Update in Hospital Medicine: Emergency Rashes

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- Assistant Professor, Harvard Medical School

Disclosures

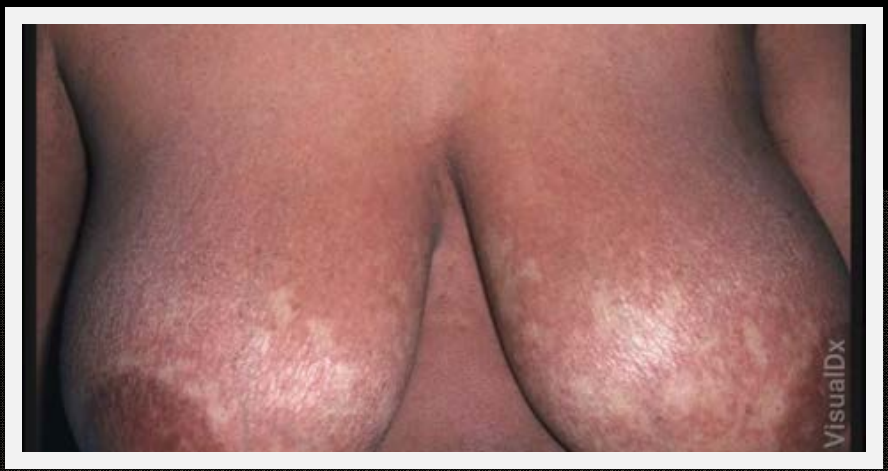
- Consultation and/or Advisory Boards for: Novartis, UCB, Wedbush, Q32, Avalo, and Moonlake.
- Clinical trials ongoing with: Incyte and Sonoma
- Above disclosures are not relevant to this presentation

Goals

- Develop tools to diagnose, differentiate, and treat the most severe and worrisome (and common) rashes:
  - Morbilliform rash
  - Stevens-Johnsons Syndrome
  - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  - Acute generalized exanthematous pustulosis (AGEP)
- Identify instances in which consultation/elevation of care will be most helpful

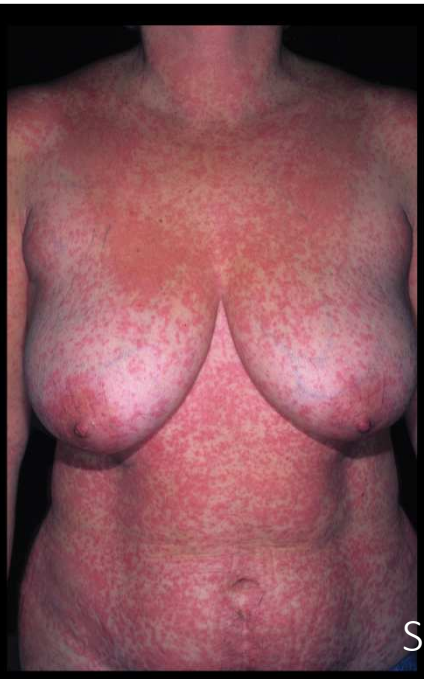
Case 1

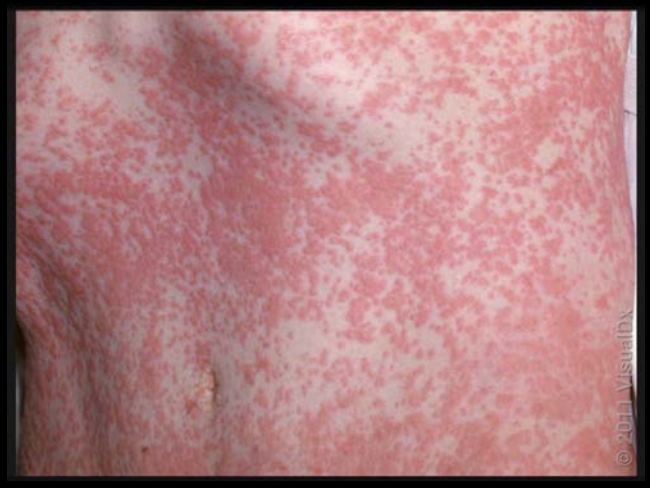
54-year-old woman with past medical history of knee replacement 1 month ago who presents with a rash



Similar rash in darker-skinned individual

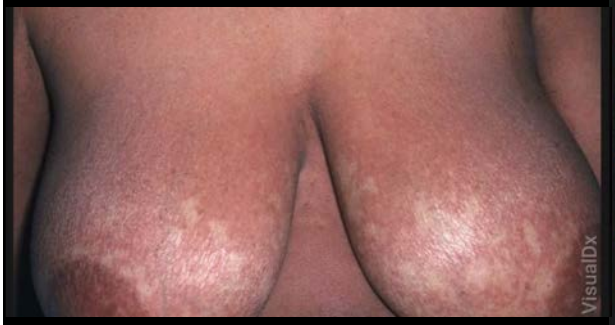
Photos sourced from VisualDx

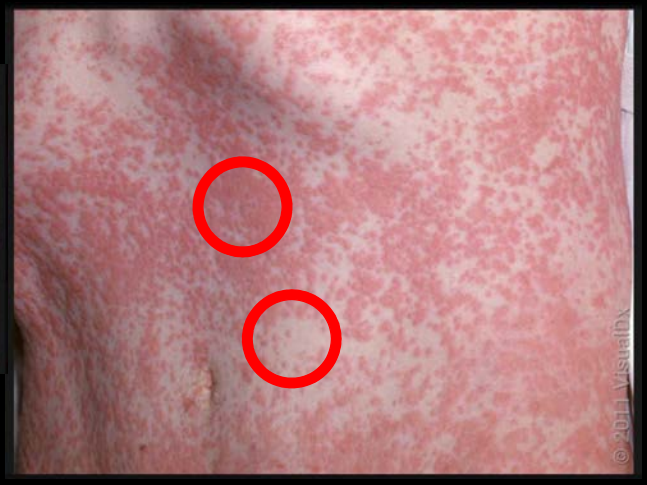




Similar rash in other skin types

Photos sourced from VisualDx





Photos sourced from VisualDx

What additional information will help you assess this patient?

- HISTORY:
  - Medication history
  - Infection history
  - Immunologic status
- SYMPTOMS and SIGNS:
  - Systemic Symptoms (Fevers, lymphadenopathy)
  - Skin pain vs skin itch
  - Mucosal involvement
- LABS:
  - CBC with DIFF, LFTS, BMP

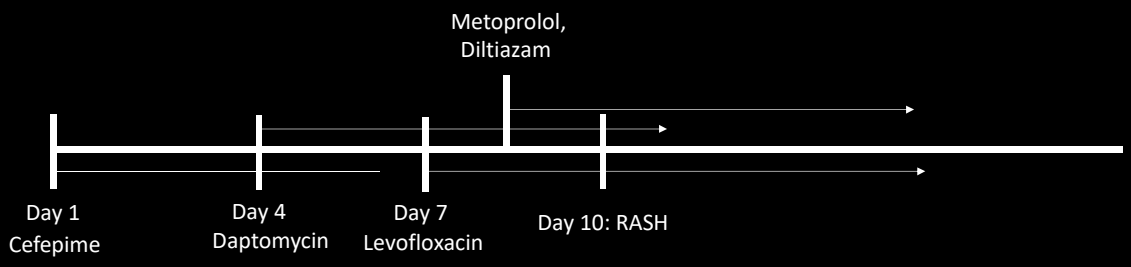
Always the same

History

- Total knee replacement (TKR complicated by infection. Admitted and started on Cefepime → Narrowed to daptomycin (PICC and discharged)
- Febrile again, Dx with PNA, 5 days ago, levofloxacin added
- Afib with RVR 4 days ago, initiated on metoprolol, diltiazam, then discharged home

Re-presents to the ED now with RASH

HOW TO MAKE A DRUG CHART



Dermatology Online Journal 2020 Feb 15;26(2):13030/qt1b20z

Determining Mucosal Involvement

1) Mouth pain, ulceration, difficulty eating
2) Gritty sensation in the eyes
3) Pain with urination or sexual activity
4) Abnormal urinary stream

Archives of Disease in Childhood - Education and Practice 2022;**107:**265-267

History (continued)

- Labs:
  - CBC: WBC today is 8
  - Diff is normal, 2% eos
  - CMP: normal
  - Coags: normal
- Symptoms:
  - No mucosal involvement
  - No skin pain
  - NO Systemic Symptoms (Fevers, lymphadenopathy)

*Based on the information provided what is the most likely diagnosis?

A. Stevens-Johnson's Syndrome (SJS)
B. Acute generalized exanthematous pustulosis (AGEP)
C. Morbilliform drug eruption
D. Drug reaction with eosinophilia and systemic symptoms (DRESS)
E. Atypical betablocker-induced desquamating eruption

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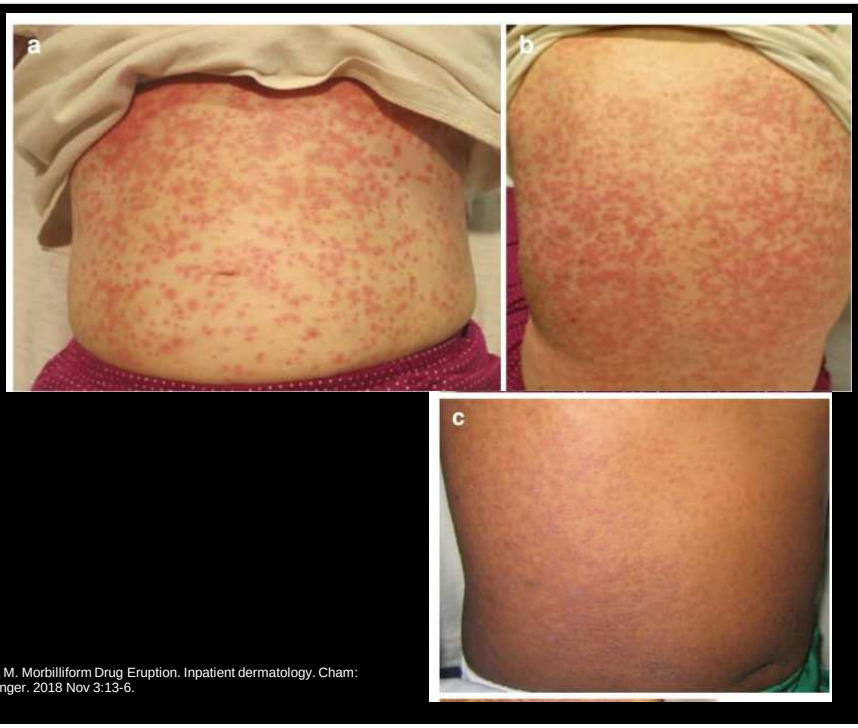
Diagnosis

- Morbilliform Rash- **Type 4 hypersensitivity reaction**
- Lacks mucosal involvement, rarely has skin pain (generally itch > pain)
- Medication history suggestive of rash
- Medication within 7 - 14 days of rash

Semin Immunopath 2016 Jan;38(1):75-86



Noe M. Morbilliform Drug Eruption. Inpatient dermatology. Cham: Springer. 2018 Nov 3:13-6.

*What is the most likely drug culprit for this morbilliform drug eruption?

A. Cefepime
B. Daptomycin
C. Levofloxacin
D. Metoprolol
E. Diltiazam

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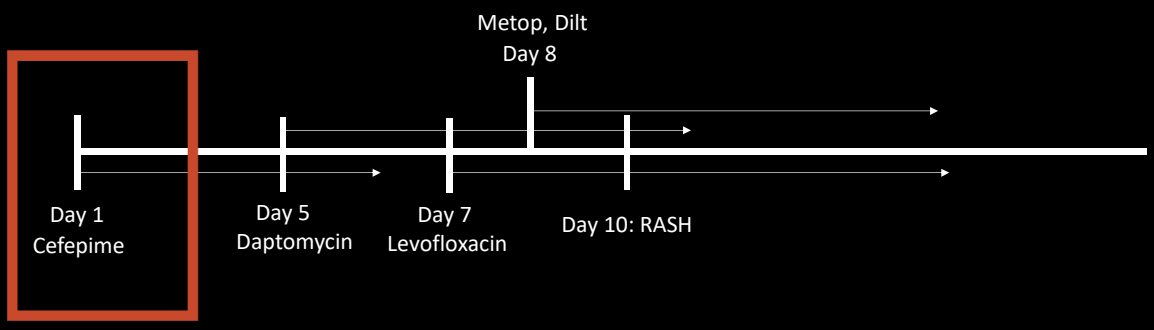


Table 2. Allergic Cutaneous Reactions to Drugs Received by at Least 1000 Patients (BCDSP)*

Drug	Reactions, No.	Recipients, No.	Rate, %	95% Confidence Interval
Amoxicillin	63	1225	5.1	3.9-6.4
Ampicillin	215	4763	4.5	3.9-5.1
Co-trimoxazole	46	1235	3.7	2.7-4.8
Semisynthetic penicillins	41	1436	2.9	2.0-3.7
Red blood cells	67	3386	2.0	1.5-2.4
Penicillin G	68	4204	1.6	1.2-2.0
Cephalosporins	27	1781	1.5	0.9-2.1
Gentamicin	13	1277	1.0	0.5-1.6

SKIN REACTIONS TO "DRUGS" RECEIVED BY AT LEAST 1000 PATIENTS

Drugs	Reaction rate (per 1000 recipients)
Ampicillin	52
Penicillin G	16
Cephalosporins	13
Packed red blood cells	8.1
Heparin	7.7
Nitrazepam	6.3
Barbiturates	4.7
Chlordiazepoxide	4.2
Diazepam	3.8
Propoxyphene	3.4
Guaifenesin	2.9
Furosemide	2.6
Phytonadione	0.9
Flurazepam	0.5
Chloral hydrate	0.2

Table 5. Allergic Cutaneous Reactions to Drugs Received by at Least 1000 Patients (van der Linden et al[2])

Drug	Reactions, No.	Recipients, No.	Rate, %	95% Confidence Interval
Floroquinolones	16	1015	1.6	0.8-2.3
Amoxicillin	40	3233	1.2	0.9-1.6
Augmentin (SmithKline Beecham,	12	1000	1.2	0.5-1.9
Penicillins	63	5914	1.1	0.8-1.3
Nitrofurantoin	7	1085	0.6	0.2-1.1
Tetracycline	23	4981	0.5	0.3-0.7
Macrolides	5	1435	0.3	0.0-0.7

Morbilliform Rash Causes

In J Dermatology. 2020 Jun;59(6):647-655
Arch Dermatol. 2001;137(6):765-770.
J Clin Empidemiology 1998 Aug;51(8):703-8.

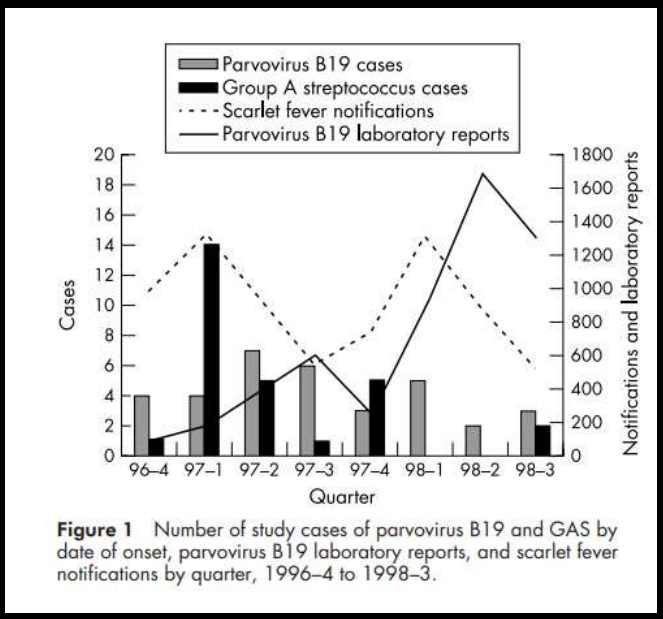


Figure 1 Number of study cases of parvovirus B19 and GAS by date of onset, parvovirus B19 laboratory reports, and scarlet fever notifications by quarter, 1996–4 to 1998–3.

Archives of Disease in Childhood. 2002 Sep 1;87(3):202-6.

Treatment

- **High potency topical steroid ointment** applied BID to the body, avoiding face, genitals for up to 14 days.
- Stop medication
- Continue to monitor for signs of other skin reactions (mucosal involvement)
- Morbilliform rash will NEVER evolve into a more serious rash but should monitor for other symptoms incase of misdiagnosis.

Case 2

27 year-old female with no past medical history presents to the ED with rash, skin pain, chapped lips.

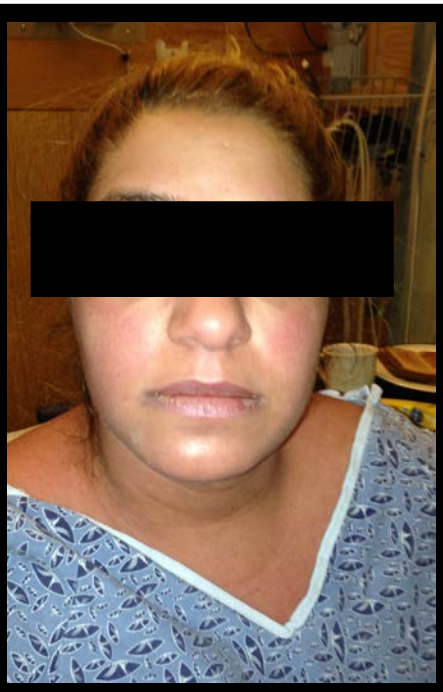


Photo courtesy of Alexandra Charrow, MD. Do not reprint

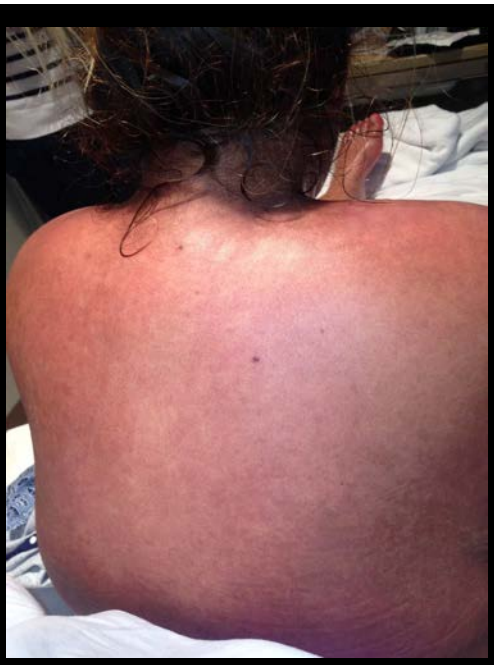
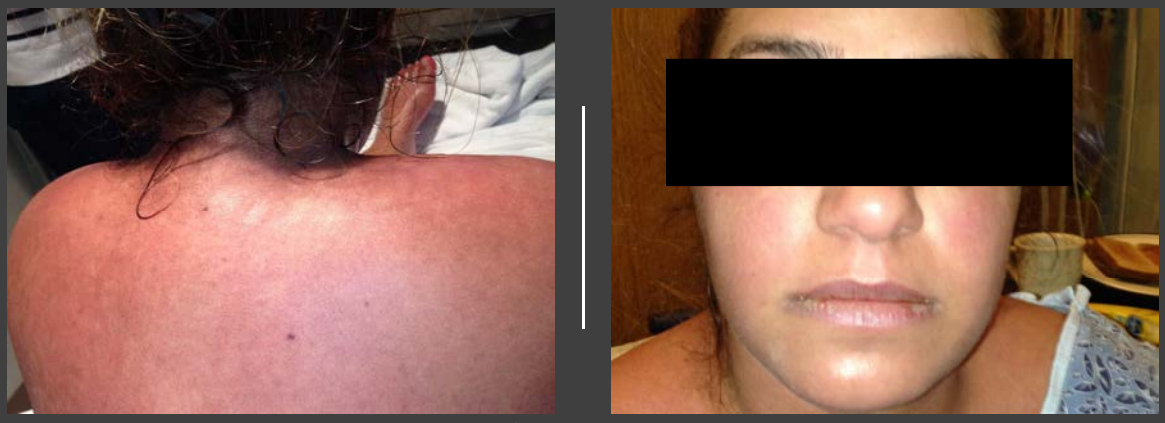


Photo courtesy of Alexandra Charrow, MD. Do not reprint

Take 30 seconds to write down a description of the rash



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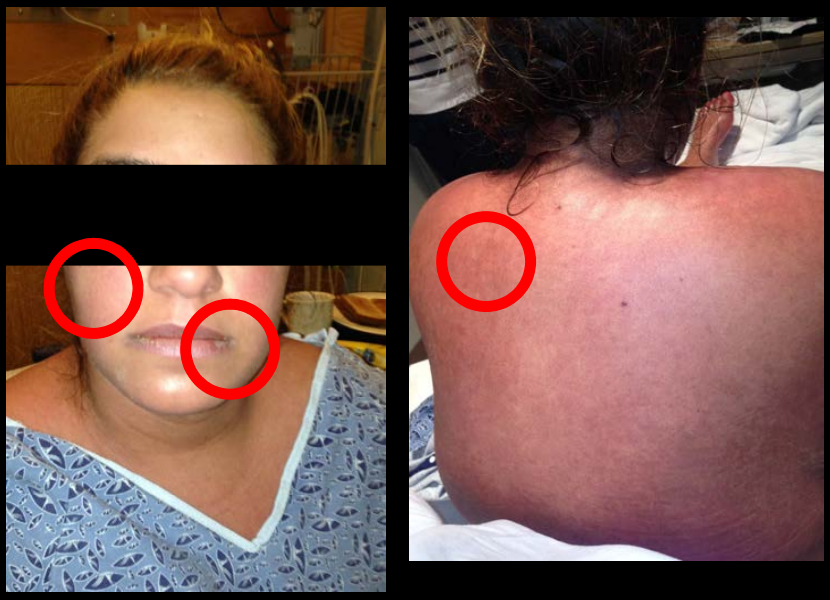

Photo courtesy of Alexandra Charrow, MD. Do not reprint

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- HISTORY:
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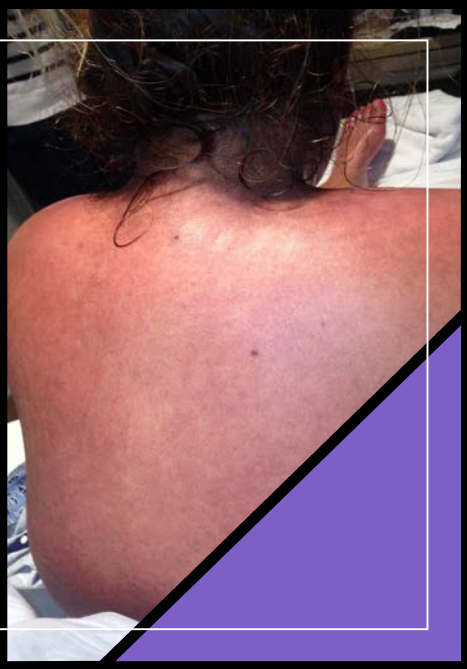


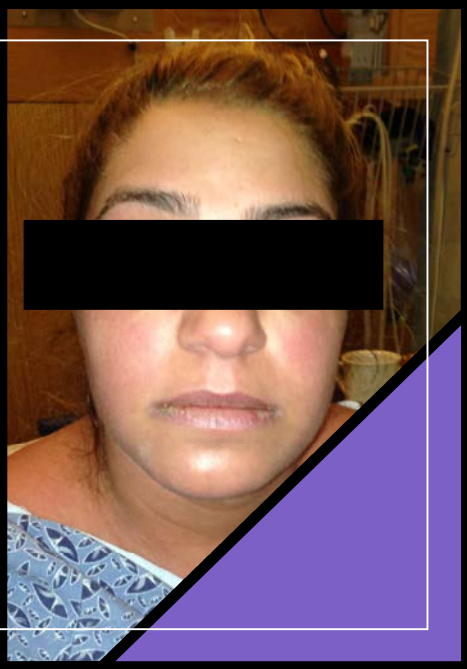
Determining Mucosal Involvement

1) Mouth pain, ulceration, difficulty eating
2) Gritty sensation in the eyes
3) Pain with urination or sexual activity
4) Abnormal urinary stream

Full History

27-year-old female, presented to her primary care 10 days ago with paronychia

- 10 days ago started on **Cephalexin, ibuprofen, acetaminophen**
- 7 days ago, no improvement, initiated **TMP SMX**
- 1 day ago noted **skin pain**, initiated on **prednisone**
- **Notes some eye itchiness**
- **Labs: Mild leukocytosis to 10**



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Diagnosis

- Concern for Stevens-Johnson Syndrome (SJS)
- Diagnosis can me made based on following:
  - Patients must have convincing **medication** history (>95% of cases associated with a medication)
  - **Skin pain** (not just itch)
  - **Mucosal involvement**
  - **Biopsy can help to demonstrate skin necrosis**

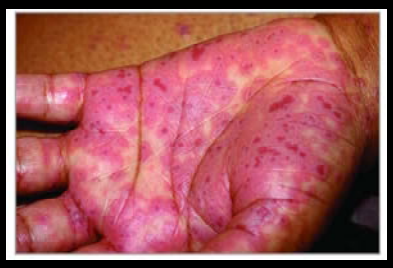
JAAD 2013 Aug;69(2):187.e1-16;

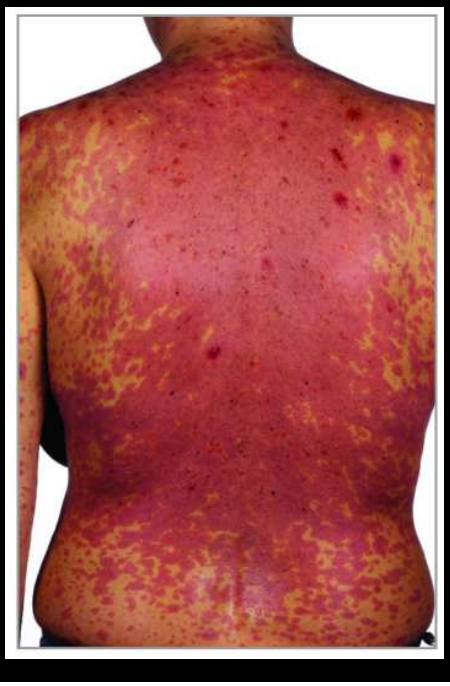
Table III. Diagnostic features of toxic epidermal necrolysis*

Clinical features	Histologic features
Constitutional symptoms: fever, malaise, anorexia, and pharyngitis	Full thickness epidermal necrosis
Erythematous, dusky, violaceous macules, morbilliform or atypical targetoid macules starting on the trunk and spreading distally; confluence on face, trunk, and elsewhere: TEN > SJS/TEN overlap > SJS	Subepidermal split, lymphocytic infiltrate at the dermoepidermal junction, $CD4^+$ T cells in dermis, and $CD8^+$ T cells in epidemis
Manifests in flaccid bullae, epidermal sloughing, and necrosis with gray hue	Endothelial apoptosis
Exfoliation of the epidermis involving 10% of body surface area for SJS, 10-30% for SJS/TEN overlap, and >30% for TEN	
Oral, genital, and ocular mucositis in nearly all patients	
Tender skin and painful mucosal erosions	
Positive Nikolsky sign	
Positive Asboe–Hansen sign	
Systemic symptoms always present in SJS/TEN overlap and TEN	
Respiratory tract epithelial involvement in 25% of patients with TEN	

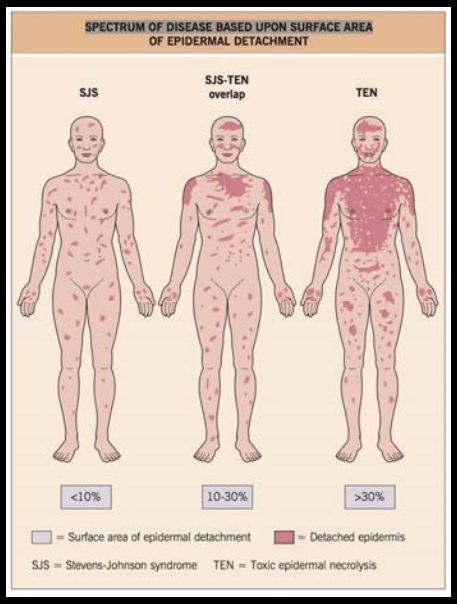
SJS, Stevens–Johnson syndrome; *TEN*, toxic epidermal necrolysis.
*Data from Hazin et al,[27] Kamada et al,[34] Sedghizadeh et al,[35] and Edell et al.[36]

Other Examination Features





British Journal of Dermatology (2016) 174, pp1194–1227



SJS and TEN

JAAD 2013 Aug;69(2):187.e1-16;

Table 3 SCORTEN calculation

Age > 40 years
Presence of malignancy
Heart rate > 120 beats min^{-1}
Epidermal detachment > 10% BSA at admission
Serum urea > 10 mmol L^{-1}
Serum glucose > 14 mmol L^{-1}
Bicarbonate < 20 mmol L^{-1}

BSA, body surface area.

Table 4 SCORTEN predicted mortality

Number of parameters	Predicted mortality (%)
0	1
1	4
2	12
3	32
4	62
5	85
6	95
7	99

British Journal of Dermatology (2016) 174, pp1194–1227

*Which is the most common cause of the patient's rash?

A. Cephalexin
B. TMP SMX
C. Acetaminophen
D. Ibuprofen
E. Antecedent bacterial infection

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DRUG CHART

Table 2. Most Common Causes of Drug-Induced SJS/TEN (N = 338)[1]

Class of Medication	n (%)
Antibiotics	165 (48.8)
Trimethoprim/sulfamethoxazole	89 (26.3)
β-lactam antibiotics	42 (12.4)
Fluoroquinolones	12 (3.6)
Antiepileptics/mood stabilizers	83 (23.7)
Phenytoin	32 (9.5)
Lamotrigine	30 (8.9)
Carbamazepine	7 (2.1)
Phenobarbital	4 (1.2)
Allopurinol	29 (8.6)
NSAIDs[2]	18 (5.3)

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; SJS/TEN, Stevens-Johnson syndrome; toxic epidermal necrolysis.

[1]See Supplementary Table S2 for a complete list of suspected causes of SJS/TEN.

[2]NSAIDS are listed individually in Supplementary Table S2.

Journal of Investigative Dermatology. 2018 Nov 1;138(11):2315-21.

*Based on the morbidity that patients experience from SJS-TEN, who should be consulted earliest?

A. Dermatology
B. Ob/GYN
C. Ophthalmology
D. Oral medicine
E. Urology

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Table 3 Spectrum of chronic ocular complications in Stevens–Johnson syndrome/toxic epidermal necrolysis

Anatomic site	Complications
Lids	Ectropion, entropion, trichiasis, distichiasis, lagophthalmos
Conjunctiva	Persistent hyperaemia, symblepharon, ankyloblepharon, forniceal shortening
Cornea	Superficial punctate keratopathy, loss of palisades of Vogt, epithelial defects, corneal scarring, neovascularization, keratinization, infectious keratitis, corneal thinning
Others	Chronic photosensitivity, decreased visual acuity, lacrimal duct obstruction, dry eyes

British Journal of Dermatology (2017) 177, pp924–935

MANAGEMENT

- **STOP the causative medication**
- **Supportive care:**
  - Petroleum jelly, xeroform to affected areas, do not break blisters
  - Mouth care: Lidocaine mouthwash, topical steroids to the mouth, dexamethasone wash
  - Topical high-potency steroids
- **Consultants:**
  - Dermatology
  - Optho for corneal protection
  - Gyn for dilator placement; foley placement for men
  - +/- burn depending on degree of insensible losses

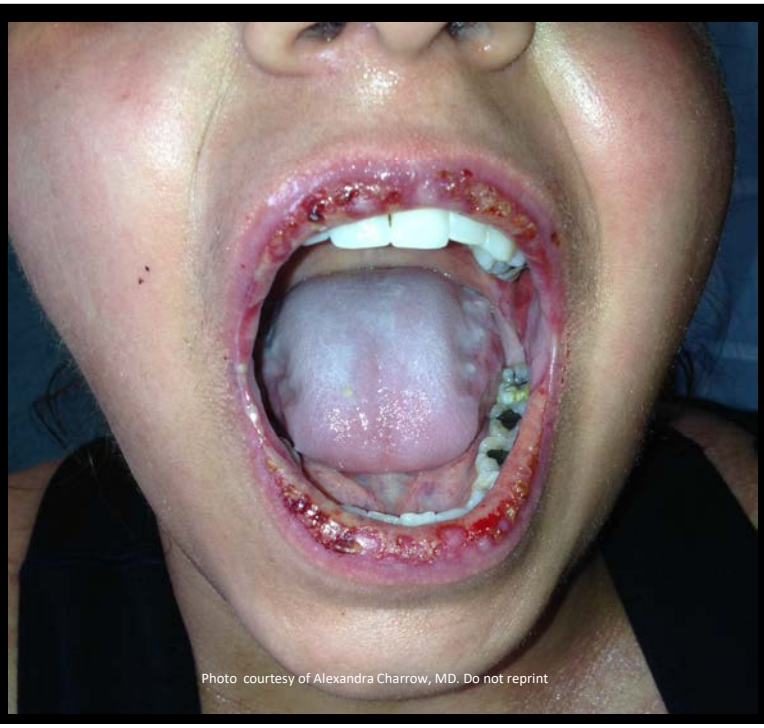
Kirchhof et al. JAAD. 2014

Treatment

- IV Methylprednisolone (0.5 mg/kg) OR
- Cyclosporine OR
- IVIG OR
- Etanercept

JAAD 2021 Aug;85(2):512-513.

With ideal management, fast recognition, in healthy patients…



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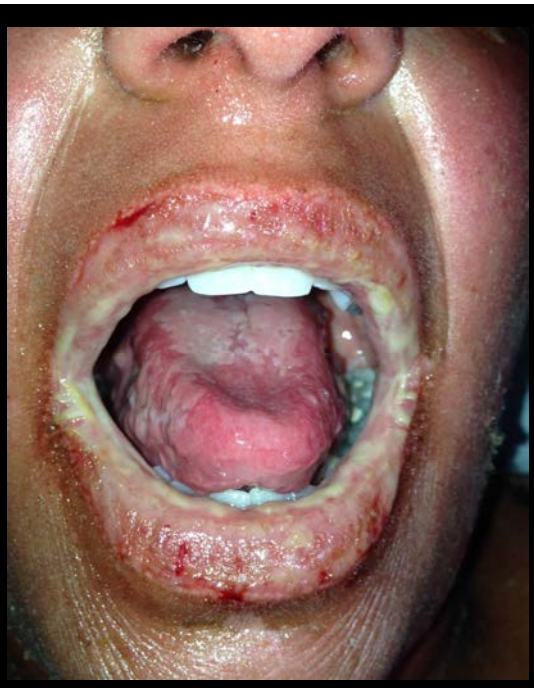

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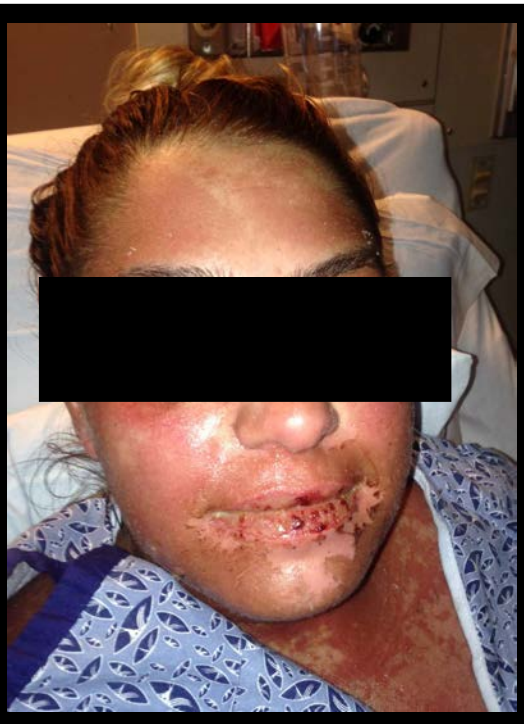

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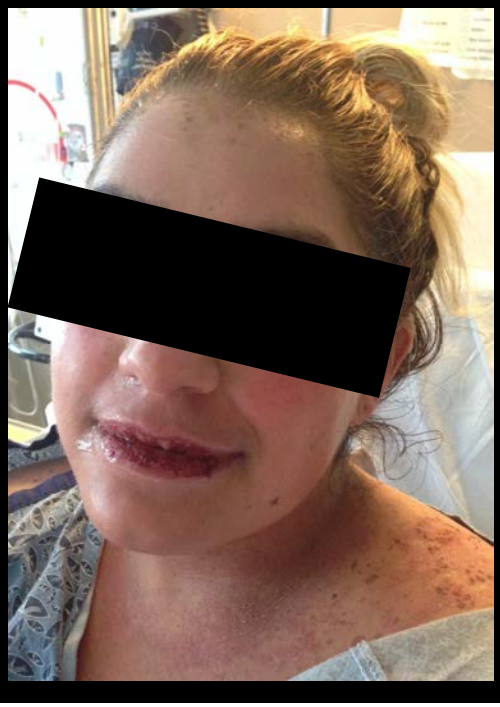

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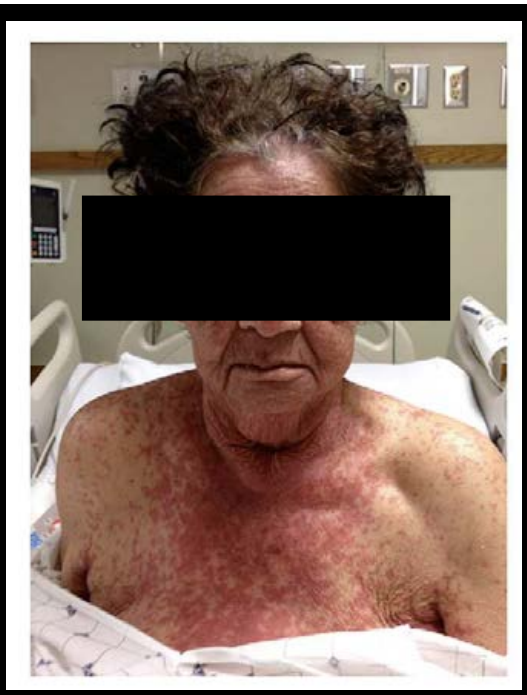
CASE 3

64-year-old female with history of bullous pemphigoid, s/p rituximab with fevers daily and rash



Please take 30 seconds to write down a description of the rash:

- Confluent
- Violaceous
- Non-blanching
- ?Mucosal involvement
- Prominent Facial involvement
- Scattered papules

What additional information will help you assess this patient?

- HISTORY:
  - Medication history
  - Infection history
  - Immunologic status
- SYMPTOMS and SIGNS:
  - Systemic Symptoms (Fevers, lymphadenopathy)
  - Skin pain vs skin itch
  - Mucosal involvement
- LABS:
  - CBC with DIFF, LFTS, BMP

Patient History

- 64-year-old female with history of bullous pemphigoid, s/p **rituximab**, prednisone 3 months ago
- Newly diagnosed gout → initiated on **NSAIDs**, colchicine.
- Following acute resolution, 6 weeks ago, uric acid level was elevated, and **patient** was initiated on allopurinol
- Beginning 2 week ago, developed fevers daily and rash

Labs

- Creatinine is 4 (from baseline of 1)
- Liver function tests are normal
- Absolute eosinophil count is 3000
- Atypical lymphocytes present on smear

*Based on the information provided what is the most likely diagnosis?

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E. Infectious process

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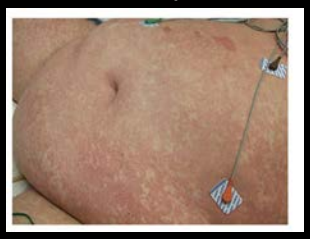
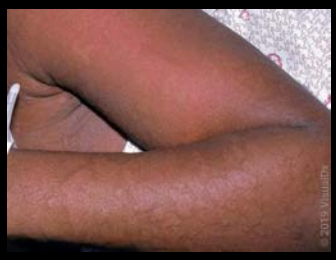
E. Infectious process (THIS MUST BE RULED OUT TOO)

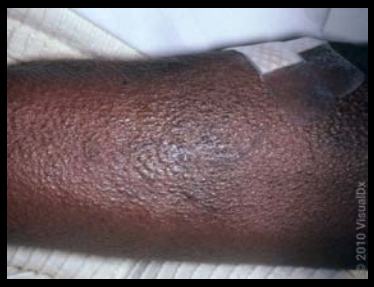
DRESS/DIHS

- Drug exposure 3 – 6 weeks prior to rash
- Rash: any morphology
- Exam findings: Fevers; Facial edema; LAD; Arthralgias/Arthritis
- Labs findings:
  - CBC abnormalities: Atypical lymphocytes; Eosinophilia
  - CMP abnormalities: Nephritis, elevated liver enzymes
  - Troponin elevation
  - Thyroiditis
  - HHV6/HHV7 reactivation

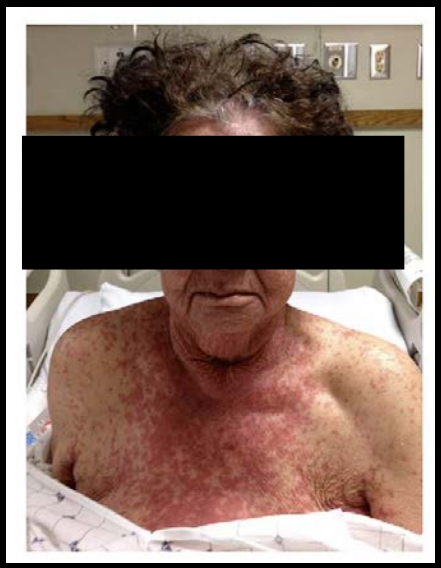
Non-specific rash







Photos sourced from VisualDx



Photos sourced from VisualDx

DIAGNOSTIC SCORING SYSTEM FOR DRESS/DIHS

Criteria	No	Yes	Unknown/ unclassifiable
Fever (≥ 38.5°C)	–1	0	–1
Lymphadenopathy (≥ 2 sites; > 1 cm)	0	1	0
Circulating atypical lymphocytes	0	1	0
Peripheral hypereosinophilia	0		0
0.7–1.499 × 10^9/L - *or* - 10–19.9%*		1	
≥ 1.5 × 10^9/L - *or* - ≥ 20%*		2	
Skin involvement			
– Extent of cutaneous eruption > 50% BSA	0	1	0
– Cutaneous eruption suggestive of DRESS**	–1	1	0
– Biopsy suggests DRESS	–1	0	0
Internal organs involved†	0		0
One		1	
Two or more		2	
Resolution in ≥ 15 days	–1	0	–1
Laboratory results negative for at least three of the following (and none positive): (1) ANA; (2) blood cultures; (3) HAV/HBV/ HCV serology; and (4) *Chlamydia* and *Mycoplasma* serology	0	1	0
Final score: < 2, no case; 2–3, possible case; 4–5, probable case; >5, definite case			

*If leukocytes < 4.0 x 10^9/L

**At least two of the following: edema, infiltration, purpura and scaling.

†Liver, kidney, lung, muscle/heart, pancreas, or other organ and after exclusion of other explanations.

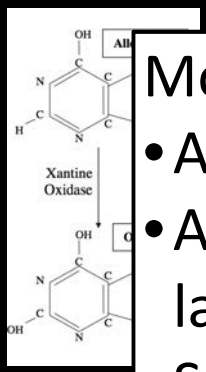
Bolongnia, et al. 2012

Diagnosis

Table III. Diagnostic criteria for drug reaction with eosinophilia and systemic symptoms syndrome

Bocquet et al[4]	RegiSCAR[72]	J-SCAR[73]*
Cutaneous drug eruption	Acute rash†	Maculopapular rash developing >3 weeks after starting offending drug
Hematologic abnormalities	Reaction suspected to be drug-related†	Prolonged clinical symptoms after discontinuation of the causative drug
Eosinophils ≥ 1.5 × 10^9/L	Hospitalization†	Fever >38°C
Presence of atypical lymphocytes	Fever >38°C‡	Liver abnormalities (ALT >100 U/L) or other organ involvement
Systemic involvement	Enlarged lymph nodes involving ≥ 2 sites‡	Leukocyte abnormalities (≥ 1)
Adenopathy: lymph nodes ≥ 2 cm in diameter	Involvement of ≥ 1 internal organ‡	Leukocytosis (>11 × 10^9/L)
Hepatitis with liver transaminases ≥ 2 times normal	Blood count abnormalities‡	Atypical lymphocytes (>5%)
Interstitial nephritis	Lymphocytes above or below normal limits	Eosinophilia (>1.5 × 10^9/L)
Interstitial pneumonitis	Eosinophils over laboratory limits	Lymphadenopathy
Carditis	Platelets under laboratory limits	HHV-6 reactivation

Hussain et al. JAAD 2013



592 The American Journal of Medicine, Vol 124, No 7, July 2011

Table 2 Classification of Published DRESS Cases According to the RegiSCAR's Score[11]

Drugs	Classification of DRESS cases n = 172: No case n = 13 (8%)	Possible n = 35 (20%)	Probable n = 77 (45%)	Definite n = 47 (27%)	Nb of Cases n (%)
Abacavir[12-16]	4	1			5 (3)
Allopurinol[17-29]	1	6	8	4	19 (11)
Amoxicillin plus clavulanic acid[30]			1		1 (0.6)
Amitriptyline[31,32]			2		2 (1)
Spironolactone[125]				1	1 (0.6)
Streptomycin[126]				1	1 (0.6)
Strontium ranelate[127]			1	1	2 (1)
Sulfalazine[62,93,128-135]	3		2	5	10 (6)
Sulfamethoxazole[14,136]			2		2 (1)
Tribenoside[53]				1	1 (0.6)
Vancomycin[137-140]	1		2	1	4 (2)
Zonisamide[18]				1	1 (0.6)

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom.

Most Common Causes

- Allopurinol
- Anti-epileptics (carbamazepine, lamotrigine, phenobarbitol)
- Sulfalazine

Cacoub et al. American Journal of Medicine 2011.

DRUG CHART

*What is the best treatment for this patient?

1. Supportive care
2. Low-dose prednisone (0.25 mg/kg) for 7 days
3. High-dose prednisone (1 mg/kg) for 2-4 weeks and slow taper
4. IV acyclovir for 7 days
5. Ibuprofen standing

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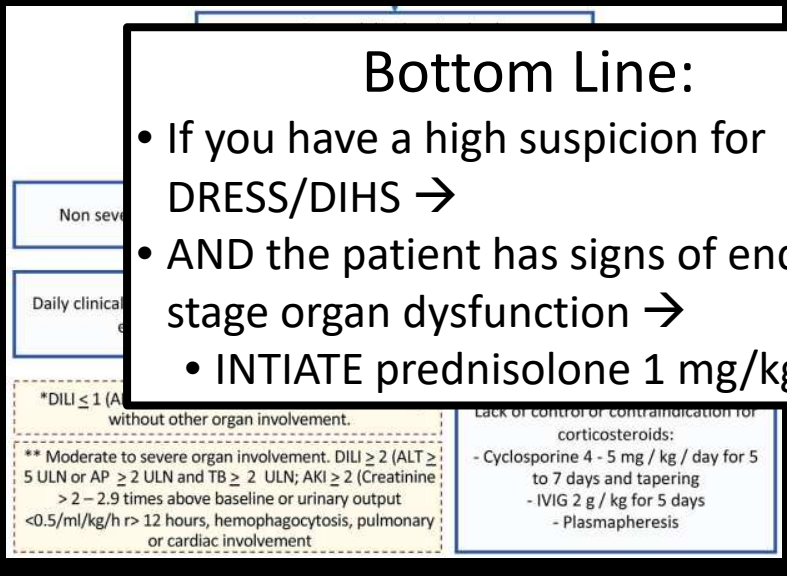
DRESS/DIHS MANAGEMENT



Bottom Line:

- If you have a high suspicion for DRESS/DIHS →
- AND the patient has signs of end stage organ dysfunction →
  - INTIATE prednisolone 1 mg/kg

Calle et al. World Allergy Organization Journal (2023) 16:100673

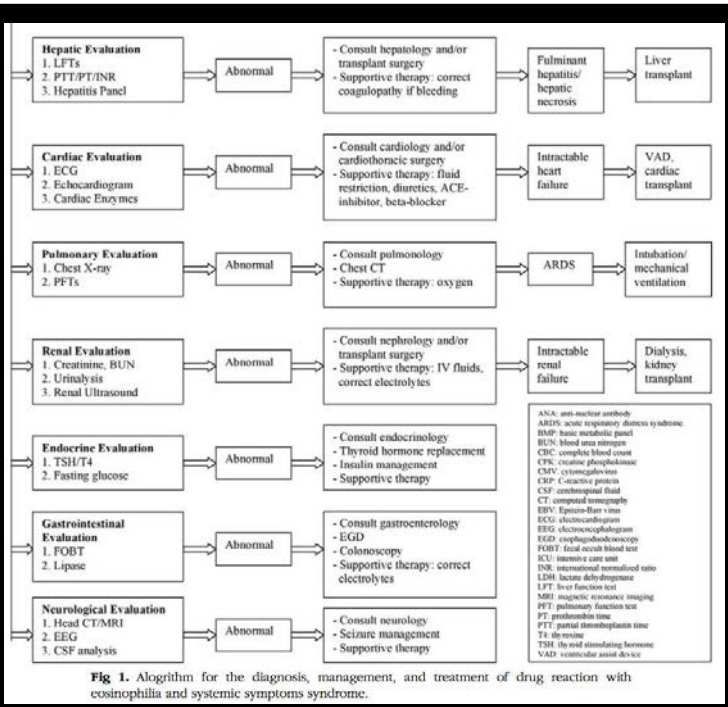
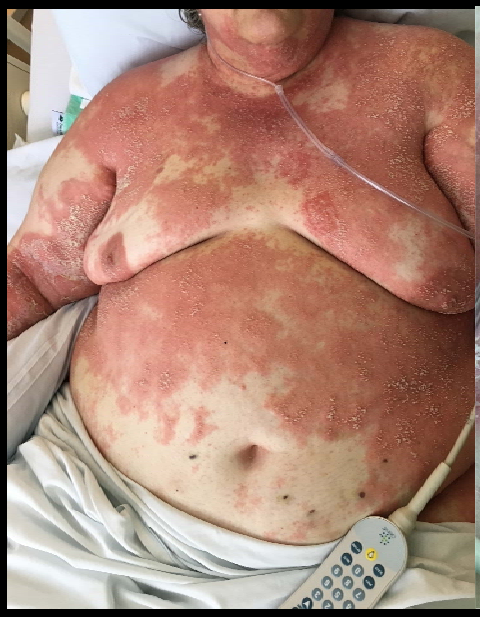


Fig 1. Alogrithm for the diagnosis, management, and treatment of drug reaction with eosinophilia and systemic symptoms syndrome.

Case 4

A 65 year-old female with history of Stevens Johnson's Syndrome previously, presents with new rash and fevers.



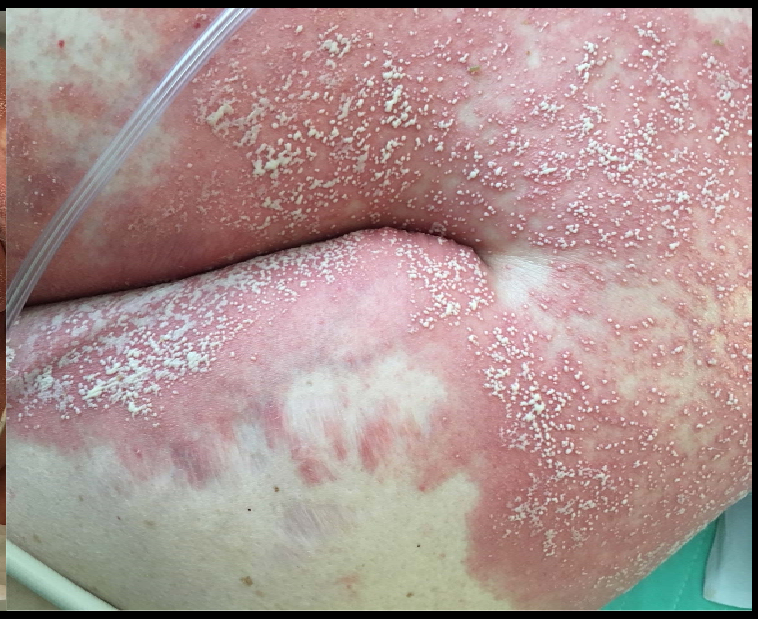
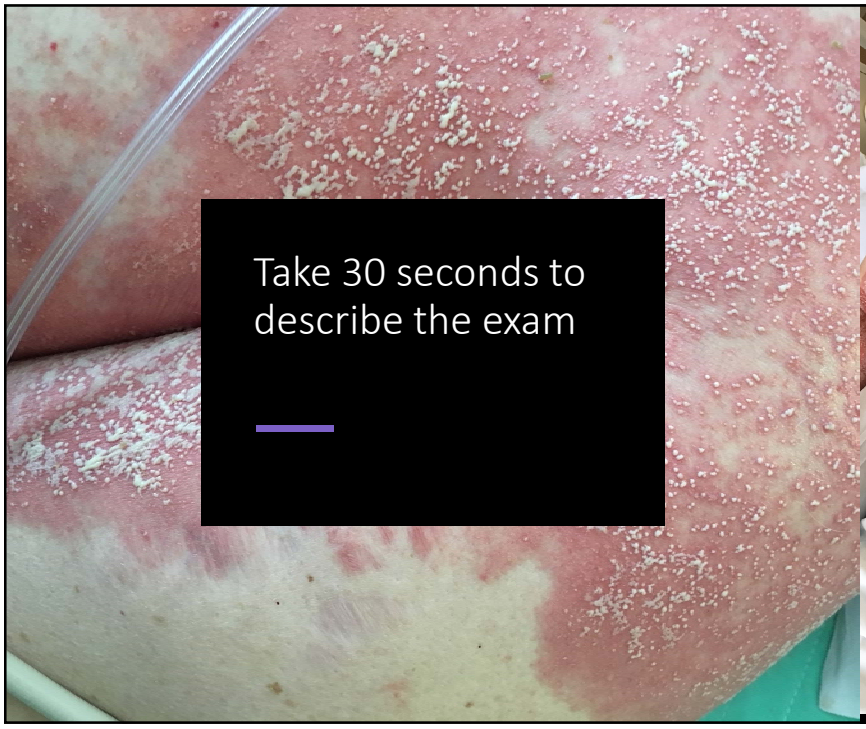
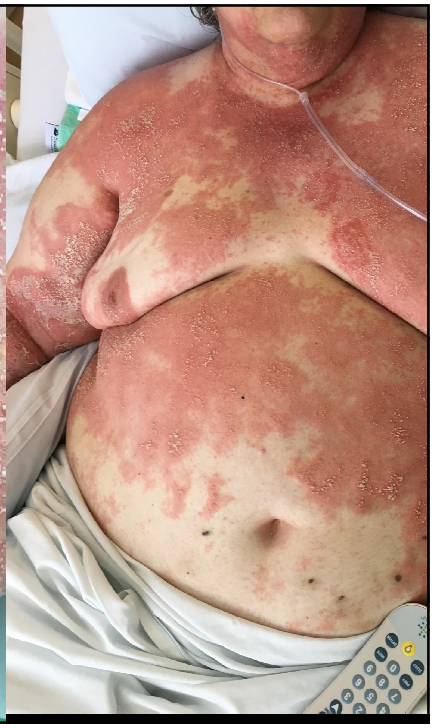


Photo courtesy of Alexandra Charrow, MD. Do not reprint



Take 30 seconds to describe the exam



Full history

- A 65 year-old female with history of Stevens Johnson's Syndrome previously, presents with new rash and fevers.
- 14 days prior to developing rash, the patient started doxycycline for lyme infection.
- She then developed atrial fibrillation with rapid ventricular response and was initiated on diltiazem 5 days prior to rash

DRUG CHART

What is the most likely diagnosis?

A. Stevens-Johnson's Syndrome (SJS)
B. Acute generalized exanthematous pustulosis (AGEP)
C. Generalized impetigo
D. Morbilliform drug eruption
E. Drug reaction with eosinophilia and systemic symptoms (DRESS)

What is the most likely diagnosis?

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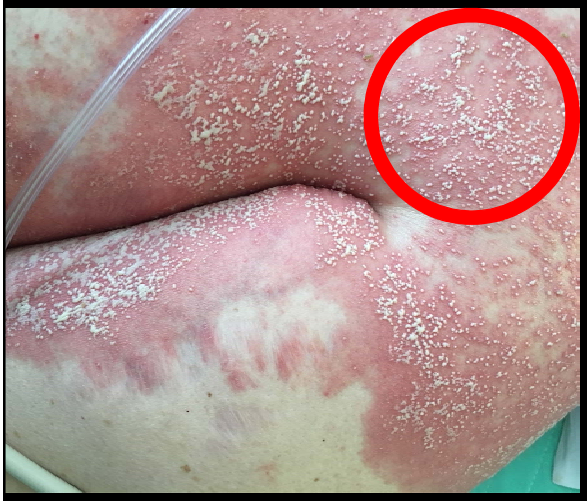


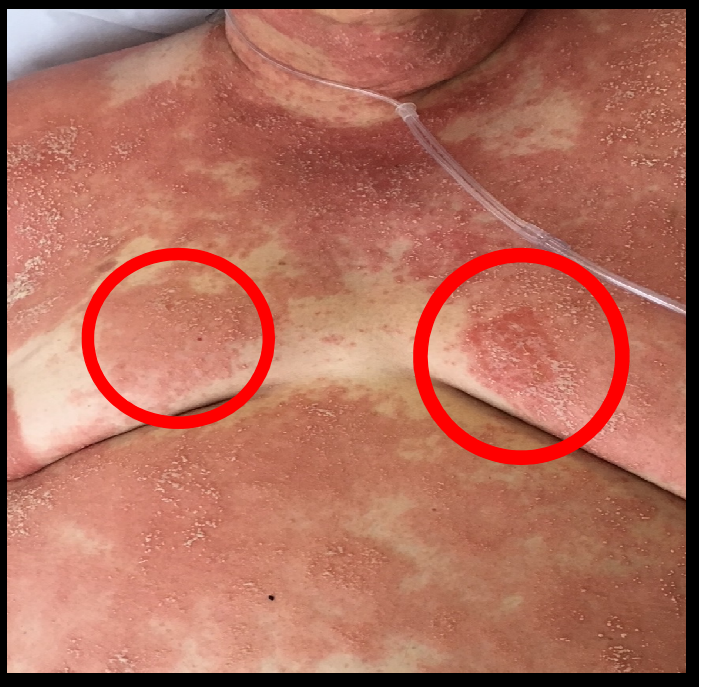
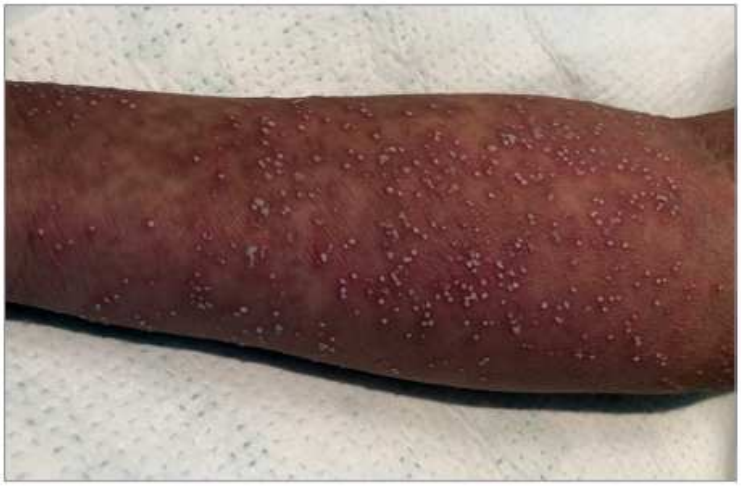


Figure. Numerous Monomorphous Nonfollicular Pustules on a Background of Erythema on the Arm



JAMA Derm 2021 May 1;157(5):589

Figure 1 Erythematous plaques and papules studded with sterile pustules, characteristic of typical acute generalized exanthematous pustulosis (AGEP).

JEADV 2015, 29, 209–214

AGEP (Acute Generalized Exanthematous Eruption)

- Acute rash that is associated with medication in 90% of cases (rarely viral infections in adults)
- Rash occurs quickly following exposure (usually 2-5 days following exposure)
- Generally rash self-resolves without intervention
- May require prednisone or other systemic medication

COMMON Drug causes

- Beta-lactam antibiotics (penicillins, aminopenicillins, cephalosporins)
- Macrolides (azithromycin)
- Calcium channel blockers (eg, diltiazem, nifedipine)
- Antimalarials
- Isoniazid
- Carbamazepine

J Eur Acad Dermatol Venereol. 2015 Feb;29(2):209-214.

RASH	Skin Pain	Tell-tale sign	Urgent escalation of care needed?	Treatment
Morbilliform Drug	Rarely; generally itchy	Convincing drug, Convincing time course, no mucosal involvement	NO	Symptomatic and supportive
SJS	YES	**Mucosal involvement, Skin desquamation or targets**	YES	YES; Nursing care + immune suppression
DRESS	VARIABLE	**Fevers, LAD, facial swelling, Lab abnormalities**	YES	YES; 1 mg/kg prednisone
AGEP	YES + ITCH	**Pustules or superficial skin peeling, fevers**	NO	Symptomatic and supportive