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Pattern of inappropriate antibiotic use among patients in the medical wards of a tertiary hospital in southwest Nigeria

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Abstract:

Background: The inappropriate use of antibiotics results in the emergence of antimicrobial resistance and adverse clinical and economic outcomes in hospital in-patients. A lack of institutional and national antibiotic guidelines promotes inappropriate antibiotic use. The objectives of this study are to evaluate the appropriateness of antibiotic prescribing, and the quality of antibiotic use in medical wards of the Lagos University Teaching Hospital, Lagos, Nigeria.
Methodology: This was a descriptive cross-sectional study of patients admitted and placed on antibiotics in the medical wards of Lagos University Teaching Hospital between July 2013 and August 2014. The appropriateness of antibiotic therapy was determined by compliance with the guidelines of the Infectious Diseases Society of America (IDSA).
Results: A total of 350 hospitalized patients on antibiotic therapy during the period of the study were reviewed, including 197 (56.3%) males and 153 females (43.7%). The mean age of the patients was 48.7±17.6 years and a total of 539 initial antibiotics were empirically prescribed. Antibiotic therapy was considered inappropriate in 290 (82.9%) patients, of which 131 (37.4%) patients had no evidence of infection. Pneumonia (23.1%) was the most common indication for antibiotic use, out of which 59.3% had inappropriate antibiotic therapy. Overall, the most frequently prescribed initial empirical antibiotic classes were imidazole derivatives (32.4%) and cephalosporins (22.0%), while the most frequently prescribed inappropriate antibiotic classes were carbapenems (100.0%) and quinolones (89.3%).
Conclusion: The study revealed a high rate of inappropriate antibiotic therapy. There is an imperative need to establish antimicrobial stewardship programmes to curb the inappropriate use of antibiotics in the hospital.

Keywords: Antibiotic use; Prescribing practice; Empirical; Antimicrobial resistance; Antimicrobial stewardship

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Modèle d'utilisation inappropriée d'antibiotiques chez les patients des services médicaux d'un hôpital tertiaire du sud-ouest du Nigeria

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Résumé:

Contexte: L'utilisation inappropriée d'antibiotiques entraîne l'émergence d'une résistance aux antimicrobiens et

des résultats cliniques et économiques défavorables chez les patients hospitalisés. L'absence de directives institutionnelles et nationales sur les antibiotiques favorise une utilisation inappropriée des antibiotiques. Les objectifs de cette étude sont d'évaluer la pertinence de la prescription d'antibiotiques et la qualité de l'utilisation des antibiotiques dans les services médicaux de l'hôpital universitaire de Lagos, Lagos, Nigeria.
Méthodologie: Il s'agissait d'une étude transversale descriptive portant sur des patients admis et placés sous antibiotiques dans les services médicaux de l'hôpital universitaire de Lagos entre juillet 2013 et août 2014. La pertinence de l'antibiothérapie a été déterminée par le respect des directives de l'Infectious Diseases Society. d'Amérique (IDSA).
Résultats: Au total, 350 patients hospitalisés sous antibiothérapie au cours de la période de l'étude ont été examinés, dont 197 (56,3%) hommes et 153 femmes (43,7%). L'âge moyen des patients était de 48,7±17,6 ans et un total de 539 antibiotiques initiaux ont été prescrits de manière empirique. L'antibiothérapie a été jugée inappropriée chez 290 (82,9%) patients, dont 131 (37,4%) patients ne présentaient aucun signe d'infection. La pneumonie (23,1%) était l'indication la plus courante d'utilisation d'antibiotiques, dont 59,3% avaient un traitement antibiotique inapproprié. Dans l'ensemble, les classes d'antibiotiques empiriques initiales les plus fréquemment prescrites étaient les dérivés de l'imidazole (32,4%) et les céphalosporines (22,0%), tandis que les classes d'antibiotiques inappropriés les plus fréquemment prescrites étaient les carbapénèmes (100,0%) et les quinolones (89,3%).
Conclusion: L'étude a révélé un taux élevé d'antibiothérapie inappropriée. Il est impératif d'établir des programmes de gestion des antimicrobiens pour lutter contre l'utilisation inappropriée des antibiotiques à l'hôpital.

Mots clés: Utilisation d'antibiotiques; Pratique de prescription; Empirique; Résistance aux antimicrobiens; Gestion des antimicrobiens

Introduction:

The introduction and use of antimicrobial agents in modern medicine contributed to a reduction in the morbidity and mortality of humans (1). However, inappropriate use of antibiotics has become a global concern (1,2), which results in adverse clinical and economic outcomes in patients (3). The adverse clinical outcomes include increased length of hospital stay, morbidity, and mortality (3), increased consumption of antibiotics by hospital in-patients (4), and emergence of drug resistance (5). The adverse economic outcomes include increased costs of healthcare borne by patients (3).

The problem of inappropriate antibiotic therapy and its adverse clinical and economic outcomes is exacerbated by a paucity of new and effective antimicrobials due to diminishing research and development efforts in antibiotic discovery (6). This scenario infers the possibility of a post-antibiotic era, in which simple infections would no longer be treatable due to a lack of effective antibiotics (5).The impact of a post-antibiotic era would be particularly severe in Africa and other resource constrained parts of the world due to an already existing vicious circle of therapeutic failures from multidrug resistant organisms, weak regulatory systems, inadequate diagnostic facilities, poorly funded healthcare delivery systems, and a paucity of antibiotic stewardship programs (7). It is therefore absolutely necessary to safeguard currently available and effective antibiotics (8).

There is however, a paucity of data in Africa regarding the appropriateness of antibiotic prescribing (9). Sadly, this knowledge gap frustrates effective policy making to curtail inappropriate antibiotic use and antimicrobial resistance in healthcare facilities in Africa (9). The aim of this study was therefore to evaluate the appropriateness of initial antibiotic therapy and the quality of antibiotic use in Lagos University Teaching Hospital, Nigeria.

Materials and method:

Study location and design:

This study was a cross sectional study conducted between July 2013 and August 2014 on patients admitted and placed on antibiotics in the medical wards of the Lagos University Teaching Hospital, southwest Nigeria. The hospital has 761 beds while its medical wards have 152 beds. Each ward admits about 30 patients monthly.

Study participants:

The study participants were adult patients over 18 years old, who were hospitalized in any of the medical wards for a minimum, of 24 hours and who were on antibiotics for treatment and not for prophylaxis.

Data collection:

Data were collected from the patients' case notes, observation charts, prescription sheets, microbiology and pathology, and radio-diagnostic results. Data collected included: patient's bio-data; diagnosis; site of infection; indication for antibiotic therapy; length of hospital stay in days; whether clinical samples were obtained for culture before antibiotic treatment; information related to the micro-organisms isolated from culture; and details of antibiotics prescribed including name, dose, duration, route and frequency of administration while on admission.

With regards to initial antibiotic use, all antibiotics were documented using the Anatomic Therapeutic Chemical (ATC) classification (10) and by the WHO Access, Watch and Reserve (AWaRe) classification of antibiotics

(11). To ensure confidentiality all data collected were de-identified and given study identification numbers.

Determining appropriateness of initial antibiotic therapy:

The antibiotic prescribing guidelines of the Infectious Diseases Society of America (IDSA) (12) was used to determine the appropriateness of initial antibiotics. In this study, inappropriate initial antibiotic therapy was categorized as; (i) inappropriate indication (no indication) where there was no evidence of infection and antibiotics were not needed; (ii) inappropriate choice where wrong choice of antibiotic based on the indication was used, and (iii) inappropriate dosing where there was wrong dose or dosage interval or route or duration. Antibiotic therapy was assessed to be inappropriate when any of the above criteria was fulfilled.

Ethical approval:

Ethical approval was obtained from the Health Research and Ethics Committee (HREC) of the hospital.

Data analysis:

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20.0. Categorical variables were summarized using percentages for inappropriate and appropriate initial antibiotic therapy based on demographics, clinical features, site of infection and patterns of antibiotic use

Results:

Three hundred and fifty in-patients on antibiotics for treatment in the medical wards of the hospital were recruited into the study between July 2013 and August 2014. There were 197 (56. 3%) males and 153 (43.7%) females in the study, with mean age of 48.7 ± 17.6 years (Table 1). A total of 539 antibiotic prescriptions were given for 350 patients over the period of study. One hundred and forty-four in-patients (41.1%) were prescribed one initial empirical antibiotic while 206 (58.9%) patients were prescribed a combination of initial empirical antibiotics (Table 1).

Table 1: Demographic characteristics and antibiotic prescribing pattern of the inpatients in Lagos University Teaching Hospital, Lagos, Nigeria (2013-2014)

Characteristics	Frequency	Percentage (%)
Gender		
Male	197	56.3
Female	153	43.7
Mean age (years)	48.7 ± 17.6	
Initial Antibiotic therapy		
Single antibiotic use	144	41.1
Combination therapy	206	58.9
Route of antibiotic administration		
Parenteral/Intravenous	322	92.0
Oral	28	8.0
Indication for antibiotic therapy		
Healthcare associated infection	4	1.1
Community acquired infection	215	61.4
Unknown or no identified infection	131	37.4
Appropriateness of antibiotic therapy		
Appropriate	60	17.1
Inappropriate	290	82.9
Inappropriate indication	131	37.4
Inappropriate choice of antibiotic	142	40.6
Inappropriate dosing/duration	17*	4.9*
Wrong dose	10*	2.9*
Wrong duration of administration	16*	4.6*

*=One prescription can include more than one inappropriate dosing.

Table 2: Indication for antibiotic prescribing and inappropriateness of antibiotic therapy among inpatients in Lagos University Teaching Hospital, Lagos, Nigeria (2013-2014)

Indication for antibiotic prescribing	No of patients receiving antibiotics (%)	No of inappropriate use (%)
Pneumonia	81 (23.1)	48 (59.3)
Sepsis	67 (19.1)	56 (83.6)
Skin and soft tissue infection	32 (9.1)	25 (78.1)
Urinary tract infection	17 (4.9)	15 (88.2)
Intra-abdominal infection	11 (3.2)	10 (90.9)
Central Nervous System Infections	11 (3.2)	5 (45.5)
No evidence of infection	131 (37.4)	131 (10.0)
Total	**350 (100.0)**	**290 (82.9)**

Three hundred and twenty-two (92%) in-patients were prescribed parenteral antibiotics while 28 (8.0%) were prescribed oral antibiotics. Most of the patients (61.4%) were treated with antibiotics for community acquired infection. A total of 219 (62.6%) patients had evidence of infections and the most common indications for antibiotic therapy were pneumonia, accounting for 23.1% of patients in the study, followed by sepsis (19.1%) and skin and soft tissue infections (9.1%) (Table 2). Antibiotic therapy was appropriate in 60 patients (17.1%) while in 290 (82.9%) patients, antibiotic therapy was inappropriate (Table 1).

Specifically, in 131 (37.4%) patients, there was no indication for antibiotic therapy because there was no evidence of infection and therefore antibiotic therapy was unnecessary. In 142 (40.6%) patients, antibiotic choice was inappropriate and in 17 (4.9%) patients, there was inappropriate antibiotic dosing based on the dose and/or duration of treatment. The highest level of inappropriate antibiotic use (90.9%) was seen in patients with presumptive intra-abdominal infection while the lowest level of inappropriate antibiotic use was seen in patients with central nervous system infections (45.5 %) (Table 2).

Of the 131 inpatients with no evidence of infection, 36 (27.5%) had an admission diagnosis of cardiac failure, 24 (18.3%) had cerebrovascular disease, and 22 (16.8 %) had chronic kidney disease (Fig 1). Out of the 142 patients with inappropriate choice of antibiotics, only 39 (27.5%) were treated with a single antibiotic while the rest were treated with multiple antibiotics. A total of 539 initial empirical antibiotics were prescribed. Overall, the most frequently prescribed initial empirical antibiotics were metronidazole (32.5%), amoxicillin-clavulanate (18.9%), levofloxacin (18.7%) and ceftriaxone (18.7%). These four antibiotics accounted for 479 (88.9%) prescriptions (Table 3).

Out of the total antibiotics prescribed, 449 (83.3%) antibiotic prescriptions were assessed as inappropriate antibiotic use. The most frequently prescribed inappropriate antibiotic classes were carbapenems (100%), quinolones (89.3%), imidazole derivatives (86.9 %) and third generation cephalosporins (86.4%).

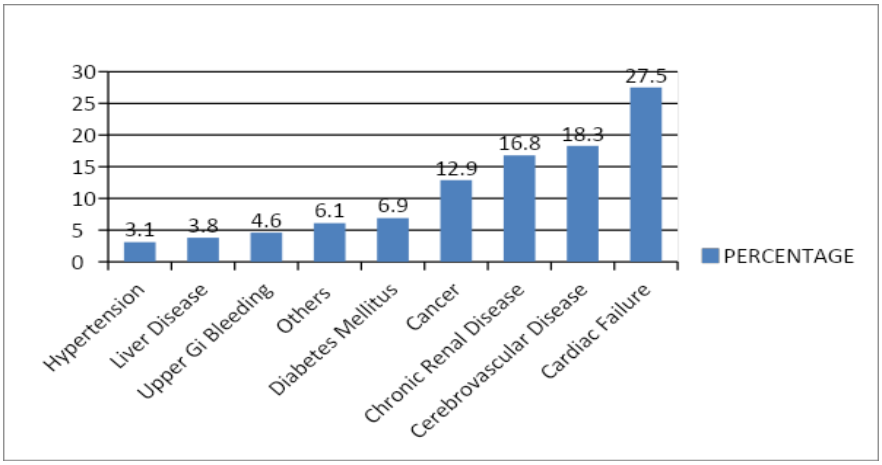

Fig 1: Admission diagnosis for 131 inpatients on antibiotic therapy with no evidence of infection in Lagos University Teaching Hospital, Lagos, Nigeria (2013-2014)

Table 3: Frequency and Anatomical Therapeutic Chemical (ATC) Codes of antibiotics prescribed to inpatients in Lagos University Teaching Hospital, Lagos, Nigeria (2013-2014)

Antibiotics prescribed	ATC Code	Frequency	Percentage (%)
Penicillins	J01C	**106**	**19.7**
Penicillin G	J01CE09	1	0.2
Amoxicillin	J01CA04	1	0.2
Flucloxacillin	J01CF05	1	0.2
Penicillin with B lactamase inhibitor	J01CR	103	19.1
Amoxycillin-clavulanate	J01CR02	102	18.9
Piperacillin-tazobactam	J01CR05	1	0.2
Cephalosporins		**119**	**22.0**
2nd Generation	J01DC	9	1.6
Cefuroxime	J01DC02	9	1.6
3rd Generation	J01DD	110	20.3
Ceftriaxone	J01DD04	101	18.7
Cefixime	J01DD08	2	0.4
Ceftazidime	J01DD02	7	1.2
Carbapenems	**J01DH**	**8**	**1.4**
Meropenem	J01DH02	8	1.4
Quinolones	**J01MA**	**113**	**21.0**
Ciprofloxacin	J01MA02	12	2.3
Levofloxacin	J01MA12	101	18.7
Macrolides	**J01FA**	**12**	**2.2**
Clarithromycin	J01FA09	3	0.6
Azithromycin	J01FA10	9	1.6
Imidazole derivatives	**J01XD**	**175**	**32.5**
Metronidazole	J01XD01	175	32.5
Other antibiotics		**6**	**1.2**
Clindamycin	J01FF01	1	0.2
Trimethoprim-sulphamethoxazole	J01EE01	1	0.2
Gentamicin	J01GB03	1	0.2
Vancomycin	J01XA01	3	0.6
Total		**539**	**100**

Of the total 539 antibiotics prescribed, 35.1% were due to inappropriate indication, 43.4% were inappropriately chosen, and 4.8% were inappropriately dosed. Inappropriate indication of antibiotics was highest for the cephalosporins (38.7%) (Table 4). The carbapenems were inappropriately used, mainly because of inappropriate choice (62.5%).

Most of the inappropriate use of the 2nd generation cephalosporins (66.7%) was due to inappropriate choice. The macrolides (58.3%) were the antibiotics with the least inappropriate use, and most of the macrolides were inappropriately used mainly because of inappropriate choice (41.7%).

A total of 256 of 539 (47.5%) antibiotics prescribed were in the "Watch" group of the WHO AWaRe category of antimicrobials, with 221 of 449 (49.2%) inappropriately prescribed, while there was no antibiotic prescribed (appropriately or inappropriately) from the "Reserve" group (Fig 2).

Table 4: Frequency distribution of types of inappropriate antibiotic usage among inpatients of Lagos University Teaching Hospital, Lagos, Nigeria (2013-2014)

Antibiotics prescribed	**Inappropriate antibiotic usage**			
	Inappropriate indication (%)	**Inappropriate choice (%)**	**Inappropriate dosing (%)**	**Total inappropriate use (%)**
Penicillins (n=106)	36 (33.9)	37 (34.9)	1(0.9)	74 (69.8)
Penicillin + beta lactamase inhibitor (n=103)	35 (34.0)	36 (35.0)	1 (1.0)	72 (70.0)
Other Penicillins (n=3)	1 (33.3)	1 (33.3)	0	2 (66.7)
Cephalosporins (n=119)	46 (38.7)	54 (45.4)	2 (1.7)	102 (85.7)
2nd Generation (n=9)	1 (11.1)	6 (66.7)	0	7 (77.8)
3rd Generation (n=110)	45 (41.0)	48 (43.6)	2 (1.8)	95 (86.4)
Carbapenems (n=8)	0	5 (62.5)	3 (37.5)	8 (100.0)
Quinolones (n=113)	42 (37.2)	48 (42.5)	11 (9.7)	101 (89.3)
Macrolides (n=12)	2 (16.7)	5 (41.7)	0	7 (58.3)
Imidazole derivatives (=175)	63 (36.0)	83 (47.4)	6 (3.4)	152 (86.9)
Other antibiotics (n=6)	0	2 (33.3)	3 (50.0)	5 (83.3)
Total (n=539)	**189 (35.1)**	**234 (43.4)**	**26 (4.8)**	**449 (83.3)**

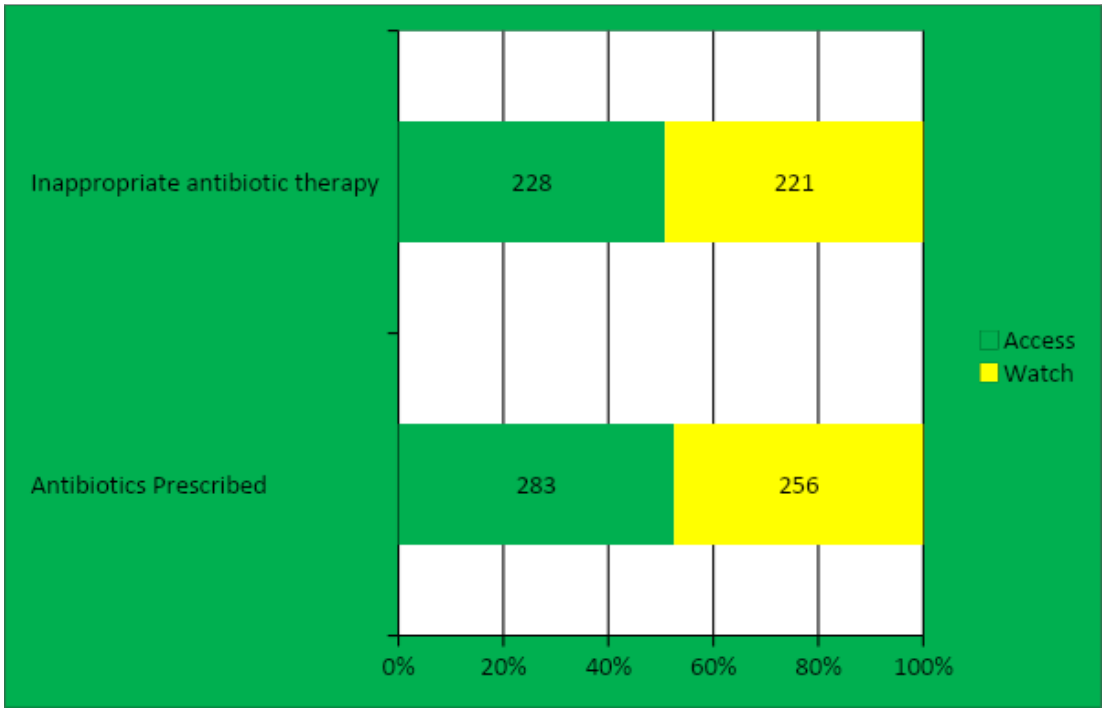

Fig 2: Frequency of inappropriate antibiotic therapy among inpatients of Lagos University Teaching Hospital, Lagos, Nigeria (2013-2014) using the WHO Access, Watch and Reserve (AWaRe) classification

Discussion:

The inappropriate use of antibiotics is a major driver of antibiotic resistance. Regrettably, this study showed that about 4 out of every 5 (82.9%) in patients; treated with antibiotics were placed on inappropriate antibiotic therapy. These findings are higher than those reported in previous studies on inappropriate antibiotic use in hospital in-patients, for example, 50.0% in Nigeria (13), 75.7% in Ethiopia (14), 72.2% in Iran (15), 54.9% in South Africa (16), 38.0% in Namibia (16), 37.0% in Switzerland (17), and 14.0% in Ghana (18). This very high rate of inappropriate antibiotic therapy might lead to increased length of stay in the hospital, cost of hospital stays, morbidity and mortality and also puts the hospital at risk of the emergence of antimicrobial resistance. It is needful to actually develop local

antibiotic guidelines for the hospital's department of medicine and ascertain the compliance rates to show appropriateness of antibiotic prescribing.

Clearly, inappropriate antibiotic prescribing is a complex process which is driven by several factors including lack of antibiotic prescribing guidelines, absence of antimicrobial stewardship programmes and inadequate knowledge of appropriate antibiotic prescribing (19,20). In addition, a major factor driving inappropriate antibiotic prescribing, is an effort by the physicians to use antibiotics to prevent infections i. e. prophylaxis (21). This implies that physicians prescribe antibiotics as a prophylactic measure, even when unnecessary (21). Therefore, it is likely that the antibiotic prescriptions for non-communicable diseases, which occurred in this study, may have been for prophylaxis. However, the IDSA guidelines do not recommend prophylaxis for non-communicable conditions such as hypertension and cerebrovascular disease (12).

In addition, it is important to understand the factors which drive inappropriate prescribing particularly in scenarios where an infection is clearly absent (20). If these factors are not clearly understood, efforts that seek to stimulate behavioural change such as antimicrobial stewardship programmes and antibiotic prescribing guidelines may fail (20,22). Such factors that drive inappropriate antibiotic prescribing will however serve as future areas for research. Data from such research will definitely guide the hospital's antimicrobial stewardship programme in designing effective interventions to curb inappropriate antibiotic use in the hospital.

Furthermore, simple biomarkers of infection such as white blood cell counts, serum procalcitonin (PCT) or C-reactive protein (CRP) are useful to screen for infection in patients admitted to the hospital. For example, a study done in Nigeria showed that 96.2% of patients with culture proven sepsis had high levels of serum PCT (23). The inclusion of such biomarkers in patient management can obviate the inapp- ropriate use of antibiotics (23,24). In addition, the management of patients on antibiotics should involve adequate utilization of the clinical microbiology laboratory in order to ensure guided antibiotic therapy and optimized appropriate antibiotic use (25).

It is noteworthy that most of the patients who had inappropriate choice of antibiotics were placed on multiple antibiotics when the guidelines recommended a single antibiotic. This is similar to other studies done in Nigeria which showed high usage of multiple antibiotic therapy (26). The use of, multiple antibiotic therapy, especially those with similar antibiotic spectrum, results in redundant therapy which could lead to increased costs, increased risk of adverse effects and antagonism and the development of resistance (27). In this regard, it would be important, to educate physicians about the indications for combination therapy.

The rate of inappropriate antibiotic use was lowest among inpatients receiving antibiotics for central nervous system (CNS) infections. This may be due to the fact CNS infections such as meningitis are life threatening conditions and considered medical emergencies; which may have made the physicians pay more attention to the treatment. Overall, the most frequently prescribed initial empiric antibiotics were metronidazole (32.5%), amoxicillin-clavulanate (18.9%), levofloxacin (18.7%) and ceftriaxone (18.7%).

Most of the point prevalence surveys of antimicrobial consumption in Nigeria have shown ceftriaxone and metronidazole as the most commonly prescribed antibiotics in tertiary healthcare facilities like ours (13,26). Similarly, a study done in Uganda showed that the most frequently prescribed antibiotics for in-patients were ceftriaxone (66%), metronidazole (41%), co-trimoxazole (27%), ciprofloxacin (19.0%) and amoxicillin (10.0%) (28). Furthermore, another study done in Pakistan showed that the five most commonly prescribed antibiotics in hospitalized patients were ceftriaxone (21.0%), amikacin (15.2%), cefoperazone plus sulbactam (11.4%), ciprofloxacin (6.4%), metronidazole (5.9%), amoxicillin-clavulanate (5.6%) and clarithromycin (2. 4%) (29).

In this study, the antibiotics most com monly prescribed inappropriately were carbapenems, quinolones, metronidazole and third generation cephalosporins. Nearly half of the total antibiotics prescribed were in the "Watch" group of the WHO AWaRe category of antimicrobials and none in the "Reserve" group. These figures are clearly a deviation from the WHO recommendations (30). According to the WHO, about 60% of antibiotic consumption should be from the Access group (30). Clearly there is a need to curb the inappropriate use of antibiotics in the hospital in order to delay the emergence of antibiotic resistance.

Going by the guidelines, the carbapenems were an inappropriate choice all the time they were used in our study. Carbapenems are the last line of defense against multidrug resistant (MDR) Gram-negative bacterial infections and should be used based on culture results or when there are risk factors for MDR infections (31). Also, narrow spectrum antibiotics such as aztreonam and temocillin, with proven efficacy against MDR infections should be included in antibiotic guidelines (32). The use of such narrow spectrum antibiotics can reduce the inappropriate use of broad-spectrum antibiotics such as the carbapenems (32). Furthermore, in this study, the macrolides had the lowest rate of inappropriate use. This may

be because they were majorly used to treat community acquired pneumonia, which is in accordance with the IDSA guidelines. These findings differ from a study done in Pakistan where 3rd generation cephalosporins (54.2%) were the most frequently prescribed inappropriate antibiotics (29), and in Eritrea where imipenem (100%), amikacin (100%) and piperacillin-tazobactam (100%) were described as the most inappropriately prescribed antibiotics (33).

From the foregoing it is absolutely clear that inappropriate antibiotic therapy is a challenge that must be urgently curbed at the hospital where this study was conducted. Fortunately, antibiotic stewardship programmes can curb the inappropriate use of antibiotics in hospitals (34). However, adequate funding of antibiotic stewardship programmes and the robust support of the hospital's management are necessary to ensure successful programme outcomes (34). Furthermore, efforts such as hospital guidelines and frequent education of physicians on proper antibiotic prescribing are also useful interventions (34).

Conclusion:

In conclusion, a high rate of inappropriate antibiotic therapy (82.9%) was found in this study. The inappropriate antibiotic therapy was due to inappropriate indication where antibiotic therapy was unnecessary, wrong choice of antibiotics according to IDSA guidelines and inappropriate dose and or duration where the choice of antibiotic was correct. The most frequently prescribed antibiotics were metronidazole, amoxicillin-clavulanate, levofloxacin and ceftriaxone. The carbapenems were the antibiotic most prescribed inappropriately. The presence of an antimicrobial stewardship programme in the hospital will curb the problem of inappropriate antibiotic use.

Contributions of authors:

IIO drafted the manuscript and was responsible for data acquisition and analysis. POO and OOO critically reviewed the manuscript for important intellectual content. All authors approved the manuscript for publication.

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Authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

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