Organisms cultured and resistance patterns seen in a secondary referral centre ICU and burns unit

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Background. Infections are common in intensive care units (ICUs) and burns units. Empiric antibiotic therapy is often required, and as such it is important to have a good knowledge of the resident organisms in these departments. Antibiotic resistance is becoming an increasing problem both internationally and in South Africa (SA) and it is important to monitor organism sensitivity.

Objectives. To establish the spectrum and sensitivity of nosocomial pathogens in an SA government referral hospital ICU and burns unit.

Methods. We report the findings from a retrospective audit of all cultures sent from the ICU and burns unit of an SA urban hospital for a 6-month period between January and June 2008.

Results. The results showed a prevalence of Gram-negative organisms in the ICU department, in particular *Klebsiella pneumoniae* and *Escherichia coli*. There was a prevalence of Gram-positive organisms in the burns unit. Overall resistance to co-amoxiclav and erythromycin was found to be high (49% and 53%, respectively), resistance to ciprofloxacin and gentamicin was moderate (30% and 35%, respectively) and resistance to piperacillin-tazobactam and the carbapenems remained low (21% for piperacillin-tazobactam, 2% for ertapenem and 19% for meropenem). When looking at individual species, it was noted that *K. pneumoniae* had high resistance to ampicillin (97%), moderate resistance to co-amoxiclav and ciprofloxacin (35% and 43%, respectively) and low resistance to piperacillin-tazobactam, ertapenem, meropenem and colistin (12%, 0%, 5% and 0%, respectively). *E. coli* was seen to have high resistance to ampicillin (79%), but low resistance to co-amoxiclav (4%), ciprofloxacin (9%), piperacillin-tazobactam (0%), ertapenem (0%), meropenem (4%) and colistin (0%).

Conclusion. This study demonstrates the prevalence of Gram-negative organisms in an SA government hospital ICU. It also demonstrates the presence of resistance mechanisms in the organisms cultured for almost all available classes of antibiotics, albeit some at low levels. The development of multi- and pan-resistant pathogenic organisms is both an SA and worldwide problem. In particular, the threat posed by resistant Gram-negative bacteria is likely to manifest itself in ICUs where septic patients unresponsive to standard antimicrobial regimens will inevitably end up. Frequent assessment of resistance patterns and appropriately designed empirical treatment protocols must remain a priority for all critical care departments.

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Invasive infections are common in intensive care units (ICUs) and burns units, and mortality from severe sepsis in the critical care setting ranges from 28 to 50%.[1] Antibiotics are commonly prescribed to critically ill patients. The use of antibiotics that are ineffective against the causative organism is associated with increased morbidity and mortality, and is an unnecessary additional strain on what are often stretched healthcare resources.[2,3] A study from 2005 looking at prescribing practices in ICUs across South Africa (SA) identified inappropriate empirical antibiotic choice in 54.9% of patients.[3] Inappropriate use can also result in the development of antibiotic resistance among bacteraemic pathogens.[4] As such, it is important to ensure that empirical antibiotic choice is based on good knowledge of the resident organisms in critical care departments. It is also well known that resistance among pathogens is increasing rapidly both internationally and in SA.[5,6] New forms of antibiotic resistance can spread between countries with ease. Of particular concern are the so-called 'ESKAPE' pathogens: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.[7] Of the aforementioned pathogens, while there is still concern around methicillin-resistant *Staphylococcus aureus* (MRSA), it is infections secondary to the Gram-negative bacteria that are causing greater concern due to the existence of pan-resistant strains and the

paucity of novel antibiotics.[8] A recently published audit from an ICU in Durban, South Africa, revealed that from samples sent from ventilated patients, 62% of the positive results were Gram-negative bacteria. Extended spectrum β-lactamase production was found in 19% of *Escherichia coli* cultured and 25% of *Klebsiella* spp. isolates.[9] Over time, as antibiotics are used within a department, the resident organisms will adapt and develop resistance mechanisms such as the production of β-lactamases. Therefore, it is important to monitor organisms and their spectrum of resistance on a regular basis.

Objectives

To establish the spectrum and sensitivity of nosocomial pathogens in an SA government referral hospital ICU and burns unit.

Methods

We report the findings from a retrospective audit of all cultures sent from the ICU and burns unit of Edendale Hospital, Pietermaritzburg, SA, for a 6-month period between January and June 2008. All culture and sensitivity testing was carried out at an on-site laboratory. The data that were assessed were kept in hard-copy form in the microbiology department of the hospital.

Edendale is a government hospital with 900 beds, which included at the time of the audit a 6-bed adult ICU and an 8-bed acute burns unit. There were no isolation rooms. There were no ventilators in

the burns unit; patients requiring invasive respiratory support were admitted to the ICU. It was not policy in either the ICU or burns unit to send surveillance cultures at the time the audit was performed. As such, all specimens were sent in response to suspected infection. Specifically, neither tracheal aspirates nor wound swabs were sent routinely. Bronchoscopy and bronchoalveolar lavage were not possible for sputum sample collection in the ICU.

All data were recorded in an Excel (Microsoft, USA) spreadsheet, including those samples with no growth. The data that were recorded included the type of sample sent, any organisms grown and their susceptibility to any antibiotics tested. Any results which were from the same patient, during the same visit and which grew the same organism were only counted once. Results for which the genus was given, but not the specific name, were categorised separately under the title spp. (for example, *Klebsiella* spp.).

Results

Table 1 shows the organisms cultured from patients in the ICU. The total number of positive cultures was 127. Gram-negative organisms predominated, in particular *K. pneumoniae*, which represented 27% of cultured isolates, *E. coli* (22%) and *A. baumannii* (17%). Table 2 shows the organisms cultured from patients in the burns unit. The total number of positive cultures was 20. There was prevalence for Gram-positive organisms, in particular *S. aureus* and *S. epidermidis*.

Table 3 shows the number and type of cultures sent from the ICU during the 6-month period, and the percentage of cultures that came back positive. Blood was the most common sample type sent (158 samples), of which 60 were growth positive. Despite fewer samples of sputum and tracheal aspirate being sent (76 samples), the number of samples that were growth positive was higher than for blood, at 68. The high percentage of positive growth seen in sputum and tracheal aspirates may reflect the techniques used to collect the samples. The number of growth-positive wound swabs was also high, at 62, a proportion of which almost certainly represented skin commensals. Table 4 shows the number and type of cultures sent from the burns unit. As might be expected, the majority of samples sent were wound swabs (38 samples). Similarly

to what was seen in the ICU, a high proportion (84%) of wound swab cultures came back positive.

Table 5 demonstrates the resistance rates of each genus to all of the antibiotics routinely tested. Low levels of resistance were seen to linezolid (0%), amikacin (8%), vancomycin (10%) and colistin (12%). Moderate levels of resistance were seen to piperacillin-tazobactam (21%), ciprofloxacin (30%), gentamicin (35%) co-amoxiclav (49%) and the 3rd-generation cephalosporins cefotaxime and ceftazidime (49% and 44%, respectively). The level of resistance to the carbapenems varied from 2% for ertapenem up to 23% for imipenem.

Table 6 demonstrates resistance rates among individual species. *A. baumannii* displayed the highest levels of resistance with 80% and 78% resistance to piperacillin-tazobactam and meropenem, respectively. By comparison, 12% of *K. pneumoniae* was resistant to piperacillin-tazobactam, while 5% was resistant to meropenem.

Discussion

Nosocomial infections cause significant morbidity and mortality among patients. Of these infections, those affecting the lower respiratory tract, urinary tract, bloodstream and postsurgical account for the majority. [10] The increasing resistance rate seen in nosocomial pathogens combined with a paucity of new antimicrobials presents a serious challenge for physicians. [11] There

are concerns that we are entering a post-antibiotic era where the treatment of previously curable infections becomes impossible. It is likely that this phenomenon will be seen most acutely in ICUs, as they are often the final destination of patients with septic shock who are not responding to initial, empirical antimicrobial therapy.

The organisms that were grown from the samples sent during the 6 months of this audit represent a combination of community-acquired and nosocomial pathogens. Distinguishing which are hospital acquired is not possible from our data. However, knowing the patterns of resistance across all pathogenic species helps us to establish more effective empirical antibiotic protocols.

Organisms grown

In this study, Gram-negative bacteria made up the majority of the growth-positive cultures (114 cultured organisms of a total of 127) in the ICU, the three most prevalent of which were *K. pneumoniae* (26.8% of cultured isolates), *E. coli* (22.0%) and *A. baumannii* (17.3%). *S. aureus* was the only Gram-positive organism cultured in the ICU in significant numbers (10.2%). The preponderance for Gram-negative organisms is consistent with the findings of Brink *et al.*[4] for private institutions in

Table 1. Organisms cultured from patients in the ICU

Gram-negative bacteria cultured	Number of positive cultures (*N*=127), *n* (%)
K. pneumoniae	34 (26.8)
E. coli	28 (22.0)
A. baumannii	22 (17.3)
Klebsiella spp.	18 (14.2)
S. aureus	13 (10.2)
P. aeruginosa	12 (9.4)

Table 2. Organisms cultured from patients in the burns unit

Gram-positive bacteria cultured	Number of positive cultures (*N*=20)
S. aureus	7
S. epidermidis	7
P. mirabilis	6

Table 3. Number and type of cultures sent from the ICU

Type of culture	Total number	% growth positive
Blood	158	38
Sputum/ tracheal aspirate	76	89
Urine	71	44
Wound swab	69	90
Central venous line tip	33	73

Table 4. Number and type of cultures sent from the burns unit

Type of culture	Total number	% growth positive
Wound swab	38	84
Urine	7	29
Blood	6	33
Central venous line tip	2	50

Table 5. Resistance rates to all antibiotics routinely tested across each genus

Antibiotic	% resistance	Antibiotic	% resistance
Amikacin	8	Colistin	12
Ampicillin	85	Ertapenem	2
Co-amoxiclav	49	Erythromycin	53
Benzyl penicillin	100	Gentamicin	35
Cefotaxime	49	Imipenem	23
Cefoxitin	49	Linezolid	0
Ceftazidime	44	Meropenem	19
Cephamdole	84	Piperacillin-tazobactam	21
Ciprofloxacin	30	Trimethoprim	77
Cloxacillin	22	Vancomycin	10

Table 6. Resistance rates among individual species (%)

Antibiotic	K. pneumoniae	E. coli	A. baumannii	S. aureus	P. aeruginosa
Amikacin	5	0	17	-	0
Ampicillin	97	79	100	42	-
Cloxacillin	-	-	-	33	-
Co-amoxiclav	35	4	91	-	-
Cefotaxime	61	8	91	-	-
Ciprofloxacin	43	9	90	12	7
Colistin	0	0	0	-	14
Ertapenem	0	0	-	-	-
Erythromycin	-	-	-	36	-
Gentamicin	63	7	100	27	0
Meropenem	5	4	78	-	15
Oxacillin	-	-	-	63	-
Piperacillin	-	-	-	-	16
Piperacillin-tazobactam	12	0	80	-	7
Vancomycin	-	-	-	7	-

SA in 2008. They found that *K. pneumoniae* made up 24.9% of cultured isolates, while *E. coli* and *A. baumannii* made up 18.5% and 7.4%, respectively. *S. aureus* made up 24.6%. Notably, unlike Brink *et al.*,[4] we saw very few *Enterobacter* spp. (*n*=7 positive cultures, all *E. cloacae*). We also saw very few *Enterococci* spp. (*n*=8), none of which were resistant to vancomycin. In 2013, when looking at an SA trauma ICU, Ramsamy *et al.*[9] found that Gram-negative organisms made up the majority of the cultured organisms. However, in their study, Gram-positive organisms made up a much bigger proportion of the total (119 out of 323). This emphasises the importance of knowing the common pathogenic organisms in a unit when designing empirical antimicrobial protocols.

In contrast to the ICU, Gram-positive organisms were the most common organism cultured in the burns unit, in particular *S. aureus*. This isn't surprising perhaps, given the fact that most of the cultures were wound swabs and therefore possibly represented skin flora rather than invasive pathogens. However, immediate colonisation of burns by patients' normal skin flora is well documented and, depending on the individual organism's virulence, can often lead to an invasive burn wound infection.[12]

Specific organisms of concern

K. pneumoniae (*n*=34)
K. pneumoniae showed similarly high rates of resistance to ampicillin, co-amoxiclav, ciprofloxacin and the 3rd-generation cephalosporins to those seen by Brink *et al.*[4] in private institutions. In contrast to their findings, however, we found low levels of resistance to piperacillin-tazobactam (12% compared with 40%). Resistance to the carbapenems was also comparably low. Despite the increasing prevalence of carbapenemase-producing *Klebsiella* isolates in Europe (8.3% in 2013)[13] and the US (11% for all *Klebsiella* spp. in 2013),[14] documented rates of carbapenem resistance in Africa remain low, at between 0 and 4% (although there is a paucity of data).[15]

E. coli (*n*=28)
Although resistance to ampicillin among *E.coli* isolates was also high (79%), they were surprisingly sensitive to all other classes of antimicrobials (4%, 9% and 8% for co-amoxiclav, ciprofloxacin and cefotaxime, respectively). This is in contrast to the findings of both Brink *et al.*,[4] who documented resistances of 37%, 20% and 10%, respectively, for the same three antimicrobials, and the World Health Organization (WHO)[15] data for 2014, which showed resistance in Africa to fluoroquinolones of between 34 and 53% in invasive isolates and resistance to 3rd-generation cephalosporins of between 28 and 36%. There was no documented resistance to either piperacillin-tazobactam or ertapenem, and only 4% to meropenem.

A. baumannii (*n*=22)
Of all the organisms cultured from patients in the Edendale ICU, *A. baumannii* exhibited the most extensive range of antimicrobial resistance. This is in contrast to Brink *et al.*,[4] who saw significantly lower levels of resistance to ciprofloxacin (90% compared with 36%), 3rd-generation cephalosporins (91% compared with 43%) and piperacillin-tazobactam (80% compared with 42%). Even more concerning, however, was the level of resistance to meropenem (78%). The Centers for Disease Control reported in 2013 that 63% of all nosocomial *A. baumannii* infections in the USA were multidrug resistant. The only effective antimicrobial tested at Edendale was the polymyxin, colistin (0% resistance). The use of colistin as monotherapy, part of combination therapy and via novel routes such as nebulisation has seen a renewed interest in recent years. While there have been doubts in the past about the virulence of *A. baumannii*, given the ability of micro-organisms to transfer resistance genes between genus, the presence of bacteria with such an extensive spectrum of resistance is a large concern.

S. aureus (n=20)

The overall resistance to cloxacillin or oxacillin, thus conferring methicillin-resistant status, was 46%. This is within the range reported by the WHO[15] for the African continent in 2014 (12 - 80%). However, it is slightly greater than that seen by Brink *et al.*[4] (36%) and significantly higher than the EU average for 2013 of 18% (although the EU intercountry variation is 1 - 60%). It should be noted that MRSA rates in both the US and Europe have been falling over the past 6 years, possibly secondary to focused national infection control campaigns.[13,14] In line with most other studies, resistance to vancomycin was low at 7%.

P. aeruginosa (n=12)

Resistance to ciprofloxacin, gentamicin and piperacillin-tazobactam was low at 7%, 0% and 7%, respectively. This is in marked contrast to Brink *et al.*,[4] who saw resistance in the private sector of 46% for ciprofloxacin, and 48% for both amikacin and piperacillin-tazobactam. Resistance to both colistin and meropenem was around 15%, again lower than Brink *et al*. The CDC have reported that ~8% of all healthcare-associated infections were caused by *P. aeruginosa* and that 13% of these were multi-drug resistant.

Study limitations

These data are historical, and while useful in guiding empirical antimicrobial protocols at the time they were collected, it is likely that the spectrum of antimicrobial resistance has changed significantly since. To guide current protocols, further data should be collected. Data regarding length of stay before cultures were taken was not collected, so no distinction can be made between community- and hospital-acquired infections. Distinguishing the hypermetabolic response to burns from sepsis is challenging, and as such, the wound swabs sent from the burns unit may often reflect colonising bacteria rather than invasive pathogens.

Conclusions

This study demonstrates the prevalence of Gram-negative organisms in an SA government hospital ICU. It also demonstrates that while at low levels for certain classes of antibiotics, specifically carbapenems, resistance mechanisms exist in the organisms cultured for almost all available classes of antibiotics. The development of multi- and pan-resistant pathogenic organisms is both an SA and worldwide problem. In particular, the threat posed by resistant Gram-negative bacteria is likely to manifest in ICUs where septic patients unresponsive to standard antimicrobial regimens will inevitably end up. Frequent assessment of resistance patterns and appropriately designed empirical treatment protocols must remain a priority for all critical care departments.

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