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A Practical Approach to Demystifying Drug Allergy in the Intensive Care Unit. A Review Article

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Abstract

Drug hypersensitivity reaction (DHR) is defined as an immunologically mediated response to a pharmacology agent. Some reactions require prior sensitization and some do not. The interactions between different drugs and the immune system occur by different mechanisms leading to variable clinical features. Some reactions are simple and do not alter patient quality of life. Some are life threatening and require immediate recognition and appropriate therapy. Confirming the diagnosis of DHR is often challenging. The environment in the Intensive care units (ICU) is considered high risk place for DHR development as it offers most of the risk factors. In this review, we offer a delicate combined approach that allows an accurate diagnosis of most of the DHRs encountered in the ICU.

1. Introduction

Adverse drug reactions are one of the leading causes of morbidity and mortality in healthcare. The cost of drug-related morbidity and mortality in the USA alone has been estimated to be US$136 billion annually, which is more than the total cost of cardiovascular or diabetic care [1].

DHR is defined as an immunologically mediated response to a pharmaceutical

or formulation (excipient) agent in a sensitized person [2]. An allergic reaction is induced by pre-existing Ig-E antibodies against an epitope within that drug or within one of its metabolites. Obviously not all drug reactions are Ig-E mediated. DHR is a broader term and it involves reactions that mount a cascade of immune response with or without Ig-E pathways and involves T cell activations. However, these two terms have been used in the literature interchangeably

The most common signs and symptoms of DHR are hives, rash or fever. DHR however, may cause serious reactions, including anaphylaxis and death. DHR is different than drug side effects, which are defined as known possible reactions that are listed on the drug label. DHR is also distinct from drug toxicity caused which is caused by drug overdose.

The incidence of all adverse drug reactions is estimated to be 15% of all hospitalized patients. DHR constitutes about 5% of all these reactions. Antibiotics are the most frequent cause of these reactions [3]. Risk factors for developing DHR are host or drug related (Table 1). It is obvious that ICU environment provides most of these factors [4].

The presence of atopy is not considered a risk factor for DHR except for Penicillin anaphylaxis [5] and allergic reactions induced by Latex and Radio Contrast Media (RCM).

Once suspected, offending drug should be discontinued immediately. Drug desensitization protocols are available and should be used in cases where a specific medication cannot be substituted. In the event of anaphylaxis, the treatment of choice is injectable epinephrine and circulation support. Other treatment modalities may include systemic steroids, antihistamines, broad spectrum antibiotics, and treatment in burns units.

2. Aim and Objective

The purpose of this review article is to describe different syndromes of DHR that might be encountered while treating patients in the ICU. Some of the reactions are simple and self-limited, however others are life threatening and require immediate recognition and cessation of the culprit drug.

3. Classification of Drug Allergy

DHRs are clinically and functionally heterogeneous. Different sub-classifications

Table 1. Identified risk factors for developing DHRs.

Drug related	Host related
High dose	Female gender
Parenteral administration	Age (less frequent in infants and elderly)
Large molecular weight agent	Diseases requiring repeated courses of therapy (such as cystic fibrosis)
Concomitant use of other medications	Genetics (specific HLA types)
Repetitive courses of the same medication.	

based on timing of symptoms appearance or type of immune mechanisms have been proposed and been used by many practitioners. **Figure 1** is a depiction for different proposed ways that are used in classifying different types of DHR.

3.1. Timing

Based on The World Allergy Organization classification of DHRs, time elapsed till symptoms appear is the simplest, useful and widely accepted way of differentiating DHRs [6]. Acute DHR are usually caused by either antigen-specific preformed Ig-E antibodies or by direct degranulation of mast cells. Anaphylaxis, urticaria, and asthma attack are manifestations of immediate DHR. Delayed reactions are usually due to T cell immune response and give rise to syndromes like severe cutaneous skin reactions and eczema.

3.2. Pharmacology Phenotypes

As per the World Health Organization, drug reactions are classified into two categories based on their pharmacology features: type A and type B [6] [7] (**Table 2**). It is important to realize that drug allergic/immunologic reactions lie within the B type.

3.3. Immunopathology

In early 1968 Gell and Coombs have classified drug allergies and their diseases into four different types [8]. Immediate reaction (type 1) is mediated by
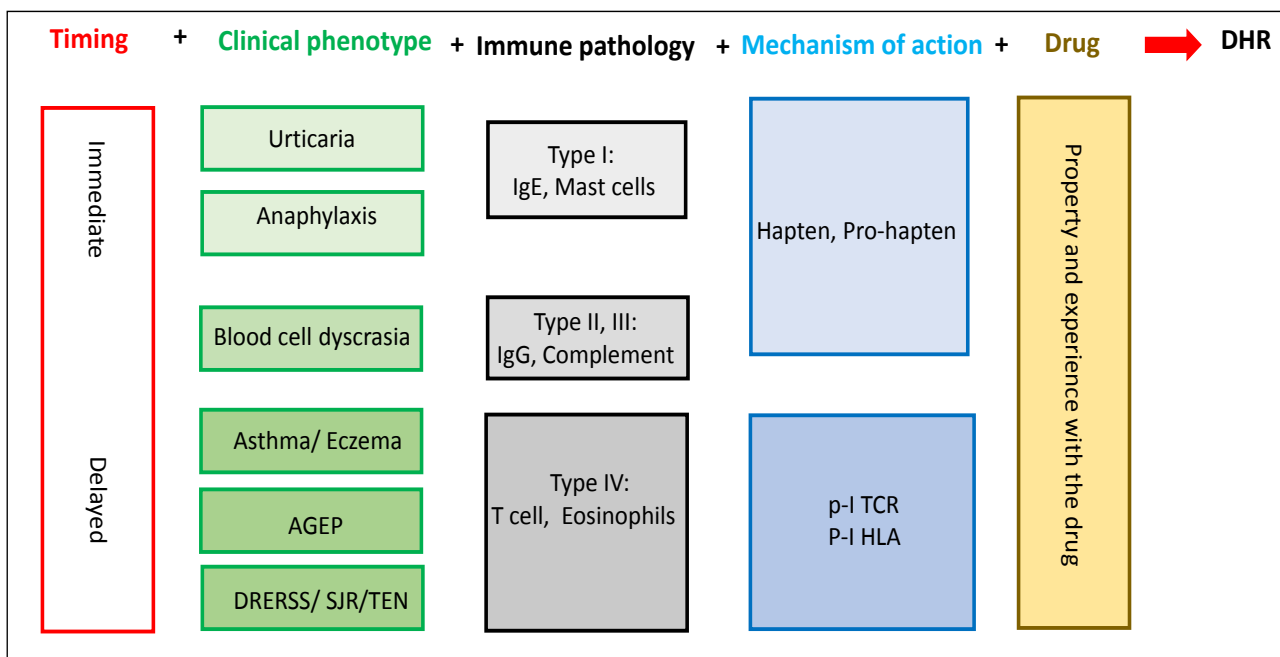
Figure 1. A simple combined approach for differentiating DHR sub-classifications. The first column shows that timing of DHR occurrence can be immediate or delayed. Clinical phenotypes in the second column include many syndromes that range from urticaria to severe skin reaction. The corresponding immune reactions and mechanisms are contained in the third and fourth columns. The last column is designated for any known reaction that is reported to be linked to a particular drug.

drug-specific Ig-E antibodies and mainly causes urticaria or anaphylaxis. The symptoms normally occur within less than 1 hour after drug administration. Immunoglobulin-mediated cytotoxic reaction is called type 2 and it concerns mainly blood cell dyscrasia. Type III reaction is immune-complex mediated, and it is the basic mechanism behind vasculitis. Finally, type IV reactions are mediated by T lymphocytes. Since T cell stimulation and migration to the tissues takes more times, Type IV presentation is usually delayed [7].

Table 3 shows all those types of DHR with the involved cellular elements [7].

Table 2. Adverse drug reactions are sub-classified as type A and B reactions. Type B reactions correspond to DHR.

Type A reaction	Type B reaction
Predictable	Unpredictable
Common, rational	less common, bizarre, not rational
Related to drug pharmacologic actions	Related to individual susceptibility.
Dose dependent	Not dose dependent
Examples: • Toxicity: renal failure from aminoglycosides. • Side effect: sedation from antihistamines. • Secondary effect: diarrhea from antibiotics. • Drug-drug Interaction: theophylline toxicity from concomitant erythromycin	Examples: • Intolerance: tinnitus from Aspirin • Idiosyncratic reaction: hemolysis from Dapsone in G6PD deficiency. • DHR: anaphylaxis from penicillin. • Pseudo allergic anaphylaxis due to radio contrast media.

Table 3. DHR classification based on Gell & Coombs.

	Immune reaction	Effector cells	Examples
Type I	Ig-E	Mast cells	Acute Asthma, Acute Allergic Rhinitis, Anaphylaxis
Type II	Ig-G	Phagocytes Natural Killer cells	Hemolysis
Type III	Ig-G	Complement	Serum Sickness, Drug Fever
Type IV			
Type IV a	IFNγ, TNFα	Macrophages T_H1 cells	Tuberculin Reaction, Contact Dermatitis, Eczema
Type IV b	IL-5, IL-4/IL-13	Eosinophils T_H2 cells	Chronic Asthma, Chronic Allergic rhinitis
Type IV c	Perforin/GranzymeB	T cells	Contact Dermatitis, Maculopapular or Bullous Exanthem, Hepatitis
Type IV d	CXCL-8. GM-CSF, IL-17	Neutrophils T cells	AGEP, TEN, SJS, Behçet Disease

3.4. Mechanisms

Based on how the drug first came in contact with the immune system, two mechanisms can be delineated (Figure 2).

3.4.1. Hapten and Pro-Hapten Hypothesis

In this mechanism, the drug is not able to elicit a specific immune reaction unless it is covalently bound to a self-protein such as albumin (Hapten theory). Sometimes the reaction occurs when some of the drug metabolites is bound to a self-protein (Pro-Hapten theory).

The covalent binding creates a new complex that could elicit innate and adaptive immune responses.

A classic example of the Hapten hypothesis is Penicillin (PCN) [9]. Sulfamethoxazole is a large molecule that has to be metabolized first to one of its constituents (Sulfamethoxazole-Nitroso) before it could trigger a DHR [10].

3.4.2. Pharmacologic-Interaction (P-I) Hypothesis

In this interaction, the drug is small enough to fit into some of the immune system cell receptors without the need for a covalent binding to self-protein. In this theory, the drug is bound to T-cell receptors (TCL) or Human Leukocyte Antigen (HLA) in a non-covalent fashion. This bond does not involve any engagement into the immunogenic peptides presented by HLA, and therefore the drug is not considered an antigen agent [11] [12].

In the P-I theory this new altered TCR-drug molecule (or HLA-drug molecule) activates the involved T cell and mount a DHR (Figure 2). Unlike Hapten
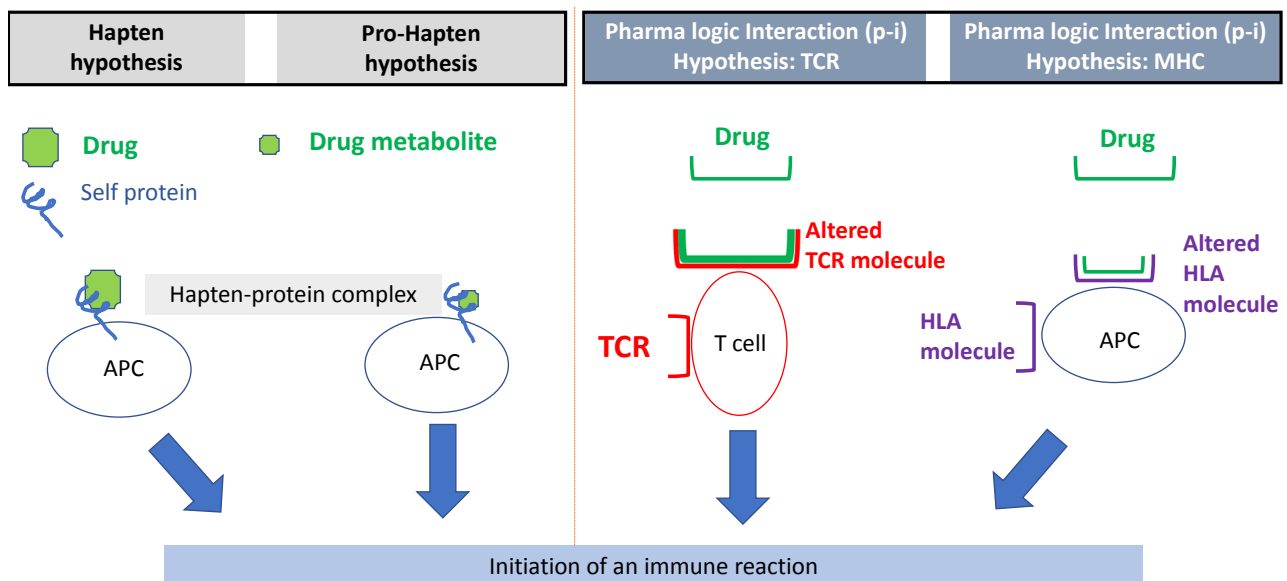

Figure 2. Drug and immune system interactions. The left side shows how small drug or its metabolites(in green) can be attached to a self-protein (in blue) and form a Drug-Protein Complex which in turn attaches itself to an antigen presenting cell (APC) and stimulate an immune reaction. The right side of the figure illustrates the P-i hypothesis. A drug (in green) is able to attach itself to a specific T cell receptor molecule TCR (in purple) or to a specific Human Leukocyte Antigen HLA molecule (in red). The surface of either molecules (TCR or HLA) is altered and could lead therefore to an immune reaction resulting in DHR.

theory, P-i based DHR does not lead to stimulation of B-cells (like IgE and IgG), but rather T-cell stimulation. Once T-cell is activated, significant number of different cytokines are released and different cytotoxic reactions occur and lead to different DHRs. This reaction occurs usually late and symptoms typically appear 7 days after the initiation of the culprit agent. This delay is explained by the time needed for the T-cell expansion and migration to the involved tissues. This is unlike the hapten based reaction that takes place usually much earlier. Clinical features related to the p-i reactions are maculopapular eruptions, acute generalized exanthematous pustulosis (AGEP) [12], drug-induced liver injury [13], Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) [14] [15], and drug reaction with eosinophilia and systemic symptoms (DRESS) [16].

The P-i reaction is specific, and affects only certain individuals who carries certain types of HLA or TCR [11] [17].

Examples for such genetic association is carbamazepine-induced Stevens-Johnson in individual with HLA-B*1502 alleles [18], and Abacavir hypersensitivity in individual with HLA-B*5701 alleles [19].

The strong MHC associated drug hypersensitivity reactions are nowadays interesting examples of personalized medicine. Commercial kits are available in order to detect susceptible HLA types to avoid using any drug that is linked to a severe DHR in that particular HLA (HLA-B*5701 for Abacavir and HLA-B*1502 typing in Han Chinese) [20] (Table 4).

4. Clinical Features

Hives, rash, and fever represent the most common clinical features of DHRs. Certain clinical syndromes have been reported due to certain medications and vice versa (Table 5). On the other hand, certain drugs are reported to cause certain types of DHRs (Table 6). Most of the DHRs seen in the ICU are described

Table 4. Genetic association with particular drugs among different ethnic groups.

Drug	Allele	Ethnic association	Drug reaction type	Availability of Genetic screening
Carbamazepine	HLA-B 15:02	Han Chinese	SJS	Yes
Carbamazepine	HAL-A 31:01	European	SJS	No
Allopurinol	HLA-B 58:01	Han Chinese, European, Japanese	SCAR	No
Abacavir	HLA-B57:01	Multiple	Abacavir hypersensitivity syndrome	Yes
Dapsone	HLA-B13:01	Asian	Dapsone Hypersensitivity Syndrome	No
Hydralazine	HLA-DRw4	None identified	SLE	No

Table 5. Examples of some clinical syndromes caused by specific drugs. PCN: Penicillin. IVIG: Intravenous Immune Globulin. NSAID: Non-Steroidal Anti-Inflammatory Drugs.

Drug Reaction	Clinical Features	Examples
Hematologic	Hemolytic anemia, Thrombocytopenia, Granulocytopenia	PCN, Quinine, Sulfa
Hepatic	Hepatitis, Cholestatic jaundice	Sulfanamides, Aminosalacylic Acid
Pulmonary	Pneumonitis, Lung Fibrosis	Nitrofurantoin, Blemomycin, Methotrexate
Renal	Interstitial Nephritis, Glomerulonephritis	PCN, Sulfa, Allopurinol
Vascular	Vasculitis, SLE	Hydralazine, Procainamide, Isoniazid
CNS	Meningitis	NSAID, IVIG

Table 6. Examples of specific drugs causing specific clinical DHR.

Drug	Reported clinical reactions
Amiodarone	Pneumonitis, Bronchiolitis Obliterans, ARDS
Methotrexate	Acute Granulomatous Interstitial Lung Disease
Chemotherapeutics: Bleomycin, Mitomycin-C, Busulfan, Cyclophosphamide	Interstitial Lung Disease
Nitrofurantoin	Pleural effusion, Pneumonitis, Fibrosis

in the following paragraphs.

4.1. Simple Skin Drug Reactions [21]

Cutaneous reactions account for approximately 2% to 3% of all adverse drug reactions. Most skin drug eruptions are benign and simple such as simple exanthemas (46%), urticaria (23%), fixed drug eruptions (10%), and erythema multiform (5.4%).

It usually develops days after drug administration. It is typically described as maculopapula rash, however drug induced blistering and bullous reactions have been described with some medications (Figure 3). Some drugs are known to cause a fixed drug eruption which characteristically recurs in the same site or sites each time a particular drug is taken (Figure 4).

4.2. Drug Fever [22]

Drug fever is a febrile response that coincides temporally with the administration of a drug (within 7 - 10 days) and disappears rapidly after its discontinuation. The fever however could recur as early as few hours if the same medication is administered again (Re-challenge). This might be considered a confirming diagnostic tool. Drug fever might proceed some more severe reactions, and re-challenge may be potentially very harmful [22].
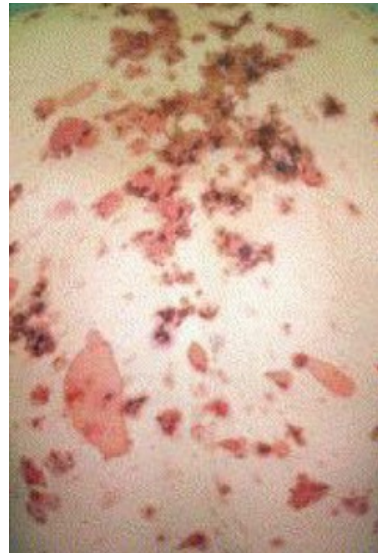
Figure 3. Skin blistering caused by Angiotensin converting enzymes inhibitors (ACE-I).

Figure 4. Fixed drug reaction from Vancomycin.

Failure to recognize drug related fever often has undesired consequences including extra testing, unnecessary therapy, and longer hospital stay.

4.3. Serum Sickness Reaction (SSR)

SSR is an example of type III hypersensitivity reaction (see above). The major clinical features of SSR include: fever, facial puffiness, malaise, lymphadenopathy, arthralgia, and rash. However renal failure, gastrointestinal bleeding, and neurological complications are life-threatening syndromes that might evolve and progress into mortality [23].

SSR typically occurs 1 - 3 weeks after the drug administration, therefore one may forget the name of the used drug. This might make it difficult to detect the culprit medication.

The erythematous rash is usually Urticarial in nature, followed by bruise-like changes, and is associated with intense pruritus (**Figure 5**).

Figure 5. Skin rash due to SSR in patient received Ciprofloxacin.

Serum sickness is typically self-limited and resolves within days once the medication is stopped. The prognosis without internal organ involvement is good.

SSR has been classically described with the use of Antivenins, Streptokinase, Vaccines (Tetanus Antitoxin), Polyclonal Antibodies, Cephalosporin, Ciprofloxacin, Metronidazole, Penicillin, Streptomycin, Sulfonamides, and Tetracycline. More recently several monoclonal antibodies (such as Infliximab, Omalizumab, and Rituximab) have been reported also to cause serum sickness-like syndrome [24] [25] [26].

Removal of the offending agent is usually enough for the reaction to abate. Some case reports have shown that antihistamines and steroids may shorten the duration of the disease. The drug be avoided in the future. Desensitization is not recommended (some exceptions are reported [27]).

4.4. Severe Cutaneous Adverse Reactions (SCAR) [28]

As we mentioned above, most skin drug eruptions are benign, but a in small percentage the DHRs could be extremely dangerous. We describe herein three major severe cutaneous adverse reactions that could be seen in the ICU.

4.4.1. Drug Rash Eosinophilia Systemic Symptoms (DRESS)
It is also called Drug-induced hypersensitivity syndrome (DIHS). It is a distinct, severe, idiosyncratic reaction to certain drugs. It is characterized by a prolonged latency period, then followed by a variety of clinical manifestations including: fever, rash, lymphadenopathy, and eosinophilia. A wide range of mild to severe systemic presentations have been reported [29].

The most important clinical feature of DRESS is the rash. The rash is described as exanthema, erythema multiform, or purpura like (**Figure 6**). The rash could evolve into more blistering or necrotic eruptions. DRESS may evolve into hypotension (up to 40% in all cases), pancytopenia, liver failure (in more than 60%), renal failure (in 30%), myocarditis, pericarditis and eosinophilic pneumonitis [30]. Facial edema can be seen in 25% of the cases, and it may be mistaken for angioedema, and it can be general.

DRESS reaction occurs 2 - 8 weeks after starting the culprit drug. The symptoms may even worsen after the drug discontinuation.

Common drugs that are reported to cause this syndrome include: anticonvulsants, antibiotics, antiviral (Abacavir), antihypertensive (Amlodipine, Captopril) and biologics (Imatinib) [31].

The Pathogenesis of DRESS is not well understood. reactivation of chronic persistent viruses such as human herpes virus family (HHV), CMV and EBV have been suggested [32].

Re-challenge with the suspected drug cannot be done as this may lead to life threatening consequences. The diagnosis then has to be clinically based [33].

The treatment includes prompt recognition, discontinuation of the culprit medication and relatively long course of corticosteroids. Other immune suppressive agents such as Cyclosporine have been used [34]. Prognosis depends on how early the syndrome is recognized and how quickly the causative agent is withdrawn.

4.4.2. Acute Generalized Eczematous Pustulosis (AGEP)

This disease is distinct by its rash. It is characterized by areas of red skin with small sterile pustules filled with white or yellow fluid (Figure 7).

AGEP may be associated with fever and malaise, but the patient does not particularly feel unwell. The rash may last 1 - 2 weeks. Eventually the skin peels off. The presentation could be unusual with mucous membrane involvement (20% of cases).

Figure 6. Rash due to DRESS caused by phenytoin.

Figure 7. Distinct skin pustules due to AGEP caused by Meropenem.

Other but rare systemic manifestations may include renal failure, hyperthermia, and hemodynamic instability. Lethality in AGEP is ~1% for older patients [35].

While drugs are the usual cause of AGEP (in more than 90% of cases), it may also be caused by contact sensitivity to some chemical like mercury. AGEP could also be elicited by viral infections.

Antimicrobials, antiepileptic agents, calcium channel blockers, NSAIDS, herbal medications and corticosteroids have all been reported to cause AGEP [36].

The treatment is supportive and includes: withdrawal of the offending medication, anti-pyretic, intravenous fluid, hospitalization and nutritional support. Sometimes topical or systemic corticosteroids are needed. The Prognosis of AGEP is usually very good with complete resolution of the rash in most of the cases.

4.4.3. Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

This syndrome is the most severe skin manifestation of DHR. Both reactions (SJS and TEN) are thought to represent a spectrum of a single reaction [37]. The percentage of skin involvement defines the difference between SJS (less than 10%) and TEN (more than 30%). The syndrome consists of a triad of mucous membrane erosions (mouth, eye, urethra and vagina), skin target lesions, and epidermal necrosis with detachment (Figure 8).

This particular SCAR does usually cause multi-organ involvements with gastro intestinal bleeding, hepatic abnormalities, pulmonary hemorrhage and renal failure. Sloughing of mucosal membranes can result in significant fluid loss, hypovolemia, acute renal tubular necrosis, and shock. Mortality for SJS is less than 5%, whereas it is 10% - 50% for TEN [38].

As explained in p-i mechanism, a genetic prediction toward the development of this syndrome has been reported for some drugs with certain HLA alleles [39]. Common drugs include: Antimicrobials (Sulfa, Macrolides, Erythromycin, PCN, and Ciprofloxacin), Anticonvulsants (Phenytoin, Phenobarbital, Carbamazepine, Valporic Acid, and Lamotrigine), Sertraline, Allopurinol, Tramadol and NSAID's.
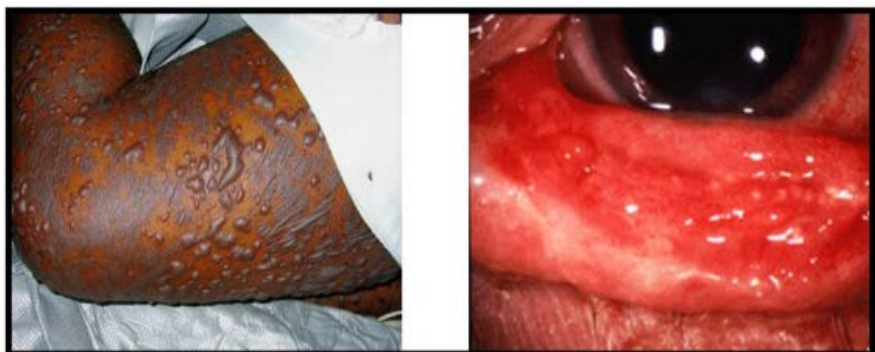

Figure 8. Mucocutaneous lesions due to TEN caused by Sulfamethoxazole.

The treatment is supportive. Most of the time the patient is admitted to the ICU or Burn Units. The use of IVIG (in higher dose and longer duration than usual) has been reported to be beneficial) (0.75 to 2 mg per kg per day for three to five days then lower dose for 12 days) [40]. Glucocorticoids however are contraindicated.

5. Specific Drugs and DHR

5.1. Penicillin Allergy

B-lactams Antibiotics are probably the most common antibiotics used in the ICU. Skin testing is the most rapid, sensitive, and cost-effective test modality for evaluating patients with immediate allergic reaction to Penicillin (PCN) and its related drugs. PCN skin testing is contraindicated in patients with chronic urticaria and severe dermatographism. It should not be performed as well If the history of PCN allergic reaction involves severe skin blistering such as TEN [41].

Negative predictive value for PCN skin test for anaphylaxis reaction with no suggestive past history for such a reaction is close to 100% [42].

It is worth to note that 90% of patients with a history of PCN allergy will tolerate PCN (the history is either inaccurate or the reaction is too remote and faded away). 80% of PCN allergic patients will lose their PCN specific Ig-E antibodies after 10 years. This means that remote history of allergic reaction carries less clinical significance.

Regarding PCN and Carbapenem cross reactivity, it is really important to realize that true cross reactivity is not 10% as usually taught in medical rounds. Most of the studies that quoted that number were remote and used older forms of the medication. In addition, cross contamination during preparation was a major concern in those studies. It is safe to state that clinical cross-reactivity is variable but much lower than older reports (may be 1%).

It is known that Aztreonam (Monobactam) does not cross-react with other beta-lactams except for Ceftazidime as both medications share an identical R-group side chain [43]. Table 7 highlights the most important recommendation in managing cases of PCN allergy.

Most of PCN allergy is due to a reaction toward to the B-lactam ring. B-lactam ring is shared between all PCN's, Cephalosporins, and Monobactam antibiotics. Some patients, however, have Ig-E antibodies directed at the R-group side chain. This type of allergy is frequently found in Europe but it is rare in the U.S. In this case PCN skin tests will be negative (as the testing materials are B-lactam ring derivatives). Table 8 shows examples of the B-lactams that share the same R chain.

5.2. Cephalosporin Allergy [44]

DHR to Cephalosporin is pointed against the R side group rather than the B lactam ring. Therefore, PCN skin testing per se is not predictive for Cephalosporin allergy (only 2% of penicillin skin test-positive patients reacts to treatment with

Table 7. General recommendations regarding Penicillin allergic reactions.

History of PCN allergic reaction
If there is no good suggestive history for PCN allergy, or the history of the reaction is remote, we advise to give the PCN (or its derivatives).
If the history is suggestive for non-anaphylactic reaction to PCN we recommend to perform the commercially available PCN skin test: • If the test is negative, give the PCN. • If the test is positive perform graded challenge (see below).
If the history is suggestive for non-anaphylactic DHR and PCN skin test is not available, we would also recommend performing PCN graded challenge.
If the history is confirmative for anaphylaxis, an alternative drug is recommended. If the PCN is absolute, then performing PCN desensitization is recommended (see below).
Graded challenge (also called provocation challenge): give 1/1000th to 1/10th of the therapeutic dose in a 30 minutes' interval till reach the recommended dose. **Desensitization** refers to a process of giving a medication in a controlled and gradual manner, which allows the person to tolerate it temporarily without an allergic reaction. Several protocols are available for certain medications.

Table 8. Examples of the B-lactams that share the same R side chain. Antibiotics in each column share the same R1 or R2 chains. Antibiotics in each group should not be substituted one for another.

Groups of B-lactam Antibiotics that share identical R1-Group side chains					
Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Ceftazidime	Cefamandole
Cefadroxil	Cefaclor	Cefotaxime	Cephalothin	Aztreonam	Cefonicid
Cefprozil	Cephalexin	Cefpodoxime	Cephaloridine		
Ceftazidime	Cephradine	Ceftizoxime			
Groups of B-lactam Antibiotics that share identical R2-Group side chains					
Cepphalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefmetazole	Loracarbef	Ceftizoxime
Cephradine	Cephaprin		Cefpiramide		

cephalosporin). Patients with a history of non-severe reaction to penicillin rarely react to cephalosporin [45]. Patients who are allergic to a Cephalosporin should avoid all Cephalosporins that share similar R-group side chains. As stated above; most of older studies of cross-reactivity among beta-lactam antibiotics have overestimated the risk due to multiple factors.

It important to know that skin test for cephalosporin is not commercially available. Some physicians use the pharmacy preparations of the product for prick testing. These preparations are usually irritating, carry lots of false positive results, and generally not recommended. Table 9 outlines the general recommendations regarding Cephalosporins allergic reactions.

5.3. Sulfonamide Allergy [46]

A sulfonamide is any compound that contains a sulfonamide (SO_2NH_2) moiety. Sulfa allergy is usually manifested by a delayed maculopapular eruption. It can

Table 9. General recommendations regarding Cephalosporins allergic reactions.

Cephalosporin allergic reaction
If there is no good previous history for PCN or Cephalosporin allergies, give the Cephalosporin.
If the history is suggestive for non-anaphylactic reaction to PCN or Cephalosporin, perform Cephalosporin graded challenge.
If the history is confirmative for anaphylaxis to PCN or Cephalosporin, use an alternative or perform Cephalosporin desensitization.
Graded challenge (provocation challenge): give 1/1000th to 1/10th of the therapeutic dose in a 30 minutes' interval till reach the recommended dose.   **Desensitization** refers to a process of giving a medication in a controlled and gradual manner, which allows the person to tolerate it temporarily without an allergic reaction. Several protocols are available for certain medications.

however, cause any of the SCAR's mentioned above. Sulfonamide antimicrobial drugs are different from other sulfonamide-containing medications (Furosemide, Thiazide diuretics) by an aromatic amine at the N4 position and a substituted ring at the N1 position. Therefore, there is no Cross-Reactivity between Sulfonamide antibiotics and Sulfonamide Non-antibiotics (Furosemide) [47]. Sulfa tolerance protocol (desensitization) is available for sulfa induced type I reaction (Ig-E mediated) [48]. Desensitization however is contraindicated with sulfa induced SCAR.

5.4. Vancomycin Allergy

Vancomycin is used very frequently in the ICU and it could cause three kinds of reactions. Red Man syndrome is characterized by Pruritus, flushing and erythroderma. It is due to non-specific release of histamine, and it does not usually evolve into anaphylaxis. Treatment would be premedication with H1-antagonists and slow administration of the drug [49]. Vancomycin is famous in causing fixed drug reactions as explained above, and the medication probably should be avoided if possible. Finally, like any other drugs, Ig-E mediated Anaphylaxis has been reported with Vancomycin. Like many medications, desensitization protocol is available for patients who has history of Vancomycin induced anaphylaxis and the medicine cannot be substituted [50].

5.5. Perioperative Allergic Reactions

Ig-E mediated or direct mast cell activation is usually the cause for this kind of DHR. The reaction varies from simple hives to full anaphylaxis. Among these medications, Quaternary Ammonium muscle relaxants are the most common particularly in females. Antibiotics, Latex, Barbiturates, Opiates, Propofol, Colloids, Antiseptics, Albumin, and many other medications all have been reported to cause some kind of allergic reaction peri-operatively. Prompt recognition is very important so appropriate management is not delayed [51].

5.6. Local Anesthetics Allergy

Local anesthetic is used widely in the ICU. Most adverse reactions are due to non-allergic factors such as vasovagal and anxiety. There are two groups of local anesthetics. Each group has several anesthetics that cross react to each other. Group 1 is the Benzoic Acid Esters group and includes Procaine and Benzocaine. Group 2 is the Amides group and includes lidocaine, Bupivacaine, and Mepivacaine. If one anesthetic from one group is known to cause a DHR, then one should not use any anesthetic from the same group (cross-reactivity). Graded challenge is the test of choice for evaluating potential local anesthetic allergy. Skin prick testing however, carries high false positive rate and is not useful [52].

5.7. Chemotherapeutic Agents Related Allergies

Chemo therapy drugs have been linked to multiple drug reactions particularly anaphylaxis and anaphylactoid reactions. The rate varies among these medications [53]. Desensitization protocol is highly successful for severe cases. Premedication with steroids and anti-histamine has been very helpful as prophylaxis [54].

5.8. Radio-Contrast Media (RCM) Reactions

The immediate reaction that can be encountered from administration of RCM occurs usually in less than 1 hour [55]. The mechanism is due to direct mast cell and complement activation rather than Ig-E antibodies. The clinical features include: hives, Urticaria, and life-threatening anaphylaxis. Delayed reactions occur after 1 hour to 7 days after contrast administration. As mentioned above this delayed reaction is mainly due to T cell activation through p-i hypothesis. Contrast-induced acute kidney injury is actually a type A adverse complication and is not considered DHR.

A history of previous RCM allergy is considered the most significant risk factor for developing a future reaction. Female gender, young and old age, and history of asthma are all risk factors. Shellfish and sea food allergy however are not risk factors as commonly thought. The allergy for fish and shellfish are usually toward a major protein called Tropomyosin. Iodine is not considered an allergen by all means (iodine is a biological element needed for thyroxin hormone synthesis) [56].

As contrast media have evolved from ionic, high-osmolality to nonionic, low-osmolality formulations the number of DHRs due to RCM is decreasing [57].

Pre-medication with anti-histamine and steroids are considered very effective prophylactic measures (Prednisone 50 mg: 13, 7 and 1 hours prior to the RCM administration).

5.9. Allergy to Aspirin and NSAID

Aspirin and NSAID allergies could cause symptoms that range from mild to se-

vere [58]. Reactions may include hives, allergic rhinitis, swelling lips, asthma like reaction, and anaphylaxis. Desensitization protocols have been used to prevent such reaction in patients who are required to take Aspirin [59].

5.10. Adverse Reactions to Biologics

Biologic agents are important therapeutic tools and their use has rapidly expanded in oncology, immunology, and inflammatory diseases. Following their increased utilization, hypersensitivity reactions linked to these drugs have become more frequent, sometimes preventing the use of first-line therapies. The clinical presentation of hypersensitivity reactions to biologics ranges from mild cutaneous manifestations to life-threatening reactions and some agents are linked to cytokine release syndrome. In this scenario, rapid desensitization is a groundbreaking procedure that enables selected patients to receive the full treatment dose in a safe way, in spite of their immediate hypersensitivity reaction to the drug, and protects them against anaphylaxis. It is best to carefully review the safety profile of each biological agent before using it [60].

6. Summary

In summary, drug reaction is not always due to drug allergy, and it demands detailed past medical history. We suggest a combined approach to distinguish the different sub-forms of DHRs. This approach uses timing of symptoms, clinical phenotypes, mechanisms of the immune responses. Previous and known experience of a drug is also a important (**Figure 1**). Immunological tests such as drug skin tests or in vitro serological tests may be required.

If the type of DHR is confirmed, recommendations including supportive care, drug avoidance, use of alternative drug, and other management modalities are implemented. The concept of cross reactivity should be considered before prescribing substituting drugs. Desensitization protocols are available for high-risk drug reaction when true allergy is expected. Performing tolerance protocols (graded challenge) in some reactions such as in SCAR are contraindicated, as this could lead to severe relapse and even mortality. And finally, physicians should be familiar with cross reactivity concepts when choosing alternatives.

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