Undressing DRESS: When Medications Dress to Kill

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

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Undressing DRESS: When Medications Dress to Kill

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Drug Reaction with Eosinophilia and Systemic Symptoms

- It’s one of the most severe and life-threatening drug reactions we encounter
- Rare but it can turn life-saving TB medications into a deadly threat
- Multi-organ involvement, delayed onset, and a high risk of mortality

Immediate vs. Delayed Reactions

Drug-induced skin reactions can be classified according to timing:

- Immediate reactions: occur less than 1 hour of the last administered dose
  - Urticaria, angioedema, anaphylaxis

- Delayed reactions: occur >24 hour after drug but can be days, weeks or 1-2 months later

  - **DRESS** – begins 2-12 weeks into continuous treatment
  - Toxic Epidermal Necrolysis (TEN) 5-28 days after drug start
  - Steven Johnson Syndrome (SJS) 5-28 days after drug start
    - ✓ TEN and SJS usually characterize by necrosis of skin

DRESS Epidemiology

Frequency varies depending on:

- Type of drug and immune status of the patient
- Incidence is estimated between 1/1,000-1/10,000 drug exposures
- Fatality rate may be up to 10%
- **Signs and symptoms typically begin 2 to 12 weeks after start of the medication or after increasing the dose**
- Symptoms may continue or recur despite the discontinuation of the culprit drug or after introduction of a new medication
- Average the recovery period is 6 to 9 weeks

DRESS from Anti-TB Therapy: A U.S. Inpatient Review

SKIN HEALTH AND DISEASE
Open Access

Skin Health Dis. 2024 Feb 28;4(2):e337. doi: 10.1002/ski2.337

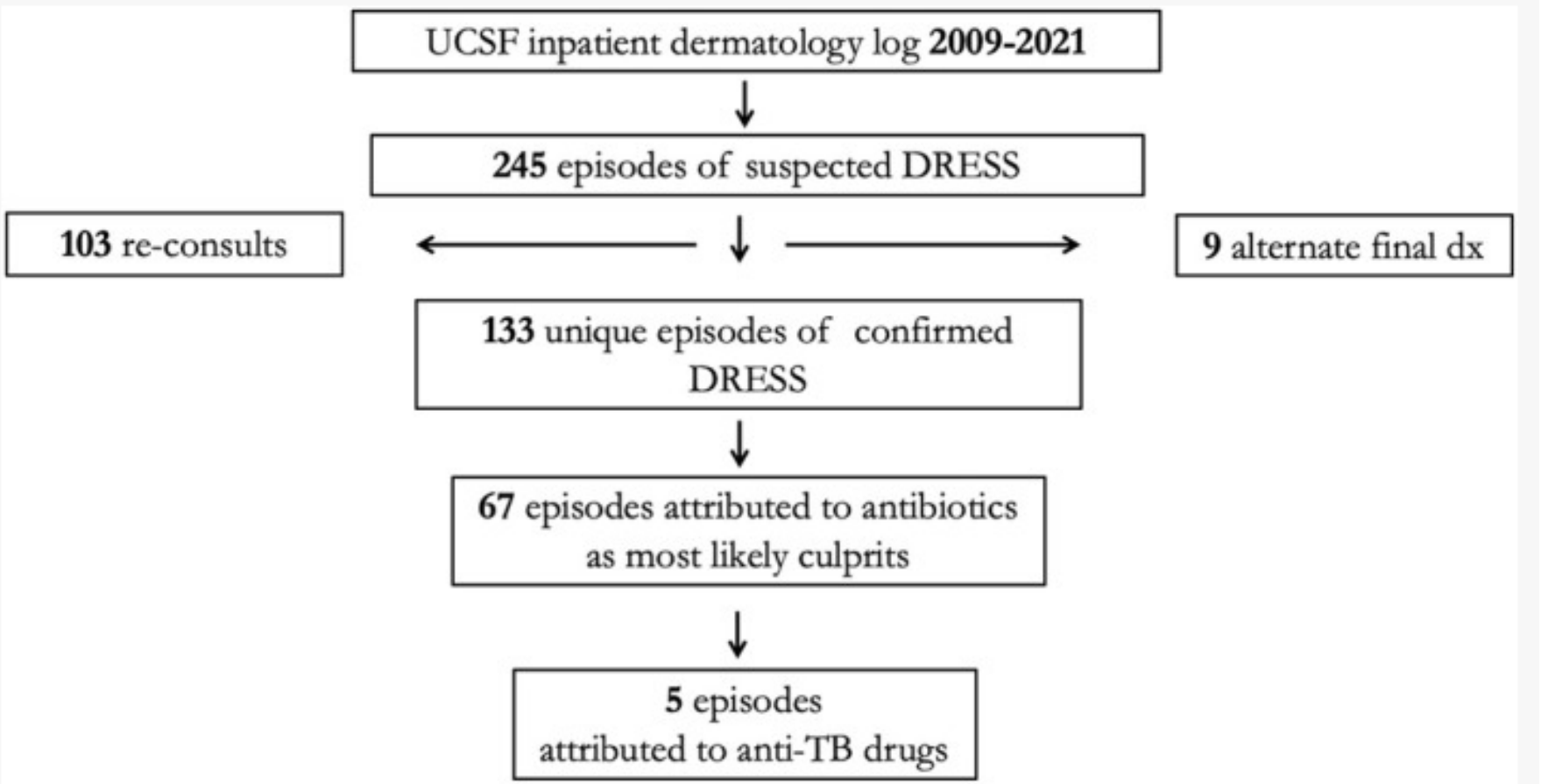
Drug rash with eosinophilia and systemic symptoms to anti-tuberculosis therapy: A retrospective review of inpatients at an academic medical centre in the United States

Rodrigo A Gutierrez [1], Maha Kazmi [2], Lindy Fox [2], Kanade Shinkai [2], Ryan Arakaki [2], Allison Dobry [2], Anna Haemel [2]

Anti-TB drugs accounted for **7.5% of all antimicrobial-induced DRESS cases** at a large academic medical center.

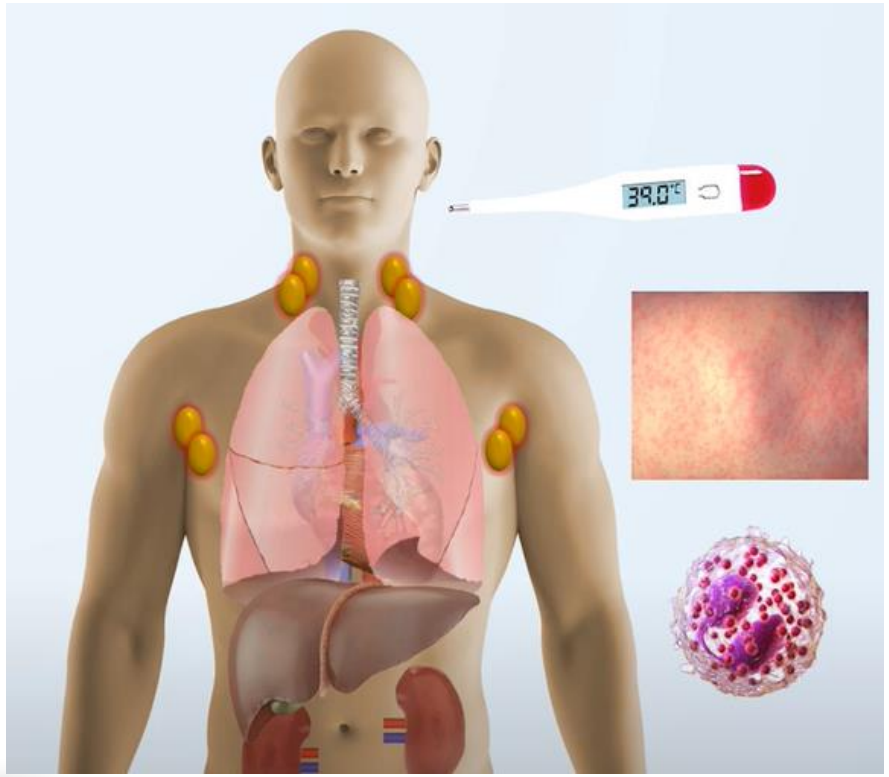
https://pmc.ncbi.nlm.nih.gov/articles/PMC10988693/

Study Findings Overview



https://pmc.ncbi.nlm.nih.gov/articles/PMC10988693/

DRESS Clinical Manifestations



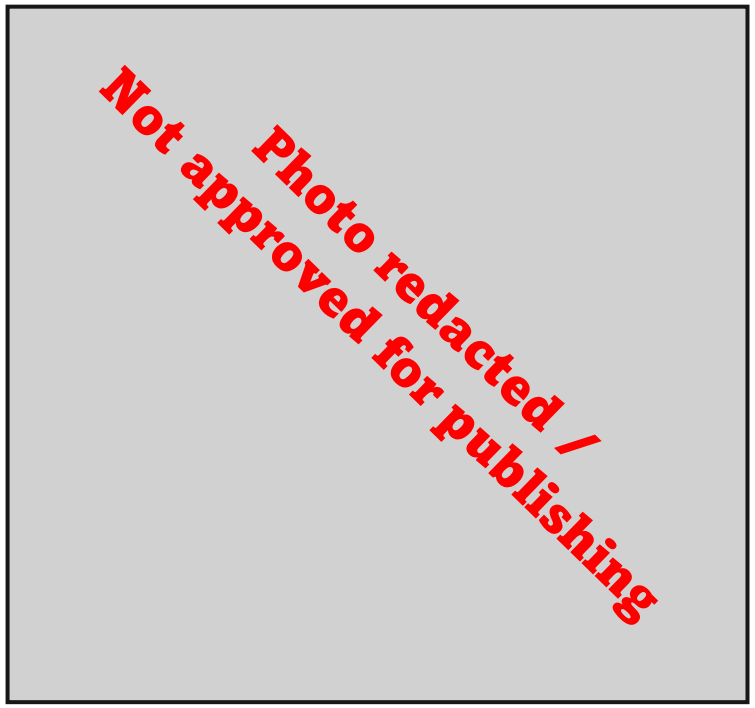
- Prodrome: General malaise, pruritus, macular exanthem, followed by fever and facial swelling
- Skin eruption, rash
- Lymphadenopathy (75% of patients)
- Internal organ involvement (liver, kidney, heart, lung)
  - Liver transplant could be considered if the liver disfunction is severe
  - If kidney failure patient could end having dialysis
- Hematologic Eosinophilia, atypical lymphocytosis (>70% of patients have eosinophilia)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10112187/pdf/main.pdf

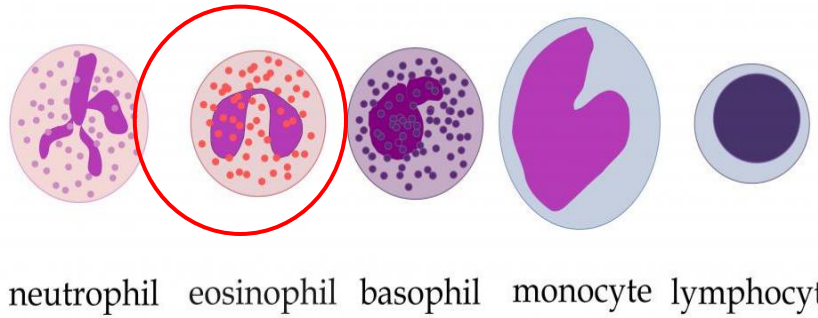
DRESS Clinical Manifestations

Skin eruption (Morbilliform rash) rapidly progresses becoming diffuse and infiltrating; >50% of body

- ✓ Usually rash starts in face, upper part of trunk, upper extremities and finally lower extremities
- ✓ Mucous membrane involvement up to 50%



Eosinophils



Eosinophilia is an increase in number of eosinophils

- **CBC: Normal Value:** Differential **1-6%**
- **Absolute Eosinophils:** 15-500 cell/uL

Most often indicates: a parasitic infection, **an allergic reaction** or cancer

Medications Most Commonly Associated with DRESS

Group	Drugs
Antiepileptics	Aromatic antiepileptic drugs (Carbamazepine, lamotrigine phenobarbital, phenytoine, oxcarbazepine)
Antibiotics	Amoxicillin, ampicillin, azithromycin, levofloxacin, minocycline, sulfamethoxazole-trimethoprim, vancomycin
Antituberculosis agents	Ethambutol, isoniazid, pyrazinamide, rifampin
NSAIDS	Aspirin, celecoxib, diclofenac, ibuprofen, piroxicam
Others	Allopurinol, amitriptyline, dapsone, hydroxychloroquine, imatinib, nevirapine, omeprazole, sulfasalazine

Diagnosing DRESS

- A clinical diagnosis
- No test results
- Combination of skin findings, labs and consistent medication history
- Different criteria – RegisCAR scoring

RegiSCAR Scoring System

International Registry of Severe Cutaneous Adverse Reactions (RegiSCAR)

Criteria	SCORE			
	−1	0	+1	+2
Fever greater than or equal to 38.5 °C	No	Yes		
Lymph node enlargement		No/U	Yes	
Eosinophils			700–1499/µL	≥1500/µL
Eosinophils, if leukocytes are <4,000			10–19.9%	≥20%
Atypical (or reactive) lymphocytes		No/U	Yes	
Extensive rash (>50% TBSA)		No/U	Yes	
Rash suggestive of DRESS	No	U	Yes	
Biopsy suggestive of DRESS	No	Yes/U		
Hepatic impairment		No/U	Yes	
Renal impairment		No/U	Yes	
Lung manifestations		No/U	Yes	
Muscle/Heart manifestations		No/U	Yes	
Pancreatic impairment		No/U	Yes	
Impairment of other organs		No/U	Yes	
Resolution in ≥15 days	No/U	Yes		
Evaluation of other potential causes: ✔ ANAS ✔ Blood cultures ✔ Serology for Hepatitis A/B/C ✔ Chlamydia/Mycoplasma pneumoniae ✔ Other serologies/PCR/cultures If none is (+) and ≥3 of those mentioned are (−)			Yes	

<2 negative case

2-3 possible

4-5 probable

>5 definitive case

Approach to the Patient with Suspected DRESS

- Complete skin exam
- Order CBC, LFTs, BUN, creatinine
- Identify the offending medication
- Medical history to identify medications known to precipitate DRESS:

  i.e., *anticonvulsants, allopurinol, antibiotics, NSAID's, and ART*

  - ✓ Review clinical history for timing of drugs and other symptoms
- **STOP** all suspect medications to let skin heal
- Seek expert consultation; many need hospitalization

Time for a Case Study

Case Study

Young adult male, resided in Northeastern region of the U.S. with his sister.

- Foreign born.
- Moved to the U.S. in 2023.

May 22, 2024 he went to the ED with fever, cough and respiratory symptoms. Chest X-ray RUL patchy opacities, diagnosed with **pneumonia** was discharged with Augmentin and Azithromycin.

Two Weeks Later

June 4, 2024

Presented to the hospital with worsening symptoms that included generalized weakness, night sweats, cough, and blood in his sputum.

June 4, 2024 Hospitalization

Findings:

- CXR showed bilateral opacities
- CT abnormal with cavitation and mediastinal and hilar adenopathy.
- Sputum PCR (+) for MTB with no rifampin resistance noted
- QFT (+)
- HIV and hepatitis screen (-)
- LFTs normal
- Started **RIPE June 6, 2024.**
- Discharged from the hospital on June 11, 2024

After Hospital Discharge

He went to the health department where he continued on TB treatment by **DOT June 17, 2024 – June 21, 2024, then set up for VDOT.**

DOT&VDOT

Out of Town Family Visit

July 8, 2024 went to visit family in the South

Family noted patient was weak, had poor appetite, a rash, and felt feverish.

- Taken to the hospital
  - Diffuse maculopapular rash
  - Elevation of liver enzymes
  - Clinical picture of sepsis with elevated lactic acid, elevated WBC, and tachycardia.
  - Diagnosed with acute liver failure due to TB medications
  - RIPE stopped July 9,2024
  - Acute kidney injury was noted, and dialysis was required starting July 12, 2024.

Maculopapular Rash

- Macules: Flat, discolored patches on the skin, less than 1 cm in diameter. Not raised or depressed compared to the surrounding skin.
- Papules: Raised, solid bumps on the skin, also less than 1 cm in diameter. Can feel them when you touch them.
- Color: Can vary depending on the underlying cause, but it's often red/pink
- Distribution: Can appear on various parts of the body, including the trunk, limbs, and sometimes the face.

Date	6/4/24 (Baseline)	7/08/24	7/14/24	07/22/24	Normal Range:
Weight		122 lb			
WBC	8.40	2.0 (L)	18.5 (H)	17.4 (H)	3.8-1.6 x10*3/uL
Eosinophils		9% (H)	1.7 %	18%	0-5%
AST	23	1037(H)	506 (H)	342	8-42 U/L
ALT	15	1160 (H)	502 (H)	180	0-<50 U?L
Alk. Phos	71	378 (H)	573 (H)	512	38-126 U/L
T. Bili	0.4	5.0 (H)	11.4 (H)	9.9	0.0-1.4 mg/dL
Creatinine	0.80	1.30 (H)	2.20 (H)	6.60 (H)	0.70-1.40 mg/dL

DRESS Diagnosis

No criterion standard for diagnosis of DRESS

European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) developed a scoring system based on:

- ✓ Extent of skin involvement
- ✓ Organ involvement
- ✓ Clinical course
- ✓ Scoring cut-off points: **< 2 no DRESS**, **2-3 Possible**, **4-5 Probable**, **≥6 Definite**

RegiSCAR: http://tools.farmacologiaclinica.info/index.php?sid=10001

– **Tools to help score for DRESS**

RegiSCAR Scoring System

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Atypical (or reactive) lymphocytes		No/U	Yes	
Extensive rash (>50% TBSA)		No/U	Yes ✓	
Rash suggestive of DRESS	No	U	Yes ✓	
Biopsy suggestive of DRESS	No	Yes/U	✓	
Hepatic impairment		No/U	Yes ✓	
Renal impairment		No/U	Yes ✓	
Lung manifestations		No/U	Yes ✓	
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Evaluation of other potential causes: ✓ ANAS ✓ Blood cultures ✓ Serology for Hepatitis A/B/C ✓ Chlamydia/Mycoplasma pneumoniae ✓ Other serologies/PCR/cultures If none is (+) and ≥3 of those mentioned are (+)			Yes	

<2 negative case

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4-5 probable

>5 definitive case

Timeline of Events

May 22, 2024

Went to ED on with fever, cough , abn CXR; dx CAP

June 4-6, 2024

Pt symptomatic, abnormal CXR and CT, PCR (+)

labs are WNL

Started RIPE

June 11, 2024

Discharged with "unremarkable LFTs"

June 16-21, 2024

DOT for 4 days, then VDOT

July 8-9, 2024

Went to ED:

Diffuse maculopapular rash

Elevation in LFTs

Increased Creatnine

Elevated lactic acid

Elevated WBC

Tachycardia

Acute liver inure

Acute kidney injury

RIPE stopped

Medical Consultation Request – Heartland National TB Center

July 30, 2024 *(during 2nd hospitalization)*

Switched from RIPE to a liver-friendly regimen:

- Moxifloxacin 400 mg daily
- Linezolid 600 mg BID *(held 7/18 for thrombocytopenia; later restarted)*
- Ethambutol 800 mg, three times/week
- Imipenem

July 30, 2024: Clinical Status

- Improved with better appetite,
- No N/V
- no further cough or SOB
- O2 sat 99% on room air
- Sputum 7/28/2024 smear negative.
- Liver failure resolved
- No change in radiograph

July 30, 2024: Ongoing Concerns & Planning:

- **Acute kidney injury**: Concern about potential need for long-term dialysis

Discharge planning for August 7, 2024:

- Patient clinically stable and ready for discharge
- Coordination with Health Department for continued TB treatment

HNTC Recommendations August 1, 2024

Drug induced liver toxicity/ **DRESS Syndrome** likely:

Acute liver failure, Acute kidney injury with biopsy proven AIN likely due to rifampin, diffuse maculopapular rash with elevated WBC 13,000 and 9% eosinophils

HNTC Consultant Recommendations

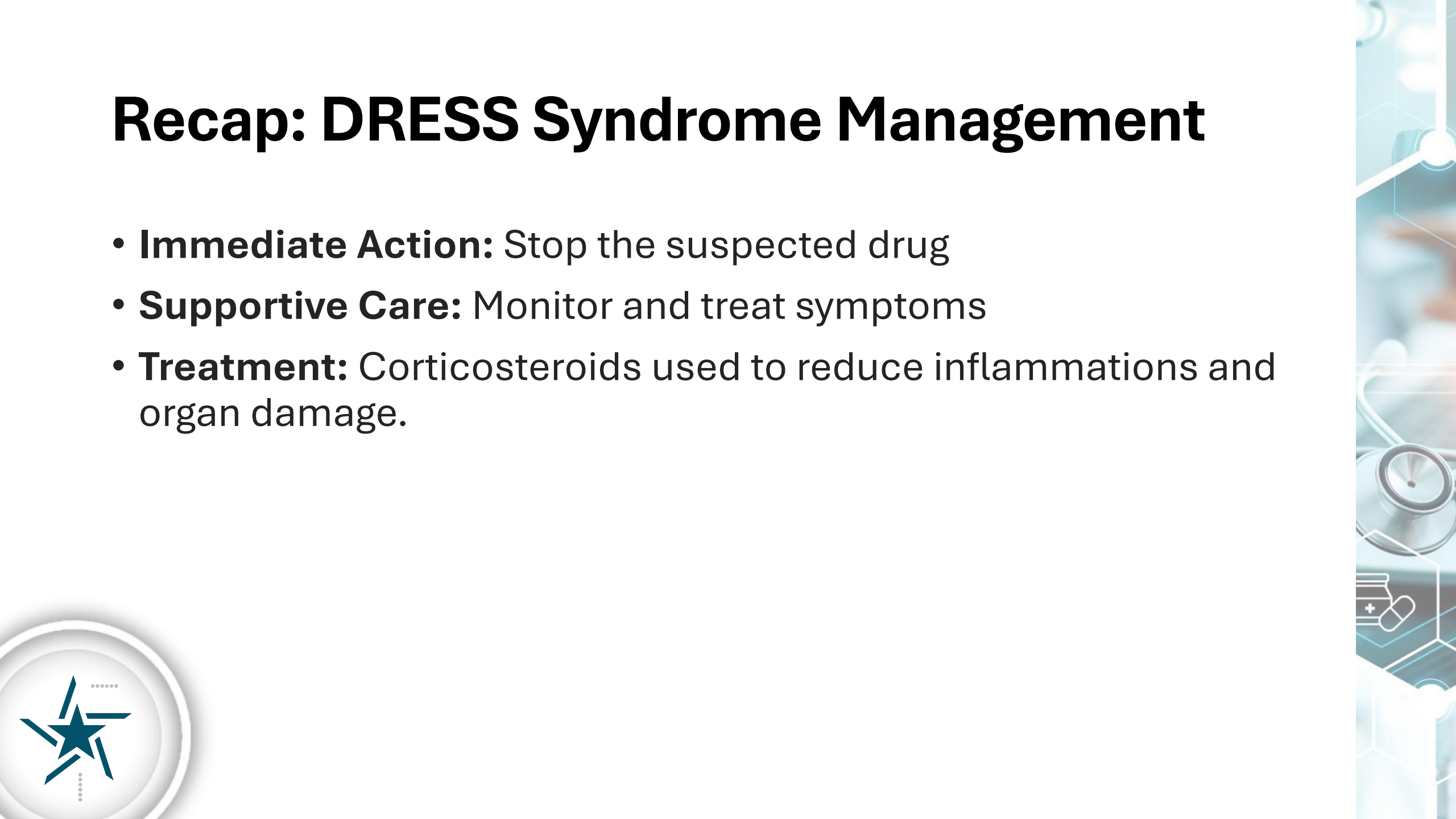
- Never take rifampin again or use of another rifamycin (would be very risky given severe nature of his illness)

- Do not recommend rechallenge with either rifampin, INH or PZA.

- Strongly recommend a regimen for rifampin intolerant TB:
  - BPaLM regimen (Bedaquiline, Pretomanid, Moxifloxacin and Linezolid) for at least 26 weeks

Recap: DRESS Syndrome Management

- **Immediate Action:** Stop the suspected drug
- **Supportive Care:** Monitor and treat symptoms
- **Treatment:** Corticosteroids used to reduce inflammations and organ damage.



Case Study continuation…

Discharged from hospital end of July followed by the health department

Patient was receiving **BPaLM** regimen

8/30: Readmitted with the following symptoms:

- Fever
- Elevated creatinine (1.48)
- Swollen face and hands
- Mild eosinophilia
- Rapid steroids withdrawal in two occasions
- Both episodes of facial swelling and rash flare likely linked to rapid steroid tapering

Clinical Course and Outcomes

August 31

Desquamative rash on trunk resolving skin lesions

Skin Reactions

September 2024

October 2024

Clinical Course and Outcomes

BPaLM treatment re-started in **September**

Patient continued hospitalization, with **TB medications temporarily stopped** due to reactions

Challenges included **rapid steroid withdrawal** on two occasions

TB medications were **discontinued**, and **high-dose steroids** were initiated

Once the reaction was controlled, **TB medications** were reintroduced

Dermatology team recommended **Benralizumab (**(IL-5 Inhibitor) which was well tolerated

Patient was **discharged** on full **BPaLM regimen**

TB Treatment in Patients with DRESS due to Rifampin Intolerance

- Traditional second-line therapy (e.g., moxifloxacin, ethambutol, linezolid, amikacin) requires 18 months
  - Effective but prolonged and difficult to tolerate
- New 6-month BPaLM regimen:
  - Bedaquiline, Pretomanid, Linezolid, Moxifloxacin
  - Major improvement, especially for DRESS patients:

What's Next in Treating DRESS? A Look Beyond Steroid

- Steroids are still the first-line treatment for DRESS.
- But long-term use has serious side effects.
- New research is exploring alternative treatments for eosinophilic inflammation
- Some promising options include:
  - IL-5 inhibitors (like *mepolizumab*)
- Early results show good outcomes with less toxicity
- Stay tuned for future webinars on these exciting developments

IL-5 Inhibitor Treatment in Drug Reaction With Eosinophilia and Systemic Symptoms | Clinical Pharmacy and Pharmacology | JAMA Dermatology | JAMA Network

Patient Education

- Most patients with DRESS recover completely in weeks or months after drug withdrawal
- Educate about the need to strictly **avoid** the offending drug as well as cross-reacting drugs
- Autoimmune diseases have been reported in some patients, months or years *after the resolution of the drug reaction*
  - Thyroiditis, diabetes mellitus type 1, and autoimmune hemolytic anemia. Medical follow up is needed for several years
- Active TB can be treated successfully despite DRESS using an alternative regimen
  - However, if patient is stable, it is best to wait for the skin to heal as recurrent DRESS can be mistaken for a reaction to a second drug which also occurs

Teaching Points

- **THINK IS THIS DRESS?** When a patient presents with a combination of rash and facial swelling
- **<u>STOP</u>** all suspect medications to let skin heal**!!!** 

- A detailed medication history is important to identify medications known to precipitate DRESS: i.e., *anticonvulsants, allopurinol, antibiotics, NSAID's, and antiretrovirals*
- Careful daily evaluation & document all reactions with detailed description in patient's chart/pictures

Teaching Points

- Signs and symptoms of DRESS may persist and recur for many weeks even after cessation of the offending medication
- DRESS is **severe** & requires **immediate medical attention**
- Fatality rate may be up to 10%
- Seek expert consultation; many need hospitalization

HNTC Rash Assessment Tool

Rash Assessment and Description Guide

1. Evaluate the Rash

1) Identify the type of lesion (size, layers of skin involved, and characteristics)
2) Identify location and distribution of lesions
3) Identify the configuration
   - The shape of one lesion:
     - **Linear** – straight line
     - **Target** – Bullseye or iris appearance; rings with central duskiness; purplish center, surrounded by pale pink, outer ring darker pink
   - The arrangement of clusters of lesions:
     - **Confluent** – Flowing into or coming together
     - **Random**
     - **Patterned**
4) Evaluate the texture
5) Color
6) Warm to the touch
7) Inspect oral mucosa

See back-side for terms and examples

2a. Gather Pertinent Information

1) Where is the rash? Is it unilateral or bilateral?
2) Where on the body did it start?
   - To where is it spreading?
   - Is it symmetrical or asymmetrical?
3) When did you notice the rash?
4) Are there any accompanying symptoms?
   - Itching, burning, fever
   - Shortness of breath, tingling of lips
5) Do you have any thoughts on what caused the rash?
   - New detergent, perfume, cleaners, lotion, soap
   - Outdoor activities, hiking, picnic, sunbathing
   - Environmental factors, vacation, travel, hotels
   - Any change in diet?
6) Complete a drug reconciliation; are their any medications known to cause drug-drug reactions?
   - Are TB Medications taken as directed?
   - Any new prescriptions?
   - New over the counter medications or supplements?
7) Have you tried any remedies?
8) What makes it better?
9) What makes it worse?
   - Is it worse at night?
10) Palpate the skin for texture and temperature changes

2b. Investigative Considerations

1) Is the eruption indicative of an infection, fungus, infestation, or drug rash?
2) HIV, Diabetes, Auto-Immune Disorders, Eczema, and Asthma increase rash prevalence, and drug-drug interactions
3) Is sunlight sensitivity a factor?

2c. Types of Reactions

Exanthemata (external rash) – Diffuse macule and papule, evolve over days after drug initiation
Urticaria & angioedema – Onset within minutes to hours after drug administration; potential for anaphylaxis
Fixed drug eruption – Hyper-pigmented plaques; upon drug re-exposure, plaques reoccur at same site.
DRESS – Cutaneous eruption, fever, eosinophilia, lymphadenopathy
Anaphylaxis – Urticaria, angioedema, bronchospasm, gastrointestinal
Stevens-Johnson Syndrome – Lesions, ulcers on mucous membranes, mouth, lips, truncal area; fever, fatigue, sore throat, ocular involvement

Seek immediate medical attention

HEARTLAND NATIONAL TB CENTER
THE UNIVERSITY OF TEXAS AT TYLER HEALTH SCIENCE CENTER

Consultations

Heartland National TB Center's Toll-Free Warm-Line
(800) TEX-LUNG *or* (800) 839-5864
https://www.heartlandntbc.org/

Rash Assessment and Description Guide

Rash Terms with Photo Examples

Bullae – Vesicle >1cm in diameter

Photo Credit: whitemay/Getty Images

Patch – Irregular shaped macule; >1cm in diameter

Photo Credit: jaojormami/Shutterstock

Erosion – Loss of epidermis; depressed, moist; follows rupture of vesicle

Photo Credit: https://www.medicinenet.com/skin_ulcer/article.htm

Plaque – Elevated, firm, rough lesion; >1cm in diameter

Photo Credit: https://www.medicalnewstoday.com/articles/323152#what-is-psoriasis

Excoriation – Loss of epidermis, linear, hollowed out, crusted area

Photo Credit: https://dermnetnz.org/topics/compulsive-skin-picking-images

Pustule – Vesicle filled with purulent fluid

Photo Credit: https://www.healthdirect.gov.au/acne

Erythema – A redness of the skin caused by congestion of the capillaries in the lower layers of the skin

Photo Credit: https://dermnetnz.org/topics/sunburn

Scale – Heaped-up accumulation of keratinized cells; flaky, can be dry or oily, varying in size

Photo Credit: AboutnuyLove

Lichenification – Rough, thickened epidermis from scratching or rubbing; normal skin markings are observable; often found on flexor surface of extremity

Photo Credit: https://www.healthline.com/health/lichenification#pictures

Urticaria – Hives, raised, itchy wheals; of varying size

Photo Credit: https://www.nidirect.gov.uk/conditions/urticaria-hives

Macule – Flat, non-palpable, circumscribed area; with change in skin color; <1cm in diameter

Photo Credit: CRISTINA PEDRAZZINI/SCIENCE PHOTO LIBRARY/Getty Images

Vesicle – Elevated, circumscribed, superficial, filled with serous fluid; <1cm in diameter

Photo Credit: Jere Mammino, DO

Papule – Elevated, firm, palpable, circumscribed area; <1cm in diameter

Photo Credit: https://www.healthline.com/health/skin/maculopapular-rash#pictures

Wheal – Elevated, irregular-shaped area of cutaneous edema; solid welt, pale red, transient; or varying diameters

Photo Credit: https://www.nidirect.gov.uk/conditions/urticaria-hives

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https://www.heartlandntbc.org/

HNTC Rash Assessment Tool

Photo redacted / Not approved for publishing

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Thank You!

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