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Discordant rate between empirical antibiotics administered and antimicrobial susceptibility in infections caused by *Pseudomonas aeruginosa* in a tertiary hospital in Nigeria

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Abstract:

Background Early initiation of appropriate antibiotics is key to the effective management of severe bacterial infections. The initiation of targeted antibiotic therapy is possible only when the causative organism is isolated. As a result, antibiotics are usually administered on an empirical basis guided by the clinical presentation, local antibiotic guidelines and other relevant histories. Generally, empirical antibiotics differ for both community- and hospital-acquired infections (HAIs), as a result of which common HAI pathogens such as *Pseudomonas aeruginosa* should be deliberately targeted, because most routine antibiotics are ineffective against them.

Methodology: This was a retrospective cross-sectional study involving the review of the clinical consults sent to clinical microbiologists at the University of Benin Teaching Hospital (UBTH) between January and December 2022. The consults were analyzed for the initial diagnosis, reasons for the invitation and empirical antibiotics administered. Other relevant informations were obtained from the laboratory records. Susceptibility profiles of *P. aeruginosa* isolates were compared with the empirical antibiotics administered. Discordant empirical antibiotic therapy was defined as the administration of antibiotic regimen with no anti-pseudomonal activity.

Results: Of the 256 consults received over the period of study, *P. aeruginosa* was isolated from 57 (22.3%) patients as pathogens. Out of this, 24.6% (n=14) received at least one anti-pseudomonas antibiotic, which puts the total discordant rate at 75.4%. Metronidazole (22.7%) and ceftriaxone-sulbactam (Tandak) (21.5%) were the most commonly prescribed empirical antibiotics. The most common reason for consultation was a diagnosis of sepsis at 40.2% followed by pan-resistant isolates at 34.8%

Conclusion: Although the commonly prescribed antibiotics in our setting are broad spectrum, they lack coverage for *P. aeruginosa* which is one of the most common pathogens implicated in HAIs.

Keywords: *Pseudomonas aeruginosa,* discordant antibiotics, empiric antibiotics

Taux de discordance entre les antibiotiques empiriques administrés et la sensibilité aux antimicrobiens dans les infections causées par *Pseudomonas aeruginosa* dans un hôpital tertiaire au Nigeria

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Résumé:

Contexte: L'instauration précoce d'un traitement antibiotique approprié est essentielle à la prise en charge efficace des infections bactériennes graves. L'instauration d'une antibiothérapie ciblée n'est possible que lorsque l'organisme causal est isolé. En conséquence, les antibiotiques sont généralement administrés sur une base empirique, guidée par la présentation clinique, les directives locales en matière d'antibiotiques et d'autres antécédents pertinents. En général, les antibiotiques empiriques diffèrent à la fois pour les infections nosocomiales et celles nosocomiales (IAS), de sorte que les agents pathogènes courants des IAS, tels que *Pseudomonas aeruginosa*, doivent être délibérément ciblés, car la plupart des antibiotiques courants sont

inefficaces contre eux.

Méthodologie: Il s'agit d'une étude rétrospective transversale portant sur la revue des consultations cliniques adressées aux microbiologistes cliniciens de l'Hôpital Universitaire du Bénin (UBTH) entre janvier et décembre 2022. Les consultations ont été analysées pour le diagnostic initial, les raisons de l'invitation et antibiotiques empiriques administrés. D'autres informations pertinentes ont été obtenues à partir des dossiers de laboratoire. Les profils de sensibilité des isolats de *P. aeruginosa* ont été comparés à ceux des antibiotiques empiriques administrés. Une antibiothérapie empirique discordante a été définie comme l'administration d'un régime antibiotique sans activité anti-pseudomonas.

Résultats: Parmi les 256 consultations reçues au cours de la période d'étude, *P. aeruginosa* a été isolé comme pathogène chez 57 (22,3%) patients. Sur ce total, 24,6% (n=14) ont reçu au moins un antibiotique anti-pseudomonas, ce qui porte le taux discordant total à 75,4%. Le métronidazole (22,7%) et la ceftriaxone-sulbactam (Tandak) (21,5%) étaient les antibiotiques empiriques les plus couramment prescrits. Le motif de consultation le plus fréquent était un diagnostic de sepsis à 40,2% suivi d'isolats pan-résistants à 34,8%.

Conclusion: Bien que les antibiotiques couramment prescrits dans notre contexte soient à large spectre, ils manquent de couverture pour P. aeruginosa qui est l'un des plus courants agents pathogènes courants impliqués dans les IAS.

Mots clés: *Pseudomonas aeruginosa*, antibiotiques discordants, antibiotiques empiriques

Introduction:

Early initiation of appropriate antibiotics is key to the effective management of bacterial infections. However, initiation of targeted antibiotic therapy is possible only when the causative organism is isolated and subsequently, antimicrobial susceptibility testing performed (1). As a result, antibiotics are often given on an empirical basis guided by the clinical presentation, other relevant clinical histories and local antibiotics guidelines, as complete culture results usually take 24 to 48 hours (2). It has been shown that delay and or administration of inadequate antibiotics for infections in the critically ill is often associated with adverse outcomes including higher morbidity and mortality as well as extended length of hospital stay (1,3).

Empirical therapy is simply defined as the initial antibiotic regimen selected in the absence of definitive microbiological pathogen identification and susceptibility testing. On the hand, targeted or definitive therapy is the antibiotic regimen selected after pathogen identification and susceptibility testing is completed (4). The common approach to prescribing on empirical basis include; the use of broad-spectrum antimicrobial agents as initial therapy, which could be achieved by mono-therapy or a combination of antimicrobial agents, with the aim of covering multiple possible organisms commonly associated with the specific clinical syndrome including Gram-positive, Gram-negative, anaerobes as well as atypical bacteria (3).

Worthy of note is that empirical choices differ for both community and hospital-acquired infections. For example, adults with community-acquired pneumonia should be started on either a respiratory fluoroquinolone such as levofloxacin or combination of a beta-lactam (amoxicillin/amoxicillin-clavulanic acid) and a macrolide (5). However, in hospital-acquired pneumonia, antibiotics regimen for empirical coverage should include antipseudomonals such as piperacillin-tazobactam, cefepime, levofloxacin, imipenem or meropenem (6).

In the case of hospital-acquired infections (HAI)s, which are frequently associated with the presence of invasive devices and procedures that compromises the normal barriers to infection such as intravascular catheter–associated bacteraemia, ventilator-associated pneumonia, and catheter-associated urinary tract infections (CAUTI), the offending pathogens are frequently multi-drug-resistant organisms, which is true for both Gram-positive (e. g. MRSA) and Gram-negative (e. g. *Pseudomonas aeruginosa*) bacteria (4). The sources of these resistance phenotypes have been linked to the hospital environment which often serves as a reservoir for these pathogens, primarily due to selection pressure from frequent antimicrobial use in the hospital (4).

Therefore, to select empirical antimicrobial therapy for HAIs, the following should be considered; (i) the site of infection and the most likely organisms colonizing that site, for example, central-line associated blood stream infection frequently results from skin flora such as staphylococci inoculated into the bloodstream by the process of catheterization, (ii) prior knowledge of bacteria known to colonize a given patient e .g. screening by the use of nasal swab and faecal screening for the carriage of carbapenem-resistant Gram-negative bacteria pathogens, which is currently been conducted routinely by many hospitals before admitting patients to the intensive care unit or before highly invasive surgeries, and (iii) the local bacterial resistance profile or antibiograms (7).

Initial antibiotic therapy in critically ill does not only need to be timely, but should be appropriate. Appropriateness can be defined as antimicrobial coverage that provides adequate *in vitro* activity against all likely pathogens at the clinical infection site of interest (8). When considering targeted therapy, appropriateness is defined as antimicrobials with *in vitro* activity against the isolated pathogen, or appropriate for the underlying clinical syndrome even if no pathogen was isolated.

Empirical antibiotic therapy is considered discordant if the bloodstream isolate does not display *in vitro* susceptibility to any systemic antibiotic administered on the day of blood culture sampling. Such a scenario includes meningitis and antibiotic regimen that crosses the blood-brain barrier (8).

Common predictors of discordant empirical antibiotic therapy (DEAT) include but are not limited to high prevalence of antibiotic-resistant phenotypes in the setting, infections due to non-glucose fermenting Gram-negative organisms (*Acinetobacter baumannii* and *P. aeruginosa*) and presence of *Enterococcus* spp and infection due to resistant phenotypes (9). Among Gram-negative infections, *P. aeruginosa* is one of the most common Gram-negative bacteria causing HAIs in hospitalized patients (10).

The World Health Organization (WHO) has placed carbapenem-resistant *P. aeruginosa* among critical priority pathogen that desperately requires new treatment options (11). Increasing rates of multidrug-resistant (MDR) *P. aeruginosa* in HAIs and among hospitalized patients is a major public health problem (12). Multidrug-resistant *P. aeruginosa* infections in the hospital setting are associated with poor outcomes including increased resource utilization and costs, morbidity, and mortality (10). In the USA, MDR *P. aeruginosa* accounts for 13–19% of the annual HAI burden. The increasing level of resistance in MDR *P. aeruginosa* is often attributed to patient-to-patient transmission of resistant strains, increasing rate of environmental colonization, as well as newly acquired resistance owing to previous antibiotic exposure (13).

In the management of severe systemic infections, multidrug-resistant *P. aeruginosa* must be part of the consideration when selecting empirical treatment to ensure timely and appropriate initial therapy. Instead of universal broad-spectrum antibiotics, specific antibiotic regimens should be determined using a more scientific approach. Such an approach should include acquiring site-specific diagnosis such as previous blood culture information to predict probable causative organisms based on epidemiological and host risk factors including recent infection exposures, evidence of colonization, indwelling devices, comorbidity, recent infections, recent antibiotic exposure in the preceding 3 months and host immunologic status (4).

Initiation of antibiotics such as ceftriaxone and amoxicillin-clavulanic acid with no *P. aeruginosa* coverage often leads to inappropriate initial therapy that adversely impacts health outcomes (14). This study aimed to determine the rate of inappropriate empirical therapy in patients with *P. aeruginosa* infections at the University of Benin Teaching Hospital, Nigeria

Materials and method:

Study setting, period and design:
The study was conducted at the University of Benin Teaching Hospital, Edo State, Nigeria between January and December 2022. This was a retrospective cross-sectional study involving the review of the clinical consults sent to consultant clinical microbiologists at the University of Benin Teaching Hospital for a period of one year.

Study procedure and data collection:
The clinical consults were analyzed for the following parameters; initial diagnosis, reasons for the invitation, and empirical antibiotics administered. Isolates and the *in vitro* susceptibility profile of the initial samples sent for microbiology culture before or immediately after initiating antibiotics were also included in the analysis. Samples that yielded growth of *P. aeruginosa* were included for further evaluations to determine the extent the *in-vitro* susceptibility profiles differ (discordant empirical antibiotic therapy) or aligned with the initial empiric antibiotics prescribed. In cases where multiple samples from one patient grew *P. aeruginosa*, only one isolate was included.

Clinical samples included in the study were blood culture, urine, body fluid aspirates and wound swabs. Empirical antibiotic therapy was considered discordant (DEAT) if *P. aeruginosa* isolate did not display *in vitro* susceptibility to any systemic antibiotic administered shortly before or immediately after sample collection. Pan-resistant isolate was defined as resistance to all antibiotics tested (15).

Results:

Of the 256 consults received during the study period, all but two patients were on antibiotics before review, giving antibiotic prevalence rate of 99.2%. *Pseudomonas aeruginosa* was isolated from 57 (22.3%) patients as pathogens. Of this, only 14 (24.6%) received at least one anti-pseudomonas antibiotics which puts the total discordant rate at 75.4% (Fig 1).

The ICU had the highest number of *P. aeruginosa* infected patients closely followed by the surgical ward at 18 (31.6%) and 15 (26.3%) respectively. The percentage of DEAT was 66.7% each for ICU and Paediatrics wards (Table 1). Metronidazole (22.7%) and ceftriaxone-sulbactam (Tandak) (21.5%) were the most commonly prescribed empirical antibiotics (Fig 3) while the most common reasons for consultation were the diagnosis of sepsis, followed by pan-resistant isolates respectively at 40.2% and 34.8% (Fig 4). The distribution of *P. aeruginosa* by specimen sources shows that urine had the highest yield of the studied pathogens followed by wound swabs at 43.9% and 29.8% respectively (Fig 4)
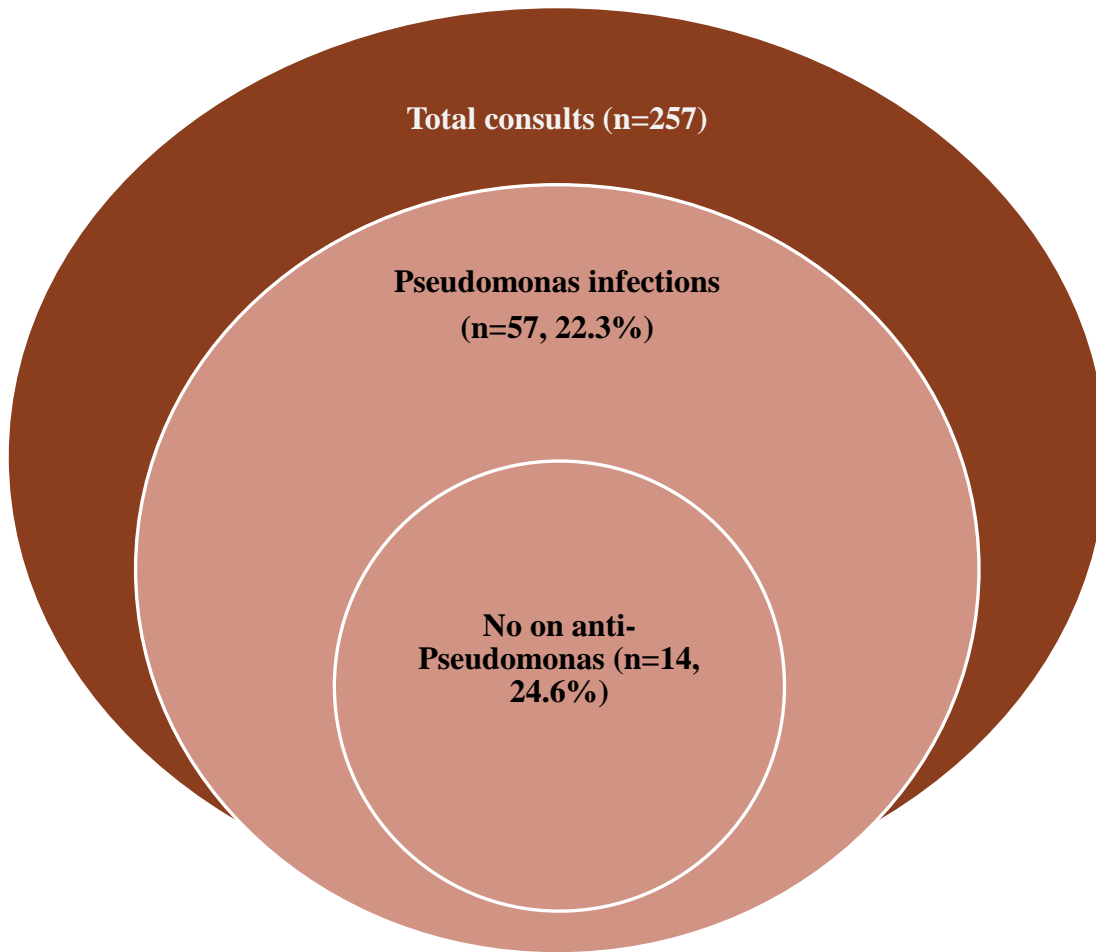
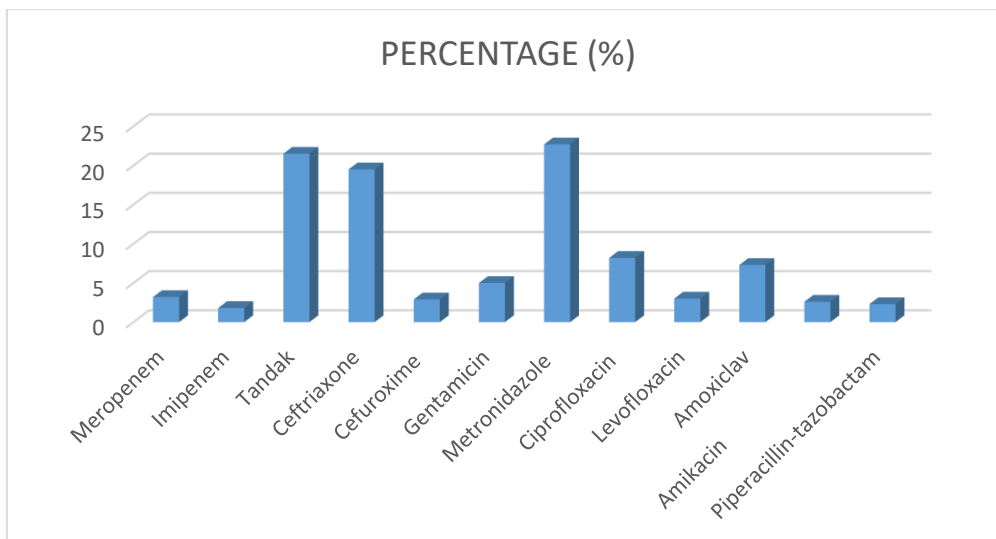Fig 1 Frequency of *Pseudomonas aeruginosa* isolate and anti-pseudomonas prescribed

Fig 2: Patterns of empirical antibiotics prescribed before or after sample collection
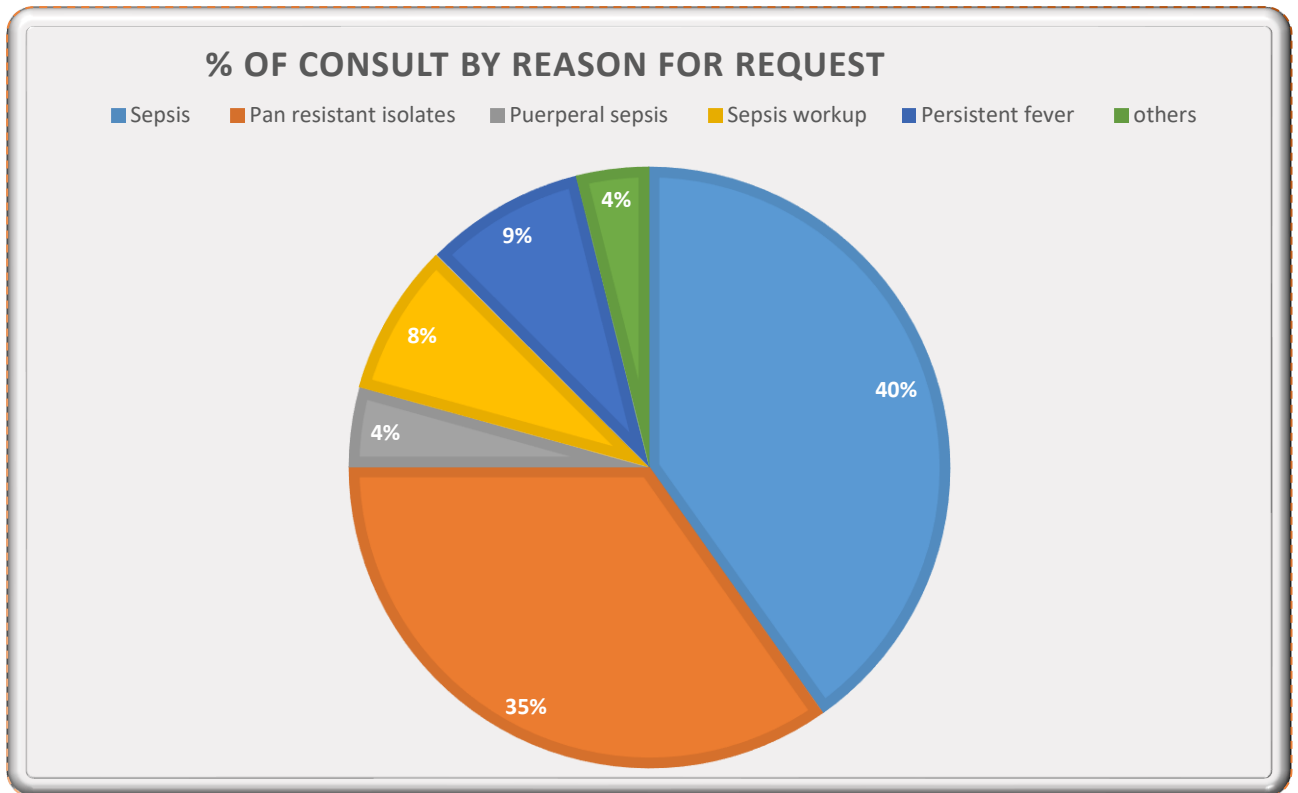
Fig 3: Frequency (%) of consults by reason for request

Table 1: Distribution of *Pseudomonas aeruginosa* infection by ward and discordant empirical antibiotic therapy

Ward/units	No of patients with *Pseudomonas aeruginosa* infection (%)	No on anti-*Pseudomonas aeruginosa* coverage (%)	No of DEAT (%)	x^2	*p* value
ICU	18 (31.6)	6 (33.3)	12 (66.7)	1.806	0.7714
Surgical ward	15 (26.3)	3 (20.0)	12 (80.0)		
O&G	7 (12.3)	1 (14.3)	6 (85.7)		
Medicine	11 (19.3)	2 (18.2)	9 (81.8)		
Paediatrics ward	6 (10.5)	2 (33.3)	4 (66.7)		
Total	**57**	**14 (24.6)**	**43 (75.4)**		

DEAT = Discordant empirical antibiotic therapy; ICU=Intensive Care Unit
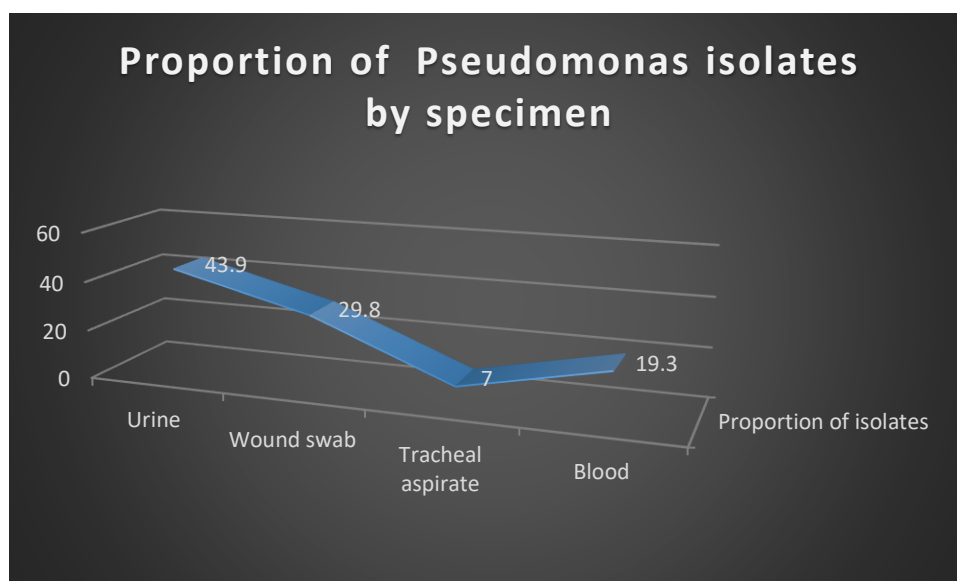
Fig 4: Frequency of *Pseudomonas aeruginosa* isolates by specimen types

Discussion:

Timely administration of effective antibiotic therapy is associated with improved outcomes in patients with severe infections such as sepsis and bloodstream infections (9). However, the uncompromisable lag between sampling of cultures and the availability of *in vitro* susceptibility report make empirical antibiotic selection challenging especially when infection involves pathogen such as *P. aeruginosa* which besides being intrinsically resistant to a number of common antibiotics, are known to possess various mechanism of resistance to different classes of antibiotics (4,9). The key predictors of discordant empirical antimicrobial therapy which include antibiotic-resistant phenotype such as *P. aeruginosa* and high antimicrobial resistance prevalence setting (16) are common features seen in this study. As demonstrated by various studies, there is high degree antibiotics resistance from isolates obtained from clinical samples in Nigerian's hospitals (17).

In this study, the discordant empirical antimicrobial therapy rate was 75.4%. This is much higher than findings from other studies (16) probably because our study was done in a setting with high prevalence of resistance to antibiotics and the focus was on a notable resistant pathogen. Also, the studies with low DEAT rate besides the low resistant prevalence setting were focused on only blood stream infections (9,16). Empirical antibiotics reported as the most administered in the study were ceftriaxone-sulbactam (Tandak) and metronidazole. Although this combination is broad spectrum sufficient to cover most Gram-positive, Gram-negative and anaerobic organisms, it does not have sufficient coverage for

*P. aeruginosa (*18). This pattern of prescription was similar to a report by Abubakar et al., (19) and other studies (20,21) which reported metronidazole and ceftriaxone as the most administered antibiotics among patients admitted to tertiary healthcare. The need for a broad-spectrum antibiotic therapy may have informed the general choice of ceftriaxone and metronidazole as among the common empirical antibiotics across most studies, even if it lacks potency for most pathogens with resistant encoding genes.

Sepsis closely followed by pan-resistant isolates were the common reasons for referrals to the clinical microbiologists, which accounted for 40.2% and 34.8% respectively. This is likely due to the understanding that the management of sepsis involves multidisciplinary approach and also clinical microbiologists largely play the roles of infectious diseases physician in our settings (22). In the analysis of the distribution of *P. aeruginosa* by ward/ unit, it somewhat showed direct correlations with HAI, with ICU having the highest recovery of *P. aeruginosa* at the rate of 31.6%. This could be explained by the fact that ICU admission is a strong determinant of HAI, and *P. aeruginosa* is a prominent pathogen in this category of infection (23).

Pseudomonas aeruginosa is a notable pathogen for serious infection especially in the immunocompromised hosts including those with severe burn, surgical site infection and those with indwelling devices such as urethral catheter (24). In this study, the highest number of *P. aeruginosa* were isolated from urine (42.9%) followed by wound swabs (29.8%). A similar observation was reported in another study with urine also the highest source for this pathogen (24,25). The high

yield of *P. aeruginosa* from the urine samples in our study may be due the fact that most of the patients were in patient who have stayed more 48 hours on admission, and many of whom would have been on urethral catheter or other devices which usually encourage bio-film formation by this organism (26).

Our study has some limitations. First, the study findings were based only on sample of patients whose consults were sent to the clinical microbiologists, which might not nece-ssarily be the true picture, and secondly, some of the cases reviewed had no sample collected for culture before clinical microbiologist's rev-iew. These were excluded and could have fur-ther reduced the number of *P. aeruginosa* in the study

Conclusion:

In general, the routine antibiotics pre-scribed on the empirical basis in our setting are broad spectrum, however, they lack cove-rage for the common multi-drug resistant pat-hogens associated with HAIs such as *P. aeru-ginosa.* As a result*,* the unintended use of these antibiotic regimens often results in in-appropriate initial therapy that adversely im-pacts health outcomes.

Contributions of authors:

IJA conceptualized and designed the study, conducted the analysis and wrote the first draft. LPVO reviewed the manuscript. The authors read and approved the final manu-script

Source of funding:

No funding was received for the study.

Conflict of interest:

No conflict of interest is declared.

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