Original Research Article

Empirical antibiotic prescription pattern among patients in a Nigerian tertiary hospital, Is there evidence of irrationality?

ABSTRACT

Background: Resistance to antibiotics is spreading rapidly around the world with its associated morbidity and mortality. Infections are becoming increasingly difficult to treat resulting in increasing cost of medical care. In low income countries with high infectious disease burden, antibiotic resistance is reported to be accelerated by irrational prescriptions in health facilities. In the absence of adequate resources, many clinicians engage in empirical antibiotic prescriptions some of which their appropriateness is questionable. There is need to for laboratory evidence to justify empirical antibiotic use in the light of increasing resistance to commonly prescribed antibiotics

Aims: This study aims to determine empirical antibiotic prescription pattern and to determine rationality using resistance profile of common bacterial isolates in the hospital.

Methods: Antibiotic prescriptions in the NHIS department and antibiogram records were obtained from pharmacy and laboratory records respectively. Analysis was carried out using descriptive statistics and comparism between antibiotics prescribed and their respective resistance pattern were compared to determine rationality.

Results/Discussion: The Penicillins and Quinolones were the most prescribed class of antibiotics and resistance range between 30 – 90% and 3 – 23% respectively. Resistance to other antibiotics was high thus making empirical prescriptions irrational in most of the cases. These findings have been consistently reported in several studies so widespread empirical antibiotic prescriptions are not in tandem with principles of rational drug use.

Conclusion: Antibiotic resistance is common among hospital isolates, so there is need to emphasize that prescriptions be based on laboratory evidence of microbial sensitivity.

Keywords: Antibiotics, Empirical prescription, rational drug use, Microbial resistance

INTRODUCTION

Antibiotics have been the cornerstone of modern medical care particularly in bacterial infections. Since the introduction of antibiotics over eight decades ago, infections that would have otherwise caused life threatening are now treatable. Infections from surgery, immunosuppression, traumatic injuries and prophylaxis have dramatically improved survival. In recent years however, reports of increasing microbial resistance have become consistent across a broad range of microorganisms [1,2,3,4,5]. Infections that were once treatable are now becoming difficult to treat resulting in increased morbidity and mortality, high cost of medical care and threatening global public health [6,7,8,9,10]. There is global evidence of the decline of effectiveness of antibiotics across all classes, there is however country and regional variations in antimicrobial resistance pattern [11].

Microbial resistance is reported to be a significant factor in mortality related to infectious diseases annually [12]. In less developed countries with high infectious disease burden and absence of reliable data, estimates of mortality also run into hundreds of thousands annually [13,14,15]. The rise in antimicrobial resistance in low income countries is related to a number of factors including easy availability of antibiotics, self-medication, extensive use in agriculture, and failure in infectious disease control system in healthcare facilities etc.[16,17] and irrational prescription practices[18,19.20,21,22].

Antibiotic prescription practices vary widely between countries and healthcare facilities; factors which have been reported to influence antibiotic use includes infectious disease burden, prescription habit of clinicians, microbial resistance pattern, regulatory control, standard treatment guidelines, availability and economic factors[23,24,25,26,27,28,29,30,31]. In resource scarce setting where routine empirical antibiotic use is widespread, prescription pattern vary widely [22]. For instance, some studies reported that Fluoroquinolones, Penicillins and Cephalosporins are the most prescribed class of antibiotics [22,32] while other studies reported high level use of Beta lactams [17,33].

The relationship between irrational antibiotic use and microbial resistance is well established and the current trend of antibiotic use is suggestive of an ongoing problem irrespective of healthcare setting. Among the most commonest microorganisms whose resistance to antibiotics is of global concern are *Escherichia coli, Streptococcus pneumoniae, Shigella species Neisseria gonorrhea* and non typhoidal *Salmonella Typhi* [34,35,36,37,38,39,40]. Empirical antibiotic use is widely reported in literature either in the form of self-medication or irrational use in healthcare facilities, studies have reported that up to 50% of antibiotic prescriptions may be in the form of empirical prescriptions [41]. Microbial sensitivity results are rarely used in many health facilities because of poor healthcare infrastructure and paucity of qualified manpower [42,43]. In many healthcare facilities where laboratory services are available, antibiotic prescriptions are not routinely based on microbial sensitivity result which is a common cause of irrational antibiotic use[26,41,44], antibiotic prescription studies have reported high levels of irrational use and an increasing level of resistance to commonly used antibiotics[23,45].

While it may be impractical to wait for antibiotic sensitivity tests before in all clinical situations, it is important that empirical prescription of antibiotics is regulated so as preserve their effectiveness and limit risk of treatment failure due to microbial resistance. It's not clear if microbial resistance containment measures such as antibiotic stewardship programs, continuing education for prescribers, patient education and regulatory control are contributing to improved antibiotic use in developing countries due to absence of reliable data [46,47,48]. In Nigeria there are few published studies that used microbial sensitivity pattern as a basis for determining level of irrational antibiotic prescriptions in healthcare facilities, so this study is an attempt in that direction.

In addition using World Health Organization quality prescribing indicators, it is important that antibiotic use should reflect the dynamics of prevailing microbial sensitivity pattern. Physicians have for a long time viewed antibiotics as "magic bullets" for all infectious disease, that perception should now give way to the new reality that "bugs" no long respond to therapy as before. It is expected that treatment of bacterial infections should have been based on laboratory evidence to qualify as rational antibiotic use. This appears not to be the case at the moment even in many tertiary healthcare facilities in the country; this must change as high level of microbial resistance is a potential threat to public health.

Objectives: To determine empirical antibiotic use pattern and compare with resistance of common bacterial isolates so as to assess rationality of prescriptions

METHODS

Setting: The study was carried out among patients insured by national health insurance scheme receiving at the University of Maiduguri teaching hospital, North east Nigeria.

Study design: This is a cross sectional retrospective study of prescriptions given to outpatients that filled their prescriptions in the NHIS pharmacy of the hospital.

Data collection: Prescription records were obtained from National health insurance scheme [NHIS] pharmacy covering the period between January 2017 and May 2018. A total of 5079 antibiotic containing prescriptions were used for this study. All eligible prescriptions selected had patient NHIS numbers clearly indicated. Prescription records that are incomplete, illegible and those not written on NHIS prescription forms were excluded. Information relating to antibiotics, duration of therapy, number of drugs per prescription, antibiotic prescription errors and demographic data were extracted

Data analysis: The data was entered into SPSS 21 and analyzed using descriptive statistics. Irrational prescriptions were determined by comparing antibiotics prescribed and resistance level from laboratory results. Prescriptions were also reviewed for prescription errors, dosage errors, formulation errors and frequency of administration errors.

Ethical approval: This was obtained from the health research ethics committee of University of Maiduguri teaching hospital

RESULTS

Demographic data showed that females were about two thirds of patients and majority of them are below 40 years old [Figure 2 and 2].

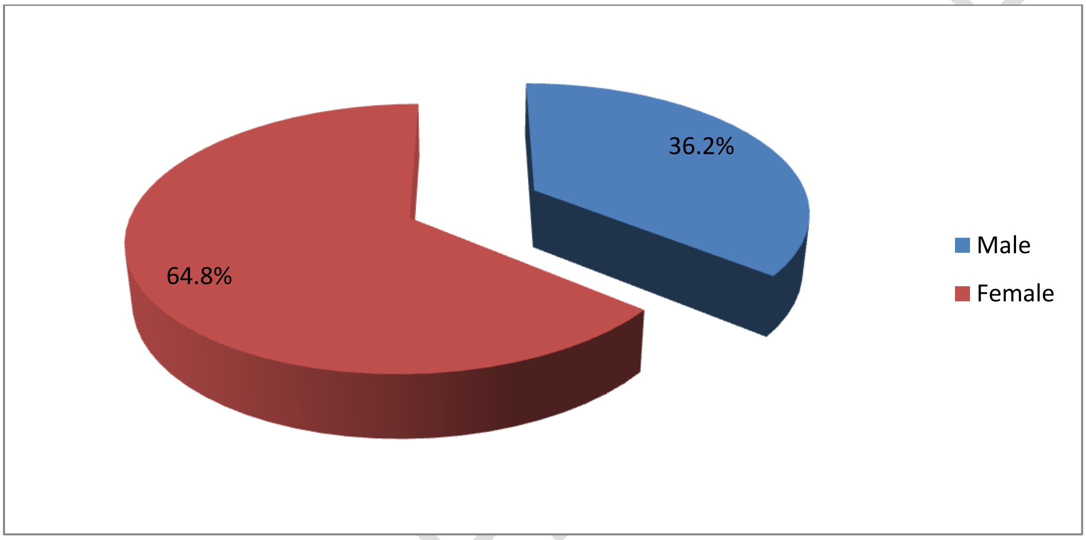

Figure 1: Gender distribution

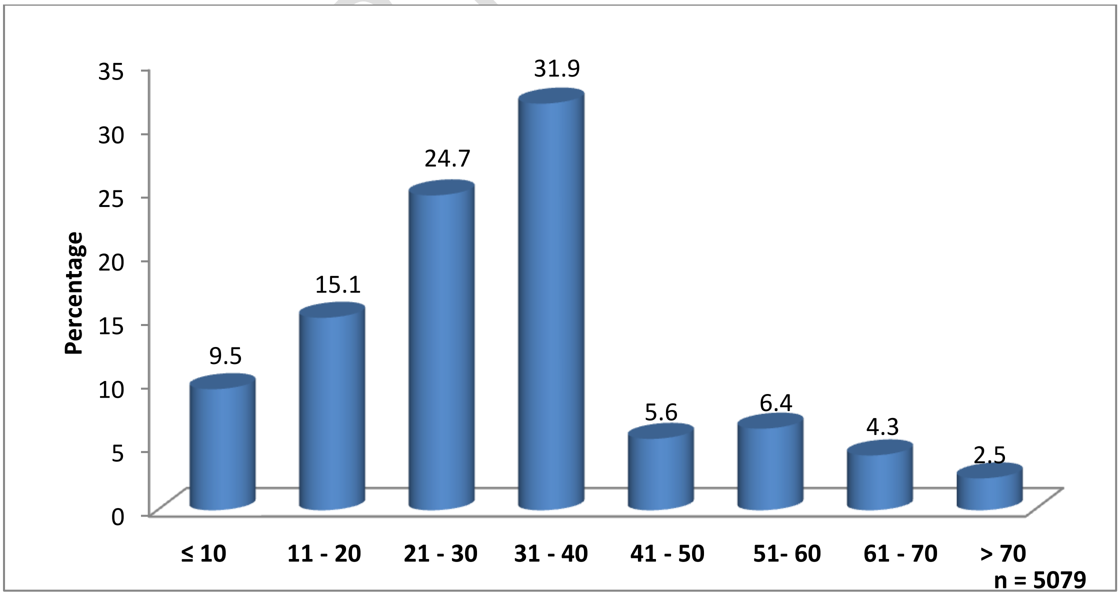

Figure 2: Age distribution

Prescription analysis showed that Penicillins [39%] accounted for the largest group of antibiotics given to patients. This is followed by Quinolones and Metronidazole with prescription rate of 25% and 17.8%

respectively. Among individual antibiotics Amoxicillin + Clavulanic acid, Metronidazole and Ciprofloxacin were the most prescribed representing 28.2%, 17.8% and 13.1% respectively.

Table 1: Antibiotics prescription pattern [n = 5079]

Name of drug	Number [%]
Amoxicillin + Clavulanic acid	1433 [28.2]
Amoxicillin	448 [8.8]
Ampicillin + Cloxacillin	108 [2.1]
Ciprofloxacin	663 [13.1]
Azithromycin	75 [1.5]
Cefuroxime	217 [4.3]
Ceftriaxone	13 [0.3]
Cephalexin	11 [0.2]
Erythromycin	294 [5.8]
Clarithromycin	56 [1.1]
Clindamycin	17 [0.3]
Levofloxacin	378 [7.4]
Metronidazole	906 [17.8]
Ofloxacin	146 [2.9]
Sparfloxacin	58 [1.1]
Doxycycline	187 [3.7]
Cotrimoxazole	38 [0.7]
Nitrofurantoin	23 [0.5]
Lincomycin	8 [0.2]

Antibiotic combination therapies were present in 12.8% of prescriptions; the most common is Penicillins + Metronidazole accounting for more than half of combination therapies. Metronidazole was found in 93.8% prescriptions in combination with different classes of antibiotics. The Quinolones were also found in 24.4% of prescriptions with other classes of antibiotics.

Table 2: Antibiotic combination therapy [n = 652]

Antibiotic combinations	Number [%]
Quinolones + Metronidazole	138 [21.2]
Penicillins + Metronidazole	357 [54.8]
Penicillins + Macrolides	13 [1.9]
Cephalosporins + Metronidazole	7 [1.1]

Macrolides + Metronidazole	49 [7.5]
Lincomycin + Metronidazole	6 [0.9]
Cotrimoxazole + Metronidazole	6[0.9]
Quinolones + Tetracycline	21 [3.2]
Penicillins + Tétracycline	7 [1.1]
Tetracycline + Metronidazole	48 [7.4]

Prescription errors involving wrong dosage and frequency of dosing were found in 15.6% of prescriptions. A breakdown of errors showed that dosage errors accounted for 51.3% and wrong dosing frequency occurred in 48.7% of prescriptions with errors. The highest number of errors occurred with Cephalosporins and macrolides representing about 45% for each of them.

Table 3: Prescription errors [n - 797]

Drugs	Dosage errors [%]	Dosing frequency errors [%]
Penicillins	17 [2.1]	18 [2.2]
Cephalosporins	178 [22.3]	189 [23.7]
Macrolides	187 [23.5]	173 [21.7]
Quinolones	19 [2.4]	4 [0.5]
Lincomycins	8 [1.1]	4 [0.5]
Total	**409 [51.3]**	**388 [48.7]**

A comparism of empirical antibiotic prescription pattern and bacterial resistance pattern [Table 4] reveal that most antibiotics given to patients without laboratory confirmation of sensitivity may be considered to be irrational. For instance, resistance to most commonly prescribed Amoxicillin + Clavulanic acid, Cotrimoxazole and Clindamycin may be inappropriate because resistance is as high as 20 – 90%. Resistance to Quinolones is generally below 20% while that of the Macrolides is between 6 – 40%. Empirical prescription of antibiotics against these isolates is likely to result in treatment failure as many strains are becoming resistant to commonly used antibiotics. The result also highlights the problem of resistance to third generation Cephalosporins and older generation Quinolones.

Table 4: Comparism of microbial resistance level and antibiotic prescription pattern [%]

Drug	*SA* [n= 259]	*EC* [n = 138]	*KP* [n = 109]	*CF* [n = 99]	*PS* [n = 25]	*PA* [n = 23]	*HS* [n = 38]	*Average resistance* [%]	PIA [%] Range
Amoxicillin+ Clavulanic acid	73.4	88.0	90.3	73.3	90.9	64.4	39.7	74.3	39 - 90
Cloxacillin	66.4	32.1	23.0	31.7	---	29.8	51.2	39.0	NA
Clarithromycin	25.8	6.9	22.2	19.4	---	32.5	14.6	20.2	6 - 32

Clindamycin	49.4	20.7	21.5	22.8	---	32.5	42.7	31.6	20 – 49
Cotrimoxazole	71.3	74.2	73.5	55.5	84.1	53.5	29.7	63.1	29 – 84
Erythromycin	33.7	12.3	21.7	16.9	13.6	29.8	40.6	24.1	12 – 40
Gentamycin	12.2	30.8	40.9	26.9	27.8	10.5	9.1	22.6	NA
Ceftriaxone	10.9	41.4	50.6	30.6	42.4	36.8	6.1	31.3	6 – 50
Ampiclox	13.2	---	1.9	5.7	4.5	---	22.1	9.5	1 – 22
Amoxicillin	13.7	1.6	5.4	14.1	18.2	5.3	29.7	12.6	1 – 29
Norbactin	9.6	3.1	10.9	11.4	9.1	5.3	23.6	10.4	NA
Ciprofloxacin	11.8	14.1	8.7	6.2	4.5	5.3	22.1	10.4	4 – 23
Perfloxacin	3.9	1.6	8.9	5.7	4.5	5.3	----	4.9	NA
Nalidixic acid	6.1	10.7	15.2	14.9	13.6	5.1	6.1	10.2	NA
Streptomycin	6.4	1.6	5.4	8.6	4.5	----	6.1	5.4	NA
Ofloxacin	3.8	14.5	17.2	14.6	21.2	----	----	14.3	3 – 21
Levofloxacin	6.9	14.2	12.3	9.3	----	5.3	----	9.6	5 – 14
Chloramphenico	5.9	5.9	1.9	5.7	----	----	17.6	7.4	NA
Tetracycline	15.1	40.3	41.1	34.7	77.3	47.4	17.1	39.0	15 – 77

Key: SA = Staph aureus, EC = Escherichia coli, Klebsiella pneumonia, CF = Coliform species, PS = Proteus species, PA = Pseudomonas aeruginosa, HS = Haemolytic streptococci, PIA = potentially inappropriate antibiotic , NA = not applicable

DISCUSSION

Antibiotic prescription pattern in a healthcare facility represents the overall influence of multiple factors. The result of this study showed that Penicillins, Quinolones and Macrolides were the most frequently prescribed antibiotics. Individual antibiotics prescription prevalence showed that Amoxicillin + Clavulanic acid, Metronidazole and Ciprofloxacin were the most prescribed. This result is in contrast to other studies [24,28,49,50,51,52]. Several studies have reported high rate of irrational antibiotic prescription and a significant percentage were empirically prescribed for patients [26,41,53,54].

High rate of empirical prescription of antibiotics is generally related to poor health infrastructure, inadequate human capacity, poor regulatory control and lack of antibiotic stewardship program in many developing countries like Nigeria [42,55,56] . There have been suggestions that empirical antibiotic use is not only related to inadequate or absent laboratory services, but also due to failure to utilize them even where they are available [57].

There is ample evidence in literature that variations in antibiotic prescribing practices have both clinical and non-clinical factors. Irrational empirical antibiotic prescription practice is said to be one of the major contributors to microbial resistance which is reported to be rising globally. The results of this study showed that 39 – 90% of seven common bacterial isolates were resistant to Amoxicillin + Clavulanic acid, similar high level of microbial resistance was also observed for Cotrimoxazole [29 –

84%], Tetracycline [17 – 77%], Ceftriaxone [6 – 50%] and Gentamycin [9 – 40%]. The high level of antibiotic resistance level in this study is comparable to many other studies, though differences exist in the magnitude [58,59,60,61,62].

This high level of multidrug resistance to commonly encountered pathogens is suggestive of the fact that empirical antibiotic prescription is no longer justified. Many patients will not achieve clinical and/or bacteriological clearance of infections. Literature evidence showed that high level of resistance have been reported *for E. coli, Staphylococcus aureus*, *Klebsiella pneumoniae, Pseudomonas aeruginosa* etc. [10,63,64,65]. Antimicrobial resistance is a global phenomenon and no region or country is spared, so there is need accelerate containment effort at the facility level. To preserve low cost broad spectrum antibiotics there should be renewed focus on laboratory confirmation of microbial susceptibility results before antibiotics are prescribed [66,67,68,69].

This is particularly urgent with increasing evidence of multidrug resistant strains of microorganisms being found in healthcare facilities [45,70]. Apart from the Quinolones, Methicillin and Chloramphenicol other antibiotics recorded more than 20% resistance to seven bacterial isolates; this should be a cause of concern to facility level providers and policy makers.

Prescription errors frequently occur and it's a common cause of irrational antibiotics use particularly as it relates to dosage, frequency of administration, formulation, timing, duration of treatment, appropriateness [71,72,73]. The prevalence of errors observed in this study associated with correct dosage and frequency of administration is totally preventable if basic standard of prescription writing are implemented. These errors can negatively affect clinical outcomes, prolong morbidity and may ultimately result in death; there is also increased risk of adverse drug reactions particularly among the most vulnerable [74,75].

There is urgent need to change current antibiotic prescribing practice in the light of increasing multidrug microbial resistance to the most commonly prescribed antibiotics. Results of this study suggest that apart from the Quinolones with relatively lower resistance profile, other antibiotics may be associated with higher frequency of treatment failure. In order to achieve improvement in antibiotic prescription practices multidisciplinary teams should be set up to manage antibiotic stewardship program in the hospital. This program is being implemented worldwide as an attempt to slow down resistance in many healthcare facilities. There is evidence that successful implementation of stewardship programs in hospitals has improved antibiotic prescribing practices and use elsewhere

[76,77,78]. A number of studies that looked at the impact of antibiotic stewardship programs showed that most studies have differing assessment tools and there are challenges with quality of evidence [79,80,81,82]. Majority of outcomes studies showed positive improvement in both clinical and economic outcomes for patients [76,83]. While it is acknowledged that empirical antibiotic use is permissible in acute clinical conditions, it should be reserved for emergencies where laboratory confirmation of microbial sensitivity may be delayed. The healthcare system in this country and patients cannot afford further explosion of microbial resistance to cheap commonly available antibiotics.

Conclusion: Resistance to commonly prescribed antibiotics is high and that makes most empirically prescribed antibiotics to be irrational. It is imperative that emphasis be placed on laboratory confirmation of microbial sensitivity as the basis antibiotic prescription.

Competing interests: The declare no competing interests

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