Review Article

Ceftriaxone Resistance – A caution for judicial antibiotic use

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ABSTRACT

Ceftriaxone is a broad-spectrum antibiotic that is effective against both Gram-negative and Gram-positive isolates. Ceftriaxone resistance research is useful in determining its current status. As a result, we aimed to understand the prevalence of Ceftriaxone resistance in bacteria isolated from various clinical specimens. Resistance to ceftriaxone has been steadily increasing and demands immediate attention. Ceftriaxone resistance prevention mechanisms must be strictly enforced. The appropriate drugs should be chosen based on susceptibility patterns. In summary, ceftriaxone should be considered in the initial treatment of seriously ill patients with infections of unknown aetiology when Gram-negative aerobes (other than Pseudomonas species) are the suspected pathogens, and in patients with Gram-negative organisms with suspected or demonstrated resistance to other antibiotics. This review summarizes the advent of ceftriaxone resistance among various organisms across the globe.

Keywords – Ceftriaxone, Resistance, Gonorrhoea, Salmonella, Shigella, Aeromonas, Enterobacter

The third-generation cephalosporin ceftriaxone has good effectiveness against numerous gram-negative pathogens and excellent activity against the majority of gram-positive infections. Ceftriaxone has generally more antibacterial action against Gram-negative bacteria than the "first" and "second generation" cephalosporins, but less antibacterial activity than the previous generations of cephalosporins against numerous Gram-positive bacteria. Ceftriaxone has a long elimination half-life, allowing for twice- and once-daily treatment, the latter of which may result in significant cost savings. Ceftriaxone may replace other third-generation cephalosporins as the treatment of choice for a range of serious infections due to its proven efficacy, safety, and practical dose schedule [1].

In patients with bacterial meningitis, respiratory tract infections, urinary tract infections, soft tissue infections of the bone and joints, and gonorrhoea, clinical investigations have shown their effectiveness and safety. Except for diarrhea, which has often not necessitated changing the course of treatment, ceftriaxone has been well tolerated. Despite having modest action against *Pseudomonas aeruginosa*, ceftriaxone is not currently advised as the only antibiotic therapy for pseudomonal infections based on the available data. Infections caused by other "difficult" organisms, such as multidrug-resistant Enterobacteriaceae, have been successfully treated with ceftriaxone [2].

With the discovery of penicillin by Sir Alexander Fleming in 1928, the modern era of antibiotics began [3]. Since that time, antibiotics have revolutionized contemporary medicine and helped save countless lives [4]. In the 1940s, doctors began using antibiotics to treat severe infections. Unfortunately, almost all antibiotics that have been produced have eventually been associated with resistance, and this is also true of cephalosporins, notably ceftriaxone [5].

Mechanism of ceftriaxone resistance development

There are multiple mechanisms that infectious agents use to resist the lethal action of antibiotics such as mutational resistance, acquisition of genetic material, increased drug efflux or, decreased drug intake [6]. Other complex mechanisms involve are biofilm formation and quorum [7]. Quorum sensing and biofilm formation is the common mechanism for antibiotic resistance among *E. coli*. In this, the cells adhere to each other on their surface using a self-produced matrix called the extra polymeric substance. This extra polymeric substance creates a barrier for the antibiotic to enter the bacteria, this promotes the emergence of antibiotic resistance and this is referred to as quorum sensing [8].

However, this mechanism may not be applicable to gonococci. Gonococci develop resistance to beta-lactam antibiotics primarily by two mechanisms – one that is quickly acquired through the transfer of resistance plasmid that produces beta-lactamases and the second one is the gradual acquisition of multiple resistance genes that promotes beta-lactam resistance [9]. The production of extended-spectrum beta-lactamases is the most commonly attributed mechanism of ceftriaxone

resistance in *E.coli* [10]. Additionally, a molecular analysis of *Salmonella* isolates with ceftriaxone resistance has demonstrated a higher production of the CMY-2 and the CTX-M-3 beta-lactamases [11]. On the other hand, ceftriaxone resistance in *Neisseria gonorrhoeae* is a result of chromosomally mediated mutations at the three loci of penA, mtrR, and penB [12].

Furthermore, the production of cephalosporinases also degrades cephalosporins and this is one such mechanism that promoted ceftriaxone resistance among *Salmonella* species. Since extended-spectrum beta-lactamases are mobile genetic materials and bacteria can acquire them through horizontal gene transfer from resistant bacteria, sensitive bacteria can acquire resistance to cephalosporins [13]. Also, several studies on the mechanism of resistance to third-generation cephalosporins, particularly ceftriaxone have suggested that clinical strains of *Enterobacter cloacae* are linked to the excessive production of chromosomal beta-lactamases [10, 14].

Neisseria gonorrhoeae

Antimicrobial resistance in *Neisseria gonorrhoeae* is a major public health concern globally. The most frequently prescribed antibiotics for Gonorrhoea are ceftriaxone, cefixime, azithromycin, spectinomycin, ciprofloxacin, and ofloxacin. *Neisseria gonorrhoeae* was initially susceptible to the majority of antimicrobials since the mid-1930s [15, 16]. But recently the resistant patterns in *Neisseria gonorrhoeae* have developed owing to its ability to develop or acquire antimicrobial resistance through most of the existing mechanisms. A few examples of the mechanisms *Neisseria gonorrhoeae* undergo to cater to antimicrobial resistance are as follows – inactivation, degradation of antimicrobials, alteration of the target antimicrobial, decreased antimicrobial influx, and increased generation of efflux transporters.

Resistance of *Neisseria gonorrhoeae* to fluoroquinolones and ceftriaxone came into prominence after its first appearance in Japan which then further spread globally [17-20]. Furthermore, the first global failure for treating pharyngeal gonorrhoea with dual antibiotics (both 500 mg ceftriaxone and 1g azithromycin) was first reported in the United Kingdom in 2016 [21]. Dual therapy has been instituted due to the emerging resistance patterns, but countries such as Japan, China, Azerbaijan, Netherlands, Belarus, and Ukraine still use ceftriaxone 500mg-1g as empirical mono-therapy [22-24].

With the evolving resistance patterns, what are the options available to the medical community? Repurposing the old antimicrobials, use of newer antimicrobials with mainly non-human or invitro data availability, and novel antibiotics in clinical trials. Spectinomycin is a long-used antimicrobial for gonorrhoea with excellent susceptibility, but relatively lower success in treating pharyngeal gonorrhoea [25]. Therefore, spectinomycin can be used as a part of the dual regimen along with azithromycin to prevent the emergence of antimicrobial-resistant strains [26].

New antimicrobials with only non-human evidence have demonstrated relative potency against *Neisseria gonorrhoeae* and include avarofloxacin, delafloxacin, sitafloxacin, tigecycline, 2-acyl carbapenems and many others which have been reviewed elsewhere [27-29]. However, many of them are in stages of early development thus posing a challenge for their use within the clinical setting. Three antimicrobials solithromycin, zoliflodacin, and gepotidacin are novel orally administered drugs in clinical evaluation for uncomplicated gonorrhoea and particularly zoliflodacin appears very promising and requires attention [30]. Until a promising new effective treatments, rational use of ceftriaxone and azithromycin will help treat gonorrhoea with its severe complications.

Aeromonas spp.

Aeromonas species can cause a wide spectrum of intestinal and extra-intestinal infections (gastrointestinal tract syndromes, wound and soft tissue infections, urinary tract infections, and rarely septicaemia) [31]. They are Gram-negative rods, facultative anaerobes and oxidase-positive. *Aeromonas* species that are pathogenic for humans include *Aeromonas hydrophila*, *Aeromonas sobria*, *Aeromonas trota*, and *Aeromonas caviae* and are most commonly found in the aquactic life forms particularly fishes [32, 33].

The sensitivity of *Aeromonas* can vary based on geographical location and diversity. The most common antibiotics employed for *Aeromonas* infections are fluoroquinolones and tetracyclines. Furthermore, third-generation cephalosporins have also been recommended but in recent years, there has been an upward trend for resistance to ceftriaxone attributed to the beta-lactamase activity of *Aeromonas* [34].

Aeromonas has been linked to the development of beta-lactamases (ESBLs, AmpCBLs, and carbapenemases), efflux pumps, and changes in the outer membrane that result in decreased permeability as the mechanisms of resistance to third-generation cephalosporins. *Aeromonas* is known to carry various drug-resistance genes and has also demonstrated the ability to transfer such genes to various gram-negative bacteria. Multiple drug resistance among *Aeromonas* spp. have been reported from many parts of the world as well. Also, a concerning aspect of drug resistance among the *Aeromonas* spp. is the ability to bring about extra-intestinal infections that can be fatal with the existing multiple drug-resistance genes [35]. A plausible cause for such increased spread of antibiotic resistance is rapid urbanization and the evolution of bacteria to survive such threats [36].

Salmonella spp.

An alarming health issue that exists everywhere is salmonella infection. Effective steps should be taken to stop the issue from getting worse [11]. The preferred treatment for typhoid fever is ceftriaxone, however, the introduction of *Salmonella Typhi* which is resistant to it creates serious treatment problems. There are more and more sporadic instances of ceftriaxone-resistant *S. Typhi*, therefore reducing the chance that the patient won't respond to therapy and that outbreaks will spread throughout the neighbourhood must take precedence. Since 1988, Salmonella resistant to extended-spectrum cephalosporins has become an international problem. This public health issue had been reported in 43 countries by 2004. Traditional extended-spectrum beta-lactamases, plasmid-mediated cephalosporinases, and most recently a class a carbapenemase were responsible for mediating resistance. The most extensively distributed of them is *CMY-2*. The two most prevalent serovars connected to extended-spectrum cephalosporins resistance in human infections are *Salmonella enterica* serotype Typhimurium and *Salmonella enterica* serotype Enteritidis [37].

The invasive infection caused by *Salmonella enterica* serotype Choleraesuis is usually typical. Most often extended-spectrum cephalosporins or fluoroquinolones are utilized to treat resistant Salmonella infections [38]. However, there are increasing reports of fluoroquinolone resistance in the invasive serotype of *Salmonella*. In SC-B67, ceftriaxone resistance was linked to a plasmid-mediated *bla*$_{CMY-2}$ that is commonly present on a particular IS*Ecp1*-*bla*$_{CMY-2}$-*blc*-*sug*E structure [39]. This conserved DNA segment, later given the designation Tn*6092*, has been identified in numerous Enterobacteriaceae and Salmonella serotypes from across the globe [40, 41]. In addition, ceftriaxone-resistant serotype *Salmonella Typhimurium* infections, which were previously uncommon in western Kenya, appeared quickly between 2009 and 2014 in countries in western Kenya, restricting the range of available treatments for serious infections. In order to direct proper therapy in diverse Asian and African nations, there is an urgent need for increased microbiologic diagnostic capability in clinical settings [42].

Extended-spectrum –lactamases whose genetic elements can be found in plasmids or the chromosome, are typically responsible for the creation of resistance to ceftriaxone. Organisms that produce CTX-M-type ESBLs constitute a particularly major public health danger globally among the variety of antibiotic-resistant Gram-negative bacteria pathogens that are currently recognised [43]. An extremely invasive zoonotic bacterium called *S. choleraesuis* produces a devastating systemic infection in people. A significant treatment issue has arisen due to the emergence and growth of *S. choleraesuis* resistance to ceftriaxone and ciprofloxacin. Sirirat et al have demonstrated high frequency of antimicrobial resistance in Salmonella Choleraesuis among 414 nontyphoidal Salmonella isolates from bacteremic patients in Thailand. *S. choleraesuis* isolates had high rates of ceftriaxone (58.3%) and ciprofloxacin (19.6%) resistance. The clonal spread of *S. choleraesuis* isolates harbouring bla$_{CMY-2}$ as well as the dissemination of the self-transferable bla$_{CTX-M-14}$-carrying IncFII$_s$, IncFII, and IncI1 plasmids and the bla$_{CMY-2}$-carrying IncA/C plasmid as well as the high frequency of resistance to extended-spectrum cephalosporins (3rd and 4th generation cephalosporins).

The first occurrence of ceftazidime-hydrolyzing CTX-M-55 in *S. choleraesuis* isolates has been documented; between 2012 and 2016, this variant's abundance among ESC-resistant *S. choleraesuis* isolates grew rapidly. The dispersion of IncA/C plasmids carrying both bla$_{CTX-M-55}$ and qnrS1 among ciprofloxacin-resistant *S. choleraesuis* isolates expressing D87G in GyrA was the cause of the spread of clone pulsotype B3. The high frequencies of co-resistance to ESCs and ciprofloxacin (51.3%) from 2012 to 2016 were reportedly caused by these isolates. As a result of travel and commerce in animal food items, this study highlights the significance of having an action plan to prevent the spread of antibiotic resistance in *S. choleraesuis* [44-46].

Shigella spp.

In the underdeveloped world, shigellosis is one of the major causes of diarrheal illnesses. An estimated 165 million cases and 1.1 million fatalities worldwide (mainly in underdeveloped nations) occur each year. Shigellosis patients have been advised to have antibiotic therapy because it can shorten the duration of the causative organism's faecal excretion and limit the clinical course of the illness, lowering the risk of complications and infection transmission [47, 48]. The growing resistance of *Shigella spp.* to effective antimicrobial treatments, however, is a significant issue [49]. Shigella isolates that are resistant to a variety of medications, including sulphonamides, tetracyclines, ampicillin, trimethoprim-sulphamethoxazole (SXT), and nalidixic acid, have been reported from many different nations over the years [50].

Azithromycin, mecillinam, ciprofloxacin, ceftriaxone, and cefixime are examples of novel antimicrobials that have been proven to be successful in treating multidrug-resistant Shigella-associated illnesses. However, Shigella strains resistant to ceftriaxone have emerged [51, 52]. Fluoroquinolones are the sole available antibiotic therapy for such MDR Shigella-associated illnesses due to the dearth of other options. Fluoroquinolones must be used carefully and wisely to prevent the rapid emergence and spread of resistance, as evidenced by the discovery of decreased susceptibility to fluoroquinolones in a significant fraction of Shigella strains and completely fluoroquinolone-resistant *S. dysenteriae* Type 1 [53, 54]. According to a study conducted by Gu B et al, a lower average

prevalence of ceftriaxone resistance among *Shigella spp.* was found in Europe-America countries. In contrast, Asia and Africa saw a clear increasing trend in ceftriaxone resistance, especially after 2007. Ceftriaxone resistance was present on average at a rate of 5% in Asia and Africa, which is 6 times higher than that of Europe and North America. In addition, Asia-Africa had resistance rates to ceftriaxone, cefotaxime, and ceftazidime that were up to 142%, 226%, and 62%, respectively, between 2010 and 2012. This warrants rapid action [55].

This phenomenon could have a number of explanations. The major cause is regional variations, which have a direct impact on socioeconomic position. Individuals in more developed regions (such as Europe and America) typically receive better care after contracting an infection than people in less developed nations (Asia-Africa). Second, flaws in medical infrastructure and facilities are also significant factors. Pakistan and other Asian-African nations lack the infrastructure necessary to track antimicrobial resistance on a national scale [56]. In addition, cheap antibiotics are widely accessible from both licensed and unlicensed sources in many Asian and African nations, which contributes to drug addiction and a high rate of resistance [57]. Third, the lack of access to safe drinking water and inadequate sanitation lead to the emergence of MDR strains of *Shigella*. Malnutrition is one of the underlying factors that raise the risk of diarrhoea and is widespread in Asian and African nations [58].

Enterobacter cloacae

The environmental pathogen Enterobacter cloacae complex (ECC), which is common, is a significant cause of nosocomial infections. The therapeutic importance of each species within ECC is less understood since standard techniques used in clinical laboratories cannot distinguish between species within ECC.Gram-negative rods resistant to third-generation cephalosporins are included in the broad spectrum of antibacterial activity of carbapenems. The main cause of ceftriaxone resistance is the pre-existing presence of resistant clones (also known as "derepressed mutants") in the Enterobacter populations. The majority of resistant clones generate substantial levels of beta-lactamases, and some of them exhibit decreased Porin F expression together with enhanced Porin C expression.

In a HPLC-based approach conducted by Pechere et al the author used HPLC to determine the outer membrane permeability in intact cells, and the results revealed that imipenem penetrated three times more quickly than ceftriaxone. Furthermore, imipenem penetration was unaffected in a Porin F defective mutant, in contrast to ceftriaxone. This implied that imipenem has a different route, possibly Porin C, then ceftriaxone. The affinity for PBPs, as determined by computation, and the rate of beta-lactamase hydrolysis under experimental settings that were believed to be physiologically relevant were comparable for the two antibiotics. Thus, selective permeability of the outer membrane appears to be the main cause of imipenem's action against ceftriaxone-resistant *E. cloacae* [59]. Because ECC isolates display intrinsic AmpC -lactamases, such as CMH, ACT, and MIR with numerous variations, they are innately resistant to ampicillin, amoxicillin-clavulanate, and first and second-generation cephalosporins [60]. Antibiotic usage has led to the emergence and global spread of multidrug resistant (MDR) ECC strains [61]. Third-generation cephalosporin resistance is also brought on by the acquisition of genes encoding extended spectrum -lactamase (ESBL). Additionally, treatment is becoming challenging due to the advent and rising prevalence of carbapenem-resistant ECC. MDR strain infections typically result in increased mortality, lengthier hospital stays, and higher expenses, having a significant influence on worldwide public health [62].

CONCLUSION

Antibiotic resistance should be prevented by reducing the irrational misuse of antibiotics, but designing successful interventions to do so will require a greater knowledge of the practices and financial incentives associated with antibiotic administration. Although increased cephalosporin resistance is frequently attributed to a single factor (PBP modification, beta-lactamase action, or impermeability), an organism's response to a drug frequently reflects the interaction of several factors. There is a need to develop methods, such as mathematical models, to aid in identifying the interplay of factors that lead to ceftriaxone resistance.

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