Antimicrobial Allergy Evaluation Tool

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, May 2016)

Reaction (as indicated in the patient's chart ☐ or described by the patient ☐)

Personal history

☐Asthma ☐Autoimmune disease ☐Atopic dermatitis ☐Latex allergy ☐Prior anaphylaxis
☐ Multiple drug intolerance syndrome ☐ Multiple drug allergy syndrome ☐Food allergy: _____
☐Other:_____

Patient questionnaire

1. When did the reaction take place? _____
2. How old was the patient at the time of the reaction? _____
3. Does the patient recall the reaction? If not, who informed them of the reaction? _____
   _____
4. Does the patient remember which medication? _____
5. What was the medication prescribed for? _____
6. What was the route of administration? _____
7. How long after starting the medication did the reaction begin? _____
   _____
8. Describe the reaction: _____
   _____
9. Did the patient seek medical care due to the reaction? _____
10. Was the medication discontinued? If so, what happened after it was discontinued? _____
    _____
11. Did the patient have any other ongoing medical problem at the time of the reaction? _____
    _____
12. What other medications was the patient taking? Why and when were they prescribed? _____
    _____
13. Has the patient taken any similar medications before or after the reaction? If so, what was the result? ____
    _____
14. Has the patient ever experienced this reaction without intake of the suspected medication? _____
    _____

Assessment

☐ Probable **non-severe delayed hypersensitivity reaction (non-IgE mediated)**
☐ Probable **non-allergic adverse reaction or intolerance**
☐ Probable **type 1 immediate hypersensitivity reaction (IgE mediated)**
☐ Probable **severe delayed hypersensitivity reaction (non-IgE mediated)**

Completed by:_____ Date/time:_____

Table 1: Patient questionnaire[1,2,4,5,6,7,12,13,14]

Question	Comments
When did the reaction take place?	Patients with type 1 immediate (IgE-mediated) hypersensitivity reactions to penicillin may lose their sensitivity over time (50% after 5 years, and 80% after 10 years)
How old was the patient at the time of the reaction?	Certain confounding factors may be more common depending on the patient's age. (Example: viral exanthems in pediatric patients)
Does the patient recall the reaction? If not, who informed them of the reaction?	Vague histories **do not** rule out serious reactions. However, it is less likely to be a serious hypersensitivity reaction if the patient or family cannot recall the specifics of the reaction.
Does the patient remember which medication?	Knowing the specific antimicrobial which caused the reaction can help in determining safe alternatives.
What was the medication prescribed for?	Sometimes patients confuse symptoms of the condition with adverse reactions of the medication. (e.g.: *Strep. pyogenes* scarlet fever rash being confused as a drug-reaction)
What was the route of administration?	Hypersensitivity reactions can be more common when medications are administered intravenously compared to orally.
How long after starting the medication did the reaction begin?	Timeframe is essential to distinguish between an IgE-mediated immediate hypersensitivity reaction or non-IgE mediated delayed reaction.
Describe the reaction.	Obtain specific information from the patient. (Ex: if a rash; determine location, morphology, etc.)
Did the patient seek medical care due to the reaction?	Can be of value to stratify how severe the reaction was.
Was the medication discontinued? If so, what happened after it was discontinued?	Discontinuing the medication will have varying results. (e.g.: depending on the type of skin reaction, symptoms may or may not improve after discontinuation)
Did the patient have any other ongoing medical problem at the time of the reaction?	Certain viral infections [e.g. Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Human immunodeficiency virus (HIV), Cytomegalovirus (CMV)] are associated with non-IgE mediated cutaneous drug reactions that are often misdiagnosed as "allergic reactions".
What other medications was the patient taking? Why and when were they prescribed?	Concomitant medications could cause or contribute to the reaction.
Has the patient taken any similar medications before or after the reaction? If so, what was the result?	Tolerance of structurally similar medications is not always indicative of tolerance of the suspected medication; however, it can assist in determining safe alternatives.
Has the patient ever experienced this reaction without intake of the suspected medication?	If the same reaction has occurred without exposure to the suspected medication, it may be caused by other factors.

Therapeutic review

Allergy evaluation is an essential component of patient care. Beta-lactams, as a class, are generally safe; allergic and adverse reactions are over diagnosed and over reported. For example, up to 10% of the population will report a penicillin allergy; but up to 95% (or more) of these patients do not have a true allergy.[4,6,11]

Fearing a potential anaphylaxis secondary to beta-lactam use, many clinicians will over diagnose penicillin allergy or simply accept a diagnosis of penicillin allergy from patients without a proper history of the reaction.[2] Studies have shown that physicians are more likely to prescribe antimicrobials from other classes when patients have a documented penicillin or cephalosporin allergy.[2,9] Non beta-lactam alternatives may be: less effective, more toxic, broader spectrum, more expensive and more likely to lead to infection or colonization with resistant organisms.[6,9] Unfortunately, a penicillin allergy label is not benign. Simply being labelled as having an allergy to penicillin increases the likelihood of prolonged hospital stay and increases the risk of infections due to *Clostridium difficile*, vancomycin-resistant *Enterococcus* (VRE), and methicillin-resistant *Staphylococcus Aureus* (MRSA).[10]

Most patients have no current physical findings that can either prove or disprove their allergy label.[2] The initial probability of a true allergy is almost always determined by the allergy history.[2] The included patient questionnaire can assist clinicians in obtaining a detailed allergy history.

A detailed investigation of the patient's allergy history is necessary to differentiate between true type 1 (IgE-mediated) immediate hypersensitivity reactions (true allergic reactions) and non IgE-mediated hypersensitivity reactions or intolerances/adverse reactions. While some of the non IgE-mediated reactions are minor, other types of reactions can be severe (e.g. interstitial nephritis, immune hepatitis, hemolytic anemia, serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, etc.). Table 2 below subdivides the reactions based on the Coombs and Gell classification of hypersensitivity reactions:

Table 2: Coombs and Gell Classification of Hypersensitivity Reactions [6,7]

Type	Mediator	Onset	Clinical Reaction	Comments
I - Immediate and Acute hypersensitivity	IgE antibodies	Within 1hr (Rarely up to 72 hours)	Anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis	Anaphylaxis: Penicillins 0.01-0.05% Cephalosporins 0.0001-0.1%
II – Delayed cytotoxic antibody-mediated hypersensitivity	IgG and IgM antibodies	Greater than 72 hours	Hemolytic anemia, thrombocytopenia, neutropenia	Drug specific
III – Antibody complex-mediated hypersensitivity	IgG and IgM complexes	Greater than 72 hours	Serum sickness, glomerulonephritis, small vessel vasculitis, drug fever	Antibody-antigen complexes precipitate in tissues and potentially affect any end organ
IV – Delayed type hypersensitivity	T-Cells	Greater than 72 hours	Contact dermatitis, pustulosis	Incidence is low. Ex: Eosinophilia, bullous exanthems, severe exfoliative dermatoses (ex. SJS/TEN), interstitial nephritis, immune hepatitis and some morbilliform or maculopapular rashes
Idiopathic Reactions	Unknown	Usually greater than 72 hours	Maculopapular or morbilliform rashes	1 – 4% of patients receiving beta-lactams

The time to onset of the reaction can be a helpful tool in determining if the reaction was in fact a true type 1 immediate (IgE-mediated) hypersensitivity reaction. Type 1 reactions usually occur within an hour of exposure, with the possibility of occurring up to 72 hours post-exposure, and can include anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor and pruritis.[5,6,7]

Cutaneous reactions

Many patients may report a "rash" as an allergic reaction; however more information should be sought to assist in defining the true nature of the reaction. Cutaneous reactions can range from non-severe delayed maculopapular rashes to life-threatening toxic epidermal necrolysis; therefore it is essential to further question the patient.

Certain infections can either cause cutaneous reactions or predispose patients to reacting to antimicrobials. Patients suffering from certain bacterial infections (e.g. *Streptococcus pyogenes*, *Mycoplasma pneumoniae*) can develop cutaneous symptoms, irrespective of which antibiotic is used.[18,22] Certain viral infections [e.g. Epstein-Barr virus (EBV), Herpes simplex virus (HSV), Human immunodeficiency virus (HIV), Cytomegalovirus (CMV)] can also directly cause cutaneous symptoms.[14,18,22] Patients suffering from these viral infections may also be at a higher risk to react to certain antimicrobials.[2,4,12,13] A notable example is the delayed morbilliform rash that often develops when patients suffering from EBV are treated with an aminopenicillin, such as amoxicillin.[4,18]

Please see table 3 below for a brief description of certain cutaneous reactions.

Table 3 – Cutaneous reactions [1,2,15,16,18,19,20,21]

Type of skin reaction	Chronology	Description
Angioedema	Onset: Usually immediate (0-6 hours) Duration: Resolution within 24-72 hours	Region(s) affected: Lips, eyelids, earlobes, tongue, mouth, larynx, genitalia Morphology: Skin-coloured circumscribed edema involving the subcutaneous tissues. (can be asymmetrical/unilateral) More details: Non-pruritic; often very frightening for patients; can be painful
DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms)	Onset: 1-8 weeks after exposure Duration: Weeks-months (even after discontinuing the suspected medication)	Region(s) affected: Classic distribution: Face, upper trunk, extremities (but can progress anywhere on the surface of the skin and can sometimes have mucosal involvement) Morphology: Most commonly begins as an erythematous, pruritic, morbilliform rash More details: Pruritis and fever usually precede cutaneous eruptions. Can cause facial edema, which can be mistaken for angioedema. Systemic systems involved: - Lymphatic: lymphadenopathy is very common - Hematologic: leukocytosis, eosinophilia, lymphocytosis - Hepatic: hepatosplenomegaly, hepatitis, elevated liver transaminases, elevated alkaline phosphatase - Renal: hematuria, proteinuria, elevated BUN and creatinine - Other: pulmonary, cardiac, neurologic
Erythema multiforme	Onset: Within 3-5 days (May include prodromal symptoms of an upper respiratory infection) Duration: Approximately 2 weeks	Region(s) affected: Often appear on the extremities (hands, palms, extensor of the forearms, soles of the feet, etc.) and can spread inwards towards the trunk. May involve mucous membranes of the mouth and genitalia. Morphology: Well-demarcated, circular, erythematous papules; often "target" or "iris"-like. More details: - Can be difficult to discern from Stevens-Johnson Syndrome - Often associated with HSV or mycoplasma infections - Fever, if present, is usually mild

Type of skin reaction	Chronology	Description
Maculopapular rash / Morbilliform rash / Exanthems	Onset: Delayed (often more than 72 hours), within the first 2-4 weeks following the initial dose Duration: Usually fades within 2 weeks	Region(s) affected: Commonly begin on head, neck or upper torso, and progress downward to the extremities. Morphology: Often bilateral and symmetrical. Usually flat, barely raised, erythematous patches (one to several mm in diameter). Can also include papules. More details: - With or without pruritis - Can develop into confluent areas - Can be the result of several mechanisms (ex: viral infection, idiopathic, etc.) - Mild eosinophilia is possible, but not common - Fever rarely associated; but is mild if present
Photosensitivity / Phototoxicity	Onset: 5-20 hours after drug + UV light exposure Duration: N/A	Region(s) affected: Areas most often exposed to the sun (ex: face, back of the hands, back and sides of the neck, extensor surfaces of the forearm, etc.). Classical presentation spares shaded areas, such as under the chin, under the nose, behind the ears. Morphology: Often resembles exaggerated sunburn, sometimes with blisters. Sharp demarcation at sites where clothing or jewelry were present during light exposure. More details: Not common with beta-lactam antibiotics
Pruritis	Onset: N/A Duration: N/A	Region(s) affected: Localized or generalized itching; more often generalized when drug induced. Morphology: Does not require visible cutaneous signs of a reaction. More details: Mechanism not always clear
Stevens-Johnson syndrome	Onset: Delayed (within 8 weeks of first exposure), but with abrupt onset of symptoms. Duration: Up to 6 weeks	Region(s) affected: Less than 10% of the body surface is affected. Can affect the skin, eyes, and mucous membranes; such as the lips, mouth, and genital mucous membranes. Morphology: Often begins with dusky red, flat lesions (sometimes target-like, similar to erythema multiforme), progressing to bullae and necrotic lesions. Leads to blisters and dislodgement of the epidermis. More details: - Is accompanied by any (or all) of: high fever, malaise, myalgia, arthralgia, headache, ocular involvement, painful stomatitis - A medical emergency; in-hospital mortality = 5-12 %
Toxic epidermal necrolysis	Onset: Delayed (within 8 weeks of first exposure), but with abrupt onset of symptoms. Duration: Up to 6 weeks	Region(s) affected: Greater than 30% of the body surface is affected. Can affect the skin, eyes, and mucous membranes; such as the lips, mouth, and genital mucous membranes. Hairy regions of the skin are often spared. Morphology: See Stevens-Johnson Syndrome; eventually can resemble extensive second degree burns More details: - Is accompanied by any (or all) of: high fever, fatigue, vomiting, diarrhea, malaise, myalgia, angina, arthralgia, headache, ocular involvement, painful stomatitis - A medical emergency; in-hospital mortality more than 30%

Type of skin reaction	Chronology	Description
Urticaria	Onset: Immediate, usually within 36 hours Duration: Rarely persist for more than 24 hours	Region(s) affected: Can occur in any location. Involves the superficial portion of the dermis, and not subcutaneous tissues. Morphology: Raised, erythematous areas of edema (wheals), sometimes with central pallor. Will often blanch with pressure. More details: - Often pruritic - May or may not be accompanied by angioedema, can progress to anaphylaxis

For more information, please see the **Management of Penicillin and Beta-Lactam Allergy** guideline prepared by the NB Provincial Health Authorities Anti-Infective Stewardship Committee.

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