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365 Desensitization

■ ■PREVENTION

Avoidance The simplest and most straightforward approach to the long-term management of a patient with a history of anaphylaxis is strict avoidance of known anaphylactic triggers and education on acute management, specifically, instructing the patient on proper use and indications for use of self-administered epinephrine. Lifelong avoid ance is not easy if the trigger is an occupational exposure, Hymenop tera sting, a common food (i.e., peanut), or a drug representing the sole or best therapeutic option for the patient. Special management options may exist for these patients. PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Venom Immunotherapy Patients of any age who have had docu mented anaphylaxis from Hymenoptera sting should be formally eval uated and started on venom immunotherapy (VIT) if skin or serologic IgE testing confirms the history. Immunotherapy is a means of “toler izing” patients to allergen by means of serial subcutaneous administra tion of escalating doses of extract containing relevant allergen until a target maintenance dose is achieved. Anaphylaxis can sometimes occur during the course of administering immunotherapy extracts, so formulating extracts and administering them is typically done under the care of a specialist familiar with this type of treatment. In the case of Hymenoptera allergy, patients receive VIT extracts containing actual Hymenoptera venom with a maintenance dose equivalent to 2–5 stings. The recommended duration of treatment is 3–5 years; however, some patients who have experienced severe respiratory or cardiovascu lar anaphylaxis are put on lifelong therapy. Patients with mastocytosis may also require such lifelong treatment. Preventative Tolerance Induction to Peanuts IgE sensitiza tion to foods occurs most frequently in infants and young children, especially those with atopic dermatitis, and is a risk factor for anaphy laxis (although detection of specific IgE through skin or serum testing has relatively poor predictive value). While most allergy to egg, milk, soy, and/or wheat resolves spontaneously during childhood, ~80% of children with peanut allergy remain sensitive for life. A sharp rise in the prevalence of peanut allergy was also observed in the late 1990s to early 2000s, especially in countries with Western diets where the aver age age of peanut introduction was age ≥3 years. Curiously, in cultures where peanut was introduced much earlier into children’s diets, the prevalence of peanut allergy remained low. The landmark Learning Early About Peanut Allergy (LEAP) study demonstrated that early introduction of peanut protein to the diet of high-risk infants (4–11 months of age with atopic dermatitis and/or egg allergy) prevented the development of most (80% or more) peanut allergy compared with children who did not consume peanuts (avoidance group), even when IgE sensitization (based on positive skin test) had already developed at the time of study entry. While the induction of tolerance at an early age seems to be key to preventing clinical reactivity later in life, it is not yet clear if this principle holds true for other foods commonly associated with hypersensitivity reactions. A relatively new treatment for patients who already

suffer from severe peanut allergy is peanut oral immunotherapy (OIT) in which patients receive a titrating regimen of precisely dosed peanut protein in the form of an oral capsule. The goal of peanut OIT is to raise a patient's threshold tolerance for accidental peanut exposure before anaphylaxis occurs, and it is not a cure for peanut allergy. At the current time, pea nut is the only food for which a U.S. Food and Drug Administration (FDA)-approved treatment exists, but research on developing OIT for other foods, such as milk and egg, remains ongoing. Desensitization For patients who have experienced anaphylaxis from drug allergy and whose treatment regimen requires the admin istration of the offending drug, desensitization may be a short-term treatment option to prevent reactions. Desensitization elicits a tem porary state of tolerance to the drug in sensitized, clinically reactive patients. While it has been a proven technique for penicillin-allergic patients for decades, desensitization has more recently been proven to be effective for certain chemotherapy agents, especially platin-based chemotherapy agents that can induce IgE-mediated sensitization with

repeated exposures. The exact mechanisms underlying desensitiza tion are not fully understood; however, temporary tolerance can be achieved through the serial administration of gradually escalating doses of drug, starting from extremely low doses, over the course of hours. As long as the patient continues to receive the drug in question at regular intervals based on drug half-life, a "desensitized" state can also be maintained until the drug is no longer needed. While drug desensitization certainly works for IgE-mediated reactions, it has been performed in cases of non-IgE-mediated anaphylaxis from Cremophor-

solubilized paclitaxel as described earlier in this chapter. Drug desensitization has also been shown by multiple groups to work for non-IgE-mediated reactions from a variety of biologic agents, various chemotherapy drugs, and NSAIDs. Given the complexity and variety of possible drug reactions, the decision to desensitize, challenge, or avoid should be made in conjunction with an allergy specialist for complete evaluation and proper risk stratification of the different pos sible approaches to take. ■ ■FURTHER READING Brennan PJ et al: Hypersensitivity reactions to mAbs: 105 desensiti zations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol 124:1259, 2009. Castells MC et al: Hypersensitivity reactions to chemotherapy: Out comes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 122:574, 2008. Chung CH et al: Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med 358:1109, 2008. Du Toit G et al: LEAP Study Team. Randomized trial of peanut con sumption in infants at risk for peanut allergy. N Engl J Med 373:803, 2015. Du Toit G et al: Immune Tolerance Network LEAP-On Study Team. Effect of avoidance on peanut allergy after early peanut consumption. N Engl J Med 374:1435, 2016. Lieberman P et al: Anaphylaxis—A practice parameter update 2015. Ann Allergy Asthma Immunol 115:341, 2015. McNeil BD et al: Identification of a mast cell-specific receptor crucial for pseudoallergic drug reactions. Nature 519:237, 2015. Valent P et al: Why the 20% + 2 tryptase formula is a diagnostic gold standard for severe systemic mast cell activation and mast cell activa tion syndrome. Int Arch Allergy Immunol 180:44, 2019. Mariana Castells

Desensitization DRUG ALLERGY AND THE NEED FOR DRUG DESENSITIZATION Drug allergy is a rising problem, paralleling the worldwide increased use of medications, the plethora of new targeted therapies, and the greater longevity of patients. Allergic drug reactions decrease patients' quality of life, limit treatment options, and can lead to vaccine hesi tancy, as seen for the COVID-19 mRNA vaccines. The first cases of reported drug-induced anaphylaxis occurred shortly after the dis

covery and therapeutic applications of penicillin in 1945, and today, 10–20% of the world's population engaged in health care claims to have a penicillin allergy. Truly allergic patients cannot use penicillin and are negatively impacted by the decreased efficacy, increased costs, and limited availability of second-line antibiotics. Similarly, the need to avoid the offending medications in allergic patients with malignancies and chronic inflammatory diseases can increase morbidity and impact life expectancy.

To address the needs of drug-allergic patients, a novel modality of drug delivery aimed at curtailing allergic symptoms has culminated in drug desensitization (DD), a treatment option that takes advantage of immune inhibitory mechanisms. Rapid multistep protocols that deliver sequential small doses of drug until the target therapeutic dose is reached in a few hours have shown outstanding safety, efficacy, and wide applicability in thousands of patients with infections, chronic inflammatory diseases, malignancies, and other conditions. ■ ■DRUG ALLERGY DEFINITIONS AND RISK FACTORS Drug allergy and drug hypersensitivity are interchangeable terms that refer to acute and delayed symptoms occurring after exposure to medications. While there is a need to address drug-allergic patients, those with unconfirmed allergy labels should be dela beled, and single-dose oral challenges have been shown to be safe in children and adults at low risk for penicillin allergy. Drug allergy is multifactorial and associated with female gender, specific human leukocyte antigen (HLA) haplotypes, atopy, polypharmacy, older age, chronic diseases, microbiome changes, and drug-dependent factors such as the route of administration, repeated and high doses, excipients, and glycosylation. ■ ■CLASSIFYING HYPERSENSITIVITY REACTIONS The modern classification of reactions has incorporated timing, sever ity, biomarkers, and new presentations to the classical Gell and Coombs definitions. Acute or immediate reactions occur during or within 1–6 h of drug exposure, while delayed reactions occur 6 h to several days or weeks after drug exposure. Reactions can be mild (affecting one organ; grade 1), moderate (affecting two or more organs; grade 2), or severe (associated with changes in vital signs; grade 3). ■ ■PHENOTYPES, ENDOTYPES, AND BIOMARKERS The symptom presentation (phenotype) depends on the mechanisms of the reactions (endotype). Acute reactions include infusion reactions, type I IgE-dependent and -independent reactions, cytokine release reactions (CRRs), and mixed reactions (type I and CRR symptoms). Delayed reactions include type II antibody-mediated cytotoxicity; type III immune complex–mediated reactions; and type IV reactions, which include benign reactions, typically skin limited, and severe cutaneous reactions with systemic symptoms (SCARS) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized eosinophilic pustulosis (AGEP) (Fig. 365-1). Symptoms are drug specific, and acute musculoskeletal pain is common in reactions to taxanes, oxaliplatin, doxorubicin, and rituximab. Type I Reactions Type I reactions result from the activation of mast cells and basophils through IgE-dependent and -independent mechanisms. While IgE sensitization requires repeated exposures and is typical for antibiotics, chemotherapy, and some biologicals, IgE-independent reactions typically occur at first exposure through either complement activation, inhibition of COX-1, or activation of the MRGPRX2 receptor by quinolones, vancomycin, icatibant, and general anesthetics with THIQ binding motif and by basic compounds. Symp toms of type I reactions include itching, flushing, hives, angioedema, dyspnea, wheezing, oxygen desaturation, throat tightening, nausea, vomiting, and hypotension with cardiovascular collapse and are associ ated with elevated serum tryptase, a specific biomarker of anaphylaxis released from mast cells and basophils granules. Tryptase levels above the normal range (11.4 ng/mL) or above a patient's baseline (× 1.6) obtained within 30 min to 4 h of initial symptoms are diagnostic

of type I and mixed reactions. Patients with baseline levels of 7.5 ng/mL or higher may have duplications of the TPSAB1 tryptase gene located on chromosome 16, known as hereditary alpha tryptasemia (HαT), a familial autosomal dominant trait present in 4–6% of Caucasian populations, which modulates anaphylaxis severity. Other mast cell– derived mediators include urine N-methylhistamine, prostaglandins, and leukotrienes.

Cytokine Release Reactions CRRs can occur at first exposure or after several exposures and are thought to be due to activation of T cells and other immune cells. Patients present with fever; chills; back, chest, or pelvic pain; headache; oxygen desaturation; and hyper- or hypoten sion; these reactions are associated with a transient serum elevation of interleukin (IL) 6.

CHAPTER 365 Mixed Reactions Mixed reactions present with symptoms of type I and CRR reactions and are associated with tryptase and IL-6 elevations (Fig. 365-1). Desensitization Delayed Type IV Reactions Delayed type IV reactions amenable to DD present as benign maculopapular rashes without associated systemic symptoms, whereas SCARS, type II, type III, vasculitis, and single-organ toxic reactions are contraindications for DD because min ute amounts of medication can trigger severe reactions. DIAGNOSTIC TESTING Skin testing (ST) elicits a local wheal-and-flare reaction upon epicuta neous or intradermal injection of drugs inducing IgE-mediated reac tions. Its use is limited by the availability of drug components including excipients, skin toxicity, costs, and the time elapsed since the patient’s initial reaction (the longer the time, the lower the likelihood that an ST will be positive) and the severity of the reaction (anaphylactic reactions can deplete mediators inducing false-negative ST). Positive and nega tive predictive values are drug specific, and anaphylaxis to penicillin or carboplatin has not been reported in ST-negative patients. The basophil activation test (BAT) provides evidence of IgE sensi tization by challenging the patient’s basophils in vitro with the culprit drug, eliminating the need for direct ST, which has a small risk for anaphylaxis. Serum-specific IgE antibodies to penicillin and platins are found in allergic patients with low sensitivity. Skin patch testing is helpful to evaluate β-lactams, anticonvulsants, corticosteroids, and other drugs that cause delayed type IV reactions with high specific but low sensitivity. Lymphocyte transformation tests (LTTs) measure the activation and/or cytokine release of lymphocytes exposed to culprit drugs and can be used to identify drugs inducing SCARS. Certain HLA haplotypes place patients at risk for SCARS when exposed to abacavir, anticonvulsants, allopurinol, vancomycin, and other drugs, and geno typing is available. DRUG DESENSITIZATION ■ ■DEFINITIONS AND MECHANISMS DD is a temporary immunotherapy modality, delivered through multi step protocols to safely and timely reintroduce a drug that has induced an acute or delayed allergic reaction. IgE-mediated desensitization takes advantage of inhibitory mast cell/basophil pathways, which are activated by low doses of drug antigens. Rapid delivery of incremental doses recruit phosphatases to IgE receptors, blocking signal transduc tion and the release of mediators when reaching the target dose and protecting against anaphylaxis. Desensitized patients have transient conversion from positive to negative ST. ■ ■PROTOCOLS Based on inhibitory pathways in mast cell models, human protocols have been generated for type I phenotypes with low starting doses and multiple steps that progress by doubling the dose administered in the previous step at constant time intervals. The first standardized and most used protocol contains three bags of 1/100, 1/10, and undiluted concentrations of the target dose and 12 doubling steps delivered every 15 min so that the target dose is reached in 5.7 h (Fig. 365-2), which has been adapted for IV, PO, SC, IM, intraperitoneal, intraocular, and intrathecal use. Protocols with four bags (starting with a 1/1000 dilution bag) are used for patients with severe initial reactions and associated

comorbidities. The recent use of one-bag protocols for type I reactions has produced mixed outcomes, with an increased use of epinephrine during breakthrough reactions (BTRs) and inability to complete treatments in highly sensitized patients.

Cytokine Release Phenotype Infusion Reaction Type I IgE/non-IgE Type II Type III Mixed Mast cell T cell NK cell Lymphocyte PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Endotype Opsonization Both TNF-α, IL-6, IL-1β TNF-α, IL-6, IL-1β IL-6, IL-1β Histamine, tryptase Biomarkers Both Flushing Pruritus Rash Urticaria Throat tightness Shortness of breath Nausea and/or vomiting Anaphylaxis and cardiovascular collapse Fever, Chills/rigors Nausea Pain Headache Dyspnea Hyper/ hypotension Back pain Fever Chills/rigors Nausea Pain Headache Both Symptoms Indicated Indicated Indicated Indicated Non indicated, regular infusion Desensitization Type IV Severe Cutaneous Adverse Reactions (SCARS); Not Indicated, Avoid Medication Eosinophils Antigen presenting cell Interferon-γ Granzyme B Granulysin Perforin HLA-1 Penicillin hapten-carrier complex TCR Neutrophils CD4+ or CD8+ cell FIGURE 365-1 Drug allergy phenotypes, endotypes, and biomarkers and indications for desensitization. AGEP, acute generalized eosinophilic pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; IL, interleukin; SJS-TEN, Stevens-Johnson syndrome–toxic epidermal necrolysis; TNF, tumor necrosis factor. (From The New England Journal of Medicine, Penicillin Allergy, M Castells, DA Khan et al: 381: 2338. Copyright @2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) The mechanisms of desensitization for other phenotypes are poorly understood, and CRRs have been successfully treated with multistep one-bag protocols, whereas multiple doses over several days have been used for delayed reactions (see specific drugs). Premedications are tailored to the initial symptoms, and steroids do not protect against anaphylaxis. Omalizumab, a monoclonal anti-IgE antibody, has been used as an adjuvant in highly sensitized patients with type I severe IgE-mediated reactions, including life-threatening anaphylaxis. Desensitization is a temporary phenomenon that does not lead to sustained tolerance and must be repeated with each exposure or if there has been a pause between doses equal to two or more half-lives of the drug. However, the desensitized state can be maintained by continued drug exposure as with antibiotics and aspirin/COX-1 inhibitors. Some

Type IV T cell Neutrophil MΦ C3a Antibody dependent cell cytotoxicity C3a C3a Antigen/ antibody complexes T cell Specific antibody or antibody/antigen complex deposition IFN-γ, IL-4, IL-5 Autoimmune Thrombocytopenia Anemia Neutropenia Serum sickness Urticaria vasculitis Arthus reaction Nephritis Fever Delayed maculopapular rash Not indicated, avoid medication Not indicated, avoid medication Clinical Phenotype Interleukin-4 Interleukin-5 Eotaxin DRESS, 2- to 8-week delay: Epidermal edema, fever, lymphadenopathy, eosinophilia, atypical lymphocytosis, and infiltration of skin and internal organs Keratinocyte death SJS–TEN, 4- to 28-day delay: Epidermal necrosis, subepidermal bullae, and involvement of multiple mucous membranes AGEP, 24- to 48-hour delay Fever, neutrophilic leukocytosis, sterile pustules in stratum corneum and epidermis, dermal edema, and infiltration of neutrophils, CD4+ T cells, CD8+ T cells, and some eosinophils Neutrophils home to the skin Interferon-γ CXCL8 GM-CSF patients reactive to taxanes and certain biologicals with uneventful DD protocols may eventually return to regular infusions. INDICATIONS, BREAKTHROUGH REACTIONS, AND OUTCOMES ■ ■INDICATIONS (FIG. 365-2) Qualifications for DD depend on the need of the medication as firstline therapy, the initial reaction phenotype, and its severity. Infusion reactions, mild CRRs, and mild delayed reactions can be addressed by symptoms targeting adjuvant medications. DD is indicated for type I IgE-dependent and IgE-independent,

CRR, mixed, and nonsevere delayed type IV phenotypes. Type I and mixed reactions

BWH desensitization 1/1000 Rate (Ml/h) 2.5 X 15min 5 X 15min 10 X 15min 20 X 15min

A Clinical Vignette 1: Rituximab Rituximab Carboplatin 59–year old, ovarian cancer, six courses of carboplatin and paclitaxel with remission 61-year old, male Marginal zone lymphoma Reaction on 8th lifetime exposure Immediate sweating, flushing, chest pain Infusion stopped and resumed after 10 minutes but symptoms recurred Treated with steroids and infusion discontinued Allergy evaluation for desensitization Change for a second-line treatment? Skin test positive (ID 1 mg/mL) Grade 2 Mixed reaction 3-bag 12-step protocol Premedication: Certirizine 10 mg Aspirin 325 mg Methylprednisolone 40 mg Famotidine 20 mg Acetaminophen 650 mg Montelukast 10 mg Tryptase 10.2 ng/mL (baseline 6.1 ng/mL) Desens # 1: step 12: Flushing, chills,

restlessness Fluids (nl saline 250 mL/h) Fever of 102.4F: Acetaminophen 650 mg

: Meperidine 25 mg IV

: Diphenhydramine 25 mg

: Famotidine 20 mg Complete rest of steps IL-6 >3000 pg/mL (normal, <17.4 pg/mL; baseline <2.9 pg/mL) B FIGURE 365-2 Desensitization: protocols and applications. A. Multibag, multistep intravenous desensitization protocols. B. Rituximab allergic reaction with mixed phenotype, positive skin test, and elevated tryptase and interleukin (IL) 6 biomarkers and successful treatment with a three-bag 12-step protocol. C. Carboplatin allergic reaction with type I phenotype, positive skin test, and elevated tryptase biomarker and successful treatment with a three-bag 12-step protocol. (Reproduced with permission from L Campos et al: Curr Treat Options Allergy 6:519, 2019.)

4-bag 16-step protcol (6.7h) 3-bag 12-step protcol (5.7h) CHAPTER 365 2-bag, 8-step protocol and 1-bag, 4-step protocol Rate (Ml/h) 1/100 Rate (Ml/h) 1/10 Rate (Ml/h) Full dose Desensitization 2.5 X 15min 5 X 15min 10 X 15min 20 X 15min 5 X 15min 10 X 15min 20 X 15min 40 X 15min 10 X 15min 20 X 15min 40 X 15min 80 X 2.9h

Clinical Vignette 2: Carboplatin Two years later, CA125 increase, mass in abdomen, stage 4, restart carboplatin and paclitaxel Second carboplatin: (8th exposure) Itchy hands Third carboplatin: (9th exposure) Flushing Generalized pruritus Shortness of breath Dizziness Hypotension O2 desaturation with syncopal episode Fluids Antihistamines Steroids Epinephrine IM: Tryptase 52 ng/mL (normal level 11.4 ng/mL) Change chemotherapy for a second-line treatment? Allergy evaluation for desensitization ANAPHYLAXIS Positive skin test to carboplatin Epinephrine 3-bag 12-step protocol Grade 3 Type
reaction Tryptase Completed rest of treatment cycle via desensitization to carboplatin C

in patients with multiple exposures to antibiotics, chemotherapeutic drugs, and biologicals indicate IgE sensitization. ST-positive patients require DD for reexposure since the risk for anaphylaxis is high. In patients with mild reactions and negative biomarkers, controlled drug challenges are indicated to assess tolerance. Large clinical series sup port outpatient settings for the majority of DD, which decreases the starting treatment time and costs and improves patients’ experiences.

AND OUTCOMES BTRs are typically mild with symptoms similar to the initial reaction. They occur in 10–30% of protocols and require symptom-specific management including epinephrine for severe reactions. BTRs do not preclude the completion of the DD protocols in 99% of cases, and no deaths due to DD have been reported. Comorbidities such as pregnancy, cystic fibrosis, decreased lung function, cardiac diseases, advanced cancer, beta blocker and/or angiotensin-converting enzyme inhibitor use, and prior severe reactions increase the risk during BTRs (Fig. 365-3). The administration of antibiotics, monoclonal antibod ies, and chemotherapy drugs through DD has shown equal efficacy as for standard administration, with the expected clearance of infec tions, decreased inflammation, and similar cancer responses. Kounis syndrome and takotsubo cardiomyopathy resulting from drug-induced anaphylaxis are contraindications for DD (Fig. 365-3). APPROACH TO SPECIFIC DRUGS ■ ■ANTIBIOTICS Antibiotics can induce all the reactions in Fig. 365-1, but the most common are type I IgE-dependent and type IV non-SCARS reactions, both of which can be addressed by DD. β-Lactams The first description of penicillin desensitization was in a World War II allergic soldier who presented with wheezing and hypotension after penicillin injection and received oral incremental Principles of Drug Desensitization No desensitization; avoid culprit drug Indications/Phenotypes Contraindications Risk Factors • SCARS* (SJS/TEN/DRESS/AGEP) • Organ specific toxicity • Cytopenias • Serum sickness • Vasculitis • Kounis and Tako Tsubo • Severe reactions • Pregnancy • Pulmonary diseases • Acute cardiac diseases • β-blockers • ACE inhibitors • Atopy • HLA haplotypes • Female gender • Polypharmacy • Advanced age • Alpha-Gal syndrome • Type 1 lgE/non-lgE • Cytokine release reaction (CRR) • Mixed reaction • Type IV +Severe cutaneous adverse reaction ‡‡Non-steroidal anti-inflammatory drugs ^Cystic fibrosis transmembrane conductance regulator potentiator FIGURE 365-3 Principles of drug desensitization: Indications, contraindications, risk factors, and drugs with successful desensitizations. ACE, angiotensin-converting enzyme; AGEP, acute generalized eosinophilic pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; SJS-TEN, Stevens-Johnson syndrome–toxic epidermal necrolysis.

doses over 30 days until he was able to tolerate a treatment course. The initial success led to shorter protocols to treat patients with bacterial endocarditis and pregnant women with syphilis who had a history of penicillin-induced anaphylaxis and positive ST. Safe rapid PO and IV desensitization protocols are currently available for all antibiotic classes and can treat high-risk patients, including cystic fibrosis patients with low pulmonary function. Sulfonamides Delayed type IV rashes to trimethoprim-

sulfamethoxazole occurred in up to 40% of patients with <100 total CD4 T cells/μL during the early 1990s HIV/AIDS epidemic, and DD included incremental doses over multiple days. Reactions have decreased since retroviral treatments, and shorter protocols have evolved. One-day PO and IV multidose protocols have shown consis tent safety and efficacy for delayed reactions in non-HIV patients. ■ ■CHEMOTHERAPY Taxanes Over 40% of patients exposed to paclitaxel and docetaxel presented with acute reactions, which have been reduced to 1% by antihistamine and corticosteroid premedication. Moderate to severe reactions attributed to lipid excipients (Cremophor and polysorbate 80) and to IgE sensitization through cross-reactive foods and envi ronmental allergens occur typically at first or second exposure with type I, mixed, and delayed phenotypes. Patients with delayed rashes can convert to acute reactions including anaphylaxis

upon subsequent exposures. The first DD to paclitaxel was reported in 2002, and an early study of 940 DDs to paclitaxel and docetaxel in 138 patients described BTRs in 20% of cases, and 22% of desensitized patients returning to standard infusions. A review of 25 studies with 976 patients and 2396 DDs to paclitaxel and docetaxel, completed in 95–100% of cases, the majority with three-bag 12-step protocols, showed 32% paclitaxel and 20% docetaxel mild BTRs and no deaths. Platinums Platinum drug (carboplatin, cisplatin, and oxaliplatin) IgE sensitization requires multiple exposures (typically six or more; Desensitization Drug Formulation • Platins: carboplatin, cisplatin, oxaliplatin • Taxanes: paclitaxel, docetaxel, cabazitaxel, nab-paclitaxel • Monoclonals: rituximab, cetuximab, tocilizumab, bevacizumab, ofatumumab, alemtuzumab, pertuzumab, nivolumab; sacituzumab, etanercept, adalimumab, infliximab, ustekinumab, vedolizumab, tezepelumab, golimumab, daratumumab, ocrelizumab, obinutuzumab, trastuzumab, margetuximab, pembrolizumab • Antibiotics: β-lactams, cephalosporins, sulfonamides, quinolones, macrolides, vancomycin, aminoglycosides, doxycycline, rifampin, metronidazole • CFTCRP^: elexacaftor/tezacaftor/ivacaftor • Enzymes: laronidase, elosulfase alfa, galsulfase, alglucosidease alfa, imiglucerase, taliglucerase alfa, sebelipase alfa, idursulfase • Iron: sodium ferric gluconate, ferumoxytol, iron sucrose, iron dextran • NSAIDS‡‡: aspirin, naproxen • Hormones: progesterone, aromatase inhibitor, letrozole • Small molecules: lenalidomide, imatinib, osimertinib, olaparib

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