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ORIGINAL ARTICLE

Antibiotic Guidelines for Critically Ill Patients in Nigeria

Directives Sur Les Antibiotiques Pour Les Patients Gravement Malades Au Nigeria

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ABSTRACT

BACKGROUND: It is well documented that inappropriate use of antimicrobials is the major driver of antimicrobial resistance. To combat this, antibiotic stewardship has been demonstrated to reduce antibiotic usage, decrease the prevalence of resistance, lead to significant economic gains and better patients' outcomes. In Nigeria, antimicrobial guidelines for critically ill patients in intensive care units (ICUs), with infections are scarce. We set out to develop antimicrobial guidelines for this category of patients.

METHODS: A committee of 12 experts, consisting of Clinical Microbiologists, Intensivists, Infectious Disease Physicians, Surgeons, and Anesthesiologists, collaborated to develop guidelines for managing infections in critically ill patients in Nigerian ICUs. The guidelines were based on evidence from published data and local prospective antibiograms from three ICUs in Lagos, Nigeria. The committee considered the availability of appropriate antimicrobial drugs in hospital formularies. Proposed recommendations were approved by consensus agreement among committee members.

RESULTS: *Candida albicans* and *Pseudomonas aeruginosa* were the most common microorganisms isolated from the 3 ICUs, followed by *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Escherichia coli*. Targeted therapy is recognized as the best approach in patient management. Based on various antibiograms and publications from different hospitals across the country, amikacin is recommended as the most effective empiric antibiotic against Enterobacterales and *A. baumannii,* while colistin and polymixin B showed high efficacy against all bacteria. Amoxicillin-clavulanate or ceftriaxone was recommended as the first-choice drug for community-acquired (CA) CA-pneumonia while piperacillin-tazobactam + amikacin was recommended as first choice for the treatment of healthcare-associated (HA) HA-pneumonia. For ventilator-associated pneumonia (VAP), the consensus for the drug of first choice was agreed as meropenem. Amoxycillin-clavulanate +clindamycin was the consensus choice for CA-skin and soft tissue infection (SSIS) and piperacillin-tazobactam + metronidazole ±vancomycin for HA-SSIS. Ceftriaxone-tazobactam or piperacillin-tazobactam + gentamicin was consensus for CA-blood stream infections (BSI) with first choice +regimen for HA-BSI being meropenem/piperacillin-tazobactam + amikacin +fluconazole. For community-acquired urinary tract infection (UTI), first choice antibiotic was ciprofloxacin or ceftriaxone with a catheter-associated UTI (CAUTI) regimen of first choice being meropenem + fluconazole.

CONCLUSION: Data from a multicenter three ICU surveillance and antibiograms and publications from different hospitals in the country was used to produce this evidence-based Nigerian-specific antimicrobial treatment guidelines of critically ill patients in ICUs by a group of experts from different specialties in Nigeria. The implementation of this guideline will facilitate learning, continuous improvement of stewardship activities and provide a baseline for updating of guidelines to reflect evolving antibiotic needs. **WAJM 2023; 40(9): 962–972.**

Keywords: Antimicrobials, Antimicrobial resistance, Antibiotic stewardship, Guidelines, Critical care, Intensive care unit, Healthcare associated infections.

RÉSUMÉ

CONTEXTE: Il est bien établi que l'utilisation inappropriée des antimicrobiens est le principal moteur de la résistance aux antimicrobiens. Pour lutter contre ce phénomène, il a été démontré que la bonne gestion des antibiotiques permettait de réduire l'utilisation des antibiotiques, de diminuer la prévalence de la résistance, de réaliser des gains économiques significatifs et d'améliorer les résultats pour les patients. Au Nigéria, les directives antimicrobiennes pour les patients gravement malades dans les unités de soins intensifs (USI), souffrant d'infections, sont rares. Nous avons entrepris d'élaborer des lignes directrices sur les antimicrobiens pour cette catégorie de patients.

MÉTHODES UTILISÉES: Un comité de 12 experts, composé de microbiologistes cliniques, d'intensivistes, de médecins spécialistes des maladies infectieuses, de chirurgiens et d'anesthésistes, a collaboré à l'élaboration de lignes directrices pour la prise en charge des infections chez les patients gravement malades dans les unités de soins intensifs nigérianes. Les lignes directrices sont basées sur des données publiées et des antibiogrammes prospectifs locaux provenant de trois unités de soins intensifs de Lagos, au Nigeria. Le comité a pris en compte la disponibilité des médicaments antimicrobiens appropriés dans les formulaires des hôpitaux. Les recommandations proposées ont été approuvées par consensus entre les membres du comité.

RÉSULTATS: *Candida albicans* et *Pseudomonas aeruginosa* étaient les micro-organismes les plus fréquemment isolés dans les trois unités de soins intensifs, suivis par *Klebsiella pneumoniae, Acinetobacter baumannii* et *Escherichia coli.* La thérapie ciblée est reconnue comme la meilleure approche pour la prise en charge des patients. Sur la base de divers antibiogrammes et publications provenant de différents hôpitaux du pays, l'amikacine est recommandée comme l'antibiotique empirique le plus efficace contre les entérobactéries et *A. baumannii,* tandis que la colistine et la polymixine B se sont révélées très efficaces contre toutes les bactéries. L'amoxicilline-clavulanate ou la ceftriaxone ont été recommandées comme médicaments de premier choix pour les pneumonies communautaires, tandis que la pipéracilline-tazobactam + amikacine ont été recommandées comme médicaments de premier choix pour le traitement des pneumonies associées aux soins. Pour les pneumonies acquises sous ventilation mécanique (PAV), le consensus sur le médicament de premier choix est le méropénem. L'amoxycilline-clavulanate +clindamycine était le choix consensuel pour les infections de la peau et des tissus mous et la pipéracilline-tazobactam + métronidazole ±vancomycine pour les infections de la peau et des tissus mous. HA-SSIS. Ceftriaxone-tazobactam ou pipéracilline-tazobactam + gentamicine a fait l'objet d'un consensus pour les infections de la circulation sanguine de l'AC (BSI), le premier choix de régime pour les HA-BSI étant le méropénem/pipéracilline-tazobactam +amikacine +fluconazole. Pour les infections urinaires communautaires, l'antibiotique de premier choix était la ciprofloxacine ou la ceftriaxone, le régime de premier choix pour les infections urinaires associées à un cathéter étant le meropenem +fluconazole.

CONCLUSION: Les données issues d'une surveillance multicentrique de trois unités de soins intensifs, d'antibiogrammes et de publications de différents hôpitaux du pays ont été utilisées par un groupe d'experts de différentes spécialités nigérianes pour élaborer ces lignes directrices sur le traitement antimicrobien des patients gravement malades dans les unités de soins intensifs, fondées sur des données probantes et spécifiques au Nigeria. La mise en œuvre de ces lignes directrices facilitera l'apprentissage, l'amélioration continue des activités de gestion et fournira une base de référence pour la mise à jour des lignes directrices afin de refléter l'évolution des besoins en antibiotiques. **WAJM 2023; 40(9): 962–972.**

Mots clés: Antimicrobiens, Résistance aux antimicrobiens, Gestion des antibiotiques, Lignes directrices, Soins intensifs, Unité de soins intensifs, Infections associées aux soins de santé

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INTRODUCTION

In the past, the management of intensive care units (ICUs) patients was interventional which was often supported with little clinical evidence.[1] Many of the patients admitted into these early ICUs were managed by their various primary admitting specialists, who could be internal medicine physicians, anaesthesiologists, or surgeons. The concept of critical care became necessary as it became apparent that severely ill or injured patients could benefit from closer attention than was provided to less severely ill patients.[1] Since the establishment of ICUs in the late 1950s, there has been an improved understanding of the pathophysiology and pathogenesis of disease processes in critically ill patients. In addition, the care of the critically ill has improved tremendously over the years and the need for a multidisciplinary approach to patient care has become apparent and accorded necessary recognition.[2] Increasingly, infectious disease/ clinical microbiology consultants, nutritionists, pharmacists, physiotherapists, and members of other relevant specialities are included in the care of critically ill patients. It is noteworthy that many tertiary hospitals in Nigeria have established critical care facilities for the care of the critically ill patients.[3–6]

One of the major indications for intensive care of patients is infectious disease which is often associated with high morbidity, mortality and cost of care. Healthcare-associated pneumonia (HAP) and ventilator-associated pneumonia (VAP), urinary tract infection (UTI) (usually catheter-associated), primary bloodstream infection (BSI) (associated with the usage of an intravascular device) and surgical site infections (SSI), account for most ICU infections.[7–8] Such infections are often acquired while receiving care in the ICU as some of the patients admitted into these units have impaired immunity and thus are at high risk of acquiring nosocomial infections. In addition, they are susceptible to secondary infections such as candidiasis and pseudomembranous colitis (*Clostridioides difficile* infection (CDI)) which arise from the elimination of protective microorganisms by the administration of broad-spectrum antibiotics and instrumentation.[8–10]

Antibiotics have been used successfully to treat infections thus decreasing associated morbidity and mortality.[11] However, recent evidence suggests that the gains achieved through antibiotic therapy are threatened by the development of antimicrobial resistance (AMR) in both hospital and community settings.[12–15]

Mounting evidence suggests that infections caused by antimicrobial-resistant bacteria are on the rise in low/ middle-income countries and in the developed world.[2,15,16] A recent World Health Organisation (WHO) report showed that Africa had the largest gap in data on the prevalence of AMR.[17] This gap is largely due to the limited laboratory capacity and surveillance network. However, some studies have revealed information regarding the prevalence of AMR in African settings. Such studies include a systematic review that documented the microbiology of major bacterial syndromes encountered in hospitals in West Africa. This review, involving 43 studies (35.8%) on UTI, 38 (31.7%) BSI, 27 (22.5%) meningitis, 7 (5.8%) diarrhoea and 5 (4.2%) pneumonia, estimated the prevalence of AMR that could compromise first-line empirical treatment such as ampicillin, cotrimoxazole, gentamicin and amoxicillin-clavulanate.[18] The authors noted that AMR is quite common in West Africa, especially hospital-acquired bloodstream infections and urinary tract infections in general.[18]

Evidence available in the literature shows that the prevalence of multidrug-resistant organisms (MDROs) in Nigeria is high.[19–23] The consequence of these observations is the drastic limitation in the options available for treating infections caused by these MDROs.[21,24–26] In addition, they constitute a major infection control challenge.[27,28] The scenario is worse in the ICUs where antibiotics are used extensively and most often irrationally.[29–32]

With the increasing incidence of AMR, there is the need to create national, regional and international surveillance systems to monitor antibiotic resistance and microbiology patterns. Furthermore, the need for clinical practice guidelines for antibiotic use in critical care cannot be overemphasized. The main objective of this study was to investigate the common etiological agents of infections in critically ill patients in Nigeria and propose guidelines for the treatment of infections in Nigerian ICUs.

MATERIALS AND METHODS

Antimicrobial Resistance Surveillance

A prospective nine-month antimicrobial surveillance study was conducted across three intensive care units in Lagos (Lagos University Teaching Hospital, Marigold Hospital and Lagoon Hospital). This study was conducted from January 2020 to September, 2020 in all three ICUs. The cosmopolitan city of Lagos has an estimated population of over 21 million people with two public tertiary hospitals, six general (secondary), several public and private healthcare facilities. Approval to carry out research was obtained from the Ethics and Research Committee of the Lagos University Teaching Hospital (LUTH), Idi-Araba-Reference number; ADM/DCST/HREC/APP/3372; on 29 November 2019. Informed consent was obtained from all study participants. Surveillance data collated from these sites was used as evidence base in the development of these guidelines, all protocols were compliant with the Helsinki Declaration of 1975.

Case Definitions

ICU-acquired infection was defined as infection developing after 48 hours of admission into ICU or infections manifesting within 48 hours of discharge from ICU. The infection was therefore not present, nor incubating on admission to the ICU. The definition of individual ICU-acquired infection adopted was that proposed by the Centers for Diseases Control and Prevention with minimal modification.[8]

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Investigating Infections in the Critically Ill Patient

A variety of samples, such as aspirate, blood, urine, sputum, abscess, wound swab, biopsy, pleural fluid, tracheostomy tube fluid, endotracheal

tube fluid, bronchoalveolar lavage, were collected from patients in the ICUs whenever there was clinical suspicion of site-specific infection. Each specimen was collected aseptically. Twenty (20) ml of blood was collected from adult patients and dispensed into a set of Bactec (BD Diagnostic. New Hampshire, USA) or BactAlert (bioMerieux) blood culture bottles for all cases of sepsis. All specimens were processed within 1–2 hours of collection to enhance recovery of pathogens.[1] Aspirates and biopsies from the sites of infection were collected and inoculated onto blood and MacConkey agar (Oxoid Reading, UK) for ambient air culture and onto gentamicin-blood agar for anaerobic culture. Tissue samples were kept moist during transportation to preserve viability of pathogens.

Identification of the organisms and antimicrobial susceptibility testing was done using Vitek-2 compact (bioMerieux, Marcy-l'Etoile, France).

Data Analysis

The analysis was done with Statistical Package for the Social Sciences (SPSS) software (version 24). Continuous variables were presented as the mean ± standard deviation. Categorical variables were presented as actual numbers and percentages or as bar charts.

Formulating of Antibiotic Guidelines

A committee of 12 relevant experts; made up of Clinical Microbiologists, Intensivist, Infectious Disease Physicians, Chest physician and Surgeon was assembled. The committee of experts, consisting of individuals with a range of specialized knowledge and experience, was carefully selected to ensure that all aspects of infection management were adequately covered. The committee members worked collaboratively to review and analyze the available evidence-based data, including published literature, local and regional antibiograms, and hospital formularies.

Prospective antibiograms from three ICUs in different parts of Lagos, Nigeria, were examined to identify local patterns of antimicrobial resistance and guide the selection of appropriate antibiotics. The committee also reviewed the availability of antimicrobial agents in hospital formularies to ensure that the recommended antibiotics were readily accessible and could be easily obtained by healthcare providers.

Throughout the process, the committee members engaged in active discussions and debates to ensure that all recommendations were evidence-based and supported by available data. They worked to reach a unanimous consensus agreement on the recommended antibiotics, dosages, and durations of treatment for specific infections. The final guidelines were based on a thorough review of the available evidence, taking into consideration local patterns of antimicrobial resistance, the availability of antimicrobial agents, and patient-specific factors.

RESULTS

A total of 311 samples were obtained from 157 patients. The leading source of these samples was blood, accounting for 43.9% (n=129), followed by UTI with 31.6% (n=93), RTI with 12.9% (n=38), SSTI with 11.6% (n=34), and the remaining 1% (n=1) from other sources. The analysis showed that gram-negative bacteria were the most prevalent, found in 65.4% of the samples, followed by gram-positive bacteria in 13.0% and fungi in 21.6%.

The most common microorganisms isolated from across hospital ICUs, were *Candida albicans* 24 (14.8%) and *Pseudomonas aeruginosa* 23 (14.2%). Other common organisms were *Klebsiella pneumoniae* 23(14.2%), followed by *Acinetobacter baumannii* 16(9.9%) and *Escherichia coli* 11(6.8%). The complete profile of the various microorganisms isolated and the corresponding infection types is shown in Figure 1. *Klebsiella pneumoniae* was the most isolated pathogen from BSI. *Candida albicans* was observed as the most isolated pathogen from UTI while *Pseudomonas aeruginosa* was the most isolated pathogen from skin and soft tissue infections (SSTI) and reproductive tract infections RTI.

The efficacy of 22 antibiotics against 58 Enterobacteriaceae, 23 *P. aeruginosa*, 18 *A. baumannii*, and other bacteria showed that amikacin was the most effective against Enterobacteriaceae (57.9%) and *A. baumannii* (55.6%). Colistin and polymixin B showed high efficacy against all the bacteria (96–100%). On the other hand, nitrofurantoin was least effective against Enterobacteriaceae (25.0%). As depicted in Table 1, amoxicillin/clavulanic acid, Ampicillin/sulbactam, cefuroxime, and tobramycin showed low efficacy against the bacteria. The presence of ESBL was detected in 16 isolates (28.1%).

When findings were disaggregated across different infections, for infections caused by gram-positive bacteria, there was universal susceptibility to Vancomycin and Tigecycline as shown in Table 2.

We found all isolates across all gram-negative isolates across all infection types in this study were universally susceptible (100.0%) to colistin and polymixin B. Both BSI and UTI isolates had universal susceptibility to tigecycline. Isolates from BSI were 91.0% susceptible to linezolid. As shown in Table 3, isolate susceptibility was lowest with penicillin beta-lactam combination across all infections. The only central nervous system (CNS) infection was caused by pan-drug-resistant *Enterobacter cloacae*.

Consensus Empirical Treatment Recommendations

Management of Sepsis in Critically ill Patients

Respiratory Tract Infections

Recommended empirical antibiotic treatments for respiratory tract infections is shown in supplemental Table 1. It differentiates between community-acquired pneumonia, healthcare-associated, and ventilator-associated pneumonia, and lists the expected causative organisms for each type of infection. For community-acquired pneumonia, amoxicillin-clavulanate or ceftriaxone is recommended as the first choice, while for healthcare-associated pneumonia, the first choice is piperacillin-tazobactam plus amikacin. For ventilator-associated pneumonia, meropenem is the first choice for both *Pseudomonas* and non-*Pseudomonas* infections, and

Table 1: A Comparison of Antibiotic Susceptibility Profile of *Enterobacteriaceae A. baumannii*, *P. aeruginosa*, and other non-Fermenters

Antibiotic Name	*Enterobacteriaceae* N = 58 (S%)	*P. aeruginosa* N = 23 (S%)	*A. baumannii* N = 18 (S%)	*Burkholderia cepacia N=5 Stenotrophomonas maltophilia N=2*
Amikacin (AMK)	33 (57.9)	4 (17.4)	10 (55.6)	–
Amoxicillin/Clavulanic acid (AMC)	2 (3.5)	–	–	–
Ampicillin/Sulbactam (SAM)	2 (3.5)	–	3 (16.7)	–
Aztreonam (AZT)	6/26 (23.1)	1/15 (6.7)		–
Cefepime (FEP)	15 (25.9)	2 (8.7)	3 (16.7)	–
Cefoxitin (FOX)	16 (27.7)	–	–	–
Ceftazidime (CAZ)	11 (19.0)	3 (13.0)	4 (22.2)	5/5 (100.0)
Ceftriaxone (CRO)	8 (13.8)	–	1 (5.6)	–
Cefuroxime (CXM)	3 (5.2)	–	–	–
Ciprofloxacin (CIP)	10 (17.2)	3 (13.0)	6 (33.3)	–
Colistin (COL)	24/25 (96.0)	15/15 (100.0)	6/6 (100.0)	–
Ertapenem (ETP)	30 (51.7)	–	–	–
Gentamicin (CN)	16 (27.6)	4 (17.4)	7 (38.9)	–
Imipenem (IPM)	32 (55.2)	3 (13.0)	4 (22.2)	–
Levofloxacin (LVX)	18 (31.0)	4 (17.4)	7 (38.9)	3/5 (66.7)2/2 (100.0)
Meropenem (MEM)	32 (55.2)	3 (13.0)	4 (22.2)	5/5 (100.0)
Nitrofurantoin (F)	7/29 (24.1)	–	–	–
Piperacillin	10 (17.2)	1 (4.4)	3 (16.7)	–
Piperacillin/Tazobactam (TZP)	9/26 (34.6)	1/15 (6.7)	0/6 (0.0)	–
Polymixin B (POL)	24/25 (96.0)	15/15 (100.0)	6/6 (100.0)	–
Tobramycin (TOB)	5/38 (13.2)	4 (17.4)	10 (55.6)	–
Cotrimoxazole (SXT)	6/35 (16.7)	–	3/13 (23.1)	5/5 (100.0) 0/2 (0.00)
ESBL	16 (28.1)			

Table 2: A Comparison of Antibiotic Susceptibility Profile of *Enterococcus species, Staphylococcus species, S. pneumoniae* and *Candida species*

Antibiotic Name	*Enterococcus spp* n = 7	*S. aureus* N = 5	*Staphylococcus spp* N = 8	*S. pneumoniae N = 1*	*Candida species* N = 15 (S%)
Amikacin (AMK)		0 (0.0)	2/4 (50.0)	–	–
Ampicillin (AMP)	3/5 (60.0)				–
Cefoxitin (FOX)		0 (0.0)	5/8 (62.5)	–	–
Ciprofloxacin (CIP)	2/7 (28.6)	0 (0.0)	1/8 (12.5)	–	–
Clindamycin (CLI)		0 (0.0)	3/8 (37.5)	0 (0.0)	–
Doxycycline (DOX)		1 (20.0)	3/8 (37.5)	0 (0.0)	–
Erythromycin (ERY)	1/5 (20.0)	0/5 (0.0)	0/8 (0.0)	0 (0.0)	–
Gentamicin (CN)	3/6 (50.0)	0 (0.0)	2/8 (25.0)	–	–
Levofloxacin (LVX)	2/7 (28.6)	0 (0.0)	1/8 (12.5)	1 (100.0)	–
Linezolid (LNZ)	6/7 (85.7)	5 (100.0)	7/8 (87.5)	0 (0.0)	–
Nitrofurantoin[B] (F)	3/3 (100.0)	–	1/1 (100.0)	–	–
Oxacillin (OXA)		–	0/4 (0.0)	0 (0.0)	–
Penicillin (PEN)	3/5 (60.0)	0 (0.0)	0/8 (0.0)	0 (0.0)	–
Rifampin (RIF)		–	4/4 (100.0)	–	–
Cotrimoxazole (SXT)		0 (0.0)	2/6 (33.3)	0 (0.0)	–
Vancomycin (VAN)	7/7 (100.0)	–	4/4 (100.0)	–	–
Quinupristin /Dalfopristin (QDA)	3/6 (50.0)	–	4/4 (100.0)	–	–
Streptomycin (STH)	1/4 (25.0)				–
Tetracycline (TCY)	2/5 (40.0)	–	2/4 (50.0)	–	–
Tigecycline (TIG)	7/7 (100.0)	–	2/2 (100.0)	–	–
Fluconazole	–	–	–	–	14 (93.3)
Voriconazole	–	–	–	–	14 (93.3)
Caspofungin	–	–	–	–	14 (93.3)
MRSA		5 (100.0)	6/8 (75.0)	–	–

R, Resistant; S, Sensitive; I, Intermediate; NT, Not tested. Numbers are percentage-resistant.

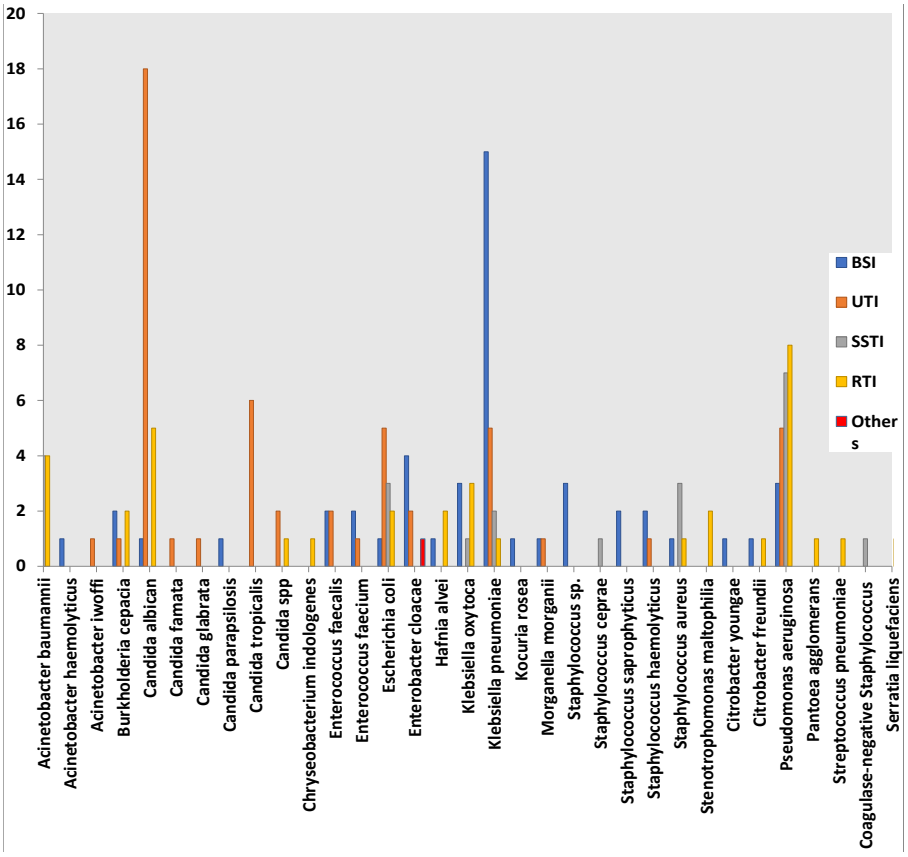

Fig. 1: Pathogen Distribution Across Site of Infection.
Key: RTI – Respiratory Tract Infection. SSTI – Skin and Soft tissue infection. UTI – Urinary tract infection. BSI – Blood stream infection.

meropenem plus colistin or polymyxin B is recommended as second choice for *Pseudomonas* infections and meropenem + tigecycline recommended for non-*Pseudomonas* infections.

Footnote:
Community-acquired pneumonia/ Healthcare-associated pneumonia in CKD patients who have undergone dialysis, piperacillin-tazobactam + doxycycline is recommended. For non-*Pseudomonas* VAP, meropenem + tigecycline combination is recommended while meropenem + polymyxin B is for *Pseudomonas* VAP. Nebulized amino-glycosides and polymyxins are recommended for severe VAP. CKD = chronic kidney disease; VAP = ventilator-associated pneumonia.

Surgical Site Infections: For repeated surgeries, meropenem + tigecycline is recommended. For abdominal surgical site infection, we recommend cefepime-tazobactam + metronidazole. Where there is polymicrobial infection or suspected toxic shock syndrome, β-lactam + clindamycin combination is recommended.

Urinary Tract Infections: Fluconazole 20mg 12 hourly is recommended when *Candida* spp. are isolated from urine samples.

Skin and Soft Tissue Infections (Including Surgical Site Infections)

The supplemental Table 1 above, provides guidance on what antibiotics to use for skin and soft tissue infections. It breaks down the recommendations into two categories: Community and healthcare-associated. The first choice of antibiotics for community-acquired infections is a combination of amoxicillin-clavulanate and clindamycin, while for healthcare-associated infections, the first choice is a combination of piperacillin-tazobactam and metronidazole.

Blood Stream Infections (BSI)

For community-acquired blood stream infections as in supplemental table 1 above, the most likely causative agents are *Streptococcus pneumoniae* and *Klebsiella pneumoniae*, and the first choice of treatment is either ceftriaxone-tazobactam or piperacillin-tazobactam and gentamicin. In the case of healthcare-associated blood stream infections, a wider range of organisms can cause the infection, including *Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus*, and others. The recommended first choice of treatment is a combination of either meropenem or piperacillin-tazobactam, along with amikacin and fluconazole.

Urinary Tract Infections (UTI)

For community acquired UTI, as shown in supplemental Table 1 above, recommended first-choice treatment is ciprofloxacin or ceftriaxone. For healthcare-associated UTI, the expected causative organisms are *Candida species, Escherichia coli, Klebsiella pneumoniae*, recommended first-choice treatment is meropenem and fluconazole. Fluconazole 20mg BD is recommended when *Candida* spp. are isolated from urine samples.

The Table 4 below, provides information about standard and high dose antibiotic treatments for various infections. Each antibiotic has a standard dose and a high dose, which is typically used in the case of more severe infections. It is important to note that the high doses listed are not applicable for all infections and should be used under the guidance of a medical professional.

Foot Note

1. Aminoglycosides given over 30–60-minute as infusion, nebulized in respiratory tract infections
2. Vancomycin infusion should be over 60 minutes.
3. Never use rifampicin as a single antibiotic or before infection shows improvement (or risk rifampicin resistance).
4. Consider that SS tablet has 80mg of TMP, DS tablet 160mg of TMP.

Table 3: Comparison of Antimicrobial Susceptibilities of Blood Stream Infection, Respiration Tract Infections, Skin and Soft Tissue Infection and Urinary Tract Infection

Antibiotic name	Blood Stream Infection (BSI) (S%)	Respiration Tract Infections (RTI) (S%)	Skin and Soft Tissue Infection (SSTI) (S%)	Urinary Tract Infection (UTI) (S%)
Amikacin (AMK)	25/39 (64.1)	8/25 (32.0)	5/20 (25.0)	11/23 (20.8)
Amoxicillin/Clavulanic acid (AMC)	2/28 (7.1)	0/11 (0.0)	0/6 (0.0)	0/12 (0.0)
Ampicillin/Sulbactam (SAM)	5/19 (26.3)	0/6 (0.0)	0/6 (0.0)	0/11 (0.0)
Aztreonam (ATM)	2/9 (22.2)	3/16 (18.8)	1/8 (12.50)	1/7 (14.3)
Cefepime (FEP)	14/35 (40.0)	4/24 (16.7)	0/16 (0.0)	2/23 (8.7)
Cefoxitin (FOX)	13/35 (37.1)	4/12 (33.3)	1/10 (10.0)	3/13 (23.1)
Ceftazidime (CAZ)	14/37 (37.8)	5/26 (19.2)	2/16 (12.5)	3/24 (12.5)
Ceftriaxone (CRO)	5/33 (15.2)	3/15 (20.0)	1/10 (10.0)	0/17 (0.0)
Cefuroxime (CXM)	2/27 (7.4)	0/10 (0.0)	–	0/10 (0.0)
Ciprofloxacin (CIP)	15/46 (32.6)	4/25 (16.0)	1/20 (5.0)	3/27 (11.1)
Clindamycin (CLI)	3/7 (42.9)	0/2 (0.0)	0/4 (0.0)	–
Colistin (COL)	11/11 (100.0)	18/18 (100.0)	8/8 (100.0)	8/8 (100.0)
Doxycycline (DOX)	–	–	–	–
Ertapenem (ETP)	18/28 (64.3)	5/11 (45.5)	3/7 (42.9)	3/12 (25.0)
Erythromycin (ERY)	1/11 (9.1)	0/2 (0.0)	0/4 (0.0)	–
Gentamicin (CN)	16/46 (34.8)	8/25 (32.0)	2/20 (10.0)	6/26 (23.08)
Imipenem (IPM)	17/29 (58.6)	6/23 (26.1)	4/16 (25.0)	5/21 (23.8)
Levofloxacin (LVX)	24/47 (51.1)	8/29 (27.6)	1/20 (5.0)	5/28 (17.9)
Linezolid (LNZ)	10/11 (90.9)	1/2 (50.0)	4/4 (100.0)	3/4 (75.0)
Meropenem (MEM)	25/37 (67.57)	9/26 (34.6)	4/16 (25.0)	6/24 (25.0)
Oxacillin (OXA)	0/3 (0.0)	0/1 (0.0)	–	–
Penicillin (PEN)	2/10 (20.0)	0/2 (0.0)	0/4 (0.0)	–
Piperacillin (PIP)	8/35 (22.9)	1/23 (4.4)	1/16 (6.3)	3/23 (13.0)
Piperacillin/Tazobactam (TZP)	4/11 (36.4)	2/19 (10.5)	2/8 (25.0)	2/8 (25.0)
Polymixin B (POL)	11/11 (100.0)	18/18 (100.0)	8/8 (100.0)	8/8 (100.0)
Tobramycin (TOB)	9/29 (31.0)	3/17 (17.7)	3/12 (25.0)	5/20 (25.0)
Cotrimoxazole (SXT)	9/32 (28.1)	4/11 (36.4)	0/10 (0.0)	3/14 (21.4)
Vancomycin (VAN)	7/7 (100.0)	–	–	4/4 (100.0)
Quinupristin /Dalfopristin (QDA)	5/7 (71.4)	–	–	2/3 (66.7)
Tetracycline (TCY)	2/7 (28.6)	–	–	–
Tigecycline (TIG)	5/5 (100.0)	–	–	4/4 (100.0)
ESBL	7/49 (14.3)	4/36 (11.1)	2/20 (10.0)	3/56 (5.4)
MRSA	5/49 (10.2)	1/36 (2.8)	4/20 (20.0)	1/56 (1.8)

5. Additional monitoring. Maximal duration of treatment: 28 days.
   IV – intravenous, PO- per oral, NB-Nebulized.

DISCUSSION

Since their introduction more than 70 years ago, antibacterial drugs (antibiotics) have become an important part of the inventory in the modern healthcare landscape, allowing the treatment of severe bacterial infections.[33] However, limiting abuse and misuse of valuable drugs by utilizing them judiciously, would reduce the risk of toxicity, selection of pathogenic organisms and the development of resistance.

Intensive or critical care is a recently improved area of medical practice and many tertiary hospitals in Nigeria have developed facilities for the care of critically ill patients. However, many of these centres do not have fully/well-equipped Intensive Care Units (ICUs) and those existing have thinned out resources resulting in unnecessary pressure placed on available resources. Therefore, intensive care services in Nigeria have remained largely in its infancy despite recent attempts by the private sector to overcome the funding impediments experienced by the public institutions.[4,5,34]

This antimicrobial guidance outlines recommendations for antimicrobial use in critically ill patients and provides accessible information on antimicrobial therapeutic management of the most common infections. However, in certain instances, it may be necessary to prescribe off the antibiotic guide, especially in a situation where the condition requiring treatment is not included here.

This guidance recommends combination therapy as empirical therapy for infections in the critically ill while

Supplemental Table 1: Empiric Therapeutic Agents for different Infections

Site of Infection: **Respiratory tract infections**

Patient Background	Expected Causative Organisms	Drug Recommendations		
		First Choice	Second Choice	Third Choice
Community acquired pneumonia	*S. pneumoniae* *S. pyogenes* *K. pneumoniae*	Amoxicillin-Clavulanate/Ceftriaxone	Amoxicillin-Clavulanate ± Amikacin	Vancomycin + Meropenem
Healthcare-associated pneumonia	*K. pneumoniae* *A. baumannii* *P. aeruginosa*	Piperacillin-Tazobactam + Amikacin	Meropenem	Meropenem + Amikacin
Ventilator associated pneumonia	*A. baumannii* *P. aeruginosa*	Meropenem	For non-Pseudomonas VAP, recommend Meropenem + Tigecycline	For Pseudomonas VAP Meropenem + Colistin/Polymyxin B

Site of Infection: **Skin and Soft Tissue Infections**

Patient Background	Expected Causative Organisms	Drug Recommendations		
		First choice	Second Choice	Third Choice
Community Acquiredpneumonia	*S. aureus* *S. pyogenes* *P. æruginosa*	Amoxicillin-clavulanate + Clindamycin	Piperacillin-Tazobactam + Clindamycin	Piperacillin-Tazobactam + Vancomycin
Healthcare Associated pneumonia	*S. aureus* *P. aeruginosa* *E. coli A. baumannii*	Piperacillin-Tazobactam + Metronidazole ±Vancomycin	Meropenem + Metronidazole ± Vancomycin /Linezolid	Meropenem + Tigecycline

Site of Infection: **Blood Stream Infections**

Patient Background	Expected Causative Organisms	Drug Recommendations		
		First Choice	Second Choice	Third Choice
Community acquired BSI	*S. pneumoniae* *K. pneumoniae*	Ceftriaxone-tazobactam or Piperacillin-tazobactam + Gentamicin	Meropenem + Vancomycin/ Levofloxacin	
Healthcare-associated BSI	*A. baumannii* *E. cloacae* *Candida spp* *K. pneumoniae* *E. coli P. æruginosa* *S. aureus* *S. marcescens*	Meropenem/ Piperacillin-tazobactam + Tigecycline + Voriconazole	Meropenem/ Piperacillin-Tazobactam + Tigecycline + Voriconazole	Colistin/ Polymixin B + Tigecycline + Caspofungin / Amphotericin B

Site of Infection: **Urinary Tract Infections**

Patient Background	Expected Causative Organisms	Drug Recommendations		
		First Choice	Second Choice	Third Choice
Community acquired UTI	*Enterobacteriaceae* *Candida species*	Ciprofloxacin or Ceftriaxone	Levofloxacin or Ceftriaxone-tazobactam + Fluconazole	Meropenem + Fluconazole
Catheter associated UTI / Healthcare associated UTI	*Candida species* *A. baumannii* *E. coli S. aureus* *K. pneumoniae* *P. aeruginosa*	Meropenem + Fluconazole	Meropenem + Fosfomycin + Voriconazole	Meropenem + Colistin/ Tigecycline + Caspofungin / Amphotericin B

Table 4: Antibiotic Dosing

Antibiotic	Standard Dose	High Dose	Paediatric Patients
Amikacin IV/NB[1]	25–30 mg/kg once daily IV or 500–750 mg x 2 doses by nebulization		15mg/kg once daily (max 1.5g/day)High dose: 7.5–10mg/kg 8hrly (Max 500mg 8hrly)
Amoxicillin + Clavulanic Acid IV	1 g amoxicillin + 0.2 g clavulanic acid x 3–4 doses	2 g Amoxicillin + 0.2 g clavulanic acid x 3 doses	1 month–12 years: 18–27mg/kg/dose bd (maximum x 1440mg/dose bd) High dose: 60mg/kg/dose BD or 30mg/kg/dose qds
Azithromycin IV/PO	0.5 g x once daily		10mg/kg once daily (max 500mg daily) for 5days (extended dose – 7days)
Cefepime IV		2 g x 3 doses	50mg/kg/dose 12hrly (max 2g, 12hrly)High dose: 50mg/kg/dose 8hrly (max 2g 8hrly)
Ceftriaxone IV	2 g once daily	2 g x 2 doses meningitis, *S. aureus:* High dose only	50–80mg/kg/day (max 4g per day)High dose: 50mg/kg/dose 12hrly
Ceftazidime IV		2 g x 3 doses	50mg/kg/dose 8hrly (max 6g per day)
Ciprofloxacin IV	0.4 g x 2 doses	0.4 g x 3 doses	10mg/kg/dose 12hrly (400mg per dose)High dose: 10mg/kg/dose 8hrly
Clarithromycin IV/PO		0.5 g x 2 doses	7.5mg/kg/dose every 12hrs (max 500mg per dose)
Clindamycin IV/PO	0.3 g x 2 oral or 0.6 g x 3 doses IV	0.9 g x 3 doses IV	3.75–6.25 mg/kg/dose every 6hrsHigh dose: 10 mg/kg/dose every 6hrs (Max 1.2 g per dose)
Cloxacillin IV	1 g x 4 doses	2 g x 6 doses	25=50mg/kg/dose every 6hrs (max 2g per dose)
Colistin IV/NB	9 MU loading dose followed by 4.5 MU x 2 doses		25,000 – 50,000U/kg/dose every 8hrs (max 3MU per dose)
Trimethoprim-sulfamethoxazole IV/PO	160/800 mg (1 DS) x 2 doses	0.24 g/1.2 g x 2 doses[4]	24mg/kg/dose every 12hrsHigh dose 120mg/kg/day 2–4 divided doses
Ertapenem IV[5]	1 g once daily over 30 minutes		15 mg/kg/dose every 12hrs (Max 1g per day)
Doxycycline IV/PO	0.1 g once daily	0.2 g once daily	Initially 4.4mg/kg/day 1-2 dosesor 200mg in 2 divided doses, then 100mg daily
Gentamycin IV[1]	6-7 mg/kg once daily		7mg/kg/dose once daily
Imipenem IV	0.5 g x 4 doses over 30 minutes	1 g x 4 doses over 30 minutes	15–20mg/kg/dose every 8hrsHigh dose: 25mg/kg/dose every 8hrs (max 1g per dose)
Levofloxacin IV	0.5 g once daily	0.5 g x 2 doses	6 months–5 years: 10mg/kg/dose twice daily, >5 years: 10mg/kg once daily (maximum single dose 500mg)
Linezolid IV/PO[5]	0.6 g x 2 doses		10mg/kg/dose every 8hrs (max 600mg per dose)
Meropenem IV	1 g x 3 doses over 30 minutes	2 g x 3 doses over 3 hours Meningitis: High dose only	10–20mg/kg/dose every 8hrsHigh dose: 40mg/kg/dose every 8hrs (Max 2g per dose)
Metronidazole IV	0.5 g x 3 doses		7.5mg/kg/dose every 8hrs (Max 500mg per dose) High dose: Loading dose 15mg/kg, then 7.5mg/kg/dose every 8hrs
Piperacillin/ Tazobactam IV	(4 g piperacillin + 0.5 g tazobactam) x 4 doses or in doses 3 by extended 4-hour infusion	(4 g piperacillin + 0.5 g tazobactam) x 4 doses by extended 3-hour infusion	90mg/kg/dose every 8 hours (maximum 4.5g every 6 hours) High dose: 90mg/kg (max 4.5g) every 6 hours
Polymyxin B IV /NB	2 MU loading dose followed by 1 MU x 2 doses		
Rifampicin IV/PO[3]	600 mg once daily	600 mg x 2 doses	15–20mg/kg daily
Teicoplanin IV	0.4 g once daily	0.8 g once daily	Initial 10mg/kg every 12hrs x 3 doses, then 6–10mg/kg/dose dailyHigh dose: 12mg/kg every 12hrs x 3–5 doses, then 12mg/kg/dose daily
Tigecycline IV	0.1 g loading dose followed by 50 mg x 2 doses		1–2mg/kg/dose every 12hrs (max 50mg per dose)
Vancomycin IV[2]	0.5 g x 4 doses or 1 g x 2 doses or 2 g once daily by continuous infusion		10–15mg/kg/dose every 6-8hrs (max 2g per dose) In severe infection 25-30mg/kg loading dose

awaiting the results of specimens that were collected prior to the commencement of antibiotics. The antimicrobial susceptibility test results of isolates from specimens sent to the clinical microbiology laboratory will determine the definitive therapy, which may require de-escalation. In settings of scarce resources, lack of laboratory support, and absence of specialist consultation, this guide provides a second-line option if the therapeutic failure occurs with the first-line options.

This represents a milestone as it is the first time that antibiotic guidelines have been created in Nigeria and the West African region with considerations for the unique characteristics of local microbiology and resistance patterns, as well as input from top experts within the country. Furthermore, it incorporates reports from several countries that have shown that BSI, UTI, SSTI (including surgical site infections) and RTI are the most common infections encountered.[9,35–43] Guidance is provided for treatment of infections caused by extended-spectrum β-lactamase-producing *Enterobacteriaceae* using carbapenems (with de-escalation to β-lactamase/β-lactamase inhibitors) and for carbapenem-resistant gram-negative bacteria using combination therapy which includes polymyxins or tigecycline.[44–48] Furthermore, treatment options for resistant Gram-positive organisms such as Methicillin-resistant *Staphylococcus aureus* (MRSA) in SSTI, BSI and RTI (VAP) are provided in second-line and third-line options.[49] The guide has been designed for easy reference for the treatment of these infections' subsets, thereby promoting the selection of the optimal antibiotic regimen including dosing, duration of therapy, and route of administration. It supports the main objectives of the antimicrobial stewardship program in the ICU setting.[50] Adherence to this guideline should decrease the rate of emergence of multidrug-resistant pathogens among critically ill patients, limit recurrences of infection and increase the likelihood of adequate initial therapy.

In the management of adults in ICUs with suspected infection, we suggest the use of serial procalcitonin (PCT) measure-ments as an antimicrobial stewardship (ASP) intervention to decrease antibiotic use and shorten antibiotic days.[51] Once culture results identify the pathogen, and susceptibility profile, a planned removal of antimicrobials that are not necessary or that provide redundant coverage should be initiated to provide more targeted therapy. This form of de-escalation also decreases the selective pressure on antibiotics recommended in the guidelines, hence reducing the rate of emergence of antimicrobial resistance.
Antimicrobial therapy should also consider fungal infections that are emerging, particularly in immuno-compromised and critically ill patients. Critically ill patients are often colonized by *Candida* and are at risk of invasive candidiasis due to their immuno-compromised status. Despite a shift in etiology from mainly *C. albicans* to non-albicans spp. which are intrinsically fluconazole-resistant, fluconazole is recommended for candiduria.[52,53] We strongly recommend species identification and antifungal susceptibility testing for cases of invasive candidiasis.[52,53]

CONCLUSION

The study identified *Candida albicans* and *Pseudomonas aeruginosa* as the most common causative agents of ICU infections, followed by *Klebsiella pneumoniae, Acinetobacter baumannii*, and *Escherichia coli*. The group of experts has provided evidence-based guidance for the management of infections commonly seen in ICU patients. This guidance recommends combination therapy as empirical therapy for infections in the critically ill while awaiting the results of specimen cultures that were collected prior to the commencement of antibiotics, but highlights that these should be used under the guidance of a medical professional. This guideline can serve as a baseline document for future updates of ICU antimicrobial guidelines that will reflect evolving antibiotic needs. Implementation and adherence to these guidelines is expected to decrease the emergence of multidrug-resistant pathogens, limit recurrences of infection, and increase the likelihood of adequate initial therapy. Further research and implementation efforts are warranted to ensure optimal antibiotic use in critically ill patients in Nigeria and beyond.

Limitations of the Study

The focus was just on the most common infections seen in the ICU. National surveillance data is not available; hence these guidelines are not drawn from a national antibiogram. However, the data presented here is most likely reflective of other ICU facilities in the country and thus can be adapted for use across the country. There will be a need to continuously revise the guidelines as the pathogens evolve in antimicrobial profiles.

Previous Publication/Presentations

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Conflict of Interest

The authors declare that there is no conflicts of interest.

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Ethical Considerations

The research was approved by the Babcock University Health Research and Ethics Committee (BUHREC 437/19). Informed consent from the participants was obtained before participating in the study.

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