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Impact of antibiotic cycling on susceptibility profiles of gram-negative pathogens in an intensive care unit: a nine-year retrospective review

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Abstract

Background—Six years after initiating a monthly antibiotic cycling protocol in the surgical intensive care unit (SICU), we retrospectively reviewed antibiogram-derived sensitivities of predominant gram-negative pathogens before and after antibiotic cycling. We also examined susceptibility patterns in the medical intensive care unit (MICU) where antibiotic cycling is not practiced.

Materials and methods—Antibiotic cycling protocol was implemented in the SICU starting in 2003, with monthly rotation of piperacillin/tazobactam, imipenem/cilastatin, and ceftazidime. SICU antibiogram data from positive clinical cultures for years 2000 and 2002 were included in the pre-cycling period, and those from 2004 to 2009 in the cycling period.

Results—Profiles of SICU pseudomonal isolates before (n=116) and after (n=205) implementing antibiotic cycling showed statistically significant improvements in susceptibility to ceftazidime (66% vs. 81%; p = 0.003) and piperacillin/tazobactam (75% vs. 85%; p = 0.021), while susceptibility to imipenem remained unaltered (70% in each case; p = 0.989). Susceptibility of *E. coli* isolates to piperacillin/tazobactam improved significantly (46% vs. 83%; p<0.0005), trend analysis showing this improvement to persist over the study period (p = 0.025). Similar findings were not observed in the MICU. Review of 2009 antibiotic prescription practices showed monthly heterogeneity in the SICU and a two-fold higher overall use of piperacillin/tazobactam in the MICU (p<0.0001).

Conclusions—Six years into antibiotic cycling, we found either steady or improved susceptibilities of clinically relevant gram-negative organisms in the SICU. How much of this effect is from cycling vs. mixing is unknown, but the antibiotic heterogeneity provided by this practice justifies its ongoing use.

Keywords

antibiotic rotation (cycling); antimicrobial resistance; intensive care units

Introduction

Infections caused by antibiotic resistant organisms have evolved into a global public health threat, leading to escalating cost, length of stay, morbidity, and mortality (1). To mitigate drug resistance and its detrimental consequences, a number of approaches with varying degrees of evidence-based substantiation have been advocated. Broadly speaking, these include: 1) implementing preventive measures (e.g. meticulous device utilization with timely discontinuation); 2) containing resistant species (e.g. isolation practices); 3) targeting and treating infections appropriately (e.g. timely antibiotic initiation); and 4) optimizing antibiotic use (e.g. antibiotic stewardship, cycling, or mixing) (2–5).

Although promising, no conclusive data exists to support the routine use of either antibiotic cycling or mixing (5–14). Antibiotic cycling (or rotation) signifies the sequential use of antimicrobials that ideally do not share a common resistance mechanism (15). This is in contrast to mixing, whereby at any given time, equal portions of a target population receive different antimicrobial agents (16).

In 2003, a monthly antibiotic cycling protocol was instituted in the surgical intensive care unit (SICU) of our institution. One year after initiating this protocol, review of unit-specific antibiogram data for the three most common gram-negative organisms showed improvement in select antibiotic susceptibility profiles (17). This effect was not observed during the same period in the medical intensive care unit (MICU) where antibiotic cycling is not practiced. The objective of the present study was to retrospectively compare antibiotic susceptibility profiles of predominant gram-negative pathogens in the SICU before and during antibiotic cycling, 6 y into the program. We reviewed these patterns in the MICU during the same time period.

Methods

The study involves data from the SICU and MICU of an academic medical center, each of which has 16 private beds. Characteristics of the units have been previously reported (17). The study qualified for IRB Exempt Status, as it only involves retrospective examination of existing secondary data (with no patient identifiers) from antibiograms prepared by our microbiology laboratory.

A series of infectious control clinical practices implemented over the years in the intensive care units are as follows: availability of alcohol hand rub solutions (2001), implementation of central line bundles (2005), unit-specific infection control data collection (2006), contact isolation practices and routine screening for MRSA and VRE (2006), collection of unit-specific infection control data (2006), implementation of independent observer model for hand washing (2007), real-time review of blood stream infections (2007), routine use of chlorhexidine gluconate impregnated dressings for central venous catheters (2007), replacement of trauma/emergency department central lines within 24 hrs (2007), and placement prioritization of peripherally inserted central catheters (2008).

This work represents an extension of our previously published work [17], in which we reported results for the years 2002 (pre-cycling) and 2004 (after instituting cycling in 2003). In the current work, we have added another year (2000) of data to the pre-cycling period, and have added cycling data from years 2005e2009 to the previously reported 2004 data to determine if, after an extended period of cycling and adherence to the infectious control practices implemented after 2004, susceptibilities to the cycled antibiotics remained steady or showed improvement.

2.1 Antibiotic Cycling Protocol

The SICU antibiotic protocol was implemented in May 2003, with monthly rotation of piperacillin/tazobactam (PIP/T), imipenem/cilastin (IMI), and ceftazidime (CAZ). The order of antibiotic rotation has remained the same, with PIP/T starting off the rotation scheme each January. Ciprofloxacin (CIP) was part of the core of antibiotics until May 2004, when it was removed in response to susceptibility data from clinical microbiology laboratory and ad lib use as a second agent during non-rotation months. Whenever specific culture data became available, antibiotic choices were tailored or de-escalated accordingly. A cycling protocol is not followed in the MICU.

2.2 Culture Methodology and Antimicrobial Susceptibilities

Culture methodology is as previously described (17). Susceptibility to antimicrobial agents was determined by broth microdilution, alternative MIC methods, or disk diffusion according to Clinical and Laboratory Standards Institute methods. Results were reported for each organism as percentage of isolates susceptible to the antibiotic being tested. Before 2008, repeat isolates from the same patient were included. For each intensive care unit, clinical microbiology laboratory prepared a specific antibiogram for the following calendar years: 2000, 2002, 2004, 2006, 2007, 2008, and 2009. Years 2000 and 2002 form the pre-cycling period, and the rest constitute the cycling period. There were no unit-specific antibiograms for the missing intervening years. Using all positive clinical cultures, we compared susceptibility profiles of the most common SICU gram-negative isolates, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* before and during the cycling period. The same was done in the MICU for the first three pathogens.

2.3 Antibiotic Prescribing Patterns

We examined antibiotic prescription patterns for 2009, the last year of the study. New orders for the target drugs and patient locations were extracted from the pharmacy management system database. Orders were totaled by the calendar month when therapy began and the intensive care unit where the patient was located.

2.4 Statistics

For each organism-antibiotic pair, changes in sensitivity before and after implementation of antibiotic rotation protocol were assessed using Pearson's chi square test. Trends in sensitivity for each pair either before or after implementing the protocol were assessed using both chi square test for trend and nonparametric test for trend. A p value of <0.05 was accepted as statistically significant. Susceptibilities of isolates during the pre-cycling period, as well as overall antibiotic use in 2009 were compared between the two intensive care units using unpaired t-test. P values <0.05 were considered statistically significant. All p values were two-sided.

3. Results

Susceptibility profiles for *P. aeruginosa*, *E. coli*, and *K. pneumoniae* isolates are outlined in Table 1. During the pre-cycling period, susceptibilities between SICU and MICU isolates showed no statistically significant difference (data not shown).

3.1 *Pseudomonas aeruginosa*

Profiles of SICU pseudomonal isolates before (n = 116) and after (n = 205) implementing antibiotic cycling showed improved susceptibility to both CAZ (66% vs. 81%; p = 0.003) and PIP/T (75% vs. 85%; p = 0.021) (Fig. 1a). Susceptibility to IMI remained unaltered

(70% in each case; $p = 0.989$), while susceptibility to ciprofloxacin (not a protocol drug after 2004) fell, but did not reach statistical significance (65.5% vs. 54.6%; $p = 0.057$). When examining the entire study period, this organism's overall susceptibility profile to the studied antibiotics remained steady. In the MICU, there was no improvement in any pseudomonal susceptibility profiles, and sensitivity to IMI declined significantly (71 % vs. 52%; $p = 0.01$).

3.2 *Escherichia coli*

Susceptibility of SICU *E. coli* isolates to PIP/T improved significantly during the cycling period (46% vs. 83%; $p < 0.0005$). Trend analysis showed this improvement to persist over the entire study period ($p = 0.025$) (Fig. 1b). Of note, there was no significant difference between 2000 and 2002 susceptibilities to PIP/T ($p = 0.23$). Susceptibilities to CAZ remained high before and during intervention periods (97% and 92%, respectively; $p = 0.23$), and those to IMI remained 100% throughout. The drop in sensitivity to ciprofloxacin before and during cycling reached statistical significance (94.6% vs. 71.8%; $p = 0.004$), with a persistent declining trend over the study interval ($p = 0.018$). In the MICU, *E. coli* susceptibility profiles remained unchanged except for a statistically significant decline in sensitivity to ciprofloxacin (81% vs. 47%; $p = 0.0004$), the trend also showing a decline over the entire study period ($p = 0.04$).

3.2 *Klebsiella pneumoniae*

No statistically significant difference was noted in susceptibilities to any of the studied antibiotics in the SICU (Fig. 1c). Sensitivity to IMI remained at 100%. The number of MICU *K. pneumoniae* isolates in 2009 was < 10 , excluding specific susceptibility determination by the clinical microbiology laboratory. As such, data in Table 1 are exclusive of 2009. Susceptibilities of this organism to CAZ, PIP/T, and CIP were low in 2000 (44%, 31%, and 44%; $n = 29$). Compared to those in 2000, statistically significant improvements were seen in susceptibility to CAZ (85%) and CIP (85%) in 2002 ($n = 21$; $p = 0.003$ for both). Difference in PIP/T sensitivity between the two years did not reach statistical significance, remaining stably low (31% vs. 47%; $p = 0.23$).

3.4 *Enterobacter cloacae*

Compared to the pre-cycling period, there was no significant difference in susceptibilities of *Enterobacter cloacae* to any of the study antibiotics (data not shown). Susceptibilities to *Enterobacter aerogenes* were not analyzed, as the number of isolates was insufficient, as was the total number of MICU *Enterobacter* isolates.

3.5 Antibiotic Prescribing Patterns

Fig. 2 shows the average monthly prescription frequency of the three cycled antibiotics from 2004 to 2009 during the months when each was either the antibiotic of the month (AOTM) (4 mo yearly per antibiotic), or not the designated AOTM. Compliance with the cycling protocol was lowest when CAZ was AOTM, and the most frequently used drug outside the protocol was PIP/T (Fig. 2). Compared with periods as AOTM, the prescription frequency of cycled antibiotics fell by 63% when not AOTM. Fig. 3 shows the pattern of prescription counts amongst the target drugs in SICU (top) and MICU (bottom) from 2004 to 2009. Amongst the three study antibiotics, mean monthly prescription frequency from 2004 to 2009 showed statistically significant differences between the MICU and SICU, with PIP/T twice as frequently used in the MICU (41.5 ± 8.7 (SD) versus 19.5 ± 12.3 respectively; $P < 0.0001$), and IMI half as often (7.6 ± 3.4 versus 14.8 ± 12.7 ; $P < 0.0001$). CAZ ordering frequency was not different between the two units (8.5 ± 5.3 versus 8.7 ± 9.9 ; NS).

Discussion

Antibiotic cycling is an attempt, amongst other strategies, to achieve either stability or a steady decrease in resistance to the cycled antimicrobial agents (3,18,19). Our findings suggest that since implementing a cycling protocol in the SICU six years ago, susceptibility profiles of predominant gram-negative pathogens against cycled antibiotics either remained steady or improved. Specifically, improvement was noted in susceptibilities of *P. aeruginosa* against ceftazidime and PIP/T, and *E. coli* against PIP/T, while sensitivities to *E. cloacae* and *K. pneumoniae* remained steady. Further, the overall trend in *E. coli* susceptibility profile showed a sustained improvement over the study period. Of note, comparison of susceptibility data between the two pre-cycling years in the SICU did not yield a statistically significant difference, suggesting that antimicrobial sensitivities were not on the rise before initiating the cycling program (data not shown). During the same time period, findings were different in the MICU. We observed no improvement in MICU resistance patterns for *P. aeruginosa* or *E. coli*, and the former isolates exhibited significantly worsened resistance to IMI. Although susceptibilities of MICU *Klebsiella* species against PIP/T, CAZ, and CIP improved between the two study periods, this largely stems from the remarkably low susceptibility profiles in 2000 to all studied antibiotics except IMI. Further, sensitivities against CAZ and CIP were already significantly higher in 2002 compared to 2000.

Given inherently different patient populations and prescribing practices, one cannot draw any conclusions regarding merits of antibiotic cycling in the MICU. It was not our intention to directly compare findings in the two locations, but to examine data from another intensive care unit during the same timeline to see if similar trends surfaced regardless of antibiotic cycling practices. We chose the MICU because susceptibility profiles of the study organisms were most comparable between the two units during the baseline period. Both units also employed routine isolation practices and screening for MRSA and VRE (the MICU a few months ahead in implementation), and displayed comparable hand-washing compliance rates.

The mechanism for a protective effect, if any (16, 20), from antibiotic cycling is debatable. Mathematical models comparing cycling with mixing strategies have proposed the latter to more effectively achieve antibiotic heterogeneity (16). Such theories remain unanswered clinically, as the number of prospective studies addressing them is limited. In a prospective comparative study of two medical intensive care units involving 346 patients admitted for > 48 hours, Martinez et. al. compared four months of cycling vs. mixing in each unit, and vice versa (15). A higher percentage of patients acquired resistant strains of *P. aeruginosa* during mixing compared to cycling periods. Caveats were compliance with antimicrobial protocols that was no better than 45% of the time, and study duration of only 8 months (15). In our study, ideally each AOTM would have shown similar prescription frequencies, (i.e., 33% per y per antibiotic for the three target drugs). We found the 6-y compliance with the cycling protocol to be roughly similar between PIP/T and IMI, and lowest with CAZ (40%, 35%, and 25%, respectively, of overall prescription as AOTM). The cyclical pattern of antibiotic prescription counts in the SICU portrayed in Fig. 3 at times resembles mixing rather than cycling, with at least two of three antibiotics used in comparable proportions. Fridkin has remarked that controlled mixing may in fact be occurring in cycling studies [21]. Further confounders such as patient allergies, established antimicrobial treatment at the time of ICU admission, and infectious disease consultant input invariably lead to antibiotic heterogeneity but, in the absence of prospective analysis, we cannot definitively delineate the degree of mixing interposed onto cycling. Whether de-escalation into a different class of antibiotic is against the tenet of cycling is also unknown.

Similar to other aspects of antibiotic rotation, there is no clarity on the optimal duration of each cycle. The overall influence of a cycling protocol is ideally cumulative, such that a specific time period or even the antibiotic choice itself become less consequential [3]. Reported cycles have spanned from proposed once daily [22] regimens to that upwards of 4 y [9]. In theory, the cycle should be short enough to discourage development of resistance to a rotated antibiotic while allowing its use in a future cycle, as any potential resistance after withdrawal would presumably drop rapidly. Of practical significance is a regimen conducive to compliance.

Yet another of many unanswered questions on antibiotic cycling is whether to periodically examine sensitivity profiles against antibiotics that are not part of the protocol, but used ad lib. For example, use of ciprofloxacin is not restricted in our intensive care units. In both SICU and MICU, we found worsening sensitivity of *E. coli* isolates to ciprofloxacin, with a statistically significant declining trend over the study period. A look at ciprofloxacin use in both units showed steady and comparable monthly use. Close monitoring of susceptibility profiles with worsening trends may call for restrictions in use of a target antibiotic to potentially foster improved sensitivities in the future.

This report spans nine years, six of which comprise the antibiotic cycling period in the SICU. Several study limitations are acknowledged. This is a single-center, retrospective study without a controlled comparison group. Although unclear as to what gold standard endpoints for antibiotic cycling entail, e.g. clinical outcomes vs. control of antibiotic resistance, we did not examine factors such as length of stay or mortality. The success of cycling and other antimicrobial control strategies is partly attributed to vigilance by invested individuals attuned to appropriate prescribing practices (8). In addition, culture sites of origin were not defined in our study, although any source can contribute to resistance. In a study by Barie et. al., site of infection was not found to influence mortality in a surgical ICU where antibiotic cycling was performed (23). Another study limitation is that microbiologic data were only derived from antibiograms created from clinical cultures, and those for years 2003 and 2005 were not performed by the microbiology laboratory. Antibiograms are tools to gauge susceptibility profiles and aid empiric therapy, and by nature only reflect submitted specimens, with potential to underestimate actual number of infections. Our antibiogram data collection was also changed in 2008 so as to only include one isolate per patient per admission. Further, we did not explore colonization, which is an immense reservoir for spread of antibiotic resistance, although routine screening for MRSA and VRE in both units was started in 2006. Lastly, no molecular investigation was done to identify clonal spread.

In summary, since 2003, we have utilized a monthly antibiotic cycling protocol in the surgical intensive care unit of our institution. Six years into this program, clinically relevant gram-negative isolates have either sustained steady susceptibilities to the cycled antibiotics or have shown significant improvement. How much of this effect is from cycling is unknown, but the antibiotic heterogeneity provided by this routine alongside other infectious control practices justifies its ongoing use.

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References

1. Levy SB, Marshall B. Antibacterial resistance worldwide: Causes, challenges and responses. *Nat Med*. 2004; 10:S122–129. [PubMed: 15577930]
2. Kollef MH. Optimizing antibiotic therapy in the intensive care unit setting. *Crit Care*. 2001; 5:189–195. [PubMed: 11511331]

3. Raymond DP, Pelletier SJ, Sawyer RG. Antibiotic utilization strategies to limit antimicrobial resistance. *Semin Respir Crit Care Med.* 2002; 23:497–501. [PubMed: 16088644]
4. Niederman M. Appropriate use of antimicrobial agents: Challenges and strategies for improvement. *Crit Care Med.* 2003; 31:608–616. [PubMed: 12576973]
5. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. *Clin Infect Dis.* 2007; 44:159–177. [PubMed: 17173212]
6. Cadena J, Taboada CA, Burgess DS, Ma JZ, Lewis JS 2nd, Freytes CO, Patterson JE. Antibiotic cycling to decrease bacterial antibiotic resistance: A 5-year experience on a bone marrow transplant unit. *Bone Marrow Transplant.* 2007; 40:151–155. [PubMed: 17530005]
7. Kollef MH, Vlasnik J, Sharpless L, Pasque C, Murphy D, Fraser V. Scheduled change of antibiotic classes: A strategy to decrease the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 1997; 156:1040–1048. [PubMed: 9351601]
8. Kollef MH, Ward S, Sherman G, Prentice D, Schaiff R, Huey W, Fraser V. Inadequate treatment of nosocomial infections is associated with certain empiric antibiotics. *Crit Care Med.* 2000; 28:3456–3464. [PubMed: 11057801]
9. Gerding DN, Larson TA, Hughes RA, Weiler M, Shanholtzer C, Peterson LR. Aminoglycoside resistance and aminoglycoside usage: Ten years of experience in one hospital. *Antimicrob Agents Chemother.* 1991; 35:1284–1290. [PubMed: 1929283]
10. Gruson D, Hilbert G, Vargas F, Valentino R, Bui N, Pereyre S, Bebear C, Bebear C-M, Gbikpi-Benissan G. Strategy of antibiotic rotation: long-term effect on incidence and susceptibilities of gram-negative bacilli responsible for ventilator-associated pneumonia. *Crit Care Med.* 2003; 31:1908–1914. [PubMed: 12847382]
11. Gruson D, Hilbert G, Vargas F, et al. Rotation and restricted use of antibiotics in a medical intensive care unit: Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. *Am J Respir Crit Care Med.* 2000; 162:837–843. [PubMed: 10988092]
12. Warren DK, Hill HA, Merz LR, Kollef MH, Hayden MK, Fraser VJ, Fridkin SK. Cycling empirical antimicrobial agents to prevent emergence of antimicrobial-resistant gram-negative bacteria among intensive care unit patients. *Crit Care Med.* 2004; 21:2450–2456. [PubMed: 15599150]
13. Masterson RG. Antibiotic cycling: more than it might seem? *J Antimicrob Chemother.* 2005; 55:1–5. [PubMed: 15574474]
14. Raymond DP, Pelletier SJ, Crabtree TD, Gleason TG, Hamm LL, Pruett TL, Sawyer RG. Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. *Crit Care Med.* 2001; 29:1101–1108. [PubMed: 11395583]
15. Martinez JA, Nicolás JM, Marco F, et al. Comparison of antimicrobial cycling and mixing strategies in two medical intensive care units. *Crit Care Med.* 2006; 34:329–336. [PubMed: 16424711]
16. Bergstrom CT, Lo M, Lipsitch M. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. *Proc Nat Acad Sci.* 2004; 101:13285–13290. [PubMed: 15308772]
17. Bennett KM, Scarborough JE, Sharpe M, Dodds-Ashley E, Kaye KS, Hayward TZ III, Vaslef SN. Implementation of antibiotic rotation protocol improves antibiotic susceptibility profile in a surgical intensive care unit. *J Trauma.* 2007; 63:307–311. [PubMed: 17693828]
18. Kollef MH, Micek ST. Strategies to prevent antimicrobial resistance in the intensive care unit. *Crit Care Med.* 2005; 33:1845–1853. [PubMed: 16096464]
19. Kollef MH. Is antibiotic cycling the answer to preventing the emergence of bacterial resistance in the intensive care unit? *Clin Infect Dis.* 2006; 43:S82–88. [PubMed: 16894520]
20. Evans HL, Milburn ML, Hughes MG, et al. Nature of gram-negative rod antibiotic resistance during antibiotic rotation. *Surg Infect.* 2005; 6:223–231.
21. Fridkin SK. Routine cycling of antimicrobial agents as an infection-control measure. *Clin Infect Dis.* 2003; 36:1438–1444. [PubMed: 12766840]

22. Smith RL, Evans HL, Chong TW, et al. Reduction in rates of methicillin-resistant *Staphylococcus aureus* infection after introduction of quarterly linezolid-vancomycin cycling in a surgical intensive care unit. *Surgical Infections*. 2008; 9:423. [PubMed: 18759679]
23. Barie PS, Hydo LJ, Shou J, Larone DH, Eachempati SR. Influence of antibiotic therapy on mortality of critical surgical illness caused or complicated by infection. *Surg Infect*. 2005; 6:41–54.

Figure 1.

Trend in antimicrobial susceptibilities of common gram-negative isolates: (A) *Pseudomonas aeruginosa*; (B) *Escherichia coli*; and (C) *K. pneumoniae*. CAZ = ceftazidime; IMI = imipenem/cilastin; PIP/T = piperacillin/tazobactam

Fig. 2.

Average monthly prescription frequency of each of the three target drugs from 2004 to 2009 when designated as AOTM (4 mo yearly per study antibiotic), and when not the designated AOTM. Compared with periods as AOTM, the overall prescription frequency of target antibiotics fell by 63% when not AOTM.

AOTM =antibiotic of the month.

Fig. 3.
Antibiotic prescription patterns in SICU (top) and MICU (bottom) from 2004 to 2009.

SICU and MICU antibiotic susceptibility profiles for *P. aeruginosa*, *E. coli*, and *K. pneumoniae* during pre-cycling and cycling periods.

Table 1

	% Susceptibility — SICU		<i>p</i> Value	% Susceptibility – MICU		<i>p</i> Value
	Pre-cycling period	Cycling period		Pre-cycling period	Cycling period (in SICU)	
<i>P. aeruginosa</i>	n = 116	n = 205		n = 65	n = 165	
Ceftazidime	66.4	81.0	0.003	70.8	60.0	0.13
Imipenem/cilastin	69.8	70.0	0.99	70.8	52.1	0.01
Piperacillin/tazobactam	75.0	85.4	0.02	72.3	69.1	0.63
Ciprofloxacin	65.5	54.6	0.06	56.9	43.6	0.07
<i>E. coli</i>	n = 37	n = 142		n = 32	n = 127	
Ceftazidime	97.3	91.6	0.23	96.9	92.9	0.41
Imipenem/cilastin	100	100	NS	94.1	96.2	0.59
Piperacillin/tazobactam	46.0	83.1	<0.0005	59.4	73.4	0.12
Ciprofloxacin	94.6	71.8	0.004	81.3	46.5	0.0004
<i>K. pneumoniae</i>	n = 32	n = 112		n = 50	n = 73	
Ceftazidime	96.9	90.2	0.23	62.0	93.2	<0.0005
Imipenem/cilastin	100	100	NS	96.2	92.3	0.37
Piperacillin/tazobactam	71.9	83.9	0.12	38.0	81.3	<0.0005
Ciprofloxacin	87.5	81.3	0.41	62.0	81.3	0.016