Journal of Bacteriology and Mycology

Open Access

Austin Publishing Group

Mini Review

Bacteria Resistance to Cephalosporins and its Implication to Public Health

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Received: March 25, 2016; **Accepted:** April 06, 2016; **Published:** April 07, 2016

Abstract

Cephalosporins have proven to be of immense importance in surgery and as first line therapy for a wide variety of infections, hence its continuous relevance and usage. Unfortunately, most bacteria of clinical importance have become resistant to these antibiotics, therefore, a worldwide problem. This phenomenon can be spread by bacteria through mobile genetic element such as integrons, insertion sequences, transposons and plasmids. However, recent discoveries have developed novel cephalosporins which have demonstrated high bactericidal activity *in vitro* to an extended spectrum of pathogenic bacteria, but have also been inactivated by certain group of bacteria. Therefore, here we review the rate of emergence and spread of bacteria resistance to these antibiotics, the public health implications as well as determine if recent discoveries and modifications in the cephalosporin structure could provide a lasting solution to the problem of bacteria resistance. This review will thereby help clinicians and public health workers to tackle cephalosporin resistance.

Keywords: Antibiotics; Antibiotic resistance; Cephalosporin; Public health

Introduction

Cephalosporins are a family of antibiotics originally isolated in 1945 from the fungus *Cephalosporium acremonium* by G.Brotzu. They contain a β-lactam structure that is very similar to that of the penicillins, and as might be expected from their structural similarities to other beta-lactams like the penicillins, cephalosporins also inhibit the transpeptidation reaction during peptidoglycan synthesis [1].

The cephalosporin antibiotics have become a major part of antibiotic formulary for hospitals in affluent countries. They are prescribed and administered many times as first-line therapy for infections ranging from mild to severe ones, from an uncomplicated cellulitis or urinary tract infection, to pyelonephritis, bacteraemia or septic shock [2], and their use have gradually increased, especially the third and fourth generations [3]. As a matter of fact, some hospitals in developed countries use enormous amounts of these antibiotics in surgery departments as their preferred prophylaxis [4]. Their undoubted popularity relies upon lesser allergenic and toxicity risk as well as a broad spectrum of activity. The microorganisms mainly involved in conferring resistance to this antibiotic includes *Enterococcus faecium, Staphylococcus aureus, Clostridium difficile, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa,* and *Enterobacteriaceae* [5,6]. These can be identified with the acronym ESCKAPE. The rapid emergence of this resistance poses serious threat to the continuous relevance of the antibiotic. Hence, it is necessary to study the trend in Cephalosporin resistance and likewise efforts made towards sustaining the relevance of this antibiotic to the present day world (through the modification of the Cephalosporin side chain)

There are basically two categories of enzymes which are responsible for conferring resistance to cephalosporins; they include the Extended Spectrum Beta-lactamases (ESBLs) and AmpC beta-lactamases. Antimicrobial resistance is enhanced by abuse and inappropriate use of antibiotics in human, veterinary medicine and agriculture [7]. As a matter of fact, clinicians are running out of therapeutic options to combat this rapid development [5]. Hence, the aim of this paper is to review bacteria resistance to cephalosporin, its implication on public health and recent advances in combating this drug resistance.

Bacteria Resistance to Cephalosporins around the World

Certain *E. coli* strains which cause bovine calf scours have shown resistance to ceftiofur in Dakota, U.S.A [8] with the prevalence of Enterobacteriaceae and non-fermenting bacteria also reported to be on the increase [5]. Likewise in the U.S, *Neisseria gonorrhoeae* has been found to show resistance to cefixime and ceftriaxone, and this has resulted to a reduction in bacteria susceptibility to them (Figure 1). Also in South America, a group of ESBLs – cefotaximases (CTX-M) have been implicated in major outbreaks of cefotaxime-resistant enterobacteria (although not having a substantial effect on ceftazidime) [9].

Although, in 2008 just 14 out of 33 European countries reported their resistance levels against third generation cephalosporins to be under 5%, since 2004 the proportion of third generation cephalosporins resistance has increased in 19 European countries. [3] with a steady increase in the rates of invasive *E. coli* and *K. pneumoniae* isolates that are resistant to these 3rd generation cephalosporins reported in European hospitals since 2000 [10]. A novel type of ESBL resistant to cefotaxime but did not significantly affect ceftazidime has been isolated in Spain, Germany among other European countries [9,11,12].

(Figure 2) below shows the proportion of invasive *E. coli* isolates with resistance to third generation cephalosporins as at 2008.

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Citation: Adesoji AT, Onuh JP and Okunye OL. Bacteria Resistance to Cephalosporins and its Implication to Public Health. J Bacteriol Mycol. 2016; 3(1): 1021.

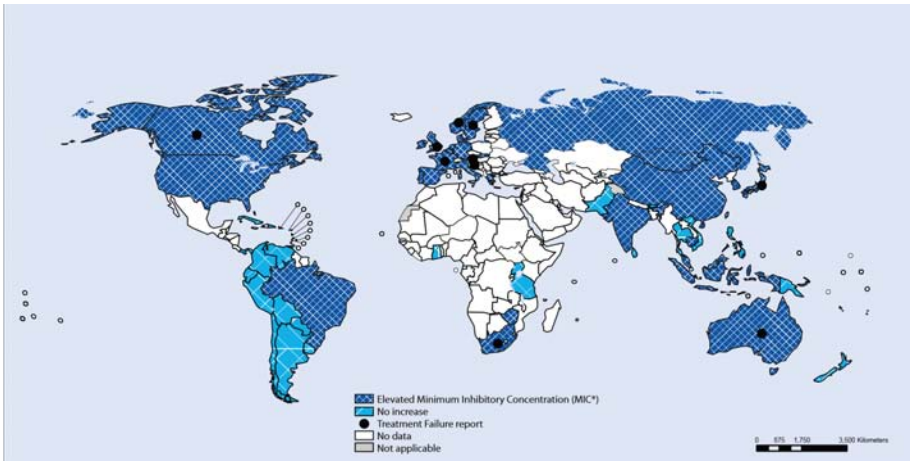

Figure 1: Detection of decreased susceptibility to third-generation cephalosporins in *Neisseria gonorrhoeae* and treatment failure up to 2010.
Note: *cefixime > 0.25µg/L or ceftriaxone > 0.125µg/L. The definition of decreased susceptibility to third generation cephalosporins differs across AMR testing methods. Countries are shaded where there has been any report of decreased susceptibility within their jurisdiction (Source:* World health Organization 2014 Antimicrobial Resistance global report on surveillance*).*

A study from Northern India in 2000 has shown an incidence of 58.06% for ESBL producing *E. coli* resistant to third generation cephalosporins. Its prevalence in the Asia Pacific region has also been reported to be more than 20% [13]. Also in India, the $bla_{\text{CTX-M-15gene}}$ in *E. coli* or *Klebsiella spp* which has been implicated in cefotaxime resistance has been isolated [14].

Available data indicates that the African region shares the worldwide trend of increasing drug resistance and this is because significant resistant bacteria that are likely to be transmissible not only in hospitals but also in the community has been reported in these African countries. A recent study conducted at the Treichville Teaching Hospital (Abidjan, Ivory Coast) to investigate the bacterial pathogenic diversity and antimicrobial resistance rates of uropathogenic bacteria over a 12-year period (2000–2011), reveals that, (compared to other antibiotics which has recorded high bacteria resistance such as amoxicillin [78.9%], trimethoprim/ sulfamethoxazole [77.9%] andtetracyclin [76.4%]), cefotaxime, ceftazidime, ceftriaxone have maintained their effectiveness(13.9%, 15.5%, 21.0% respectively). However bacterial resistance is increasing over a time for all antibiotics except chloramphenicol [15].

Antimicrobial resistance has become a worldwide phenomenon spreading rapidly into most countries with Nigeria not being an exception. A number of bacteria isolates (318 isolates) has been isolated from Nigerian indigenous herbal medicines, with about 4.13 – 9.92 % resistant to cephalexin, a first generation cephalosporin [16]. Other findings by Egbebia and Famurewa have shown antibiotic resistance to third generation cephalosporins in south western Nigeria. These isolates showed resistance to cephalothin (64.7%) a first generation cephalosporin and cefotaxime (52.0%) a third generation cephalosporin, among other antibiotics [17]. *E. coli* and *S. aureus* resistant to some cephalosporins have been isolated from chickens in Maiduguri arid zone. About 50% of the tested strains of *E. coli* were resistant to cephalexin [18]. However, there are few reports from Nigeria showing the mechanisms these bacteria are using in cephalosporin resistant. Extensive studies therefore have to be carried out in this area.

Inherently Resistant Microorganism

Coagulase-negative staphylococci (CNS)

CNS is the most prevalent skin commensals gotten mostly from hospitals. A relationship has been found to exist between antibiotic usage and antibiotic resistances of CNS in hospitals [19], especially due to the heavy continuous exposure of the hospital staff and patients to antibiotics [20] and the consequent selective pressure exerted by the broad-spectrum cephalosporins [21]. CNS is usually connected with infections of artificial prostheses, including plastic catheters and will generate persistent low-grade infections unless prosthesis is removed [22], the removal of which increases the overall usage of these antibiotics [23].

Oxidative non-fermentative gram negative bacilli

An example of these is *P. aeruginosa* and has been isolated from hospitals where a relatively high amount of cephalosporins are consumed [24]. Apart from ceftazidime and other new cephalosporins, *P. aeruginosa* is resistant to almost all other cephalosporins [25], although ceftazidime use has led to a significant reduction in susceptible *P. aeruginosa* to this antibiotic, a reduction in its use has been found to increase the proportion of susceptible *P. aeruginosa* [26].

Enterococci

Infection by *Enterococci* usually occurs in the urinary tract, but can occur in various other sites in patients who have taken cephalosporins [27], this is because the organism is inherently resistant and is able to colonize gastrointestinal sites previously populated by cephalosporins-susceptible organisms [21]. Taking antibiotics that decrease the colonization resistance of the alimentary canal may further encourage the overgrowth of potentially pathogenic bacteria, and this overgrowth can also be associated with development or acquisition of resistance to the antibiotic taken [28].

Microorganisms with Acquired Resistance

Extended spectrum beta-lactamase-producing coliforms

Beta-lactamase has been found by certain authors to be low in

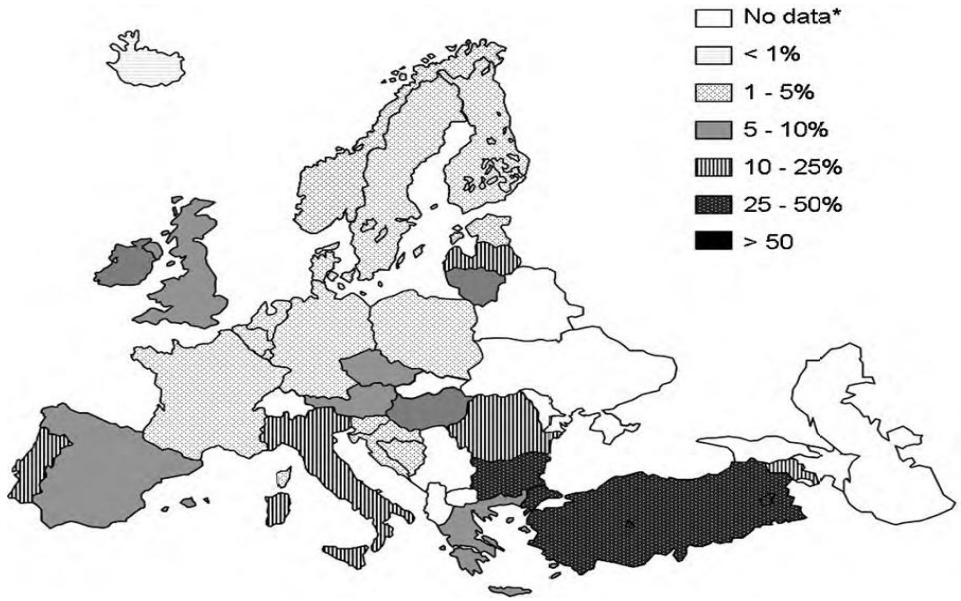

Figure 2: Proportion of invasive isolates of Escherichia coli with resistance to third-generation cephalosporins in 2008. *These countries did not report any data or reported less than 10 isolates. (Source: http://www.rivm.nl/earss/)

coliforms isolated from places not habited by humans but induced in a variety of species exposed to beta-lactam drugs [29,30]. Initially, these were susceptible to cefotaxime and ceftazidime, but later plasmid-mediated resistance emerged [31] and in no distant time plasmid-mediated ESBLs was recorded almost every year and most of which were derivatives of the TEM and SHV-1 beta-lactamase [32].

Another mechanism of resistant is the capture on plasmids of normally chromosomal genes from *Enterobacter cloacae, Citrobacter fruendii* or *P. aeruginosa*, which can provide *K. pneumonia* or *E. coli* with resistance to α-methoxy-β-lactams (cefoxitin and cefotetan) as well as to oxyimino-β-lactams (cefotaxime, ceftriaxone and ceftazidime) [33]. A resistant organism isolated during therapy to one cephalosporin may thus demonstrate reduced susceptibility to other antibiotics, not necessarily within the same class [34].

Penicillin-resistant *pneumococci*

Clinically significant infections with penicillin-resistant pneumococci (PRP), has become an epidemic [35] and are associated with extensive prior antimicrobial therapy [36], particularly beta-lactams [37]. But the aminopenicillins have also been implicated for selecting PRP, although this may only be because the emergence of this pathogen coincided with increased consumption of these antibiotics [38]. PRP have greater potential to spread than susceptible strains [39] and the pathogenicity of this organism is such that the increasing incidence worldwide is of major concern to clinicians [40].

Methicillin-resistant *Staphylococcus aureus* (MRSA)

A direct relationship has been established between MRSA and cephalosporins. A study revealed that patients who had received cephalosporin therapy for more than 5 days were more likely to acquire MRSA than those who had not received these agents [41]. This relationship was further affirmed by a study demonstrating the effects of reducing cephalosporins usage in three acute medical wards for the elderly. This study revealed that the number of MRSA infections reduced by half including a 42% drop in the number of *C. difficile* infections [42]. Another finding reported a reduction in the number of MRSA isolates from 35% to 23%, owing to the decreased use of cephalosporins in favor of piperacillin-tazobactam [43].

Public Health Implications of Bacteria Resistance to Cephalosporins

Hospital acquired/originated infections are also referred to as nosocomial infections. These infections are most frequently caused by *E. coli* (including clones of ESBL-producing *E. coli* ST131 responsible for wide spread nosocomial infections [5]); others include *A. baumannii, P. aeruginosa, K. pneumoniae, S. epidydermis, E. Faecium, E. Faecalis, S. marcescens* and *S. aureus*. These infections are significantly associated with antibiotic type and quantities used in hospitals [7]. These bacteria contain genes coding for the production of ESBL and/or AmpC transmitted by integrons (mostly Class I); insertion sequences (*Ecp*1 and *CR1* which are part of the so-called *sul1*-type integron structures) and transposons (The Tn*3* class II transposon); and plasmids (FII, A/C, L/M, N, K, and I1 groups, with IncF, IncI and IncN plasmid families being largely prevalent in commensal faecal flora of healthy animals) [10], hence are easily spread within and between hospitals through patients who move into and/or out of these hospitals [12].

With the continuous emergence of antibiotic resistance, the antibiotics used to treat bacterial infections lose their efficacy. The loss of effective antibiotic treatments will not only cripple the ability to fight routine infectious diseases but will also undermine treatment of infectious complications in patients with other diseases. Many of the advances in medical treatment—joint replacements, organ transplants, cancer therapy, and treatment of chronic diseases such as diabetes, asthma, rheumatoid arthritis—are dependent on the ability to fight infections with antibiotics. If that ability is lost, the ability to safely offer people many life-saving and life-improving modern

medical advantages will be lost with it [44]. Regrettably, the multi-resistant nature of bacteria that produce ESBLs and AmpCs can affect the selection and timely administration of appropriate antimicrobials for combating these community-acquired and healthcare-associated infections, since many first-line antimicrobials are no longer active against them [10], and this could increase the mortality rate. The health implications of this phenomenon have also been discovered to have a direct impact on the economy [45].

The high reported proportions of resistance to thirdgenerationcephalosporins means that treatment for severe infections for which *E. coli* and/or *K. pneumoniae* are a likely cause, may need to be initiated with broader therapy (e.g.carbapenems) in these populations. This implies highercosts and stimulus to the expansion of carbapenem resistant strains. Of even greater concern is that infections with carbapenem-resistant strains need to be treated with the last-resort drugs tigecycline orcolistins, which are not only less effective but also not widely available. Patients with such resistant infections (especially *K. pneumoniae*) carry a risk of worse clinical outcomes and consume more health-care resources than patients infected by susceptible strains [46].

Recent Advances in Cephalosporin Development against Resistant Bacteria

One cephalosporin that has shown relevance in tackling resistance in a wider variety of bacteria is Cefovecin. Although initially unclassified, cefovecin is now classified as a member of the third generation [47]. Isolates from dogs and cats have shown that cefovecin is very active against gram-negative organisms like *E. coli*, *P. multocida, Proteus spp*, *Klebsiella spp* (including *K. pneumoniae*) and Enterobacter [48]). In cats, cefovecin showed good activity against *Fusobacteriumspp*, *Bacteroidesspp*, and *Prevotellaoralis* [47]. However, it is not active against *P. aeruginosa* [48].

Recently, basically two new cephalosporins have been synthesized to combat resistance in bacteria, these are together called the fifth generation cephalosporins, and they include Ceftobiprole and Ceftaroline. The most advanced among these molecules is ceftobiprole and it is usually administered intravenously as a prodrug because of its low water solubility [49]. This fifth generation cephalosporin has been discovered to be the most potent cephalosporin tested against *S. pneumoniae* with MIC_{50} (0-0.15microg/mL) and MIC_{90} (0-5microgr/mL) with values two-fold lower than ceftriaxone [50]. They can bind effectively (due to modifications to the carbapenem structure [51]) to Penicillin Binding Proteins 2a (PBP2a) in MRSA including Vancomycin Intermediate Staphylococcus aureus (VISA) and Vancomycin Resistant *S.aureus* (VRSA) [52]. It has also been found to be highly active against penicillin-susceptible isolates of *S. pneumoniae* (MIC_{90}, 0.03μg/mL) [53]. Despite the wide spectrum of its activity making it resistant to inactivation by a wide range of beta-lactamase, ceftobiprole is not active against *E.faecium* [54], and is hydrolyzed by ESBLs found in *E. coli* and *Klebsiellaspp* (and Metallo-beta-lactamases (MBLs) [5]).

The second of the fifth generation cephalosporins which has also shown affinity for PBP2a is Ceftaroline. It is active against methicillin – sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *S. epidermidis* and Methicillin – resistant *Staphylococcus aureus* (MRSA). When tested against a collection of Community – associated MRSA (CA-MRSA) strains, the Minimum Inhibitory Concentrations MIC_{50} and MIC_{90} were 0.5μg/ml [55]. It has also shown activity against vancomycin-intermediate *S. aureus* (VISA) and hetero-VISA as well as non-extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter fruendii* and *Enterobacter cloacae* [49]. Ceftaroline is also active against strains of *S. pneumoniae* that are resistant to ceftriaxone, as well as *Haemophilus influenzae* and *Moraxella catharralis*. Similar to ceftobiprole, Ceftaroline inhibited strains of both vancomycin-susceptible and –resistant *E. faecalis*, but was inactive against *E. faecium*. It has a weak activity against Gram-negative bacteria compared to other extended spectrum cephalosporins.

Ceftolozane/tazobactam formerly referred to as CXA-201, is another novel antibiotic which comprises a combination of anoxyimino-aminothiazolyl cephalosporin (ceftolozane) and β-lactamase inhibitor (tazobactam). The addition of tazobactam to ceftolozane resulted in an improved activity compared to other antibiotics. This excellent activity has been demonstrated *in vitro* against a panel of >900 *P. aeruginosastrains*, (including cephalosporin- and carbapenem-resistantisolates) and Gram-negative organisms such as *E. coli* and *K. pneumoniae* [6]. CXA-101, another novel cephalosporin under development, in combination with tazobactam, just like CXA-201 has also shown improved *in vitro* activity against *P. aeruginosa*, *E. coli*, and *K. pneumoniae* and is not affected byAmpC over expression, porin mutations or efflux pumps [5].

In vitro Studies on the Pharmacodynamics Effects of Cephalosporins

The effect of cephalosporins depends on the time above MIC. Ceftobiprole, a novel parenteral cephalosporin with high affinity for most penicillin-binding proteins (PBPs), including the mecAproduct PBP2a, making it active against MRSA [56], however, lacks affinity against Ampicillin-resistant *Enterococci* as a result of poor affinity for PBP5, which is mutated and over expressed in Ampicillin-resistant *enterococci* [57]. The typical minimum inhibitory concentration (MIC) of ceftobiprole against MRSA is 2μg/ml, contrasted with an MIC of > 64μg/ml for ceftriaxone [51].

Ceftaroline has higher MICs against penicillinase-producing *E.coli* and *Klebsiella* spp. And *Enterobacter*, *Citrobacter* and *Serratia spp*. (0.12–1 μg/ml) compared to ceftriaxone, cefotaxime, ceftazidime, and cefepime [58].

Ceftobiprole has been found to be highly active against penicillin-susceptible isolates of *S. pneumoniae* (MIC_{90}, 0.03μg/mL) [53]. Not only that, Penicillin-intermediate and –resistant isolates of *S. pneumoniae* are also highly susceptible to ceftobiprole *in vitro* with MIC_{50} and MIC_{90} values of 0.06 and 0.5 μg/mL (penicillin-intermediate isolates) and 0.5 and 1.0 μg/mL (penicillin-resistant isolates) [59]; making Ceftobiprole a therapeutic option for infections caused by pneumococci resistant to conventional cephalosporins. This renders ceftobiprole a promising candidate for empirical treatment of community and hospital-acquired pneumonia [56].

Bustos and Del Pozo. (2010) in an invitro study, discovered that serial dilution with increasing concentrations of ceftobiprole performed with 3 MRSA isolates and 1 MSSA isolate shows that the

emergence of resistance to ceftobiprole (from 1.7 × 10–3 to 1.2 × 10–8, at the MIC to <1.4 × 10–8 to <1 × 10–9 at 8 times the MIC) as a result of mutations in chromosome, occur less often, if ever, in MRSA [56]. However, a recent study by *Banerjee et al*., (2008) suggested that MRSA can develop high level ceftobiprole resistance *in vitro* mediated by mutations in PBP2a [60].

Conclusion

Based on our review, bacteria (including causative agents of life threating infections) have developed resistance to virtually all generations of cephalosporins including the recently developed fifth generation. Despite the fact, that this new generation (just like the previous ones) was developed to curb the menace of bacteria resistance, but unfortunately, ceftobiprole has been reported to be inactivated by ESBLs found in *E. coli* and *Klebsiellaspp* includingmetallo-beta-lactamases (MBLs). Ceftaroline has also been found to be hydrolyzed by organisms producing ESBLs and AmpC beta-lactamases

However, with the pandemic nature of bacteria resistance to cephalosporins and the thousands of annual deaths reportedly to have been caused by this phenomenon and perhaps more alarming, its fast emergence and spread, a restriction in the use of these antibiotics (especially the third and fourth generations), would be recommended, and then the ceftolozane – tazobactam combination encouraged since it has demonstrated an excellent activity *in vitro* against *P. aeruginosastrains* and Gram-negative organisms such as *E. coli* and *K. pneumoniae*, organisms which have been reported to be resistant to almost all the other cephalosporin generations.

Authors' Contributions

AAT made substantial contributions to conception and design of this review. AAT and OJP were involved in drafting the manuscript. AAT revise it critically for important intellectual content. All authors read and approved the final manuscript.

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J Bacteriol Mycol - Volume 3 Issue 1 - 2016
ISSN : 2471-0172 | www.austinpublishinggroup.com
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Citation: Adesoji AT, Onuh JP and Okunye OL. Bacteria Resistance to Cephalosporins and its Implication to Public Health. J Bacteriol Mycol. 2016; 3(1): 1021.