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Road Less Traveled: Drug Hypersensitivity to Fluoroquinolones, Vancomycin, Tetracyclines, and Macrolides

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Abstract

While fluoroquinolones, vancomycin, macrolides, and tetracyclines are generally safe antibiotics, they can induce both immediate and delayed hypersensitivity reactions (HSRs). Historically, less has been published on allergies to these antibiotics compared to beta lactams, but the prevalence of non-beta lactam HSRs is increasing. To fluoroquinolones, immediate HSRs are more common than delayed reactions. Both IgE and non-IgE mechanisms, such as the mast cell receptor Mas-related G protein-coupled receptor X2 (MRGPRX2), have been implicated in fluoroquinolone-induced anaphylaxis. Skin testing for fluoroquinolones is controversial, and the gold standard for diagnosis is a graded dose challenge. To vancomycin, the most common reaction is vancomycin infusion reaction (previously called “red man syndrome”), which is caused by infusion rate-dependent direct mast cell degranulation. Severity can range from flushing and pruritis to angioedema, bronchospasm, and hypotension that mimic type I HSRs. MRGPRX2 has been implicated in vancomycin infusion reactions. IgE-mediated HSRs to vancomycin are rare. Vancomycin skin testing yields high false positive rates. Thus, direct provocation challenge with slower infusion rate and/or antihistamine pre-treatment is preferred if symptoms are mild to moderate, and desensitization can be considered if symptoms are severe. To tetracyclines, non-IgE-mediated and delayed HSRs predominate with cutaneous reactions being the most common. There is no standardized skin testing for tetracyclines, and avoidance is generally recommended after a severe reaction because of the paucity of data for testing. Graded dose challenges and desensitizations can be considered for alternative or index tetracyclines if there are no alternatives. With macrolides, urticaria/angioedema is the most common immediate HSR, and rash is the most common delayed HSR. The predictive value for skin testing to macrolides is similarly poorly defined. In general, HSRs to fluroquinolones, vancomycin, macrolides, and tetracyclines are challenging to diagnose given the lack of validated skin testing and in vitro testing. Direct

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provocation challenge remains the gold standard for diagnosis, but the benefits of confirming an allergy may not outweigh the risk of a severe reaction. Skin testing, direct provocation challenge, and/or desensitization to the index non-beta lactam antibiotic or alternatives in its class may be reasonable approaches depending on the clinical context and patient preferences.

Keywords

Drug hypersensitivity; Drug allergy; Fluoroquinolones; Vancomycin; Macrolide; Tetracyclines

Background

Antimicrobial drug allergy has largely focused on beta lactam antibiotics such as penicillin and cephalosporins. However, the frequency of HSRs to non-beta lactam antibiotics is increasing and is likely associated with increased use in both adults and children [1, 2]. Fluoroquinolones, vancomycin, macrolides, and tetracyclines are widely available and commonly prescribed to treat a range of infections in the inpatient and outpatient settings. Here, we review the spectrum of adverse drug reactions associated with fluoroquinolones, vancomycin, macrolides, and tetracyclines. We will discuss diagnostic tools and their limitations and management approaches to these drug allergies. We will review MRGPRX2, a mast cell–specific receptor that may be implicated in anaphylaxis to fluoroquinolones and vancomycin [3].

Fluoroquinolones

Introduction

Quinolones are potent, synthetic antibiotics composed of a bicyclic skeleton with carboxylic acid and ketone groups [4]. Since the introduction of the first quinolone nalidixic acid in 1964, the basic structure has been modified to expand antimicrobial spectrum and increase bioavailability [5]. Current options include ciprofloxacin, moxifloxacin, levofloxacin, ofloxacin, delafloxacin, and gatifloxacin. Fluoroquinolones are routinely used in both inpatient and outpatient settings for respiratory, urinary, intraabdominal, bone, joint, and skin and soft tissue infections (SSTIs) and have overlapping spectrums of activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria [4].

Prevalence/Incidence

The incidence of fluoroquinolone allergy differs between Spanish and North American data. In a Spanish cohort, fluoroquinolones were the second most common antibiotic associated with HSRs after beta lactams [1], and the fifth most common antibiotic associated with anaphylaxis in the United States (US), after penicillin, sulfonamides, cephalosporins, and macrolides [6]. Fluoroquinolone HSRs increased from 0.54% in 2005 to 6.85% of confirmed drug HSRs in 2010 in Spain, likely due to increased fluoroquinolone use [1, 2]. In the US, the prevalence of reported fluoroquinolone-induced anaphylaxis was 3.7 per 10,000 patients [6] and the absolute risk of an emergency department (ED) visit for fluoroquinolone-induced HSR was approximately 44 ED visits per 100,000 prescriptions [7]. Variations in definitions of fluoroquinolone HSR may account for these observed differences. Additionally, those

with fluoroquinolone HSR were more likely to have a beta lactam allergy compared to fluoroquinolone-tolerant patients [6].

Moxifloxacin is the most frequently implicated fluoroquinolone in immediate HSRs and anaphylaxis [2, 8, 9]. Moxifloxacin is associated with a 5.4-fold and 3.5-fold increased risk for seeking ED care relative to ciprofloxacin and levofloxacin respectively [7]. For delayed reactions, ciprofloxacin and moxifloxacin were the most frequent offenders [2, 4].

Immediate Reactions

The most common immediate symptoms to fluoroquinolones are rash, hives, nausea/vomiting, swelling, pruritis, and anaphylaxis [10]. For confirmed cases of fluoroquinolone-induced immediate HSRs, the most frequent reactions were anaphylaxis (62.5–64.3%), followed by urticaria (30.4–35.7%), and angioedema (7.1%) [2, 8]. Anaphylaxis has occurred upon first fluoroquinolone exposure [9].

Delayed Reactions

Delayed reactions are less common than immediate reactions [2, 8, 11]. Non-immediate reactions typically consist of delayed urticaria, angioedema, fixed drug eruption, or maculopapular exanthem [2, 12]. Fluoroquinolones and tetracyclines were both observed to be the third most common antibiotic culprit for electronic health record (EHR) reported drug reaction with eosinophilia and systemic symptoms (DRESS), each accounting for 3 of the 69 cases [13]. Reports of acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), and leukocytoclastic vasculitis have also been described [11, 14, 15].

Adverse Reactions

Non-allergic adverse reactions include tendonitis/tendon rupture, photosensitivity, thrombocytopenia, hemolytic anemia, hepatitis, *Clostridium difficile*-associated diarrhea, seizures, and peripheral neuropathy [5, 16]. Fluoroquinolones that are associated with hematologic and hepatic toxicity, such as trovafloxacin and temafloxacin, are unavailable or have strict restrictions limiting their use [5, 14]. Additionally, the US Food and Drug Administration (FDA) has issued Boxed Warnings for fluoroquinolones for disabling and potentially permanent side effects involving tendons, muscle and joints (tendon rupture, tendonitis), worsening of myasthenia gravis, irreversible peripheral neuropathy, inattention, disorientation, agitation, nervousness, memory impairment, and hypoglycemia [17].

Pathophysiology

Both IgE and MRGPRX2, a mast cell-specific receptor, have been implicated in immediate HSR [18–20]. Mast cells are classically activated when antigen binds to antigen-specific IgE, triggering cross-linking of high-affinity IgE receptors (FcεRI), resulting in release of inflammatory mediators. Quinolone-specific IgE has been previously detected in 30/55 (54.5%) patients who reported an immediate HSR to a quinolone [20].

Mast cells can also be triggered by a variety of cationic substances called basic secretagogues in an antibody-independent manner [3]. In 2015, McNeil et al. first identified the mast cell–specific receptor for these basic secretagogues in mice as Mrgprb2, which is the orthologue of human G-protein-coupled receptor, MRGPRX2 [3]. Activation of MRGPRX2 induced a quicker release of smaller, spherical granules in vitro and a faster, more localized reaction in vivo compared to FcεRI-dependent mast cell activation, which triggered a gradual degranulation of heterogenous granules in vitro and a more prolonged and systemic reaction in vivo [21]. The tetrahydroisoquinoline (THIQ) motif is a potent MRGPRX2 agonist, and a very similar motif is found on fluoroquinolones [3]. In a murine model, ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin induced a mast cell response in peritoneal mast cells that was impaired if Mrgprb2 was non-functional [3]. Mrgprb2 knockout mice exhibited a significantly reduced anaphylactic response to ciprofloxacin and recovered faster compared to wild type [3]. These findings suggest fluoroquinolone-induced mast cell degranulation employs Mrgprb2. All nine fluoroquinolones, including levofloxacin and moxifloxacin, activated mast cells through MRGPRX2 in another study [22]. Fluoroquinolones activated MRGPRX2 in a dose-dependent manner that involved increased intracellular calcium mobilization [22]. Non-IgE-mediated mechanisms, such as MRGPRX2, are hypothesized to be a mechanism for fluoroquinolone-induced anaphylaxis, especially in drug-naïve patients [19].

Delayed hypersensitivity to fluoroquinolones is thought to be T cell-mediated. T-cell assays, such as lymphocyte proliferation and patch tests, have been reported, but their significance has yet to be established. Previous studies have used increased lymphocyte proliferation and patch testing to identify the culprit quinolone, though one study only showed 50% (3/6 patients) had a positive patch test to the culprit fluoroquinolone after 24 and 48 h [23].

Diagnosis

Allergy labels are not a reliable predictor of reproducible fluoroquinolone HSRs: approximately 70% of patients labeled as allergic tolerated a challenge [11]. Skin testing for fluoroquinolones is controversial. Although some studies consider skin prick (SPT) and intradermal skin testing (IDT) useful [24, 25], most authors acknowledge skin testing has low sensitivity and low specificity [11, 14, 26]. Empedrad et al. were unable to determine a non-irritating concentration (NIC) for ciprofloxacin but found levofloxacin NIC to be 0.025 mg/mL (Table 1) [27]. High rates of false positives have been attributed to fluoroquinolone-induced direct histamine release, possibly via MRGPRX2-dependent mast cell activation [12, 14, 25]. More restrictive criteria for IDT (Table 2) were retrospectively applied to 163 patients who reported a fluoroquinolone allergy to identify candidates for DPT [25]. All 82 patients whose IDT was negative by the proposed criteria who underwent DPT tolerated the oral challenge; 29–57% of these 82 would have a positive IDT by expert consensus criteria and would have been ineligible for DPT [25]. This study highlights the challenges with skin testing and how applying more stringent criteria may help distinguish between IgE-mediated and non-specific/non-IgE-mediated mast cell activation.

In vitro tests for fluoroquinolones, such as basophil activation test (BAT), may have increased sensitivity compared to skin testing but are also poorly predictive and not

commercially available [2, 11, 28, 29]. Interestingly, the average level of quinolone-specific IgE was higher in patients who were sampled within 8 months of their reaction (14.4% ± 10%) compared to those sampled more than 8 months later (8.1% ± 3%, $p = 0.095$) [20]. The timing may account for the high degree of variability in testing results, and caution should be taken with more recent reactions. Diagnostic testing for delayed fluoroquinolone reactions is quite limited. Patch testing has low sensitivity, 0–50% positivity in patients with delayed symptoms by clinical history [11, 23]. Two of 28 patients with negative patch testing and underwent DPT developed skin reactions 15–20 h after ingestion [11].

DPT is the only reliable diagnostic tool to definitively confirm or rule out a fluoroquinolone allergy [11]. DPT can be useful after mild cutaneous reactions [8, 11]. However, DPTs carry risks and are often avoided after severe index reactions, especially severe cutaneous adverse reactions (SCARs).

Management

There are no definitive guidelines to predict cross-reactivity among fluoroquinolones. Most patients with one positive fluoroquinolone skin test or in vitro test also test positive for another [4, 20, 24]. However, studies that include a drug challenge suggest lower levels of cross-reactivity. Of patients who reacted to ciprofloxacin, 2/5 (40%) tolerated levofloxacin in one study and 4/5 (80%) tolerated levofloxacin in another [2, 30]. Similarly, 3/5 (60%) and 3/4 (75%) of levofloxacin-reactive patients tolerated ciprofloxacin [2, 30]. In a case series, three patients with immediate HSR to moxifloxacin all tolerated ciprofloxacin [31]. Cross-reactivity could be a consequence of their common basic structure, although moxifloxacin notably has unique side chains on positions 7 and 9 of its bicyclic ring [20, 31]. Alternatively, fluoroquinolones could exhibit a nonspecific class effect via MRGPRX2-mediated mast cell activation [25].

For patients with confirmed immediate HSR to one fluoroquinolone, avoidance of the class is often recommended, but alternative fluoroquinolones can be considered on a case-by-case basis [12, 25]. Desensitization can be considered if the benefit outweighs the risks (Table 6) [32]. For delayed HSR to fluoroquinolones, cross-reactivity appears to be low [12], so challenging to other fluoroquinolones may be pursued as clinically necessary.

Vancomycin

Introduction

Vancomycin, a tricyclic glycopeptide, is one of the oldest antimicrobials against Gram-positive cocci bacteria. It originated from compound 05865, which was first isolated in 1952 from a dirt sample from Borneo. After purification methods to remove its brown color, compound 05865 (also known as “Mississippi mud”) became vancomycin and was approved by the FDA in 1958 [33]. Vancomycin use has escalated in the last 20 years with the spread of methicillin-resistant *Staphylococcus aureus* (MRSA), enterococcal, and *Clostridium difficile* infections. It is one of the most frequently used antibiotics today, with vancomycin inpatient use increasing by 32% from 2006 to 2012 [34]. Vancomycin is used in empiric treatment of Gram-positive infections and is a mainstay for MRSA SSTI,

bacteremia, endocarditis, bone and joint infections, and meningitis [35]. Oral vancomycin is the first-line therapy for *C. difficile* colitis [36].

Prevalence/Incidence

In a large, cross-sectional study of EHR-documented allergy, 14,426 (0.32%) of 4.5 million patients had a vancomycin allergy label between January 2017 and December 2019 (population estimate of 3 vancomycin-allergic individuals per 1000) [37]. No further confirmation of vancomycin allergy was performed in this study. The incidence of new vancomycin allergy increased over time, from a quarterly mean of 200 in April–June 2017 to 290 in October–December 2019, while the rate of vancomycin allergy deletion was stable at 12 per quarter [37]. The prevalence of EHR-reported vancomycin-induced anaphylaxis was 0.9 per 10,000 patients in the US without distinguishing between severe infusion reactions and true HSRs [6].

Immediate Reactions

The most common immediate vancomycin-induced reaction in both pediatric and adult populations has historically been called “red man syndrome,” a term with racist undertones that some have called to replace with “vancomycin infusion reaction (VIR)” [37, 38]. VIR is mediated by infusion rate–dependent direct mast cell degranulation, resulting in a rise of plasma histamine levels and symptoms of flushing, pruritis, and/or erythematous rash, typically on the face, neck, and upper torso [39, 40]. Nine of 11 healthy, vancomycin-naïve volunteers developed VIR with vancomycin 1 g/h, and the severity of their symptoms were proportional to the amount of histamine released [39]. The incidence of VIR in infected patients appears to be lower, ranging from 3.4 to 47% in small prospective studies [41, 42].

As mast cell involvement is common to both, VIR can mimic type I HSRs with angioedema, chest pain, dyspnea, bronchospasm, and hypotension [40, 43, 44]. Certain aspects of the history can help distinguish between VIR and type I HSRs: rapid symptom onset, rapid resolution of symptoms with drug withdrawal, and appearance on first exposure to vancomycin favor VIR over IgE-mediated HSR [45]. While 6% of vancomycin allergies were coded as anaphylaxis in one EHR-based study [37], IgE-mediated anaphylaxis is exceedingly rare: only 7 cases were identified in a systematic literature review from 1982 through 2015 [46]. These cases were deemed to likely be type I HSRs because of positive skin testing using a NIC, symptoms of anaphylaxis despite decreased infusion rate and antihistamine premedication, or IgE-mediated symptoms during a vancomycin desensitization [47–53]. Although uncommon, VIR and type I HSRs have also been reported with oral vancomycin and intraperitoneal vancomycin [48, 54].

Delayed Reactions

While rash is the prevailing delayed reaction to vancomycin, SCARs are uncommon, accounting for 3.5% of delayed HSRs [37]. DRESS is the most frequent EHR-documented vancomycin-associated SCAR [37]. Vancomycin is one of the most common antibiotic culprits of DRESS, accounting for 39–60% of the cases depending on the study [13, 55–57] and the second most common culprit of DRESS reported in the FDA Adverse Event Reporting System [58]. Onset of DRESS is typically 21 days after the start of vancomycin,

but can range from 12 days to 4 weeks [46, 59]. Renal injury occurs in DRESS and is strongly associated with vancomycin-induced DRESS in particular [13, 60]. Vancomycin is the most common culprit in drug-induced linear IgA bullous dermatosis (LABD), a rare autoimmune disease characterized by linear IgA deposition in the basement membrane zone [61, 62]. LABD symptoms occur, on average, 7 days after vancomycin initiation and typically consists of tense bullae in an older, predominantly male population [46, 63]. Vancomycin can also cause SJS and TEN, which can mimic drug-induced LABD [61, 62]. The median onset of SJS/TEN is approximately 9 days from starting vancomycin [46]. Other non-immediate reactions to vancomycin include acute interstitial nephritis, fixed drug eruption (FDE), and AGEP [37, 46]. For patients with impaired renal clearance, vancomycin should be considered a potential cause even if the reaction occurred weeks after the last dose [12]. Delayed reactions, such as maculopapular rash, can occur with enteral vancomycin therapy [64].

Adverse Reactions

Other adverse effects of vancomycin include nephrotoxicity, ototoxicity, neutropenia, thrombocytopenia, and phlebitis [33].

Pathophysiology

Immediate reactions to vancomycin are mediated by non-IgE mechanisms such as VIR and, less commonly, IgE mechanisms. MRGPRX2 has been implicated in VIR via in vitro studies in which vancomycintriggered mast cell degranulation of human mast cells was reduced in mast cells with decreased MRGPRX2 expression [65]. Sera from patients experiencing anaphylaxis during anesthesia demonstrate mast cell degranulation in a MRGPRX2-dependent manner [65]. Additionally, glutaminyl-D-tryptophylphenylalanine (QWF), a MRGPRX2 antagonist, significantly inhibited vancomycin-induced degranulation in human mast cells [66].

HLA-A*32:01 is strongly associated with vancomycin-induced DRESS among patients with European ancestry [67]. In a cohort of 23 patients diagnosed with probable DRESS, 19 had HLA-A*32:01 allele compared to 0 of 45 vancomycin-tolerant–matched controls [67]. For those carrying the HLA-A*32:01 allele, the risk for DRESS approaches 20% at 4 weeks of vancomycin therapy [67].

Diagnosis

Validated diagnostic tests for vancomycin-associated hypersensitivity reactions are lacking. Serum tryptase has been proposed as a method to distinguish between VIR and IgE-mediated anaphylaxis, but the data are conflicting. One study of non-IgE mediated anaphylaxis induced by vancomycin found no change in tryptase levels, but they were drawn at ≤ 20 min, earlier than the expected time to tryptase elevation [68, 69]. Cases of severe VIR with elevated tryptase levels have also been described [70].

Skin testing to vancomycin has high false positivity rates, likely due to direct cutaneous mast cell degranulation upon administration. All 12 healthy volunteers without prior exposure to vancomycin had positive IDTs at concentrations of 10 μg/mL or greater, all developed

VIR, and there was no significant relationship between the skin test flare size and symptom severity [40]. Currently, published drug allergy guidance recommends vancomycin NICs of 50 mg/mL and 0.005 mg/mL for SPT and IDT respectively (Table 3), although the positive and negative predictive values of the results are unknown [12, 27, 47]. A recent study suggests that the sterile water as the diluent worsens vancomycin's irritant side effects, and that alternatives like human serum albumin-based sterile saline may be more favorable for skin testing [71]. A risk assessment is necessary before any type of skin testing in suspected SCARs.

In vitro testing, such as BAT for immediate reactions and IFN-γ cytokine release assay or lymphocyte transformation tests for delayed reaction, has been performed but is not commercially available. For vancomycin-induced DRESS, a rapid allele-specific assay for HLA-A*32:01 has 100% sensitivity and 100% specificity, but it is not commercially available, and the test characteristics can change if the methods are modified [72]. Based on the 6.8% prevalence of HLA-A*32:01 in individuals with European ancestry, Rwandamuriye et al. estimate that 75 patients will need to be tested to prevent 1 case of DRESS [72].

DPT with a slower infusion rate and/or antihistamine pre-medications remains the gold standard for differentiating between VIR and type I HSR, but is generally avoided in the setting of severe symptoms, positive skin testing, or elevated tryptase levels [73].

Management

For mild to moderate VIR, symptoms can typically be mitigated with antihistamine pretreatment and by reducing the infusion rate by 50% or more, or 1 g over 2 h or more [74–76]. For severe or refractory VIR or likely IgE-mediated anaphylaxis, rapid desensitization should be considered, along with discontinuation of concurrent narcotics (Table 6) [12, 69, 77]. Mild transient reactions occur in approximately 30% of patients during desensitization, and slower protocols are reserved for patients who fail rapid desensitization [50, 69].

As with all SCARs, avoidance is recommended, and desensitization is generally contraindicated. Topical and oral corticosteroids, dapsone, cyclosporine, other immunosuppressants, and intravenous immunoglobulin have been used with unknown benefit [46, 59, 63].

Data on vancomycin cross-reactivity with other similarly structured glycopeptide antibiotics are mixed. In a review of the literature from 1994 to 2019, nine studies concluded cross-reactivity between glycopeptides while the other six did not [45]. In the largest study, 58 of the 304 hospitalized patients who received teicoplanin for the first time had an adverse reaction to teicoplanin and 55 demonstrated adverse reactions to both teicoplanin and vancomycin. The incidence of teicoplanin adverse reactions was higher in patients with prior vancomycin adverse reactions compared to those who did not (23.1% vs. 5.1%, $p < 0.001$) [78]. However, teicoplanin does not activate MRGPRX2 to induce mast cell degranulation, and multiple cases reports/series also demonstrate lack of clinical cross-reactivity [45, 79]. Cross-reactivity with vancomycin may be less with dalbavancin and oritavancin as they are less structurally similar, but data are lacking. Sera from all 15 HLA-A*32:01 restricted

vancomycin-induced DRESS patients demonstrated positive ELISpot to vancomycin and a negative ELISpot for dalbavancin, but 2 showed cross-reactivity with teicoplanin and telavancin [58].

Tetracycline

Introduction

Tetracyclines were first discovered in the early 1940s from soil samples and are naturally produced by Streptomyces species [80]. Tetracyclines share a naphthacene core with similar side groups that have been modified over the years to improve pharmacokinetics and overcome bacterial resistance [80]. Doxycycline, minocycline, and tetracycline are the most heavily used agents in this class, providing broad spectrum activity against Gram-positive aerobic and Gram-negative bacteria, atypical pathogens, and protozoan parasites and are used to treat a variety of infections, from community-acquired pneumonia (CAP) to acne to tick-borne illnesses [81]. Rarely utilized as an antibacterial, demeclocycline is used to treat syndrome of inappropriate antidiuretic hormone secretion [82]. In 2018, FDA-approved omadacycline for CAP and SSTI and eravacycline for intraabdominal infections [83–85]. Tigecycline, a glycylcycline, is a tetracycline derivative approved for CAP and complicated SSTI, but excess associated mortality seen in clinical trials has limited its use [81].

Prevalence/Incidence

Prevalence data is limited because a significant portion does not distinguish between HSR and side effects, and most suspected HSR are not confirmed by diagnostic testing. The prevalence of tetracycline HSR has been noted to be 4.2% (69/1624 reactions to antibiotics) [86]. Minocycline has been implicated in more adverse reactions than doxycycline despite being less commonly prescribed [87, 88]. In one retrospective review, 22 HSRs to tetracycline, minocycline, or doxycycline were identified (3 were confirmed by a positive rechallenge), and minocycline was implicated in 86% of these cases [89]. The prevalence of tetracycline-induced anaphylaxis was 0.8 per 10,000 patients in an EHR study [6].

Serious HSRs to minocycline occur more frequently compared to other tetracyclines, and it has been theorized that minocycline’s structure and metabolism may be responsible given its unique dimethylamino group in the 7th position [80, 89]. Although it is unknown whether minocycline produces a reactive metabolite that can act as hapten, it is unique in its potential to generate an iminoquinone derivative [89, 90].

Immediate Reactions

While immediate HSRs are infrequent, anaphylaxis to minocycline [90, 91], tetracycline [92, 93], and doxycycline [94, 95] have been reported. Most reactions occurred within 1 h of drug intake and consisted of urticaria, angioedema, dyspnea, wheezing, tachycardia, and/or hypotension [81]. In a few cases, patients were subsequently confirmed to have an IgE-mediated hypersensitivity by either positive skin testing [91–93] or oral challenge [90].

Delayed Reactions

The majority of HSRs to tetracyclines are non-IgE mediated. Delayed reactions to tetracyclines include erythematous rash, DRESS, SJS/TEN, serum sickness like reaction (SSLR), FDE, hypersensitivity pneumonitis, drug-induced lupus, hepatitis, and myocarditis with cutaneous reactions being the most common [81, 89, 96–98]. Reactions ranged from mild to very severe, and more serious reactions were associated with minocycline [81, 89]. FDEs occur most frequently with tetracycline and doxycycline, and typically appear within 24 h and in various locations, including genitals [96, 99–101]. Minocycline poses the highest risk for DRESS amongst tetracyclines and can manifest with pneumonitis and myocarditis in addition to hepatic and renal involvement [88, 102, 103]. Minocycline-induced DRESS may have a prolonged course, particularly in patients with darker skin [104].

Adverse Reactions

Common and dose-dependent adverse reactions to tetracyclines include gastrointestinal upset (predominantly doxycycline and minocycline), photosensitivity (tetracycline, doxycycline), blue-gray hyperpigmentation (minocycline), vestibular dysfunction, and headaches (minocycline) [87, 89, 105]. Less commonly, intracranial hypertension, hepatic disorders, autoimmune disorders (including lupus), Sweet's syndrome, and drug-induced fever without rash have been reported with minocycline [106–108]. Minocycline-induced eosinophilic pneumonia and hypersensitivity pneumonitis have also been reported [109, 110]. While most adverse reactions occur within several months of initiation, late reactions, such as drug-induced lupus, occur on average 2 years after therapy initiation [89]. Generally, minocycline has lower benefit to risk ratio compared with doxycycline, and extreme caution should be taken in patients with lupus, hepatic or renal disease, and history of HSR [88, 89].

Tigecycline, a glycylcycline derived from tetracyclines, is rarely used and less is known about its ability to induce HSR. Drug fever with leukemoid reaction, TEN, and delayed bronchospasm have been reported in association with tigecycline [111–113].

Diagnosis

Skin testing regimens for tetracyclines are not standardized, and their negative and positive predictive values are unknown (Table 4). To date, Maciag et al. has published the most comprehensive skin testing protocol for tetracyclines in a case series of 10 patients, 8 of whom were pediatric [113]. This protocol was based on maximum NICs after testing 3 control patients for doxycycline, 2 for minocycline, and 1 for tigecycline [113]. While passive transfer and hemagglutination tests were described for tetracycline in the 1960s, more recent in vitro diagnostic testing has not been reported in the literature.

DPT remains the gold standard for diagnosis. For patients with non-severe reactions, Maciag et al. offered a graded challenge of 1%, 10%, and 90%, the goal dose to tetracyclines with negative skin testing [113]. All DPTs (3 doxycycline, 2 minocycline, 2 tigecycline) were successful, although the challenge tetracycline was not the index reaction tetracycline if skin testing was positive [113].

Management

Because of the limited data on skin testing for immediate reactions and the lack of data in non-immediate reactions, avoidance is recommended after serious reactions. DPT to alternative tetracyclines can be considered on a case-to-case basis. Cross-reactivity among tetracyclines is not well defined. In a study of 16 patients with tetracycline-induced FDEs, there was higher rate of co-allergy with doxycycline (62.5%) than minocycline (18.7%) [100]. Case reports of cross-reactivity between minocycline/doxycycline and possibly minocycline/tigecycline have also been described [99, 113].

For patients with positive skin testing or high pretest probability of HSR by history, tetracycline rapid desensitization can be performed if there are no alternative treatments. Successful oral and parental desensitization protocols to doxycycline typically consist of 10–16 steps with a starting dose of 0.0001–0.125 mg (Table 6) [95, 113–115]. Breakthrough symptoms during desensitization were treated with antihistamines, leukotriene inhibitors, a brief pause in the protocol, and/or skin cooling measures [113]. Minocycline and tigecycline desensitization have also been performed without adverse reactions [113].

Macrolides

Introduction

Macrolides consist of a macrocyclic lactone ring that contains 14, 15, or 16 carbon atoms with 1 or more sugar attached and were first isolated from *Streptomyces venezuelae* [116]. The first macrolide erythromycin had 14 carbons in lactone ring (14-C) and gained prominence in the 1950s, but its use was limited by significant gastrointestinal side effects [117]. Newer macrolides, azithromycin (15-C) and clarithromycin (14-C), have broader antimicrobial coverage, improved pharmacokinetics, and better tolerability. Azithromycin and clarithromycin have been commonly prescribed for respiratory tract, sexually transmitted, non-tuberculous mycobacterial, and *Helicobacter pylori* infections [117, 118]. Additionally, macrolides have anti-inflammatory properties with therapeutic benefit in chronic respiratory disease, such as chronic obstructive pulmonary disease and chronic bronchiectasis [116]. Less commonly used macrolides include roxithromycin (14-C), dirithromycin (14-C), spiramycin (16-C), and josamycin (16-C) [118].

Prevalence/Incidence

Macrolides generally have an excellent safety profile and hypersensitivity reactions are uncommon. The prevalence of reported macrolide-induced anaphylaxis was 3.8 per 10,000 patients in one large US healthcare system, with erythromycin accounting for the majority of cases [6]. Self-reported adverse reaction to macrolides was 3.5% and occurred predominantly in outpatient medicine clinics [86]. However, the true prevalence may be lower as these studies do not confirm HSR and/or differentiate HSR from side effects. In a smaller study that included a DPT, only 7.5% (8/107) of patients with history of HSR had a positive DPT to their suspected macrolide [119]. Positive DPT rates are similarly low in other studies, including among children [120–122].

Immediate Reactions

Urticaria is the most commonly reported immediate HSR to macrolides, followed by urticaria/angioedema [119, 121]. Anaphylaxis is rare but has been described for azithromycin, clarithromycin, and erythromycin with some cases subsequently confirmed by positive allergy testing [121, 123–125]. Interestingly, a case report of anaphylaxis to azithromycin determined the culprit to be the carmine dye in the coating of the tablet rather than azithromycin [126].

Delayed Reactions

The most common delayed reaction to macrolides is a maculopapular exanthem or undefined rash [119, 121]. Other more severe delayed HSRs include FDE, DRESS, SJS/TENS, and bullous skin reaction [118, 127]. HLA-A*02:07 allele is associated with clarithromycin-induced cutaneous ADRs in Han Chinese patients and may be a genetic risk factor [128]. Occupational exposure to powdered azithromycin and its intermediates can also cause allergic contact dermatitis [129].

Adverse Reactions

The major adverse reactions to macrolides are nausea, diarrhea, abdominal pain, and vomiting due to gut contractility, which are reduced in extended-release formulations [117, 130]. Rare side effects include QTc prolongation, sensorineural ototoxicity, myasthenia gravis, and hepatoxicity [97, 130]. In a study of drug-induced liver injury, azithromycin was the most frequent culprit drug in patients with preexisting chronic liver disease [97]. Macrolides also interact with many drugs, via 14-C macrolides' affinity for CYP450 and clarithromycin's effects on CYP3A metabolism [117, 118, 130, 131].

Diagnosis

Similar to other non-beta lactam antibiotics, the clinical history does not reliably prognosticate reproducible HSRs [119] and the predictive value of skin testing is controversial. Empedrad et al. established NICs of 0.05 and 0.01 mg/mL for erythromycin and azithromycin respectively in 25 healthy controls [27]. While some have found IDTs to be useful [132], others have not [125, 133]. However, the skin testing concentrations varied by study and may account for their differences (Table 5). In vitro tests such as BAT [122] and macrolide-specific IgE [121, 134] have been studied for immediate reactions and lymphocyte transformation test [122] for delayed reactions, but these tests are neither validated nor commercially available.

DPT remains the standard for diagnosis, but the rate of positivity appears varied. In a retrospective cohort study of 107 patients with reported HSR to macrolides, only 7.5% had a positive DPT [119]. The timing of symptom onset was telling as the majority of positive DPTs occurred in patients whose index reaction was within 24 h of ingestion [119]. The severity of the index reaction did not correlate with DPT results [119]. Other studies have similarly low rates of positive challenges (2.7% to 6%), although patients with positive skin testing were excluded from DPTs in some studies [120, 122, 125, 132]. In contrast, Ünal et al. found that 16 of 25 patients with history of macrolide HSR (64%) had positive DPTs to either the culprit or alternative macrolide [125]. This difference may be due to higher

percentage of immediate reactions (84%) included in this study as well as timing of the allergy test, which occurred on average 24 months after the drug reaction [125].

Management

In the setting of low clinical suspicion of IgE-mediated HSR or SCAR, skin testing and/or DPT may be considered. Extra caution should be taken with a history of immediate (< 1 h) and more recent reactions. With high pre-test probability of a severe HSR, avoidance is recommended. Rapid desensitization for immediate HSR is an option if the there are no other antibiotic alternatives, and successful protocols to spiramycin [135] and clarithromycin [136, 137] have been described (Table 6).

There is limited data on cross-reactivity between macrolides. While the majority of patients can tolerate an alternative macrolide, particularly a macrolide with differing number of carbon atoms, 2 of 20 clarithromycin (14-C)-allergic patients reacted to azithromycin (15-C) and 1 of 2 azithromycin-allergic patients had a positive clarithromycin DPT [125]. Other case reports of azithromycin and clarithromycin cross-reactivity have been described [121, 136]. Cross-reactivity between antibiotic and macrolide immunosuppressants (e.g., 23-C tacrolimus, 29-C sirolimus) has been reported, but the diagnosis was made by clinical history, and no subsequent allergy evaluation was performed [138].

Conclusion

Confirming fluoroquinolone, vancomycin, tetracyclines, and macrolide HSR is challenging. A thorough clinical history, particularly the onset of the symptoms from drug intake, is necessary and can help distinguish HSR from a side effect, but history alone does not consistently correlate with HSR reproducibility. The value of skin testing to fluoroquinolones, vancomycin, tetracyclines, or macrolides is controversial because protocols vary and the negative and positive predictive values are poorly defined. DPT remains the gold standard of diagnosis, but the risk of a severe reaction on challenge may outweigh the benefit of confirming the allergy. Allergy testing to antibiotics within the same class and desensitization to index reaction antibiotic may be considered on a case-to-case basis when indicated for directed treatment of specific infections.

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Abbreviations

AGEP	Acute generalized exanthematous pustulosis
BAT	Basophil activation test

CAP	Community acquired pneumonia
DPT	Direct provocation test
DRESS	Drug reaction with eosinophilia and systemic symptoms
ED	Emergency department
HER	Electronic health record
FcεRI	High-affinity IgE receptor
FDA	US Food and Drug Administration
FDE	Fixed drug eruption
HSR	Hypersensitivity reaction
IDT	Intradermal skin test
LABD	Linear IgA bullous dermatosis
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRGPRX2	Mas-related G protein-coupled receptor X2
NIC	Non-irritating concentration
SCAR	Severe cutaneous adverse reaction
SDRIFE	Symmetrical drug-related intertriginous and flexural exanthema
SJS	Stevens-Johnson syndrome
SPT	Skin prick test
SSLR	Serum sickness like reaction
SSTI	Skin and soft tissue infections
TEN	Toxic epidermal necrolysis
THIQ	Tetrahydroisoquinoline
US	United States
VIR	Vancomycin infusion reaction (red man syndrome)

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Table 1

Fluoroquinolone skin testing concentrations

Drug	Skin prick test (mg/mL)	Intradermal (mg/mL)	References
Ciprofloxacin	2	NP	[11]
	0.02 and 0.2	NP	[2]
	0.02	0.02	[24]
	NP	0.025 and 0.005	[25]
Moxifloxacin	1.6	NP	[11]
	400 mg tablet suspended in NaCl	NP	[2]
	400 mg tablet suspended in NaCl	NP	[24]
	NP	0.025 and 0.005	[25]
Levofloxacin	5	NP	[11]
	0.05 and 0.5	NP	[2]
	5	0.05	[24]
	NP	0.025*	[27]
	NP	0.025 and 0.005	[25]

NP - not performed

*NIC

Table 2

Criteria for positive IDT for fluoroquinolone

Expert consensus	Proposed criteria by Krantz et al.
Criteria 1: Fluoroquinolone wheal ≥ saline wheal + 3 mm Criteria 2: Fluoroquinolone wheal ≥ saline wheal + 3 mm and flare present Criteria 3: Fluoroquinolone wheal ≥ 5 mm and flare > wheal	Criteria 4: Specific fluoroquinolone flare at 0.025 mg/mL ≥ histamine flare, specific fluoroquinolone flare at 0.005 mg/mL ≥ 5 mm, and no flare ≥ 5 mm for either of the two other fluoroquinolones (non-culprit) tested at 0.005 mg/mL

Table 3

Vancomycin skin testing concentrations

Drug	Skin Prick Test (mg/mL)	Intradermal (mg/mL)	References
Vancomycin	50	0.005*	[27, 47]

*NIC

Table 4

Tetracycline skin testing concentrations

Drug	Skin prick test (mg/mL)	Intradermal (mg/mL)	References
Doxycycline	10	0.0001 and 0.001	[113]
Minocycline	0.2	0.0002 and 0.002	[113]
Tetracycline	25	NP	[92]
	0.5		[93]
Tigecycline	1	0.01 and 0.1	[113]

NP - not performed

Table 5

Macrolide skin test skin testing concentrations

Drug	Skin Prick Test (mg/mL)	Intradermal Test (mg/mL)	References
Erythromycin	NP	0.05 *	[27]
	10	0.1, 1, 10	[119]
Azithromycin	NP	0.01 *	[27]
	250 mg tablet suspended in saline solution	NP	[125]
	100	0.01	[121]
	10	0.1, 1, 10	[119]
Clarithromycin **	50	0.05, 0.5 * and 5	[132]
	50	0.05–0.5	[121]
	50	0.0005, 0.005 and 0.05	[133]
	0.1	0.001–10	[125]
	10	0.1, 1, 10	[119]

NP - not performed

* NIC;

** Not available in intravenous form in the USA

Table 6

Desensitization protocols for fluoroquinolones, vancomycin, tetracyclines, and macrolides

Drug class	Drug	Sample protocol	References
Fluoroquinolone	Ciprofloxacin	13 steps for cumulative dose of 450.55 mg: 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8, 25, 50, 100, 250 mg in 15-min intervals	[32]
Vancomycin	Vancomycin	11 steps for goal cumulative dose (e.g., 1 g): 0.0060, 0.020, 0.060, 0.20, 0.60, 2.0, 6.0, 20, 60, 125 mg/hr in 15-min intervals, followed by 250 mg/hr for remainder of dosage	[12] Alternative rapid desensitization protocols: [69, 77] Slow desensitization protocols: [50, 139]
Tetracycline	Doxycycline	12 steps for a cumulative dose of 102 mg: 0.00001, 0.0001, 0.001, 0.01, 0.1, 1, 2, 4, 8, 12, 25, 50 mg in 30-min intervals	[113] Alternative protocols: [95, 114, 115]
	Minocycline	14 steps for cumulative dose of 140 mg: 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1.28, 2.56, 5, 10, 20, 40, 60 mg in 15 min intervals	[113]
	Tigecycline	12 steps for cumulative dose of 50 mg: 0.0010, 0.0025, 0.0050, 0.01, 0.025, 0.05, 0.1, 0.2, 0.4961, 0.9921, 1.9843 in 15 min intervals, followed by 46.134 mg over 186 min	[113]
Macrolide	Clarithromycin	14 steps for cumulative dose of 503 mg: 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 125, 250 mg in 15-min intervals	[136] Alternative protocols: [137]