Bacterial resistance to commonly prescribed antibiotics in a tertiary care hospital: a retrospective review of evidence

Abstracts

Background: Antibiotic resistance is a growing global healthcare challenge and efforts to contain it are being outpaced by rapid emergence of resistant microbes. Common environmental pathogens have been reported to manifesting resistance to several antibiotics to which they were once sensitive. In the hospital close contact of patients and caregivers allow resistant strains to easily spread in hospital wards. Evidence of antibiotic resistance is needed to inform rational selection of drugs for infectious diseases.

Aim: The aims of this study are to determine common pathogens in patients' bacterial isolates and their antibiotic sensitivity profiles.

Methods: This was a cross sectional retrospective study using antibiotic resistance profiles of bacterial isolates obtained from patients. Antibiogram records for one year period were obtained and relevant data extracted for analysis

Results/Discussion: The most commonly isolated bacteria included *Staphylococcus aureus, Escherichia coli* and *Klebsiella pneumoniae* which together accounted for over two thirds of isolates. Most of the bacterial isolates were resistant to at least four antibiotics with Penicillins, Sulphonamides and Tetracyclines having the highest level of resistances. Resistance to these antibiotics is well reported in literature and thus threatens their efficacy in treatment of infectious diseases.

Conclusion: Antibiotic resistance is high and there is need to emphasize evidence based rational prescriptions to preserve the efficacy of current antibiotic stock.

Introduction: Antimicrobial resistance is a rising global problem particularly in low to middle income countries where health care systems are weak. A combination of high infectious disease burden, poor access to quality medicines and diagnostic services as well as low availability of second line antibiotics all combine to increase morbidity and mortality [WHO 2012, WHO 2004, Frean *et al*, 2012]. Antimicrobial resistance is now widespread threatening future public health and making infectious diseases difficult to manage. In recent years emerging evidence is showing that irrational use of antibiotics in both animals and humans is accelerating the development of multiple microbial resistance to commonly prescribed antibiotics particularly in low income countries [Levy *et al*, 2004, Lateef 2004, Nsofor and Iroegbu 2012, Ohi and Luther 2011].

In many developing countries where a combination of weak healthcare systems and poor regulatory controls allow antibiotics to be freely available without medical prescription. Irrational prescription and misuse of antibiotics contribute to emergence of resistance [Lim *et al*, 2015, Zimmer 2015]. In Nigeria, several studies have reported high level of irrational prescription of antibiotics in healthcare facilities [Umar *et al*, 2018, Eshiet *et al*, 2015, Akinyandenu *et al*, 2014, Oduyebo *et al*, 2017]. While prevalence may vary widely between countries, frivolous antibiotic prescription is a global problem [Kourlaba *et al*, 2016, Akram *et al*, 2014, Kaur *et al*, 2018].

Antibiotic resistance to antibiotics is well documented particularly among five bacterial pathogens [*Staphylococcus aureus*, *Escherichia coli*, *Proteus spp*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, alpha *Haemolytic streptococci* etc.]. In China, resistance of *Escherichia coli* to Quinolones is in the range of 53 – 56% and 31 – 70% with third generation Cephalosporins. Resistance of *Klebsiella pneumoniae* is reported to be between 25 – 52% [Cui *et al*, 2017].

In sub Saharan Africa, some studies reported resistance to Ampicillin by *Escherichia coli* and *Klebsiella pneumonia* averaged 75.4% and 97% of strains respectively; a third of these organisms are resistant to Amoxicillin + Clavulanic acid [Adjei *et al*, 2012, Oli *et al*, 2010, Oladeinde *et al*, 2011, Muoneke *et al*, 2012, Rabasa et al 2002, Okwori *et al*, 2010, Mava *et al*, 2012, Sire *et al*, 2007]. *Escherichia coli* which is said to be the leading cause of urinary tract infections globally [Stamm *et al*, 2001, Russo *et al*, 2003] and often result in increased morbidity and mortality [Dehbanipour *et al*, 2016].

Resistance to Quinolones by many microbes is becoming a major concern among clinicians globally [Pitout *et al*, 2008, Urban *et al*, 2010, Amabile-Cuevas *et al*, 2010, Silva-Sanchez *et al*, 2013, Paniagua-Contreras *et al*, 2017, CDDEP 2015]. Prevalence of Methicillin resistant *Staphylococcus aureus* [MRSA] varies widely between countries and sometimes between various departments of the same hospital [Robicsick *et al*, 2008, Gordon *et al*, 2008, Jarvis *et al*, 2007, Haznedaroglu *et al*, 2010, Ramirez-Castillo et al, 2018] and while its occurrence is decreasing in developed countries because of sustained action, the reverse is the case in many developing countries.

The emergence of multidrug resistant strains of *Pseudomonas aeruginosa*, *Klebsiella* spp and MRSA in hospital settings is well reported in literature {Rice 2006, Misic *et al*, 2014, Iredell *et al*, 2016]. For instance resistance of gram negative bacterial isolates to Aminoglycosides and Quinolones is reported to have increased in recent years [Bubonja-Sonje *et al*, 2015, Labarca *et al*, 2016]. While prevalence is highly variable, there is consistent evidence to conclude that high levels of resistance of both gram positive and negative bacteria pose significant risks to public health [Nsofor *et al*, 2016, Jombo *et al*, 2011,, Muluye *et al*, 2014, Ruiz *et al*, 2016, Trojan *et al*, 2016, CDDEP 2015].

Multidrug resistance above 50% have been reported with many bacterial strains in many sub Saharan African countries [Kariuki *et al*, 2015]. In one study, it was observed that 84% of *Klebsiella pneumonia* strains were resistant to Cephalosporins; about 47% of Enterobacteriacea isolates were resistant to third generation Cephalosporins and 31 – 94% of isolates were resistant to Chloramphenicol [Le Daore *et al*, 2014]

Overall, high rates of resistance of gram positive pathogens in hospital acquired infections are reported to be highly resistant to first line antibiotics [Leopold *et al*, 2014]. Evidence of high level resistance to commonly prescribed antibiotics is yet to significantly influence treatment guidelines of many common invasive bacterial infections. The impact of rising antimicrobial resistance on empirical antibiotic prescription practices is yet to be widely evaluated in healthcare facilities in low income countries including Nigeria. The cost of microbial resistance and impact on patient clinical outcomes has also received little research attention in low income countries [Blomberg *et al*, 2005]. Microbial sensitivity to antibiotics has changed and evidence from healthcare facilities can provide valuable insight into trends, spread and severity. This will help in formulating antibiotic use guidelines in hospitals and the evidence to guide cautious use of broad spectrum and new generation antibiotics.

Objectives

- To determine level of microbial resistance to common antibiotics
- To investigate prevalence of pathogenic bacteria in laboratory samples

Methods

Setting: The study was carried out in the microbiology department of the University of Maiduguri teaching hospital, Borno State Nigeria.

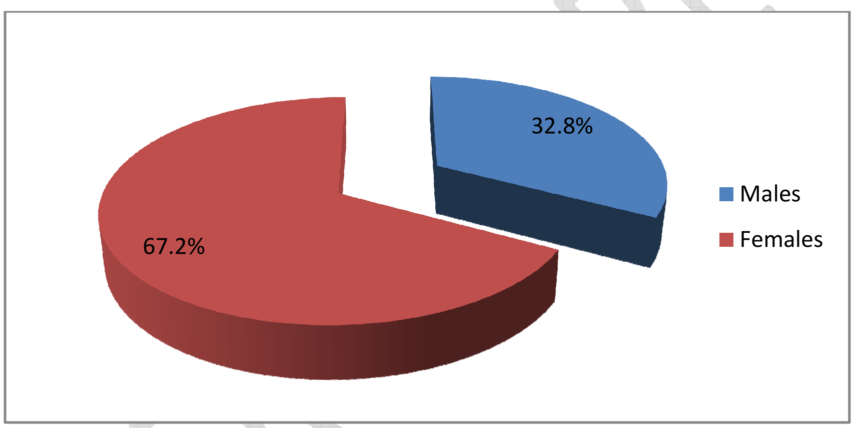
Study design: This was a cross sectional retrospective study using microbial sensitivity test records in the Microbiology laboratory of the hospital

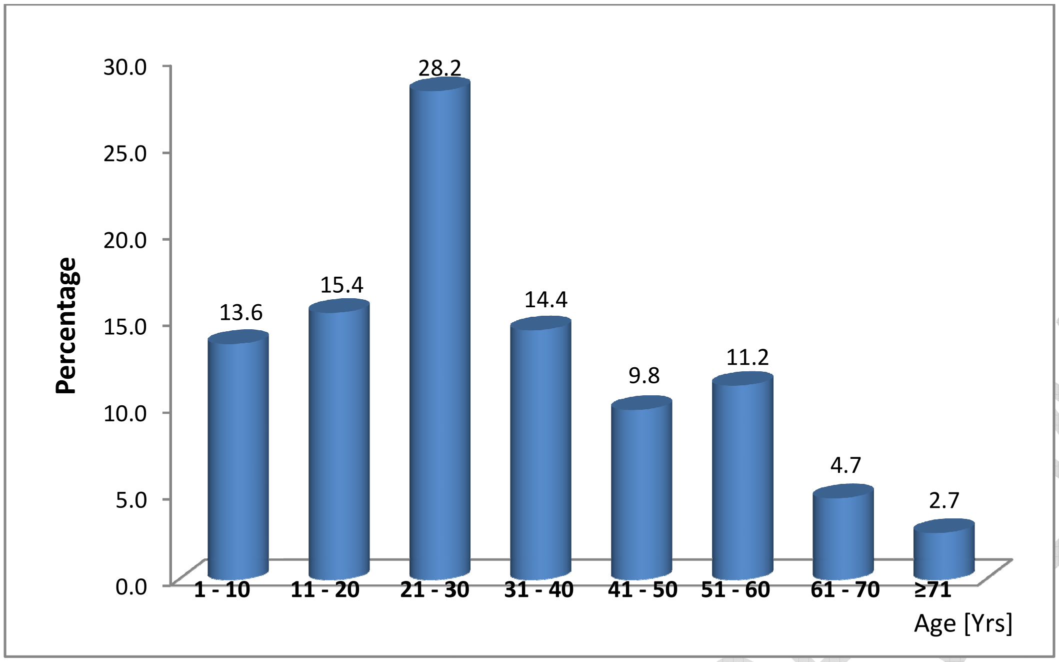
Data collection: Records of bacterial isolates from all patient samples and their sensitivity/resistant results were extracted into data collection forms. Isolates were from Urine, Blood, Sputum, swab [HVS, wound and pus]. Antibiogram followed standard test procedures resistance for each bacteria is summarized as a range and average.

Data analysis: The data was entered into SPSS 20 for descriptive analysis. Results were express as percentages and average.

Ethical approval: It was received from human ethics research committee of University of Maiduguri teaching hospital.

Results:





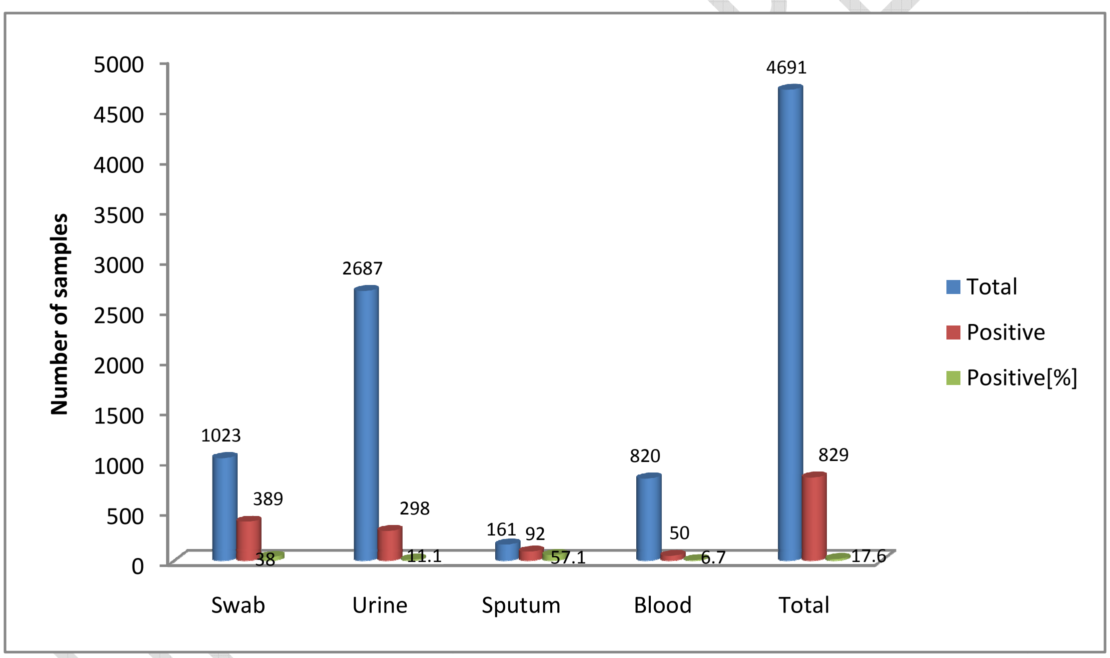


Figure 1: Distribution of positive cultures

Table1: Distribution of isolates among clinical samples

Specimen	SA	EC	KB	PT	PS	HS	CF
Swab	**244**	**64**	**58**	**27**	**29**	**7**	**36**
Urine	**23**	**114**	**36**	**8**	**10**	**--**	**52**
Sputum	**10**	**3**	**9**	**--**	**4**	**39**	**4**
Blood	**32**	**7**	**6**	**--**	**--**	**--**	**7**

Total	**309**	**188**	**109**	**35**	**43**	**46**	**99**

Key: SA = Staph aureus, EC = E.Coli, KP = Klebsiella pneumoniae, PT = Proteus spp, PS =Pseudomonas aeruginosa, Haemolytic streptococci HS, CF = Coliforms

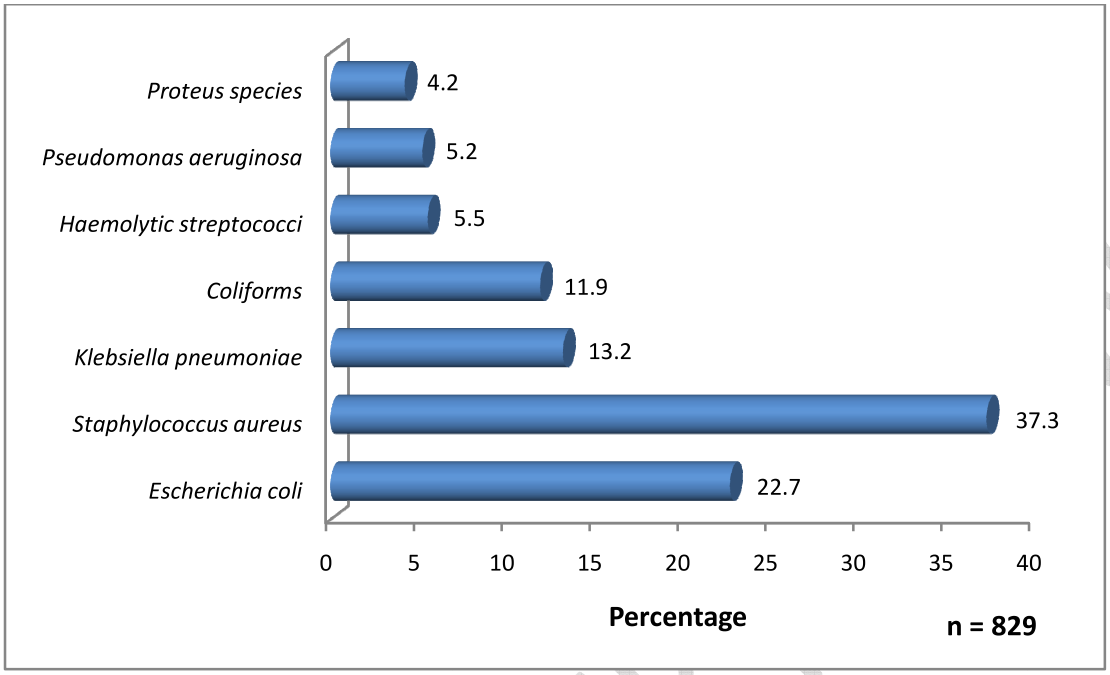


Figure 2: Prevalence of isolates

Table 2: Mean number of resistant antibiotic strains [n = 829]

Bacteria	**Number**	**Antibiotic resistant strains** Mean ± SD
Escherichia coli	188	4.06 ± 1.78
Staphylococcus aureus	309	4.11 ± 1.92
Klebsiella pneumonia	109	4.82 ± 1.57
Coliforms	99	4.18 ± 1.72
Proteus spp	35	4.56 ± 1.18
Pseudomonas aeruginosa	43	4.58 ± 1.38
Haemolytic streptococci	46	3.78 ± 1.42

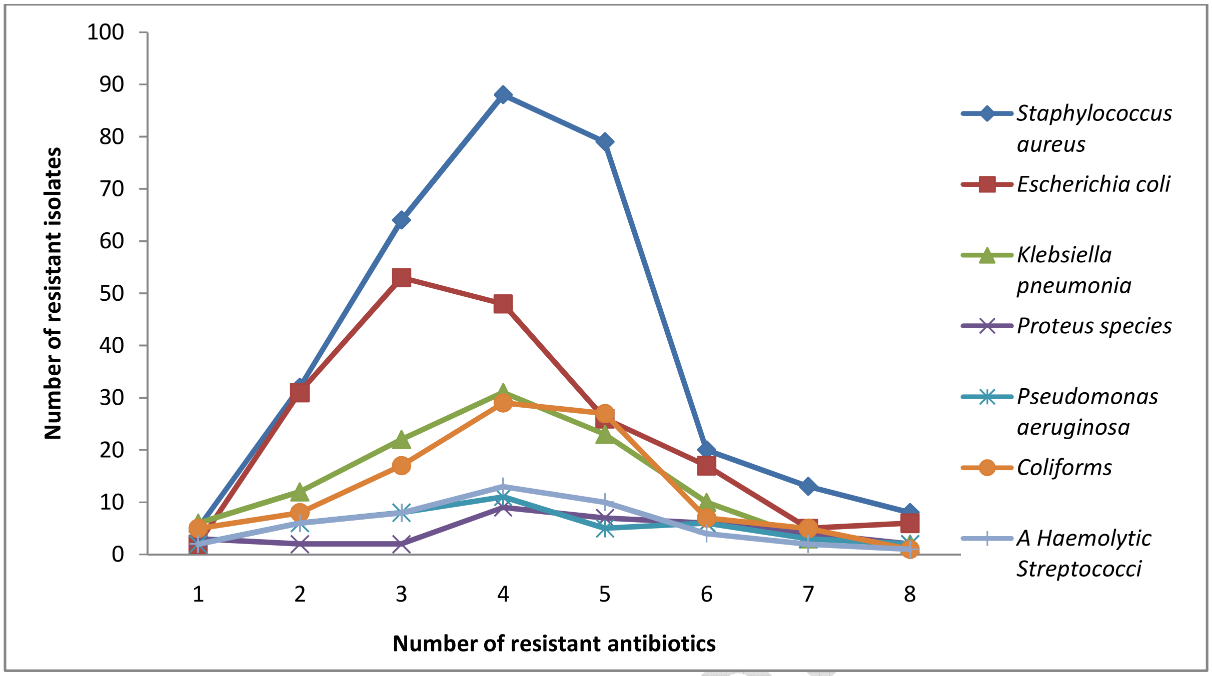


Table 3: Resistance to antibiotics

Drug	EC[%] n = 188	SA[%] n = 309	COL[%] n = 99	KP[%] n = 109	PT[%] n = 35	PS[%] n = 43	HS[%] n = 46	Resistance range [%]
Cloxacillin	30[15.9]	154[49.3]	22[22.2]	29[26.6]	4[11.4]	6[13.9]	17[36.9]	11.4 – 49.8
Clindamycin	21[11.2]	36[11.5]	17[17.2]	21[19.3]	1[2.1]	7[16.3]	17[36.9]	2.1 – 36.9
Amx + CLA	131[69.7]	208[66.7]	86[86.9]	94[86.2]	23[65.7]	20[46.5]	15[32.6]	32.6 – 86.9
Cotrimoxazole	110[58.5]	183[58.7]	67[67.7]	81[74.3]	18[47.4]	15[34.9]	18[39.1]	34.9 – 74.3
Clarithromycin	19[10.1]	74[23.7]	18[18.2]	22[20.2]	6[17.1]	7[16.3]	4[8.7]	8.7 – 23.9
Tetracycline	60[31.9]	56[17.9]	38[38.4]	51[46.8]	17[48.6]	9[20.9]	5[10.8]	10.8 – 48.6
Ceftriaxone	51[27.1]	46[14.7]	31[31.3]	50[45.9]	6[17.1]	7[16.3]	2[4.3]	4.3 – 45.9
Gentamycin	36[19.1]	33[10.6]	28[28.3]	41[37.6]	9[23.7]	2[4.7]	NA	4 7 – 37.6
Methicillin	11[5.9]	8[2.6]	10[10.1]	9[8.2]	5[14.3]	NA	NA	2.6 – 14.3
Erythromycin	12[6.4]	108[34.6]	14[4.1]	21[19.3]	3[3.6]	7[16.3]	10[21.7]	3.6 – 34.9
Ofloxacin	19[10.1]	10[3.2]	13[13.1]	14[12.8]	3[8.6]	NA	NA	3.2 – 13.1
Levofloxacin	7[3.7]	8[2.6]	5[5.1]	10[9.2]	NA	NA	NA	2.6 – 9.2
Ciprofloxacin	4[2.1]	23[7.4]	5[5.1]	9[8.2]	1[2.9]	1[2.3]	9[19.6]	2.1 – 19.6
Nalidixic acid	9[4.8]	18[5.8]	9[9.1]	12[11.0]	3[8.6]	1[2.3]	2[4.3]	2.3 – 11.0
Ampiclox	NA	15[4.8]	2[2.0]	1[0.9]	1[2.9]	NA	9[19.6]	1.0 – 19.6
Amoxicillin	1[0.5]	20[6.4]	5[5.1]	3[2.7]	4[11.4]	1[2.3]	14[30.4]	1.0 – 30.4
Norbactin	2[1.1]	20[6.4]	4[4.0]	6[5.5]	2[5.7]	1[2.3]	10[21.7]	1.1 – 21.7

Perfloxacin	1[0.5]	8[2.6]	3[3.0]	5[4.6]	1[2.9]	NA	NA	1.0 – 4.6
Streptomycin	1[0.5]	13[4.2]	3[3.0]	3[2.7]	1[2.9]	NA	NA	1.0 – 4.2

***Key**: EC = Escherichia coli, SA = Staphylococcus aureus, COL = Coliforms, KP = Klebsiella pneumonia, PT = Proteus spp, PS = Pseudomonas aeruginosa, HS = Haemolytic streptococci, AMX+CLA = Amoxicillin + Clavulanic acid, NA = not applicable*

Discussion: The emergence and rapid spread of antibiotic resistance in sub Saharan Africa is endangering efficacy of limiting treatment options in the face of high infectious disease burden. Healthcare facilities are recognized as a place where resistance to antibiotics can easily be spread among patients. The results of this study showed that *Staphylococcus aureus* accounted for more than a third of all isolates from clinical samples followed by Escherichia coli. These two bacteria account for more than two thirds of all isolates which is comparable to earlier study by Masyeni *et al*, 2018 but lower than that reported in several studies [Sewunet *et al*, 2013, Dilnessa *et al*, 2016]. While many clinical samples had *Staphylococcus aureus* identified*; Escherichia Coli* was predominantly found in urine samples [Ragbetli *et al*, 2016, Ramirez – Castillo *et al*, 2018]. Several studies reported that S. aureus is found in many clinical specimens across African countries with prevalence as high as 60.9% [Acquah *et al*, 2013, Opoku-Okrah *et al*, 2013]. A number of gram negative bacteria such as *Klebsiella, Proteus* and *Pseudomonas aeruginosa* have been reported clinical specimens with varying level of prevalence [Mordi *et al*, 2009, Kehinde *et al*, 2004, Fadeyi *et al*, 2016]. Majority of alpha *haemolytic Streptococci* were isolated from sputum specimens similar to previous studies [Masyeni *et al*, 2018]

In many developing countries prevalence of Klebsiella infections is high compared to the findings of this study [Hansen *et al*, 2004, Chakraborty *et al*, 2016, Olowe *et al*, 2012]. Similar pattern of varying prevalence of bacterial isolates was reported for *Pseudomonas aeruginosa*, *Proteus* species ,*Klebsiella* and *coliforms* which are in contrast to the results of this study [Mahmoud et al 2016, Patil *et al*, 2017, Akter *et al*, 2014, Raiz *et al*, 2012, Sarathbau *et al*, 2012, Prasad *et al,* 2016, Bahashwan *et al*, 2013]

The emergence of antibiotic resistance is known to be due to a complex interplay of several factors including overuse/irrational use and environment. Evidence from antibiograms used in this study showed that bacterial isolates were resistant to 3 – 6 antibiotics on the average. This high level of resistance presents a unique challenge in low and medium income countries where empirical antibiotic treatment is widespread. It also raises doubt as to the efficacy and appropriateness existing guideline recommendations for syndromic treatment of several infections {Bernabe *et al*, 2017]. Antibiotics with high level resistance included Amoxicillin + Clavulanic acid, Cotrimoxazole, Cloxacillin, Tetracycline and Ceftriaxone in that order of decreasing frequency. Quinolones have the least resistance which is below 20% for these commonly isolated bacteria.

The level of resistance to Amoxicillin + Clavulanic acid by Staph aureus in this study is lower than that reported by Ragbetli *et al*, 2016, Saba *et al*, 2017, Bernabe *et al*, 2017 but comparable to that reported by Masyeni *et al*, 2016 . Resistance of Staph aureus to Cotrimoxazole and Macrolides in this study is considerably higher compared to some previous studies [Aydin *et al*, 2001, Ozkalp *et al*, 2003]. In the case of *Escherichia coli*, resistance to Amoxicillin + Clavulanic acid, Cotrimoxazole and Ceftriaxone are comparatively high [Ray *et al*, 2015, Ali Abdel Rahim *et al*, 2014]. Penicillins and macrolides have showed consistently comparable level of resistance to several previous studies [Dash *et al*, 2013, Niranjan *et al*, 2014, Dugal *et al*, 2013], Quinolone resistance in this study is lower than in these reported studies, though other studies [Olorunmola *et al*, 2013, Akter *et al*, 2014[reported high level of bacterial resistance.

A similar pattern of resistance to these common drugs was also observed with *Pseudomonas aeruginosa* and *Haemolytic Streptococci*, however while Quinolones have been reported to have higher levels of resistance [Sharma *et al*, 2016, Khan *et al*, 2014], other studies reported lower level of resistance [Naik *et al*, 2016]. The high level of multidrug resistance observed in this study has been earlier reported around the world [Rossolini *et al*, 2014, Golkar *et al*, 2014]. One of the major driving factors is inappropriate prescribing and self-medication in the community [Bartlett *et al*, 2013, Luyt *et al*, 2014]. In, Nigeria, poor regulatory controls and inappropriate prescription of antibiotics is compounding the problems of resistance development. Many patients only report to hospital when self-medication fails to address their health problems

Evidence from several studies clearly suggests that routine empirical antibiotic prescription can no longer be justified as rational. There is an urgent need to review antibiotic use policies to emphasize microbial susceptibility testing to ensure that patients' treatment outcomes are guaranteed.

Conclusion: Antibiotic resistance to commonly used antibiotics is very high. There is need to de-emphasize empirical prescriptions and give way for evidence based susceptibility testing of pathogens before a suitable course of antibiotic therapy is initiated.

Limitations: There are a number of limitations of this study and they include.

- The data were extracted from records and there may be errors in entry and/or test procedures
- The quality of materials and adherence to standard test procedures could not be ascertained
- The presence of antibiotic tainted samples because previous therapy or self-medication may influence results

Conflict of interest: The authors declare no conflict of interest

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