DERM ROUNDS:
A day in the life of the inpatient consult service

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Saturday June 29th, 9:30-10:15 am

Conflicts of Interest

- *I have no relevant conflicts of interest for this lecture.*

Learning Objectives

- Discuss how best to utilize the dermatology service in the inpatient setting and common pitfalls.
- Review common and uncommon skin conditions seen in hospitalized patients including drug reactions and infections, among others.
- Recognize those conditions that would require urgent diagnosis and intervention in the inpatient setting.

Outline

- Drug eruptions (cutaneous drug eruptions):
  - Morbilliform, drug hypersensitivity reactions, SJS/TEN
- Infectious related eruptions
  - Eczema cocksackium
  - Staph scalded skin syndrome
  - Unusual presentations of common bugs: lice, scabies
  - Strep infections
  - Mycoplasma induced eruptions
- Reaction patterns:
  - Urticaria multiforme
  - Urticaria

- **Drug eruptions (DE): drug eruption diagnoses are heavily based on clinical appearance and *history*. Ensure you consider a broad differential and rule out other causes. A drug timeline can be very helpful in patients on polypharmacy.**
  - *Morbilliform eruptions*
  - Drug hypersensitivity reaction (DHS)
  - SJS/TEN continuum
  - Reactions to chemotherapy/targeted-drugs

Cutaneous drug eruptions (general)

- Estimated that 50 to 100 of every 10,000 patients will develop a cutaneous eruption after starting a new drug.
- No comparison between adult and pediatric eruptions
- Age related pharmacokinetics
- Lack of clinical trial data for some drugs in children
- Genetics in family

Warning signs for CDEs

- Presence of mucosal involvement
- Systemic clinical manifestations
  - Facial swelling
  - Lymphadenopathy
- Blister formation
- Pustules and denuded skin
- Fever N 38°C (100.4°F)

Morbilliform drug eruption (MDE)

- 35% of children (compared to 85% of adults) with adverse CDRs
- Genetic risk factors
- Type IV delayed type hypersensitivity
- Immune reaction to viral and drug haptens
- Higher risk for further MDEs

MDEs

- It is important to rule out severe cutaneous adverse reactions, which can mimic a simple morbilliform drug reaction.
- Estimated 0.5-0.7% of children develop MDE when exposed to a new drug during hospitalization.
- It is important to accurately label a patient as allergic to a medication.

Type of DE	Onset	Incidence	Clinical	Common drugs
Morbilliform*	**4-21 days**	**35% of children**	**Pink to violaceous macules and papules on truck and extremities; rare MMs, can have low grade fever**	**Beta-lactam Abx, AED^, NSAIDS**
DHS*	2-6 weeks	Unclear (1 in 1,000 to 1 in 10,000 in adults)	Febrile prodrome, morbilliform skin changes, facial edema, conjunctivitis, mucositis, lymphadenopathy	Aromatic AEDs, lamotrigine, sulfa antibiotics
SJS/TEN (continuum)	Prodrome 1-3 weeks after medication	10% of all cases occur in children; overall rare	Morbilliform to targetoid plaques to full epidermal necrosis, bullae and vesicles; prodrome of fever, fatigue, sore throat, LAD	Phenobarbital, sulfa antibiotics, lamotrigine, carbamazepine

*(Virtually any drug can cause simple MDE)

Photos from Hurwitz Pediatric Dermatology

Treatment for MDEs

- Withdrawal offending agent^
- Symptomatic treatment
- Bland emollients
- Topical corticosteroids
- Oral antihistamines
  - Avoid topical antihistamines due to allergic contact dermatitis

^if drug is felt to be necessary and no viable alternatives, may consider continuing

Keys to diagnosing a MDE

- Careful history and physical exam
  - Ask about prescription, non-prescription drugs, herbal supplements, vitamins
  - Dates are important → make a drug chart
- *Morbilliform eruption that started within 48-72 hours of starting a drug is likely to be infectious in etiology*
- Consider medications taken for longer and recently discontinued

Drug induced hypersensitivity reactions (aka DRESS/DIHS)

- Average age in children: 9 years
- Incidence in children unknown, may be lower than adults
- Racial and gender (?) predilections, due to HLA types and genetic mutations in specific drug detoxification enzymes
- Role of drugs and viral reactivation; drug metabolites may alter immune function
- Children have lower mortality than adults

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DIHS*	**2-6 weeks**	**Unclear (1 in 1,000 to 1 in 10,000 in adults)**	**Febrile prodrome, morbilliform skin changes, facial edema, conjunctivitis, mucositis, lymphadenopathy; Begins on face and spreads downward, over time becomes more violaceous and exfoliative**	**Aromatic AEDs, lamotrigine, sulfa antibiotics (dapsone), allopurinol, other antimicrobials (vancomycin, cephalosporins, minocycline)**
SJS/TEN (continuum)	Prodrome 1-3 weeks after medication	10% of all cases occur in children; overall rare	Morbilliform to targetoid plaques to full epidermal necrosis, bullae and vesicles; prodrome of fever, fatigue, sore throat, LAD	Phenobarbital, sulfa antibiotics, lamotrigine, carbamazepine

Internal complications: hematologic and hepatic ☹
Other: renal, pulmonary, endocrine, cardiac

RegiSCAR[17]	J-SCAR Criteria[30]
Acute rash	Maculopapular rash >3 weeks after initiating offending drug
Reaction suspected to be drug related	Prolonged clinical symptoms after drug discontinuation
Hospitalized	Fever > 38°C
Fever >38°C	Liver abnormalities or other organ involvement
Lymphadenopathy at two or more sites	Leukocyte abnormalities (leukocytosis, atypical lymphocytosis, or eosinophilia)
Involvement of at least 1 internal organ	Lymphadenopathy
Blood count abnormalities (lymphopenia, eosinophilia, or thrombocytopenia)	HHV-6 reactivation

HHV, human herpesvirus; *J-SCAR,* Japanese Research Committee on Severe Cutaneous Adverse Reaction; *RegiSCAR,* European Registry of Severe Cutaneous Adverse Reactions.

*RegSCAR and J-SCAR are not validated in children or adults with drug hypersensitivity syndrome but can be useful to asses likelihood of DIHS/DRESS.

From: Waldman R, Whitaker-Worth D, Grant-Kels JM. Cutaneous adverse drug reactions: Kids are not just little people. Clin Dermatol. 2017 Nov - Dec;35(6):566-582. doi: 10.1016/j.clindermatol.2017.08.007. Epub 2017 Aug 4. Review. PubMed PMID: 29191348.

Work-up for DIHS

- History and physical examination
- Drug history and timelines
- Family history of drug reactions
- Assess other organ involvement (cardiac, pulm)
- CMP with LFTs, CBC with diff, peripheral smear
  - PT/PTT
  - UA with microscopy
  - HHV-6/HHV-7 (?), test for other infections in differential
  - Thyroid function
- *SKIN BIOPSY generally does not have a role*

Treatment and follow-up for DIHS

- Stop offending agent!
  - Beware of cross reactivity if replacement drug is needed
- Skin limited: topical corticosteroids, anti-histamines, fluids
- Organ involvement: systemic corticosteroids (oral or IV)
  - Consider taper over 3-6 months to prevent relapse
- Failure of CSs: Immunosuppressants (cyclosporine), IVIG, plasmapheresis, can have efficacy in children
- Long term follow-up needed

  thyroid function testing at 3 months, repeat labs until normal off steroids

Stevens-Johnson syndrome/toxic epidermal necrolysis

- Two of the most grave ACDEs
- Keratinocyte apoptosis and widespread skin sloughing
  - Improper t-cell activation
- Spectrum of severity
- Genetic risk factors
- Incidence may increase with age, children 10% of cases
  - Overall RARE
- Children have lower mortality rate compared to adults

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SJS/TEN (continuum)	**Prodrome 1-3 weeks after medication**	**10% of all cases occur in children; overall rare**	**Often starts on face and upper trunk; morbilliform to targetoid violaceous plaques to full epidermal necrosis, bullae and vesicles; acral involvement; mucosal involvement; prodrome 1-2 weeks prior of fever, fatigue, sore throat, cough, LAD** Nikolsky sign++	**Phenobarbital, sulfa antibiotics, lamotrigine, carbamazepine** **Less common: Tylenol, NSAIDS, macrolide antibiotics, other antiepileptic drugs**

SJS: epidermal attachment of <10% BSA	SJS/TEN overlap: epidermal detachment from 10-30% BSA	TEN: epidermal attachment >30% BSA
Widespread violaceous or purpuric macules and atypical targets	Widespread violaceous or purpuric macules and atypical targets	Widespread violaceous or purpuric macules and atypical targets or diffuse erythroderma with epidermal sloughing
*More common in children than TEN, more mucosal involvement		
BX= interface dermatitis	BX=interface dermatitis +necrolysis	BX= necrolysis

SJS/TEN is mainly drug induced

No longer categorized with "EM/EM major"

Waldman R, Whitaker-Worth D, Grant-Kels JM. Cutaneous adverse drug reactions: Kids are not just little people. Clin Dermatol. 2017 Nov - Dec;35(6):566-582.

Management of SJS/TEN

- History, PE, role of biopsy (H and E and snap frozen)
- Medical history to help discern mortality risk
- Involve dermatology team early/wound care
- Detailed serial skin and mucous membrane exams
- Ophthalmology consult (regardless of eye exam findings)
- CMP, CBC (volume status and infection, neutropenia)
- Scoring systems not validated but could be helpful

TABLE 20.5 Features of Stevens–Johnson syndrome and toxic epidermal necrolysis

- Constitutional
  - Fever
  - Dehydration
- Mucocutaneous
  - Stomatitis with hemorrhagic crusts
  - Oral and genital erosions
  - Dysphagia
  - Purulent conjunctivitis with photophobia
  - Occasionally esophageal and pulmonary mucosal sloughing
  - Dusky erythematous macules, targetoid lesions, bullae, and skin sloughing
- Visceral
  - Lymphadenopathy
  - Hepatosplenomegaly with hepatitis
  - Uncommonly, pneumonitis, arthritis, myocarditis, and nephritis
- Laboratory abnormalities
  - Increased erythrocyte sedimentation rate (100%)
  - Leukocytosis (60%)
  - Eosinophilia (20%)
  - Anemia (15%)
  - Elevated hepatic transaminase levels (15%)
  - Leukopenia (10%)
  - Proteinuria, microscopic hematuria (5%)

TABLE 20.6 Most common pharmacologic triggers of SJS and TEN

- Allopurinol
- Barbiturates
- Carbamazepine
- Lamotrigine
- NSAIDs
- Penicillins
- Phenytoin
- Sulfonamides

Tables from Hurwitz Pediatric Dermatology

Morbidity and mortality in SJS/TEN

- Eyes, airway**, GI system, kidney, cardiac
- Up to 50% of children develop long term complications
- Skin dyspigmentation to corneal scarring
- Main cause of death is infection
- Overall children have a better prognosis!

Treatment of SJS/TEN

- Immediate withdrawal of offending agents
- Limit new drug exposures
- >30% BSA should be transferred to a burn unit
- Supportive care is mainstay
- Alternatives with some evidence: high dose IVIG, pulsed high dose corticosteroids, cyclosporine, plasmapheresis, TNF-alpha inhibitors

Mimickers of severe drug eruptions

- Erythema multiforme
- Mycoplasma induced mucositis and rash
- Staph scalded skin syndrome
- Kawasaki syndrome

Mycoplasma pneumoniae associated cutaneous eruptions

- Morphologically diverse group
- Mucositis alone
- Mucositis with sparse cutaneous involvement
- Mucositis with moderate skin involvement

- Erythema multiforme, SJS, TEN
- Only mucositis: “incomplete SJS”, “Fuchs syndrome”, and “Mycoplasma pneumoniae-associated mucositis”

Canavan T. N. et al. J Am Acad Dermatol 2014

Mycoplasma induced mucositis and rash: Introducing “MIMR” (aka “murms”)

- Mucocutaneous reaction to *Mycoplasma pneumoniae* infection
- Used to be considered SJS variant due to MP infection
- Younger patients (mean=12), male predominance
- Universal prodromal symptoms for ~ 1 week
- Ocular involvement (82%)
- Urogenital lesions (63%)

Canavan T. N. et al. J Am Acad Dermatol 2014

Mycoplasma induced mucositis and rash: contin’

- Polymorphic skin lesions
  - Vesiculobullous (majority)
  - Targetoid
  - Papules/macules
- BSA is often sparse (47%) or severe mucositis alone (34%)
- Mucositis in majority
  - Isolated erosions
  - Ulcers
  - Vesiculobullous lesion
  - Severe involvement of buccal mucosa and denudation

Canavan T. N. et al. J Am Acad Dermatol 2014

Mycoplasma pneumoniae–induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: A systematic review

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Birmingham, Alabama, and San Francisco, California

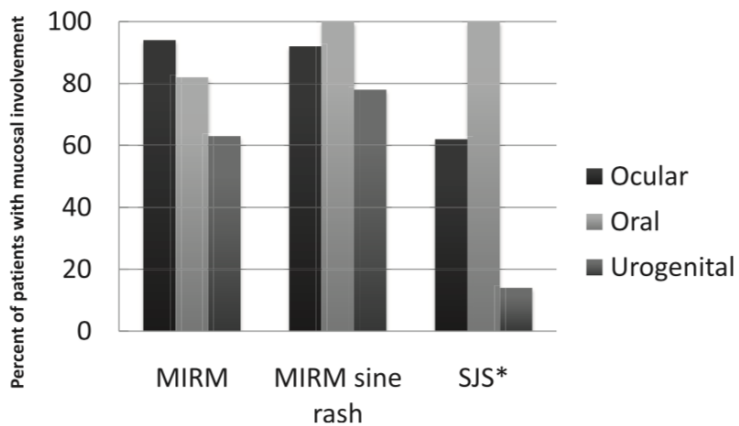

Fig 3. Rates of mucositis in patients with *Mycoplasma*-induced rash and mucositis (*MIRM*), MIRM sine rash, and Stevens-Johnson syndrome (*SJS*). *Data from Wetter and Camilleri,[19] 2010; Kunimi,[107] 2011; and Ting,[120] 1985.

Table II. Proposed diagnostic criteria for classic cases of *Mycoplasma*-induced rash and mucositis

Classification	MIRM
Detachment	<10% BSA
No. of mucosal sites involved*	≥2
Few vesiculobullous lesions, or scattered atypical targets	Yes
Targetoid lesions	±
Evidence of atypical pneumonia	
1) Clinical	Fever, cough, positive auscultatory findings
2) Laboratory	Increase in MP IgM antibodies, MP in oropharyngeal or bullae cultures or PCR, and/or serial cold agglutinins

BSA, Body surface area; *MIRM*, *Mycoplasma*-induced rash and mucositis; *MP*, *Mycoplasma pneumoniae*; *PCR*, polymerase chain reaction.
*Rare cases have <2 mucosal sites involved.

Canavan T. N. et al. J Am Acad Dermatol 2014

Table III. Proposed diagnostic criteria for variants of *Mycoplasma*-induced rash and mucositis (MIRM), including MIRM sine rash and severe MIRM

Classification	MIRM sine rash
Detachment	<10% BSA
No. of mucosal sites involved	≥2
Few and fleeting morbilliform lesions, or few vesicles	±
Evidence of atypical pneumonia	
1) Clinical	Fever, cough, positive auscultatory findings
2) Laboratory	Increase in MP IgM antibodies, MP in oropharyngeal or bullae cultures or PCR, and/or serial cold agglutinins

Classification	Severe MIRM
Detachment*	<10% BSA
No. of mucosal sites involved†	≥2
Extensive widespread blisters or flat atypical targets	Yes
Evidence of atypical pneumonia	
1) Clinical	Fever, cough, positive auscultatory findings
2) Laboratory	Increase in MP IgM antibodies, MP in oropharyngeal or bullae cultures or PCR, and/or serial cold agglutinins

BSA, Body surface area; *MIRM*, *Mycoplasma*-induced rash and mucositis; *MP*, *Mycoplasma pneumoniae*; *PCR*, polymerase chain reaction.
*Rare cases may have >10% BSA involvement.
†Rare cases may have <2 mucosal sites involved.

Canavan T. N. et al. J Am Acad Dermatol 2014

Treatment of MIMR

- Review of cases showed diverse treatments
  - Antibiotics
  - IVIG
  - Systemic corticosteroids
  - Supportive care
- Ophthalmology, urology, nutrition and dermatology consults
- *Supportive care is primary, IVIG in mucositis only cases failing supportive care*

Canavan T. N. et al. J Am Acad Dermatol 2014

Prognosis and sequela of MIMR

- Majority of patients have full recovery, mortality very low
- Respiratory and oral/esophageal involvement, higher acuity
- Skin: PIH
- Ocular: conjunctival shrinkage, corneal ulcerations, dry eyes, blindness, ocular synechiae, loss of lashes
- Oral or genital synechiae

(my) Lessons learned from MIMRs cases

- **Distinct from SJS/TEN**, in young males
- <<<mucositis predominant, milder skin findings
- Don’t trust respiratory PCR, use serum PCR or Ab panel for Mycoplasma
- Often 2-3 mucosal sites
- Avoid NSAIDS if sever oropharyngeal involvement
- Get nutrition involved early, may need TPN
- Prolonged hospital course due to mucositis, pain

Urticaria and related reaction patterns

- “Urticaria multiforme”
- Acute urticaria
- Serum sickness-like reaction

“Urticaria multiforme”—not your average hives

- Children 4 months to 3-4 years, preceded by infection
- Urticarial plaques with bruise-like pattern/dusky centers (no true targets)
- Polycyclic to annular pattern
- Angioedema or acral edema
- Fever w/w/o other URI type symptoms for 1-3 days prior
- Lesions last < 24 hour
- Favorable response to antihistamines
- NOT an allergic reaction but a hypersensitivity reaction

TABLE 4 **Distinguishing Features of Urticaria Multiforme, Erythema Multiforme, and Serum-Sickness–Like Reactions**

Feature	Urticaria Multiforme	Erythema Multiforme	Serum-sickness–Like Reactions
Appearance of individual lesions	Annular and polycyclic wheals with central clearing or ecchymotic centers	Classis target lesion with annular lesions with purpuric or dusky, violaceous center (may blister), middle ring of pallor and edema, outer ring of erythema or blisters	Polycyclic urticarial wheals with central clearing; may appear purpuric
Location	Trunk, extremities, face	Involvement of palms, soles common	Trunk, extremities, face, lateral borders of hands and feet
Duration of individual lesions	<24 h	Days to weeks	Days to weeks
Fixed lesions	No	Yes	Yes
Total duration of rash	2–12 d	2–3 wk	1–6 wk
Mucous membrane involvement	Oral edema common, no erosions or blisters	May see oral erosions or blisters of lips, buccal mucosa, and tongue; rarely involves conjunctivae, nasal, or urogenital mucosa; usually involving only a single site	Oral edema common, no erosions or blisters
Facial or acral edema	Common	Rare	Common
Dermatographism	Yes	No	No
Fever	Occasionally, low-grade	Occasionally, low-grade	Prominent, high-grade
Associated symptoms	Pruritus	Mild pruritis or burning	Myalgias, arthralgias, lymphadenopathy
Common triggers	Antibiotics, immunizations, viral illness	Herpes simplex virus, other viral illness	Antibiotics
Treatment	Discontinue any new or unnecessary antibiotics or medications; combinations of H1 and H2 antihistamines may be helpful; systemic steroids can be helpful in more recalcitrant cases	Supportive care; early institution of systemic steroids can sometimes be helpful	Discontinue any new antibiotics or medications; H1 and H2 antihistamines; supportive care; consider systemic corticosteroids

Streptococcal skin infections (with AD)

- Bacterial colonization/infection is higher in AD flares
- Correlates with severity of skin lesions
- Strep as a pathogen in poorly controlled AD*
- Thick pustules and crusts with GAS, pain^
- Facial and periorbital >>>> GAS than *S. aureus (3.4X likely febrile)^*
- *Higher rate of hospitalization (3X more than with SA)^*
- GAS+ were 3.7X more likely to have invasive infections
- Mixed infections with *S. aureus* are common

*Arkwright PD et al. Arch Dermatol 2002
*Adachi J et al. J Dermatol Sci 1998
*Hayakawa K et al. Clin Exp Dermatol 2009
^Sugarman JL et al. Pediatr Dermatol 2011

GAS infections (with AD), take homes

- “Emerged” pathogen in skin and soft tissue infections, and AD
- More likely to be sicker kids in the hospital with fever
- Often co-cultured with *staph aureus*
- Importance of culture and sensitivities
  - Prior to initiation of therapy
  - Consider when choosing empiric therapy
- Be on alert for more invasive infections with streptococcus
- Consider in acutely worsening AD patients

“Eczema Coxsackium (EC)” and other atypical findings of hand, foot and mouth disease

- Caused by cocksackie virus A6
- High fever and often severe cutaneous lesions common
- Accentuated in eczematous areas (eczema coxsackium)
- Vesiculobullous and erosive eruption
- Perioral, **extremity** and truncal involvement in addition to classical HFMD areas (palms/soles/buttocks)
- Accentuation in areas of previous skin injury (diaper rash, sunburn)

Mathes E. et al. Pediatrics 2013

Forms of HFMD

- Diffuse form (lesions extending to trunk) (all ages)
- Classic acral form (infants, <2 years)
- Eczema cocksackium-on preexisting eczema areas (2 years and older)
- Other morphologies:
  - Petechial/purpuric form
  - Blistering form
  - Gianotti-crosti-like

- Sequelae: acral peeling and nail changes

Mathes E. et al. Pediatrics 2013

These atypical eruptions could be confused with other dermatoses:

- Bullous impetigo
- Eczema herpeticum
- Vasculitis
- Auto-immune bullous disease

Diagnosis and treatment

- High suspicion with symptoms of HFMD and cutaneous findings
- Genotyping of coxsackie virus
  - PCR on swabs of skin vesicles, oropharynx, perirectal skin, stool or blood
- Respiratory PCR for enterovirus can help support
- Rule out HSV when indicated, bacterial cultures
- Supportive care, minimal need for hospitalization
- Self-limited

TABLE 4 Clinical Features and Differential Diagnosis of Severe CVA6-Associated HFMD

Findings Suggestive of HFMD [a]: 1) Fever, 2) Oral erosions, 3) Mild gastrointestinal symptoms, 4) Oval vesicles on hands and feet, 5) Known sick contacts

	Atypical Cutaneous Morphology	Clinical Differential Diagnosis
Vesiculobullous and erosive eruption	• Widespread (>5% BSA distribution) • Perioral, acral, buttock predilection • Bullae more common aged <1year	• Bullous impetigo • Varicella • Primary immunobullous disorders
Eczema coxsackium	• Vesicles and erosions in areas of eczematous dermatitis	• Eczema herpeticum • Secondary bacterial infection in setting of AD
Gianotti Crosti-like eruption	• Acrofacial papulovesicles and erosions with relative sparing of the trunk similar to Gianotti-Crosti syndrome	• Gianotti Crosti syndrome • Other viral exanthems • Urticaria multiforme
Petechial and purpuric rash	• Most often seen in patients > 5 years of age • Often acral	• Leukocytoclastic vasculitis • Glove and stocking purpura (parvovirus infection)
Delayed cutaneous findings	• Onychomadesis (nail shedding) and Beau's lines (tranverse grooves) • Acral desquamation	• Onychomadesis: Medication induced (tetracyclines), after severe systemic illness • Acral Desquamation: after toxin or superantigen-mediated disease (Group A *Streptococcus* infection, Kawasaki disease, or toxic shock syndrome)

Diagnosis can be confirmed by enterovirus PCR (serum; oropharyngeal and skin swab as available). As indicated, rule out other entities with viral and bacterial cultures, viral DFA or PCR, and skin biopsy.

[a] May be variably present.

Mathes E. et al. Pediatrics 2013