CEPHALOSPORINS DRUG RESISTANCE, A GUIDE FOR SELECTING AN ALTERNATIVE ANTIBIOTICS

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***Abstract*- Antibiotic resistance in bacteria can be innate or acquired. For example, cephalosporin resistance in Enterococcus species originates from a feature that occurs naturally in that species, and consequently, all members of that species will have that resistance pattern. A wide variety of hypersensitivity responses (HSRs) with various immune pathologies can be brought on by cephalosporin's. Over the past 20 years, new HLA associations and drug hypersensitivity syndromes have had a significant impact on both the safety of medications and our understanding of the immune pathogenesis of these events. The aforementioned studies showed the value of taking into account the antigenic determinants of both side chains when choosing alternative cephalosporin's in cephalosporin-allergic subjects as well as the ability of STs to identify subtle structural variations among cephalosporins in allergic subjects. Antibiotic resistance genes may also be carried on mobile gene cassettes which can be integrated into or deleted from their receptor elements.**

Key Words: **Antibiotic resistance, cephalosporin, immune-pathogenesis, hypersensitivity reaction.**

INTRODUCTION

Antibiotic resistance in bacteria can be innate or acquired. For example, cephalosporin resistance in Enterococcus species originates from a feature that occurs naturally in that species, and consequently, all members of that species will have that resistance pattern. Not all strains will have acquired resistance because acquired resistance results from mutation of an already present gene or acquisition of new DNA encoding a novel gene. The occurrence of mutation is a spontaneous process that takes place whether or not an antibiotic is present [1]. The DNA gyrase gene (gyrA) of Escherichia coli is frequently subject to mutations that result in a Ser83-Leu or Trp substitution. These strains are particularly resistant to fluoroquinolone antibiotics like ciprofloxacin, and the resistant mutants overwhelm the susceptible population quickly. In the United States, cephalosporins are among the most often prescribed antibiotics for hospitalised patients and the most typical antibiotic class given to patients upon discharge [2]. Cephalosporins make up 11.4% of all outpatient antibiotics in Europe, and their usage has grown over time [3]. A wide variety of hypersensitivity responses (HSRs) with various immune pathologies can be brought on by cephalosporins. This essay will concentrate on how we now understand cephalosporin hypersensitivity, with a focus on acute reactions to cephalosporins and current methods for patient de-labelling [4]. Like other -lactams, cephalosporins bind to the bacterial penicillin-binding proteins (PBPs). The D-ala-D-ala trans-, carboxy-, and endo-peptidases that are in charge of facilitating the cross-linking of freshly synthesised peptidoglycans correspond to these [5]. When the PBPs, and in particular the transpeptidases, are altered or when they are shielded by -lactamases or "permeability barriers," resistance results. Reduced affinity of an existing PBP component or the development of an additional, -lactam-insensitive PBP are two possible outcomes of targetmediated cephalosporin resistance [6]. Bacteria produce a variety of -lactamases, the identity of which can be identified by chromosomal or plasmid DNA [7]. Although species-specific, the chromosomal -lactamases can be divided into a few major categories. The interspecific and intergeneric barriers are crossed by the plasmid-mediated enzymes. The amount of enzyme produced with or without induction, the location of the enzyme (extracellular for Gram-positive organisms and periplasmic for Gram-negative ones), and the kinetics of the enzyme's activity all have an impact on the level of -lactamase-mediated resistance [8]. Because the PBPs in Gram-positive organisms are found on the outside of the cytoplasmic membrane, there is less need for permeability barriers to protect them. However, in Gramnegative organisms, PBPs are shielded by the outer membrane, which the majority of -lactams pass through through diffusion through aqueous pores made of "porin" proteins [9]. The number of porins and cephalosporin resistance in enterobacteria clearly correlate, indicating that the outer membrane is the only physical barrier to drug entrance. For Pseudomonas aeruginosa, where the cell may have additional barriers between the outer membrane and the PBPs, these correlations are less obvious [10]. Although PBP-modification, -lactamase activity, or impermeability are frequently cited as the causes of enhanced cephalosporin resistance, an organism's response to a medicine frequently reflects the interaction of multiple variable [11]. The susceptibility to eight cephalosporins, both alone and in combination with a subinhibitory concentration of the beta-lactamase inhibitor clavulanic acid, was tested in 35 beta-lactamresistant isolates of the Bacteroides fragilis group. In the presence of clavulinic acid, the majority of strains tested became fully susceptible to cephaloridine, cefotaxime, and ceftriaxone, whereas the effect of the inhibitor on the susceptibility to substances like cefsulodin and ceftazidime, and to a lesser extent cefoperazone, varied depending on the species. The MICs of Bact. fragilis strains nearly always decreased significantly, but those of other species, particularly Bact. thetaiotaomicron, were only little impacted. The inhibitor had no effect on cefoxitin susceptibility, while clavulanic acid made certain organisms with high levels of latamoxef (moxalactam) resistance vulnerable. The nitrocefin test revealed that all bacteria produce beta-lactamase, and these were distinguished by isoelectric focusing [12].

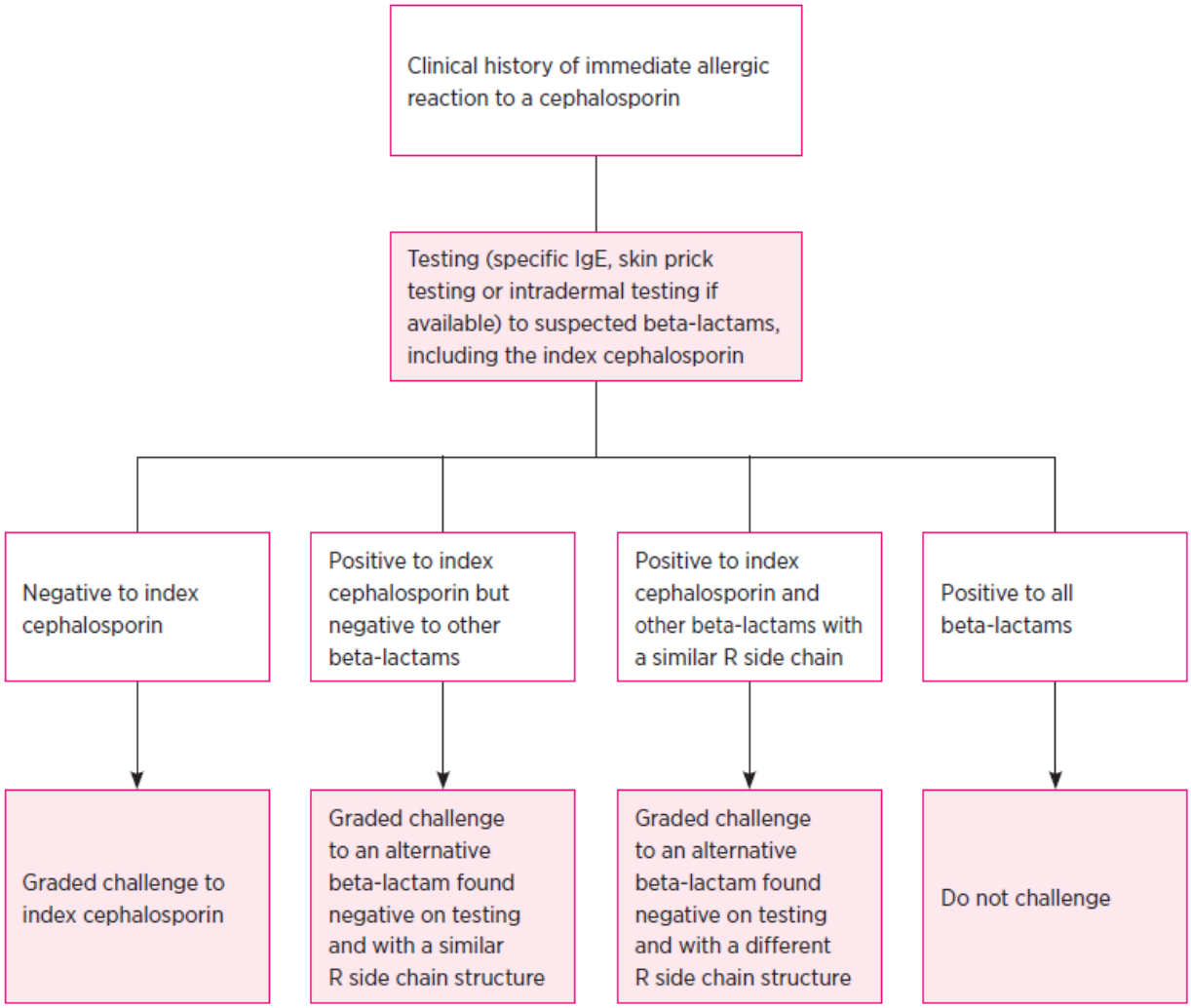
PHARMACOGENETICS

Over the past 20 years, new HLA associations and drug hypersensitivity syndromes have had a significant impact on both the safety of medications and our understanding of the immunopathogenesis of these events[13, 14-15]. Most antimicrobials, including beta-lactams, have not yet have HLA correlations with drug hypersensitivity events documented. Penicillin and drug-induced liver damage have been linked in the most important ways to date (DILI) [15-17]. The rarity of the DILI in comparison to how frequently these medications are used has prevented the translation of HLA use in screening for both flucloxacillin (which is available in Europe and Australia) and amoxicillin-clavulanate. Neither amoxicillin-clavulanate nor flucloxacillin are currently known to have any cross-reactivity with other beta-lactams for DILI [18]. An link between the HLA- haplotype and drug- and non-drug-induced interstitial nephritis was discovered in a recent investigation [19]. It is unknown whether this haplotype has any particular relevance for beta-lactam-associated acute interstitial nephritis (AIN). Although AIN is frequently brought on by semi-synthetic penicillin, these individuals frequently tolerate cephalosporins like cefazolin [20, 21]. There haven't been many studies done yet that link HLA variation and instant reactions. Asparaginase rapid reactions are significantly associated with the only HLA allele that has been linked to drug-induced anaphylaxis [21]. Studies particularly powered to look at genetic risk factors for cephalosporin allergy do not exist. It is believed that HLA may be necessary but not sufficient and subject to other ecological and epigenetic factors, especially for IgE-mediated reactions where sensitivity will wane significantly over time and almost 80% of cephalosporin allergic individuals have lost skintest reactivity to the implicated drug by 5 years after the acute reaction [22, 23]. The genes involved in IgE synthesis (STAT6, IL4RA, IL13), expression of pre-formed mediators (LGALS3), HLA class II antigen presentation genes, NOD2 genes regulating class II expression, and cytokines have shown the strongest relationships with genetic variation for beta-lactam allergy (IL-4, IL10, IL-18) [24,25]. A genome-wide association analysis for beta-lactams that revealed a signal in the class II HLA region did not achieve genome-wide significance [26]. CEPHALOSPORINS ALLERGY HSRs brought on by cephalosporins can range from benign exanthema to anaphylaxis or SCAR. The most typical type of delayed reactions is maculopapular exanthema. Many cephalosporins can cause serum sickness-like reactions (SSLR), but cefaclor has the highest relative risk of doing so and, in certain series, may account for more than 80% of SSLRs linked with antibiotics [27]. The pharmacogenetic foundation of the cefaclor SSLR mechanism has not been sufficiently investigated, however it appears to be related to the formation of hazardous metabolites [28]. Children with SSLR to cefaclor seem to tolerate various cephalosporins despite the paucity of available evidence. Another typical contributor to antibiotic-associated SCAR is cephalosporins[30]. HSRs can be fatal during the perioperative period because they are unpredictable. Perioperative HSR incidence is probably underreported, however literature reports range from 1:1380 to 1:20,000[29-32]. Antibiotics and neuromuscular blocking drugs (NMBAs) are the primary etiological agents of perioperative anaphylaxis, albeit this varies by country. Antibiotics account for 50% of IgE-mediated perioperative HSRs in the United States, making them the most common cause of HSRs in the operating room. According to multiple studies, the most frequent cause of perioperative anaphylaxis in the United States and some other countries is cefazolin, the first-line prescribed perioperative antibiotic for the majority of surgeries [33, 34].

CROSS REACTIVITY

According to several studies, those who are allergic to cephalosporins typically tolerate other cephalosporins with different R1 group side chains. The largest .'s study to date analysed 102 individuals (89 with anaphylactic histories) from Italy who underwent skin testing to alternative cephalosporins and had rapid reactions to cephalosporins [35]. Based on the distribution of skin test reactions, they separated the subjects into 4 groups. Patients in Group A (71% of subjects) were hypersensitive to Group A cephalosporins, which included ceftriaxone, cefuroxime, cefotaxime, cefepime, and cefodizime and shared a common R1 methoxyamino group. Patients belonging to Group B (13%) were hypersensitive to cefaclor, cephalexin, and cefadroxil, which share the same R1 amino group as ampicillin and amoxicillin. 7 percent of Group C patients were hypersensitive to Group C cephalosporins, such as cefazolin, cefamandole, cefoperazone, and ceftibuten, which have distinctive R1 groups and are structurally distinct from other cephalosporins. Skin test reactivity to at least two members of groups A, B, and C was seen in group D subjects (9%) who appeared to crossreact between the groups. 60% of all patients had ceftriaxone as the offending cephalosporin, followed by cefaclor (11.6%) and ceftazidime (8.9%). All 102 participants tolerated 326 skin test-negative challenges to additional cephalosporin groups. According to this study, Groups A, B, and C side-chain structure accounts for 91% of cephalosporin allergies, while a negative skin test to a different cephalosporin with a different R1 side chain indicates tolerance. In patients with histories of allergy to cefazolin (a total of 36 patients), further investigations have demonstrated side chain specificity when skin tests and challenges to cephalosporins with various R1 side chains, such as cefuroxime, cetriaxone, ceftazidime, and ceflotin, were negative [37]. Ceftezole, which is sold in Asia but not the United States, has a side chain that is identical to that of cefazolin's and has been linked to anaphylaxis in some cases [38]. proposed patterns of cross-reactivity between cephalosporins. It is unknown if other nations, particularly the United States, where side chain specific aminopenicillin reactions are uncommon, exhibit the same pattern of cross-reactivity. Generally, but not always, tolerance to cephalosporins can be anticipated based on similarities or variances in the R1 side chains of the various cephalosporins. A pharmacological challenge is required to confirm tolerance. As previously mentioned, the negative predictive value linked to rapid skin testing for cephalosporin hypersensitivity has not been established. For this reason, challenge with the offending cephalosporin medicine is advised when skin testing does not show a notable wheal/flare reaction to a cephalosporin drug in order to conclusively rule out cephalosporin allergy [39]. The chance of negative skin tests and cephalosporin tolerance increases the longer it has been since the adverse reaction occurred in patients with histories of cephalosporin allergy that are clearly compatible with IgE-mediated pathophysiology, as has been seen with penicillin [40]. Patients who have had an adverse reaction within the past six months but have negative skin tests and a history consistent with an IgE-mediated reaction may therefore be considered to be at increased risk and candidates for safety measures like a graded-dose challenge starting at a lower dose (e.g.,

1/100th-1/10th of the full dose). However, false positive skin tests for cephalosporin medications may occur. The positive predictive value of cephalosporin skin testing has also not been established. Limited retrospective data indicate that between one-third and fifty percent of patients with positive skin tests for penicillin will experience adverse effects after being challenged [41]



MANAGEMENT/PREVENTION

The prevalence of HSRs to cephalosporins is rising, with 1-3% of the population reporting them. Cephalosporins, in particular, are one of the main contributors of SCARs and perioperative anaphylaxis [41, 42]. STs with cephalosporins are reliable and effective for identifying both immediate60-65 and delayed hypersensitivity66 to these -lactams, despite the fact that they have less validation than STs with penicillins in trials including at least 20 patients. Notably, [44]. (5.2%) of 1421 patients in a Korean research who had preoperative cephalosporin STs performed tested positive for at least one cephalosporin. All 74 participants, however, were able to tolerate a challenge dose of a cephalosporin that had been discovered to be effective in skin testing. Selecting Penicillins Several investigations evaluated the cross-reactivity between cephalosporins and the other classes of -lactams in participants with established IgE-mediated allergy to cephalosporins by administering graded challenges with substitute -lactams that tested negative for allergy. In a research by Antunez et al.,[42-45]. 22 of the 24 cephalosporin-allergic participants were ST negative to penicillin reagents and tolerated PG challenges, whereas 2 of the 24 subjects were ST positive to them. In a study of 98 people with confirmed cephalosporin allergy, 25 subjects (25.5%) tested positive for penicillin allergies after undergoing sIgE assays, STs with penicillin reagents, as well as STs with carbapenems and aztreonam. Amoxicillin challenges were tolerated by all 73 patients who tested negative for penicillin reagents. Of the 55 people who had previously experienced rapid reactions to cephalosporins, Yuson et al [46]. identified 24 (46.3%) as having a hypersensitivity to the index cephalosporins. Twenty-three of them were ST negative to penicillin reagents; seven of them undertook amoxicillin challenges (six subjects) or flucloxacillin challenges (one subject), and they all tolerated them. The final suspect tested positive for ST to amoxicillin but was not questioned. In 40 patients who had allergic reactions to cefazolin and positive STs to it, Li et colleagues [47, 48]. evaluated the feasibility and safety of amoxicillin challenges without penicillin STs. All 4 patients in this study exhibited positive STs to the causing cephalosporins and negative STs to penicillin. This study also included 2 patients with cephalothin anaphylaxis and 2 patients with ceftriaxone anaphylaxis. A 3-day amoxicillin challenge was carried out on all 44 individuals without any adverse effects being reported. One patient stopped taking amoxicillin after experiencing a delayed benign rash at 24 hours. Selecting Carbapenems or Aztreonam The incidence of any type of HSR to a carbapenem was 25% (3 of 12) for patients with prior proven, suspected, or possible IgE-mediated cephalosporin reactions (n = 12), including 2 nonIgE mediated reactions and 1 possible IgE mediated reaction. This included children and adults

reporting immediate reactions to penicillins and/or cephalosporins who were then given a carbapenem. One person in the previously described study with 98 cephalosporin-allergic subjects was ST positive to both meropenem and imipenem/cilastatin as well as to all other testing reagents, indicating a sensitivity to an antigenic determinant Three people tested positive for aztreonam, including the one just stated, another who also tested positive for cefodizime and PV in allergy tests, and the last who tested positive for both the causative medications, aztreonam and ceftazidime. It's noteworthy that the other 10 people who had ceftazidime allergies also tested ST-negative for aztreonam. With the exception of one patient who had an adverse reaction to imipenem/cilastatin in this investigation, all 68 subjects tolerated the alternative lactams that were examined and shown to be ineffective in skin testing. Selecting Alternative Cephalosporins There aren't many trials where at least five patients with cephalosporin allergies were tested with an alternate cephalosporin and the ST results came out negative [49, 50]. In a study cefaclor IgE tests and STs with a panel of 11 cephalosporins were used to assess 102 persons who had rapid reactions to cephalosporins and positive STs to the medicines that caused them. The subjects were divided into four groups based on the outcomes of both allergy tests: group A (73 subjects), positive to one or more of the following antibiotics: ceftriaxone, cefuroxime, cefotaxime, cefepime, cefodizime, and ceftazidime; group B (13 subjects), positive to amino cephalosporins; group C (7 patients), positive to antibiotics other than those in the aforementioned groups; and group D (9 participant) In group A, 32 of the participants displayed a pattern of cross-reactivity, while 41 of the subjects tested positively solely to the relevant cephalosporins. 11 individuals in group B only tested positive to the offending aminocephalosporins, and 2 displayed a pattern of cross-reactivity. The other person, who had reacted to cefoperazone, was positive to both cefoperazone and cefamandole. Of the 7 subjects in group C, 6 were positive just to the offending compound (5 to cefazolin and 1 to cefamandole). Different patterns of positivity were displayed by Group D participants, and the majority of these patterns cannot be explained by either similar or identical side chains or by the common -lactam ring. These instances raise the probability of concurrent sensitivities; as a result, the frequency of positive allergy test results to other cephalosporins is not only attributed to the shared chemical properties of side-chain determinants. Cefuroxime axetil, ceftriaxone, cefazolin, and ceftibuten were given to group B participants, while cefuroxime axetil, ceftriaxone, ceftibuten, and other cephalosporins that were chosen for group C and D participants based on their patterns of positive, were given to group A individuals. A total of 323 challenges with different cephalosporins were well tolerated (ceftibuten in 101, cefazolin in 96, cefaclor in 82, and cefuroxime axetil and ceftriaxone in 22 patients). These findings suggest that it is unlikely that cephalosporin hypersensitivity is a type of class hypersensitivity. There are actually 2 classes (or groups) of cephalosporins. ere identified: Those belonging to group A—those with a methoxyimino group in their R1 side chains—plus ceftazidime, whose R1 side chain has an alkoxyimino group rather than a methoxyimino group, and those belonging to group B—aminocephalosporins—are combined here. It was impossible to distinguish further categories due to the small number of cephalosporin-sensitive participants who did not belong to the aforementioned groups. It is possible to speculate about additional groups, such as one made up of cephalosporins like cefamandole, cefoperazone, and cefotetan that share an identical R2 side chain with an N-methyltetrazole-thiol group. This hypothesis is based on the case of a group C subject who had reacted to cefoperazone and was ST positive to both cefoperazone and cefamandole. Then, in a research by Sadleir et al., [50, 51] 21 individuals with acute cefazolin hypersensitivity, including 19 with definite anaphylaxis, tested negative for cephalothin in IDTs and withstood challenges. Five patients received ceftazidime from Van Gasse et al., [52, 53] who noted instantaneous HSRs to cefuroxime and positive STs to cefuroxime but negative ones to ceftazidime. With ceftazidime, all participants tolerated the difficulties. This study established that clinical tolerance and a lack of cross-reactivity may be caused by minor structural differences. In a study by Stone et al., [54, 55]. 17 of 22 individuals with a documented acute allergy to cefazolin, cefuroxime, ceftriaxone, ceftazidime, or cefepime tolerated an oral challenge with cephalexin, a different cephalosporin with an R1 side chain. A challenge with cefuroxime was tolerated by a different patient who had a known allergy to cefazolin. The aforementioned studies showed the value of taking into account the antigenic determinants of both the R1 and R2 side chains when choosing alternative cephalosporins in cephalosporin-allergic subjects as well as the ability of STs to identify subtle structural variations among cephalosporins in allergic subjects. In actuality, no symptoms were observed in any of the 367 challenges that were carried out with other cephalosporins and proven to be negative to STs. As a result, cephalosporin STs seem to be a trustworthy and useful tool for choosing substitute cephalosporins in people who are allergic to cephalosporins [56-59]. However, systematic IDT screening with cephalosporins before to administration of the cephalosporin in question was not clinically beneficial for the prevention of anaphylaxis and concomitant mortality in a large Korean research, In the aforementioned study [60] 65 on people who have a delayed allergy to cephalosporins, 2 of the 7 patients who had this allergy to cefazolin, cefoxitin, ceftriaxone, or cefepime undertook an oral challenge with cephalexin and both tolerated it [61]. Regarding subjects with SCARs, of the 3 subjects mentioned who had each received a DRESS from cefoxitin, cefuroxime, and/or ceftriaxone, one showed a selective response to PT with cefoxitin, another tested positive for cefuroxime as well as for ceftriaxone, cefuroxime, and penicillins, and the final subject tested positive for ceftriaxone, cefuroxime, ceftazidime [62].

CONCLUSION

A single plasmid may carry multiple antibiotic resistance genes which are capable of replicative transfer from one plasmid to another or the bacterial genome if located within a transposon (or ‘jumping gene’). Antibiotic resistance genes may also be carried on mobile gene cassettes which can be integrated into or deleted from their receptor elements, integrons, or infrequently may be integrated at other locations via site-specific recombination catalyzed by an integron-encoded recombinase. Instead, the cross-reactivity related to the common β-lactam ring, which entails positive responses to all β- lactams tested, is very rare in subjects with an IgE- mediated allergy and appears to be even rarer or absent in those with a T-cell-mediated allergy

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