Drug allergy: diagnosis and management

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Summary

Drug allergy is one of the most commonly encountered medical problems in family practice. The symptoms may range from trivial to life-threatening. As drug use continues to increase, the incidence of drug allergies will also continue to rise. Many drugs are available without doctors' prescriptions, which further increase the risk of fatal reactions. Drug allergy can become a major problem for patients with the multiple drug allergy syndrome, and more so with the emergence of antibiotic resistant organisms that limits the choice of antibiotics available. This article reviews the current understanding in the mechanisms of drug allergy, the management of patients with allergy to commonly used drugs such as penicillins, NSAIDs, local anaesthetics and radiocontrast media. After reading this article, the reader should be able to recognize patients at high risk of serious drug reactions and to formulate a management plan for such patients.

Introduction

Adverse reactions to drugs are important causes of morbidity and mortality and are frequently encountered in family practice. It has been estimated that the risk of an allergic reaction for most drugs is 1-3%. Such reactions might become an important reason for complaints or even malpractice litigation. It is therefore important that all doctors who prescribe medicines should have a basic understanding of this subject in order to reduce the risk of adverse drug reactions in their patients. Since the subject of adverse drug reactions covers an enormous scope, this review will concentrate on immunologically-mediated drug reactions since they are often the most dangerous types of adverse drug reactions.

Adverse drug reactions can be classified into predictable and unpredictable categories. Predictable reactions are often caused by the toxic side effects of drugs, or by the interaction of different drugs. These reactions occur commonly and are usually related to the doses of the drugs. For example, bradycardia caused by β-blockers and headache caused by nitrates. Idiosyncratic, allergic and pseudoallergic reactions are unpredictable reactions. Chloramphenicol-induced aplastic anaemia is an example of an idiosyncratic reaction. Only a very small proportion of patients is affected and the reaction cannot be predicted by animal testing.

Mechanisms of drug allergies

Allergic reactions have certain characteristics that help to distinguish them from other types of adverse drug reactions. These include:

1. Prior sensitisation. Allergic reactions to drugs, like other immunologically-mediated reactions, are acquired. In other words, the immune system must have been exposed to related drugs previously in order to be sensitised. The likelihood of sensitisation depends on the genetic predisposition of the individual, the amount of drug given, and the length, frequency and route of exposure. Genetic
predisposition to drug allergies appears not to be related to other atopic diseases such as asthma, allergic rhinitis or food allergies. In general, longer or more frequent exposure will more likely lead to sensitisation, and cutaneous exposure is more likely to sensitise than by intravenous route, and oral administration being the least likely. Some cases of allergic reactions to drugs given apparently for the first time may be due to cross-sensitisation or previous occult exposure, as antibiotic use in animal feed is widespread in the farming industry.

2. Consistency in symptoms. Allergic reactions lead to a limited and well-characterised set of symptoms. Different allergic mechanisms lead to different sets of symptoms that can often be distinguished clinically. Repeated exposure will invariably reproduce similar symptoms in any given individual.

3. The severity of symptoms is often unrelated to the dose of drug given. Even minute amounts of a drug far below therapeutic dose can lead to a fatal reaction. As a result, application of a "test dose" could be a very dangerous proposition.

4. Temporal relationship. A drug allergy reaction is always temporally related to drug exposure. The timing of the reaction is dependent on the mechanism of the reaction. For example, an IgE-mediated reaction usually occurs within 15 minutes to one hour of exposure.

As most drugs are small molecules incapable of sensitising the immune system on their own, they act as haptons by binding to serum proteins, thereby altering the antigenic determinants. The genetic predisposition to producing active drug metabolites that react with serum proteins may affect the likelihood of becoming sensitised to drugs. Drug allergies may involve many different immunological mechanisms, but can be classified along the lines described by Gell and Coombs:

Type I or Immediate-type hypersensitivity reactions

T cells sensitised to a drug stimulate B cells to produce antibodies of the IgE isotype against the drug. During re-exposure, cross-linking of IgE bound to the surface of mast cells by antigen leads to mast cell degranulation and the release of mediators such as histamine, cytokines, proteolytic enzymes, eicosanoids and platelet activating factor. Symptoms can occur from 15 minutes to 1 hour after exposure. Symptoms of anaphylaxis include generalised urticaria, angioedema, bronchoconstriction, hypotension or even cardiovascular collapse. Less severe reactions may involve the skin only. Examples of drugs causing type I reactions include penicillin, insulin and streptokinase.

Type II or antibody mediated cellular cytotoxicity reactions

IgG or IgM antibodies specific for drug antigens may bind to surface of cells such as erythrocytes, platelets or granulocytes. Binding of drug molecules to the surface bound antibody triggers a cascade of events involving complement activation, leading to cell lysis. These reactions may occur hours to days after exposure. Example may include penicillin and sulphonamides.

Type III or immune complex mediated reactions

IgG or IgM antibodies specific for drug antigens bind to drug molecules to form insoluble complexes, which get deposited in basement membrane of blood vessels. The classic reaction in this category is serum sickness characterized by fever, cutaneous eruptions, lymphadenopathy, arthralgias, nephritis, hepatitis, and vasculitis. These reactions may occur 4 to 20 days after exposure. Penicillin, anti-thymocyte globulin or heteroantisera may lead to this type of reactions.

Type IV or Delayed type hypersensitivity reactions

Sensitised T cells may directly damage the target organ, usually the skin in this type of reactions. A classic example is contact dermatitis secondary to topical antibiotics or anaesthetics. The reaction usually occurs 48 to 72 hours after exposure.

There are many reactions with complex mechanisms that cannot be neatly classified under one of these categories. These reactions include Stevens-Johnson syndrome, erythema multiforme, mobilliform drug rashes, fixed drug eruptions, toxic epidermal necrolysis and many organ-specific drug reactions.
Pseudoallergic reactions

These are reactions that are clinically indistinguishable from type I reactions. Drugs that can cause mast cell degranulation directly without sensitising the immune system include radiocontrast media, certain muscle relaxants, vancomycin and opiates. Angiotensin converting enzyme inhibitors can cause angioedema by accumulating bradykinins. Non-steroidal anti-inflammatory drugs (NSAIDs) may exacerbate pre-existing urticarial rashes or cause bronchospasm by altering eicosanoid metabolism. Since these reactions do not involve immune activation, no prior sensitisation is required.

Diagnosis of drug allergy

A detailed history is of utmost importance in diagnosing drug allergies. The symptoms, drug history and the timing of reaction in relation to drug administration will help to pinpoint the offending drug and the type of reaction. A previous history of drug allergies or a family history of drug allergies is important since these factors greatly predispose the patient to developing allergies to other drugs. Sullivan suggested that in people allergic to penicillin, there was at least a tenfold increase in reaction rate to non-beta-lactam antibiotics. As mentioned earlier, other atopic diseases do not predispose the patient to drug allergies. A history of concomitant illness is also important. Quite frequently, viral rashes are mistaken as drug rashes caused by antibiotics given to treat the viral illness. Drugs given under some circumstances may also lead to a non-immunologically mediated rash. For example, ampicillin/amoxicillin given during infection caused by Epstein-Barr virus or cytomegalovirus, or when given to a patient with acute lymphocytic leukaemia, may lead to a drug rash. Similarly, penicillin given to a patient with syphilis may lead to the Jarisch-Herxheimer reaction. Under other circumstances, these patients will not react to the antibiotics. AIDS also predisposes patients to drug allergies. Fifty percent of AIDS patients treated with trimethoprim-sulfamethoxazole develop an allergic rash.

Physical examination should focus on the skin, a frequent site of manifestation of drug allergies. It is important to distinguish between a mobilliform rash from an urticaria rash; the former is usually benign whereas the latter indicates the presence of IgE antibodies. Direct observation by the physician is important as patients' description may not be accurate, as discussed below. Mucosal involvement may indicate Stevens-Johnson syndrome or toxic epidermal necrolysis. Both are serious conditions. Chest examination may reveal wheezing secondary to bronchospasm, or stridor caused by laryngeal oedema.

Laboratory tests may be helpful in diagnosing organ-specific allergic reactions such as haemolytic anaemias, hepatitis, nephritis etc. Anti-histone antibodies may appear in patients taking hydralazine or procainamide, but do not necessarily indicate drug-induced lupus. In situations where anaphylaxis is suspected, a serum tryptase level drawn within 3 to 4 hours of the reaction may help; the assay is however expensive. Skin tests are available for diagnosing type I reactions to penicillin and insulin. Radioallergosorbent tests (RAST) for penicillin, ampicillin and cephalosporin specific IgE are available but are unreliable and tend to over-diagnose allergies.

Management of drug allergies

Penicillin and other β-lactam antibiotics

β-lactam antibiotics are some of the most widely used drugs and are responsible for the majority of drug allergies. These drugs can cause many different types of allergic reactions, from minor drug rashes to fatal anaphylaxis. Fatal reactions are rare, but it is important to distinguish the serious reactions from the trivial. One often encounters patients with a vague history of allergy to penicillin in the past. Mendelson et al. skin-tested 240 children and adolescents with a history of penicillin or amoxicillin allergy and found only 8.75% to be truly allergic to these antibiotics. Similarly, Macy et al. skin-tested 348 patients referred to their allergy clinic with a history of penicillin allergy, and only 60 (17.2%) were found to have positive skin tests. These results suggest that without skin testing, the majority of patients labelled as ‘penicillin allergic’ would be avoiding these drugs unnecessarily.

Before starting a patient on β-lactam antibiotics, the physician must ascertain whether the patient is allergic to the drug, and the seriousness of the allergic reaction. In general, trivial drug rashes are not contraindications to the use of these drugs if they are
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absolutely needed, since the symptoms of the reaction can often be managed to allow the patient to complete the course of treatment. However, these drugs must be completely avoided if the patient has a history of Stevens-Johnson syndrome, toxic epidermal necrolysis or type I hypersensitivity reactions. The first two entities, both serious conditions, should be easily recognisable. However, the patient may not be able to distinguish a mobilliform or maculopapular rash from an urticarial rash. Pichichero reported that 22% of patients with a history suggestive of a non-IgE mediated rash nevertheless had positive skin tests to penicillin.7

Skin testing has proven to be very reliable in predicting the risk of anaphylactic reactions. Penicillin is metabolised to major and minor determinants. The major determinant is penicilloyl and the minor determinants include penilloate, penilloate and benzylpenicillin (Table 1). Skin testing reagent for the major determinant is available (penicilloyl polylysine, PrePen). Although the minor determinants are responsible for a substantial proportion of serious anaphylactic reactions, no skin testing reagent for minor determinants is commercially available. Sodium amoxicillin is usually included in the panel since some patients react to its side-chain instead of the β-lactam group. In Macy’s study, 12 out of 60 (20%) penicillin allergic patients reacted to penilloate and/or penicilloate only* (Table 2). When skin testing is carried out using major and minor determinants and amoxicillin, a very high negative predictive value is achieved. In Macy’s study, only 5.2% of patients with negative skin tests developed a reaction on oral challenge, and all were mild. Skin testing is also safe, and only 0.3% of patients is known to develop urticaria during the tests.

Skin tests for penicillin should be by intradermal injections only, since prick puncture is not sufficiently sensitive. Appropriate solutions for skin testing include penicilloyl polylysine (Schwarz Pharma), penilloate (0.01M), penilloate (0.01M), benzylpenicillin (0.01M) and amoxicillin (0.01M). Since penilloate and penilloate are not commercially available, they must be prepared and stored in the freezer. 0.02 ml of the solutions are injected intradermally and the wheal and flare reaction is read after 15 minutes. Histamine and saline are used as positive and negative controls respectively. Positive responses consist of a wheal of 5 mm or more in diameter with surrounding erythema greater than the wheal, a negative response to control solution and a positive response to histamine.

The incidence of skin test positivity declines with time following the initial reaction, and is down to less than 10% after 10 years. This is because of waning penicillin-specific IgE levels in the absence of antigenic stimulation. A new course of penicillin in this situation may provoke IgE production again by the memory B cells. Skin testing with penicillin can theoretically also restimulate IgE synthesis. It is therefore important to tell patients that a negative skin test does not

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Table 1: Skin-test reagents for penicillin allergy

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major determinant</td>
<td></td>
</tr>
<tr>
<td>- Penicilloyl polylysine (PrePen)</td>
<td>10^+ M</td>
</tr>
<tr>
<td>Minor determinant mix (MDM)</td>
<td></td>
</tr>
<tr>
<td>- Potassium penicillin G</td>
<td>0.01 M</td>
</tr>
<tr>
<td>- Sodium benzylpenicilloate</td>
<td>0.01 M</td>
</tr>
<tr>
<td>- Benzylpenicilloyl-n-propylamine</td>
<td>0.01 M</td>
</tr>
<tr>
<td>Sodium amoxicillin</td>
<td>0.01 M</td>
</tr>
<tr>
<td>Histamine</td>
<td>1 mg/ml</td>
</tr>
<tr>
<td>Saline control</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Type and specificity of positive penicillin skin test reactions in 384 patients

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Puncture (no. of patients)</th>
<th>Intradermal (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrePen</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Penicilloye</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Penilloate</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Penilloate + penilloate</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Penicilloate + PrePen</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Penicilloate</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>All other combinations*</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>54</td>
</tr>
</tbody>
</table>

* All of these subjects had positive responses to at least one of the commercially available skin test materials: amoxicillin (5 of 15), PrePen (11 of 15), and penicillin (1 of 15).

guarantee any safety to take repeated courses of penicillin; retesting is required before each subsequent course of penicillin. It is best to perform skin testing just before the course of antibiotics is needed. Since anaphylaxis is a first dose phenomenon, the danger is minimal after the first dose of a course is tolerated, as long as there is no interruption in treatment. An interruption of 3 days or longer runs the risk of resensitisation and subsequent reaction when the course of treatment is resumed.

The issue of cross-reactivity between penicillins and cephalosporins is less clear. Both classes of drugs contain a β-lactam ring structure. Some studies suggested that increased hypersensitivity to first-generation cephalosporins exists in those patients who have histories of penicillin allergy. However, these studies were not supported by skin-test results. The incidence of cross-reactivity between penicillin and second- and third-generation cephalosporins appears to be low. Cross-reactivity between penicillins and cephalosporins with similar side chains appears to be more frequent. Miranda reported that in 21 patients allergic to amoxicillin, 8 (38%) also reacted to cefadroxil, but none reacted to cefamandole. If a cephalosporin is used in a penicillin allergic patient, inclusion of the drug in the skin test panel is advisable. In a patient with known allergy to a cephalosporin, another cephalosporin with a different side chain structure is usually safe. Imipenem, a carbipenem antibiotic widely used in hospitals in Hong Kong, carries a 50% risk of cross reactivity with penicillin. Aztreonam, a monobactam, does not cross-react with penicillin.

In summary, if a patient with a history of penicillin allergy requires antibiotics, substituting a chemically unrelated antibiotic should be the first course of action. If penicillin is absolutely required, skin testing with major and minor determinants and amoxicillin will reliably assess the risk of a serious reaction. If the patient's skin test is negative, a test dose of oral amoxicillin should be given under medical supervision and the patient observed for one hour before starting the course of treatment. The patient must understand that skin testing will only predict anaphylactic reactions and minor skin rashes may still occur. If the patient's skin test is positive, an alternative antibiotic should be used. Under exceptional circumstances where penicillin is absolutely necessary, e.g. tertiary syphilis, the patient can be desensitised. Desensitisation can be achieved by the oral or intravenous methods. In both methods, the patient is given minute doses of the β-lactam drug starting at 0.05 mg orally or 0.01 mg intravenously. The next higher dose is given after a 15-minute interval if there is no reaction. The dose is gradually increased over the next 4 hours until the patient can tolerate a full therapeutic dose of the drug. This should be carried out by an allergist experienced with the procedure under strict medical observation. After desensitisation, treatment must begin immediately and must not be interrupted. After a successful course of treatment, the patient must be desensitised again just before subsequent courses of penicillin in the future.

Aspirin and other NSAIDs

NSAIDs are some of the most frequently prescribed drugs in the world. They are also hidden components of many over-the-counter cold and flu remedies. Allergic reactions to NSAIDs are common and involve many different mechanisms. They can cause exacerbation of rhinitis and asthma in patients with aspirin sensitive asthma. They may also exacerbate symptoms in patients with idiopathic urticaria and angioedema. True immune-mediated allergic reactions to NSAIDs also lead to urticaria, angioedema and anaphylaxis. Lastly, these drugs may rarely cause aseptic meningitis and pneumonitis.

Up to 15% of adult asthmatics have been estimated to have aspirin sensitive asthma (ASA). ASA is a distinct disease entity. The typical patient with ASA is an adult of either sex aged 20 to 40, suffering from asthma, rhinitis, sinusitis and nasal polyps. Anosmia is frequently found as is sinus opacification on x-ray. The lower airway is sometimes spared but most patients have moderate to severe asthma, they require high dose inhaled corticosteroids or even oral corticosteroids. The severity of asthmatic symptoms appears to parallel the severity of rhinosinusitis, as treatment of the sinus disease, e.g. by surgery, will also improve asthma control. Improvement after surgery is usually short-lived as nasal polyps and sinusitis tend to recur.

The hallmark of this disease is the exacerbation of asthma within 15 min to 3 hours of NSAID ingestion. Patients may develop conjunctivitis,
rhinorrhea, nasal congestion, a slow and sustained bronchoconstriction and occasionally laryngospasm. These reactions may last 1 to 24 hours. This is followed by a refractory period of 2 to 5 days when patients can take NSAIDs without any reaction. The aetiology of this disease is known to be a disorder of leukotriene synthesis. The cysteinyl-leukotrienes leukotriene C4 (LTC4) and LTD4, are the most potent naturally-occurring bronchoconstrictors known, and can also mediate eosinophilic inflammation. ASA patients produce increased amounts of LTC4 and LTD4, reflected by the raised levels of urinary LTE4 (breakdown product of LTC4 and LTD4) as compared to control asthmatics. The urinary LTE4 is substantially increased after aspirin challenge in ASA subjects but not control asthmatics. Their bronchial responsiveness to inhaled LTE4 is also higher than non-ASA asthmatics.

The diagnosis of ASA can be confirmed by nasal lysine-aspirin challenge, inhaled lysine-aspirin challenge or oral aspirin challenge. Nasal challenge test is less reliable but is useful in diagnosing aspirin-sensitive upper airway disease. Inhaled lysine-aspirin challenge is the test of choice for diagnosing ASA. It is safe, the symptoms are usually limited to the lower airways and are rapidly reversed. Oral challenge may produce prolonged symptoms and is therefore more hazardous. However, oral challenge can be followed by aspirin desensitisation. Following desensitisation, patients can take NSAIDs indefinitely as long as the course of treatment is not interrupted by more than 2 days. Furthermore, desensitisation leads to improvement in both upper and lower airway symptoms and should be considered for patients with difficulty in controlling ASA.

It is important to bear in mind that ASA is a class effect and all strong inhibitors of cyclooxygenase will provoke reactions in these patients. Paracetamol has been shown to cross-react at high doses (1000 mg or greater) in 28% of ASA patients. Recent anecdotal evidence claims that nimesulide, a new COX-2-selective inhibitor, does not provoke symptoms in ASA patients. Although Zileuton, a 5-lipoxygenase inhibitor, has been found to protect ASA patients from aspirin-induced bronchospasm, this has not been shown in clinical practice. The new anti-leukotriene drugs, while useful in improving asthma control in ASA patients, should not be used to enable patients to take NSAIDs. ASA patients requiring NSAIDs should undergo desensitisation.

Aspirin and other NSAIDs have been found to exacerbate symptoms in some patients with idiopathic urticaria. This is probably related to inhibition of prostaglandin synthesis common with all NSAIDs. However, NSAIDs can also elicit IgE-mediated reactions leading to urticaria, angioedema and anaphylaxis. Since this effect is immunologically-mediated, cross-reactivity between different NSAIDs is low and only confined to drugs with similar chemical structure. Unfortunately, there is no reliable test in vivo or in vitro to confirm the diagnosis. Treatment is by avoidance since previous attempts at desensitising these patients have failed.

Local anaesthetics

Allergy to local anaesthetics is a frequent complaint from patients, especially in dental practice. The usual symptoms include flushing, tachycardia and syncope during or immediately after injection. While contact dermatitis to topically applied local anaesthetics is common, systemic allergic reactions to these drugs are extremely rare. It is possible that some of the reported cases were caused by reactions to preservatives in the multidose vials. Most of the cases were anxiety reactions, vasovagal syncope or reactions caused by direct intravenous injections of preparations containing adrenaline. In these situations, test by subcutaneous injections of incremental doses of the anaesthetic in question would be very useful in allaying the patient's fear.

Drugs which cause pseudoallergic reactions

Many clinicians and radiologists still believe that allergy to radiocontrast media (RCM) is related to allergies to iodine or even seafood. While iodine can cause dermatitis, allergy to shellfish is caused by IgE directed against muscle proteins, components that are not present in any radiocontrast medium. RCMs, by virtue of their hyperosmolar nature, can directly cause mast cell degranulation when injected intravenously. The use of RCM in procedures such as cystograms and myelograms poses no risk. Patients with cardiac disease, atopy or drug allergies, or who are taking β-blockers are at risk of serious reactions. A history of prior RCM reactions increases the risk of future reactions to 30% or greater. The use of premedications with prednisolone 40 mg, 13, 7 and 1 hour before, and
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Key messages
1. Allergic drug reactions should be distinguished from other forms of adverse drug reactions.
2. Allergic drug reactions are immunologically mediated. This requires prior exposure and the clinical manifestations are diverse.
3. The more serious types of allergic drug reactions such as anaphylaxis, Steven-Johnson syndrome and toxic epidermal necrolysis should be recognised.
4. Some drugs such as radiocontrast media, opiates, muscle relaxants, dextran and vancomycin can cause anaphylactoid reactions by directly causing mast cell degranulation.
5. Skin testing is useful in predicting the risk of anaphylaxis to drugs such as penicillin in patients with prior history of allergic reactions to those drugs. Skin testing patients without a prior history is not indicated.
6. In most cases, an alternative drug that does not cross-react should be substituted. Under certain circumstances, drug desensitisation can be performed.

Prevention of drug allergies and the multiple drug allergy syndrome
As mentioned previously, patients with allergy to penicillin are 10 times more likely to become allergic to other drugs. This susceptibility not only applies to anaphylactic type reactions, but also extends to drug rashes, exfoliative dermatitis, toxic epidermal necrolysis and Stevens-Johnson syndrome. In a study of 120 patients with antibiotic allergies, 19% were allergic to at least one other antibiotic; 15.8% reacted to three or more antibiotics. Forty-two percent of those patients allergic to two or more antibiotics were allergic to NSAIDs, in contrast to only 18% of those patients allergic to one antibiotic. The presence of atopy was not a risk factor for multiple drug allergies.

Preventing drug allergy is the responsibility of medical practitioners. Frequent, short courses of antibiotics are responsible for sensitising many patients to these drugs. I once saw a 4-year-old girl referred to me by a hospital paediatrician because he could not find an antibiotic that he could use to treat the girl’s pneumonia. The girl’s mother listed 21 occasions in the past three years when the girl was given antibiotics for the treatment of viral upper respiratory tract infections. She was otherwise a normal healthy child and there was no sign of immunodeficiency. By the time she visited my clinic, she had already been admitted three times for drug-induced anaphylaxis, once requiring intubation. Examples such as this are admittedly rare, but I see a fair number of patients with antibiotic allergies caused by overuse. We must educate our patients and ourselves when antibiotics are truly indicated. By avoiding inappropriate use, the incidence of drug allergies will decrease, which will ultimately benefit our patients and prevent a lot of problems for ourselves.

References

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