Antimicrobial susceptibility profile of selected bacteraemic pathogens from private institutions in South Africa

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Objectives. The National Antimicrobial Surveillance Forum is a continuous surveillance organisation comprising all academic/public and private sector laboratories in South Africa.

Methods. The antibiotic susceptibility of blood culture isolates of *Escherichia coli, Klebsiella pneumoniae, Enterobacter* species, *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Staphylococcus aureus* from patients in private hospitals in five major centres were investigated. Antimicrobial susceptibility tests were performed by 12 participating laboratories according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. Extended-spectrum β-lactamase (ESBL) production was determined in selected species of Enterobacteriaceae irrespective of source.

Results. The overall prevalence of ampicillin resistance in blood culture isolates of *E. coli* ($N = 471$) was 84%, and 20% were resistant to the fluoroquinolones. Considerable geographical differences were noted between the centres with regard to the *K. pneumoniae* ($N = 636$) resistance rates for ceftriaxone and/or cefotaxime (39 - 87%). The most active agents in the *Enterobacter* spp. ($N = 244$) were imipenem/meropenem, ertapenem, ciprofloxacin, levofloxacin and cefepime, with 100%, 94%, 88%, 87% and 80% susceptibility, respectively. Carbapenem resistance in *P. aeruginosa* ($N = 382$) varied between 42% and 45%, and in the case of *A. baumannii* ($N = 190$) resistance varied between 32% and 33% for meropenem and imipenem respectively. The nationwide incidence of oxacillin resistance in *S. aureus* ($N = 629$) was 36%. Overall, the prevalence of ESBL production among all isolates of *K. pneumoniae* was 26% ($N = 7\,514$), while in *Enterobacter* spp. it was 12% ($N = 4\,031$) and in *E. coli* 5% ($N = 28\,412$).

Conclusions. The data highlight the widespread problem of antibiotic resistance among important bacteraemic pathogens in private institutions in South Africa. Continued surveillance is vital to guide appropriate empirical therapy for invasive infections.

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For several reasons, including selective pressure from overuse of antibiotics, there has been worldwide emergence of multidrug-resistant (MDR) bacteria – reports of hospital outbreaks resulting from such strains are cause for concern. In South Africa, the increased use of carbapenems is driven by an increase in cephalosporin and fluoroquinolone resistance among extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.[1] Although extensive published data[2] are available on antibiotic susceptibility of community-acquired respiratory tract pathogens, especially *Streptococcus pneumoniae*, very few data have been documented for Gram-negative pathogens such as *Acinetobacter baumannii* or *Pseudomonas aeruginosa* or for Gram-positive pathogens, particularly *Staphylococcus aureus*. In the past, one private laboratory in Johannesburg, which participated in the SENTRY international antimicrobial surveillance programme,[3] documented the prevalence rate of ESBL production in *Enterobacter cloacae* from hospitalised patients at 20% ($N = 11/54$), and oxacillin resistance in blood culture isolates of nosocomially acquired *S. aureus* at 40%.[4] These results may not be representative of the rest of the private hospitals in South Africa. This prompted a nationwide study in clinical private practice to examine the susceptibility of important invasive Gram-negative pathogens and *S. aureus*, including ESBL production in selected Enterobacteriaceae.

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Materials and methods

Collaborating centres

The study was conducted from 1 January 2006 to 30 June 2006. Twelve laboratories of 7 private pathology practices in all the private hospitals in Johannesburg, Pretoria, Durban, Cape Town and Bloemfontein participated in the survey, namely Drs Bouwer and Partners (Ampath), Drs Dietrich and Voigt (Pathcare), Drs du Buisson, Bruinette and Partners (Ampath), Drs Mauf and Partners (Lancet), Drs Swart and Marais (Ampath), Drs van Rensburg Pathologists, and Drs Vermaak and Partners. The participants from these laboratories are listed in the Acknowledgements.

Bacterial isolates and susceptibility testing

Inclusion criteria for bacterial isolates were any isolate cultured from blood of hospitalised patients irrespective of whether infections were regarded as being community or nosocomially

acquired. Duplicate isolates from the same patient were avoided. Isolation and identification were done according to standard methods. All species of *Enterobacter* were included in the study. Participating laboratories (9/12) performed disc diffusion susceptibility testing according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[5] Quality control strains recommended by the CLSI were used and results of testing were accepted if results of control strains were within published limits. The other 3 laboratories reported susceptibility results using the automated Vitek 2 system (BioMerieux, Marcy L'Etoile, France). External quality control was performed on a regular basis (National Health Laboratory Service Quality Assessment Programme, External Quality Assessment Unit, National Institute for Communicable Diseases, Sandringham, Johannesburg, South Africa as well as Thistle Quality Assurance Programme, Northcliff, Johannesburg, South Africa).

The antibiotics tested for lactose-fermentative Gram-negative bacilli were ampicillin, cefuroxime, ceftriaxone and/or cefotaxime, cefepime, amoxicillin-clavulanate, piperacillin-tazobactam, ciprofloxacin, levofloxacin, ertapenem, imipenem and meropenem. Aminoglycoside susceptibility was not reported. In the case of non-lactose fermentative isolates the following were tested: ceftazidime, cefepime, piperacillin-tazobactam, amikacin, tobramycin, ciprofloxacin, levofloxacin, imipenem and meropenem. For *S. aureus* isolates, cefoxitin or oxacillin (reported as cloxacillin), rifampicin, trimethoprim/sulfamethoxazole, fusidic acid, gentamicin, teicoplanin, vancomycin and linezolid were tested.

In most laboratories (8/12), teicoplanin and vancomycin susceptibility of *S. aureus* was determined by disc diffusion using the CLSI parameters for teicoplanin.[5] One laboratory used brain-heart-infusion agar screening with vancomycin (6 µg/ml) and with teicoplanin (12 µg/ml) to test these isolates for glycopeptide resistance, while another 3 laboratories used the automated Vitek system. In all laboratories, reduced susceptibility was confirmed by determining minimum inhibitory concentrations (MICs) using teicoplanin and/or vancomycin E-tests (AB Biodisk, Solna, Sweden).

ESBL production was determined in all strains of *Klebsiella pneumoniae*, *Enterobacter* spp. and *Escherichia coli* over the study period irrespective of the source and whether the isolates were regarded as being community or hospital acquired. The production was determined using the Vitek automated system in 3 laboratories and the double-disc synergy test in the rest.[6]

Once susceptibility testing was completed, data from each laboratory were sent to a central data collection point where collation and intra- and intercity comparisons were performed. Patient names and hospital and laboratory numbers were not referred to at any stage and therefore patient consent was not sought as surveillance data were submitted anonymously.

Results

Over the study period a total of 2 552 blood culture isolates were tested. Twenty-eight thousand four hundred and twelve isolates of *E. coli*, 7 514 *K. pneumoniae* and 4 031 *Enterobacter* spp. cultured from various sources, were tested for ESBL production.

E. coli

Table I shows the susceptibility of 471 isolates of *E. coli*. Eighty-four per cent of the isolates were resistant to ampicillin, with overall cefuroxime, ceftriaxone and cefepime resistance of 11%, 10% and 6% respectively. Of the beta-lactam/beta-lactamase inhibitor combinations, piperacillin-tazobactam was the most active, with 89% susceptible to this agent, while susceptibility to co-amoxiclav was 63%. Ciprofloxacin resistance ranged from 12% to 26% (Fig. 1), with a nationwide average of 20% (95/471) and 19% (90/471) for ciprofloxacin and levofloxacin, respectively. No resistance to ertapenem, imipenem and meropenem was detected.

K. pneumoniae

Of 636 isolates isolated, 98% were ampicillin resistant (Table I). Cephalosporin resistance was high: 52% (330/636), 46% (292/636) and 44% (279/636) with regard to cefuroxime, ceftriaxone and cefepime, respectively. Resistance to piperacillin-tazobactam and co-amoxiclav was similar (40% and 52%, respectively). Fluoroquinolone resistance was higher than in *E. coli* with 31% (197/636) and 32% (203/636) resistant to ciprofloxacin and levofloxacin, respectively. Two per cent of the isolates were resistant to ertapenem and none to imipenem and meropenem.

Enterobacter spp.

As shown in Table I, antibiotic resistance in 244 isolates of *E. cloacae* and other species was also high. All the strains were resistant to ampicillin. The most active cephalosporin was cefepime, with 80% susceptibility. Activity of levofloxacin and ciprofloxacin was similar (87 - 88% susceptibility, respectively). Piperacillin-tazobactam resistance was 30% (73/244) overall, with some centres reporting up to 79% resistance (Fig. 1). Six per cent of isolates were resistant to ertapenem, while no resistance to imipenem and meropenem was detected.

P. aeruginosa

Overall, carbapenem resistance in isolates of *P. aeruginosa* (N = 382) varied between 42% and 45% for meropenem and imipenem, respectively (Table I). Ceftazidime resistance was 45%; a similar prevalence of resistance to cefepime was noted (53%). Resistance to piperacillin-tazobactam varied between 21% and 61%, with an average of 48% (183/382) (Fig. 2). Fluoroquinolone resistance was similar, with 46% (175/382) resistant to both ciprofloxacin and levofloxacin. Of

Table I. Antibiotic resistance (%) among bacteraemic strains of selected pathogens in private practice in South Africa, January - June 2006

Antibiotic	*E. coli* (*N* = 471)			*K. pneumoniae* (*N* = 636)			*Enterobacter spp.* (*N* = 244)		
		%			%			%	
	N	Overall	Range	*N*	Overall	Range	*N*	Overall	Range
Ampicillin	396	84	78 - 90	623	98	88 - 100	244	100	-
Cefuroxime	52	11	5 - 37	330	52	31 - 62	195	80	50 - 100
Ceftriaxone/cefotaxime	47	10	3 - 14	293	46	13 - 61	110	45	28 - 100
Cefepime	28	6	0 - 11	280	44	12 - 59	49	20	15 - 25
Co-amoxiclav	78	37	15 - 52	330	52	22 - 61	237	97	89 - 100
Piperacillin-tazobactam	52	11	4 - 18	254	40	26 - 53	73	30	9 - 79
Ciprofloxacin	95	20	12 - 26	197	31	0 - 49	29	12	8 - 21
Levofloxacin	90	19	9 - 31	203	32	0 - 49	32	13	8 - 22
Ertapenem	0	0	-	12	2	0 - 10	15	6	4 - 8
Imipenem	0	0	-	0	0	-	0	0	-
Meropenem	0	0	-	0	0	-	0	0	-

	P. aeruginosa (*N* = 382)			*A. baumannii* (*N* = 190)		
		%			%	
	N	Overall	Range	*N*	Overall	Range
Ceftazidime	172	45	11 - 90	82	43	21 - 81
Cefepime	202	53	21 - 70	82	43	10 - 83
Piperacillin-tazobactam	183	48	21 - 61	80	42	14 - 83
Ciprofloxacin	176	46	30 - 67	68	36	10 - 75
Levofloxacin	176	46	21 - 67	59	31	10 - 75
Amikacin	183	48	11 - 67	55	29	7 - 70
Tobramycin	202	53	11 - 100	36	19	7 - 40
Imipenem	172	45	23 - 63	63	33	3 - 72
Meropenem	160	42	15 - 64	61	32	3 - 72

	S. aureus (*N* = 629)		
		%	
	N	Overall	Range
Cloxacillin	226	36	29 - 46
Trimethoprim/sulfamethoxazole	182	29	4 - 33
Fusidic acid	19	3	0 - 7
Rifampicin	69	11	3 - 27
Gentamicin	75	12	6 - 20
Teicoplanin	0	0	-
Vancomycin	0	0	-
Linezolid	0	0	-

N = number of strains.
Range = variation between centres.

the aminoglycosides tested, amikacin was more active than tobramycin (52% versus 47% susceptible respectively).

A. baumannii

The most active agent in the 190 isolates was not a carbapenem but tobramycin, with 81% testing susceptible (Table I). As depicted in Fig. 2, carbapenem resistance ranged between centres from 3% to 72%, with an overall prevalence of 32% (60/190) and 33% (62/190) for meropenem and imipenem, respectively. Activity of the cephalosporins, piperacillin-tazobactam and the fluoroquinolones was similar; resistance ranged from 43% for ceftazidime and cefepime to 31% for levofloxacin.

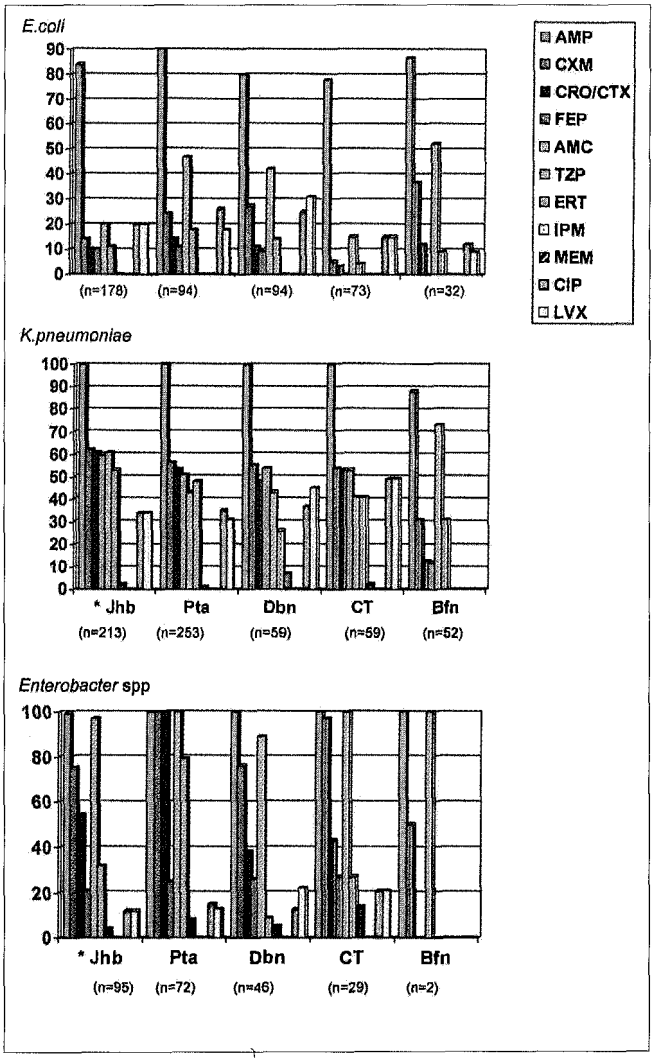

Fig. 1. Antibiotic resistance (%) of bacteraemic strains of fermentative Gram-negative bacilli in different centres in private practice in South Africa, January - June 2006. (AMP = ampicillin; CXM = cefuroxime; CRO/CTX = ceftriaxone/cefotaxime, FEP = cefepime; AMC = co-amoxiclav; TZP = piperacillin-tazobactam; ERT = ertapenem, IPM = imipenem; MEM = meropenem; CIP = ciprofloxacin; LVX = levofloxacin; Jhb = Johannesburg; Pta = Pretoria; Dbn = Durban; CT = Cape Town; Bfn = Bloemfontein; N = total number of isolates.)

S. aureus

The prevalence of oxacillin resistance varied from 29% to 46% (Fig. 3), with an overall average of 36% (226/629) (Table I). Together with teicoplanin, vancomycin and linezolid (for which no resistance was detected), fusidic acid had excellent activity, with only 3% of the isolates resistant. Rifampicin, gentamicin and trimethoprim/sulfamethoxazole resistance was documented as 11%, 12% and 29% overall, respectively.

Extended-spectrum β-lactamase production

As shown in Table II, 26% of *K. pneumoniae* isolates overall produced an ESBL, with detection rates varying between 8%

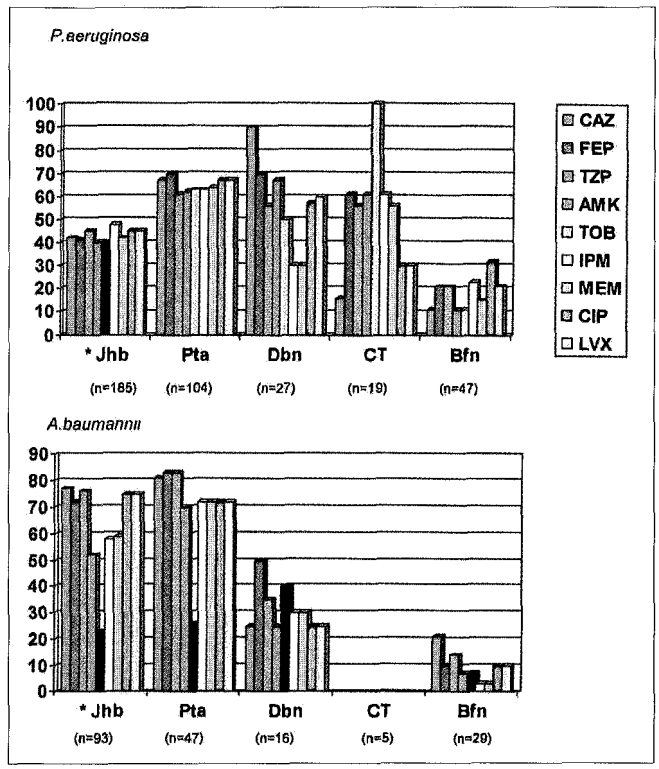

Fig. 2. Antibiotic resistance (%) of bacteraemic strains of non-fermentative Gram-negative bacilli in different centres in private practice in South Africa, January - June 2006. (CAZ = ceftazidime; FEP = cefepime; TZP = piperacillin-tazobactam; AMK = amikacin; TOB = tobramycin; IPM = imipenem; MEM = meropenem; CIP = ciprofloxacin; LVX = levofloxacin; Jhb = Johannesburg; Pta = Pretoria; Dbn = Durban; CT = Cape Town; Bfn = Bloemfontein; N = total number of isolates.)

and 42% at the different centres. Similarly, ESBL production detection in *Enterobacter* spp. varied, with Cape Town recording a prevalence of 27%. Overall, 12% of these isolates produced an ESBL. In contrast, the prevalence of ESBL production in *E. coli* was the lowest (5%) of the Enterobacteriaceae tested and did not differ significantly between the cities.

Discussion

Overall, the results for *E. coli* in this study are similar to those reported from Europe,[7] where up to 23% of invasive isolates were resistant to the third-generation cephalosporins. Fluoroquinolone resistance was also comparable (19% and 20% for levofloxacin and ciprofloxacin, respectively).[7] The rate of ESBL production (5%) is also similar to that reported for some European countries. The worldwide emergence of novel ESBLs,[8] specifically cefotaximases (CTX-M) in *E. coli* predominantly causing urinary tract infections, has not been documented in South Africa.[8] However, the emergence of CTX-M β-lactamases in *K. pneumoniae* has been described.[1] The rate of MDR was not determined in this study; Bell *et al.*[9] have previously shown the prevalence among bacteraemic isolates to be 4%.

Table II. Incidence (%) of ESBL production (number of isolates) in selected strains of Enterobacteriaceae in private practice in South Africa (all sources), January - June 2006

	K. pneumoniae % (*N*)	*Enterobacter* spp. % (*N*)	*E. coli* % (*N*)
Overall	26 (7 514)	12 (4 031)	5 (28 412)
Centre			
Johannesburg	42 (3 010)	11 (1 486)	4 (12 600)
Pretoria	27 (2 244)	10 (1 061)	3 (7 406)
Durban	8 (1 359)	5 (1 093)	4 (5 637)
Cape Town	40 (805)	27 (328)	4 (1 380)
Bloemfontein	15 (96)	6 (63)	12 (1 389)

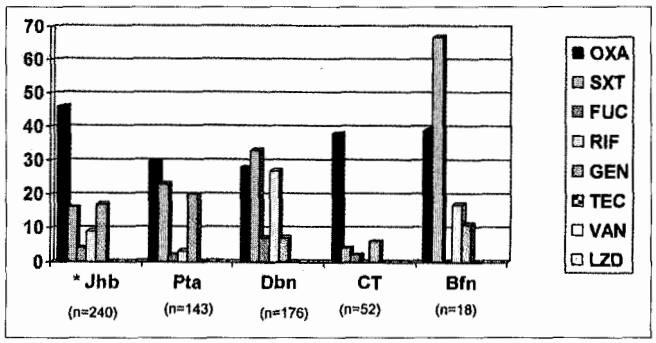

Fig. 3. Antibiotic resistance (%) of bacteraemic strains of S. aureus in different centres in private practice in South Africa, January - June 2006. (OXA = oxacillin; SXT = trimethoprim/sulfamethoxazole; FUC = fusidic acid; RIF = rifampicin; GEN = gentamicin; TEC = teicoplanin; VAN = vancomycin; LZD = linezolid; Jhb = Johannesburg; Pta = Pretoria; Dbn = Durban; CT = Cape Town; Bfn = Bloemfontein; N = total number of isolates.)

The high level of ampicillin (84%) and co-amoxiclav resistance (37%) among *E. coli* isolates generally preclude these agents as empirical choices when invasive infections due to this pathogen are suspected. Similarly, with 20% fluoroquinolone resistance, these antibiotics should probably be reserved for directed therapy.

The high rate of cephalosporin resistance among the blood culture isolates of *K. pneumoniae* (52% for cefuroxime, 46% for ceftriaxone or cefotaxime and 44% for cefepime) most probably reflects the high overall incidence of ESBL production in this species (26%). However, the incidence among blood culture isolates specifically is now under investigation. Nationwide, piperacillin-tazobactam resistance was 40%. It was recently demonstrated[10] that the mechanisms of inhibitor-combination resistance in ESBL-producing *K. pneumoniae* (*N* = 139) in Johannesburg is due to modification of outer membrane proteins (porin-deficiency) changes in 12 (9%), high-level Bush group 2b β-lactamase production in 6 (4%), and oxacillinase (OXA)-type enzymes (Bush group type 2d) in 1 isolate (0.7%), respectively.[10] Inhibitor-resistant (IRT) Bush group 2br enzymes were not detected. Fluoroquinolone resistance was 31% and 32% for ciprofloxacin and levofloxacin, respectively. Similarly, among *Klebsiella* spp. collected from intensive care units (ICUs) in Southern and Western Europe in 1998, Babini and Livermore[11] documented the proportion of ESBL-producers co-resistant to piperacillin-tazobactam to be 63%, with fluoroquinolone resistance 31%. In New York,[12] 25% of non-ESBL-producing isolates of *K. pneumoniae* were resistant to piperacillin-tazobactam and ciprofloxacin, but among ESBL-producing isolates, 54% and 50% were resistant respectively.

Recently, co-resistance to three unrelated classes of antibiotics (trimethoprim/sulfamethoxazole, gentamicin or amikacin, and fluoroquinolones) among ESBL-positive *Klebsiella* spp. (*N* = 139) and *E. coli* isolates (*N* = 988) in South Africa were reported to be 57% and 72%, respectively.[10] The problem of drug-resistant *K. pneumoniae* and *E. coli* might be exacerbated by failure of infection control practices in the community, hospitals, long-term care facilities and old-age homes, all of which might be important reservoirs for ESBL-containing multiple antibiotic-resistant Gram-negative pathogens. MDR in these Gram-negatives severely limits therapeutic options. Based on the results from most major centres, mild to moderate infections due to *K. pneumoniae* would be best treated empirically with ertapenem and in the future with tigecycline, reserving imipenem and meropenem for more serious bacteraemic cases, particularly those admitted to ICUs. To reduce selection pressure on both groups of carbapenems, mandatory de-escalation to narrow-spectrum antibiotics (once culture and susceptibility become available) is necessary. In this regard, few therapeutic options remain because of current international practice according to which in the presence of ESBL production all penicillin, cephalosporin and aztreonam results are edited as resistant irrespective of phenotypic susceptibility pattern.

In contrast, where infections caused by *Enterobacter* spp. are suspected more empirical options besides ertapenem or imipenem and meropenem are available. These include cefepime and levofloxacin or ciprofloxacin, with 80%, 87% and 88% of the isolates respectively being susceptible. The susceptibility pattern with regard to cefepime probably reflects excellent activity against chromosomal-located cephalosporinase (Amp-C)-producing isolates. However, caution has been expressed in respect of cefepime use in

cases of high-inoculum ceftazidime-resistant *Enterobacter* infections as treatment failures have been described in a murine experimental model as well as in the clinical setting.[13] Tazobactam does not inhibit these chromosomal enzymes and therefore piperacillin-tazobactam is not appropriate for such infections. Similarly, although 55% of invasive *Enterobacter* spp. in this study were susceptible to the third-generation cephalosporins, these agents should also be avoided empirically, as it has been demonstrated that the 30-day mortality rate of bacteraemic patients with resistant infections treated using this group of agents is significantly higher than mortality among patients with third-generation susceptible *Enterobacter* bloodstream infections (33.7% v. 18.6%; $p = 0.021$).[14] The nationwide prevalence of ESBL production in this pathogen was 12%, which is lower than that reported previously in hospitalised patients from South Africa.[3] One possible explanation is that in this study all *Enterobacter* spp. were tested irrespective of whether they were regarded as nosocomial or community acquired. In addition, it is clear that geographical differences (5 - 27%) exist in private practice in South Africa.

Antibiotic resistance in *P. aeruginosa* was overall higher than in *A. baumannii*. Carbapenem resistance in the former was 42% and 45% for meropenem and imipenem respectively, compared with 32% and 33% in *A. baumannii*. Similarly, cefepime and piperacillin-tazobactam resistance was 53% v. 43% and 48% v. 42% for these non-fermentative bacilli, respectively. The prevalence of fluoroquinolone resistance was also noted to be less in *A. baumannii* than *P. aeruginosa*, namely 31% v. 46% for levofloxacin and 36% v. 46% for ciprofloxacin, respectively. Tobramycin was the most active agent against *A. baumannii* (81% susceptibility). In the present survey the prevalence of resistance to antipseudomonal agents in bloodstream isolates of *P. aeruginosa* was considerably higher than reported elsewhere[15] (with resistance to piperacillin 29%, ceftazidime 19%, ciprofloxacin 17% and imipenem 15%, respectively) ($N = 190$). Significantly, in the study by Kang *et al.*[15] the 30-day mortality rate was 44% (33/75) in patients infected with isolates resistant to any of the antipseudomonal agents, compared with 33.9% (39/115) in patients with strains susceptible to all antipseudomonal antibiotics ($p = 0.161$). Patients infected with imipenem-resistant strains had the highest mortality. Clearly, the impact of outcome in our setting needs to be determined. In respect of the mechanism of carbapenem resistance in *A. baumannii*, it was reported previously that resistance was due to OXA-23 enzymes; metallo-β-lactamases (bla_{VIM-2}) were also found in some South African isolates.[16]

Internationally, the prevalence of oxacillin-resistant *S. aureus* (ORSA) varies greatly by region, site of infection and whether the infection is of nosocomial or community onset. Previous studies[4] of *S. aureus* isolates from blood cultures which included hospitalised patients from Johannesburg, reported 40% to be oxacillin-resistant. However, in this study no distinction was made between nosocomial and community-acquired infections. Furthermore, geographical differences (29 - 46%) do exist in private practice. No resistance to teicoplanin, vancomycin or linezolid was detected and high rates of sensitivity to fusidic acid (97%), rifampicin (89%), gentamicin (88%) and trimethoprim/sulfamethoxazole (71%) were demonstrated. This suggests that a significant proportion of ORSA isolates may not be multi-resistant. In a previous study,[17] including South African ORSA isolates (SENTRY-Asia-Pacific), it was shown that 10% (40/394) of ORSA isolates from Johannesburg were not multi-resistant (resistance to less than 3 of the following antibiotics: erythromycin, tetracycline, gentamicin, chloramphenicol, rifampicin, ciprofloxacin and trimethoprim/sulfamethoxazole) and that the increase was attributed to the so-called British epidemic methicillin-resistant *S. aureus* (EMRSA) clone (resistance to erythromycin and ciprofloxacin only), in this case being EMRSA-16 and not EMRSA-15. Further investigations are warranted to confirm this trend. Therefore, in contrast to serious Gram-negative infections, several empirical treatment options do exist for ORSA infections.

Tigecycline, the first agent of the new broad-spectrum class of glycylcyclines, has been shown to have excellent activity against Gram-negative pathogens including ESBL-producing isolates, *Acinetobacter* spp. including carbapenem-resistant isolates, and *Stenothrophomonas maltophilia*,[18] as well as Gram-positive bacteria including ORSA.[19] In our study susceptibility to this new antibiotic was not determined. In future, surveillance should also be extended to aminoglycosides among the fermentative Enterobacteriaceae, and polymyxin and aztreonam among isolates of *P. aeruginosa* and *A. baumannii*. Clindamycin and erythromycin susceptibility in *S. aureus* should also be reported.

The study clearly has several limitations and also highlights some problems. The study was performed in private practice in South Africa and therefore the relevance on a wider geographical scale is less clear. Typically in routine clinical laboratory practice, susceptibility testing of the study isolates was not performed at a single site, nor was uniform methodology used. Other limitations include the low numbers of isolates tested in some smaller centres and a lack of distinction between community and hospital acquisition. No clinical information was documented relating to colonisation or clinical significance; this includes the impact of resistance on outcome. Typing of isolates was not performed. It is therefore uncertain whether cross-infection or clonal spread may have occurred to possibly account for the differences in resistance rates in different localities.

Additional problems highlighted in this study include the lack of standardisation in detection of glycopeptide resistance among isolates of *S. aureus*. Another problem is the lack of standard criteria for determination of ESBL production in

Enterobacter spp. in which production of de-repressed AMP-C β-lactamase enzymes can interfere with clavulanate synergy tests. In addition, concomitant ESBL production as described in *E. aerogenes* may be present.[13] To detect such cases, Pitout *et al.*[20] described a modified double disc test that was not utilised in participating laboratories. Overreporting of ESBL production in our study is also possible as 3 laboratories used Vitek 2, which has shown false-positive ESBL results with chromosomal K1 β-lactamase hyperproduction among *Klebsiella* species.[21] With all the diversity of ESBLs, appropriate testing among Enterobacteriaceae in routine clinical practice has become very complex. However, the results of the study should serve as the basis for comparing changes in resistance patterns as surveillance continues over time.

In conclusion, there were significant regional differences in antibiotic resistance patterns in South Africa, and accurate surveillance of regional centres and preferably individual private hospitals, even at unit level, is necessary to optimise empirical antibiotic treatment for bacteraemic infections. Based on the results for *K. pneumoniae*, with the carbapenems currently the only empirical treatment option, antibiotic susceptibility patterns would also need close monitoring. The very high levels of antibiotic resistance prevalent throughout the study period in bloodstream isolates of *P. aeruginosa* and *A. baumannii* are of great concern as limited therapeutic options threaten the successful management of these infections, particularly in critically ill patients. No currently available single agent tested had adequate activity to be regarded as a suitable empirical option as monotherapy when either pseudomonal or *Acinetobacter* bacteraemia/septicaemia is suspected. Combination therapy is therefore advocated until susceptibility results are available, with the choice dictated by geographical and/or hospital-specific susceptibility patterns.

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