全身性皮疹之鑑別診斷

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皮疹鑑別診斷之大方向

- 局部性皮疹
  - 多為皮膚病或局部感染
- 全身性皮疹
  - 急性或亞急性多為藥物疹
  - 慢性要考慮免疫性疾病
- 皮疹伴隨血壓不穩或休克
  - 敗血症併皮膚移轉性感染

Drug Eruptions

Introduction

- Drug eruptions can mimic a wide range of dermatoses and should be considered in any patient who is taking medications and who suddenly develops a symmetric cutaneous eruption.
- occur in approximately 2-5% of inpatients and in greater than 1% of outpatients.
- Most drug eruptions are mild, self-limited, and usually resolve after the offending agent has been discontinued. Severe and potentially life-threatening eruptions occur in approximately 1 in 1000 hospital patients.
- antimicrobial agents, nonsteroidal anti-inflammatory drugs (NSAIDs), cytokines, chemotherapeutic agents, anticonvulsants, and psychotropic agents

Pathophysiology

Immunologically mediated reactions

- Type I reactions (ie, immediate hypersensitivity reactions) involve immunoglobulin E (IgE)–mediated release of histamine and other mediators from mast cells and basophils which result in urticaria, angioedema, and anaphylaxis.
- Type II reactions (ie, cytotoxic hypersensitivity reactions) involve immunoglobulin G or immunoglobulin M antibodies bound to cell surface antigens, with subsequent complement fixation. , which result in hemolysis and purpura .
- Type III reactions (ie, immune-complex reactions) involve circulating antigen-antibody immune complexes that deposit in postcapillary venules, with subsequent complement fixation. , which result in vasculitis, serum sickness, and urticaria.
- Type IV reactions (ie, delayed hypersensitivity reactions, cell-mediated immunity) are mediated by T cells rather than by antibodies , which result in contact dermatitis, exanthematous reactions, and photoallergic reactions.

Table 23.3 Mechanisms of cutaneous drug-induced reactions.

MECHANISMS OF CUTANEOUS DRUG-INDUCED REACTIONS	
Immunologic mechanism (unpredictable)	• IgE-dependent drug reactions • Cytotoxic, drug-induced reactions • Immune complex-dependent drug reactions • Cell-mediated reactions
Nonimmunologic mechanisms (sometimes predictable)	• Overdose • Pharmacologic side effects • Cumulative toxicity • Delayed toxicity • Drug-drug interactions • Alterations in metabolisms • Exacerbation of disease
Idiosyncratic with a possible immunologic mechanism (unpredictable)	• DRESS • TEN/SJS • Drug reactions in the setting of HIV infection • Drug-induced lupus

Jarisch-Herxheimer phenomenon

- Jarisch-Herxheimer phenomenon is a reaction due to bacterial endotoxins and microbial antigens that are liberated by the destruction of microorganisms. The reaction is characterized by fever, tender lymphadenopathy, arthralgias, transient macular or urticarial eruptions, and exacerbation of preexisting cutaneous lesions. The reaction is not an indication to stop treatment because symptoms resolve with continued therapy. This reaction can be seen with penicillin therapy for syphilis, griseofulvin or ketoconazole therapy for dermatophyte infections, and diethylcarbamazine therapy for oncocerciasis

History

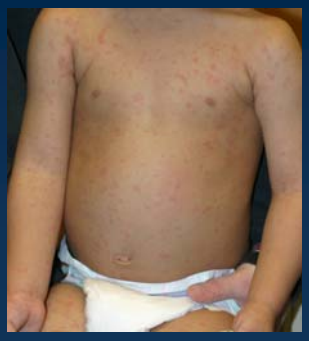
- All prescription and over-the-counter drugs, including topical agents, vitamins, and herbal and homeopathic remedies .
- The interval between the introduction of a drug and onset of the eruption .
- History of previous adverse reactions to drugs or foods.
- Consider alternative etiologies, especially viral exanthems and bacterial infections.
- Concurrent infections, metabolic disorders, or immunocompromise (eg, due to HIV infection, cancer, chemotherapy) .

Physical

- Evaluate for certain clinical features that may indicate a severe, potentially life-threatening drug reaction Such features include the following:
  - Mucous membrane erosions
  - Blisters (Blisters herald a severe drug eruption.)
  - Nikolsky sign (epidermis sloughs with lateral pressure; indicates serious eruption that may constitute a medical emergency)
  - Confluent erythema
  - Angioedema and tongue swelling
  - Palpable purpura
  - Skin necrosis
  - Lymphadenopathy
  - High fever, dyspnea, or hypotension

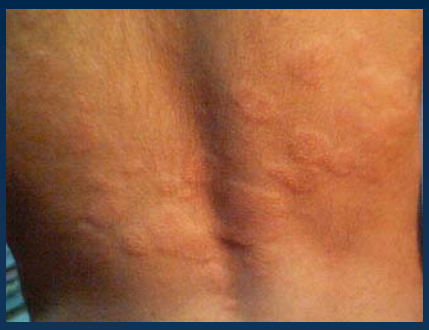
Exanthematous (maculopapular)

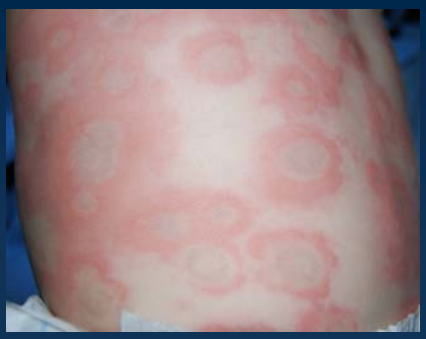
- Commonest
- Erythematous morbilliform maculopapular eruption on trunk and extremeties that usually fade with desquamation.
- Antimicrobials (penicillin, ampicillin) phenytoin, gold….



Urticaria

- 2nd most common.
- Type 1 or type 3 hypersensetivity reaction.
- Firm erythematous oedematous plaque with normal overlying epidermis lasting less than 24 hrs.
- Angioedema may be associated
- Ampicillin, salicylates, blood product, vaccines, radiocontrast agents…





Management of Urticaria

- The most important step in the treatment of drug induced urticaria is withdrawal of causative agent with administration of systemic antihistamine.

Angioedema

- Is transient edema involving deep dermis and subcutaneous & submucosal tissues which can affect airway, mucosa, and bowels.
- Usually affect the eyelid ,lips, ears, extremities & genetalia
- Associated with urticaria in 50% of cases.
- The major drugs involved in angioedema are:
  - ✓ ACE inhibitors , Penicillin , NSAIDS.

Angioedema

- may be complicated by life-threatening anaphylaxis which present with hypotension & tachycardia .

Management : Angioedema

- Withdrawal of drug
- Antihistamines, corticosteroids
- Epinephrine may be needed if airway is affected.
- Report of FFP used in refractory case (to above and IVIg, CSA)

DRESS Syndrome: I

- Drug Rash with Eosinophilia and Systemic Symptoms
- Formerly called Hypersensitivity Syndrome (HSS)
- Typically presents with rash and fever (87%), classically erythematous papules and pustules associated with facial oedema .
- Other severe systemic manifestations such as hepatitis (51%), arthralgias, lymphadenopathy (75%), interstitial nephritis (11%), or hematologic abnormalities (30%).
- Hematologic abnormalities include eosinophilia, thrombocytopenia, neutropenia, and atypical lymphocytosis.
- Can affect any organ system (lungs, CNS, GI, etc.)
- Skin biopsy is non-specific.

DRESS Syndrome: II

- Common causes:
  - aromatic anticonvulsants (carbamazepine, phenytoin, phenobarbital, etc.) and sulfonamides.
- Other drugs implicated:
  - lamotrigine
  - allopurinol
  - NSAIDs.
  - Minocycline

DRESS Syndrome: III

- Usually occurs 2-6 weeks after initiation of the medication, which is later than most drug eruptions.
- Treatment is supportive.
- Medication should be stopped as soon as the diagnosis is suspected.
- Corticosteroids have been required in some cases, but their use is controversial.

Erythema multiforme (EM)

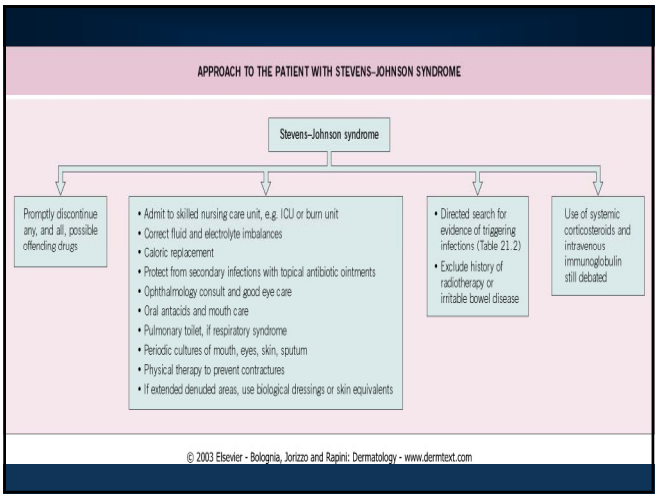
- This includes a spectrum of diseases (eg, EM minor, EM major); however, many authorities categorize SJS and TEN as EM major and differentiate them by body surface involvement
- EM minor - this is a mild disease; patients are healthy. It is characterized by target lesions distributed predominantly on the extremities . Mucous membrane involvement may occur but is not severe. Patients with EM minor recover fully, but relapses are common. Most cases are due to infection with herpes simplex virus, and treatment and prophylaxis with acyclovir is helpful.

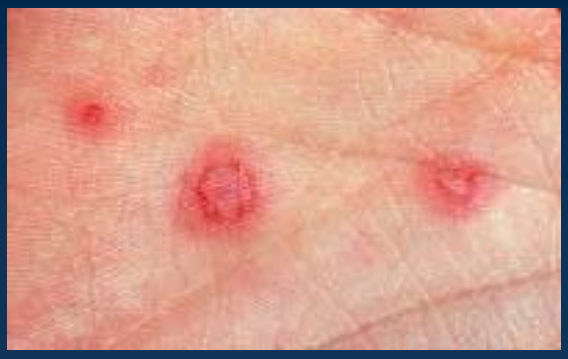
Stevens-Johnson syndrome (SJS)

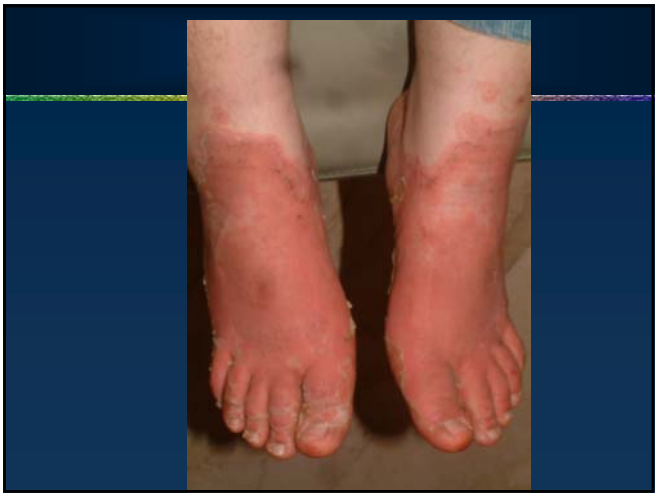
- Widespread skin involvement, large and atypical targetoid lesions, significant mucous membrane involvement, constitutional symptoms, and sloughing of 10% of the skin. SJS can be caused by drugs and infections (especially those due to *Mycoplasma pneumoniae*).
- SJS/TEN overlap: Epidermal detachment involves 10-30% of body surface area.

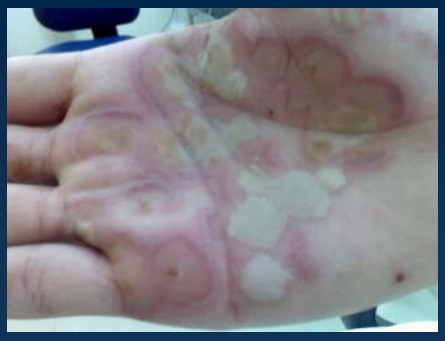
Toxic Epidermal Necrolysis (TEN)

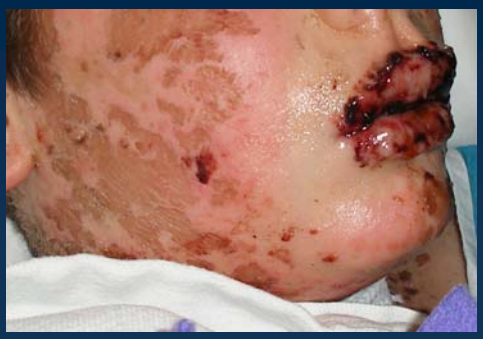
- This is a severe skin reaction that involves a prodrome of painful skin (not unlike sunburn) quickly followed by rapid, widespread, full-thickness skin sloughing. It typically affects 30% or more the total body surface area. Secondary infection and sepsis are major concerns, and pneumonia may develop from aspiration of sloughed mucosa. Most cases are due to drugs.
- The risk of TEN in HIV-positive patients is 1000-fold higher than in the general population.











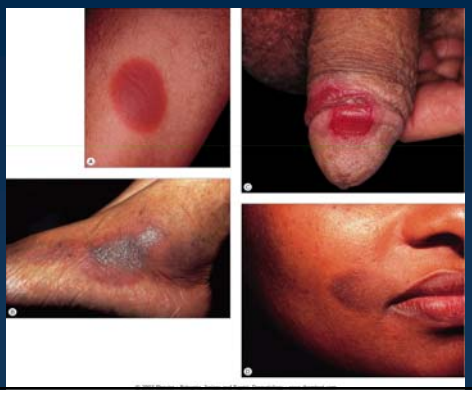
Fixed drug eruptions

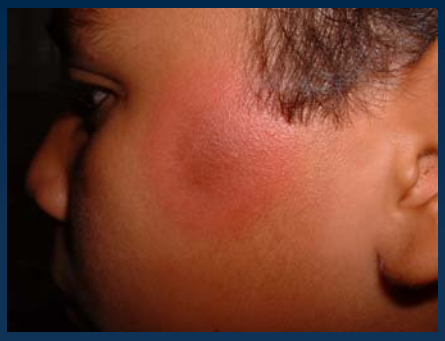
- Lesions recur in the same area when the offending drug is given . Circular, violaceous, edematous plaques that resolve with macular hyperpigmentation is characteristic. Lesions occur 30 minutes to 8 hours after drug administration. the hands, feet, and genitalia are the most common locations

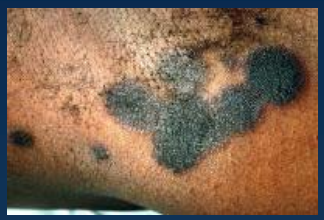
Leukocytoclastic vasculitis

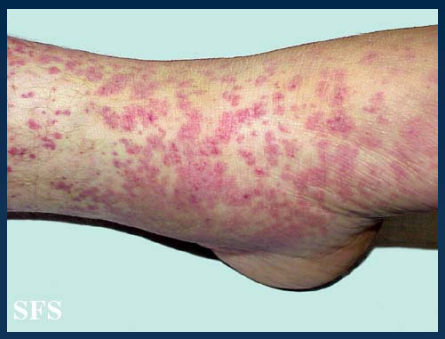
- This is the most common severe drug eruption seen in clinical practice . It is characterized by non blanching erythematous macules quickly followed by palpable purpura. Fever, myalgias, arthritis, and abdominal pain may be present. It typically appears 7-21 days after the onset of drug therapy, and a laboratory evaluation to exclude internal involvement is mandatory.

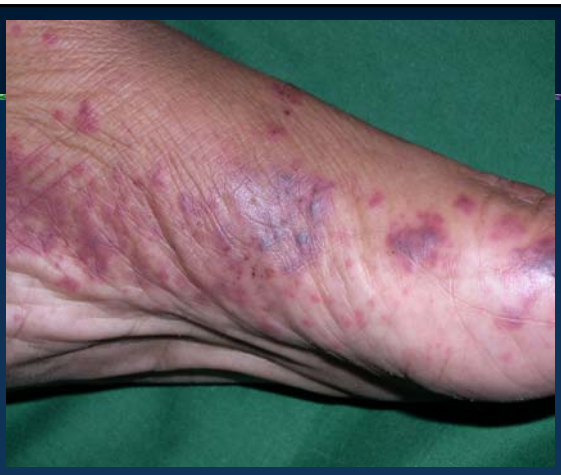
Fixed Drug Eruptions











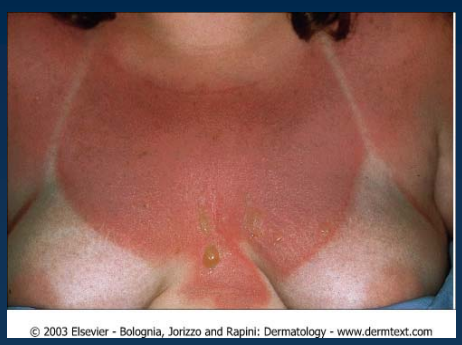
Photosensitivity

- Two types include phototoxic eruptions and photoallergic eruptions.
- Phototoxic eruptions are due to absorption of UV light (usually UVA) by the drug, which causes a release of energy and damage to cells. Looks like a bad sunburn, which may blister.
- Photoallergic eruptions are a lymphocyte-mediated reaction caused by exposure to UVA, which converts the drug to an immunologically active compound that activates lymphocytes, causing an eczematous reaction in a photodistribution.

Photosensitivity

- Usually due to topical agents including fragrances and sunscreens.
- Both types can be caused by phenothiazines, chlorpromazine, sulfa, and NSAIDS, although phototoxic reactions are more common with these agents.

Photosensitivity

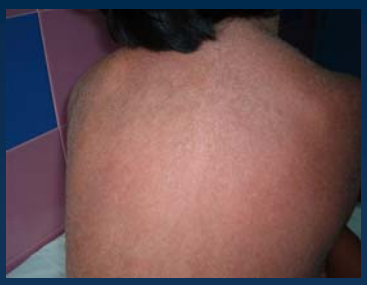


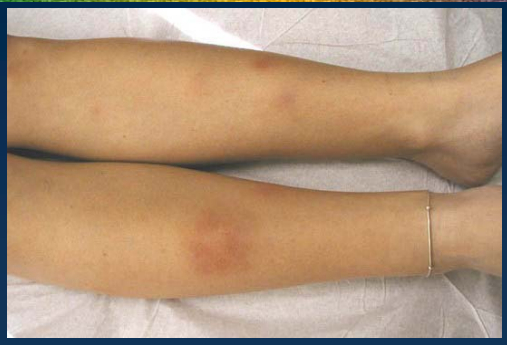
Erythroderma

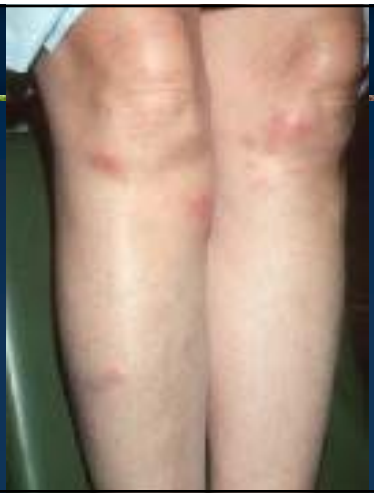
- This is widespread inflammation of the skin , and it may result from an underlying skin condition, drug eruption, internal malignancy, or immunodeficiency syndrome. Lymphadenopathy is often noted, and hepatosplenomegaly, leukocytosis, eosinophilia, and anemia may be present.

Erythema nodosum

- This is characterized by tender, red, subcutaneous nodules that typically appear on the anterior aspect of the legs. Lesions do not suppurate or become ulcerated . It is a reactive process often secondary to infection, but it may be due to medications, especially oral contraceptives and sulfonamides



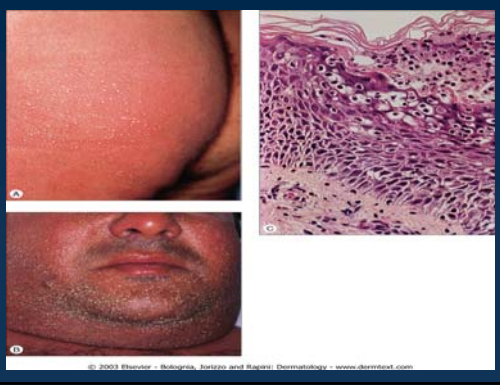




Acute generalized exanthematous pustulosis (AGEP)

- Acute-onset fever and generalized scarlatiniform erythema occur with many small, sterile, nonfollicular pustules.
- The clinical presentation is similar to pustular psoriasis, but AGEP has more marked hyperleukocytosis with neutrophilia and eosinophilia.
- Most cases are caused by drugs (primarily antibiotics) often in the first few days of administration. A few cases are caused by viral infections, mercury exposure, or UV radiation.
- AGEP resolves spontaneously and rapidly, with fever and pustules lasting 7-10 days then desquamation over a few days.

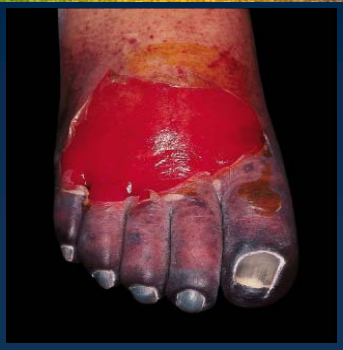
Acute generalized exanthematous pustulosis (AGEP)



Anticoagulant Skin Necrosis

- A rare [1: 10000], some times life-threatening reaction by warfarin due to ischemic infarcts by occlusive thrombi.
- Typically begin 3-5 days after therapy.
- Clinically erythematous, painful plaques → hemorrhagic blisters and necrotic ulcers.
- Most common site : breast, thighs and buttocks.
- Those with hereditary protein C deficiency are at high risk.
- Heparin → induction of platelet aggregates →thrombosis + skin necrosis both at site of injection and at distant sites as well as internal organs.
- Thrombocytopenia , but other coagulation profile are normal.

Anticoagulant Skin Necrosis



Approach to drug eruptions

Table 23.4 Logical approach to determine the cause of a drug eruption.
*Often inadvertant.

LOGICAL APPROACH TO DETERMINE THE CAUSE OF A DRUG ERUPTION	
Drug responsibility assessment	
Clinical characteristics	• Type of primary lesion • Distribution and number of lesions • Mucous membrane involvement • Associated signs and symptoms: fever, pruritus, lymph node enlargement, visceral involvement
Chronological factors	• Document all drugs to which the patient has been exposed and the date of introduction • Date of eruption • Timing of interval following initial administration and skin eruption • Response to removal of the suspected agent • Response to re-challenge*
Literature search	• Bibliographic research (e.g. Medline) • Drug Alert Registry or Medwatch • Data collected by pharmaceutical companies • In the case of recently released medications, extrapolation based on the class of drug

Lab Studies

- History and physical examination are often sufficient for diagnosing mild asymptomatic eruptions.
- Severe or persistent eruptions may require further diagnostic testing.
  - Biopsy can be helpful in confirming the diagnosis of a drug eruption.
  - CBC count with differential may show leukopenia, thrombocytopenia, and eosinophilia in patients with serious drug eruptions.
  - Serum chemistry studies may be useful. Liver involvement leading to death can occur in persons with hypersensitivity syndromes. Special attention should be paid to the electrolyte balance and renal and/or hepatic function indices in patients with severe reactions such as SJS, TEN, or vasculitis

Treatment: I

- Treatment of drug eruptions is generally supportive and depend on severity.
- There are five issues to be considered in possible drug eruptions:
  - ✓ The assessment of the cutaneous eruption
  - ✓ The probability of a relation between the cutaneous eruption and the drug
  - ✓ If a drug eruption is probable, clinical and laboratory factors that might alert the clinician to the potential seriousness of the eruption
  - ✓ The management of the eruption
  - ✓ The prevention of future eruptions to include patient education

Treatment: II

- Symptomatic treatment primarily is predicated on the discontinuation of the offending agent, if possible.
- Antihistamines help to relieve pruritus and the signs and symptoms of urticaria and angioedema.
- Topical and systemic corticosteroids can provide additional relief. Topical corticosteroids are most beneficial for eczematous disease, but provide little benefit in urticaria.

Treatment: III

- **Life-threatening reactions such as angioedema and anaphylaxis** require prompt treatment with epinephrine, antihistamines, and/or systemic corticosteroids.
- **Treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis** includes fluid replacement, pain control, and often antibiotics to prevent secondary infection. The role of systemic corticosteroids, intravenous immunoglobulin, and plasmapheresis in these conditions is controversial.

Treatment: IV

- **Warfarin necrosis** treated by its discontinuation, parenteral vitamin K, and monoclonal protein C concentrate.
- **Desensitization** is a reasonable approach for patients with an allergy to penicillins, cephalosporins, or sulfonamides.

懇請賜教