An Original Research Paper

REVIEW OF ANTIBIOTICS USAGE IN THE MANAGEMENT OPEN FRACTURE IN A NIGERIAN HOSPITAL

ABSTRACT

BACKGROUND. Antibiotics are adjuncts in the management of open fractures, and microbial characteristic of open fractures will guide the use of antibiotics. With changing pattern in microbial colonization of wounds, the need to review antibiotic usage in hospitals becomes imperative. The study aimed to evaluate the antibiotic protocol of managing open fractures at the Accident and Emergency department, with the advent of new antibiotics introduced into the hospital drug formulary.

MATERIALS AND METHODS. This study is a hospital-based prospective evaluation of the antibiotic sensitivity of cultured microorganisms from the patients with open fractures presenting between January 2013 and December 2013 in the Accident and Emergency Department, of a tertiary hospital in Nigeria. Swabs of superficial and deeper parts of the wound were taken at the presentation of the patients before wound debridement and commencement of antibiotics. Other two samples and biopsies were taken at the deeper parts of the wound on the 3rd and 7th day of admission. Culture and Sensitivity pattern of isolates were determined for positive cultures using antibiotics impregnated disks. Descriptive and inferential statistics of the findings are presented.

RESULT. One hundred and thirty patients with open fractures were recruited for the study, but 81 patients completed the study. . Forty patients discharged themselves against medical advice and while nine patients were referred to other hospitals. Sterile swabs were taken from the surface and deeper portion of the wounds at a presentation before treatment was commence and at day 3 and day 7 of admission, *Staphylococcus aureus* and *Clostridium perfringens* were the most common aerobic and anaerobic isolates from the wounds respectively. The aerobic isolates and anaerobes were susceptible to ceftriaxone, ciprofloxacin, co-Amoxyclav, gentamycin, and cefotaxime and metronidazole respectively.

CONCLUSION. The antibiotic sensitivity pattern in the emergency department of the Hospital has changed not significantly as previously reported about 12 years earlier. Therefore, the hospital antibiotic protocol in the treatment of open fractures in the Accident and Emergency department should be retained.

Keywords: Open fracture. Antibiotics sensitivity, Antibiotic usage, Ibadan, Nigeria

Introduction

The choice of antibiotics in the treatment of open fractures as an adjunct to debridement and wound care, is determined by established microbial characteristics of open fractures in the locality or empirically using combination therapy to cover most of the available organisms such as Gram-positive and Gram-negative aerobes as well as the anaerobes. The choice of antibiotics in the treatment of infections is determined by the potential bacterial contamination based on historical or research documented patterns for each locality [1]. On account of their findings, Wilkins and Patzakis recommended the use of a combination of cephalosporins, penicillins and aminoglycosides in open fractures depending on the severity of the wound and extent of contamination [2]. However, Alonge et al. in Ibadan Nigeria, found that pefloxacin, ciprofloxacin and ceftriaxone were the antibiotics which exhibited relatively higher sensitivity to the micro-organisms isolated [3], which is in agreement with the findings in other studies [4] [5] [6] [7][8][9].

Research have helped refine surgical protocols, change in antibiotic prescriptions, and in defining the appropriate timing for interventions including debridement, modalities of fracture fixation, and soft tissue coverage [10][11][12][13][14][15][16]. Infections in open fractures becomes more likely after six hours of injury if adequate surgical treatment is not carried out along with the administration of appropriate antibiotics early enough after the injury. Deep fracture site infections could lead to complications of chronic osteomyelitis, fracture non-union and sometimes limb loss. Majority of infections in open fractures are caused by *Staphylococci* species especially *Staphylococcus aureus* and coagulase-negative *Staphylococci*, gram-negative bacilli which include *Acinetobacter spp, Escherichia coli, Pseudomonas* spp, *Klebsiella* spp and *Proteus* spp amongst others [4][14][17]. Resistance to available antimicrobial drugs is an established and ever-growing challenge in clinical practice. Such resistance can result from two mutually non-exclusive phenomena: mutations in house-keeping structural or regulatory genes and the horizontal acquisition of foreign genetic information [18]. Outbreaks of infections due to *Klebsiella* pneumonia harboring plasmid-encoded cephalosporinases and the spread of this resistance mechanism to bacterial species naturally susceptible to cephamycins have been reported [19] as well as poor response to antibiotics identified as sensitive to isolated organisms especially in the presence of biofilm infections [20].. This study aimed to review the antibiotic treatment protocol for open fractures in the A&E of a tertiary hospital in Nigeria with the view for recommendations for possible change in practice.

MATERIALS AND METHODS

This study is a hospital-based prospective evaluation of antimicrobial pattern and antibiotics sensitivity pattern in open fractures presenting in the Accident and Emergency Department of the University College Hospital, Ibadan from January 2013 to December 2013 following approval of the Hospital Ethical and Research Committee according to Helsinki Declaration of 1977 modified in 2000. Hospital Ethical Approval Number: UI/FC/12/0431.

Emergency Room Protocol: Proforma for the study was completed for all patients seen in the Accident and Emergency department of the hospital with open fracture after obtaining securing informed consent from the included patients. Patients with open fractures who had wound debridement and antibiotics before presenting at the Accident and Emergency of the University College Hospital, Ibadan were excluded.

Patients with open fractures were resuscitated and treated using the advanced trauma life support (ATLS) protocol. The associated open fractures were inspected, and clinical photographs obtained as appropriate.. Four sterile wound swabs, (superficial aerobic and anaerobic, deep aerobic and anaerobic) were collected from the superficial and deep parts of open fracture wounds using the Levine's technique. The swabs of the wounds were obtained aseptically before wound debridement and antibiotics were commenced within 30 minutes of patient's arrival at the Accident and Emergency Department. Two other samples and biopsies were taken at the deeper parts of the wounds on the 3^{rd} and 7^{th} day of admission. Samples were collected into sterile Stuarts transport medium, and sterile Robertson cooked meat medium for aerobic and anaerobic organisms respectively. The samples were labelled "S" for superficial swab samples, "D" for deep swab samples, "BS" and "BD" for superficial and deep biopsy samples with the patient's research number on the laboratory request form and also on the bottle. Having collected the samples, the open fracture was treated according to the hospital established protocol of early antibiotic administration, analgesics, tetanus prophylaxis, early wound debridement, fracture stabilization and early soft tissue coverage.

Laboratory Protocol: All obtained samples arrived the laboratory within 30 minutes to 3 hours of collection. The samples were stored at room temperature in a cupboard for less than 6 hours until ready for analysis. Microscopy, culture and sensitivity patterns of the samples to various antibiotics (penicillin, cephalosporin, quinolone, aminoglycoside, clindamycin, sulphonamides and trimethoprim, and metronidazole) were carried out. The samples for aerobic cultures were plated out on sterile Sheep blood agar and MacConkey agar aseptically and incubated at 37^0C for 24 hours. The direct Gram staining of the swabs was carried out, and the slides examined to identify the presence of organisms and pus cells. After 24 hours of incubation, the plates were analyzed for the growth of the bacteria and gram staining of the bacteria colonies were carried out.

The confirmatory test of all the isolated gram-negative bacilli was based on the use of API 20 E while the gram-positive cocci were based on the use of control organisms for coagulase test. Sensitivity testing was carried out using the disc diffusion technique (Bauer Kirby method), The anaerobic samples were inoculated aseptically into a sterile Sheep blood agar and MacConkey agar within five minutes of sample collection. The inoculated plates were incubated in the anaerobic gas chamber containing anaerobic catalytic agent, Anaero Gen kit and anaerobic control kit (Oxoid Ltd of United Kingdom). Strict anaerobic control bacteria and strict aerobic bacteria were also included as an added quality control. The anaerobic organisms were left in the chamber to incubate at 37^0C for three days to isolate the fast-growing anaerobes which are mostly contaminants while the late growing anaerobes were further incubated for ten days and these are the bacteria of medical importance.

Data was managed and analysed using IBM SPSS Statistics for Windows Version 20.0 Software (Armonk, NY: IBM Corp). Descriptive statistics were presented as proportions, percentages and with appropriate scientific figures. Chi-square ($\chi 2$) was used to test for statistical significance for observed differences for categorical variables. P -values less than 0.05 were accepted as significant.

RESULTS

Eighty-one of the 130 recruited patients completed the study with superficial and deep swab samples taken from all patients on the first day and other swabs and biopsy samples taken on the third and seventh day of admission. Forty patients took their discharges against medical advice while nine patients were referred to other hospitals of their choice. There were 93 (71.5%) male and 37 (28.5%), female patients, as shown in figure 1 while figure 2showed open fractures in different regions of the body with the tibia and fibula constituting 78 (60%) of the cases while the femur accounted for 19 (14.6%). Gustilo and Anderson type 3B [21] was the most common grade of open fracture 48 (36.9%), while type 3A occurred in 43 (33.1%) as presented in figure 3. The microbial cultures showed that *Staphylococcus aureus* and *Clostridium perfrigens* were the predominant aerobic and anaerobic isolates.

Figure 1: Showing the sex distribution

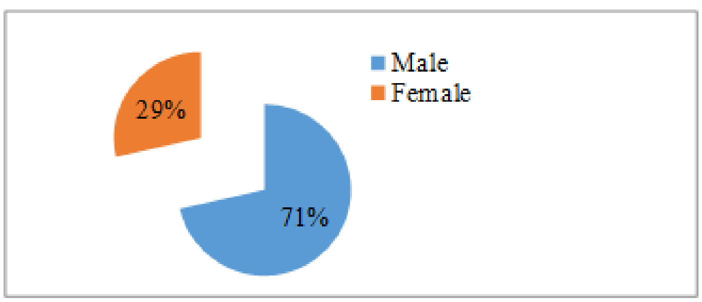
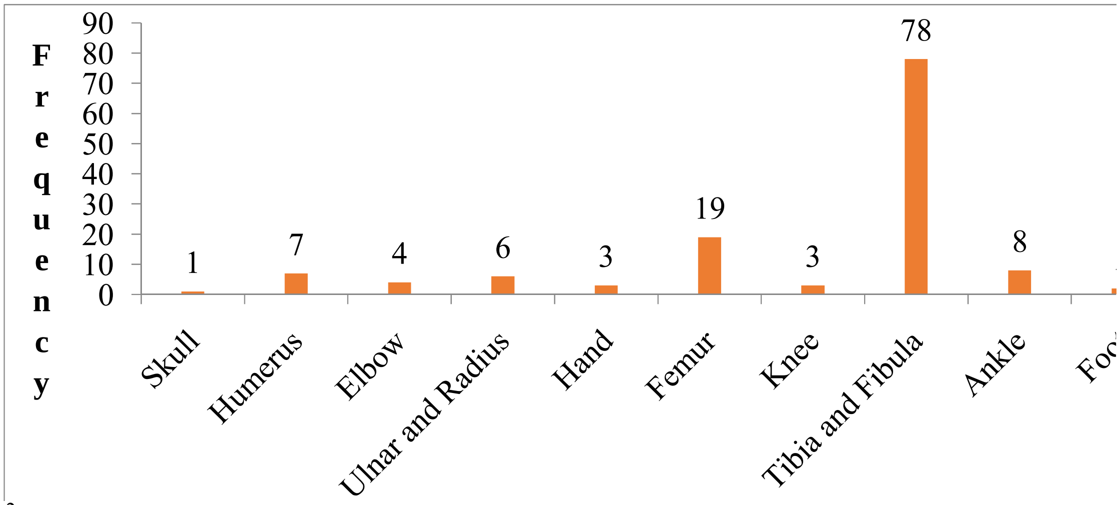
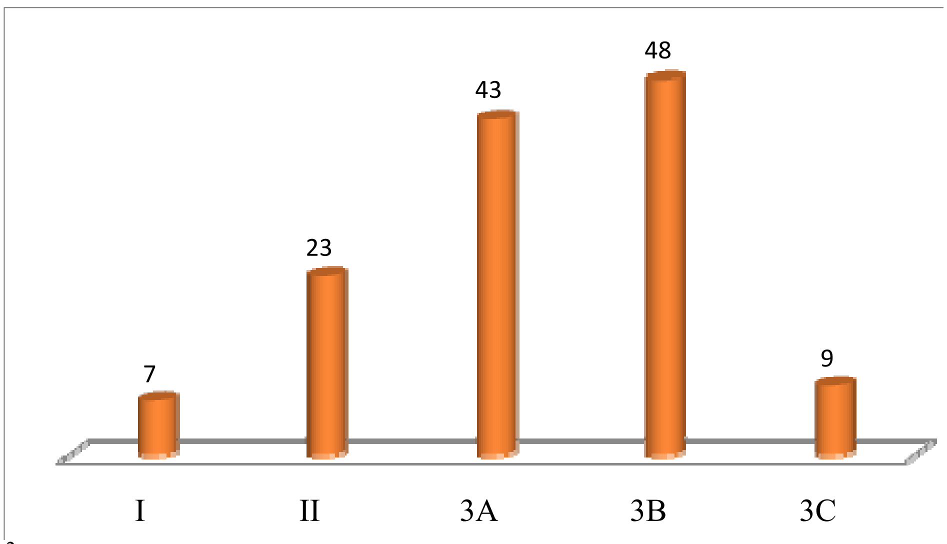


Figure 2: Shows open fracture in the various regions of the body



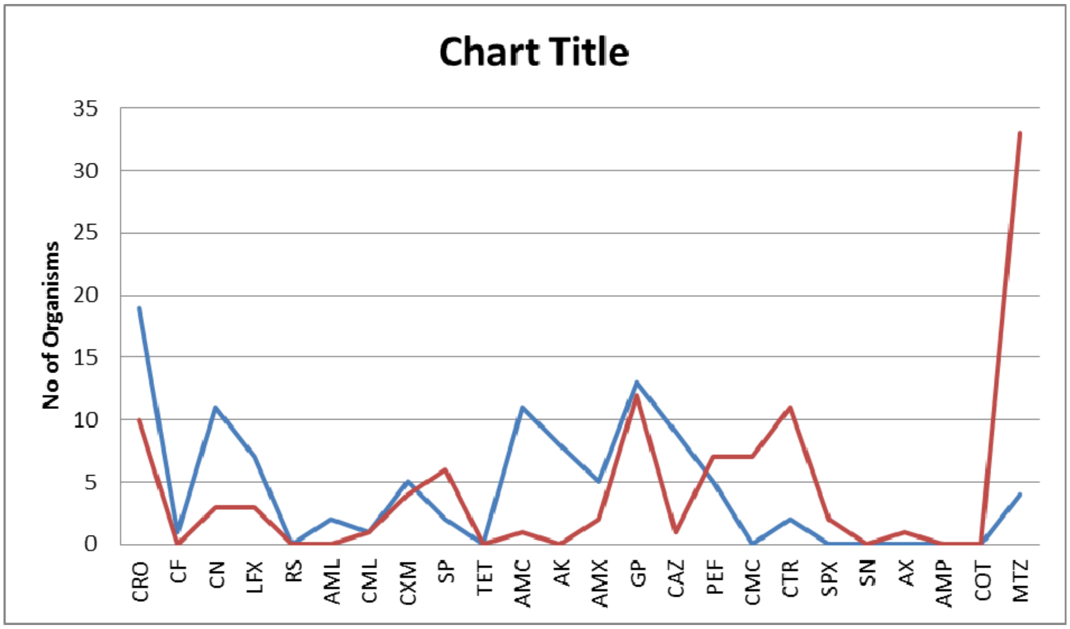
χ^2 =132.154 P < 0.001

Figure 3: Shows the grades of open fracture



χ^2 = 55.077 P <0.001

Figure 4: Antibiotic sensitivity pattern for aerobes (blue) and anaerobes (red)



Abbreviations

CRO – cephtriaxone, CF – cefazolin, CN – gentamycin, LFX – levofloxacin, RS –rosoxacin, AML –amoxycillin, CLM – clindamycin, CXM – cefuroxime, SP – sparfloxacin, TET – tetracycline, AMC – co-Amoxyclav, AMX – amoxycillin, GP – ciprofloxacin, CAZ – ceftazidime, PEF- pefloxacin, CTR – cefotaxime, SPX – sparfloxacillin, SN-sulphonamides, AX – amoxycillin, AMP – ampicillin, MTZ – metronidazole and COT –cotrimoxazole.

The antibiotic sensitivity pattern are shown in figure 4 and tables 1and 2. Ciprofloxacin (GP), ceftriaxone (CRO), co-amoxiclav (AMC) and gentamycin (CN) were the drugs most aerobic organisms were sensitive to, while anaerobic microorganisms were highly sensitive to cefotaxime (CTR), and metronidazole (MTZ).

Table 1. Aerobic Organism sensitivity

Organism	**Antibiotics**										**X^2; P value**
.	CRO	CN	LFX	CXM	AMG	AMX	GP	CAZ	CTR	MTZ	
SA	5	4	1	2	3	3	4	0	0	0	3.33; 0.50
EC	0	1	2	0	1	0	1	2	0	0	2.0; 0.74
KS	3	1	0	1	5	1	4	0	0	0	8.0; 0.09
PsA	2	1	1	0	0	0	2	1	0	0	2.0; 0.74
X^2; P value	2.67 0.45	3.0 0.39	2.0 0.57	2.0 0.57	5.0 0.17	6.0 0.11	1.3 .72	2.0 0.57			

Key: *S A – Staphylococcus aureus, E C – Escherichia coli, K S – klebsiella spp, and PsA - Pseudomonas auregenosa.*

Table 2. Anaerobic Organism sensitivity

Organism	Antibiotics										χ^2; P value
	CRO	CN	LFX	CXM	AMG	AMX	GP	CAZ	CTR	MTZ	
CP	3	0	2	2	0	0	3	1	3	20	41.33 <0.001
BS	0	0	0	0	0	0	0	0	0	5	20.00 <0.001
CT	1	0	1	0	0	0	1	0	2	9	15.33 0.004
AI	4	1	0	2	0	0	4	2	1	0	5.0 0.29
χ^2; P value	5,0; 0.17	- -	2.0 0.57	4.0 0.26	- -	- -	5.0 .17	2.0 0.57	1.0 0.80	24.89 <0.001	

Key*: C P – Clostridium perfringens, C T – Clostridium tetani, B S –Bacteroides spp and A I –Actinomyces isrealii*.

Discussion

The place of early wound debridement and antibiotic administration are recognized as important in the management of open fractures. Appropriate antibiotics are administered according to the established hospital protocol following the identified historical and sensitivity patterns of wound swabs [22]. The value of antibiotics in the treatment of open fractures has been established, but this does not substitute for proper wound debridement and adequate skeletal stabilization as an essential aspect of open fracture management. The choice of antibiotic should be guided by the knowledge of possible contaminating organisms at presentation. Since subsequent infections are often by multiple organisms, these microorganisms should be adequately covered by the choice of antibiotics. Evidence-based guidelines for prophylactic antibiotic use in open fractures recommend short-course, narrow-spectrum antibiotics for Gustilo Grade I or II open fractures and broader coverage with gram-negative coverage for Grade III open fractures [23].

The antibiotic protocol for the treatment of open fractures in the Accident and Emergency Department of the hospital where this study was undertaken, has been a combination of ceftriaxone, quinolones (ciprofloxacin) and metronidazole-based on findings of Alonge et al.

in 2002 [3]. The observation of Alonge et al. with*Escherichia coli* being the most common single gram-negative aerobic isolate was slightly at variance to the findings from this study which showed that Staphylococcus *aureus* and Clostridium perfrigens were the most common single aerobic and anaerobic isolates respectively..

The predominant aerobic gram-positive organism isolated in this study (Staphylococcus aureus) was sensitive to ceftriaxone (CRO), Gentamycin (CN), co-amoxiclav (AMC), cefuroxime (CXM) and amoxycillin (AMX) while the aerobic gram-negative organisms (Escherichia coli and Klebsiella spp) were sensitive to ceftriaxone, amoxycillin, levofloxacin and ceftazidime. However, amongst the aerobic isolates tested to antibiotics, only Staphylococcal aureus was marginally significantly sensitive to ceftriaxone, $P = 0.50$, but significantly insensitivity to metronidazole ,$P < 0.05$. The observed antibiotic sensitivity pattern was not too different from the findings by *Alonge et al.*in 2002 and other studies [3][4][5]. Also, isolated anaerobes were significantly sensitive to metronidazole (MTZ) but moderately sensitive to ceftriaxone, levofloxacin, cefuroxime, ciprofloxacin and cefotaxime (CTR), justifying the inclusion of metronidazole in the hospital antibiotic protocol.

The micro-organisms cultured in this study showed high resistance to ampicillin (AMP), cotrimoxazole (COT), sulphonamides (SN), clindamycin (CML), rosoxacin (RS), amoxycillin, cefazolin (CF), and tetracycline (TET). The aerobic gram-positive organisms were resistant to ceftazidime (CAZ), cefotaxime (CTR) and metronidazole while the aerobic gram-negative microorganisms were resistant to cefotaxime, metronidazole, amoxycillin, cefuroxime). The anaerobic organisms also showed significant resistance to co-amoxyclav, amoxycillin, gentamycin and ceftazidime. These findings were comparable to a similar study in another African hospital by Sitali and colleagues in 2017 [24].

Apart from antibiotic sensitivity and microbial patterns, the hospital antibiotic protocol is also influenced by the cost and availability of the drugs. In the centre where this study was undertaken as well as in most hospitals in the region, availability of some of the antibiotics can be challenging. Even when the drugs are available, affordability often becomes another challenge as the majority of persons in the region live below the WHO poverty line [25]. The use of generic forms of these antibiotics, therefore, is common in the region.

It is worth noting that cultured isolates from a wound especially in the presence of biomaterials and biofilms may not be truly representative of the actual organisms causing infections. Since an infection engrafted on a biomaterial (thick, adherent biofilm) responds poorly to antimicrobial therapy and is not usually cured until the biomaterial is removed, the reliance on only antibiotics for cure of infections in open fractures without appropriate debridement of dead tissue should be with caution. Antimicrobials that are chosen from the swab culture results may not be effective against all of the bacterial species in these biofilm infections [26]. Incidentally, it takes some time before biofilm develops. However, since the cultures in this study were all done within seven days of admission, the identified sensitivity patterns may not be entirely reflective of the antibiotic sensitivity and resistance in open fractures with chronic wounds when there are the existence of biofilms.

CONCLUSION

The hospital antibiotic protocol which recommends the combination of ceftriaxone, quinolones, gentamycin, co-amoxyclav and metronidazole in treating open fractures in the Accident and Emergency department of the hospital, was based on the antibiotics sensitivity patterns to cultured microbial organisms in the hospital. Since the existing microbial and antibiotic sensitivity patterns had not changed significantly since the establishment of the protocol 12 years preceding this syudy, there was no reason for a recommendation for change in the current practice.

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