A decade of change in susceptibility patterns of Gram-negative blood culture isolates: a single center study

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Abstract

Background **Gram-negative bacteremia is one of the leading causes of mortality and morbidity in Indian hospitals. We hereby describe changing trends in Gram-negative isolates from blood cultures from a single center over a ten-year period.**

Methods **Antibiotic susceptibility patterns were collected for a total of 4128 non-repetitive blood culture isolates from 2003 to 2013. We analyzed clinically important Gram-negative isolates (*Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*) and their susceptibility pattern. *A. baumannii* was studied between 2009 and 2013 only.**

Results **There was a steady increase in extended-spectrum beta-lactamase (ESBL) production in *E. coli* (56% to 80%) and an even steeper increase in *K. pneumoniae* (50% to 81%). Susceptibility to carbapenems fell marginally for *E. coli* (p = .242) but significantly for *K. pneumoniae* (p = .000) and *P. aeruginosa* (.0005). All these changes were seen irrespective of the source of the isolate (outpatient, inpatient and critical care unit – CCU), with a statistically significant fall among CCU isolates of *K. pneumoniae* and *P. aeruginosa*. *P. aeruginosa* was more susceptible to carbapenems than beta-lactam /beta-lactamase inhibitors until 2009, but thereafter the pattern reversed. *A. baumannii* was isolated from the CCU only: 75% were resistant to carbapenems and susceptible only to polymyxin E and tigecycline.**

Conclusion **There was a progressive increase in antimicrobial resistance in isolates of *E. coli, K. pneumoniae, P. aeruginosa* and *A. baumannii* isolated from blood cultures. ESBL production was seen in the majority of isolates of *E. coli* and *K. pneumoniae*. Carbapenem resistance in *K. pneumoniae* and *E. coli* is increasing rapidly. Resistance to even tigecycline and polymyxin E, antibiotics of last resort, has begun to emerge. There is an urgent need for antimicrobial stewardship and other measures to limit worsening of Gram-negative resistance in India.**

Keywords **Antibiotic resistance, bacteremia, Enterobacteriaceae, Gram-negative infections**

Background

Bloodstream infections caused by multidrug-resistant Gram-negative organisms continue to be leading causes of morbidity and mortality in hospitalized patients.[1-3] Knowledge of longitudinal trends in antimicrobial susceptibility patterns will help both clinicians and infection control practitioners. Unlike many developed

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countries, India does not have a nationwide antimicrobial resistance monitoring network and therefore long term longitudinal single center studies can give important information regarding emerging resistance patterns. Most studies from India have been performed over 1 to 4 years;[4-11] only one has analyzed data over an 8 year period.[12] We herewith describe antibiotic susceptibility patterns of important Gram-negative blood culture isolates at a single center over 10 years.

Methods

A retrospective observational study was carried out at a 550-bed tertiary care referral center in South India. We studied the antimicrobial susceptibility patterns of 4128 non-repetitive blood culture isolates of *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* from 2003-2013. *Acinetobacter baumannii* was included from 2009-2013 as blood culture isolates were uncommon prior to 2009. We collected the susceptibility patterns of all the four organisms both together and separately based upon whether collected from ward inpatients (IP), outpatients (OP) and patients in the critical care unit (CCU). Subsequent cultures of the same organism from the same patient were not included.

Isolation and identification was done with BacT/ALERT (bioMérieux, Marcy-l'Étoile, France) and VITEK 2 (bioMérieux, Marcy-l'Étoile, France) and also through standard microbiological tests. Susceptibility testing was done with the disc diffusion method (modified Kirby-Bauer method) using Mueller-Hinton agar and VITEK 2 antimicrobial susceptibility testing (AST) cards. The results were interpreted as per CLSI (Clinical and Laboratory Standards Institute) guidelines corresponding to that period.[13] All antibiotic discs were obtained from OXOID (Oxoid Ltd, Altrincham, Cheshire, United Kingdom) and BD BBL (Becton, Dickinson and Company Ltd, Franklin Lakes, New Jersey, USA). Extended-spectrum beta-lactamase (ESBL) production and carbapenem resistance was interpreted based on Kirby-Bauer disc susceptibility testing and the minimum inhibitory concentration (MIC) criteria by the VITEK COMPACT 2 as per CLSI guidelines. Tigecycline susceptibility was not performed for *P. aeruginosa* as it is inherently resistant. Meropenem was taken as a representative of the Group 2 carbapenems (meropenem, imipenem, doripenem).

Data was entered in Microsoft Excel worksheet and susceptibility percentages were calculated. Comparison of resistance of 2003 and 2013 was done with Z test for 2 population proportions.

We obtained institutional ethics committee clearance for the study.

Results

During the study period, susceptibility patterns of 4128 blood culture isolates of *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* were analysed. *E. coli* predominated in outpatient isolates whereas *K. pneumoniae and P. aeruginosa* predominated in CCU isolates. All *A. baumannii* isolates were from the CCU. Details of isolates are in Table 1. The overall susceptibility pattern of all blood isolates is depicted in Figure 1.

Table 1. Details of number of isolates included in the study

	Outpatient	Inpatient	CCU	Total
All isolates	1111	1365	1652	4128
E. coli	687	774	457	1918
K. pneumoniae	286	396	568	1250
P. aeruginosa	138	195	295	628
A. baumannii	-	-	332	332

CCU critical care unit.

Outpatient isolates (Tables 2 and 5): Amikacin susceptibilities fell between 2003 (85%) and 2013 (74%), not statistically significant (p = .136). ESBL production rates increased from 45% to 67%. Susceptibility to ciprofloxacin was low throughout the study period (37%-40%). There was a significant drop in susceptibility to beta-lactam – beta-lactamase inhibitor (BL-BLIs) from 80% to 60% (p = .006 for cefoperazone-sulbactam and p = .0003 for piperacillin-tazobactam).

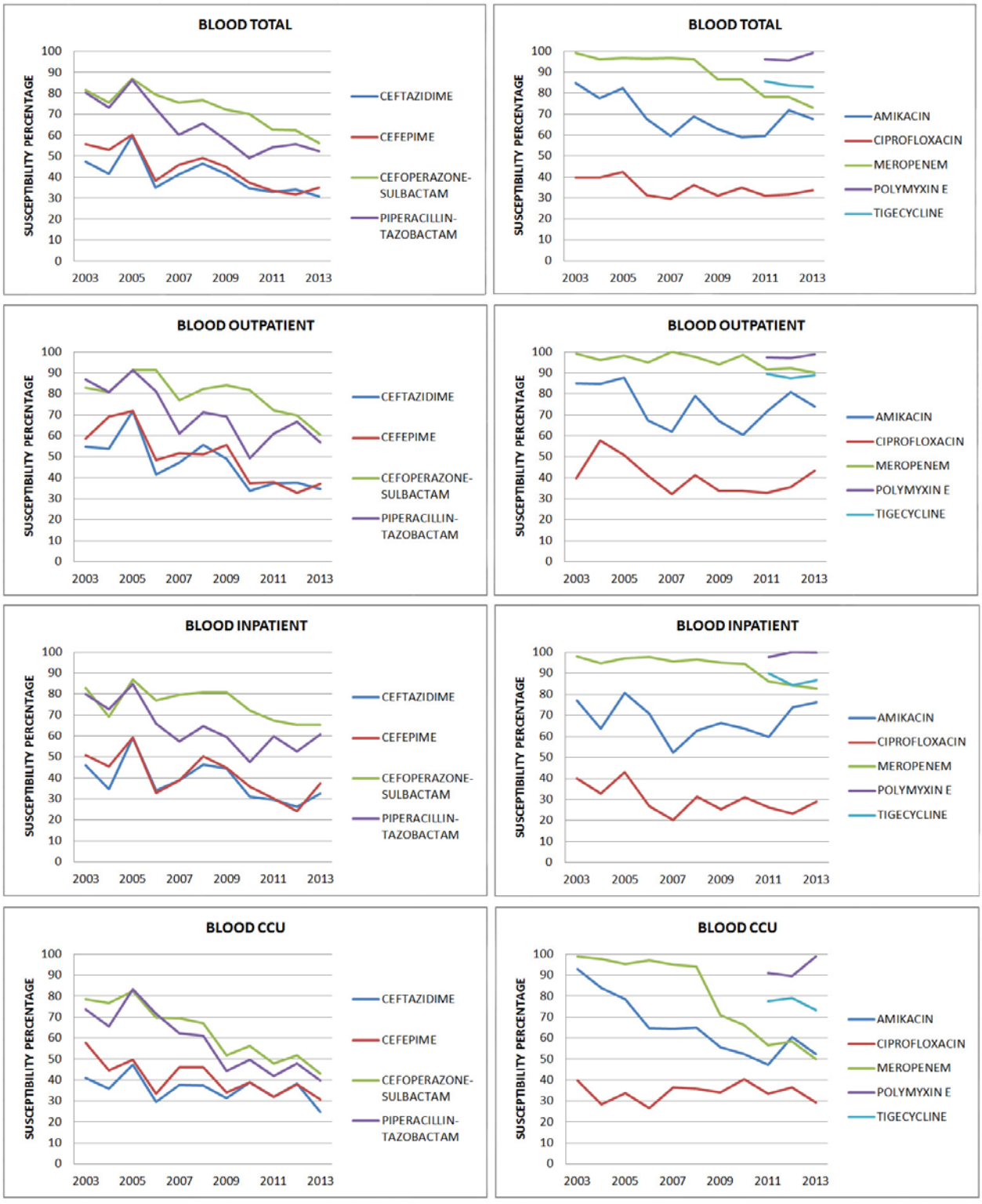

Figure 1. Susceptibility patterns of all blood isolates

Table 2. Comparison of resistance of all blood culture isolates in 2003 vs. 2013

	2003 %	2013 %	Resistance comparison 2003 vs. 2013	
OUTPATIENT			Z score	*p* value
Amikacin	85	74	1.4888	.13622
Ceftazidime	55	35	2.3068	**.02088**
Cefepime	58	37	2.4384	**.01468**
Ciprofloxacin	40	43	-0.4112	.6818
Cefoperazone-sulbactam	83	60	2.7667	**.0056**
Piperacillin-tazobactam	87	57	3.6607	**.00026**
Meropenem	96	79	2.7931	**.00528**
INPATIENT				
Amikacin	77	76	0.128	.89656
Ceftazidime	46	32	2.0772	**.03752**
Cefepime	51	37	2.014	**.0444**
Ciprofloxacin	40	29	1.7445	.08186
Cefoperazone-sulbactam	83	65	2.7752	**.00544**
Piperacillin-tazobactam	80	61	2.2309	**.00338**
Meropenem	88	83	0.9845	.32708
CCU				
Amikacin	93	52	6.6121	0
Ceftazidime	41	25	2.838	**.00452**
Cefepime	58	31	4.4315	0
Ciprofloxacin	40	29	1.8114	.0703
Cefoperazone-sulbactam	78	43	5.5771	0
Piperacillin-tazobactam	73	40	5.3191	0
Meropenem	99	50	7.9709	0
TOTAL				
Amikacin	86	66	5.2925	0
Ceftazidime	46	30	4.3462	0
Cefepime	56	34	5.335	0
Ciprofloxacin	40	31	2.3333	**.0198**
Cefoperazone-sulbactam	81	56	6.4772	0
Piperacillin-tazobactam	79	52	6.8697	0
Meropenem	95	69	7.3563	0

CCU critical care unit.

Meropenem susceptibility dropped from 96% to 79% (p = .005). Most isolates were susceptible to polymyxin E and tigecycline (97% and 89% respectively).

Inpatient isolates (Table 2): Susceptibility to amikacin was maintained throughout this period (77% to 76%). A drop in the susceptibility to ciprofloxacin was noted (40% to 29%) but it was not statistically significant (p = .082). There was a statistically significant drop in the susceptibility to ceftazidime and cefepime (p = .038 and .044). The drop in BL-BLIs (statistically significant – p = .005 and .003) and meropenem (not statistically significant, p = .327) susceptibilities was similar to outpatient isolates.

The detailed antibiotic susceptibility patterns are in Table 3a, 3b, 4, 5 and 6.

CCU isolates (Tables 3 and 5): Amikacin susceptibility fell from 93% to 52% (p = .000). ESBL production rates increased from 60% to 80%, higher than among outpatient and inpatient isolates. There was a drop in meropenem susceptibility (from 99% to 77%). The drop in susceptibility to all antibiotics except for ciprofloxacin was statistically significant**.** The only antibiotics with susceptibilities greater than 80% were polymyxin E and tigecycline.

E. coli (Figure 2, Tables 3a and 3b): Amikacin susceptibility was maintained for OP/IP/CCU isolates at 90%. ESBL rates increased from 56% in 2003 to 71% in 2013. The increase was more important in CCU isolates. There was a significant drop in ceftazidime susceptibility in CCU isolates (p = .037). Among the BL-BLIs, cefoperazone-sulbactam susceptibility was about 10% higher overall than that to piperacillin-tazobactam, although susceptibility to both fell by about 10% between 2003 and 2013. The statistically significant drop in cefoperazone-sulbactam (p = .024) susceptibility was more contributed by the inpatient isolates (p = .046). For piperacillin-tazobactam, the drop in susceptibility was significant (p = .012), more from the outpatient isolates (p = .038). There was a reduction in susceptibility to meropenem from 2003 to 2013 (100% to 95%), falling to as low as 91% among CCU isolates but this was not statistically significant.

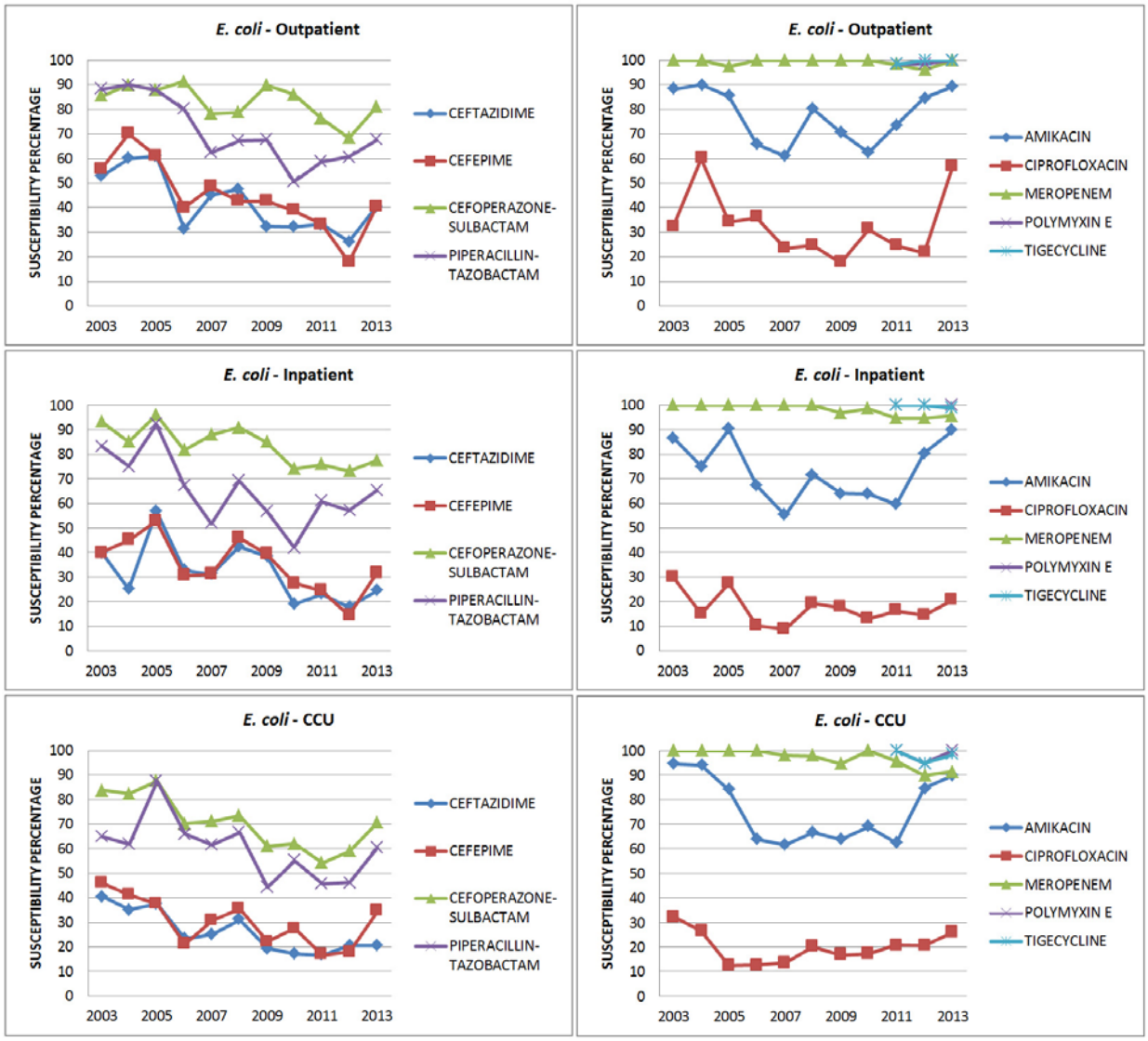

Figure 2. Susceptibility patterns of *E. coli*

Susceptibility to polymyxin E and tigecycline was high (100% to 95%).

K. pneumoniae (Figure 3, Tables 3a and 3b): There was a significant drop in the susceptibility to amikacin in CCU isolates from 94% in 2003 to 44% in 2013 (p = .000). ESBL production rates were 75% in outpatient isolates and 81% in CCU isolates. The susceptibility rates to BL-BLIs were as low as 40% in both outpatient and inpatient isolates and just 30-35% in CCU isolates. The drops in the susceptibility to BL-BLIs of all isolates (outpatient, inpatient and CCU) were statistically significant. Meropenem susceptibility fell from100% in outpatient isolates in 2003 to 60% in 2013 (p = .019). A similar trend was seen in CCU isolates (p = .000). Even though there was a drop for inpatient isolates, it was not statistically significant. In 2013, only 59% of inpatient isolates and 43% CCU isolates were susceptible to meropenem. Susceptibility to tigecycline (76%) was lower than that to polymyxin E (100%) in CCU isolates (Table 5).

P. aeruginosa (Figure 4, Tables 3a and 3b): Amikacin susceptibility was maintained throughout the study period in inpatient isolates whereas there was a 20% reduction in CCU isolates (87% to 66%). The number of isolates susceptible to piperacillin-tazobactam was higher

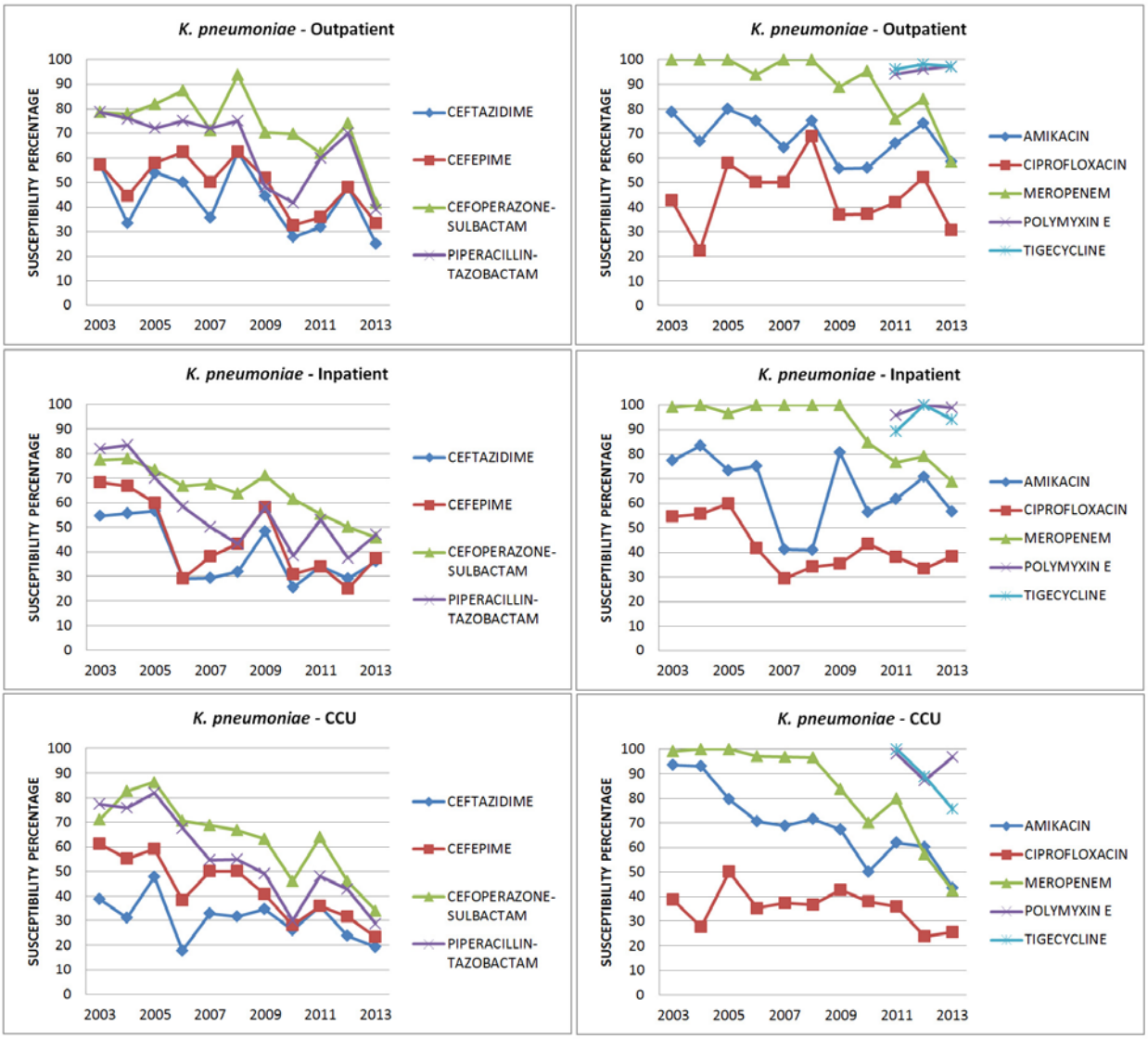

Figure 3. Susceptibility patterns of *K. pneumoniae*

than that for ceftazidime and cefoperazone-sulbactam and the susceptibility to piperacillin-tazobactam was maintained throughout the study period. In 2003 strains were more susceptible to meropenem compared to BL-BLIs but from 2009, the trend got reversed. Even though there was a drop in the susceptibility to all antibiotics, the only statistically significant drop was for meropenem from CCU isolates (p = .0006). More than 90% of isolates were susceptible to polymyxin E (Table 5).

A. baumannii (Figure 5): We analyzed data from 2009 to 2013 only, all from the CCU. Susceptibility to amikacin was low but steady (35% to 25%) between 2009 and 2013. Susceptibility to third generation cephalosporins/BL-BLIs was low at 33% to 23%. Meropenem susceptibility was low throughout the study period (33% to 26%). Polymyxin E and tigecycline susceptibility fell from 100% to 95% and 80% respectively, both not statistically significant.

Discussion

The rapid emergence of multidrug-resistant Gram-negative bacteria is an enormous problem not only in India but also globally.[14-17] We hereby demonstrate steadily increasing resistance

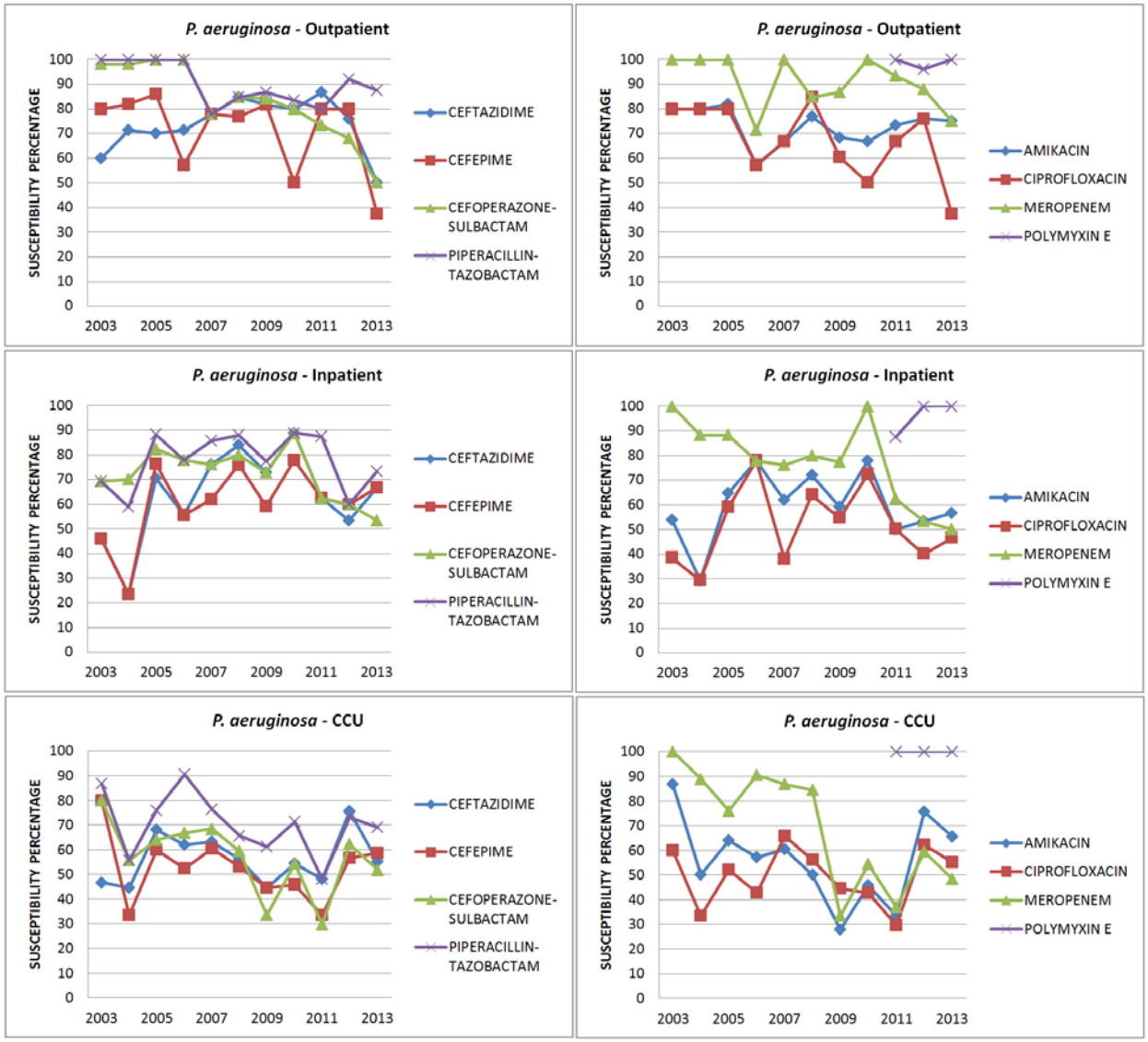

Figure 4. Susceptibility patterns of *P. aeruginosa*

rates among Gram-negative blood culture isolates with the greatest rise among CCU isolates, compared to outpatient and inpatient isolates.

ESBL production in Enterobacteriaceae in India has been increasing steadily in various studies. In our study ESBL production rate in *E. coli* increased from 56% in 2003 to 71% in 2013 and was as high as 80% in the CCU, which is higher than previous studies where it was between 45-70%.[5-8] Our ESBL rate in *E. coli* was similar to the rates in the study by Rajeevan et al.[9] ESBL production in *K. pneumoniae* similarly increased from 50% in 2003 to 73% in 2013. A worrying trend in our study was the increasing ESBL production rate even in outpatient isolates (from 45% in 2003 to 67% in 2013). This increase in rates unfortunately may require clinicians to use high end antibiotics such as carbapenems even for community-acquired bacteremias.

The increase in ESBL rates may have resulted in widespread carbapenem usage in many Indian hospitals during the first decade of this century, which in turn probably fuelled emergence of carbapenem resistance. Carbapenem resistance in Enterobacteriaceae increased over this period in our study: *E. coli* isolates were fully susceptible

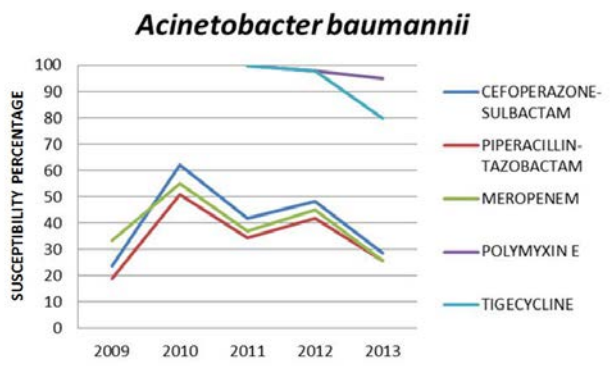

Figure 5. Susceptibility patterns of *A. baumannii*

to carbapenems in 2003 but not in 2013, when 4% of isolates were resistant. *K. pneumoniae* showed an even greater increase in carbapenem resistance (1% in 2003 to 46% in 2013 – Table 3b). The changes in carbapenem resistance were statistically significant in isolates from outpatient and CCU. This was similar to two other studies that showed that carbapenem resistance increased from 10% to 40% over a two year period.[6,16] A similar increase in carbapenem resistance from 2008 was reported in another study done in South India.[12] This probably reflects the emergence and subsequent dissemination of New Delhi metallo-beta-lactamase (NDM-1)-producing Enterobacteriaceae in multiple Indian hospitals in this period.[17]

A similar rise in carbapenem resistance was noted in *P. aeruginosa* and *A. baumannii*. Carbapenem resistance in *P. aeruginosa* was not seen in 2003 but in 2013, 52% of CCU isolates were resistant, the difference being statistically significant. The drop in susceptibility in other isolates was not statistically significant. In another study done in India, 30-37% of *P. aeruginosa* isolates were resistant to carbapenem.[18] *P. aeruginosa* isolates were more susceptible to piperacillin-tazobactam (70% to 80%) than cefoperazone-sulbactam (50%) or carbapenems (65%). Again, the widespread use of carbapenems instead of BL-BLIs to treat ESBL Enterobacteriaceae may have contributed.

In our study *A. baumannii* isolates were all from the CCU. Susceptibility to meropenem was just 33% and decreased further to 26% in 2013 similar to another study which analyzed isolates between 2011 and 2012 and showed 20% susceptibility to carbapenems.[19] Carbapenem-resistant *A. baumannii* is a common cause of hospital-acquired bacteremia and pneumonia at our center. Carbapenems are therefore currently inappropriate as empiric therapy for hospital-acquired infections where *A. baumannii* may be a pathogen.

Beta-lactam/ beta-lactam inhibitors have been used as carbapenem-sparers for nosocomial infections, but susceptibility rates declined over time in our study (Table 4). Cefoperazone-sulbactam susceptibility of outpatient isolates declined from around 83% in 2003 to 60% in 2013 (p = .005). Susceptibility to piperacillin-tazobactam also declined from 87% in 2003 to 57% in 2013 for outpatient isolates (p = .0003) – Table 2. Although the drop in the susceptibility to BL-BLIs was statistically significant in all isolates ($p \leq .005$), it was more pronounced in CCU isolates (40%) than in outpatient (60%) and inpatient isolates (60%). These findings have important implications for therapy: these drugs are no longer reliable as empiric choices for hospital-acquired infections and may not be effective as empiric choices for severe community-acquired bacteremias.

Polymyxin E and tigecycline were the most effective antibiotics for *E. coli* and *K. pneumoniae* (susceptibility ranged between 90-100%). However resistance to these antibiotics of last resort is clearly emerging at our center. Although there was a drop in overall susceptibility to polymyxin E and tigecycline in 2013, this was statistically significant (p = .0001) only for polymyxin E from CCU isolates (Table 6). In 2013, 3-5% of *P. aeruginosa* and *A. baumannii* isolates were resistant to polymyxin E and there was a fall in tigecycline susceptibility from 100% in 2011 to 70%-80% in 2013 among *K. pneumoniae* and *A. baumannii* isolates from CCU (Table 5). This highlights the need for careful antimicrobial stewardship to preserve polymyxin E and tigecycline as the drugs of last resort.

In 2013, 67% of the isolates were susceptible to amikacin, with a minimal fall in

susceptibilities over a 10 year period. This could be due to the fact that aminoglycosides are rarely used as empiric or definitive therapy for Gram-negative sepsis at our center due to concern about toxicity: perhaps it is time to reconsider the use of aminoglycosides as empiric agents in Gram-negative sepsis, probably in combination with beta-lactam antibiotics.

We acknowledge some limitations in our study. The increase in carbapenem resistance in 2012 and 2013 may have been because of lowered MIC breakpoints by CLSI in 2012.[13] We also did not test for molecular mechanisms of resistance, which might have yielded valuable insight into reasons behind emergence of resistance. For instance, we do not know whether carbapenem resistance was due to the production of NDM-1, other carbapenemases or still other mechanisms such as porin channel mutations or efflux pumps. We also did not test for clonality among isolates which might give useful information regarding the role of infection control efforts versus antimicrobial stewardship.

Conclusion

We hereby demonstrate significant increases in resistance in blood culture isolates of Gram-negative bacteria to all major classes of antibiotics. Inclusion of blood culture isolates alone, as opposed to cultures from non-sterile sites, increases the applicability of our findings to clinical practice. The majority of Enterobacteriaceae at our center are ESBL producers and this was true even for outpatient isolates. There was a drop in susceptibility to beta-lactam/beta-lactamase inhibitors, which are potential carbapenem-sparers. Carbapenem-resistant *A. baumannii* has established itself as a nosocomial pathogen, and almost half of *P. aeruginosa* isolates were also resistant. Rising carbapenem resistance was also noted with *K. pneumoniae*, especially for isolates from the CCU, where carbapenems can no longer be used as reliable empiric therapy. Resistance to polymyxin E and tigecycline, considered drugs of last resort, has begun to emerge in *K. pneumoniae*. Antimicrobial stewardship and other measures, such as those suggested by the Chennai Declaration,[20] are urgently needed to tackle the problem of Gram-negative resistance.

Authors' contribution statement

MA contributed to study concept, design, data collection, data analysis, and manuscript preparation. RG contributed to study concept, data analysis, and manuscript preparation. SNP contributed to study concept, data collection, data analysis, and manuscript preparation. SD contributed to study concept and manuscript editing. TMA contributed to study concept, data collection, and manuscript editing. VR contributed to study concept and manuscript editing. All authors read and approved the final version of the manuscript.

Conflicts of interest

All authors – none to declare

References

1. Biedenbach DJ, Moet GJ, Jones RN. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002). Diagn Microbiol Infect Dis 2004;50:59-69. [CrossRef] [PubMed]
2. Marra AR, Camargo LF, Pignatari AC, et al. Nosocomial bloodstream infections in Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide surveillance study. J Clin Microbiol 2011;49:1866 -71. [CrossRef] [PubMed] [FullText]
3. Lee NY, Lee HC, Ko NY, et al. Clinical and economic impact of multidrug resistance in nosocomial *Acinetobacter baumannii* bacteremia. Infect Control Hosp Epidemiol 2007;28:713-9. [CrossRef] [PubMed]
4. Gupta A, Sharma S, Arora A, Gupta A. Changing trends of in vitro antimicrobial resistance patterns in blood isolates in a tertiary care hospital over a period of 4 years. Indian J Med Sci 2010;64:485-92. [CrossRef] [PubMed]
5. Chadhary M, Kumar S, Payasi A. Prevalence and antimicrobial sensitivity of ESBL producing Gram-negative bacteria from clinical settings in India from 2010 to 2012. Int J Med Med Sci 2013;46:1212-7.
6. Jain S, Khety Z. Changing antimicrobial resistance pattern of isolates from an ICU over a 2 year period. J Assoc Physicians India 2012;60:27-8,33. [PubMed]
7. Kumhar GD, Ramachandran VG, Gupta P. Bacteriological analysis of blood culture isolates from neonates in a tertiary care hospital in India. J Health Popul Nutr 2002;20:343-7. [PubMed]
8. Kaul S, Brahmadathan KN, Jagannati M, et al. One year trends in the gram-negative bacterial antibiotic susceptibility patterns in a medical intensive care unit in South India. Indian J Med Microbiol 2007;25:230-5. [PubMed]
9. Rajeevan S, Ahmad SM, Jasmin PT. Study of prevalence and antimicrobial susceptibility pattern in blood isolates from a tertiary care hospital in North Kerala, India. Int J Curr Microbiol App Sci 2014;3:655-62.

10. Chhina D, Gupta V. Bacteriological profile and antimicrobial susceptibility pattern of blood isolates from a tertiary care hospital in North India. Int J Pharm Res Biosci 2013;2:24-35.
11. Vanitha Rani N, Kannan G, Venkata Narendra M, et al. A retrospective study on blood stream infections and antibiotic susceptibility patterns in a tertiary care teaching hospital. Int J Pharm Pharm Sci 2012;4:543-8.
12. Gopalakrishnan R, Sureshkumar D. Changing trends in antimicrobial susceptibility and hospital acquired infections over an 8 year period in a tertiary care hospital in relation to introduction of an infection control programme. J Assoc Physicians India. 2010;58 Suppl:25-31. [PubMed]
13. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; thirteenth to twenty third informational supplements. CLSI document M100-18. Wayne, PA: Clinical and Laboratory Standards Institute. 2003 -2013.
14. Nair PK, Vaz MD. Prevalence of carbapenem resistant Enterobacteriaceae from a tertiary care hospital in Mumbai, India. J Microbiol Infect Dis 2013;3:207-10. [CrossRef]
15. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infec Dis 2011;53:60-7. [CrossRef] [PubMed]
16. Mohamudha Parveen R, Harish BN, Parija SC. Emerging carbapenem resistance among nosocomial isolates of *Klebsiella pneumoniae* in South India. Int J Pharma Biosci 2010;1:1-11.
17. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis 2010;10: 597-602. [CrossRef] [PubMed] [FullText]
18. Gupta E, Mohanty S, Sood S, Dhawan B, Das BK, Kapil A. Emerging resistance to carbapenems in a tertiary care hospital in north India. Indian J Med Res 2006;124:95-8. [PubMed]
19. Sinha N, Agarwal J, Srivastava S, Singh M. Analysis of carbapenem-resistant *Acinetobacter* from a tertiary care setting in North India. Indian J Med Microbiol 2013;31:60-3. [CrossRef] [PubMed]
20. Chennai Declaration Team. "Chennai Declaration": 5-year plan to tackle the challenge of anti-microbial resistance. Indian J Med Microbiol 2014;32:221-8. [CrossRef] [PubMed]

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Table 3a. Antibiotic susceptibility patterns of Gram-negative isolates in 2003 and 2013 (in percentage, rounded to the nearest full number) and comparison of resistance in 2003 vs. 2013

	Ceftazidime				Cefepime			
	2003 %	2013 %	Resistance comparison 2003 vs. 2013		2003 %	2013 %	Resistance comparison 2003 vs. 2013	
			Z score	*p* value			Z score	*p* value
E. coli								
Total	44	29	3.466	**.00058**	47	35	2.4535	**.01428**
Outpatient	53	41	1.0466	.29372	56	41	1.2927	.19706
Inpatient	40	24	1.7747	.07672	40	32	0.8882	.37346
CCU	41	21	2.0918	**.03662**	46	34	1.1173	.26272
K. pneumoniae								
Total	50	27	3.2198	**.00128**	62	30	4.7265	**0**
Outpatient	57	25	2.1543	**.03156**	57	33	1.543	.12356
Inpatient	55	36	1.5663	.11642	68	37	2.5915	**.0096**
CCU	39	19	2.2114	**.0217**	61	23	3.8936	**.0001**
P. aeruginosa								
Total	51	57	-1.0625	.28914	57	55	0.6747	.50286
Outpatient	60	50	0.3519	.72634	80	38	1.4954	.13362
Inpatient	46	67	-1.2635	.20766	46	67	-1.2635	.20766
CCU	47	55	-0.5354	.5892	80	59	1.4181	.1556
	Cefoperazone-sulbactam				**Piperacillin-tazobactam**			
	2003 %	2013 %	Resistance comparison 2003 vs. 2013		2003 %	2013 %	Resistance comparison 2003 vs. 2013	
			Z score	*p* value			Z score	*p* value
E. coli								
Total	87	76	2.253	**.02444**	78	65	2.5117	**.01174**
Outpatient	85	81	0.4732	.63836	88	68	2.8022	**.03752**
Inpatient	93	77	1.9972	**.0455**	83	68	1.9536	.5118
CCU	84	71	1.4529	1.14706	65	60	0.4428	.65994
K. pneumoniae								
Total	78	41	4.9607	**0**	77	38	5.9395	**0**
Outpatient	79	42	2.3453	**.01878**	79	39	2.5198	**.01174**
Inpatient	77	46	2.6293	**.00854**	82	47	2.9157	**.0035**
CCU	77	34	3.5991	**.00032**	71	29	4.784	**0**
P. aeruginosa								
Total	82	52	2.2574	**.02382**	85	77	0.9561	.33706
Outpatient	98	50	1.0817	.28014	100	88	0.8229	.41222
Inpatient	69	53	0.9705	.33204	69	73	0.2755	.77948
CCU	80	52	1.8259	.06724	87	69	1.2853	.19706

CCU critical care unit.

Table 3b. Antibiotic susceptibility patterns of Gram-negative isolates in 2003 and 2013 (in percentage, rounded to the nearest full number) and comparison of resistance in 2003 vs. 2013

	Amikacin				Ciprofloxacin				Meropenem			
	2003 %	2013 %	Resistance comparison 2003 vs. 2013		2003 %	2013 %	Resistance comparison 2003 vs. 2013		2003 %	2013 %	Resistance comparison 2003 vs. 2013	
			Z score	*p* value			Z score	*p* value			Z score	*p* value
E. coli												
Total	90	89	0.147	.88076	31	31	0.8808	.37886	100	95	1.1698	.242
Outpatient	88	89	-0.127	.89656	32	57	-2.0645	**.0394**	100	100	1.0596	.29372
Inpatient	87	90	-0.481	.63122	30	21	0.1237	.26272	100	96	0.2368	.81034
CCU	95	90	0.8454	.39532	32	26	0.6924	.4902	100	91	1.8349	.06724
K. pneumoniae												
Total	88	53	4.9262	**0**	46	32	1.9986	**.0455**	99	54	5.5334	**0**
Outpatient	79	58	1.3386	.18024	43	31	0.8245	.41222	100	60	2.3496	**.01878**
Inpatient	77	57	0.7648	.0784	55	39	1.3516	.17702	99	59	1.6498	.09894
CCU	94	44	4.567	**0**	39	26	1.4054	.15854	99	43	5.274	**0**
P. aeruginosa												
Total	74	66	0.9967	.31732	59	47	0.4977	.61708	100	65	3.4913	**.00048**
Outpatient	80	75	0.2082	.83366	80	38	1.4954	.13362	100	75	1.2154	.22246
Inpatient	54	57	-0.171	.86502	38	47	0.4976	.61708	100	50	1.1662	.242
CCU	87	66	1.4932	.31732	60	55	0.3064	.75656	100	48	3.431	**.0006**

CCU critical care unit.

Table 4. Antibiotic susceptibility of Gram-negative isolates from 2003 to 2013 (in percentage, rounded to the nearest full number)

	Amikacin			Ceftazidime			Cefoperazone-sulbactam			Piperacillin-tazobactam			Meropenem		
	OP	IP	CCU	OP	IP	CCU	OP	IP	CCU	OP	IP	CCU	OP	IP	CCU
2003	85	77	93	55	46	41	83	83	78	87	80	73	99	98	99
2004	85	64	84	54	35	36	81	69	77	81	73	65	96	95	98
2005	88	81	78	72	59	47	91	87	82	91	85	83	98	97	95
2006	67	71	65	41	34	29	91	77	70	81	66	72	95	98	97
2007	62	52	64	47	39	38	77	80	69	61	58	62	100	96	95
2008	79	63	65	56	46	37	82	81	67	71	65	61	98	97	94
2009	67	66	56	49	44	31	84	81	52	69	60	44	94	95	71
2010	61	63	52	34	31	39	82	72	56	49	48	50	99	94	66
2011	72	60	47	37	29	32	72	67	48	61	60	42	92	86	57
2012	81	74	60	38	26	38	70	65	52	67	53	48	92	84	58
2013	74	76	52	35	32	25	60	65	43	57	61	40	79	83	50

CCU critical care unit; **IP** inpatient; **OP** outpatient.

Table 5. Susceptibility to polymyxin E and tigecycline of Gram-negative isolates (in percentage, rounded to the nearest full number. CCU – critical care unit)

	Total			*E. coli*			*Klebsiella*		
	2011	2012	2013	2011	2012	2013	2011	2012	2013
OUTPATIENT									
Polymyxin E	97	93	99	98	98	100	100	96	100
Tigecycline	89	87	89	98	100	100	96	98	97
INPATIENT									
Polymyxin E	98	100	100	100	100	100	88	100	100
Tigecycline	90	84	87	100	100	99	89	100	94
CCU									
Polymyxin E	91	90	99	100	95	100	100	100	100
Tigecycline	77	79	73	100	95	98	100	89	76

	Pseudomonas			*Acinetobacter*		
	2011	2012	2013	2011	2012	2013
OUTPATIENT						
Polymyxin E	94	96	97			
Tigecycline						
INPATIENT						
Polymyxin E	96	100	99			
Tigecycline						
CCU						
Polymyxin E	98	87	97	100	98	95
Tigecycline				100	98	80

Table 6. Comparison of susceptibility to polymyxin E and tigecycline in 2011 vs. 2013 (in percentage, rounded to the nearest full number. CCU – critical care unit)

	2011 %	2013 %	Comparison of resistance 2011 vs. 2013	
			Z score	*p* value
OUTPATIENT				
Polymyxin E	97	98	-0.7752	.4354
Tigecycline	89	88	0.1196	.90448
INPATIENT				
Polymyxin E	97	99	-1.866	.06148
Tigecycline	89	86	0.9364	.34722
CCU				
Polymyxin E	91	98	-3.8051	**.00014**
Tigecycline	77	73	0.9889	.32218
TOTAL BLOOD ISOLATES				
Polymyxin E	95	99	-4.1913	**0**
Tigecycline	83	81	1.0556	.28914