Antibiotic prescribing practices in the presence of Extended-spectrum β-lactamase (ESBL) positive organisms in an adult intensive care unit in South Africa – a pilot study.

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ABSTRACT
Introduction: Antimicrobial resistance is one of the most severe health threats globally. Extended spectrum β-lactamases (ESBLs) are enzymes produced by a variety of gram-negative bacteria, which lead to an increase in resistance to commonly used antibiotics and are associated with higher morbidity and mortality. Objectives: Assess the prescribing practices prior to, and after, positive ESBL producing microbiology cultures in an adult ICU setting, according to sensitivity reports obtained from the clinical laboratories from January 2013 until January 2014. Subsequently use the findings to guide future practice.
Method: Retrospective study at a private hospital in Pretoria, Gauteng Province. All adult patients older than 18 years of age that were admitted to either the MICU or the TICU with a positive producing ESBL culture during their hospitalised stay were assessed. Results: During the study period, 39 patients in the MICU and TICU had positive ESBL microbiology results. The majority of positive ESBL results were due to Klebsiella pneumonia isolates. Antibiotics prescribed post ESBL positive culture were appropriate according to the sensitivity report in 64% of patients. 22 patients survived and 17 patients died. All the patients that died were on invasive ventilatory support. Conclusion: Clinically it appears as if patients who received appropriate therapy according to the microbiology results showed a

better clinical outcome than those with inappropriate therapy. This underlines the importance of appropriate prescribing practices in combination with co-morbid conditions. Invasive ventilatory support can be identified as a clear risk for contracting an infection due to an ESBL producing organism.

1. INTRODUCTION

Antimicrobial resistance (AMR) is one of the most severe health threats, both globally and in South Africa [1]. This is illustrated by the World Health Assembly in 2015 adopting a global action plan on AMR which underlines a global consensus that AMR poses a profound threat [2]. This is illustrated in South Africa and among sub-Sahara African countries with efforts to document current antimicrobial utilization patterns, investigate antimicrobial stewardship programmes and assess antimicrobial utilization against current guidance [3-8]. Infections from resistant bacteria are becoming more common, and some pathogens have even become resistant to multiple classes of antibiotics. Extended-spectrum β-lactamase (ESBL) producing bacteria have become recognized as a challenge in South Africa with an extremely high prevalence of ESBL producing organisms. The ESBL producing organism rate for Klebsiella pneumoniae cultured from complicated intra-abdominal infections in private hospitals in South Africa is 41.2%, and that for bacteraemic isolates in the public sector varies between 55 to 74% [9].

AMR occurs when bacteria change in a way that eliminates or reduces the effectiveness of the drugs available to treat them [10]. Our ability to treat infectious diseases and to manage infectious complications in vulnerable patients is undermined by the loss of effective antibiotics leading to increased morbidity, mortality and costs [1,11].

Extended spectrum β-lactamase (ESBLs) are enzymes produced by a variety of gram-negative bacteria which leads to an increase in resistance to commonly used antibiotics. Infections caused by such enzyme-producing organisms are associated with higher morbidity and mortality [2]. The increasing prevalence rates of ESBL producing organisms worldwide, coupled with the lack of development of new antibiotics in the short term, symbolizes an appreciable danger to public health [12]. According to the latest data in the United States, patients with bloodstream infections caused by ESBL producing Enterobacteriaceae have a 57% higher mortality than those with bloodstream infections caused by a non ESBL producing strain [11].

According to Coetzee and Brink, the utilisation of ertapenem, meropenem and, imipenem in the private sector in South Africa more than doubled between January 2009 and June 2011 [13]. Whilst it is recognized that the carbapenems are the cornerstone of therapy for patients with serious infections caused by ESBL producing organisms, the high prevalence of ESBL amongst bacteraemic pathogens places a tremendous strain on the use of these agents both as empiric therapy as well as directed therapy. Not only does the increasing consumption of the carbapenems create an ideal environment for the development of carbapenem resistance among the Enterobactericeae, carbapenem use has been shown to be a risk factor for subsequent infections with ESBL producing organisms through selective pressure. Inappropriate use is selecting for the very resistance that the class is being used for [13]. In the public health care sector in South Africa, K. pneumoniae showed a higher rate of resistance than E. coli bacteraemia [14], which is also a concern.

In view of these concerns, we wanted to investigate the situation within the ICU of a leading large private hospital in South Africa to improve the future care of these patients. This is because in the beginning of 2013, a significant increase in the number of ESBL producing isolates was noticed, with 18 patients producing ESBL positive cultures in one month. Consequently, this study aimed to evaluate prescribing practices among patients in an intensive care unit (ICU) setting prior to and post positive ESBL producing organisms, according to the positive microbiology results. Subsequently, use the findings to improve future prescribing if pertinent.

2. METHODS

2.1 Study design and population

This retrospective, quantitative study was performed at a private hospital in Pretoria, Gauteng Province, South Africa, which is the largest private hospital in South Africa with 470 beds. The multi- and trauma ICU in this private hospital contains 29 beds, with the multi-intensive care unit (MICU) and Trauma intensive care unit (TICU) having 21 beds and eight beds respectively. The ICU has an average of four patients per month with positive ESBL producing organisms. The study followed an epidemiological observational design.

2.2 Data collection and analysis

Purposive sampling was used for all consecutive patient files of adult patients older than 18 years that were admitted to these two units that had cultured positive ESBL producing organisms during their hospitalised stay from January 2013 until January 2014. Since the study was a census, the data from all the files during the study period were recorded on a form designed according to recommendations by Gregory and Radovinsky [15]. The data from the patient files were collected, managed, and analysed using the IBM Statistical Package for Social Sciences Statistics® (SPSS) programme. Descriptive statistics were used to analyse data for prescribing patterns in the presence of ESBL producing organism. This was followed by determining the antibiotics that were prescribed prior to the diagnosis of ESBL producing organism and after ESBL producing organisms were diagnosed.

Antibiotic use would be considered appropriate when the antibiotic prescribed was sensitive according to the microbiology result obtained from the laboratory data. The total daily consumption (TDC) refers to the antimicrobial dose that the patients received, with this methodology used in studies to monitor antimicrobial utilization [15,16]. Defined daily doses (DDD) were also calculated with DDDs being the assumed average maintenance dose per day for a medicine used for its main indication in adults according to the World Health Organisation (WHO) [2,15,17,18].

The Fischer exact test was used to test the association between variables such as patients' gender, age, diagnosed condition and length of stay in the adult ICU and the antibiotic prescription patterns. The Pearson correlation test was used to determine the statistical correlation between the combined age/co-morbid score and the relative risk of death ratio according to the Age-Adjusted Charlson Comorbidity index (AACI).

2.3 Risk factors for infection due to ESBL producing organisms

Each patient was included as a case only once. If an ESBL producing organism was isolated on multiple occasions, only the first episode of infection was reviewed. Hospital acquired infections are defined by the Centers of Disease Control (CDC) as an infection that occurred

>48hours after admission to the hospital, infection up to 3 days after discharge and/or infection up to 30 days after an operation [19].

The presence of a central venous catheter, urinary catheter, or mechanical ventilation was also assessed. Finally, all antimicrobial therapy that was administered prior- and post to positive ESBL producing cultures were documented. The presence of the following comorbid conditions was also documented: malignancy, diabetes mellitus, renal insufficiency, HIV infection and neutropenia [20].

Several instruments have been developed to assess the extent of co-morbidity and grade the degree of comorbid burdens using ordinal scales. One of the most widely applied is the Charlson Comorbidity Index (CCI), which has been extensively used to evaluate the impact of comorbidity in a variety of medical conditions. The CCI was developed in 1987 and is a prognostic taxonomy that was initially developed to account for the influence of a patients' adverse medical conditions in longitudinal studies and has been validated in many clinical settings [21,22]. This index is calculated by the summation of weight scores for 19 medical conditions and high scores were found to be associated with poorer prognosis [21,22].

Age has also been determined to be associated with overall survival, this was the CCI modified by Charlson et al. in 1994 [23]. This modification called Age-Adjusted Charlson Comorbidity index (AACI) includes the age of the patient as a correction variable of the final score of the Charlson index. Peterson et al. reported that each decade of age ≥50 years is equivalent to a 1-point increase in comorbidity (i.e. 50–59 years=1 point; 60–69 years=2 points) [24]. The AACI was used to assess the patient's estimated relative risk of death as only two patients in this study were younger than 50 years of age. The ACCI score was calculated for these patients and were dichotomized into four groups as recommended by Yang et al., i.e. having either low comorbidity (CCI = 0-1), mild comorbidity (CCI = 2-3), moderate comorbidity (CCI = 4–6) or severe comorbidity (CCI ≥ 6) [25].

2.4 Role of ESBL-resistance in outcomes

To evaluate the effect of infections due to ESBL producing organisms on clinical outcomes, the following outcomes were assessed: clinical outcome, mortality, duration of ICU stay and ventilation status. The antimicrobial exposures before and after the positive ESBL producing organisms were cultured were also assessed.

2.5 Microbiological methods

Clinical samples were processed according to standard microbiological procedures. Bacterial isolates were identified with the Bruker MALDI Biotyper. Antibiotic susceptibility testing was performed using the Vitek 2 (bioMerieux, Johannesburg, South Africa), and interpreted according to the criteria of the 2013 Clinical and Laboratory Standards Institute (CLSI). K. pneumoniae and E. coli isolates were suspected of ESBL-production if the MIC was ≥ 2 µg/mL for ceftazidime, cefotaxime or ceftriaxone [26]. Such isolates were subjected to a phenotypic confirmatory test, performed by incubating the isolates with disks containing 30 µg of cefotaxime and ceftazidime, with and without clavulanic acid (10 µg; Oxoid Ltd, Basingstoke, UK). The zone of inhibition was measured after 16-18 hours incubation, and an increase of ≥ 5-mm in a zone diameter of either agent tested in combination with clavulanic acid vs the zone of the diameter when tested alone was considered to be positive for ESBL-production.

There are no CLSI criteria for confirmation of ESBL-production in Enterobacter spp. ESBLs are more difficult to detect in these genera that have inducible AmpC chromosomal enzymes, as these enzymes can be induced by clavulanic acid, and then hydrolyse the indicator cephalosporin. Cefepime is however a poor substrate for AmpC β-lactamases. In Enterobacter spp with MICs of ≥ 2 µg/mL for cefotaxime or ceftazidime, ESBL production was suspected. We performed a double disk potentiation test between a cefepime disk and an adjacent amoxicillin-clavulanate disk on these isolates. This test is performed by placing a cefepime disk (30 µg) 15 mm (edge-to-edge) from a disk containing amoxicillin-clavulanate (20µg/10µg) [27].

2.6 Ethical considerations

Ethical approval was obtained from the University of Limpopo - Medunsa Campus (Number MREC/H/227/2014: PG) and from the research operations committee of the private hospital were the study was conducted – (Number UNIV-2014-0050).

Participant consent was not obtained for this study. This study was considered as an epidemiological observation study. Participant personal information was only used to match the laboratory report obtained from the laboratory dataset. Once this was done, the patient's personal data was anonymised and stored in a locked cupboard.

3. RESULTS

3.1 Study population and socio-demographic characteristics

During the study period, 39 patients had positive ESBL producing isolates. Of these, more than 70% were male (Table 1). Respiratory distress was the initial admitting diagnosis for 41% of patients, with the mean age of patients being 62 years, with only two patients younger than 50 years. 36 patients received antibiotics prior to the positive ESBL producing organisms being cultured (92.3%) and the remaining three patients (7.7%) only received antibiotics after the positive ESBL producing organisms were cultured. Infections for 36 patients (92.3%) were classified as hospital-acquired infections and three patients (7.7%) as community acquired infection.

Table 1 provides an overview of the baseline characteristics for the patients. Most patients were male (72%).

The sources where the positive cultures were principally from sputum (56%), followed by urine (23%) and blood cultures (15%) (Table 1). The majority of positive ESBL producing isolates were due to Klebsiella pneumoniae isolates (79%).

Table 1: Baseline demographic and study characteristic information

Data Characteristics	No (%) of Patients (IQR)
Demographic Data	
Total Patients	39 (100%)
Male	29 (72%)
Female	11 (28%)
Age(years), Median (IQR)	62.35 (24 – 92)
LOS in ICU (days)	22.15 (2 – 63)
Clinical Data	
Admission Diagnosis	n=39
Intestinal obstruction	5 (13%)
Heart failure	1 (3%)
Malignant neoplasma	2 (5%)
Pulmonary problems	4 (10%)
Respiratory distress	16 (41%)
Sepsis	5 (13%)
Trauma	6 (15%)
UTI	1 (3%)
ICU	
MICU	22 (56.4%)
TICU	17 (43.6%)
Charlson score, median (IQR)	5 (3-8)
Community acquired infection (CAI)	3 (7.7%)
Hospital associated infection (HAI)	36 (92.3%)
Origin of the infection	
Source of culture	n=39
Blood	6 (15%)
Lung Tissue	1 (3%)
Sputum	22 (56%)
Duodenal Swab	1 (3%)
Urine	9 (23%)
Microbiology data	n=39
Citrobacter koseri.	1 (3%)
Escherichia coli	4 (10%)
Enterobacter cloacae	2 (5%)
Enterobacter aerogenes	1 (3%)
Klebsiella pneumoniae	31 (79%)

3.2 Comorbidity index

38.5% of patients had severe ACCI scores (Table 2), followed by moderate (25.6%) and mild (20.5%) (Table 2). Table 2 also categorises the relative risk of death ratio (RR) in relation to ACCI.

Table 2: Age Adjusted Charlson Comorbidity index and clinical outcome (n=39)

COMBINED AGE/CO-MORBID SCORE	AMOUNT N=39	PERCENTAGE N=39	RELATIVE RISK OF DEATH	CLINICAL OUTCOME Percentage (n=39)	
				SURVIVED	DIED
0 - 1	6	15.4%	0-1.45	100	0
2 - 3.	8	20.5%	2.10-3.40	87.5	12.5
4 - 6.	10	25.6%	4.40-9.23	70	30
>6	15	38.5%	9.23-19.37	13.3	86.7

The clinical outcome of the sample population corresponds with the prediction calculated by the AACI. According to Pearson Correlation there is a statically correlation of 0.01 between the combined age/co-morbid score and the relative risk of death ratio, which highlights the importance of co-morbid conditions in critical ill patients.

3.3 Prescribing patterns

In this study, 91 different antimicrobials were prescribed for 39 patients prior to the positive ESBL producing organisms being cultured; consequently, each patient received on average 2.3 different antibiotics. The first antimicrobials that the patients received were as follows: twenty one patients (54%) received other β-lactam antibiotics as empiric therapy, seven patients (18%) received fluoroquinolones, three (8%) patients received a carbapenem, with additional antimicrobials contained in Table 3. Eight patients received one antimicrobial agent before positive ESBL producing organisms were isolated, with others receiving more (Table 4).

Table 3 – Details of the first antimicrobials patients received

Number of patients (N=39)	Antimicrobial received and ATC code	Percentage
21	β-lactam (J01C, J01DB to DE)	54%
7	Fluoroquinolones (J01MA)	18%
3	Carbapenem (J01DH)	8%
2	Tetracyclines (tigecycline) J01AA	5%
1	Aminoglycosides (J01G)	3%
1	Imidazole derivatives (J01XD01) (Metronidazole)	3%
1	Other bacterials J01XX (Linezolid)	3%
	Others	6%

Table 4 – Number of antibiotics patients received before positive ESBL organisms were isolated

Number of patients (N=39)	Number of antibiotics prior to ESBL isolate
10	2
8	1
8	3
8	4
3	5
2	0

3.4 *Appropriate use of antibiotic's post positive ESBL producing culture*
The prescribing practices post positive ESBL producing organisms being cultured are summarised in Table 5.

Table 5: Prescribing practices after positive ESBL producing culture

Cultures obtained (n= 39)	Sensitivity Yes/No/Not reported (NR)	Initial Prescribed therapy (frequency) (and ATC code)	TDC (g)	DDD	Appropriate Prescribing Yes/No/Not reported (NR)
Blood (6)					
K.pneumoniae (5)	Yes	Doripenem (2) (J01DH04)	3	1.5	Yes
	Yes	Ertapenem (1) (J01DH03)	1	1	Yes
	Yes	Meropenem (1) (J01DH02)	6	3	Yes
	NR	Piperacillin/Tazobactam (1) (J01RA01)	13.5	14	NR
E. cloacae (1)	Yes	Imipenem (1) (J01DH)	4	2	Yes
Sputum (22)					
K.pneumoniae (18)	Yes	Cefepime (2) (J01DE01)	4	2	No
	Yes	Ceftriaxone (1) (J01DD04)	2	2	No
	Yes	Ciprofloxacin (1) (J01MA02)	0.8	0.5	No
	Yes	Doripenem (2) (J01DH04)	2.25	1.5	Yes
	Yes	Ertapenem (2) (J01DH03)	2	1	Yes
	Yes	Imipenem (4) (J01DH)	2.5	2	Yes
	Yes	Meropenem (4) (J01DH02)	4.5	3	Yes
	Yes	Moxifloxacin (1) (J01MA14)	0.4	0.4	No
	NR	Tigecycline (1) (J01AA12)	0.2	0.1	NR
No AB received (1)					
C. Koseri (1)	Yes	Meropenem (1) (J01DH02)	3	3	Yes
E. aerogenes(1)	Yes	Amikacin (1) (J01GB06)	1	1	Yes
E. Coli (1)	Yes	Cefepime (1) (J01DE01)	6	2	No
Duodenal Swab (1)					
K.pneumonia (1)	Yes	Doripenem (1) (J01DH04)	3	1.5	Yes
Lung Tissue (1)					
K.pneumonia (1)	Yes	Cefepime (1) (J01DE01)	3	2	NR
Urine(9)					

Ent.cloacae (1)	Yes	Amoxicillin (1) (J01CA04)	2	1	No
E. Coli (3)	Yes	Ciprofloxacin (1) (J01MA02)	0.8	0.5	No
	Yes	Doripenem (1) (J01DH04)	3	1.5	Yes
	Yes	Meropenem (1) (J01DH02)	4	3	Yes
K.pneumonia (5)	Yes	Cefepime (1) (J01DE01)	3	2	No
	Yes	Ertapenem (1) (J01DH03)	2	1	Yes
	Yes	Tigecycline (2) (J01AA12)	0.2	0.1	Yes
	NR	Vancomycin (1) (J01XA01)	2	2	NR

TDC = Total daily consumption; DDD = Defined daily dose; NR = not reported

The majority (64%) of all antibiotics prescribed post positive ESBL producing organism were appropriate according to the sensitivity report. Antibiotics were prescribed to nine patients (23%) despite resistance to the said antibiotics on the culture reports. One (3%) isolate was not treated as the patient passed away before the antibiotic was started. There was no sensitivity results available for four (10%) of the antibiotics prescribed after the positive culture.

3.5 Sensitivity and clinical outcome

Most (95%) of the ESBL producing organisms isolated in the 39 patients during the study period were sensitive to the carbapenem antibiotics. One E. aerogenes sputum isolate was only sensitive to imipenem, and one K. pneumonia blood isolate showed resistance to imipenem.

Twenty two (56%) patients survived and 17 (44%) patients died. It is clinically significant to note, however, that of the survivors, 32 % (n = 7) received inappropriate antibiotics. Of the 17 patients who died, eight (47%) received appropriate therapy, four (23%) received inappropriate therapy and there were no sensitivity reported for four (23%) isolates and one patient (6%) did not receive any antibiotics because he passed away before antimicrobial therapy could be started. The difference between those survivors who received appropriate therapy vs those who did not was not statistically significant (p=0.209) (Table 6).

Table 6: Clinical Outcomes for patients as compared to appropriate vs inappropriate therapy received

Clinical Outcome of Patients (N = 39 and %s)	Appropriate Therapy Received	Inappropriate Therapy Received	Other		Fischer Exact Test
			Sensitivity reports not done	Antibiotics Not Received	
Survived (n = 22) - 56.4%	15 (68 %)	7 (32 %)	-	-	
Deceased (n = 17) - 43.6%	8 (47 %)	4 (23 %)	4 (24 %)	1 (6 %)	p=0.209

4. DISCUSSION

ESBL producing organisms were most frequent in patients aged between 51 to 60 years, similar to the findings of Dey et al [28].

The mean length of stay in the ICU in our study was 22.15 days (range 2 to 63 days – Table 1), with ICU stay known to increase the patients' risk of contracting infections caused by ESBL producing organisms [29]. According to a study conducted by Kramer and Zimmerman [30], there are distinct differences between patients with an ICU stay < 5 days versus those with an ICU stay ≥ 5 days. Patients with an ICU stay ≥ 5 days had significantly higher severity of illness, frequency of mechanical ventilation, ICU readmission and emergency surgery. Patients with an ICU stay ≥ 5 days accounted for 21% of all admissions but 63% of total ICU days; and their outcomes were uniformly poorer [30]. In this study, 90% of patients were in the ICU for longer than five days.

Of the 39 patients with ESBL producing organisms, 31 (79%) had infections due to K. pneumoniae and four (10%) were due to E. coli. Most isolates were cultured out of the respiratory tract (56%) followed by the urinary tract (23%). The results seem to correspond to global findings where K. pneumoniae and E. coli remain the dominant ESBL producing organisms [31].

In this study population, 36 patients (92%) were on invasive ventilatory support and only three patients were on non-invasive ventilatory support. This might also play an important role regarding the acquisition of an ESBL producing infection with the introduction of invasive devices. Twenty two patients survived (56%) and 17 patients died (44%). All the patients that died were on invasive ventilatory support. According to Kritsotakis et al, non-antibiotic risk factors for carbapenem sensitive ESBL producing K. pneumonia organisms included invasive ventilator support, central vascular catheterization, urinary catheterization and tracheostomy [32].

The relatively high ACCI index, the ventilation status of the patients, as well as the increased duration of stay in ICU in this study population, confirmed the appreciable contribution to the risks of patients contracting a positive ESBL producing organism and the their outcomes similar to other studies [29]. The importance of comorbid conditions was underlined by the statistical significant implication on the risk of death according to the ACCI correlation.

Having said this, the morbidity calculator does not take in account respiratory distress or dependence on ventilatory support. Consequently, additional care is needed when treating these patients.

4.1Prescribing practices before ESBL producing cultures

Numerous studies underline the impact of antimicrobial exposure and the risk of developing an ESBL producing related infection [31,32]. Antibiotic consumption, including the use of third generation cephalosporins, other β-lactams and fluoroquinolones, are also well-established risk factors shown to be associated with the acquisition of ESBL producing organisms [32]. This is similar to our study where more than 70 percent (77%) of the patients received other β-lactam antibiotics prior to positive ESBL producing organisms being cultured. These included cephalosporins, piperacillin/tazobactam and penicillins, which might play a role in enhancing an ESBL producing related infection [33]. Other antimicrobial exposure includes fluoroquinolones (36%), carbapenems (33%) and aminoglycosides (10%).

4.2 Prescribing practices after positive ESBL producing results and clinical outcome

The majority (64%) of all antibiotics prescribed post positive ESBL producing organisms were appropriate according to the sensitivity report. According to Pannell, the simple approach to sensitivity analysis, given its ease and transparency, may even be the optimal method for the purpose of practical decision making [34].

Patients who receive appropriate therapy according to the microbiology results showed a better clinical outcome than those with inappropriate therapy; however, whilst these results were not statistically significant they underline the importance of appropriate prescribing practices after positive microbiology results.

Just under half (47%) of the patients who died also received appropriate treatment after positive ESBL producing organisms, which underlines the fact that sensitivity and microbiology results cannot be interpreted without taking the patients' co-morbidity into consideration. This was also confirmed in a study done by Van Daalen et al [35].

Overall, we believe our findings provide a stimulus to establish an antimicrobial stewardship team (ASTs) in this hospital, and likely in other hospitals in South Africa, to reduce inappropriate prescribing and dispensing and reduce AMR rates [4]. Coetzee and Brink underlined the importance of an antibiotic stewardship team and suggest that restrictive measures, even when perceived as punitive measures, may be required to influence future antibiotic prescriptions [13]. Similar activities have been seen in other countries to try and reduce AMR rates [36-40]. The AST should provide advice to improve and adapt antibiotic prescriptions, and to encourage prescribers to adapt their treatment in accordance with local sensitivity reports and recommendations, with evidence-based prescribing and dispensing seen as a future standard of care [2,41,42]. Prescribing practices can be positively influenced by pharmacists through relationship building with prescribers and by leading and driving antibiotic stewardship initiatives building on the South African's government initiatives to reduce AMR rates [4,40]. As part of this, de-escalation should also be systematically proposed when clinical and microbiological data allows for this using patient co-morbidities to guide suggested therapies.

4.3 Limitations

We are aware that the study followed a retrospective, epidemiological observational approach, with some the patient files incomplete. In addition, the findings were based on the data captured by the infection prevention practitioner of the hospital where the study was conducted and we did not look at issues of mortality broken down by de-escalation or no de-escalation. We are also aware that we used the 27th edition of CLSI for our study analysis and not the 28th edition, and that the study was conducted in only one hospital in South Africa. However, this is a leading private hospital in South Africa providing guidance to others. Consequently, we believe that despite these limitations our findings are robust providing direction for the future in this and other hospitals in South Africa.

5. CONCLUSION

The length of ICU stay, ventilatory status and prior exposure to antibiotics were found to be significant risk factors associated with ESBL producing E. coli and/or K. pneumoniae acquisition status of patients. Consequently, restricting the use of antibiotics, along with implementation of infection control measures, should help control and decrease the spread of ESBL producing pathogens. Recommendations to this and other leading hospitals in South Africa in light of our findings also include writing and implementing an antibiotic policy in the MICU and TICU, taking into consideration the ventilatory status and co-morbid conditions of patients to limit antimicrobial exposure. In this study there was no indication if the antibiotic was de-escaled to avoid carbapenem use and factors associated with omission of de-escalation should be studied further especially if they have an influence on mortality rates. There should also be a strong urge to establish proactive ASTs to monitor these efforts.

There was also no indication if the infections were colonisations or an active infection, which is an important part of antimicrobial stewardship. Consequently, it is recommended that future studies of this nature be limited in scope to ensure effective focus and in depth evaluations of specific guidelines related to antibiotic prescriptions. We also believe it is important that future researchers undertake a mix of quantitative and qualitative study designs, which will allow in-depth research of the prescribers' views when prescribing antibiotics to better plan for the future.

This hospital has now established a multidisciplinary AST, and is working towards reducing irrational prescribing practices in the ICU. Future research will concentrate on assessing the impact of these initiatives including their influence on future clinical outcomes and improved management of patients in the ICU.

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