

Immediate Drug Hypersensitivity

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Abstract Drug allergy affects a large percentage of the general population. A listed drug allergy can also have broad implications for many aspects of patient care. Here, we will review recent advances in the arena of drug allergies with a focus on antibiotics, monoclonals, NSAIDs, and chemotherapeutics.

Keywords Drug allergy · Drug hypersensitivity · Antibiotic · Monoclonals · Chemotherapy

Introduction

Drug allergy affects a large percentage of the general population, and 15 % of inpatients have a listed drug allergy to penicillin (PCN) alone [1, 2]. The term “allergy” is used broadly in the health care setting and, in many electronic health records (EHR), is combined with adverse drug reactions and a host of non immune-mediated reactions. Listed medications in the allergy section of a patient’s record can have broad implications for their care in multiple arenas—cost, safety, duration of inpatient stay, and efficacy of treatment [3]. Not only is the quality and safety of care greatly affected by the items listed in the electronic medical record (EMR) but many drug allergy alerts for these listed allergens

are ignored and frequently overridden [4] stressing an urgent need for improvement in what is listed and when an alert should fire. A careful understanding of how to improve EMRs in this arena requires the collaboration of the allergist, and we will review recent advances on how to look at listed allergies in the EHR to assist with management.

As providers are increasingly utilizing multifaceted treatment regimens, the aim for drug allergic patients is not only to deliver first-line agents safely despite a spectrum of reactions but also to learn from emerging cross-reactive patterns in a growing list of chemotherapeutics and monoclonal agents.

Antibiotics

Examinations of cross-reactivity patterns and their impact on patient care continue to be important when prescribing antibiotics. Recent studies have focused on addressing listed antibiotic allergies in the EMR and their impact on patient care, especially the largest allergy-inducing category of beta-lactam antibiotics. Macy et al. demonstrate that patients who carry the PCN allergy not only have longer inpatient stays but also have higher rates of hospital associated infections with 30.1 % more VRE, 14.1 % more MRSA, and 23.4 % more *C. difficile* compared to matched non-allergic inpatients [5]. The public health implications of these findings are significant given the prevalence of listed PCN allergy of around 10 % of patients and 15 % of inpatients. Recent literature has seen a push to clarify these listed allergies with varied recommendations of protocols which include utilization of skin testing [6] and clinical history taking [7] to safely allow beta-lactam antibiotic administration in these patients.

For patients who have skin test proven IgE-mediated hypersensitivity to penicillins, a recent prospective study confirmed the tolerability of aztreonam and carbapenems after

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negative skin testing with both categories [8]. Cephalosporin cross-reactivity and best prescribing practices remain more challenging given the lower predictability of skin testing when compared to penicillins [9]. A recent study grouped 102 cephalosporin skin test-positive patients and tested for 11 cephalosporins, amoxicillin, ampicillin, and penicillin with determinants as well as serological testing [10]. They then showed all subjects were able to undergo successful challenges with alternative cephalosporins selected based on their skin test results.

Fluoroquinolone hypersensitivity occurs more often in patients with beta-lactam-confirmed hypersensitivity, and moxifloxacin has a higher rate of hypersensitivity reactions among the group of fluoroquinolones when examined in patients attending an allergy clinic and in US hospital emergency departments [11, 12].

It has been well established that outpatient protocols of varying lengths successfully allow HIV patients with a history of adverse drug reactions to TMP-SMX to tolerate administration [13, 14]. Outpatient desensitization also works well in patients without HIV infection, and 1-day protocols, when compared to longer protocols, may have greater long-term success rates without differing short-term outcomes [15].

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an additional category of medication frequently encountered in the allergy section of an EMR. They are the second largest category of reported drug hypersensitivity [16]. There are a multitude of type A (predictable) and type B (unpredictable) reactions associated with the NSAID category. NSAIDs also often cause what are termed “pseudoallergic” reactions, which occur in an immediate time frame but are thought to be due to biochemical alteration of the COX-1 pathway by these medications as opposed to an unexpected immunological response [2].

NSAID allergy is typically grouped into six main categories, the first four of which are considered pseudoallergic and types 5 and 6 are allergic and considered to be IgE mediated. A combination of history taking and aspirin challenge can help clarify in the patient with an unclear categorization.

In the subcategory of NSAID-allergic patients who have aspirin exacerbated respiratory disease (AERD), there is often a delay to diagnosis. It is notable that adult patients maintained on low dose aspirin (ASA 81 mg) may still have AERD [17]. Patients from an AERD registry were identified by chart review and subjects were identified who were on 81 mg ASA at the time of AERD evaluation and who reported no hx of sensitivity to ASA. Six patients out of the seven identified had positive challenge tests with ASA. Additionally, as explored by Cardet et al., the presence of alcohol-induced

respiratory symptoms may be a clinical clue to this diagnosis with a prevalence of 75 % of AERD patients reporting upper respiratory reactions as opposed to 33 % with aspirin tolerant asthma [18].

There is a much work that remains to be done in the NSAID allergy arena, with a need for diagnostics to clarify and confirm beyond the oral challenge, early identification of AERD patients, and improvement in our EMR specificity and prescribing guidelines.

Chemotherapy

Hypersensitivity reactions (HSR) to chemotherapy represent a complex challenge in diagnosis and management given the sheer variety of agents used in different clinical settings. These agents include synthetic compounds, naturally occurring compounds, and monoclonal antibodies, all of which have different physical properties and toxicities that affect their risk of causing allergic reactions. While many open questions still exist, much headway has been made in our understanding of the mechanism and treatment of chemotherapy-induced HSRs over the past 10 years.

Chemotherapy allergy consistent with a classic type I HSR profile has been best described for carboplatin as it is one of the mainstay treatments for ovarian cancer. Many ovarian cancer patients require long and repeated courses of chemotherapy, thus setting the stage for IgE sensitization to carboplatin. The incidence of carboplatin allergy is about 27 % after seven lifetime exposures and as high as 46 % in patients who have had at least 15 lifetime doses [19, 20]. Acute HSRs which occur during the infusion and present with symptoms consistent with anaphylaxis (i.e., flushing, hives, wheezing, hypotension) are generally amenable to treatment with drug desensitization to induce a temporary state of tolerance to the offending agent [21•, 22•, 30]. A number of protocols for various agents, including monoclonals, have been described, but most are derived from antibiotic desensitization protocols using serial dilutions of drug to gradually escalate the dose administered to the patient over a period of several hours to a day [21•, 22•]. One of the most frequently used protocols for which outcome data is available is a three-solution, 12-step protocol described by Lee et al. used to treat women with ovarian cancer and skin test-confirmed allergy to carboplatin (Table 1) [23]. Desensitization is a highly effective technique when properly applied but may not be widely available outside large medical centers. Even when available, desensitization requires a high degree of coordination between allergists, nurses, and pharmacists to successfully and safely implement. Given the time and resources required to desensitize, the decision to do so requires a thorough diagnostic evaluation

Table 1 Example of three-solution, 12-step desensitization protocol

Name of medication:		Carboplatin				
Target dose (mg)		250.0				
Standard volume per bag (ml)		250				
Final rate of infusion (ml/h)		80				
Calculated final concentration (mg/ml)		1				
Standard time of infusion (min)		187.5				
					Total mg per bag	
Solution 1	250	ml of	0.010	mg/ml	2.500	
Solution 2	250	ml of	0.100	mg/ml	25.000	
Solution 3	250	ml of	0.992	mg/ml	248.033	
*** PLEASE NOTE ***		The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are not completely infused				
Step	Solution	Rate (ml/h)	Time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0050	0.0050
2	1	5.0	15	1.25	0.0125	0.0175
3	1	10.0	15	2.50	0.0250	0.0425
4	1	20.0	15	5.00	0.0500	0.0925
5	2	5.0	15	1.25	0.1250	0.2175
6	2	10.0	15	2.50	0.2500	0.4675
7	2	20.0	15	5.00	0.5000	0.9675
8	2	40.0	15	10.00	1.0000	1.9675
9	3	10.0	15	2.50	2.4803	4.4478
10	3	20.0	15	5.00	4.9607	9.4085
11	3	40.0	15	10.00	9.9213	19.3298
12	3	80.0	174.375	232.50	230.6702	250.0000
Total time (min) =			339.375	=5.66 h		

including a detailed history, exam, and skin testing, if appropriate and available.

Because of the relatively high incidence and potential morbidity of carboplatin allergy in patients who receive more than six lifetime doses, some groups explored the idea of prospectively skin testing patients after their sixth dose of carboplatin [24]. One particularly interesting finding from this review comes from Markman et al. who performed carboplatin infusion challenges on patients who were known to be skin test-positive to carboplatin. In this group, six out of seven patients with positive carboplatin skin tests had infusion reactions of varying severity, thus giving the skin test a high positive predictive value of 86 % [25]. Skin testing is a resource-intensive task on the part of patients and providers, so in most cases, patients present to allergy specialists only after they have experienced a HSR. In this setting, the skin test is used as a risk stratification tool that is especially useful in cases where the clinical history is not entirely clear for an allergic reaction. Given the cumulative risk of anaphylaxis with subsequent infusions, even mild reactions should raise concern of more severe reactions in the future, even if the initial skin test is negative.

One approach in distinguishing patients who do and do not need desensitization is described by Patil et al. and Wang et al. in which serial skin testing after empiric carboplatin or oxaliplatin desensitizations was used to monitor for IgE sensitization [26, 27]. The authors describe a protocol in which patients with a clinical history of carboplatin- or oxaliplatin-induced HSRs with initially negative skin tests were risk-stratified to identify those patients who could return to regular outpatient infusion. Patients received three additional rounds of testing with intervening desensitizations. Patients who converted to a positive skin test remained on desensitization indefinitely while those patients who remained negative after three rounds of desensitizations were then referred to outpatient infusions without desensitization. Of the patients who were continued on chemotherapy by their oncologist, 77 and 89 %, respectively, on carboplatin or oxaliplatin were referred back to outpatient infusions and remained reaction-free with subsequent infusions (median number of observed infusions was two in the study period). While it is not known how many of these patients subsequently developed reactions after the study period ended, this approach is useful in medical centers where the demand for desensitization space and resources far

outstrips supply. Identifying those patients who can return to regular infusion is important but must be balanced with the need to maximize patient safety.

Another chemotherapeutic agent that frequently causes anaphylactic reactions is paclitaxel, a hydrophobic agent derived from the needles or bark of yew trees that requires solubilization into aqueous solutions with polyethoxylated castor oil, aka Cremaphor-EL. Unlike carboplatin, many reactions to paclitaxel occur with the first or second administration of the drug when patients would be expected to be immunologically naïve. Unless patients have a pre-existing cross-reactive IgE antibody from some other allergen, these reactions likely represent non-IgE-mediated anaphylactic reactions to an excipient such as Cremaphor which continues to be used as the solubilizing agent in paclitaxel [28]. Another taxane agent, docetaxel, is solubilized with a different surfactant, polysorbate-80, which can also potentially induce HSRs. Reactions to Cremaphor are non-IgE mediated with symptoms including flushing, urticaria, back pain, chest tightness, and wheezing [29]. The incidence of HSRs to paclitaxel is so common, many patients are routinely premedicated with antihistamine and steroids. Despite this premedication regimen, about 10 % of patients will have breakthrough reactions requiring additional intervention, and the vast majority of these patients who react are able to be treated with drug desensitization [30]. The fact that reactions to Cremaphor are amenable to desensitization speaks to the utility of this technique and mechanism of action bypassing the role of IgE. An alternative to Cremaphor-solubilized paclitaxel is Abraxane which is paclitaxel encapsulated in an albumin nanoparticle. HSRs to Abraxane are exceedingly rare [31], but its use is often limited by its significantly higher cost over paclitaxel.

Identifying the need to desensitize vs. premedicate for HSRs to taxanes is not always clear, and while sensitivity and specificity data for skin testing to taxanes is lacking, a positive skin test suggests the possible presence of IgE against the drug or excipient moieties [32]. Challenging a patient to determine if a patient can return to regular outpatient infusion has risks which can be mitigated using a suggested algorithm published by Picard et al. Analogous to the efforts of Patil et al. and Wang et al. for carboplatin allergy, skin testing to paclitaxel or docetaxel is used in this algorithm to risk-stratify patients while initially desensitizing using the Castells protocol [21•]. The algorithm also uses the clinical HSR grade as described by Brown et al. (see Fig. 1) [33] to determine if patients who present with grade 1 or 2 can receive infusions with standard premedications and “accelerated” desensitizations using fewer drug dilutions and/or higher final rate of infusion. Assuming there are no reactions, patients may then be challenged to confirm they can safely return to regular outpatient infusion. Only patients who initially present with severe grade 3 anaphylactic

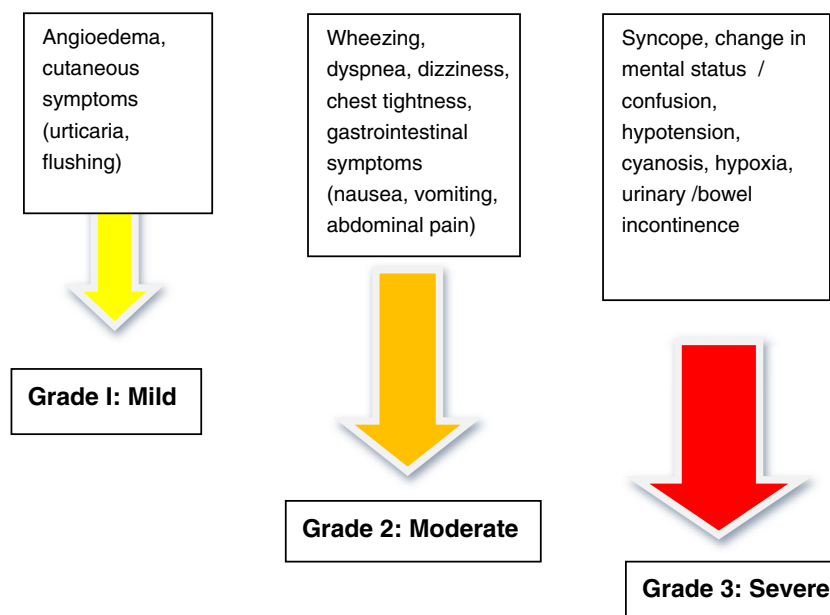
reactions are deemed too risky to subject to challenge [34]. It is important to note that data showing the efficacy and safety of this algorithm have not yet been published.

Monoclonals

Reactions to monoclonals often occur with the first or second infusion featuring cytokine release syndrome-like symptoms (high fever, rigors) and mast cell-mediated symptoms (flushing, hypotension, pruritis, urticaria). Most reactions are thought to non-IgE mediated. As mentioned previously, polysorbate-80 (P-80) is an excipient used to solubilize hydrophobic proteins, increase protein stability, and prevent losses due to adsorption on solid surfaces (i.e., container bags). It is used in a variety of monoclonals including rituximab and infliximab, two agents with the highest incidence of HSRs in this class [22•]. P-80 in solution can generate peroxide radicals when exposed to light and air, an effect further enhanced by heat [35]. Peroxide is a known activator of rat mast cells in vitro, and infusion of P-80 into dogs has been shown to induce hypotensive anaphylaxis [36]. Studies also have shown that P-80 “purity” in terms of peroxide content can vary by manufacturer suggesting there is potential for batch-to-batch variability in potential for causing inadvertent mast cell activation [37]. One group in Germany has demonstrated also the possibility of IgE-mediated sensitization to P-80 on the basis of skin testing [38]. In this case report, a patient who had an anaphylactic reaction to an infused multivitamin solution solubilized with P-80 was skin tested to the vitamin solution and another solution containing just an equivalent concentration of P-80. Skin testing was positive to both. Given the ubiquity of P-80 in household goods and medications, the potential for sensitization offers yet another possible explanation for anaphylaxis to medications to which patients would be expected to be immunologically naïve.

Allergy to monoclonals can also be due to generation of IgE against antibody moieties. While this topic has been reviewed in more depth elsewhere [39], cetuximab allergy is a particularly interesting case of monoclonal hypersensitivity in that patients may also have delayed onset anaphylaxis to consuming mammalian meat (i.e., beef and pork) which expresses the oligosaccharide epitope, galactose- α -1,3-galactose (α -gal) [40]. Cetuximab is derived from a mouse cell line that expresses a transferase that tags the Fab’ portion of the cetuximab heavy chain [41]. Another fascinating twist is demonstrated in the finding that a history of multiple bites from ticks commonly found in the Carolinas, Arkansas, and Tennessee correlates with the presence of anti- α -gal IgE antibodies as compared to serum from control patients living outside those

Fig. 1 Hypersensitivity reaction categorization (adapted from Brown et al.) “Hypersensitivity Reaction Categorization (Adapted from Brown et al.)” was captured as a figure. Please check if correct. I put a comment around this figure- why are there little dots around the middle arrow? Also the spacing looks different between the text and the arrows than what I submitted. Thank you.



states [42, 43]. The tick thought to be most likely to cause this sensitization in the USA is *Amblyomma americanum*, though alpha-gal antibodies have been found in areas where this tick is not commonly found as well.

Conclusion

Constraining therapeutic choices due to a history or fear of drug allergy can have unintended consequences that have significant implications for public health and health care delivery, as well as individual therapeutic outcomes. A high prevalence of drug allergy to beta-lactams, for example, can lead to wider use of broad-spectrum antibiotics leading to accelerated development of bacterial resistance. For institutions and insurance providers, alternative agents may be more expensive or harder to procure. For the patient, the alternative drug may be less effective or have more toxicity, potentially leading to a sub-optimal or failed therapeutic outcome. Better access to services and tools that accurately diagnose drug allergy will likely improve efficiencies in health care delivery as well as enhance patient satisfaction and quality of care.

Drug allergy parallels the expanding field of drug development. Further work in the arena of drug hypersensitivity is still needed on multiple fronts. In addition to public health and epidemiology research, more clinical work is needed to improve clinical pathways to clarify drug allergy status, to better define sensitivity/specificity of drug skin testing protocols, and to improve upon existing treatments for drug allergy. Additionally, EMRs

provide significant opportunities for sharing of allergy data across EMR systems and improving electronic drug allergy listing to improve quality care. For example, the nuances of classifying allergens as specific to individual drug vs. drug class and differentiating adverse reactions vs. immune-mediated reactions might be better standardized with future EMRs.

While desensitization has been extensively studied and proven effective in many cases of drug allergy, the role of biologic treatments directed against Th2 cytokines or IgE, has been largely unexplored in this setting. Improving in vitro diagnostics could lead to increased safety when deciding when to perform drug challenges, similar to how component-resolved IgE testing has impacted the diagnosis and treatment of peanut allergy. Further research is also needed to understand the mechanism of non-IgE-mediated reactions which constitute many cases of drug allergy (i.e., paclitaxel). What role do excipients play in these reactions? Could such reactions be secondary to a pre-existing cross-reactive antibody? Is desensitization always the best approach to such reactions? Clearly, there is the need for further study to unlock the answers to critically important questions that shape our approach to the complications inherent to drug allergy.

Compliance with Ethical Standards

Conflict of Interest Drs. Wickner and Hong declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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