ANTIBIOTICS' SUSCEPTIBILITY PATTERNS OF BACTERIAL ISOLATES CAUSING LOWER RESPIRATORY TRACT INFECTIONS IN ICU PATIENTS AT REFERRAL HOSPITALS IN NAMIBIA

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ABTRACT

Background: Lower Respiratory Tract Infections (LRTIs) are a particular public health concern especially among sub-Saharan African countries. This is especially the case in Namibia where LRTIs are currently the third leading cause of death, 300 deaths in children under 5 years of age. To reduce the burden of Lower Respiratory Tract Infection (LRTIs) on health systems and ensure appropriate patient management, it is critical to know the most prevalent pathogens leading to LRTIs and their susceptibility patterns in the local setting. Consequently, the objective was to formulate cumulative antibiograms for ICUs of referral hospitals in Namibia to guide future antibiotic use. **Methods:** A retrospective analytical cross-sectional study was conducted over two years. The cumulative antibiograms were constructed in accordance with current guidelines. **Results:** 976 first isolate cultures were obtained from ICUs of the different referral hospitals. *K. pneumoniae* (8.8%, 8.1%) was a predominant pathogen in Windhoek Central hospital ICU in 2017 and 2018. In Oshakati intermediate hospital ICU, *Enterobacter sp*. (22.2%) and *P. aeruginosa* (37.5%) were the common pathogens in 2017 and 2018, respectively. *A. baumannii* isolates were > 90% susceptibility to colistin, carbapenems and tigecycline in 2017. In 2017, *K. pneumoniae* isolates were more susceptible to carbapenems (94% and 93.8% among isolates), amikacin (89.3%) and tigecycline (88.7%). In 2018, *K. pneumoniae* isolates were 100% susceptible amikacin, colistin and carbapenems. *S. maltophilia* isolates were more than 80% susceptible to all the tested antibiotics. *S. aureus* isolates were 100% susceptible to linezolid, rifampicin, teicoplanin, vancomycin in 2017 and in 2018. Its susceptibility to these antibiotics did not change. **Conclusion:** The susceptibility patterns of the common isolated gram-negative pathogens were highly variable. Meropenem in combination with gentamicin is now the recommended antibiotic combination for empiric therapy for patients with LRTIs in Windhoek Central Hospital ICU.

Key words: Antibiograms, Antibiotics, Guidelines, Hospitals, ICUs, LRTIs, Namibia

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1.INTRODUCTION

Lower respiratory tract infections (LRTIs) are currently the sixth leading cause of death globally (1), accounting for 2.38 million deaths in 2016 of which 47.4% occurred in sub-Saharan Africa (1). Among children, lower respiratory infections account for 38.6% of all infectious disease deaths, with an appreciable number deaths among African children (14.9% of all deaths) (2). Overall, LRTIs currently cause approximately 300 deaths a year in children under five years (3).

LRTIs are a particularly important problem in Namibia as they are currently the third leading cause of death in the country (4). Alongside this, in 2015, a third of all health funds in Namibia were spent on treating infectious and parasitic diseases, with the management of respiratory infections accounting for 10% of these (5). Some organisms known to cause LRTIs are intrinsically resistant, namely *Pseudomonas aeruginosa* (6), which was the most frequent cause of LRTIs in Nepal (7). LRTI-related deaths can be prevented, or their rates reduced, with appropriate use of antimicrobials alongside vaccinations (8, 9). Once patients develop a LRTI, this requires clinicians to be aware of the causative organisms and their susceptibilities as these differ by geographical area as well as change over time due to the development of antimicrobial resistance (AMR) (10-15). Consequently, good quality updated data about the susceptibility patterns of potentially causative organisms is needed to guide appropriate antimicrobial choices among hospital patients especially those in intensive care with LRTIs (10, 16). Otherwise, valuable time and resources will be wasted adding to AMR, with its known impact on morbidity, mortality and costs (9, 17-19).

However, currently little is known about the prevalence and susceptibility of pathogens causing LRTIs among ICU patients in Namibia. ICUs were selected for this initial study in Namibia since ICU patients are more prone to infections due to their underlying diseases as well as interventional or therapeutic procedures they undergo in hospitals including ventilation increasing morbidity, mortality and costs (20-25). In addition, we are aware there can be irrational use of antibiotics in ICUs, increasing adverse drug reactions alongside healthcare costs and AMR, with the instigation of rapid diagnostic and other interventions in ICUs reducing the over use of antibiotics especially broad spectrum antibiotics (26-29).

Consequently, this study was undertaken to examine the common pathogens that caused LRTIs among ICU patients in Namibia, and their susceptibility to potential antibiotics, to formulate cumulative antibiograms for ICUs among Namibia's referral hospitals to enhance future antibiotic use. We have previously shown that in Namibia there is good adherence to guidelines generally as well as for infectious diseases among hospitals in Namibia due to their respected content and ease of handing, and we wanted to build on this (30, 31). This is not always the case among hospitals in low- and middle-income countries including sub-Saharan African countries regarding the management of infectious diseases (9, 32-35).

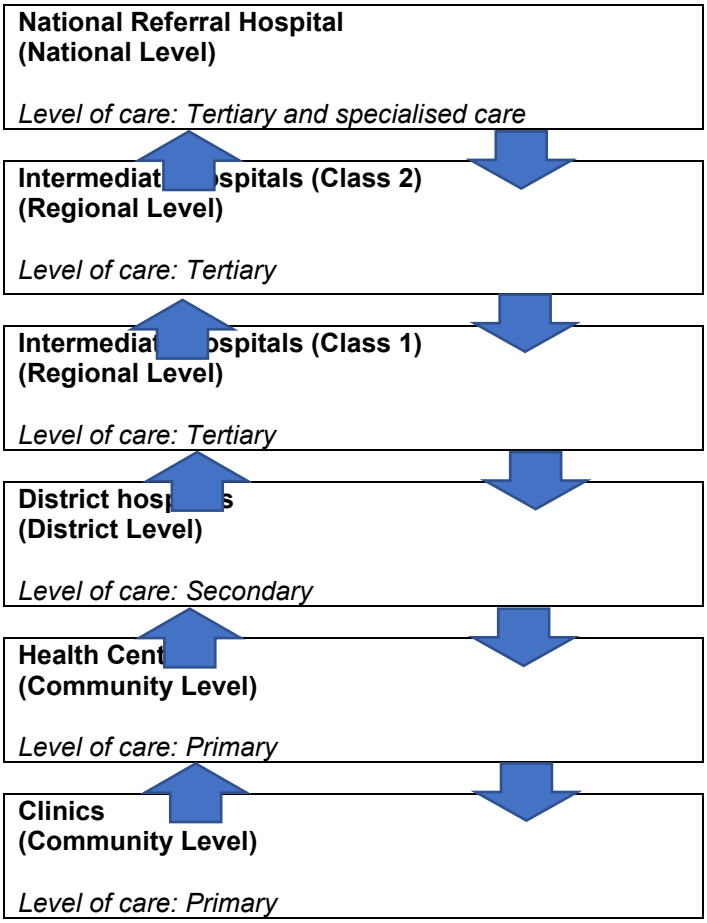
2. METHODOLOGY

We performed a retrospective analytical cross-sectional study to describe the susceptibility patterns of common isolated bacteria among patients with LRTIs in the ICU over two years from 01 January 2017 to 31 December 2018. Data were acquired from the Namibia Institute of Pathology (NIP), with NIP regularly conducting culture and sensitivity tests. Pathogen identification and antibacterial susceptibilities at NIP are performed using Wellcogen® Bacterial Antigen Kit, Gram stain, and methylene blue stain. NIP performs standard bacterial culture and sensitivity tests using horse blood agar (5%) or chocolate agar. Culture results are evaluated after 24 hours of incubation. Plates are re-incubated for another 24 hours and re-examined for additional organisms (36). The results were recorded on a worksheet and entered into a specific database known as Meditech®. From Meditech® the data are provided to users in an excel format, aggregated by geographical region, health facility, ward, patient characteristics, and specimen type.

The following specimens were of interest to this study: sputum, bronchial aspirate, and pleural fluid. As mentioned, data that was accessed from 01 January 2017 to 31 December 2018 among three referral public health facilities in Namibia, namely: for Oshakati Intermediate Hospital, Onandjokwe Hospital, and Windhoek Central Hospital. These referral hospitals were chosen as they provide specialized health care for critically ill patients in Namibia.

Currently in Namibia, the Ministry of Health and Social Services oversees 287 clinics, 37 health centres and 27 hospitals of which five are referral hospitals. These include Oshakati, Onandjokwe, Katutura, and Rundu which are intermediate hospitals (Regional level) and Windhoek Central is a national referral hospital (Figure 1). However, only Onandjokwe, Oshakati and Windhoek Central hospitals have intensive care units. The other two hospitals (Regional Level Class 1) have high care units. The public clinics and health centres provide primary health care services; however, these facilities do not have beds. Patients may be referred to a district hospital or intermediate hospital (Class 1 or 2) when secondary care is deemed necessary. Patients from district hospitals who require tertiary care or a more specialized care are referred to intermediate hospitals Class 2 or a national referral hospital.

Figure 1 - Flow chart: referral of patient in a public sector, Namibia



The data was available in Excel, subsequently cleared of missing susceptibility data and saved in BacLink for conversion to a form that could be analysed using WHONET version 5.6 (37). We used the CLSI M39 guidelines for cumulative antibiograms development - that is, a minimum of 30 isolates per species for each reporting period. The analysis of susceptibility patterns was conducted for WCH's ICU isolates, but not for Onandjokwe and Oshakati intermediate hospital ICUs, since the number of isolates from the latter two hospitals were fewer than 30.

WHONET strategies for handling multiple patient isolates, including CLSI recommendations, were used to include one isolate per species per patient in the analysis. The susceptibility data was analyzed using '% RIS and test measurement' feature in WHONET for the formulation of a cumulative antibiogram which was presented as percentage of susceptible isolates in a table (37). Intermediate susceptibility was considered resistant. The WHONET 'isolate listing and summary' feature was used to determine the commonest pathogens. Finally, the Chi-square test was used to compare the changes in susceptibility from 2017 to 2018, where p-values < 0.05 were considered statistically significant.

2.1 Validity of the study/data

NIP is an approved laboratory that provides antimicrobial susceptibility testing services to all state hospitals in Namibia. Standard operating procedures (SOPs) entail stepwise instructions and provide a full description of the activities performed in the laboratory (38). Consequently, the existence of the SOPs in the laboratories guarantees consistency, quality and reliability of the laboratory data (38). Periodic quality control reports (both internal and external) also help ensure reliability and repeatability of the laboratory results (38). Specific bacteria and the data (specimens) for this study were collected overtime, which helped enhance the validity of this study.

This study was approved by the Faculty of Health Sciences, University of Namibia, NIP and the Ministry of Health and Social Services' ethics committees (reference number 17/3/3 PS).

No participants were directly involved as the study was based on retrospectively collected data available from NIP. The data was de-identified to ensure anonymity and confidentiality as it was transferred from Meditech ® to Excel and was secured on a password protected computer.

3. RESULTS

A total of 976 first isolate cultures were obtained in 2017, with most (n=957) from Windhoek Central Hospital. In 2018, 1128 isolate cultures were obtained with again most (n=1102) obtained from Windhoek Central Hospital (Table 1).

In 2017, the isolate culture from Onandjokwe Hospital's ICU was obtained from one specimen, which was negative. In that same year, 17 isolates were obtained from Oshakati Intermediate Hospital, and all were positive (Table 1). In 2017, 421 isolates were obtained from Windhoek Central Hospital of which almost half were negative.

In 2018, ten isolate cultures from Onandjokwe Hospital's ICU were obtained from five specimens, of which 50% were negative. In that same year, isolates from Oshakati Intermediate Hospital's ICU were obtained from 15 specimens, all of which were positive, and 465 isolates were obtained from Windhoek Central hospital and almost half were negative (Table 1).

Table 1: Characteristics of lower respiratory tract specimens and isolates of ICUs of the referral hospitals

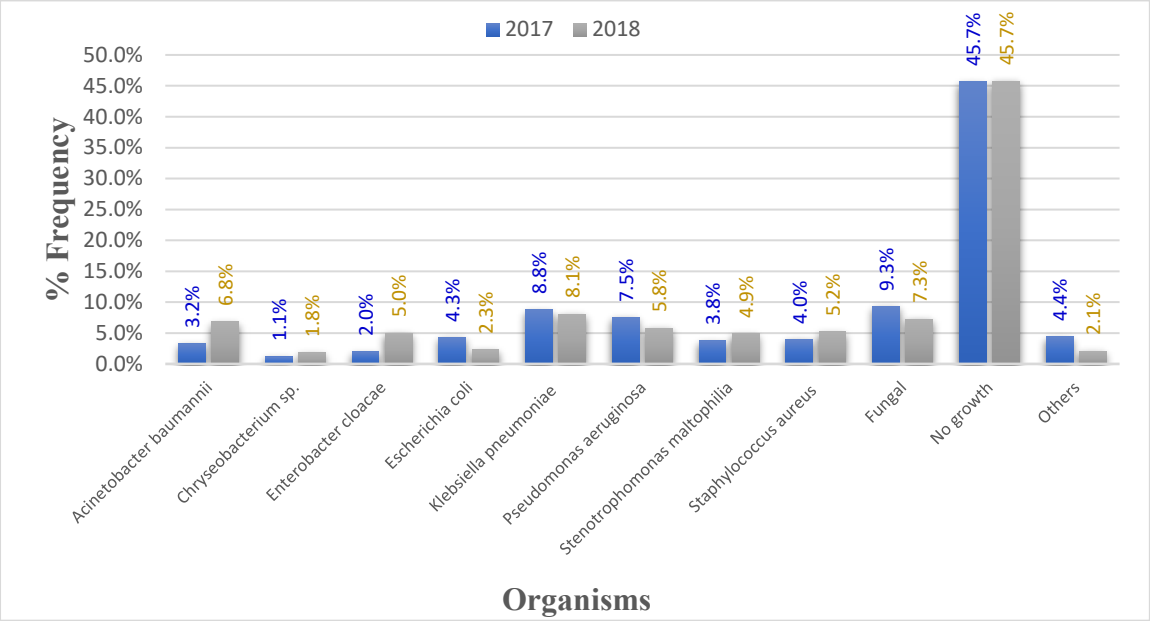
Location	**Windhoek Central Hospital ICU**		**Oshakati intermediate hospital ICU**		**Onandjokwe hospital ICU**	
Reporting period	2017	2018	2017	2018	2017	2018
Number of specimens	421	465	17	15	1	5
Sputum, n (%)	376 (89.3)	443 (95.5)	16 (94.5)	13 (86.7)	1 (100)	5 (100)
Pleural fluid, n (%)	41 (9.7)	19 (4.1)	-	1 (6.7)	-	-
Bronchial aspirate, n (%)	4 (1)	3 (0.65)	1 (5.9)	1 (6.7)	-	-
Number of isolate cultures	957	1102	18	16	1	10
Gram positive, n (%)	61(6.4)	70 (6.4)	-	2 (12.5)	-	-
Gram negative, n (%)	328 (34.3)	425 (38.5)	14 (77.8)	12 (75)	-	1 (10)
Fungal, n (%)	89 (9.3)	80 (7.3)	3 (16.7)	2 (12.5)	-	4 (40)
No growth, n (%)	437 (45.7)	504 (45.7)	-	-	1 (100)	5 (50)
Others, n (%)	42 (4.3)	23 (2.0)	-	-	-	-

Key: n (%) = Number (percentage); others = Mycobacterium tuberculosis, contaminated isolate cultures and no anaerobes found

3.1 Pathogens causing LRTIs

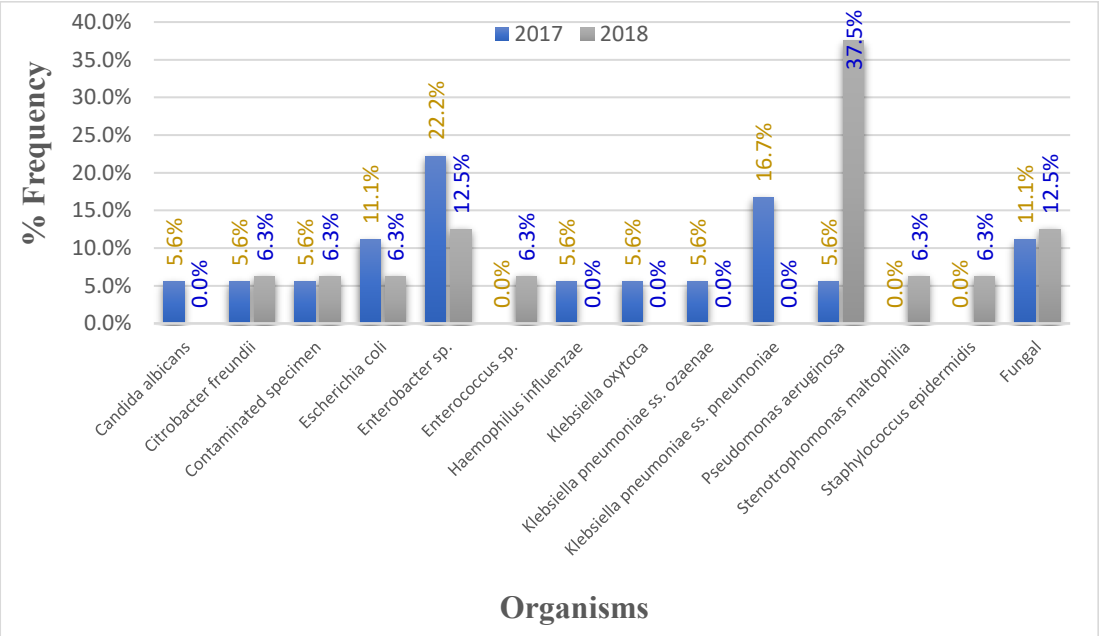
Most of the pathogens that were identified from the specimens were gram negative bacteria (Table 1). In 2017, *K. pneumoniae* (8.8% of specimens) and *P. aeruginosa* (7.5% of specimens) were the predominant isolates in Windhoek Central hospital's ICU. The other pathogens included *E. coli*, *S. aureus*, *S. maltophilia* and *A. baumannii* (Figure 1). In 2018, the same organisms were identified as the most frequent isolates, except for *E.cloacae* (5% of specimens) which was newly identified in 2018 and *E. coli* only in 2017 (Figure 2).

Figure 2: Common pathogens causing LRTIs in Windhoek Central hospital ICU in 2017 and 2018



In 2017, the most common bacterial isolates in Oshakati Intermediate Hospital's ICU were *Enterobacter sp*. (22.2% of specimens) , *K. Pneumonia* (16.7% of specimens), and *E. Coli* (11.1%). In 2018, *P. aeruginosa*, and *Enterobacter sp* were isolated from the specimen (Figure 3). *K. aerogenes* was the only isolate in 2018 for Onandjokwe Hospital's ICU.

Figure 3: Common pathogens causing LRTIs in Oshakati intermediate hospital ICU in 2017 and 2018



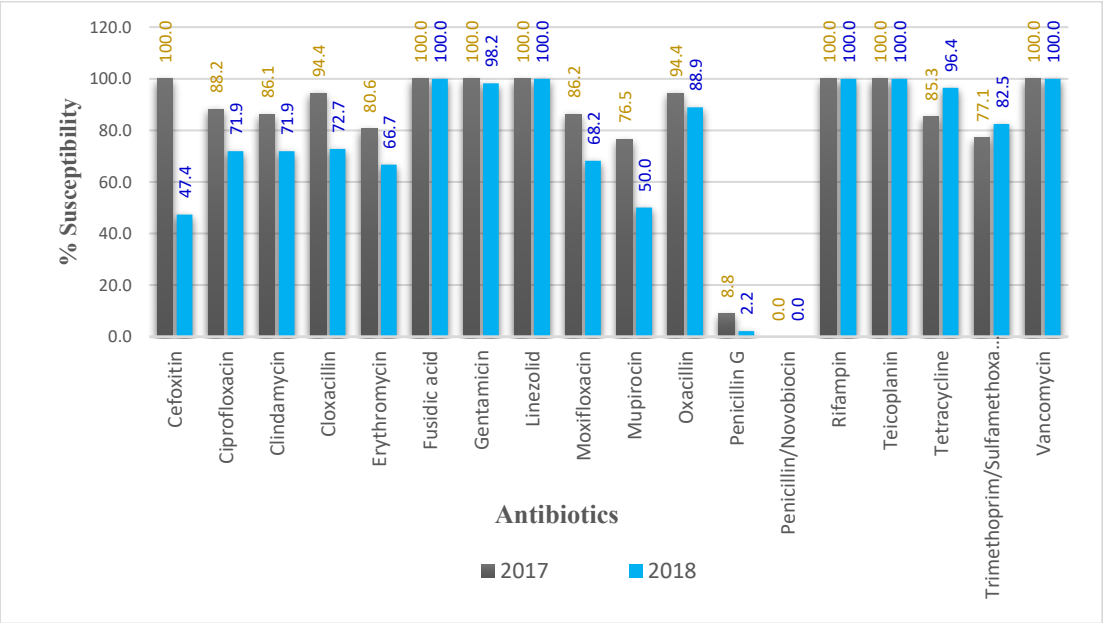
3.2 Analysis of susceptibility patterns

Analysis of the susceptibility pattern of 2018 bacteria isolates revealed a similar susceptibility pattern to 2017 for most gram-negative isolates (Appendix 1). Organism specific results include:

- *A. baumanni* isolates exhibited > 90% susceptibility to colistin, carbapenems and tigecycline (Figure 3) in 2017. In 2018, similar susceptibilities were observed except for tigecycline. Amikacin was effective in 2018 (Appendix 2).

- *E. coli* isolates were 100% susceptible to amikacin, carbapenems (imipenem and meropenem) and tigecycline in addition to colistin (Appendix 3). However, they were less than 60% susceptible to 3rd and 4th generation cephalosporines and penicillins.
- In 2017, *K. pneumoniae* isolates were more susceptible to carbapenems: ~94%, amikacin: 89.3%, and tigecycline: 88.7% (Appendix 4). These isolates were less susceptible to penicillins and all cephalosporins tested except cephamycin and cefoxitin (94.4%). *K. pneumoniae* was less than 100% susceptible to colistin (98.7%). In 2018, *K. pneumoniae* isolates were 100% susceptible amikacin, colistin and carbapenems (Appendix 4).
- In 2017, *P. aeruginosa* isolates were highly susceptible to aminoglycosides (amikacin 94.4% and gentamicin 90.1%), 3rd and 4th generation cephalosporins (cefepime 83.1% and ceftazidime 85.9%), ciprofloxacin 83.1%, carbapenems (74.3%) and piperacillin/tazobactam 84.5% (Appendix 5). In 2018, the susceptibility of *P. aeruginosa* isolates to amikacin, gentamicin, piperacillin/tazobactam, ciprofloxacin, 4th generation cephalosporins and ceftazidime ranged from >85% to 100% (Appendix 5).
- *S. maltophilia* isolates were more than 80% susceptible to all the tested antibiotics (Appendix 6).
- In 2018, *E. cloacae* isolates were 100% susceptible to amikacin and colistin, and highly susceptible to carbapenems (ertapenem 94.4%, imipenem and meropenem 98.1%), tigecycline 97.5% and piperacillin/tazobactam 83% (Appendix 7).
- *S. aureus* was the only gram-positive bacteria with >30 isolates in 2017 and 2018. Its isolates were 100% susceptible to linezolid, rifampicin, teicoplanin, vancomycin in 2017. In 2018, its susceptibility to these antibiotics did not change (Figure 4). *S. aureus* isolates' susceptibility was >85% for the following antibiotics: ciprofloxacin, moxifloxacin, clindamycin, cloxacillin, erythromycin, oxacillin, and tetracycline (100%). In 2018 a decrease in susceptibility was observed: ciprofloxacin 71.9%, moxifloxacin 71.9%, clindamycin 72.7%, cloxacillin 72.7%, erythromycin 66.7%, oxacillin 88.9% and tetracycline 96.4%.

Figure 4: S. aureus antibiotic susceptibility pattern in 2017 and 2018



The statistically significant susceptibility changes in cumulative antibiograms from 2017 to 2018 were observed in *A. baumannii, K. pneumoniae, P. aeruginosa* isolates and *S. aureus* (Table 2). It is noteworthy that the statistically significant changes in susceptibility were improvements for *A. baumannii, K. pneumoniae, and P. aeruginosa,* while for *S. aureus* they were declines (Table 2, and documented in appendix 8).

Table 2: Annual susceptibility changes from 2017 to 2018 cumulative antibiograms

Organism	Antibiotics	% susceptibility 2017	% susceptibility 2018	Difference in % susceptibility	P-value
Acinetobacter baumannii	Amikacin	75.9	93.5	17.6	0.015!
	Cefepime	27.6	28.8	1.2	0.905
	Ceftazidime	13.3	23.3	10	0.255
	Ciprofloxacin	29	30.1	1.1	0.868
	Gentamicin	32.3	47.9	15.6	0.140
	Imipenem	96.8	91.8	-5	0.353
	Meropenem	96.8	91.9	-4.9	0.360
	Piperacillin/ Tazobactam	35.5	32.9	-2.6	0.797
	Trimethoprim/ sulfamethoxazole	38.5	29.4	-9.1	0.400
Klebsiella pneumoniae	Amikacin	89.3	100	10.7	0.002!
	Amoxicillin/ Clavulanic acid	40.5	51.9	11.4	0.144
	Cefepime	42.7	83	40.3	<0.001!
	Cefotaxime	43.2	48.1	4.9	0.535
	Cefoxitin	69.9	94.4	24.5	<0.001!
	Ceftazidime	41.7	53.9	12.2	0.107
	Cefuroxime	39.3	49.4	10.1	0.179
	Ciprofloxacin	60.7	65.9	5.2	0.480
	Colistin	98.7	100	1.3	0.309
	Gentamicin	54.8	55.7	0.9	0.903
	Piperacillin/ Tazobactam	44	77.5	33.5	<0.001!
	Trimethoprim/ sulfamethoxazole	24.1	42.7	18.6	0.010
Pseudomonas aeruginosa	Amikacin	94.4	100	5.6	0.058
	Cefepime	83.1	87.5	4.4	0.478
	Ceftazidime	85.9	89.1	3.2	0.582
	Ciprofloxacin	83.1	98.4	15.3	0.003!
	Gentamicin	90.1	100	9.9	0.010!
	Imipenem	74.3	65.1	-9.2	0.628
	Meropenem	74.3	68.8	-5.5	0.478
	Piperacillin/ Tazobactam	84.5	96.9	12.5	0.015!
Staphylococcus aureus	Cefoxitin	100	47.4	-52.6	0.003*
	Ciprofloxacin	88.2	71.9	-16.3	0.069
	Clindamycin	86.1	71.9	-14.2	0.111
	Cloxacillin	94.4	72.7	-21.7	0.009*
	Erythromycin	80.6	66.7	-13.9	0.146
	Moxifloxacin	86.2	68.2	-18	0.080
	Mupirocin	76.5	50	-26.5	0.098
	Oxacillin	94.4	88.9	-5.5	0.377
	Tetracycline	100	96.4	-3.6	0.056
	Trimethoprim/ sulfamethoxazole	77.1	82.5	5.4	0.533
Stenotrophomonas maltophilia	Trimethoprim/ sulfamethoxazole	97.1	98.1	1	0.765

NB: ! = Statistically significant increase in numbers of susceptible isolates; * = Statistically significant decrease in the number of susceptible isolates

4. DISCUSSION

To the best of our knowledge, we believe this is the first study to describe the susceptibility patterns of pathogens commonly associated with LRTIs in ICUs in Namibia. In addition, the first study to formulate cumulative antibiograms for identified pathogens. Alongside this, we believe this is the first study in Namibia to analyse changes in the susceptibility of pathogens causing LRTIs among the leading tertiary hospitals in Namibia over time. Our findings showed increases in the susceptibility of *A. baumanni, K. pneumoniae,* and *P. aeruginosa* to commonly tested antibiotics, and decreases in the susceptibility of *S. aureus* to penicillinase-resistant penicillins and cephalosporins.

Six of the seven organisms associated with LRTI in ICUs in Namibia, *P. aeruginosa, K. pneumoniae, E.coli, A. baumanii, Enterobacter sp.* and *S. aureus,* have been associated with LRTIs in other countries (39-42). However, there have been different frequencies. In Romania, the most common organisms were *A. baumannii* (64%), *Klebsiella sp.* (35%) and *S. aureus* (29%) (40). In Egypt, they were *K. pneumonia* (33.5%), *Staphylococcus spp*. (23.2%) and *E. coli* (19.3%) (41); while in Uganda they were *K. pneumonia*, *A. baumanii* and *P. aeruginosa* among others (16, 43). The differences may be associated with differences in the number of samples, which may be subject to study designs.

In Namibia, we also observed differences between and within hospitals regarding isolate types and their frequencies. For instance, *Enterobacter sp.* and *E. coli* were the most frequent organisms for ICU patients in Oshakati Intermediate Hospital in 2017, while for Windhoek Central Hospital these were *K. pneumoniae* and *P. aeruginosa*. Within the surveyed hospitals, from 2017 to 2018, the most frequent isolate in Oshakati Intermediate Hospital's ICU changed from *Enterobacter sp* to *P. aeruginosa*, with *P. aeruginosa* not among the isolates in 2017. In Windhoek Central Hospital in 2017, the most frequent isolates were *K. pneumoniae, P. aeruginosa, S. aureus, and E. coli*. However, in 2018, *E. coli* was replaced by *A. baumanii*, while the others remained on the list of isolates.

Encouragingly, the different organism isolates from the ICU of Windhoek Central hospital had similar susceptibilities in 2017 and 2018. *K. pneumoniae* isolates were highly susceptible to amikacin, colistin and carbapenems in both 2017 and 2018 showing a lack of resistance emergence. This is comparable with the results of a study conducted in Uganda where *K. pneumonia* was highly susceptible to amikacin and imipenem (16). In another study, *K. pneumoniae* isolates were less than 50% susceptible to all the antibiotics tested except colistin (44). In contrast to our findings though, a study conducted in the United State of America found that *K. pneumoniae* isolates were resistant to carbapenems (39). The susceptibility of *E. coli* to ciprofloxacin in Switzerland was 92.1% (45), higher than 70.7% recorded in our study. However, the susceptibility was not assessed in 2018 because the number of isolates were less than 30. *P. aeruginosa* isolates from Windhoek Central Hospital were more than 70% susceptible to all antibiotics tested in 2017 and more than 60% susceptible to all other antibiotics tested in 2018. This though contrasts with the findings in Romania where *P. aeruginosa* ICU isolates were poorly susceptible (< 30%) to all antibiotics tested (40). Alongside this, a study conducted in Uganda found that *P. aeruginosa* isolates were less susceptible to amikacin (16), which differs from our study.

Interestingly statistically significant increases in susceptibility to amikacin, second and fourth generation cephalosporins and piperacillin-tazobactam were noted for *K. pneumoniae* in our study; however, this change could not be explained. The 2018 Windhoek Central Hospital ICU cumulative antibiogram showed that *A. baumannii* isolates were more than 70% susceptible to tigecycline, carbapenems, amikacin and colistin. In this study, there was a statistically significant increase in the susceptibility of *A. baumanni* to amikacin from 75.9% to 93.3% from 2017 to 2018 (p=0.015); however, no explanation is currently available for this change. Nonetheless, the change may be associated with an increase in the number of *A. baumanni* isolates. *E. coli* isolates were highly susceptible to amikacin, carbapenems and tigecyclines, which is similar to the findings of a study in Egypt (41). However, there was a statistically significant decrease in the susceptibility of *S. aureus* to cefoxitin from 100% to 47.4% in our study. Moreover, there was also a decrease in the susceptibility of *S. aureus* to penicillinase resistant antibiotics. According to the Centre of Disease Control, Methicillin Resistant Staphylococcus Aureus (MRSA) may also be resistant to fluoroquinolones, erythromycin and clindamycin in addition to cephalosporins and carbapenems (46). The decrease in susceptibility rates to all these antibiotics was observed except for carbapenems because they were not tested. This indicated the egression of MRSA, which should be of great concern and activities should be undertaken to try and address this including enhancing appropriate antibiotic use within hospitals.

The within and between facility differences in organisms and their susceptibilities in our study emphasizes the need to conduct such studies across hospitals and countries to develop local antibiograms and guidelines. Namibia has already made great investments in culture and sensitivity services. The next step is to establish a health facility-based system to analyse local data for the development of local antibiograms and guidelines. Subsequently, research adherence to current guidelines building on previous studies in Namibia to improve future care (30, 31).

We are aware that the study has a number of limitations. Firstly, since the study used laboratory-based data, it cannot be established whether the infection is community-acquired or hospital-acquired. In addition, we only assessed resistance patterns in 3 ICUs in the country. Consequently, the findings cannot be generalised to other hospital ICUs or wards in Namibia. There was also irregularity in NIP antibiotics testing practices since with some organisms < 30 isolates were tested per antibiotics. However, despite these limitations we believe that this study did have interesting findings to help shape future antibiotic use in these hospitals and potentially wider.

5. CONCLUSION AND RECOMMENDATIONS

This study has demonstrated that local antibiograms should be developed to enhance appropriate use of antibiotics within hospitals and within ICUs. This is particulalry important during the current pandmic with antibiotics frequently prescribed in patients with COVID-19 across countries despite limited bacterial co-infections driving up AMR rates (9, 47-51).

Meropenem in combination with gentamicin is now the recommended empiric therapy for patients with LRTIs in Windhoek Central Hospital ICU based on the findings, and we are following this up in current research projects. Meropenem will cover gram-negative pathogens and gentamicin will cover *P. aeruginosa* and *S. Aureus* with aminoglycosides recommended for use in lower respiratory tract infections in clinical practice despite known poor lung penetration (52, 53). In addition, aminoglycosides and β-lactams are known to have a synergistic effects when used in combination (54).

Conflicts of interest

The authors declare they have no conflicts of interest to declare.

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REFERENCES

1. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Infectious diseases. 2018;18(11):1191-210.
2. Reiner RC, Welgan CA, Casey DC, Troeger CE, Baumann MM, Nguyen QP, et al. Identifying residual hotspots and mapping lower respiratory infection morbidity and mortality in African children from 2000 to 2017. Nat Microbiol. 2019;4(12):2310-8.
3. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet Infectious diseases. 2017;17(11):1133-61.
4. CDC in Namibia. Top 10 causes of death. 2020. Available at URL: https://www.cdc.gov/globalhealth/countries/namibia/pdf/Namibia_Factsheet.pdf.
5. REPUBLIC OF NAMIBIA Ministry of Health and Social Services NAMIBIA 2012/13 HEALTH ACCOUNTS REPORT. 2015. Available at URL: https://www.afro.who.int/sites/default/files/2017-10/Namibia%202012-13%20Health%20Accounts%20Report%20%20%2015%20July%20%202015-FINAL.pdf.
6. Pachori P, Gothalwal R, Gandhi P. Emergence of antibiotic resistance Pseudomonas aeruginosa in intensive care unit; a critical review. Genes & diseases. 2019;6(2):109-19.
7. Khan S, Priti S, Ankit S. Bacteria Etiological Agents Causing Lower Respiratory Tract Infections and Their Resistance Patterns. Iranian biomedical journal. 2015;19(4):240-6.
8. CDC. Pneumonia Can Be Prevented—Vaccines Can Help. 2020. Available at URL: https://www.cdc.gov/pneumonia/prevention.html.
9. Godman B, Egwuenu A, Haque M, Malande OO, Schellack N, Kumar S, et al. Strategies to Improve Antimicrobial Utilization with a Special Focus on Developing Countries. Life. 2021;11(6):528.

10. Jacobs MR, Felmingham D, Appelbaum PC, Grüneberg RN. The Alexander Project 1998-2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. The Journal of antimicrobial chemotherapy. 2003;52(2):229-46.
11. Gupta S, Khan W, Krishna A. Pattern of skin diseases and common drugs prescribed in dermatology OPD of an Indian tertiary care hospital. International journal of basic and clinical pharmacology. 2016;6:203-7.
12. Brusselaers N, Vogelaers D, Blot S. The rising problem of antimicrobial resistance in the intensive care unit. Annals of intensive care. 2011;1:47.
13. Zilahi G, Artigas A, Martin-Loeches I. What's new in multidrug-resistant pathogens in the ICU? Annals of intensive care. 2016;6(1):96.
14. Bernabe KJ, Langendorf C, Ford N, Ronat JB, Murphy RA. Antimicrobial resistance in West Africa: a systematic review and meta-analysis. International journal of antimicrobial agents. 2017;50(5):629-39.
15. Leopold SJ, van Leth F, Tarekegn H, Schultsz C. Antimicrobial drug resistance among clinically relevant bacterial isolates in sub-Saharan Africa: a systematic review. The Journal of antimicrobial chemotherapy. 2014;69(9):2337-53.
16. Agaba P, Tumukunde J, Tindimwebwa JVB, Kwizera A. Nosocomial bacterial infections and their antimicrobial susceptibility patterns among patients in Ugandan intensive care units: a cross sectional study. BMC research notes. 2017;10(1):349.
17. Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. PloS one. 2017;12(12):e0189621.
18. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. The Lancet Infectious diseases. 2019;19(1):56-66.
19. Godman B, Haque M, McKimm J, Abu Bakar M, Sneddon J, Wale J, et al. Ongoing strategies to improve the management of upper respiratory tract infections and reduce inappropriate antibiotic use particularly among lower and middle-income countries: findings and implications for the future. Current medical research and opinion. 2020;36(2):301-27.
20. Sánchez-Velázquez LD, Ponce de León Rosales S, Rangel Frausto MS. The burden of nosocomial infection in the intensive care unit: Effects on organ failure, mortality and costs. A nested case-control study. Archives of medical research. 2006;37(3):370-5.
21. Dasgupta S, Das S, Chawan NS, Hazra A. Nosocomial infections in the intensive care unit: Incidence, risk factors, outcome and associated pathogens in a public tertiary teaching hospital of Eastern India. Indian journal of critical care medicine. 2015;19(1):14-20.
22. Rosenthal VD, Maki DG, Salomao R, Moreno CA, Mehta Y, Higuera F, et al. Device-associated nosocomial infections in 55 intensive care units of 8 developing countries. Annals of internal medicine. 2006;145(8):582-91.
23. Kalanuria AA, Ziai W, Mirski M. Ventilator-associated pneumonia in the ICU. Critical care. 2014;18(2):208.
24. Kollef MH, Hamilton CW, Ernst FR. Economic Impact of Ventilator-Associated Pneumonia in a Large Matched Cohort. Infection Control & Hospital Epidemiology. 2012;33(3):250–6.
25. Feng DY, Zhou YQ, Zhou M, Zou XL, Wang YH, Zhang TT. Risk Factors for Mortality Due to Ventilator-Associated Pneumonia in a Chinese Hospital: A Retrospective Study. Medical science monitor. 2019;25:7660-5.
26. Guillamet MCV, Burnham JP, Kollef MH. Novel Approaches to Hasten Detection of Pathogens and Antimicrobial Resistance in the Intensive Care Unit. Seminars in respiratory and critical care medicine. 2019;40(4):454-64.
27. Timsit JF, Bassetti M, Cremer O, Daikos G, de Waele J, Kallil A, et al. Rationalizing antimicrobial therapy in the ICU: a narrative review. Intensive care medicine. 2019;45(2):172-89.
28. Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Annals of internal medicine. 2001;134(4):298-314.
29. Nusrat T, Akter N, Rahman NAA, Godman B, DT DR, Haque M. Antibiotic resistance and sensitivity pattern of Metallo-β-Lactamase Producing Gram-Negative Bacilli in ventilator-associated pneumonia in the intensive care unit of a public medical school hospital in Bangladesh. Hospital practice. 2020;48(3):128-36.
30. Nakwatumbah S, Kibuule D, Godman B, Haakuria V, Kalemeera F, Baker A, et al. Compliance to guidelines for the prescribing of antibiotics in acute infections at Namibia's national referral hospital: a pilot study and the implications. Expert review of anti-infective therapy. 2017;15(7):713-21.
31. Niaz Q, Godman B, Campbell S, Kibuule D. Compliance to prescribing guidelines among public health care facilities in Namibia; findings and implications. International journal of clinical pharmacy. 2020;42(4):1227-36.

32. Mwita JC, Ogunleye OO, Olalekan A, Kalungia AC, Kurdi A, Saleem Z, et al. Key Issues Surrounding Appropriate Antibiotic Use for Prevention of Surgical Site Infections in Low- and Middle-Income Countries: A Narrative Review and the Implications. Int J Gen Med. 2021;14:515-30.
33. Sefah IA, Essah DO, Kurdi A, Sneddon J, Alalbila TM, Kordorwu H, et al. Assessment of adherence to pneumonia guidelines and its determinants in an ambulatory care clinic in Ghana: findings and implications for the future. JAC Antimicrob Resist. 2021;3(2):dlab080.
34. De Bruycker M, Van den Bergh R, Dahmane A, Khogali M, Schiavetti B, Nzomukunda Y, et al. Non-adherence to standard treatment guidelines in a rural paediatric hospital in Sierra Leone. Public Health Action. 2013;3(2):118-24.
35. Gasson J, Blockman M, Willems B. Antibiotic prescribing practice and adherence to guidelines in primary care in the Cape Town Metro District, South Africa. South African medical journal. 2018;108(4):304-10.
36. Mengistu A, Gaeseb J, Uaaka G, Ndjavera C, Kambyambya K, Indongo L, et al. Antimicrobial sensitivity patterns of cerebrospinal fluid (CSF) isolates in Namibia: implications for empirical antibiotic treatment of meningitis. J Pharm Policy Pract. 2013;6:4.
37. WHO. WHONET Software Version 5.6. 2020. Available at URL: https://www.whonet.org/software.html.
38. WHO Africa Region. Disease Surveillance and Response Programme Area - Disease Prevention and Control Cluster. Guide for establishing laboratory-based surveillance for antimicrobial resistance. 2013. Available at URL: https://www.afro.who.int/sites/default/files/2017-06/guide-for-establishing-lab-based-surveillance-for-amr.pdf.
39. Claeys KC, Zasowski EJ, Trinh TD, Lagnf AM, Davis SL, Rybak MJ. Antimicrobial Stewardship Opportunities in Critically Ill Patients with Gram-Negative Lower Respiratory Tract Infections: A Multicenter Cross-Sectional Analysis. Infect Dis Ther. 2018;7(1):135-46.
40. Peneş NO, Muntean AA, Moisoiu A, Muntean MM, Chirca A, Bogdan MA, et al. An overview of resistance profiles ESKAPE pathogens from 2010-2015 in a tertiary respiratory center in Romania. Romanian journal of morphology and embryology. 2017;58(3):909-22.
41. Negm EM, Mowafy SMS, Mohammed AA, Amer MG, Tawfik AE, Ibrahim AES, et al. Antibiograms of intensive care units at an Egyptian tertiary care hospital. The Egyptian Journal of Bronchology. 2021;15(1):15.
42. Senbayrak Akcay S, Inan A, Cevan S, Ozaydın AN, Cobanoglu N, Ozyurek SC, et al. Gram-negative bacilli causing infections in an intensive care unit of a tertiary care hospital in Istanbul, Turkey. Journal of infection in developing countries. 2014;8(5):597-604.
43. Aruhomukama D, Najjuka CF, Kajumbula H, Okee M, Mboowa G, Sserwadda I, et al. bla(VIM)- and bla(OXA)-mediated carbapenem resistance among Acinetobacter baumannii and Pseudomonas aeruginosa isolates from the Mulago hospital intensive care unit in Kampala, Uganda. BMC Infect Dis. 2019;19(1):853.
44. Perovic O, Ismail H, Quan V, Bamford C, Nana T, Chibabhai V, et al. Carbapenem-resistant Enterobacteriaceae in patients with bacteraemia at tertiary hospitals in South Africa, 2015 to 2018. European Journal of Clinical Microbiology & Infectious Diseases. 2020;39(7):1287-94.
45. Kuster SP, Ruef C, Zbinden R, Gottschalk J, Ledergerber B, Neuber L, et al. Stratification of cumulative antibiograms in hospitals for hospital unit, specimen type, isolate sequence and duration of hospital stay. The Journal of antimicrobial chemotherapy. 2008;62(6):1451-61.
46. CDC. Laboratory Testing - Methicillin-resistant Staphylococcus aureus (MRSA). 2019. Available from URL: https://www.cdc.gov/mrsa/lab/index.html.
47. Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clinical microbiology and infection. 2021;27(4):520-31.
48. Hsu J. How covid-19 is accelerating the threat of antimicrobial resistance. BMJ. 2020;369:m1983.
49. Moretto F, Sixt T, Devilliers H, Abdallahoui M, Eberl I, Rogier T, et al. Is there a need to widely prescribe antibiotics in patients hospitalized with COVID-19? International journal of infectious diseases. 2021;105:256-60.
50. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clinical microbiology and infection. 2020;26(12):1622-9.
51. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
52. Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: An Overview. Cold Spring Harbor perspectives in medicine. 2016;6(6).
53. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections--full version. Clinical microbiology and infection. 2011;17 Suppl 6(Suppl 6):E1-59.

54. Lippincott’s Illustrated Reviews Pharmacology - 4th Edition. Book (Pharma). 2009.