneumonia (confirmed for 125 cases by retrospective analysis of medical records). MICs of 8 commonly used antibiotics were determined by geometric microdilution in cation-adjusted Muller-Hinton broth (data on doripenem, not included in our original submission, have been added for this presentation) and susceptibilities assessed according to FDA and EUCAST breakpoints.

Results: Taking a 25 % of full resistance level (R; based on EUCAST breakpoints) as a limit for clinical usefulness in empiric therapy, only amikacin and doripenem could be considered globally effective as well as in each individual hospital. Ciprofloxacin and meropenem were globally effective, but resistance exceeded the cut-off value in 2/5 and 3/5 hospitals, respectively. Gentamicin, ceftazidime, piperacillin-tazobactam and cefepime were globally ineffective, with resistance levels exceeding 40 % of isolates for cefepime and ceftazidime in 2 hospitals. If using CLSI breakpoints (FDA for doripenem), amikacin, ciprofloxacin, piperacillin-tazobactam and gentamicin could still be considered effective; doripenem and meropenem were globally effective but resistance exceeded the cut-off value in 2/5 and 3/5 hospitals, respectively; cefepime and ceftazidime were globally ineffective.

Conclusion: The level of antibiotic resistance in PA in the ICU surveyed is high and severely limits empiric treatment options. The breakpoint used (EUCAST or CLSI/FDA) strongly influences the conclusions of the study with respect to the recommendations of antibiotic usage in this population.

Introduction

Nosocomial pneumonia (NP) in intensive care units (ICU) is a common complication of critical illness and is associated with significant attributable morbidity and mortality, including prolongation of mechanical ventilation and increased risk of death of patients [1]. *P. aeruginosa* (PA) is a major cause of nosocomial pneumonia in ICU but antibiotic selection is made difficult by its low susceptibility and frequently multiresistant character to the main classes of antibiotics [2-4].

This triggered us to evaluate the level of resistance to anti-pseudomonal aminoglycosides, β-lactams, and fluoroquinolone, of first isolates of PA collected from ICU patients during the 2004-2008 period.

While most countries have been using CLSI-defined breakpoints for assessing antibiotic susceptibility, European countries are now moving to EUCAST-defined breakpoints [5]. These are largely based on PK/PD considerations and are most often considerably lower than those of CLSI. Both breakpoints were therefore used in this study.

References

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2. Mesaros *et al.* (2007). *Pseudomonas aeruginosa*: resistance and therapeutic options at the turn of the new millennium. *Clin Microbiol Infect*. 13: 560-78.
3. Discoll *et al.* (2007) The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. *Drugs* 67: 351-68.
4. Rossolini & Mantengoli (2008). Antimicrobial resistance in Europe and its potential impact on empirical therapy. *Clin. Microbiol. Infect.* 14 S::2-8.
5. http://www.eucast.org

Results

Prevalence of clinical antibiotic resistance (global and by hospital) in 138 isolates of *Pseudomonas aeruginosa*

Figures **in bold** and with a **colored background** indicate situations (global or per hospital) in which resistance to a given antibiotic exceeds **25 %** of isolates based on breakpoints (blue: EUCAST / light red: CLSI)

ATB	Global			H1 (n=12)			H2 (n=29)			H3 (n=18)			H4 (n=22)			H5 (n=56)		
	$MIC_{50/90}$	I / R (%)		$MIC_{50/90}$	I / R (%)		$MIC_{50/90}$	I / R (%)		$MIC_{50/90}$	I / R (%)		$MIC_{50/90}$	I / R (%)		$MIC_{50/90}$	I / R (%)	
		EUCAST	CLSI		EUCAST	CLSI		EUCAST	CLSI		EUCAST	CLSI		EUCAST	CLSI		EUCAST	CLSI
GEN	**2 / 64**	**0.0 / 26**	10 / 15	2 / 64	25	17 / 8.3	**2 / 64**	**31**	10 / 21	**4 / 64**	**33**	**29**	**2 / 32**	**27**	9.1 / 18	2 / 8	20	13 / 7.4
AMK	4 / 16	9.4 / 8.0	1.0 / 7.0	4 / 8	8.3	8.3	4 / 32	14 / 14	3.4 / 10	8 / 16	11 / 5.6	0.0	4 / 32	18 / 14	14	8 / 8	3.6 / 5.4	5.6
MEM	1 / 16	0.0 / 10	3.0 / 24	1 / 4	25 / 8.3	8.3 / 8.3	**2 / 16**	**7 / 38**	**3.4 / 38**	1 / 4	17 / 5.6	4.8	**1 / 16**	**4.5 / 27**	**27**	**1 / 16**	**16 / 27**	**3.6 / 26**
DOR	1 / 8	17 / 18	24	0.375 / 2	17 / 8.3	8.3	**1 / 8**	**17 / 31**	**38**	1 / 2	19 / 4.8	9.5	1 / 16	14 / 23	23	1 / 16	20 / 20	**28**
FEP	**8 / 64**	**0.0 / 46**	**17 / 30**	**4 / 32**	**0.0 / 33**	**33**	**16 / 64**	**0.0 / 73**	**28 / 45**	**12 / 64**	**0.0 / 44**	24 / 24	**6 / 64**	**0.0 / 36**	14 / 23	**8 / 64**	**0.0 / 37**	**15 / 26**
PTZ	**8 / 128**	**0.0 / 34**	20	8 / 128	0.0 / 25	25	**16 / 128**	**0.0 / 41**	21	**8 / 128**	**0.0 / 33**	24	**8 / 128**	**0.0 / 32**	18	**8 / 128**	**0.0 / 32**	17
CAZ	**4 / 64**	**0.0 / 39**	**6.0 / 33**	4 / 16-64	0.0 / 25	8.3 / 17	**4 / 64**	**0.0 / 52**	**6.9 / 45**	**4 / 32-64**	**0.0 / 33**	**4.8 / 29**	**4 / 64**	**0.0 / 41**	**4.5 / 36**	**4 / 64**	**0.0 / 38**	**5.6 / 32**
CIP	0.25 / 8	7.2 / 23	4.0 / 18	0.25 / 8	8.3 / 25	25	**0.4 / 16**	**7 / 38**	14 / 24	**0.25 / 16**	**11 / 33**	24	0.19 / 8	0.0 /14	14	0.19 / 16	8.9 / 16.1	3.7 / 13

Methods

Bacteria: 138 strains of *P. aeruginosa* were collected from patients admitted in ICU with a diagnosis of nosocomial pneumonia in 5 Belgian hospitals.

MICs: These were determined by geometric microdilution in cation-adjusted Muller-Hinton broth. *P. aeruginosa* ATCC 27853 and PAO1 were used as a quality control. Susceptibility was assessed according to EUCAST and CLSI Breakpoints (see values in Table; EUCAST breakpoint are freely available on http://www.eucast.org; in the absence of CLSI-defined breakpoints for doripenem, FDA-defined susceptible breakpoints [as per the product information documentation] were used [FDA does not define I or R breakpoints]).

breakpoint	GEN	AMK	DOR	MEM	TZP	CAZ	FEP	CIP
EUCAST (≤ S / R >)	4 / 4	8 / 16	1 / 4	2 / 8	16 / 16	8 / 8	8 / 8	0.5 / 1
CLSI (≤ S / R ≥)	4 / 16	16 / 64	2 / –	4 / 16	64 / 128	8 / 32	8 / 32	1 / 4

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Conclusions

- The activity of current therapeutic options is highly compromised in PA from NP patients from the hospitals surveyed, with multiresistant phenotypes further complicating antibiotic selection.
- The use of EUCAST breakpoints makes resistance levels worse in those hospitals where resistance according to CLSI was already important.
- Because of the large variability of resistance rates between hospitals, susceptibilities need to be assessed, and the corresponding antibiotic policies defined locally.

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