



Cephalosporin Allergy: Updates on Diagnostic Testing

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Abstract

Purpose of Review Cephalosporins are one of the most prescribed antibiotics worldwide and are implicated in a wide range of hypersensitivity reactions (HSR). This review summarizes recent updates in cephalosporin hypersensitivity with a focus on diagnostic testing.

Recent Findings Reported testing strategies to evaluate different immediate and delayed cephalosporin HSR have included skin testing, in vitro testing, and diagnostic drug challenges. However, the diagnostic performance of in vivo and in vitro tests remains unclear across different hypersensitivity endotypes; adequately powered studies investigating the true positive and negative predictive value of these diagnostic modalities are needed using the reference standard of drug challenges to define cephalosporin hypersensitivity.

Summary Refinement of diagnostic testing should be guided by growth in our understanding of cephalosporin antigenic determinants. This growth will be crucial in driving further clarification of cross-reactivity between cephalosporins, and potentially delineating streamlined evaluation processes resulting in reduced unnecessary antibiotic avoidance.

Keywords Cephalosporin allergy · Hypersensitivity · Adverse reaction · Cefazolin · Ceftriaxone · Anaphylaxis · Testing

Introduction

Cephalosporins continue to be one of the most prescribed antibiotic classes worldwide [1–3]. Adverse reactions to cephalosporins are well-recognized, and can be the target of a spectrum of hypersensitivity reactions (HSR) [4]. While our understanding of cephalosporin hypersensitivity has increased, there are still significant gaps in our knowledge, particularly in comparison to its beta-lactam “cousin”, penicillin. This review will provide recent updates to our understanding of cephalosporin HSRs, focusing on developments in the epidemiology, diagnostic testing, and management of cephalosporin HSRs.

Clinical Presentations of Cephalosporin Hypersensitivity and Epidemiology

Cephalosporins are the most commonly prescribed antibiotic in the hospital and the second after penicillins and are used to treat a variety of infections in the outpatient setting [5, 6]. Approximately 0.5% of new exposures to cephalosporin result in an adverse reaction [4, 7]. Review of electronic health records from multiple large health systems in the US show that 1.3%–1.7% of the US general population and 0.9% of the US pediatric population report drug allergy to cephalosporins [6, 8, 9].

Cephalosporin allergy can present as immediate or delayed hypersensitivity reactions. Immediate reactions to cephalosporins are more commonly reported than delayed reactions. Of 328 patients identified as having a cephalosporin allergy label in a large, multicenter retrospective chart review, 74.7% had a history consistent with an immediate reaction while 25.3% had histories consistent with a delayed reaction [10]. Symptoms of immediate reactions often begin within one hour after exposure, although can occur for up to six hours after exposure [11]. Manifestations include

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cutaneous reactions such as urticaria and angioedema, bronchospasm, and anaphylaxis [10, 12].

Anaphylaxis to cephalosporins are rare with the estimated incidence of cephalosporin induced anaphylaxis 6.1 per 10,000 patients from review of one large US healthcare system's EMR [13]. Despite the overall low incidence of cephalosporin induced anaphylaxis, cefazolin is the leading cause of perioperative anaphylaxis in the US [4, 14]. Cefazolin is the most commonly prescribed antibiotic for surgical prophylaxis and is generally well tolerated, even in patients with verified penicillin allergy [15]. However, over 50% of perioperative anaphylaxis cases are caused by antibiotics, with b-lactam antibiotics causing 90% of these reactions and cefazolin being the most common culprit [16]. Perioperative anaphylaxis is associated with significant morbidity. Review of the National Inpatient Sample Database revealed that 5% of 5223 analyzed perioperative anaphylaxis cases were near fatal and 2% were fatal [17].

Delayed reactions occur greater than six hours after exposure to the culprit cephalosporin. Non-severe maculopapular rashes are the most common type of delayed reaction [4]. In a cross-sectional study of 162 children with parent reported cephalosporin allergy presenting to a pediatric emergency room, the most common reported reaction was rash and itching that developed greater than 6 h after medication administration [18]. Serum sickness-like reactions are delayed reactions manifesting as fever, arthralgias, and cutaneous eruptions [19]. Several antibiotics have been implicated, with some studies suggesting that cefaclor is the culprit medication for up to 80% of antibiotic induced cases [19, 20].

Cephalosporin HSRs can manifest through severe cutaneous adverse reactions (SCARs [21]. SJS/TEN represents the most severe SCAR with clinical presentation consisting of mucocutaneous blistering and epithelial sloughing. Anti-convulsants, NSAIDs, allopurinol, and antibiotics, including cephalosporins, are common culprit medications. Review of an insurance claims database in Japan yielded 170 cases of antibiotic-induced SJS/TEN. Approximately 20% of these cases were secondary to cephalosporin use [22]. A US study of almost 1.4 million courses of cephalosporins identified only 3 cases of SJS/TEN associated with cephalosporin use, all of whom also received other antibiotics [7]. Thus, it is unclear if indeed cephalosporins are a common cause of SJS/TEN or are just concomitant medications, not culprits.

Drug related eosinophilia and systemic symptoms (DRESS) syndrome is characterized by rash, fever, eosinophilia, and organ injury that can present days to weeks into a medication course and even after discontinuation of the offending medication. Cephalosporins are estimated to be responsible for 3.94 – 7% of antibiotic-induced DRESS syndrome cases [23, 24]. Retrospective chart review of 69 DRESS syndrome cases revealed 5 cases due to cephalosporins. In addition to rash and eosinophilia, two of these

patients had kidney injury, two patients had liver injury, and one patient had both liver and kidney injury [24]. One study suggests that the latency period of cephalosporin induced DRESS may be shorter than for some other commonly implicated drugs, including allopurinol and carbamazepine [25].

Cephalosporin induced acute generalized exanthematous pustulosis (AGEP) has been described primarily in case reports. One study summarized clinical presentation of cephalosporin induced AGEP across 35 articles and 43 patients and found that in addition to the development of pustules, 46.5% of patients had fever, 30.2% had pruritis, 11.6% had tenderness, and 11.6% had mucosal involvement. Two patients had SJS/TEN overlap. The most common culprit antibiotic was ceftriaxone, followed by cephalexin [26].

b-lactam antibiotics are a well-established cause of acute interstitial nephritis (AIN). The primary manifestation of AIN is acute kidney injury, which can be associated with irreversible renal injury in a minority of cases [27]. A population-based analysis of a large US health system analyzed 1.4 million courses of cephalosporins given to 820,124 individuals over a two-year period. 1658 (0.2%) individuals had new-onset serum creatinine levels of 3 mg/dL or more within 30 days of starting a cephalosporin [7]. 80% of patients with b-lactam induced AIN will have peripheral eosinophilia, compared to only 33% of patients with non-b-lactam induced AIN. The majority of patients with b-lactam induced AIN also have fever and rash [27].

Drug induced liver injury (DILI) accounts for up to 13% of acute liver failure in the US and can present as hepatocellular, cholestatic, or mixed liver injury [28]. Among 1019 cases of DILI, 33 were attributed to cephalosporins, and 19 of these were attributed to cefazolin. Symptoms developed 1–4 weeks after exposure to cephalosporin. Seventy-nine percent of patients had jaundice, nausea, and fever and 36% had rash, eosinophilia, and fever. Those with non-cefazolin cephalosporin induced DILI had a more severe course compared to those with cefazolin induced DILI, with 2 patient deaths. Cefazolin was often given as a one-time dose at the time of surgery, and patients often were unaware this was given, resulting a delay of recognition of cefazolin-induced DILI and substantial diagnostic testing [29].

Diagnostic Testing of Cephalosporin Allergy

Skin Testing

Immediate Reactions

Historically, cephalosporin skin testing experience has lagged behind penicillin skin testing [30]. One reason for this is the lack of both commercial products approved for skin

testing and the lack of metabolites for skin testing. There have been several reports of the utility of cephalosporin skin testing over the last 5 years. Romano et al. prospectively evaluated 236 Italian patients with immediate index reactions to cephalosporins [11]. These patients all underwent skin prick and intradermal testing to sterile intravenous forms of cefazolin, cefuroxime, cefodizime, cefonicid, cefotaxime, ceftazidime, ceftriaxone, and cefepime, as well as non-standardized sterile preparations produced from oral formulation capsule powders for cephalexin, cefatrizine, cefaclor, cephadrine, cefprozil, cefixime, cefpodoxime, or cefibuten. Concentrations of 2 mg/mL and 20 mg/mL were used for all cephalosporins except for cefepime. Of these 269 reactions, the index reaction consisted of anaphylaxis in 63% and the most common suspected agent was ceftriaxone (58%). The median duration between index reaction and testing was 4 months. For all cephalosporins, 167/236 (70.8%) demonstrated positive testing. For ceftriaxone, 35/157 (22%) had negative skin testing; 26.7%, 44.5%, and 10.5% were positive on skin prick test (SPT), intradermal test (IDT) 2 mg/mL, and IDT 20 mg/mL respectively. For ceftazidime, 6/17 (35.3%) had negative testing; none were positive on prick testing and 11/17 (64.5%) were positive on IDT 2 mg/mL. Rates of positive skin testing decreased with time, with positive testing rates of 85.3%, 70.3%, 63.3%, and 39.7% when testing was performed 1–3 months, 4–6 months, 7–12 months, or after 12 months after the index reaction respectively [11].

Stone et al. retrospectively evaluated 245 patients with immediate index reactions to cephalosporins, across sites in the United States and Australia [10]. All patients underwent skin testing (SPT and IDT) to ceftriaxone, cefazolin, and the implicated cephalosporin (if it was not ceftriaxone or cefazolin) with the following concentrations, ceftriaxone 2.5 mg/mL, cefuroxime 10 mg/mL, and all other cephalosporins with sterile intravenous solutions at a concentration of 1 mg/mL. The most common implicated agents were cephalexin (55.5%), ceftriaxone (24.9%), and cefazolin (17.5%). An index reaction of anaphylaxis was uncommon, only reported in 5% of cases. Twenty-two of 245 (8.9%) had a positive skin test, most commonly, cefazolin, which accounted for 50% of positive skin testing. Increasing time between index reaction and skin testing performance was also associated with decreased odds for a positive skin test (0.71 per year; 95% CI: 0.57, 0.90) [10].

In a single center, retrospective observational study in France, Touati et al. reported 160 patients with immediate index reactions to cephalosporins [31]. All patients underwent skin testing (SPT and IDT) to cefazolin, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and ceftazidime (2 mg/mL). Eighty-five of 160 patients had an index history of anaphylaxis. Positive cephalosporin testing (either skin testing or drug provocation test (DPT)) was demonstrated in 73/160

(45.6%) but was not distinguished further in the manuscript. Defining a “confirmed” allergy as either positive skin testing or DPT, the authors observed that a confirmed allergy was associated with an immediate index reaction (OR 3, 95% CI [1.6–5.5], $P < 0.001$), multiple reactions (OR = 2.0, 95% CI [1–3.5], $P = 0.04$), anaphylaxis with shock (OR = 6.5, 95% CI [3.3–13.1], $P < 0.001$), and anaphylaxis without shock (OR = 3.1, 95% CI [1.6–6.1], $P < 0.001$). This study also included 146 children, with 62.3%, 25.3%, and 12.3% reporting a delayed, immediate, or unknown index reaction respectively. Ten of 146 (6.9%) had positive skin testing and 136 children with negative skin testing underwent DPT and 11 were positive [31].

Bogas et al. prospectively evaluated a cohort of Spanish patients with cefazolin hypersensitivity [14]. All patients underwent skin testing with both 2 mg/mL and 20 mg/mL concentrations, and patients with negative skin testing underwent a 5 step DPT. Of 166 patients who underwent evaluation, 84% reported an immediate index reaction, most often in the setting of perioperative reactions, and 42% of these consisted of anaphylaxis. Forty of 152 (26.3%) had positive skin testing with a mean interval between index reaction and skin testing occurring at 14.8 ± 36.4 months. Of these 40, 5 (12.5%) had positive SPT with no further IDT. The remaining 35 all tested negative at the 2 mg/mL IDT but tested positive at the 20 mg/mL IDT [14].

It's important to note the different concentrations used for skin testing across studies as well as the different study populations, as some studies were enriched for index reactions of anaphylaxis whereas others for delayed reactions. Table 1 summarizes recent skin testing experience for immediate cephalosporin index reactions. Furthermore, numerous studies demonstrated that the time elapsed between the index reaction and skin testing appears to significantly impact the positive skin testing rate. As such, direct comparisons between studies are limited. Further studies are needed to precisely define the performance of skin testing, ideally controlling for the time elapsed from index reaction to skin testing as well as specific index reaction phenotypes. Table 2 expands the recommended concentrations for cephalosporin skin testing as outlined in the Drug Allergy Practice Parameter with updates from the above references [4, 32]. It is notable most of the studies discussed above did not perform the higher concentration IDT, with the exception of Bogas et al. and Romano et al. For cefazolin, there does appear to be a subset of patients who may only be identified using the higher concentration (20 mg/mL) IDT testing; however, this is not definitively known as these patients did not undergo subsequent challenge and as such it is not known how many of these, if any, represent false positive testing. One study from Korea, found that 5% of patients with no history of a cephalosporin allergy had a positive IDT but demonstrated

Table 1 Summary of recent experiences of skin testing for immediate cephalosporin hypersensitivity

	Romano			Stone			Bogas			
	Concentration (mg/mL)	Positive ST	Concentration (mg/mL)	Positive ST	Concentration (mg/mL)	Positive ST	Concentration (mg/mL)	Positive ST	Concentration (mg/mL)	
Cefazolin	2	9/19 (47%)	20*	2/10 (20%)	1	11/43 (25.6%)	2	5/142 (3.5%)	20*	35/137 (25.5%)
Cefuroxime	2	6/9 (66.7%)	20*	0/3 (0%)	10	3/23 (13%)				
Cefotaxime	2	7/10 (70%)	20*	0/3 (0%)	1	2/2 (100%)				
Cefoxitin	2	0/1 (0%)	20*	0/1 (0%)	1	0/3 (0%)				
Ceftazidime	2	11/17 (64.7%)	20*	0/6 (0%)	1	2/10 (20%)				
Ceftriaxone	2	112/153 (73.2%)	20*	6/42 (14.3%)	2	9/61 (14.8%)				
Cefepime	2	0/1 (0%)			1	3/18 (16.7%)				

ST (skin testing) includes skin prick test and intradermal testing

*Only patients with negative ST to 2 mg/ml underwent skin testing at 20 mg/ml

tolerance to the cephalosporin suggesting a 5% false positive rate [33]. In contrast, a study of 7 patients with perioperative anaphylaxis to cefuroxime, all of whom demonstrated positive cefuroxime skin tests, all had positive cefuroxime challenges [34]. Thus the rate of false positives skin tests may differ based on clinical history.

Delayed Reactions

Skin testing assessing delayed cephalosporin reactions through delayed intradermal testing and patch testing have been previously reported, but have been marked with very low positive testing rates as well as infrequent confirmation of delayed cephalosporin reactions [4]. There have been a few studies in the last 5 years assessing skin testing for cephalosporin reactions. Stone et al. report 83 delayed index cephalosporin reactions who underwent single delayed IDT (dIDT); 7/83 (8%) demonstrated positive dIDT testing. Seventy-one patients with negative dIDT underwent challenge with no observed reactions [10]. In the French retrospective cohort mentioned above, Touati et al. also reported 316 patients who had delayed index cephalosporin reactions; positive cephalosporin testing (either skin testing or DPT) was demonstrated in 33/316 (10.4%) but was not distinguished further in the manuscript [31]. Copaescu et al. report a unique approach of investigating patch testing and dIDT in patients with a history of severe cutaneous adverse reactions (SCARs) to cephalosporins [35, 36]. In this prospective Australian study, there were 31 patients with SCARs attributed to cephalosporins, 16 DRESS, 8 severe MPE, 3 AGEP, 1 GBFDE, 2 SJS, and 1 TEN [35]. There was not a standardized skin testing regimen; most patients underwent dIDT, fewer received patch testing. Unfortunately, the authors report their patch testing and IDT experience as a combined group including both penicillins and cephalosporins, and did not further analyze the cephalosporins as their own subgroup. With this in mind, of 21 patients with beta-lactam severe MPE, 14/15 who underwent IDT/PT had positive testing; and of 30 patients with beta-lactam DRESS, 12/17 had positive IDT/PT. While interpreting this data is very limited in that cephalosporins were not isolated for analysis, this suggests that severe delayed hypersensitivity phenotypes may have a higher skin test positivity rate compared to more benign delayed cutaneous reactions; however, further study is needed. Furthermore, the concentrations needed to elicit a T cell-mediated response may be different compared to the non-irritating concentrations used to assess immediate IgE-mediated reactions; and the use of higher irritating concentrations for drugs such as vancomycin may improve sensitivity for delayed reactions such as DRESS [4, 37]. Further study is needed to identify the role, if any, delayed skin testing has for different delayed ADR phenotypes and the optimal skin testing concentrations.

Table 2 Skin testing for immediate cephalosporin hypersensitivity

	Cefazolin	Cefuroxime	Ceftriaxone	Cefotaxime	Ceftazidime	Cefepime	Ceftaroline
Prick test	200–330 mg/mL	90 mg/mL	100 mg/mL	100 mg/mL	100 mg/mL	2 mg/mL	2 mg/mL
Intradermal test	20–33 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	2 mg/mL	2 mg/mL

While serial dilutions for cephalosporin intradermal testing have been routinely incorporated for a presumed safety benefit, it is not clear that this is necessary for most, if any, patients. Experience of the safety of using a single intradermal concentration step without serial dilutions for penicillin-related life-threatening anaphylaxis suggests that serial dilutions may be unnecessary. As such, the authors suggest simplification to a single intradermal testing step. For patients with life-threatening anaphylaxis to a suspected cephalosporin, an additional intradermal step can be considered at a 1:10 dilution of the proposed intradermal concentration above

In Vitro Cephalosporin Testing

Serologic testing assessing cephalosporin hypersensitivity reactions remains unstandardized. Immunoassays to detect cephalosporin-specific IgE have not performed well, and are likely limited by the fact that the antigenic determinants driving cephalosporin hypersensitivity are not fully characterized. In a cohort of 29 confirmed cefazolin-allergic patients, only one patient had detectable cefazolin sIgE [14]. In another study, evaluating 43 cefazolin-allergic patients and 30 controls, there was no significant difference in cefazolin sIgE levels between the two groups however the ratio of cefazolin specific IgE to total IgE had enhanced specificity [38]. Basophil activation tests (BAT), measuring basophil surface expression of CD63 or CD203c after stimulation with implicated drug, have been used to assess cephalosporin hypersensitivity reactions. The diagnostic performance of BAT may depend on the marker used to define basophil activation; in a study of 18 patients with index reactions of perioperative anaphylaxis to cefazolin and positive cefazolin IDT, CD63 expression was much less sensitive than CD203c expression with a sensitivity of 38% vs 75% respectively [39]. In the above mentioned cohort of patients with clinical history concerning for cefazolin hypersensitivity, Bogas et al. randomly selected patients using a pre-specified protocol to undergo basophil activation testing prior to cefazolin skin testing and DPT. Interestingly, of 8 patients who had negative cefazolin ST but a positive cefazolin DPT, 6/8 had a positive BAT, highlighting potential added clinical utility of BAT [14]. In this study, sensitivities for CD63 and CD203c were 43.5% and 50% respectively; it is important to note that this study population also included non-immediate reactions making it difficult to directly compare to previously mentioned BAT studies. BAT thus far has only been available in select sites with unique expertise, and commercially available cephalosporin BAT have not been validated in the United States.

Enzyme-linked immunospot (ELISpot) assays, measuring IFN- γ releasing cells when incubated with implicated drug, have been investigated as a strategy to evaluate non-immediate cephalosporin hypersensitivity. However, current

reports are limited to small case series and remain at the proof-of-concept stage [35, 40–42].

Challenge Testing

Cephalosporin drug challenge testing is an important tool in definitively confirming cephalosporin allergy, given the unclear negative and positive predictive values of cephalosporin skin testing. For patients presenting with an immediate index reaction and negative cephalosporin skin testing, positive drug challenge rates have varied from 0–19.5% [10, 11, 14, 31]. Romano et al. report 55 of 72 adult patients with negative skin testing who underwent a 3-step drug provocation challenge (DPT) to implicated cephalosporin; 52/55 (94.5%) had a negative DPT. There were 3 positive DPTs; 2 reacted to ceftriaxone, with symptoms of urticaria or angioedema, and the other reacted to cephalexin with symptoms of urticaria [11]. Stone et al. reported 230 adult cephalosporin DPT and all tolerated without reaction [10]. In another study, out of 476 patients with both immediate and delayed index reactions, 421 with negative skin testing underwent DPT. Fifty-one of 421 (12.1%) had positive DPT, and 10 of these reactions were described as anaphylaxis [31]. In the cefazolin hypersensitivity cohort reported by Bogas et al., of 112 patients with negative skin testing who underwent DPT, there were 22/112 (19.5%) positive challenges, with 77% developing isolated urticaria and 13.6% developing anaphylaxis [14]. In addition, the positive predictive value of cephalosporin skin testing is not known as patients rarely undergo confirmatory drug challenge testing, highlighting an important area of future investigation.

Direct cephalosporin challenge without preceding skin testing has been reported as a testing strategy, thus far primarily in children. There have been numerous small, single center studies evaluating a 5-day challenge protocol for children with a history of non-immediate cutaneous-only reactions, collectively evaluating 115 children across studies with no positive challenge reactions [43]. In an important study, Silcox et al. expanded this to include immediate reactions. In a prospective, multicenter study performed in

Canada, 2-step direct cephalosporin graded oral challenges (GOC) were performed in children with either immediate or delayed index reactions, including anaphylaxis [44]. 136 children underwent direct GOC, 17.5% presented with an immediate reaction, with 2 cases of anaphylaxis. The median time between index and challenge reaction was 1 year (0.3–2.5), and the median age at challenge was 3.9 years (2.3–8.7). The most common implicated cephalosporins were cefprozil (67.6%), cephalexin (18.4%), and cefixime (8.8%). 123/136 (90.4%) had a negative GOC challenge. Of the 13 positive challenges, 12 presented with mild, benign rashes (most commonly urticaria, 69.2%); 7/13 occurred within 1 h. There was one episode of anaphylaxis, which occurred in a patient with an index reaction to cephalexin who had previously required epinephrine [44]. Finally, cephalosporin GOC has also been used to evaluate serum sickness-like reactions to cephalosporins; Delli Colli et al. report safely performing this in 4 children [45]. Direct oral challenges have become widely used in evaluating low-risk penicillin allergy, particularly in children; Silcox et al. demonstrate important initial data supporting the general safety of this approach [44]. However further study is needed to define optimal risk-stratification for direct GOC testing as well as to assess this approach in adults.

Rapid Drug Desensitization

For patients with IgE-mediated cephalosporin allergy who require the implicated cephalosporin to treat an infection without reasonable alternative, rapid drug desensitization (RDD) can be a tool to safely administered as a therapeutic procedure to temporarily induce tolerance [4, 46, 47]. The role of RDD for non-immediate reactions is not clear, and is contraindicated in the setting of SCARs.

Risk Stratification

Risk stratification strategies for cephalosporin reactions have been suggested, primarily extrapolating from penicillin allergy. Stone et al. sought to retrospectively analyze the performance of history-based risk stratification for cephalosporin allergy labels to predict positive cephalosporin skin testing or challenge testing in 288 patients undergoing cephalosporin allergy evaluation [48]. Defining low risk adult patients as an index history of isolated urticaria over 5 years ago, a benign cutaneous-only reaction, isolated GI symptoms, or other non-allergic symptoms to any cephalosporin, 204 patients remained in this risk stratification group, and 201/204 had negative testing, NPV 98.5%; 95% CI, 95.8%–99.7%. The NPV increased to 100% when low risk was defined as the above history to an orally administered

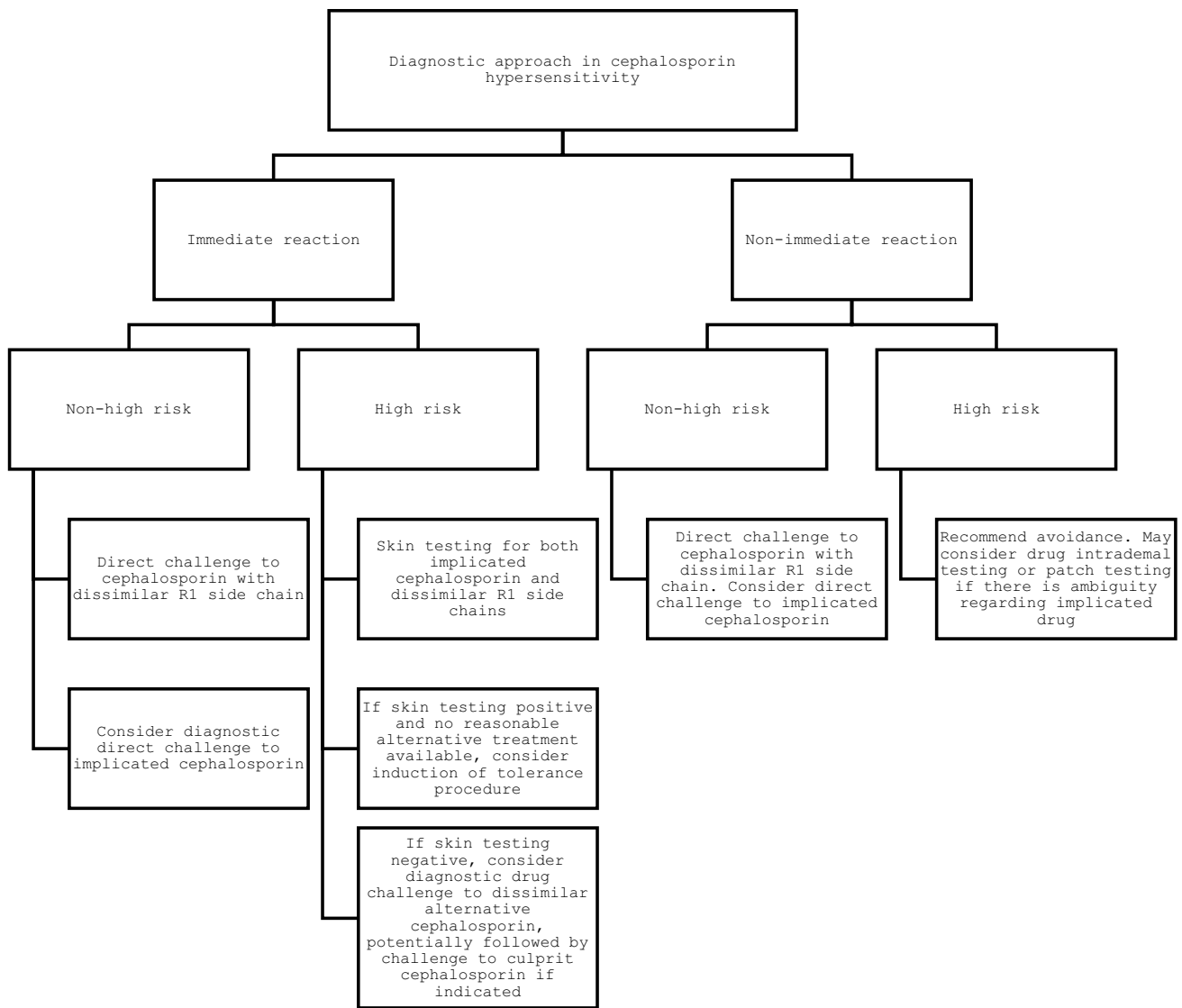
cephalosporin. In a retrospective case–control study of 72 cephalosporin allergic pediatric patients and 144 age and sex-matched controls, an index history of anaphylaxis was most strongly associated with positive cephalosporin testing [49]. Further studies are needed in both children and adults to prospectively evaluate the performance of different risk stratification strategies to guide streamlined cephalosporin allergy evaluations. A proposed diagnostic algorithm is outlined in Fig. 1.

Cross-Reactivity

Beta-lactam antibiotics are composed of a four-membered ring that is fused with a five-membered thiazolidine ring in penicillins and a six-membered dihydrothiazine ring in cephalosporins. These drugs have a side chain, known as R1, bound to the beta-lactam ring. Cephalosporins also have a second side chain, R2, bound to their dihydrothiazine ring [50]. The R1 side chain is the major component responsible for cross reactivity between cephalosporins and penicillins [51]. The R2 side chain is less studied but may have a role in the immunogenicity of cephalosporins [52].

In a meta-analysis of 21 studies exploring penicillin and cephalosporin cross-reactivity, the R1 side chains of implicated antibiotics were analyzed, and similarity scores were produced on the basis of structural and physiochemical properties. In comparing R1 side chains of penicillins and cephalosporins, cefazolin, cefuroxime, and all third and fourth generation cephalosporins have low similarity scores suggesting a low risk of cross reactivity. These similarity scores can be used to predict likelihood of cross reactivity between cephalosporins. For example, two cephalosporins with a low similarity score, such as cefdinir and cefoxitin, would be estimated to have 2% risk of cross-reactivity [53]. Conversely, cephalosporins with similar R1 side chains, such as ceftriaxone, cefuroxime, cefotaxime and ceftazidime may have a higher degree of cross reactivity [54].

The cross-reactivity between penicillins and cephalosporins has been widely studied. Historically, cross-reactivity has been cited to be as high as 10%. However, newer data suggests that this number is much lower. In a meta-analysis of 30 studies that assessed frequency of cefazolin allergy in penicillin allergic patients and 15 studies that assessed frequency of penicillin allergy in cefazolin allergic patients, a total of 6001 penicillin allergic and 146 cefazolin allergic patients were analyzed [55]. Dual allergy to cefazolin in penicillin allergic patients was 0.7%. This number was higher in individuals with confirmed penicillin allergy compared to those with self-reported allergy at 3% and 0.6%, respectively. Notably, these meta-analysis are based solely on skin testing as a measure of cross-reactivity, without confirmatory challenge testing [55]. A review of 597 surgeries in which



“Risk Definitions: non-high risk immediate hypersensitivity reaction is defined as a non-anaphylactic immediate reaction; high risk immediate hypersensitivity reaction is defined as anaphylaxis; non-immediate non-high risk reaction include benign cutaneous reaction and serum sickness like reactions, and excludes severe cutaneous adverse reactions (SCAR); non-immediate high risk reaction is defined as a SCAR. No testing indicated for hemolytic anemia, drug-induced liver injury, and acute interstitial nephritis and recommend drug avoidance for these. Drug challenges should be performed per the 2022 Drug Allergy Practice Parameter. Skin testing should be performed with sterile parenteral formulations, see Table 2. While skin testing has been suggested for non-high risk immediate reactions, the authors consider that the theoretical safety benefit of skin testing does not outweigh the significant risk of false positive skin testing leading to avoidance of diagnostic drug challenges resulting in unnecessary cephalosporin avoidance”

Fig. 1 Proposed management approach to cephalosporin hypersensitivity reactions

the patient had a documented penicillin allergy found that in 504 cases, the patient received beta-lactam prophylaxis, primarily cephalosporins. Cefazolin was used in 280 cases

and cefuroxime used in 195 cases. Among these patients, there were zero documented hypersensitivity reactions [15].

Similarly, the majority of patients with documented cephalosporin allergy are able to tolerate penicillins. The meta-analysis mentioned above found dual allergy occurring in 3.7% of cefazolin allergic patients who received penicillin and 4.4% of patients who received testing for penicillin allergy [55]. One study describes 44 patients with confirmed history of cephalosporin anaphylaxis who subsequently underwent penicillin challenge. Forty of these patients had anaphylaxis to cefazolin, two to cephalothin, and two to ceftriaxone. High risk patients underwent penicillin skin test prior to direct drug challenge, and low risk patients proceeded directly to direct challenge. All 44 patients completed a 3-day challenge of amoxicillin with no immediate reactions and 1 delayed reaction of a benign rash. Patients with cephalosporin allergy, specifically cefazolin allergy, are generally able to tolerate penicillins and may not need further testing [56].

Future Directions

Significant gaps in our understanding of cephalosporin hypersensitivity exist. The diagnostic performance of in vivo and in vitro tests remains unclear across different hypersensitivity endotypes; adequately powered studies investigating the true positive and negative predictive value of these diagnostic modalities are needed using the reference standard of drug challenges to define cephalosporin hypersensitivity, a model thus far under-utilized in drug allergy. Refinement of diagnostic testing should be guided by further growth in our understanding of cephalosporin antigenic determinants, which currently remain limited. These two core elements will be crucial in driving further clarification of cross-reactivity between cephalosporins, and potentially delineating streamlined evaluation processes resulting in reduced unnecessary antibiotic avoidance. Building on the significant progress made in understanding cephalosporin hypersensitivity reactions, these efforts will lead to increased effectiveness in the diagnosis and management of cephalosporin hypersensitivity.

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Declarations

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Conflict of Interest The authors declare no competing interests.

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