

Infection and Drug Induced Muco-cutaneous Blistering Diseases (RIME/DEN) Clinical Care Guidelines

Version: 1

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1.0 Introduction

Cutaneous blistering reactions secondary to drug exposure while rare, pose diagnostic and management challenges. Severe cutaneous drug related adverse reactions (SCARs) include acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Infectious entities such as staphylococcal scalded skin syndrome (SSSS) and reactive processes secondary to infection (e.g. RIME) may resemble these conditions and prompt recognition and treatment is necessary to improve outcomes and prevent aggressive unnecessary management.

This guideline uses the terminology proposed in the British Journal of Dermatology's 2021 publication, which is based on expert panel opinion and supportive literature mostly from adults.

1.1 Target Users

Physicians, Nurse Practitioners, Physician Assistants, Pharmacists, Nurses in the Emergency Department, Pediatric Medicine, ICU, Dermatology, and Plastic Surgery

1.2 Objectives

- To standardize management approaches and initial assessments
- To standardize treatment
- To clarify what consult service is responsible for directing care

2.0 Definition: Infection and Drug Induced Muco-cutaneous Blistering Diseases

2.1 Diagnosis of Reactive Infectious Mucocutaneous Reaction (RIME)

To make a diagnosis of RIME there has to be evidence of an infectious trigger, which can be suspected if there is a history of cough, fever, malaise or arthralgias in the preceding 7-10 days (prodrome) or a clinical examination or investigations that support a respiratory infection.

Supportive investigations may include chest radiograph or laboratory tests.

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To confirm a diagnosis of RIME, **at least 2** of the following must be present:

- Non-contributory medication history
- Erosive mucositis affecting 2 or more sites, or
- Vesiculobullous lesions/atypical, often bullous, targets most commonly affecting less than 10% BSA

Although skin involvement is more commonly limited, it can at times exceed 10% of body surface area (BSA).

Supporting features include prodromal symptoms (fever, upper respiratory symptoms, feeling unwell) and histology excluding other diagnosis.

2.2 Diagnosis of Drug Induced Necrolysis (DEN)

Rapidly progressive erythema and epidermal detachment, relevant medication history and if performed, histology that excludes other diagnoses (e.g. autoimmune blistering disorders).

To confirm a diagnosis of DEN, there has to be a relevant medication history with exposure in the prior 4-28 days. It must also have **at least 2** of the following:

- Erosive mucositis of 2 or more sites
- ≥10% detached or detachable skin
- Constitutional/site-specific signs or symptoms
- Tender skin in the absence of other features of SSSS (e.g. periorificial crusting and predominant folds involvement), generalized distribution with centrifugal spread and a morphology of flat, atypical targets also supports this diagnosis

2.3 Differentiating Features of Skin Syndromes

Features	Staphylococcal Scalded Skin Syndrome (SSSS)	Erythema Multiforme	Reactive Infectious Mucocutaneous Reaction (RIME)	Drug Induced Necrolysis (DEN)
Constitutional Symptoms (fever, malaise, unwell)	Yes	No	Yes/No	Yes
Generalized Erythema	Yes and Tender	No	No	Yes
Typical target lesions (3 rings: dusky centre, pale ring, red rim)	No	Yes	Yes/No	No
Atypical targets (have an edematous centre or blister/bulla and less often 3 rings)	No	No	Yes	Yes
Epidermal Detachment	Yes, especially folds	No	No	Yes
Body Surface Area Percentage (BSA %)	10-60	< 10	< 30	>30

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Features	Staphylococcal Scalded Skin Syndrome (SSSS)	Erythema Multiforme	Reactive Infectious Mucocutaneous Reaction (RIME)	Drug Induced Necrolysis (DEN)
Mucosa Involvement (mouth, eyes, nose, genitalia)	No, periorificial crushing	Yes, typically mouth	Yes, 1-2	Yes, severe, >2

3.0 Guideline

3.1 Initial Assessment

Evaluation at patient presentation includes a thorough history including medication history, a physical examination, and laboratory investigations.

3.1.1. History

- a. Known allergies
- b. Chronology of all medications
- c. Chronology of symptoms
- d. History of herpes virus infection or other infectious history including respiratory symptoms
 - i. Before the rash appears, there is usually a prodromal illness of several days duration, resembling an upper respiratory tract infection or “flu-like” illness
 - ii. Symptoms may include:
 1. Fever > 39
 2. Sore throat, difficulty swallowing
 3. Rhinorrhea and cough
 4. Sore red eyes, conjunctivitis
 5. Generalized pains/aches
- e. Medication history
 - i. Timeline of any and all medications exposures (including over the counter medications, eye drops, supplements, naturopathic and homeopathic medications)
 - ii. Common culprit drugs – anticonvulsants, sulpha drugs, allopurinol, cough syrups
 - iii. Drugs started in the last 2 days are less likely to be causative particularly if these are antibiotics started for cough or suspected pneumonia
 - iv. Associated symptoms – difficulty swallowing, respiratory distress, difficulty urinating
 - v. Pain

3.1.2 Physical Examination

Skin – extent of epidermal involvement (body surface and mucosal involvement)

- Ensure photos are taken of all areas that are involved including areas of erythema (diffuse redness) where red skin is still intact

- Document morphology of skin lesions
- Calculate BSA using the Lund and Browder Chart

Mucosa

- Identify areas of mucosal involvement (eyes, oral/pharyngeal, genital, rectal)
- Identify types of mucosal involvement (erosions, ulcers, crusting, apthae)

3.1.3. Laboratory Investigations

- Comprehensive blood work including CBC, CRP, ESR, liver function tests, BUN, creatinine, glucose, bicarbonates, electrolytes
- Mycoplasma PCR (nasopharyngeal/throat swab) and serology
- Nasopharyngeal viral swab panel including COVID
- Consider Herpes Virus PCR from atypical lesions in skin or mucosa
- Chest x-ray (if patient has respiratory symptoms and signs)

3.1.4. STOP ALL potentially offending/unnecessary medications

3.2 Consults

- For patients with < 10% BSA affected, notify Dermatology only.
- For patients with ≥ 30% BSA affected, notify both Dermatology and Burn Team (Plastic Surgery Department)

Additional consults for consideration depending on patient presentation:

- Clinical Pharmacology
- Ophthalmology
- Urology/Gynecology
- CCRT or PICU
- Infectious Diseases

3.3 Patient Admission

Admission location will depend on the patient’s BSA involvement and need for airway support

	Paediatric Medicine	Paediatric Medicine + Consult PICU	PICU
BSA %	< 10%	10-30%	>30%
Need For Airway Support	No	No	Yes/No

3.4 Severity Assessment

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A severity assessment is performed by the Dermatology or Burn Team

- Total body surface area (TBSA) affected at day 3
 - SCORTEN Criteria calculation within 24 hours of admission and again, on day 3 of admission
- The SCORTEN system considers independent risk factors, where each factor present adds one point to the total score.
1. Age >40 years
 2. Presence of malignancy
 3. Heart rate >120 beats per minute
 4. Initial epidermal detachment > 10% of total body surface area
 5. Serum urea > 10 mmol/L
 6. Serum glucose > 14 mmol/L
 7. Bicarbonate < 20 mmol/L

4.0 Management

4.1 Supportive Care

4.1.1. Fluids and Electrolytes

- Consider baseline needs plus additional fluids based on the estimated loss due to denuded BSA
- Fluid replacement may be required due to insensible losses from wounds, dehydration due to impaired oral fluid intake, or intravascular volume contraction if the patient is ill.

4.1.2. Nutrition

- **Immediate start of NG feeds**
- Contraindication: severe mucosal ulceration that prevents a safe tube insertion

4.1.3. Secure IV access; Consider early PICC line insertion

4.2. Pain Control

- Consider involving Acute Pain Service and Anesthesia early on
- NSAIDs should be avoided due to risk of GI bleeding
- Consider initiation of an opioid infusion (\pm adjunctive pain medication) where TBSA involvement is > 20-30%
- An appropriate time to commence opioid weaning is when skin involvement is at least 80% healed or by 8-10 days

4.3. Airway (PICU)

- An ETT may be required for cases where there is excessive oral involvement typically for 2 weeks

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- A two-part fixation is required (stability wire and suture for securement) and is reviewed daily by the RT in the PICU. External ties/tapes are not used due to facial involvement.
- Any changes of the fixation of the ETT for patients with TEN are strongly recommended to be done in the OR due to oral/pharyngeal involvement

4.4. Skin and Wound Care

The aim of skin management is to:

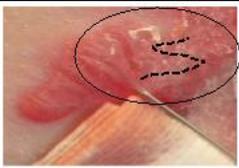
- Drain blisters and prevent blister spread and sloughing
- Decrease pain
- Prevent bacterial superinfection

BSA Involvement	Primary Consulting Team	Who provides Wound Care?
< 10%	Dermatology	Bedside Nursing Team with support from Wound Care Team and Dermatology
≥ 10%	Burn Team	Burn Team

4.4.1. Blister Management

Wherever possible, blister fluid should be released by puncturing any blister > 1 cm and draining the fluid. The skin should be left intact to serve as a biological dressing.

Steps for Blister Management

Step 1	Organize equipment: <ul style="list-style-type: none"> - Towel - Sterile needle - Sharps container - Sterile gauze - Dressings <ul style="list-style-type: none"> ○ Non-stick dressings (e.g. Telfa, Mepilex, Urgotul), and ○ Silver non-stick dressings (e.g. Mepilex Silver, Urgotul Silver) 	
Step 2	Aim for the edge of the blister where gravity is pulling the fluid. Gently tear blister roof with a needle. Using a zigzag motion with a needle, lift the roof away.	
Step 3	Use gauze to absorb blister fluid.	
Step 4	Leave the overlying roof to protect the skin underneath.	

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Step 5	If the blister is large or still draining, apply a non-adherent dressing.	
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4.4.2. Blister Dressings

Blister dressings should be non-stick, silicone dressings with silver (e.g., mepilex Ag, urgotul Ag) and covered with gauze and secured within burn net.

Change dressings every 2-3 days. During dressing changes, assess BSA blistering, denuded skin and re-epithelization, and skin infection.

4.4.3. Skin Biopsies

Dermatology considers skin biopsies if there is suspicion of other skin diseases (e.g. pemphigus vulgaris, bullous pemphigoid).

If skin biopsies are needed, 2 skin biopsies should be completed (1 for H&E and 1 for direct immunofluorescence (DIF)).

H&E	DIF (Direct Immunofluorescence)
4 mm punch biopsy is taken and sent to the pathology lab in formalin.	3-4 mm punch biopsy from uninvolved skin or perilesional skin is sent as a fresh sample on saline gauze. <i>Call pathology to pick up or place in Michel media after hours.</i>

4.4.4. Debridement

Debridement is the manual removal of skin and can be considered for necrotic skin only. It is ideally performed under sedation by the Burn Team.

Silver dressings (Acticoat or similar) should be used, with an outer layer that can be changed without causing discomfort.

Change dressings every 2-3 days. During dressing changes, assess BSA blistering, denuded skin and re-epithelization, and skin infection.

4.5. Mucosal Care

4.5.1. Eyes

Urgent referral to Ophthalmology, within 24 hours and ideally to members of the Cornea Team.

Document the extent of ocular surface ulceration and take images of the ocular surface. Where possible, to limit patient discomfort, complete eye examinations and imaging in combination with other procedures such as dressing changes.

Daily review by Ophthalmology with the administration of topical steroids, antibiotics, and lubricants, as needed. Use preservative-free formulations of topical agents, if available. Significant conjunctival membranes will be debrided under topical anesthesia.

In cases with severe ulceration, amniotic membranes may need to be placed over the ocular surface. This is ideally done within 72 hours of presentation. This can be done at the bedside in the PICU, in combination with other procedures or in the operating room.

4.5.2. Lips

Intrasite gel may be applied to keep lips moist and prevent scab formation. Gentle sterile water soaks can be used between applications.

A Telfa Gauze with saline and petroleum jelly can be used to keep lips moist. This should be changed every 2 hours to prevent bleeding from the lips. This can be used for patients with ETT tubes in situ.

Topical clobetasol ointments may be used to hasten healing for up to 5 days.

Antiseptic mouth washes can be used several times a day, especially after meals.

4.5.3. Genitals

Consult Urology/Gynecology if there is genital mucosa involvement.

Goals of treatment focus on preservation of anatomy:

- Consider insertion of a foley catheter.
- For females:
 - o Place a Telfa pad saturated with petroleum jelly between the labia minora to maintain separation.
 - o Petroleum jelly can be gently swabbed in the vagina to prevent adhesions.
- Mid-potency steroids may be used on non-denuded areas for up to 5 days

4.6. Medical Treatment

Medical Treatment is guided by the most responsible provider (Pediatrics or PICU) with a consult to Dermatology.

4.6.1 Treatment Options for RIME/DEN with < 10% BSA

- Option 1: Systemic Corticosteroids
 - o [Methylprednisolone IV](#) or [Prednisone PO](#)
 - o Consider IV if several mucosal involvement
- Option 2: Anti-TNF alpha agent Etanercept for patients ≥ 2 years
 - o To be ordered in consultation with Dermatology
 - o If ongoing new areas of blistering occurs, consider escalating therapies

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4.6.2. Treatment Options for DEN with $\geq 10\%$ BSA

- Option 1: Anti-TNF alpha agent [Etanercept](#) for patients ≥ 2 years
 - To be ordered in consultation with Dermatology
 - If ongoing new areas of blistering occurs, consider escalating therapies
- Option 2: [Cyclosporine](#) for 10 days
 - Consider IV if suspect GI involvement
 - Adjust for renal impairment
 - Evaluate need for longer treatment if there is evidence of blistering in areas that were previously unaffected or those that re-epithelized
 - Trough levels on day 2
 - Potential Adverse Events include renal dysfunction, hypertension, neutropenia, leukoencephalopathy, immunosuppression
- Option 3: Etanercept + Cyclosporine
- Option 4: Systemic Corticosteroids
 - Only in cases where the onset of disease is < 24 hours and there is $> 10\text{-}20\%$ BSA
 - [Methylprednisolone IV](#) or [Prednisone PO](#)
 - Consider IV if several mucosal involvements
- Option 5: [IVIg](#) for 1-3 days
 - Check if patient is IgA deficient
- Option 6: JAK Inhibitors ([Tofacitinib](#))
 - > 2 years and > 10 kg
 - At discretion of treating team if there is progression despite other treatments being used

5.0 Additional Recommendations

5.1 Photos of the skin are placed in the Electronic Health Record.

5.2 Disease Progression

Diagnosis can only be made by experienced clinicians that have previously viewed the wound and should not be made if the entire skin and wound is not examined. It is the responsibility of the Burn Team and Dermatology Service to see the wound when the outer dressings are changed and document skin involvement in the patient's electronic medical record.

5.3 Antibiotics

Prophylactic antibiotics are contraindicated especially in situations where severe adverse drug reactions have resulted in admission. Treatment of infections are guided by Paediatric Medicine or PICU.

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5.4 Notify all consult services when patient is discharged to ensure appropriate outpatient follow-up (e.g. ophthalmology, clinical pharmacology, etc.).

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