Abstract
The antibiotic formulary in Sudan is deficient in many injectable antibiotics necessary for the treatment of common infections. Instead cephalosporins, particularly the third generations are widely available and extensively used. This class of antibiotics is known to induce resistance among Gram-negative bacteria and Staphylococcus aureus. Indeed overuse of third generation cephalosporins has resulted in wide scale resistance among bacterial isolates in our hospitals. Adding more effective and less damaging antibiotics and reducing the use of third generation cephalosporins should improve patients’ outcome and reduce the rate of antibiotic resistance. It is vitally important, meanwhile, to educate all prescribers on the rational use of antibiotics and ensure that an appropriate policy is in place to safeguard against misuse of these agents.

Keywords: Antibiotics, resistance, cephalosporins, bacteria.

Introduction
An infection may be treated by one of several antibiotics to which the causative organism is sensitive. However, the choice of an antibiotic is based not only on susceptibility, but also on the killing capacity of the antibiotic, its rapidity of action, pharmacokinetics (adequate concentration at the infection site), toxicity and cost. The clinical microbiologist should, therefore, advise the treating doctor on the most appropriate antibiotic for his patient. However, in Sudan, serious limitations prevent microbiologists and clinicians from choosing the appropriate antibiotics. The Sudanese antibiotic formulary is deficient in essential injectable antibiotics necessary for the treatment of common and serious infections. Instead, the antibiotic formulary is overwhelmed by several brands and classes of injectable cephalosporins. Therefore, in the absence of specific antibiotics to treat common infections, clinicians have no choice, but to use variable brands of the widely available cephalosporins, probably unaware of...
the serious implications of the overuse of third generation cephalosporins (oxyimino cephalosporins). Highlighted in this article are the undesirable effects (collateral damage) associated with the overreliance on third generation cephalosporins, identify gaps in Sudan’s antibiotic formulary and recommend measures to ensure appropriate use of proposed additions to the formulary.

The problem with third generation cephalosporins

Since their introduction in the 1980s, third generation cephalosporins have been used in the treatment of a wide variety of infections. However, the association between overuse of third generation cephalosporins and development of antibiotic resistance has limited their use in many centres. Several reports have provided sufficient evidence that overuse of third generation cephalosporins is associated with increase in the prevalence of extended spectrum β-lactamase (ESBL) producing bacteria as well as methicillin-resistant *Staphylococcus aureus* (MRSA)(1,2). ESBLs are enzymes produced by Gram-negative bacteria that render them resistant to all penicillins, cephalosporins and monobactams. Kheder showed that under high consumption of cephalosporins 90% to 100% of *Enterobacteriaceae* isolates in Ibn Sina Hospital during the period 2008 to 2010 were resistant to third generation cephalosporins(3). Today antibiotic resistance particularly to β-lactam antibiotics amongst isolates in our hospitals is alarmingly high. Ali compared antibiotic susceptibilities of *Enterobacteriaceae* isolated in Khartoum Teaching Hospital (KTH) and Soba University Hospital (SUH). He found that resistance of *Escherichia coli* and *Klebsiella spp.* to ceftriaxone and ceftazidime in both hospitals ranged from 56.5% to 79%(4). In a survey done earlier at SUH, we found that 78% and 80% of *Escherichia coli* and *Klebsiella pneumoniae* respectively were ESBL producers and that 51% of *Staphylococcus aureus* were MRSA(5). In her study for MD degree in Microbiology, Yousif found that 61.9% of *Escherichia coli* and 83.8% of *Klebsiella pneumoniae* were ESBL-producers(6). Earlier reports from Khartoum have also shown high prevalence of ESBL-producers among *Enterobacteriaceae*(7).

To further confirm the association between the usage of cephalosporins and resistance, several workers have demonstrated significant reduction in MRSA and ESBL producers following reduction in the consumption of third generation cephalosporins(8,9). By reducing the consumption of third generation cephalosporins and increasing the usage of β-lactam-β-lactamase inhibitors, Landman demonstrated significant reduction in MRSA and ceftazidime resistant *Klebsiella pneumoniae*(1). Fujitsu used third generation cephalosporins for surgical prophylaxis that resulted in an increase in MRSA. But he noticed significant reduction in MRSA when he stopped using third generation cephalosporins in surgical prophylaxis(2).

Judging from the above reports, we are confident that should clinicians use effective and less damaging alternatives to cephalosporins, we would not only reduce the prevalence of ESBL producers and MRSA in our hospitals, but would also significantly reduce morbidity and mortality from infection. We must realize the serious deficiency in antibiotic formulary and revise it in order to add essential medicines needed for the treatment of common and life threatening infections.

Challenges in the treatment of infections with Gram-positive bacteria in Sudan

*Staphylococcus aureus* is one of the most commonly encountered pathogens in the community as well as in healthcare settings and is the most important cause of bloodstream infection associated death(10). In SUH *Staphylococcus aureus* accounts for 36%-39% of isolates from clinical specimens and is the most frequent bloodstream isolate.
About half of Staphylococcus aureus isolates in our settings are methicillin-sensitive (MSSA)\(^{(11,12)}\). Cloxacillin /flucloxacillin is the ideal agent for treating infections with MSSA. It is the most effective agent against Staphylococcus aureus, having a minimum inhibitory concentration (MIC) of 0.25 mg/l, lower than any other antibiotic. It is well tolerated and up to 12 grams/day may be administered in the treatment of infective endocarditis. Having high bactericidal capacity, rapid action and narrow spectrum of activity, cloxacillin provides good killing capacity with minimum collateral damage\(^{(13)}\). Ampiclox, which is often used in Sudan for treating staphylococcal infections, is not an alternative to cloxacillin. It is a combination of two penicillins, not known to be synergistic or even additive, since both compounds compete for the same binding site (penicillin-binding protein). Furthermore, high doses of cloxacillin are often needed to treat serious staphylococcal infections, which mean that an equal amount of amoxicillin must be given along with cloxacillin that may be associated with unwanted effects.

Methicillin resistant Staphylococcus aureus accounts for 50% to 60% of clinical isolates in our hospitals\(^{(11)}\). This is comparable to the prevalence of MRSA in neighbouring Arab countries. Shibl et al reported 32% in Kuwait, 52% in Oman and 60% in Egypt\(^{(14)}\). Lapse of infection control practice could have contributed to the high prevalence of MRSA in these countries. MRSA infection is treated with vancomycin. However, vancomycin is a pharmacodynamically inefficient antibiotic and is slow acting\(^{(15)}\). Among a cohort of 320 patients with MRSA bacteremia, 52.3% experienced treatment failure with vancomycin\(^{(16)}\). Vancomycin requires an additive antibiotic to augment its action when treating deep-seated or long standing staphylococcal infections. Rifampicin has been recommended as an additional drug in the treatment of infective endocarditis\(^{(17)}\) and prosthetic joint infection\(^{(18)}\). Rifampicin is also an essential component in the treatment of brucellosis and Legionnaire’s disease. However, in Sudan, rifampicin is restricted to the treatment of tuberculosis in order to delay emergence of rifampicin resistance among Mycobacterium tuberculosis. Nevertheless, rifampicin use may be controlled and restricted to the treatment of special cases only. It may be licensed to referral hospitals and issued only to specified senior medical staff or by culture report. In order to further ensure control, each pharmacy who holds rifampicin must keep a record showing the received stock and details of the issued prescriptions.

Furthermore, some patients may not respond to treatment with vancomycin if MRSA overproduces cell wall peptidoglycan and converts to glycopeptide intermediate Staphylococcus aureus (GISA)\(^{(19)}\). We reported such strain from Oman and have recently identified three strains in SUH\(^{(20)}\). GISA can be treated with linezolid or daptomycin, which, unfortunately, are not registered in Sudan. Linezolid is an oxazolidinone antibiotic with activity against Gram-positive bacteria, including those resistant to glycopeptides. Daptomycin is a semisynthetic lipopeptide antibiotic active against multi-resistant Gram-positive bacteria. Enterococcus spp. is the most common cause of bloodstream infections in the United States and Europe\(^{(21,22)}\). It is the third most frequent isolate from blood and common isolate from urine and intra-abdominal infection in our setting\(^{(11)}\). Enterococcus spp. is intrinsically resistant to several antibiotics including cephalosporins. The treatment of enterococcal infection is limited to a few antibiotics; ampicillin, co-amoxiclav and vancomycin. Being least costly and associated with least side effects, ampicillin should be the preferred antibiotic in treating all infections with susceptible enterococci. Vancomycin should be reserved for resistant cases only.
Ampicillin with or without gentamicin is the recommended treatment of *Listeria monocytogenes* infection, since *Listeria monocytogenes* is intrinsically resistant to all cephalosporins. Ampicillin is also a component in the treatment of pregnant women with chorioamnionitis\(^{(23)}\). The burden of pneumococcal invasive disease in the Arab peninsula remains significant with incidence rates of 3.4 to 53.5/100,000/year\(^{(24)}\). Penicillin-resistant strains of *Streptococcus pneumoniae* are prevalent in the region, ranging from 20% to 78%\(^{(24,25)}\). However, in Sudan, we do not know the incidence of invasive pneumococcal disease or the prevalence of penicillin-resistant *Streptococcus pneumoniae* because of difficulties in performing culture and MICs for *Streptococcus pneumoniae*, due to lack of appropriate culture media. Until we resolve this problem and judging from the level of resistance among *Streptococcus pneumoniae* in the neighbouring countries and elsewhere, we advise our clinicians not to treat pneumococcal meningitis with penicillin. While respiratory and bloodstream infections with pneumococci showing low to moderate level resistance may respond to high doses of penicillin or ampicillin, meningitis treatment failures have been documented in infections with even low level penicillin-resistant strains. Therefore, initial treatment of meningitis should include high dose of cefotaxime or ceftriaxone with vancomycin\(^{(26)}\). This is one of the few situations where the use of a third generation cephalosporin is justified.

\(\beta\)-haemolytic *Streptococci* belongs to a wide range of microorganisms that cause a variety of infections. Soft tissue infection with *Streptococcus pyogenes*, with or without *Staphylococcus aureus* may progress to necrotizing fasciitis, an infection with high morbidity and mortality. These organisms may also produce toxic shock syndrome toxin that adds insult to injury. Clindamycin is an essential additive to penicillin/flucloxacillin in the treatment of these conditions, due to its anti-toxin effect and excellent pharmacokinetic properties in penetrating infected tissues and neutrophils\(^{(27)}\). Patients with such infections are usually too sick to take oral treatment. Injectable clindamycin is needed in our formulary.

Macrolides are used as an alternative therapy for patients who are allergic to penicillin and are also the treatment of choice for atypical pneumonia and Legionnaire’s disease. Although atypical pneumonia and Legionnaire’s disease may also be treated with fluoroquinolones, which are available in Sudan, macrolides are preferred because of their safety, low cost and not being associated with collateral damage. Patients may be too sick to take oral treatment and it may be necessary to administer the medicine by intravenous route. Injectable macrolides should be added to our formulary.

**Challenges in the treatment of infections with Gram-negative bacteria in Sudan**

The prevalence of ESBL in *Enterobacteriaceae* is increasing worldwide\(^{(28)}\). This has prompted several centres to reduce the consumption of oximino cephalosporins and replace them with \(\beta\)-lactam-\(\beta\)-lactamase inhibitors that are least associated with collateral damage\(^{(1,2)}\). The addition of piperacillin-tazobactam to the hospital formulary at the Cleveland Department of Veterans Affairs Medical Centre and minimizing the administration of ceftazidime were associated with a marked decrease in ceftazidime-resistant isolates\(^{(29)}\). In a similar report, Landman et al demonstrated significant reduction in ceftazidime-resistant *Klebsiella pneumoniae* by reducing the consumption of ceftazidime and increasing the use of piperacillin-tazobactam\(^{(4)}\). \(\beta\)-lactam-\(\beta\)-lactamase inhibitors are widely used worldwide. They have broad-spectrum activity and are effective against a wide range of pathogens. They cause minimum collateral damage and can be an
alternative or compete with the notorious third generation cephalosporins. Furthermore, piperacillin-tazobactam (piptazo) and ticarcillin-clavulanic acid have activity against *Pseudomonas aeruginosa* as well as anaerobes.

In Sudan, ESBL prevalence is the highest even when compared to neighbouring Arab countries. Sixty percent to 80% of *Escherichia coli* and *Klebsiella pneumoniae* isolates in KTH and SUH were ESBL producers, while in Arab countries ESBL prevalence ranged from 6% in Saudi Arabia to 15% in Oman (14,30). The available treatment for infections with these organisms in Sudan is meropenem, which is prohibitively expensive for most patients. Furthermore, most laboratories in Sudan do not test for ESBL production and may erroneously report an ESBL producer as sensitive to cephalosporins; as such organisms may appear sensitive on an ordinary disc diffusion test. This may in turn give false impression to the clinicians and mask the true picture of the high prevalence of cephalosporin resistance. Other problem is the emergence of carbapenem-resistant strains with increasing frequency. During the period January 2011 to June 2013, we isolated 80 bacterial strains in SUH resistant to all available antibiotics including meropenem (Microbiology records SUH). Meropenem resistance may be due the notorious metallo-β-lactamases that inactivate all β-lactams except aztreonam. Recently strains of *Escherichia coli* and *Klebsiella spp* carrying genes for this resistance (*blaNDM1*) originated from the Indian Subcontinent and have spread worldwide (31). Infections with carbapenem-resistant organisms are treated with colistin (colistimethate sodium) or tigecycline, which, unfortunately, are not available in Sudan. Colistin is a polymyxin, active only against Gram-negative bacteria including carbapenem-resistant strains. Tigecycline is a glycyclycline antibiotic active against a wide range of microorganisms including anaerobes, carbapenem-resistant bacteria, chlamydia and mycoplasma.

Other mode of carbapenems resistance is intrinsic such as that with *Stenotrophomonas maltophilia*. These organisms as well as other multi resistant bacteria such as *Burkholderia cepacia*, although resistant to meropenem and colistin they are susceptible to cotrimoxazole. Eighty-seven percent of such organisms isolated in Soba hospital were susceptible to cotrimoxazole. Since patients infected with these organisms are usually treated in special care units, they require injectable cotrimoxazole, which is not available in Sudan.

In conclusion, the Sudanese antibiotic formulary contains very few injectable antibiotics other than cephalosporins. Clinicians have no option, but to prescribe cephalosporins, probably unaware of the associated resistance. On the other hand, very few laboratories reliably perform antibiotic susceptibility testing of clinical isolates. Many clinicians, unaware, of the prevailing resistance continue to prescribe cephalosporins to their patients. Some may shift to the other injectable antibiotic ‘ciprofloxacin’, not knowing of the association between ESBL production and *qnr* resistance gene of quinolones (32). The end result, in the absence of microbiology support is treatment failure. Third generation cephalosporins have been linked to infection and colonization with multi-resistant organisms (collateral damage) and do not appear suitable for sustained use in hospitals as routine antibiotic therapy (33). There is a wide variety of antibiotics with minimum collateral damage highly effective against the common clinical isolates and that are recommended for the treatment of specific clinical scenarios. The good news is that recently all the above less damaging antibiotics have been added to the essential medicines list and that third generation cephalosporins have been reduced.
to the essential ones. However, it is necessary, at this stage to start an advocacy programme to promote the new medicines and to educate medical practitioners and pharmacists on their use. This can be done through Continuing Professional Development (CPD) programmes, publishing antibiotic guides and writing newsletter about bacterial isolates and their antibiotic susceptibilities. We have recently completed writing the Standard Treatment Guide and shall be available to healthcare providers. Also an antibiotic guide was published at SUH ‘Soba Guide to Antibiotic Therapy’.

Microbiology laboratories should be encouraged to issue regular newsletters of their isolates and antibiotic susceptibilities. Education of healthcare providers to judiciously use antimicrobial agents should eventually improve morbidity and mortality of our patients and should significantly reduce the rate of antimicrobial resistance.

**Transparency declaration**

This was unfunded work. The author has no professional or financial conflicts of interest that would influence this review.

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