

HKIA GUIDELINES ON MANAGEMENT OF BETA-LACTAM ANTIBIOTIC ALLERGY

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Section I: Disease mechanisms and Clinical Presentation

Antibiotics can be classified as beta-lactam and non-beta-lactam. The former consists of 2 major classes (penicillins and cephalosporins) and 4 minor ones (carbapenems, monobactams, oxacephems, and clavams), all of which contain a 4-membered beta-lactam ring. Non-beta-lactam antibiotics (e.g.

quinolones, sulfonamides, macrolides, aminoglycosides, rifamycins, glycopeptides, and clindamycin) have very different chemical structures, antimicrobial spectra, and immunogenic properties.

Allergic drug reaction is defined as an adverse drug reaction with an established immunological mechanism. It may be classified according to the Coombs and Gell classification system into 4 types: I (mediated by drug-specific IgE antibodies), II (complement-mediated cytotoxicity), III (immune complex formation), and IV (delayed type hypersensitivity mediated by drug-specific T lymphocytes). T-cell mediated type IV reactions can be further sub-classified into IVa - IVd reactions¹. Type IVa corresponds to Th1 cell-mediated immune reaction involving interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF- α), and interleukin-2 (IL-2), such as in skin test reactions to tuberculin, and contact dermatitis. Type IVb corresponds to Th2 cell-mediated immune reaction secreting IL-4, IL-13 and IL-5, which promote B-cell production of IgE and IgG4, macrophage deactivation and mast cell and eosinophil responses, such as in maculopapular exanthema. Type IVc corresponds to cytotoxic T-cell immune reactions, such as in Steven-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), where activated CD8+ T-cells kill keratinocytes, but may also be the dominant reaction in drug induced hepatitis or nephritis. Type IVd corresponds to neutrophilic inflammation where CD8+ T-cells recruit neutrophilic leucocytes via CXCL8 release and prevent their apoptosis via GM-CSF release, such as in acute-generalized exanthematous pustulosis.

Clinically, allergic reactions to antibiotics are commonly classified as immediate or non-immediate according to the time interval between the last drug administration and their onset.

Immediate reactions occur within the first hour after drug administration and are possibly induced by an IgE-mediated mechanism. Symptoms are produced by a rapid release of histamine and other vasoactive inflammatory mediators immediately after hapten-antibody interaction. They usually manifest as urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, gastrointestinal symptoms

(nausea, vomiting, diarrhea), or anaphylactic shock.

Acute urticaria is a transient swelling on the skin lasting 2-12 hours. They are characterized by itchy well-demarcated wheals with raised pale centers and are surrounded a red flare. Angioedema is part of the spectrum of urticaria and it presents with deeper swellings of the dermis, subcutis, and submucosa, most often occurring in the mouth, eyelids or genitalia. Anaphylaxis is a potentially life-threatening systemic allergic reaction, often explosive in onset, with symptoms ranging from mild flushing (with generalized pruritis, urticaria and/or angioedema), to upper respiratory obstruction (laryngeal edema), wheezing (bronchospasm) with or without shock (vascular collapse). Tachycardia, hypotension and respiratory failure are late signs with lethal consequences.

Non-immediate reactions are those that occur more than 1 hour after drug administration and are often associated with a delayed T-cell dependent type of allergic mechanism. Typically, T-cell mediated skin reactions can resemble urticarial wheals but last days rather than hours and develop 2-4 days after commencing the causative drug. They can also present as maculopapular rashes which are usually symmetrical, may become confluent but spare the palms and the soles. Additional T cell-mediated patterns include fixed drug eruption (FDE) and acute generalized exanthematous pustulosis (AGEP). In FDE red or brownish circular lesions develop at exactly the same site(s) following each exposure to the culprit drug. In AGEP, an extensive rash of fine pustules arising on erythematous areas develops. Erythema multiforme (EM) occurs as an eruption of circular, targetoid lesions spreading from the extremities to the face and trunk and involves the palms and soles. The initial lesions provoke a 'burning' feeling or pain but not itching. Lesions differ from urticaria and toxic erythemas in that the centers in EM are darker red. Bullous EM presents with target lesions and any blistering involves <10% of body surface area (BSA); Steven-Johnson Syndrome (SJS) is characterized by widespread erythematous or purpuric lesions or flat atypical targets and blistering involving <10% BSA; overlap Steven-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN) presents with lesions

that are like those in SJS but epidermal detachment affects between 10% and 30% BSA; TEN may present with a rash which is like that in the overlap but epidermal detachment is >30% BSA. Alternatively TEN may present without 'spots' but with epidermal detachment in large sheets, affecting >10% BSA. The more severe syndromes can be life-threatening and the drug must be stopped immediately. The cutaneous 'necrolysis' is due to massive apoptotic death of epidermal cells and is very hard to stop.

Non-immediate allergic reaction to antibiotics may also involve the respiratory, hepatobiliary, and the nephritic system. Pulmonary manifestations include pulmonary eosinophilia, organizing pneumonia, interstitial pneumonitis or pleural involvement. Hepatitis, interstitial nephritis, haemolytic anemia, thrombocytopenia and neutropenia can also happen. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening, drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and internal organ (liver, kidney, lung) involvement. DRESS is characterized by a long latency (two to eight weeks) between drug exposure and disease onset, a prolonged course with frequent relapses despite the discontinuation of the culprit drug, and frequent association with the reactivation of a latent human herpesvirus infection.

Penicillin or beta-lactams are recognized as the most frequent causes of immediate and non-immediate drug reactions². Self-reported beta-lactam 'allergy' is common (up to 20% of hospitalized patients)³, but only 1-10% of these patients have evidence of type 1 hypersensitivity on testing^{4,5}. This had resulted in the prescription of alternative antibiotics such as clindamycin, quinolones and vancomycin. In a matched cohort of hospitalized patients, those with a history of penicillin 'allergy' had more hospital days⁶, more likely to have *Clostridium difficile* and more likely to have vancomycin-resistant *Enterococcus* than controls. Mean antibiotic costs in hospital patients labelled as allergic to penicillin were estimated to be 63 times greater than for those not allergic to

penicillin⁷. This guideline will only focus on management of allergy to beta-lactam antibiotics.

Diagnosis of antibiotic allergy depends on detailed clinical history, skin testing, blood tests and oral provocation test. Detailed and accurate clinical history is required as the first step to a correct diagnosis. This should include details of the drug (formulation, dose, route and timing of administration), detailed symptomatology (onset of the symptoms, evolution of symptoms, and the extent of involvement), the chronology of the symptoms (previous exposure, delay between the last dose and the onset of symptoms, effect of stopping treatment, any drug taken subsequently without the problem, as well as development of any similar presentations without taking the drug), other medications taken (both at the time of the reaction and other drugs taken after the development of reaction), and the medical background of the patient (any suggestion of a previous allergy, or of a medical condition, such as viral infection or systemic disease that can have skin lesions mimicking drug allergy). During physical examination, the most important thing is to examine the patient for any signs and symptoms of anaphylaxis (Table 1). This may require emergency treatment with adrenaline injection.

In patients with stable haemodynamic condition, thorough systemic examination should be carried out. Skin lesions are the most common presenting symptoms. The entire skin, including scalp, hair, nails, should be examined. Inspect carefully for the distribution of the skin lesions as well as their morphology (size, colour, shape, edge, any scales, blisters etc). Palpate gently for any blanching, tenderness, warmth, and epidermal detachment. Examine mucous membranes and genitals where appropriate. If the skin lesions had already resolved during the examination, written medical and nursing record as well as photographs and eye-witness accounts should be sought.

Section II. Workup for immediate reactions

For the evaluation of beta-lactam type I hypersensitivity, skin test is a crucial investigation. Other *in vitro* assays, such as serum specific IgE and flow cytometric basophil activation tests (BAT) may provide complementary information for the workup. After defining histories and negative allergy investigations, confirmation of tolerance by drug provocation test (DPT) is useful. Since IgE reactivity decreases with time and may produce negative results including DPT, in selected cases, retesting may be considered⁹. The practice to retest these cases varies. The US practice parameters stated that re-sensitization is more likely after parental than oral penicillin and suggested selective retesting depending the route of re-exposure. The European guidelines advise to retest whoever with clear past history of immediate reaction but negative initial workup⁹.

Blood tests

In vitro tests for type 1 hypersensitivity workup include serum specific IgE and BAT. These assays are safe and may be performed in cases not feasible for skin tests. In addition, it provides complementary information to skin tests. There are occasions that patients with clear hypersensitivity history may display negative skin tests but positive drug specific IgE. Guidelines by the European Network for Drug Allergy and the European Academy of Allergy and Clinical Immunology interest group on drug hypersensitivity include serum specific IgE assays as part of the workup. These guidelines also recommended performing *in vitro* tests before skin testing in high risk cases⁹. However, in view of its lower sensitivity compared to skin tests, all negative *in vitro* tests should be followed by skin test workup if possible.

In vitro cellular assays, such as BAT has been described in recent years. BAT is a flow cytometric assay, measuring the activation markers (CD63 or CD203c) of basophil after incubation with allergen *in vitro*. The sensitivity of BAT in diagnosing beta-lactam allergy is around 50 %, and is overall higher than

serum specific IgE assay. The specificity is greater than 90%¹⁰⁻¹². Despite higher sensitivity than serum specific IgE, BAT is not a commonly available test since blood sample has to be processed fresh. Moreover, it is also more technically demanding compared to serum IgE assay. Nevertheless, BAT may provide useful findings when conventional skin tests are not feasible, or when other allergic workup are negative.

Skin test

Skin testing in the workup of beta-lactam allergy is well established. In general, the test is safe and rarely leads to systemic allergic reactions if properly performed. Nevertheless, facilities and medications for managing allergic reactions, including anaphylaxis should be readily available. Skin tests normally begin with prick test. Results are usually read at 15-20 minutes. A wheal larger than 3 mm than negative control, associated with erythema is considered a positive reaction. If results are negative, intradermal testing will be performed. Intradermal test is done by injection of 0.02 ml of the test reagents intradermally, raising a small bleb. Results are considered positive if there is an increase in wheal size greater than 3 mm compared to initial wheal at 20 minutes¹³. Appropriate positive histamine and negative saline control should also be included for proper results interpretation.

Immediate reactions to beta-lactams could be directed towards the beta-lactam rings or against the side chain. Test panels commonly includes penicilloyl-polylysine (PPL), minor determinant mixture (MDM), benzylpenicillin (BP), amoxil and the suspected beta-lactam. The maximum concentrations accepted for prick and intradermal testing are: PPL 5×10^{-5} mmol/L, MDM 2×10^{-2} mmol/L, BP 10000 IU/ml and amoxil 20 mg/ml (6). In Europe, both PPL and MDM are commercially available, whereas, in US, only PPL is available. The importance of testing MDM in addition to PPL and BP is controversial. Some studies showed comparable negative predictive value with only PPL and BP to full panel including MDM, while others estimate a difference of sensitivity of around 10% to 20% with

additional MDM testing¹⁴⁻¹⁸. Clavulanic acid, which is also commercially available as a skin test reagent, is worth testing in addition to amoxicillin and penicillin panels when investigating Augmentin allergy. The dilutions employed in skin tests depend on patient's history. In cases of severe anaphylactic reactions, skin tests should begin with a higher fold dilutions before testing with the maximum concentration.

General considerations in skin test include reviewing patient recent prescriptions. Certain medications, such as anti-histamines (around 1 week) and beta blockers (around 48 hours) should be discontinued before testing. Moreover, skin test should not be performed in weeks immediate after an anaphylactic event in view of possible compromised sensitivity. A period of at least four weeks should be allowed after anaphylaxis before skin test workup.

Approximately half of the penicillin skin tested positive subjects will develop immediate hypersensitivity reactions when re-challenged¹⁷⁻²⁴. Hence, skin tested positive patients should avoid re-exposure. If an alternative is not available, the drug has to be administered under close monitoring (e.g. in intensive care unit) with desensitization protocol. Generally, the negative predictive value of penicillin skin test is high. In large scale studies, 1 to 3 percent of the subjects with negative skin tests may develop reaction upon re-exposure. Most reactions are mild^{15, 16, 18, 21, 25-28}. Nevertheless, the tolerance to the drug should be confirmed by drug provocation test (DPT).

Drug provocation test

In patients with negative penicillin skin tests, it is recommended to confirm drug tolerance by provocation test (DPT). Challenge is indicated since the negative predictive value of skin test though high, is not 100 percent. Graded drug challenge can be performed by giving an initial dose of one hundredth of the therapeutic dose followed by a one-tenth dose with one hour apart if there is no

adverse reaction observed. Finally, a full dose can be given to the patient and monitor for any reaction. DPT is the gold standard to establish a firm diagnosis. It is important to note that drug challenge is not desensitization. Desensitization is a special process for administering medication to which the patient is allergic.

Cephalosporin use in patients with a history of Penicillin allergy

Though only around 2 % of penicillin skin test positive patients react to cephalosporin, the reaction could be severe. There is a higher chance for penicillin allergic subjects to cross react with first generation than the second/third generation cephalosporin. Cephalosporin with similar side chains are more likely to cross react in case of cephalosporin allergy. For cases with suspected penicillin allergy and negative penicillin skin tests, cephalosporin may be administered with minimal concern about an immediate reaction. However, if penicillin skin tests are positive and cephalosporin use is necessary without better alternative, cephalosporin skin test, and if the result is negative, followed by graded challenge should be considered. For high risk cases, either choosing alternative non-beta-lactam antibiotics or administer cephalosporin with desensitization protocol is recommended (Figure 2).

Section III. Workup for non-immediate reactions

Non-immediate reactions to beta-lactam antibiotics are those occurring more than 1 hour after administration. Most are due to a type IV hypersensitivity mechanism and can be investigated by patch test, delayed reading of intradermal test and blood tests before considering the necessity of drug provocation test (Figure 1). Both for immediate and non-immediate types of reactions the practice of routine penicillin skin testing is discouraged. The investigation procedures described below and those described for immediate reactions should be carried out in patients only with a suggestive clinical history of beta-lactam allergy.

Patch test

Standard commercial patch test kits are available. Positive patch test has been reported in patients with non-immediate cutaneous reactions to beta-lactam antibiotics²⁹. Patch test should be performed with benzylpenicillin (BP), amoxicillin (AX), ampicillin (AM) and suspected penicillins and/or cephalosporins. If the drugs are not available commercially they can be home-made using parenteral solutions or dissolving the drug if they are soluble. Drug tablets are grounded in a mortar and then added to normal saline or petrolatum. Patch test readings should be recorded (i) at 20 minutes to check for any immediate reactions; (ii) after 48 hours when the patch is removed; (iii) after 72 hours; (iv) after 7 days. Reading score should be made according to the European Environmental and Contact Dermatitis Research Group patch test classification³⁰.

Intradermal test

Intradermal tests are performed in the same manner as for immediate reactions. Prick tests and immediate readings of intradermal tests at 20 minutes are not relevant as they are for immediate

reactions. Studies have shown that delayed readings of intradermal tests at 48 or 72 hours are predictors of non-immediate allergic reactions to beta-lactam antibiotics²⁹. Positive results consist of erythema and a variable degree of induration. In some cases, biopsy of the test areas showed typical histological features of type IV hypersensitivity³¹; in others, delayed skin test positivity were confirmed by drug challenge²⁹. For safety reasons, intradermal test is contraindicated in patients with severe reactions such as DRESS, SJS/TEN and AGEP. Patch test is considered acceptable in these situations.

Skin test interpretation

The sensitivity of skin tests for non-immediate reactions is generally lower than that for immediate reactions but still seems to be good – around 35-55% for BP, AM and AX depending on studies^{29, 32, 33}. Generally patch test is less sensitive than intradermal test but may be more specific. There is a lack of definitive data for other beta-lactam antibiotics. The specificity is not easy to determine as it is not ethical to challenge patients with positive skin tests. Nevertheless as most skin test-negative patients tolerate the drug they help to reduce the number of patients falsely labelled as allergic to penicillin.

Lymphocyte transformation test (LTT)

T cell recognition of beta-lactam antibiotics can be demonstrated by several laboratory methods. LTT is a well-established method to measure T cell proliferation *in vitro* in response to stimulation by the responsible drug. Basically peripheral blood mononuclear cells from patients are stimulated with the suspected drugs. Lymphocyte proliferation is assessed by ³H-thymidine incorporation or other means. It is considered positive if the stimulation index (SI), defined as proliferative response to drug divided by background proliferative response, is greater than 3. Theoretically apart from the parent drug *ex vivo* generated drug metabolites can also be used as stimulants. The sensitivity of LTT in beta-lactam

antibiotic allergy is highly variable, ranging from very low to 100%³⁴. This is partly due to a long period of incubation, usually 5-7 days, leading to a lot of variables which are difficult to control. T cell lines generated can lead to enhanced proliferative response which varies from culture to culture. Patient selection, choice of SI cutoff levels and culture conditions are additional factors contributing to the variability. Nevertheless LTT is considered to have a higher sensitivity and hence a better diagnostic value than skin tests in non-immediate reactions of beta-lactam antibiotics³⁵. The major limitations are the resources, facilities and expertise needed to carry out the laboratory test with good accuracy and reproducibility.

Since T cells are also involved in immediate reactions, LTT responses in patients with immediate type allergy to beta-lactam antibiotics can be demonstrated. In fact the sensitivity is higher for the immediate group than the non-immediate group³⁶. Although LTT is used to identify allergic subjects, non-allergic control subjects who are exposed to the same drug can also be positive. This may be due to the presence of memory T cells in these controls³⁴.

Enzyme-linked immunospot (ELISPOT) assay

The ELISPOT assay is a sensitive, reproducible laboratory technique that measures antigen-specific, cytokine-producing cells. Applications in non-immediate type of drug allergy are supported by work largely done on beta-lactam antibiotics. Patient peripheral blood mononuclear cells are cultured with suspected drugs and positively responding cells are detected by measuring intracellular cytokine production. Key cytokines involved in drug allergy are interferon-gamma, interleukin-5, granzyme B and granulysin. Using the interferon-gamma ELISPOT assay one study demonstrated amoxicillin-specific T cells in 20/22 (91%) of patients with known delayed hypersensitivity to amoxicillin³⁷ and in only 1/26 non-allergic patients. The sensitivity of LTT in the same study was lower (68%) but the specificity is similar (91%). In a position paper of the European Academy of Allergy and

Clinical Immunology it was recommended to combine of LTT and ELISPOT which would give the highest percentage of positivity³⁸.

Drug provocation test (DPT)

DPT is the gold standard in diagnosis of drug allergy. Because of the relatively low sensitivity of skin and/or blood tests in non-immediate reaction, DPT is often needed to confirm the diagnosis. Due to the complexity of the procedure and the associated hazards, DPT is only done after skin tests and/or blood tests have been performed. Its main uses are (i) to confirm negativity of skin/blood test results and (ii) to clarify whether the patient is allergic or not when skin/blood test results are dubious or contradictory. Protocols of DPT for beta-lactam antibiotics are published^{39, 40}. For example in one study of amoxicillin and several cephalosporins, 5 and 50 mg of the drugs were given orally or parenterally with a one-hour interval. Then 100, 250, 500 mg were followed at 48-hour intervals. For the first 8 hours the patient was monitored under close medical observation, after which they were followed up with a paging system.

Section IV. Management of Beta-lactam Allergy

When an allergic reaction to a beta-lactam antibiotic is suspected, the offending drug should be stopped immediately. Mild reactions of fever and non-pruritic skin rash often resolve spontaneously after drug cessation. Urticaria and pruritic skin rash can be effectively controlled by anti-histamines. Bronchospasm and respiratory distress requires oxygen and bronchodilator therapy. In more severe reactions that amount to impending anaphylaxis, subcutaneous or intramuscular administration of adrenaline of 0.3-0.5mg should be given immediately and the patient should be sent to the nearest medical facility for observation and further treatment. For less severe reactions, systemic corticosteroid at 0.5-1mg/kg is usually effective in controlling the symptoms. In severe non-immediate reactions such as exfoliative dermatitis, Steven-Johnson Syndrome, and Toxic Epidermal Necrolysis, rapid desquamation exposing large areas of raw dermis can occur. This is similar to a severe thermal injury and the patient should be admitted to hospital, and sometimes to the Burn Unit, so that fluid loss and electrolyte disturbance as well as secondary infection can be managed promptly.

Avoidance

The most effective measure to prevent drug allergy is by avoidance and alternative drugs should be used whenever possible. In subjects with IgE-mediated allergy to Penicillin, prescribing structurally related antibiotics including Cephalosporins, Carbapenems, and Monobactams should be done with caution. The cross-reactivity between Penicillins and Cephalosporins ranges between 1-8% with first- and second-generation Cephalosporins having higher rate⁴¹. Aminopenicillins, Cephalothin, Cephalexin, Cefadroxil, and Cefazolin should be avoided in subjects with penicillin allergy. The third- and fourth-generations Cephalosporins such as Ceftriaxone, Cefuroxime, and Ceftazidime are usually well tolerated⁴². The Monobactam antibiotic Aztreonam has a monocyclic core structure and does

not have significant cross reactivity with Penicillins. The exact rate of cross reactivity between Penicillins and Carbapenems is unknown but positive skin test to Imipenem was found in as low as 1.5% of patients with Penicillin allergy in one study⁴³.

Desensitization

In clinical situations such as infective endocarditis where Penicillin is the treatment of choice, the avoidance of the whole group of beta-lactam antibiotics because of drug allergy is challenging, particularly in serious infections caused by multi-drug resistant organisms where the choice of antibiotics is limited. Drug desensitization is indicated when there is no better alternative medication available, and where the benefits of desensitization outweigh the risks. It is a process of induction of a temporary state of tolerance by graded administration of a drug that is responsible for an immediate hypersensitivity reaction. Drug desensitization is mainly done in IgE mediated allergy and is contraindicated in non-IgE mediated allergic reactions such as immune complex reactions, acute interstitial nephritis, Steven-Johnson Syndrome and Toxic Epidermal Necrolysis. The mechanisms that leads to antigen specific mast cell desensitization are not entirely known but may involve internalization of antigen/IgE/FcεRI and cross-linking of inhibitory receptors on mast cells, reduced levels of up-stream signal transducing molecules, such as Syk which are necessary for activation and mast cell IgE-signalling⁴⁴. Penicillin desensitization has been shown to result in an increased Penicillin specific IgG antibody response as well⁴⁵.

Because of the potential risk of anaphylaxis, desensitization is indicated only if it would significantly improve the clinical outcome in patients in whom alternative antibiotics are less effective or not available. At the time of the procedure, other concomitant medical conditions must be stable and beta-blockers therapy should be ceased. Penicillin desensitization can be done orally or intravenously, and a number of protocols have been published⁴⁶. Oral desensitization is generally

safer and takes about 6 hours to reach the cumulative therapeutic dose. Intravenous administration can deliver the drug in precise concentration at a specified rate and is particularly useful in patients who cannot take oral drugs or when oral equivalents are not available. The starting dose is often \leq 1/1000th of the therapeutic dosage, with escalations being carried out in doubling doses at 15–30 min intervals, thereby reaching the therapeutic dosage within a few hours. It must be performed under the supervision of an experienced clinician in intensive care or high dependency unit where cardiopulmonary monitoring and resuscitation facilities are readily available. If an allergic reaction develops during the course, it should be treated with a combination of antihistamines, adrenaline, and corticosteroids appropriate to the severity of the reaction. In such circumstances, dose reduction would be necessary before escalation can be re-attempted to establish tolerance. Because of the potential risk of anaphylaxis, a careful risk-benefit analysis must be considered beforehand.

Penicillin desensitization is successful in at least 75% of cases⁴⁷. Those with multiple drug allergies are more difficult to desensitize. Once desensitized, patients are able to tolerate the course of antibiotic therapy at therapeutic dose with minimal adverse reactions. The patients must be given the drug daily in order for tolerance to be maintained. If the drug therapy was discontinued, the desensitized state would be lost and anaphylactic sensitivity would return within a few days to a week. Oral penicillin desensitization is usually well tolerated although mild pruritic rash has been reported by up to 30% of patients, and serum sickness, hemolytic anemia, and nephritis can also occur. However, most patients with mild reactions are able to tolerate them and complete the desensitization procedure. Although uncommon, severe and fatal reactions have been associated with parenteral penicillin desensitization⁴⁸.

Table 1. Clinical signs and symptoms of anaphylaxis (adapted from reference 8)

<p><u>Cutaneous /subcutaneous / mucosal tissue</u></p> <p>Flushing, erythema, hives (urticaria) and angioedema Pruritis of lips, tongue, and palate; edema of lips, tongue and uvula Periorbital erythema, urticaria and edema, conjunctival erythema, and tearing</p>
<p><u>Respiratory</u></p> <p>Nose: erythema, congestion, rhinorrhea, sneezing Laryngeal: erythema and tightness in the throat; dysphagia, and hoarseness; dry staccato cough; stridor; sensation of erythema in the external auditory canals Lung: shortness of breath, dyspnea, chest tightness, deep cough, and wheezing / bronchospasm (decreased peak expiratory flow)</p>
<p><u>Cardiovascular</u></p> <p>Hypotension Feeling of faintness (near-syncope), syncope, and altered mental status Chest pain Arrhythmia</p>
<p><u>Gastrointestinal</u></p> <p>Nausea and vomiting Crampy abdominal pain Diarrhea</p>
<p><u>Other</u></p> <p>Uterine contractions in women Aura or sense of impending doom</p>

Figure 1. Diagnostic algorithm of beta-lactams allergy

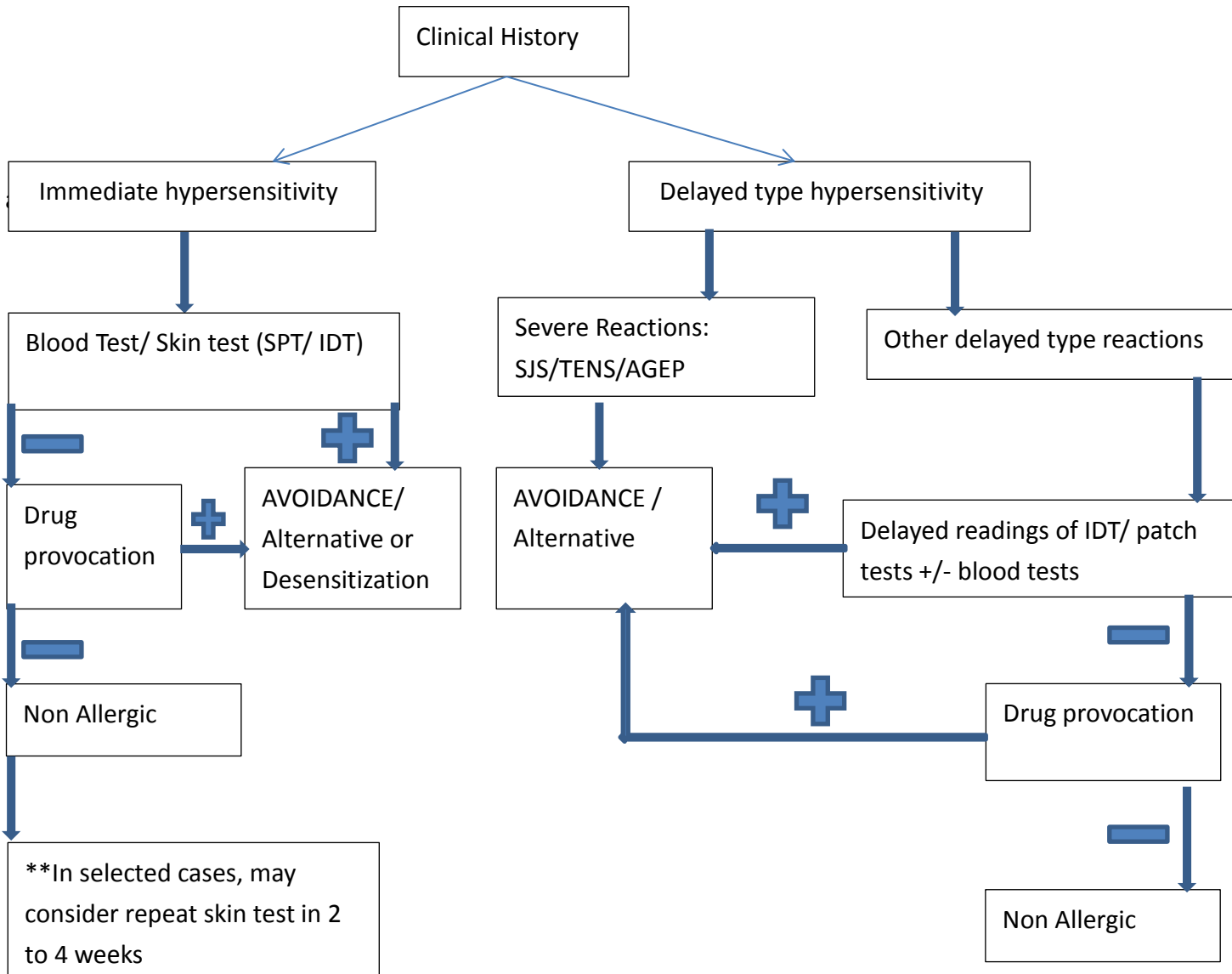
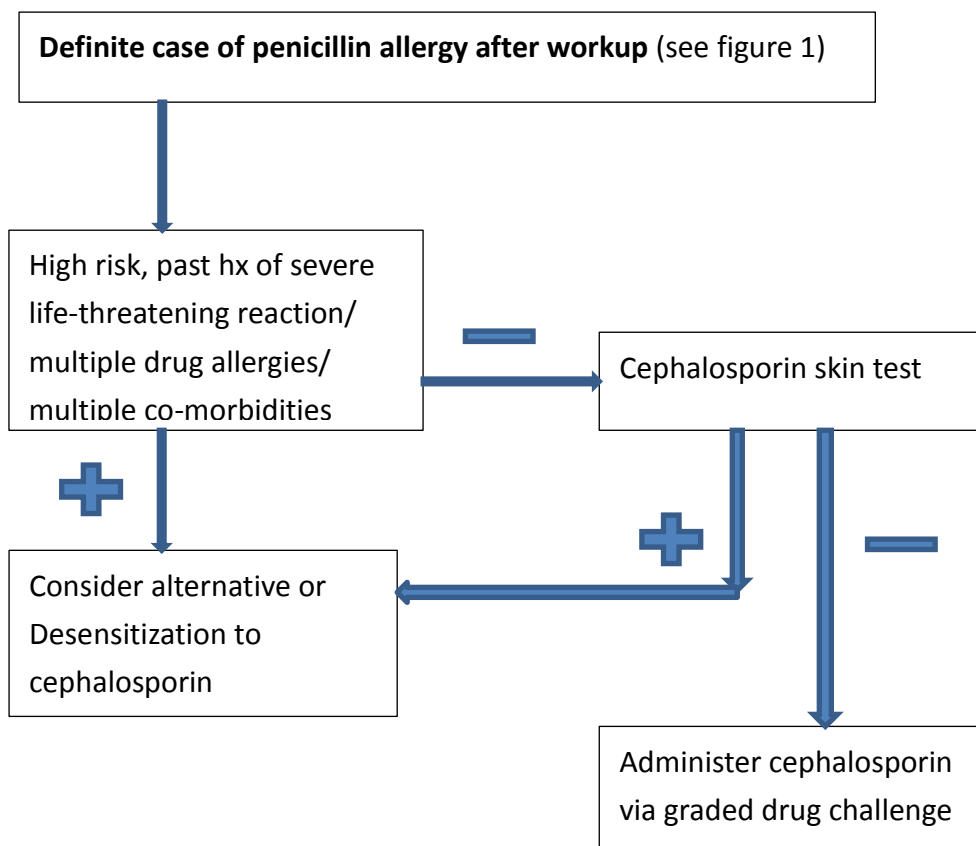


Figure 2 Cephalosporin administration in case of penicillin allergy



1. Concerning choice of cephalosporin: In general, greater risk of cross reactivity is noted with first or second generation of cephalosporins in penicillin allergic subjects, hence, third generation cephalosporins are more preferred in these cases.
2. Please note that cephalosporin skin tests are not as validated as penicillin skin test and the negative predictive value is unknown. Therefore, caution is still required.
3. All these investigations, including skin tests, drug challenge and desensitization should be conducted under close medical supervision with resuscitation facilities readily available.

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