HMS Update in Hospital Medicine Course

Common Consult Questions for Skin and Soft Tissue Infections

October 2021

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HARVARD MEDICAL SCHOOL | Postgraduate Medical Education

HMS Update in Hospital Medicine Course

Common Consult Questions for Skin and Soft Tissue Infections

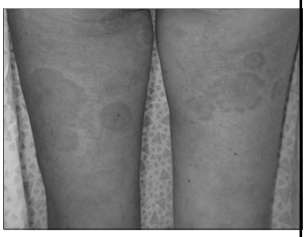
- No disclosures

Plan

- Management controversies for common skin infections
- Overlooked or underappreciated diagnoses
- Diagnostic pearls you can't easily Google

True/False

A patient is admitted with cough and hypoxia, after testing positive for COVID-19. During the intake exam, he is noted to have this widespread urticarial eruption, which was not present hours earlier.

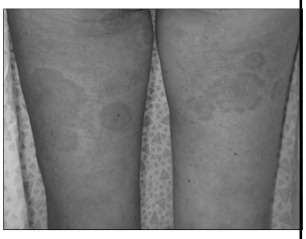


True/false: The rash is an excellent prognostic sign.

A. True
B. False

True/False

A patient is admitted with cough and hypoxia, after testing positive for COVID-19. During the intake exam, he is noted to have this widespread urticarial eruption, which was not present hours earlier.



True/false: The rash is an excellent prognostic sign.

A. True
B. False

Urticaria not an independent predictor of mortality/survival

Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: A worldwide review. JAAD Int. 2021 Mar;2:119-133. Epub 2020 Dec 16.

COVID-19 Acute Eruptions For the Hospitalist

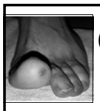
Eruptions COVID patients may be admitted ***WITH***	Eruptions COVID patients may be admitted ***FOR***

COVID-19 Acute Eruptions For the Hospitalist

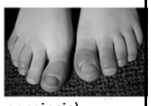
Eruptions COVID patients may be admitted ***WITH***	Eruptions COVID patients may be admitted ***FOR***
COVID Toes	
Maculopapular	
Urticarial	
Vesicular	

COVID-19 Acute Eruptions For the Hospitalist

Eruptions COVID patients may be admitted ***WITH***	Eruptions COVID patients may be admitted ***FOR***
COVID Toes	Vaso-occlusive disease
Maculopapular	
Urticarial	
Vesicular	

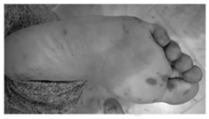


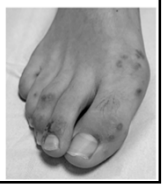
COVID-19 Acute Eruptions For the Hospitalist



Eruptions COVID patients may be admitted ***WITH***

COVID Toes (AKA chilblains, pseudo-chilblains, perniosis)





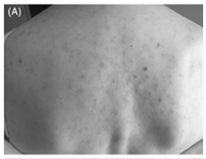
Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A, Moreno-Arrones OM, Saceda-Corralo D, Arana-Raja A, Ortega-Quijano D. Characterization of acute acral skin lesions in nonhospitalized patients: A case series of 132 patients during the COVID-19 outbreak. J Am Acad Dermatol. 2020 Jul;83(1):e61-e63. Epub 2020 Apr 24.

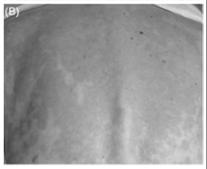
COVID-19 Acute Eruptions For the Hospitalist

Eruptions COVID patients may be admitted ***WITH***

COVID Toes

Maculopapular AKA Morbilliform





Maculopapular eruptions associated to COVID-19: A subanalysis of the COVID-Piel study. Dermatologic Therapy, Volume: 33, Issue: 6, First published: 10 August 2020, DOI: (10.1111/dth.14170)

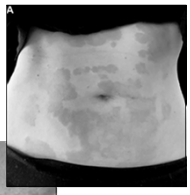
COVID-19 Acute Eruptions For the Hospitalist

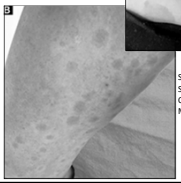
Eruptions COVID patients may be admitted ***WITH***

COVID Toes

Maculopapular

Urticarial AKA Hives





Skin manifestations of COVID-19. Sarah Young, Anthony P. Fernandez Cleveland Clinic Journal of Medicine May2020

COVID-19 Acute Eruptions For the Hospitalist

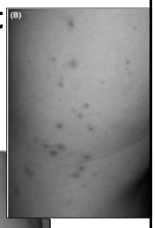
Eruptions COVID patients may be admitted ***WITH***

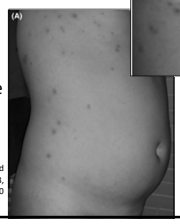
COVID Toes

Maculopapular

Urticarial

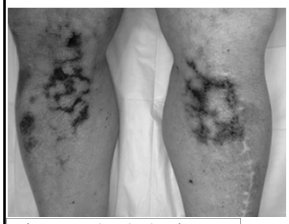
Vesicular AKA Varicella-like





Varicella-like exanthem associated with COVID-19 in an 8-year-old girl: A diagnostic clue? Pediatric Dermatology, Volume: 37, Issue: 3, Pages: 435-436, First published: 21 April 2020

COVID-19 Acute Eruptions For the Hospitalist

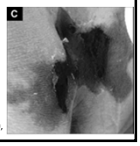


Retiform purpura as a dermatological sign of coronavirus disease 2019 (COVID-19) coagulopathy Journal of the European Academy of Dermatology and Venereology, Volume: 34, Issue: 10, Pages: e548-e549, First published: 03 June 2020

Eruptions COVID patients may be admitted ***FOR***

Vaso-occlusive disease

i.e. Retiform purpura, livedo racemose, livedo reticularis



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Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: A worldwide review. JAAD Int. 2021 Mar;2:119-133. doi: 10.1016/j.jdin.2020.12.003. Epub 2020 Dec 16. PMID: 33479703; PMCID: PMC7754879.

COVID-19 Acute Eruptions For the Hospitalist

Skin Manifestations	Eruptions COVID patients may be admitted ***WITH***	Eruptions COVID patients may be admitted ***FOR***
COVID Toes		Vaso-occlusive disease
Maculopapular		
Urticarial		
Vesicular		
Vaso-occlusive		

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COVID-19 Acute Eruptions For the Hospitalist

Skin Manifestation	**% of rashes**
COVID Toes	41%
Maculopapular	28%
Urticarial	12.5%
Vesicular	10.5%
Vaso-occlusive	4.5%
Other	3%

Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: A worldwide review. JAAD Int. 2021 Mar;2:119-133. doi: 10.1016/j.jdin.2020.12.003. Epub 2020 Dec 16. PMID: 33479703; PMCID: PMC7754879.

COVID-19 Acute Eruptions For the Hospitalist

Skin Manifestation	**% of rashes**	**Rash Onset timing**	
		With Other sxs	Late / Only
COVID Toes	41%		**70% (36 / 34)**
Maculopapular	28%	56%	32%
Urticarial	12.5%	52%	33%
Vesicular	10.5%	38%	48%
Vaso-occlusive	4.5%	**68%**	
Other	3%		

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COVID-19 Acute Eruptions For the Hospitalist

Skin Manifestation	**% of rashes**	**Rash Onset timing**		**Prognosis?**
		With Other sxs	Late / Only	
COVID Toes	41%		**70% (36 / 34)**	**Good**
Maculopapular	28%	56%	32%	**N/A**
Urticarial	12.5%	52%	33%	**N/A**
Vesicular	10.5%	38%	48%	**N/A**
Vaso-occlusive	4.5%	**68%**		**Poor**
Other	3%			

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COVID-19 Acute Eruptions For the Hospitalist

Skin Manifestation	% of rashes	Rash Onset timing		Prognosis?
		With Other sxs	Late / Only	
COVID Toes	41%		**70%** (36 / 34)	**Good**
Maculopapular	28%	**Not informative**		**N/A**
Urticarial	12.5%	**Not informative**		**N/A**
Vesicular	10.5%	**Not informative**		**N/A**
Vaso-occlusive	4.5%	**68%**		**Poor**
Other	3%			

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COVID-19 Acute Eruptions For the Hospitalist

Skin Manifestation

VASCULOPATHY

COVID Toes

Common among COVID eruptions (Late sign)
Good Prognosis

Uncommon among COVID eruptions
Poor Prognosis

Vaso-occlusive

ie retiform purpura

Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: A worldwide review. JAAD Int. 2021 Mar;2:119-133. doi: 10.1016/j.jdin.2020.12.003. Epub 2020 Dec 16. PMID: 33479703; PMCID: PMC7754879.

COVID-19 Acute Eruptions For the Hospitalist

Skin Manifestation	% of rashes	Mechanism	Onset / Severity
COVID Toes	41%	Vasculopathy	**Late** sign, **Mild** disease
Maculopapular	28%	**Other**	Contemporaneous with other symptoms; **Any** severity disease
Urticarial	12.5%		
Vesicular	10.5%		
Vaso-occlusive ie retiform purpura	4.5%	Vasculopathy	**Contemporaneous** with other symptoms; **SEVERE** disease

Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: A worldwide review. JAAD Int. 2021 Mar;2:119-133. doi: 10.1016/j.jdin.2020.12.003. Epub 2020 Dec 16. PMID: 33479703; PMCID: PMC7754879.

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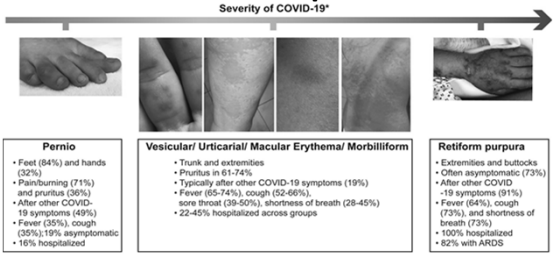


*Severity calculated based on percentage of patients hospitalized for COVID-19

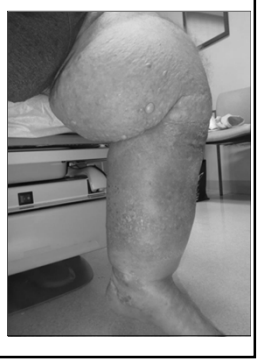
The spectrum of COVID-19–associated dermatologic manifestations: An international registry of 716 patients from 31 countries. Esther E. Freeman, MD, PhD, Devon E. McMahon, BA, Jules B. Lipoff, MD, Misha Rosenbach, MD, Carrie Kovarik, MD, Seemal R. Desai, MD, Joanna Harp, MD, Junko Takeshita, MD, PhD, MSCE, Lars E. French, MD, Henry W. Lim, MD, Bruce H. Thiers, MD, George J. Hruza, MD, MBA, Lindy P. Fox, MD. Journal of the American Academy of Dermatology, Volume 83,Issue 4,Pages 1118-1129 (October 2020)

Key COVID-19 Points

- COVID Toes suggests mild disease
- Retiform purpura suggests severe disease

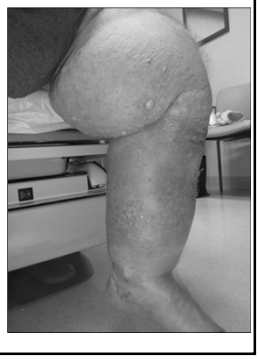
Case

- 58 yo M
- CHF, Diabetes, CAD, morbid obesity
- 3 days worsening leg swelling, redness, warmth
- Admitted for IV antibiotics



How should you manage?

A. IV Vancomycin
B. IV Cefazolin
C. IV Cefazolin + PO sulfa agent
D. PO Linezolid
E. No antibiotics



How should you manage?

~~A. IV Vancomycin~~
B. IV Cefazolin
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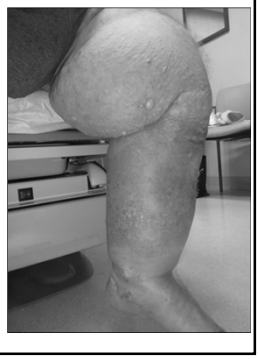
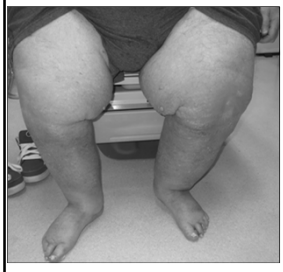
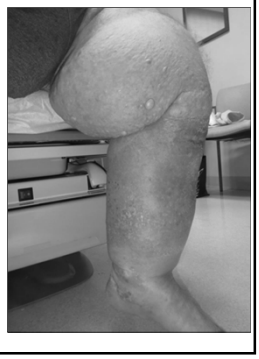
UNFAIR QUESTION!
Not enough data

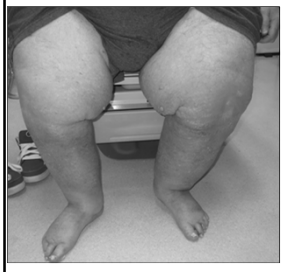


You walk in the room and see this:





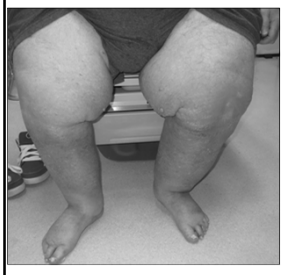
You take some additional history:



- 58 yo M
- CHF, Diabetes, CAD, morbid obesity
- 3 days worsening leg swelling, redness, warmth, pain
- Admitted for IV antibiotics

- Chronic edema for years
- Worse in past 3 days
- Symmetric progression
- No subjective fevers
- + Pruritus
- + Pain, mild to moderate

You become skeptical of the cellulitis diagnosis



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- Symmetric progression
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- + Pruritus
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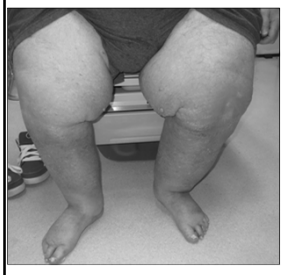
You get paged out of the room, and have time for only 1 more quick action on the way out. To best ***rule OUT*** cellulitis, you should:



A. Feel the legs for warmth
B. Press the legs to check for tenderness
C. Order a CBC
D. Check systemic temperature
E. Swab the skin surface for culture

* Alternative question phrasing: Which of the following characteristics is most *SENSITIVE* for cellulitis?

1. Local warmth
2. Local tenderness
3. Leukocytosis
4. Fever
5. Positive surface culture

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1. Local warmth
2. **Local tenderness**
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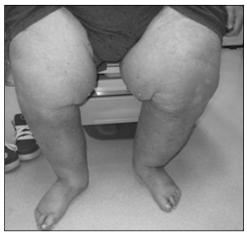
Cellulitis

- Infection of deep dermis and subcutaneous fat
- Red, warm, **tender**, edematous (rubor, calor, dolor, tumor)
- *S. aureus*, *S. pyogenes* (but cultures low yield)
- Common: fever, leukocytosis

- Risks
  - Immunosuppression: e.g. diabetes (**consider GNRs**)
  - Anatomic anomaly: e.g. lymphedema, obesity
  - Loss of skin integrity: e.g. tinea pedis, ulcer, incision

You quickly palpate his legs: they are *minimally* tender bilaterally and circumferentially. No specific points of greater tenderness anywhere.



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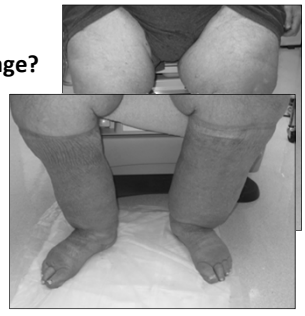

A. IV Vancomycin
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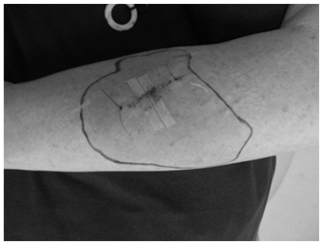
Management of Cellulitis

STEP 1: Cellulitis or NOT Cellulitis?



Step 1: Cellulitis or NOT Cellulitis?

JAMA Dermatology | Original Investigation

Costs and Consequences Associated With Misdiagnosed Lower Extremity Cellulitis

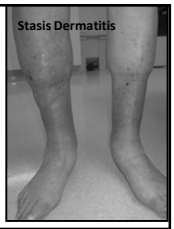
JAMA Dermatol. doi:10.1001/jamadermatol.2016.3816
Published online November 2, 2016.

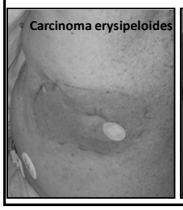
Qing Yu Weng, MD; Adam B. Raff, MD, PhD; Jeffrey M. Cohen, MD; Nicole Gunasekera, BS; Jean-Phillip Okhovat, BS; Priyanka Vedak, MD; Cara Joyce, PhD; Daniela Kroshinsky, MD, MPH; Arash Mostaghimi, MD, MPA, MPH

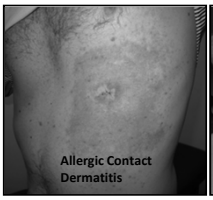
- 259 pts admitted from ED with "cellulitis"
- 79 (30.5%) did not have cellulitis
- 52 admitted specifically for "cellulitis"
  - 44 (84%) did not require hospitalization
  - 48 (92%) received unnecessary antibiotics
- **Cellulitis misdiagnosis→**
  - 50,000-130,000 unnecessary admissions (annual)
  - $195 million- $515 million avoidable healthcare $$s (annual)

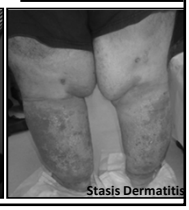
Step 1: Cellulitis or NOT Cellulitis?

- **Tender?** If not, consider alternative
- Bilateral? Consider alternative
- Pruritic? Consider alternative
- Geometric? Consider alternative









Management of Cellulitis

STEP 1: Cellulitis or NOT Cellulitis?
STEP 2: Severe or NOT Severe?

Step 2: consider SEVERITY

- Assessment of severity
  - Ill appearing patient
  - Severe co-morbidities
  - Evidence of deep infection
    - Pyomyositis, gangrenous cellulitis, necrotizing fasciitis
    - NSAIDs perhaps masking signs of deep infection?
- Management of SEVERE cellulitis:
  - Admission/Observation
  - Debride if needed
  - Broad spectrum IV antibiotics: Cover GAS, MRSA, MSSA
  - Consider GNR & anaerobe coverage in select situations

Management of <u>SIMPLE</u> Cellulitis

- Supportive care: elevation, immobilization, wound care
- Oral antibiotics

But which one?

- β-lactam?
- Clindamycin? Sulfa? Minocycline? Fluoroquinolone?
- 2 oral antibiotics together?
- IV vancomycin? PO linezolid? Other?

NOTE: Same clinical question when transitioning from IV therapy to oral antibiotics for cellulitis

Cellulitis empiric therapy: Key principles

- Common pathogens: GAS, MSSA, CA-MRSA
- Susceptibility
  - MSSA and GAS susceptible to beta-lactams
  - MSSA and CA-MRSA *generally* susceptible to TMP-SMX
  - GAS is *unreliably* susceptible to TMP-SMX
  - Susceptibility to clinda, fluoroquinolones, tetracyclines, macrolides, etc. *varies*
- Rates of MRSA: vary by region– often >50%
- Some infections will worsen despite "correct" empiric abx
- MANY infections will resolve despite "incorrect" empiric abx
- Cultures are generally low yield

Legend: GAS = Group A Streptococcus
MSSA = methicillin sensitive S. aureus
MRSA = methicillin resistant S. aureus
CA = community aquired
TMP-SMX = Trimethoprim/Sulfamethoxazole

Data: Simple Cellulitis Empiric Antibiotic Choice

Caution: The data is messy and incomplete

SSTI empiric therapy 2007-2010

Pro-B-lactam	Description	Result
Phillips et al 2007	• Cost effectiveness analysis • *Simple* SSTIs • Cephalexin vs Clindamycin vs TMP-SMX	• Cephalexin dominates nearly all situations • Unless chance of *S. aureus* (vs Group A Strep) is very high • Or, MRSA prevalence rises well above current levels
Madaras-Kelly 2008	• Retrospective case control • Multicenter, adult practices, Idaho	• Adverse effects: More with anti-MRSA therapy • Effectiveness: No differences β-lactams vs anti-MRSA therapy
Elliot et al 2009	• Retrospective case control • Multicenter, Pediatric practices	• Host factors predict failure more than antibiotic choice • TMP-SMX failed more than clinda or cephalexin

Anti-B-lactam	Description	Result
Khawcharoenpom and Tice, 2010	• Retrospective analysis, • Hawaii clinics • 405 cases	• TMP-SMX success rate > cephalexin (94% vs 71%) • MRSA rate in culture positive cases = 62% (of 117 cultured)
Pokharna et al, 2010 ABSTRACT ONLY	• Retrospective analysis, Detroit • Tertiary care **hospital (inpatients)** • **Culture positive cellulitis only**	• Success rates: vancomycin > beta-lactam (90% vs 45%, OR 11)

Phillips A, MacDougallC, Holdford DA. Analysis of Empiric Antimicrobial Strategies for Cellulitis in the Era of MRSA.*Annals of Pharmacotherapy:* 2007; Vol. 41, No. 1, pp. 13-20
Elliott DJ, Zaoutis TE, Troxel AB, et al: Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant Staph aureus. Pediatrics 123:e959-66, 2009
Madaras-Kelly KJ, Remington RE, Oliphant CM, et al: Efficacy of oral beta-lactam versus non-beta-lactam treatment of uncomplicated cellulitis. Am J Med 121:419-25, 2008
Khawcharoenpom T, Tice A. Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis. Am J Med.123 (10): 942-50, 2010
Pokharna H, Haque N, Zervos M. Vancomycin Vs B-Lactam – Drug of Choice for Empiric Treatment of Cellulitis Requiring Hospitalization. Abstract 1238 in Infectious Diseases Society of America 48th Annual Meeting; Oct 23, 2010.

SSTI empiric therapy 2007-2010

General conclusions

1. **Weak: Most studies slightly favor B-lactams**
2. **Consistent: Patient/disease characteristics predict failure better than abx choice**

Phillips A, MacDougallC, Holdford DA. Analysis of Empiric Antimicrobial Strategies for Cellulitis in the Era of MRSA.*Annals of Pharmacotherapy:* 2007; Vol. 41, No. 1, pp. 13-20
Elliott DJ, Zaoutis TE, Troxel AB, et al: Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant Staph aureus. Pediatrics 123:e959-66, 2009
Madaras-Kelly KJ, Remington RE, Oliphant CM, et al: Efficacy of oral beta-lactam versus non-beta-lactam treatment of uncomplicated cellulitis. Am J Med 121:419-25, 2008
Khawcharoenpom T, Tice A. Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis. Am J Med.123 (10): 942-50, 2010
Pokharna H, Haque N, Zervos M. Vancomycin Vs B-Lactam – Drug of Choice for Empiric Treatment of Cellulitis Requiring Hospitalization. Abstract 1238 in Infectious Diseases Society of America 48th Annual Meeting; Oct 23, 2010.

Cochrane Review 2010

Authors' conclusions:

We cannot define the best treatment for cellulitis and most recommendations are made on single trials. There is a need for trials to evaluate the efficacy of oral antibiotics against intravenous antibiotics in the community setting as there are service implications for cost and comfort.

Read the full abstract...

Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD004299.

June 2013

Clinical Trial: Comparative Effectiveness of Cephalexin Plus Trimethoprim-Sulfamethoxazole Versus Cephalexin Alone for Treatment of Uncomplicated Cellulitis: A Randomized Controlled Trial

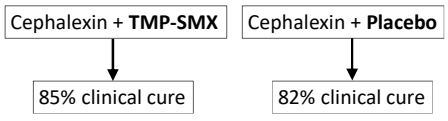
Daniel J. Pallin,[1,2] William D. Binder,[2] Matthew B. Allen,[1,4] Molly Lederman,[1,5] Siddharth Parmar,[1] Michael R. Filbin,[3] David C. Hooper,[6] and Carlos A. Camargo Jr[2]

[1]Department of Emergency Medicine, Brigham and Women's Hospital, [2]Division of Emergency Medicine, Boston Children's Hospital, and [3]Department of Emergency Medicine, Massachusetts General Hospital, Boston; [4]Perelman School of Medicine at the University of Pennsylvania, Philadelphia; [5]Department of Pediatrics, and [6]Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital, Boston

CID 2013:56 (15 June)

Pallin et al, CID 2013

- 3 Boston Emergency Depts, 2007-11
- 153 Simple Cellulitis patients randomized



- Presence of nasal MRSA: no impact on outcome
- Conclusion: **no benefit to adding sulfa**

Pallin DJ, et al. "Clinical Trial: Comparative Effectiveness of Cephalexin Plus Trimethoprim-Sulfamethoxazole Versus Cephalexin Alone for Treatment of Uncomplicated Cellulitis: A Randomized Controlled Trial." Clin Infect Dis, 56: 2013 1754-62

Moran et al, JAMA 2017

- 5 U.S. Emergency Depts, 2009-12
- 500 Simple Cellulitis patients randomized

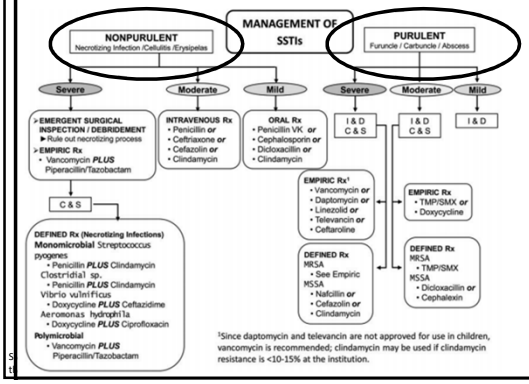
Cephalexin + **TMP-SMX**	Cephalexin + **Placebo**
↓	↓
83.5% clinical cure	85.5% clinical cure

- Conclusion: **no benefit to adding sulfa**
- Modified Intention-to-treat analysis trended toward combo therapy (7.3%, 95%CI -1.0 to 15.5%, p = 0.07)

Moran GJ, Krishnadasan A, Mower WR, Abrahamian FM, LoVecchio F, Steele MT, Rothman RE, Karras DJ, Hoagland R, Pettibone S, Talan DA. Effect of Cephalexin Plus Trimethoprim-Sulfamethoxazole vs Cephalexin Alone on Clinical Cure of Uncomplicated CellulitisA Randomized Clinical Trial. *JAMA.* 2017;317(20):2088–2096.

June 2014

IDSA GUIDELINE



2014 Updated IDSA Guidelines

- Purulent Infections (eg abscesses)
  - Always I&D
  - If moderate or severe: anti-MRSA abx empirically

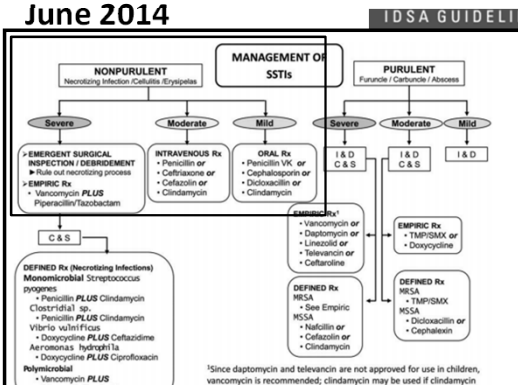
  (Daum et al, NEJM 2017: also suggests PO Abx for small abscesses)

- Non-purulent infections (eg cellulitis)
  - If severe: debride, support, broad spectrum IV Abx
  - If not severe: systemic abx with Strep coverage

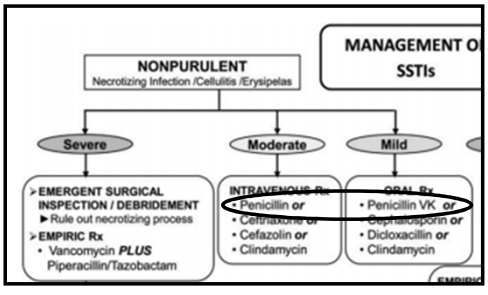
Stevens DL, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases (Advanced Access June 18, 2014)

June 2014

IDSA GUIDELINE



2014 Updated IDSA Guidelines
Caution regarding non-purulent infections



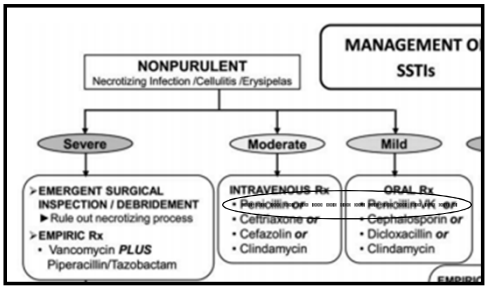
Stevens DL, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases (Advanced Access June 18, 2014)

2014 Updated IDSA Guidelines
Caution regarding non-purulent infections

- Assumes Strep is dominant, minimal MSSA/MRSA
- Cites 6 studies: mostly old culture data (5 are pre-1996)
- Exception: Jeng et al, 2010– serologies & β-lactam response
  - Claim: "73% of non-culturable cellulitis caused by BHS"
    - **BUT: Not "intention to test"– 31% lost without serologies**
  - Claim: β-lactam response rate 95.6%
    - **BUT: They recommended cefazolin or oxacillin, which cover MSSA**
  - **Only included patients admitted to hospital**

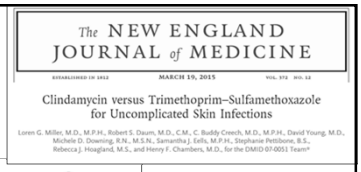
Jeng A, Beheshti M, Li J, Nathan R. The role of beta-hemolytic streptococci in causing diffuse, non-culturable cellulitis: a prospective investigation. Medicine (Baltimore) 2010; 89: 217-26
Stevens DL, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the IDSA. Clinical Infectious Diseases (Advanced Access June 18, 2014)

2014 Updated IDSA Guidelines
Caution regarding **non**-purulent infections



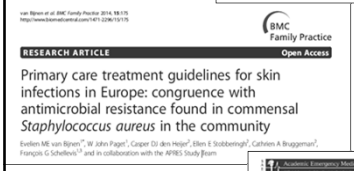
Stevens DL, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases (Advanced Access June 18, 2014)

Newer data


The NEW ENGLAND JOURNAL of MEDICINE

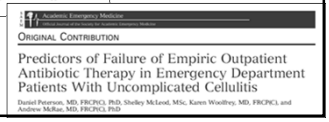
MARCH 19, 2015

Clindamycin versus Trimethoprim–Sulfamethoxazole for Uncomplicated Skin Infections


BMC Family Practice

RESEARCH ARTICLE Open Access

Primary care treatment guidelines for skin infections in Europe: congruence with antimicrobial resistance found in commensal *Staphylococcus aureus* in the community

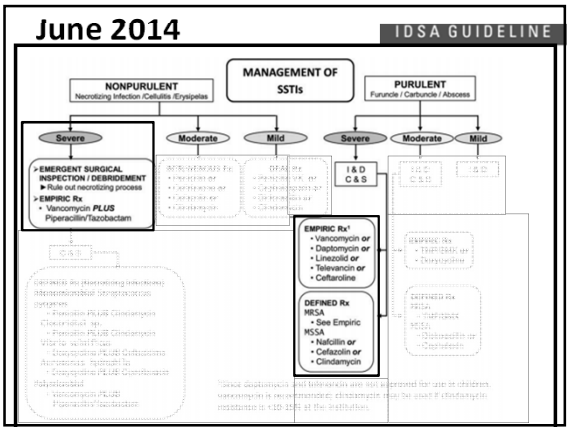

ORIGINAL CONTRIBUTION

Predictors of Failure of Empiric Outpatient Antibiotic Therapy in Emergency Department Patients With Uncomplicated Cellulitis

Cellulitis empiric therapy: Conclusions/Recommendations

- Still a moving target, but data is improving
- Anything severe: Admit, monitor, broad IV abx, surgery
- Beta-lactam likely best for most simple, outpatient cases
- Despite IDSA guidelines:
  - Strongly consider a β-lactamase resistant agent

June 2014

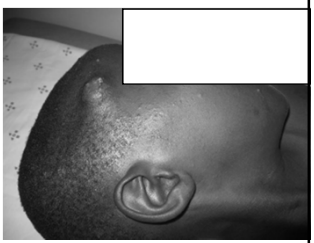


Newly Approved Antibiotics for SSTI

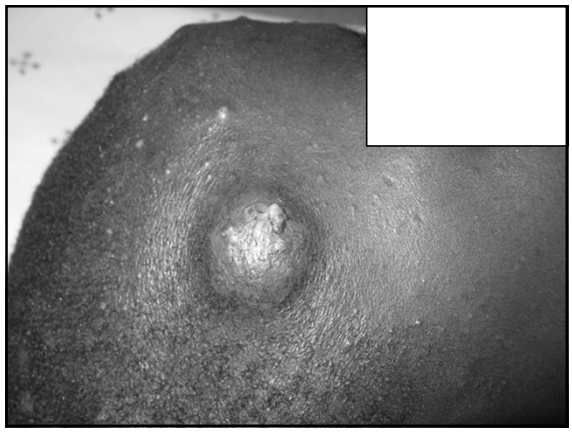
Antibiotic	Year	Route	Class	SSTI spectrum
Omadacycline	2018	IV, PO	Modernized Tetracycline	Staph spp (incl MRSA), Strep spp, VRE/VSE, *E. cloacae, K. pneumoniae,*
Delafloxacin	2017	IV, PO	Fluoroquinolone	Staph spp (incl MRSA), Strep spp, VRE/VSE, *E. coli, E. cloacae, K. pneumoniae, P. aeruginosa*
Ozenaxacin	2017	Topical	Quinolone	Impetigo (including MRSA)
Dalbavancin	2014	IV (Qwk)	Lipoglycopeptide	Staph spp (incl MRSA), Strep spp, VSE
Oritavancin	2014	IV x 1	Lipoglycopeptide	Staph spp (incl MRSA), Strep spp, VSE
Tedizolid	2014	IV, PO	Oxazolidinone	Staph spp (incl MRSA), Strep spp, VRE/VSE
Ceftaroline	2010	IV	Cephalosporine	Staph spp (incl MRSA), Strep spp (incl MDR *S. pneumoniae*), VRE/VSE (limited), *H. influenzae, E. cloacae, E. coli, K. pneumoniae,* Shigella spp.
Televancin	2009	IV	Lipoglycopeptide	Staph spp (incl MRSA), Strep spp, VSE

Case

- 12 year-old female
- Fluctuant nodule R temple
- Increasing pain x 1 week
- HIV+ (congenital)
- CD4+ > 200
- on ARVs



- Many similar lesions over past year



What is the most appropriate next step in management of the furuncle/abscess?

1. Daily chlorhexidine washes
2. Oral cephalexin
3. Oral cephalexin plus oral TMP-SMX
4. IV vancomycin
5. Incision and Drainage

~~What is the most appropriate next step in management of the furuncle/abscess?~~

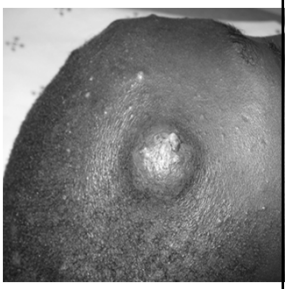
1. ~~Daily chlorhexidine washes~~
2. ~~Oral cephalexin~~
3. ~~Oral cephalexin plus oral TMP-SMX~~
4. ~~IV vancomycin~~
5. ~~Incision and Drainage~~

No longer a fair question because of data on the following slides

Furunculosis

- *Staph aureus* most common
- Treatment:
  - Warm compresses
  - Incision & Drainage if >1cm

I&D alone? I&D + PO antibiotics



??????????

Duong M, Markwell S, Peter J, Barenkamp S. Randomized, controlled trial of antibiotics in the management of community-acquired skin abscesses in the pediatric patient. Ann Emerg Med.2010;55:401-407.

Schmitz GR, Bruner D, Pitotti R, et al. Randomized controlled trial of trimethoprim-sulfamethoxazole for uncomplicated skin abscesses in patients at risk for community-associated methicillin-resistant Staphylococcus aureus infection. Ann Emerg Med 2010;56:283-287[Erratum, Ann Emerg Med 2010;56:88

Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52:e18-e55

N ENGL J MED 376;26 NEJM.ORG JUNE 29, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses

Robert S. Daum, M.D., C.M., Loren G. Miller, M.D., M.P.H., Lilly Immergluck, M.D., Stephanie Fritz, M.D., M.S.C.I., C. Buddy Creech, M.D., M.P.H., David Young, M.D., Neha Kumar, M.D., Michele Downing, R.N., M.S.N., Stephanie Pettibone, B.S., Rebecca Hoagland, M.S., Samantha J. Eells, M.P.H., Mary G. Boyle, R.N., M.S.N., Trisha Chan Parker, M.P.H., and Henry F. Chambers, M.D., for the DMID 07-0051 Team*

- 6 centers: U. Chicago, SF General, Harbor UCLA, Vanderbilt, Wash U., Morehouse
- Double Blinded, Randomized, Placebo Controlled; Appropriate exclusions/inclusion
- Single abscess, <5cm, uncomplicated, adults & children
- Clinda 300mg TID vs Bactrim DS BID vs Placebo
- 786 Enrolled

NEJM 2017: Simple Abscess Treatment
I&D + {Clinda vs TMP-SMX vs Placebo}

Table 3. Cure Rate at Test-of-Cure Visit in the Overall Population and Relevant Subgroups.*

Group	Clindamycin		TMP-SMX		Placebo	
	No. with Cure/ Total No.	% (95% CI)	No. with Cure/ Total No.	% (95% CI)	No. with Cure/ Total No.	% (95% CI)
All participants						
Intention-to-treat population	221/266	83.1 (78.3–87.9)	215/263	81.7 (76.8–86.7)	177/257	68.9 (62.9–74.9)
Population that could be evaluated	221/238	92.9 (89.3–96.4)	215/232	92.7 (89.0–96.3)	177/220	80.5 (74.8–86.1)
Children						
Intention-to-treat population	90/101	89.1 (82.5–95.7)	75/91	82.4 (74.0–90.8)	61/89	68.5 (58.3–78.7)
Population that could be evaluated	90/92	97.8 (94.3–100.0)	75/81	92.6 (86.3–98.9)	61/74	82.4 (73.1–91.8)
Adults						
Intention-to-treat population	131/165	79.4 (72.9–85.9)	140/172	81.4 (75.3–87.5)	116/168	69.0 (61.8–76.3)
Population that could be evaluated	131/146	89.7 (84.5–95.0)	140/151	92.7 (88.2–97.2)	116/146	79.5 (72.6–86.3)
S. aureus isolated						
Intention-to-treat population	157/188	83.5 (77.9–89.1)	149/179	83.2 (77.5–89.0)	102/160	63.8 (56.0–71.5)
Population that could be evaluated	157/167	94.0 (90.1–97.9)	149/160	93.1 (88.9–97.4)	102/134	76.1 (68.5–83.7)
MRSA isolated						
Intention-to-treat population	116/142	81.7 (75.0–88.4)	110/130	84.6 (78.0–91.2)	73/116	62.9 (53.7–72.2)
Population that could be evaluated	116/126	92.1 (86.9–97.2)	110/117	94.0 (89.3–98.7)	73/96	76.0 (67.0–85.1)
MSSA isolated						
Intention-to-treat population	41/46	89.1 (79.0–99.2)	39/49	79.6 (67.3–91.9)	29/44	65.9 (50.8–81.1)
Population that could be evaluated	41/41	100.0 (98.8–100.0)	39/43	90.7 (80.9–100.0)	29/38	76.3 (61.5–91.1)
No S. aureus isolated						
Intention-to-treat population	57/68	83.8 (74.3–93.3)	59/72	81.9 (72.4–91.5)	69/83	83.1 (74.5–91.8)
Population that could be evaluated	57/63	90.5 (82.4–98.5)	59/65	90.8 (83.0–98.6)	69/76	90.8 (83.6–97.9)

* The actual confidence interval was 95.6% after adjustment for the interim analysis. The intention-to-treat population includes all participants who underwent randomization, and the population that could be evaluated includes participants who received treatment or placebo and completed the required study visits.

NEJM 2017: Simple Abscess Treatment
I&D + {Clinda vs TMP-SMX vs Placebo}

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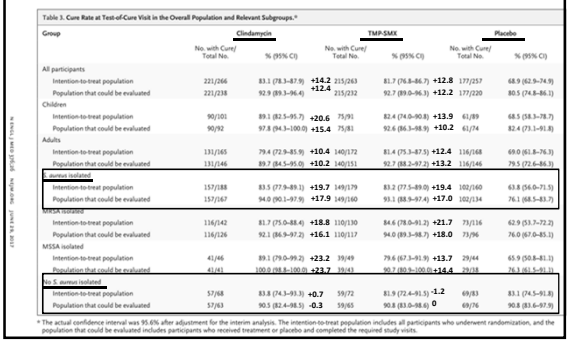
All participants						
Intention-to-treat population	221/266	83.1 (78.3–87.9)	215/263	81.7 (76.8–86.7)	177/257	68.9 (62.9–74.9)
		+14.2		+12.8		
Population that could be evaluated	221/238	92.9 (89.3–96.4)	215/232	92.7 (89.0–96.3)	177/220	80.5 (74.8–86.1)
		+12.4		+12.2		
Children						
Intention-to-treat population	90/101	89.1 (82.5–95.7)	75/91	82.4 (74.0–90.8)	61/89	68.5 (58.3–78.7)
		+20.6		+13.9		
Population that could be evaluated	90/92	97.8 (94.3–100.0)	75/81	92.6 (86.3–98.9)	61/74	82.4 (73.1–91.8)
		+15.4		+10.2		
Adults						
Intention-to-treat population	131/165	79.4 (72.9–85.9)	140/172	81.4 (75.3–87.5)	116/168	69.0 (61.8–76.3)
		+10.4		+12.4		
Population that could be evaluated	131/146	89.7 (84.5–95.0)	140/151	92.7 (88.2–97.2)	116/146	79.5 (72.6–86.3)
		+10.2		+13.2		
S. aureus isolated						
Intention-to-treat population	157/188	83.5 (77.9–89.1)	149/179	83.2 (77.5–89.0)	102/160	63.8 (56.0–71.5)
		+19.7		+19.4		
Population that could be evaluated	157/167	94.0 (90.1–97.9)	149/160	93.1 (88.9–97.4)	102/134	76.1 (68.5–83.7)
		+17.9		+17.0		
MRSA isolated						
Intention-to-treat population	116/142	81.7 (75.0–88.4)	110/130	84.6 (78.0–91.2)	73/116	62.9 (53.7–72.2)
		+18.8		+21.7		
Population that could be evaluated	116/126	92.1 (86.9–97.2)	110/117	94.0 (89.3–98.7)	73/96	76.0 (67.0–85.1)
		+16.1		+18.0		
MSSA isolated						
Intention-to-treat population	41/46	89.1 (79.0–99.2)	39/49	79.6 (67.3–91.9)	29/44	65.9 (50.8–81.1)
		+23.2		+13.7		
Population that could be evaluated	41/41	100.0 (98.8–100.0)	39/43	90.7 (80.9–100.0)	29/38	76.3 (61.5–91.1)
		+23.7		+14.4		
No S. aureus isolated						
Intention-to-treat population	57/68	83.8 (74.3–93.3)	59/72	81.9 (72.4–91.5)	69/83	83.1 (74.5–91.8)
		+0.7		-1.2		
Population that could be evaluated	57/63	90.5 (82.4–98.5)	59/65	90.8 (83.0–98.6)	69/76	90.8 (83.6–97.9)
		-0.3		0		

* The actual confidence interval was 95.6% after adjustment for the interim analysis. The intention-to-treat population includes all participants who underwent randomization, and the population that could be evaluated includes participants who received treatment or placebo and completed the required study visits.

NEJM 2017: Simple Abscess Treatment
I&D + {Clinda vs TMP-SMX vs Placebo}



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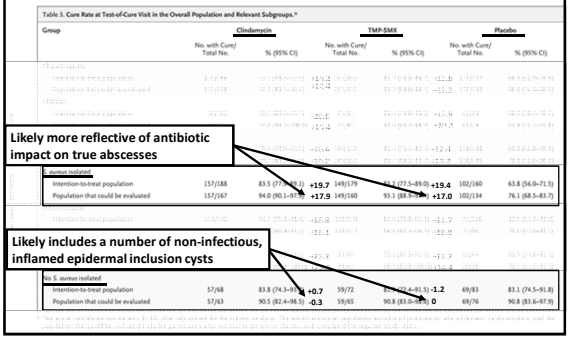

NEJM 2017: Simple Abscess Treatment
I&D + {Clinda vs TMP-SMX vs Placebo}

Table S8: Reasons for failure at the TOC in the ITT population and OMFU visit

	Clindamycin n=266	TMP-SMX n=263	Placebo n=257	Total n=786
Failures up to and including the OMFU visit	~~57~~	~~71~~	~~96~~	~~224~~
	44	45	50	
Excluded from the secondary efficacy analysis due to lost to follow up and other administrative reasons	32	37	39	108
Worsening original lesion	1	0	1	2
New infection	~~13~~	~~26~~	~~46~~	~~85~~
Used Rescue Meds	12	15	33	60
Treatment stopped within 48 hours	4	1	1	6
Unplanned surgery	3	3	3	9
Used non-study antibiotics for other lesion	5	4	3	12
Cure at 1 month	**83.5%**	**82.9%**	**80.5%**	

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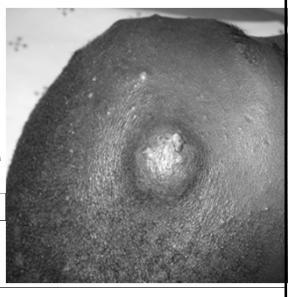
What are we treating here?

Furunculosis

- *Staph aureus* most common
- Treatment:
  - Warm compresses
  - Incision & Drainage if >1cm

~~I&D alone = I&D + PO antibiotics~~

Consider anti-staph (MRSA) Abx



N ENGL J MED 376;26 NEJM.ORG JUNE 29, 2017

My Personal Approach:

1. I&D, with culture
2. If not resolved by time of culture result, start PO abx based on culture result

S. aureus Decolonization

- Data is poor quality
- Data is highly **fragmented**
  - By setting: ambulatory, hospital, ICU, nursing home…
  - By indication: pre-op, carrier-status, recurrent infection…
  - By intervention: mupirocin, chlorhexidine, PO abx, et al...
  - By outcome: decolonization vs lower infection rate
  - By endpoint: 1 mo, 3 mo, 6 mo, 1 year, 5 year….

S. aureus Decolonization

- Cochrane review concludes:

"In people who are nasal carriers of *S. aureus*, the use of mupirocin ointment results in a statistically significant reduction in *S. aureus* infections."

van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Cochrane Database of Systematic Reviews 2008, Issue 4.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Decolonization to Reduce Postdischarge Infection Risk among MRSA Carriers

Susan S. Huang, M.D., M.P.H., Raveena Singh, M.A., James A. McKinnell, M.D., Steven Park, M.D., Ph.D., Adrijana Gombosev, M.S., Samantha J. Eells, M.P.H., Daniel L. Gillen, Ph.D., Diane Kim, B.S., Syma Rashid, M.D., Raul Macias-Gil, M.D., Michael A. Bolaris, M.D., Thomas Tjoa, M.P.H., M.S., et al., for the Project CLEAR Trial

- Large multicenter RCT
- Post-discharge decolonization vs education alone
- Chlorhexidine/Mupirocin x 5 days, once/mo x 6 mo
- Follows x 1 year
- →**30% lower risk of MRSA infection**

Huang SS, et al; project CLEAR Trial. Decolonization to reduce Postdischarge infection risk among MRSA carriers. N Engl J Med 2019;380(7):638–650.

S. aureus Decolonization

- Nasal *S. aureus* carriers:
  - Mupirocin → lower *S. aureus* infection rate
  - But, *possibly* higher rates of other nosocomial infections
- Other groups/settings:
  - Many studies demonstrate transient decolonization
    - Simple cases: mupirocin to nares, chlorhexidine wash
    - Complex cases: add 2 PO antibiotics
    - Remember benzoyl peroxide, bleach baths, hexachlorophene, et al
  - A few demonstrate lasting effect or decreased infection

Finnell SM, et al. Decolonization of children after incision and drainage for MRSA abscess: a retrospective cohort study. Clin Pediatr (Phila). 2015 May;54(5):445-50
Huang SS, et al. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 2013 Jun 13;368(24):2255-65.
Miller LG, et al. Prospective investigation of nasal mupirocin, hexachlorophene body wash, and systemic antibiotics for prevention of recurrent community-associated methicillin-resistant Staphylococcus aureus infections. Antimicrob Agents Chemother 2012;56:1084-108
Ammerlaan HS et al. Eradication of carriage with methicillin-resistant Staphylococcus aureus effectiveness of a national guideline. J Antimicrobial Chemother. 2011: 66(10):2409-17
Hughes C, Smith M, Tunney M. Infection control strategies for preventing the transmission of meticillin-resistant *Staphylococcus aureus* (MRSA) in nursing homes for older people. Cochrane Collaboration, 20 Jan 2010.
Loeb MB, Main C, Eady A, Walker-Dilks C. Antimicrobial drugs for treating methicillin-resistant Staphylococcus aureus colonization. Cochrane Collaboration, 8 Oct 2008.
Weintrob A, et al. Randomized, Double-Blind, Placebo-Controlled Study on Decolonization Procedures for Methicillin-Resistant Staphylococcus aureus (MRSA) among HIV-Infected Adults. PLoS One. 2015 May 27;10(5)

S. aureus Decolonization

- We can return to this at the end
- Bottom line:
  - Jury is still very much out
  - I do use decolonization regimens in select, usually ambulatory, patients

Finnell SM, et al. Decolonization of children after incision and drainage for MRSA abscess: a retrospective cohort study. Clin Pediatr (Phila). 2015 May;54(5):445-50
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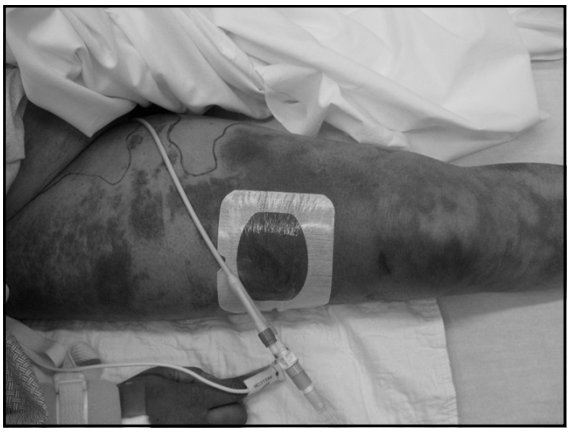
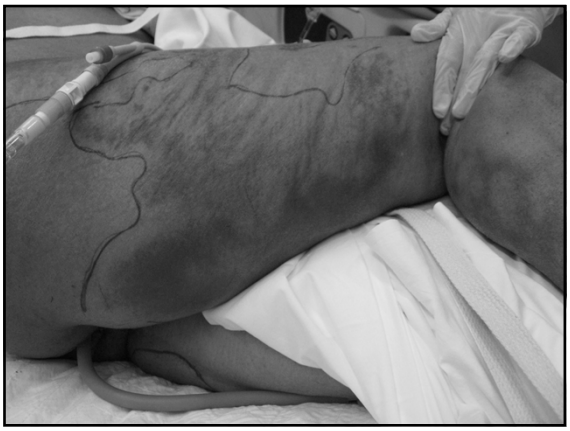
Case

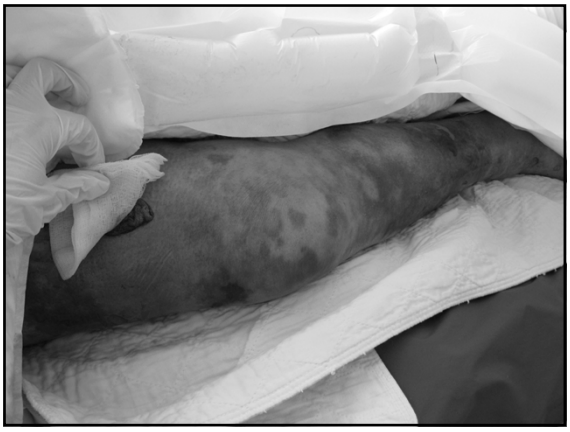
- **52 yo F with systemic lupus**
- **On mycophenolate mofetil and prednisone**
- **Presents unresponsive with rash on her right leg only**
- **Was well the night before**
- **Rapidly developed multi-organ failure in ED**

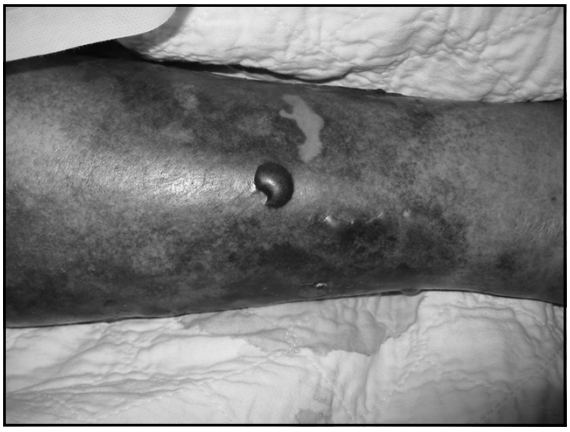
Hospital Day 1

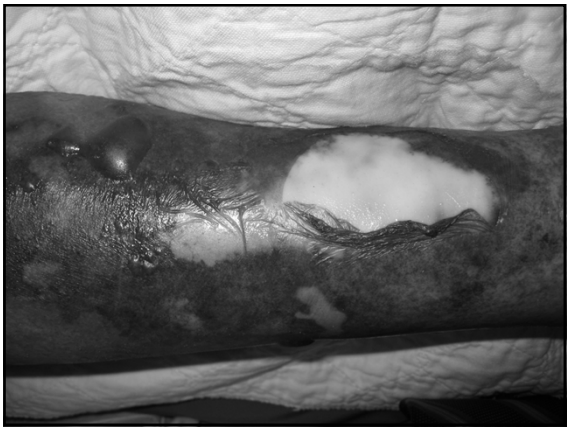




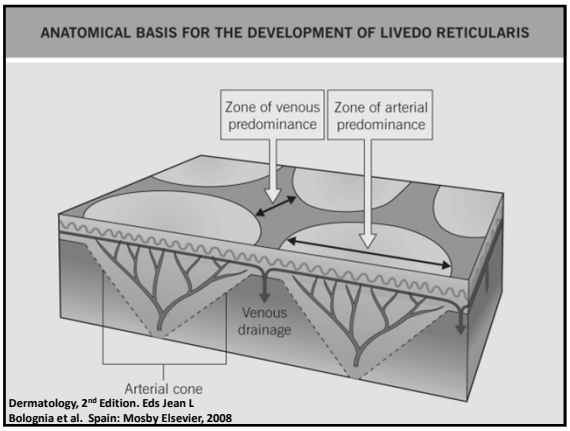
Hospital Day 3

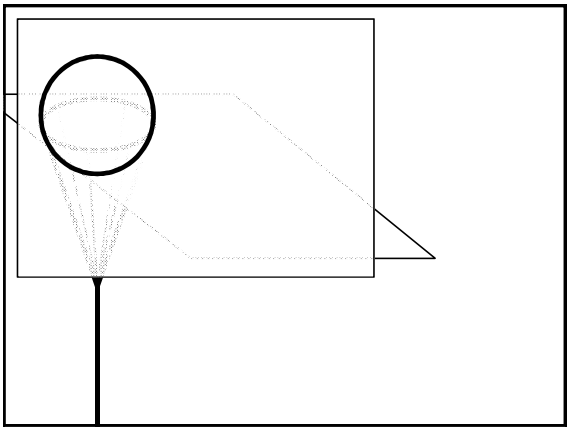


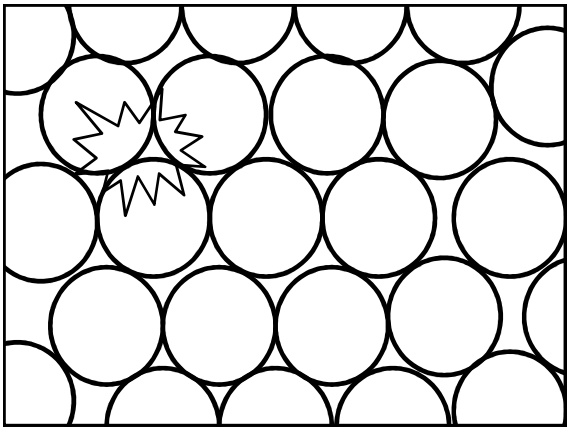


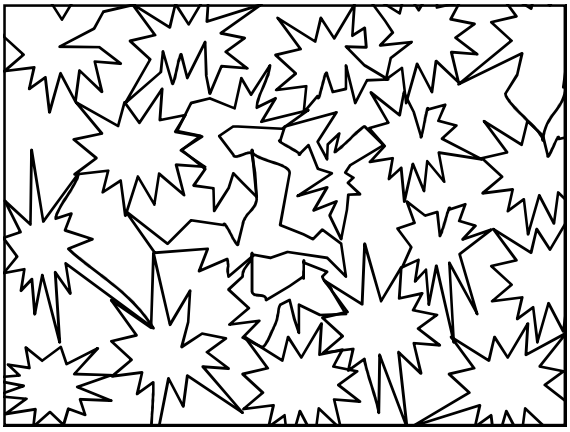


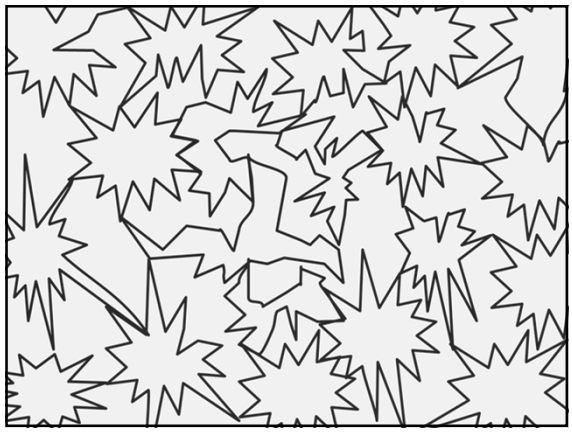

What can morphology tell us about pathophysiology?

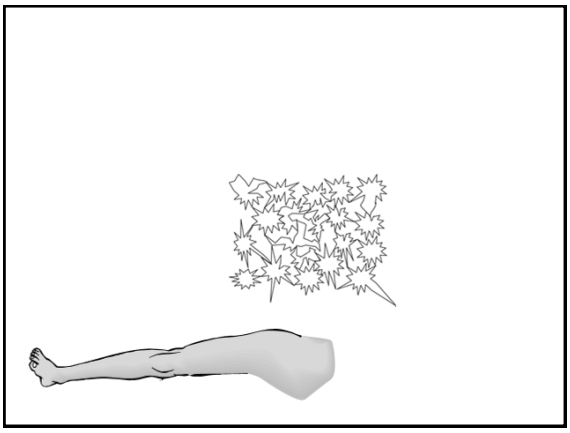

ANATOMICAL BASIS FOR THE DEVELOPMENT OF LIVEDO RETICULARIS
Zone of venous predominance
Zone of arterial predominance
Venous drainage
Arterial cone
Dermatology, 2nd Edition. Eds Jean L Bolognia et al. Spain: Mosby Elsevier, 2008

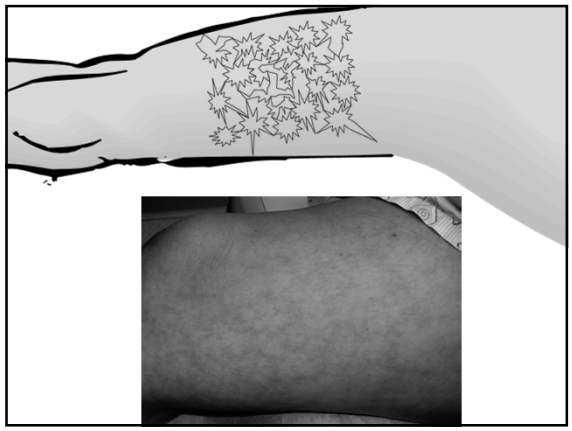










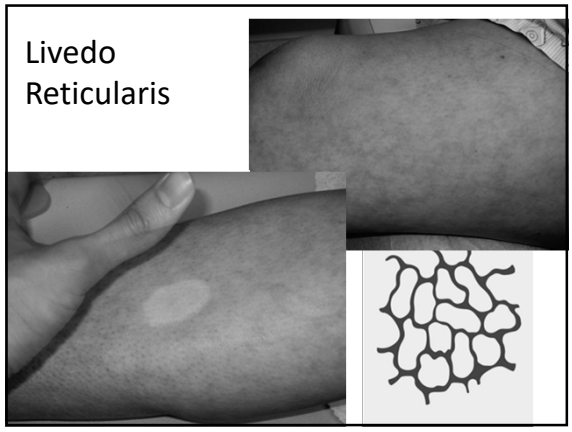


2 potential problems with this system

Problem 1: Livedo Reticularis

- Violaceous erythema
- Outlines 1-3cm stellate patches
- Surface of cones fed by individual perforating arterioles
- From enhanced visibility of zones of venous predominance
  - Increased deoxygenated blood in the venules
  - From engorged veins, constricted arterioles, local hypoxia…

Livedo Reticularis

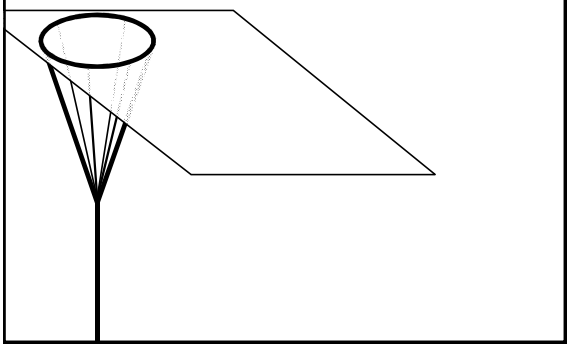


Problem 2:

<u>Retiform Purpura</u>

- Purpura of these same stellate patches/plaques
- From ***<u>occlusion</u>*** of the perforating arterioles.

Retiform Purpura



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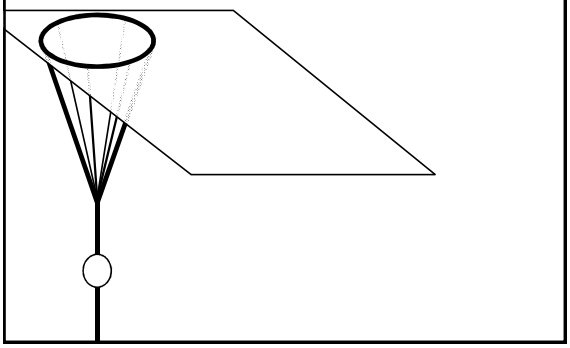
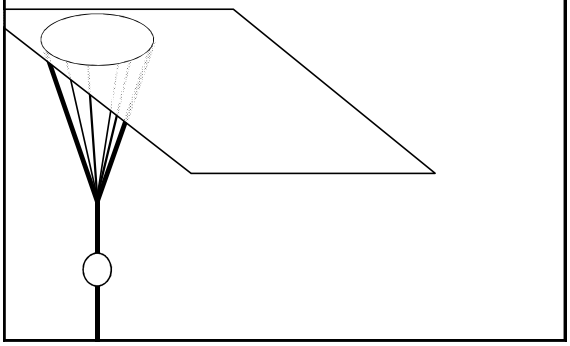
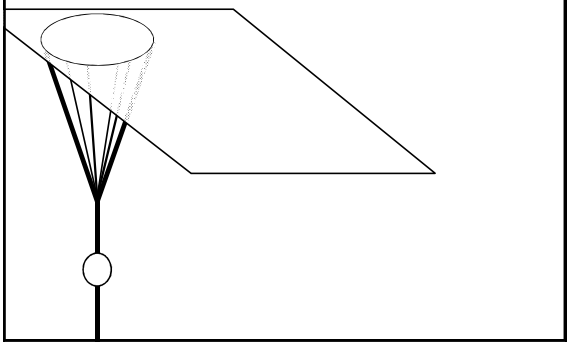


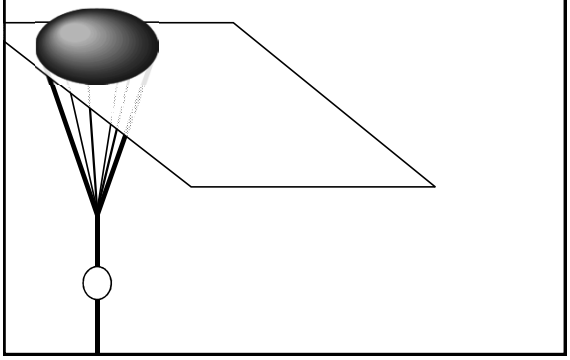
Retiform Purpura



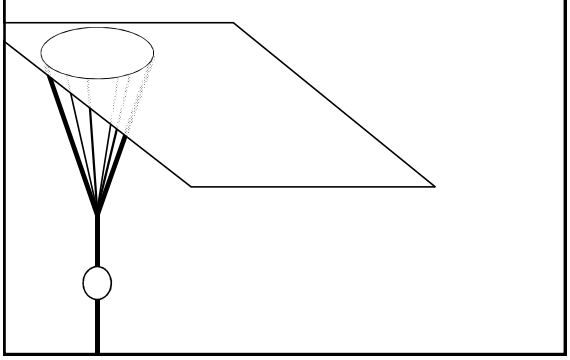
Retiform Purpura

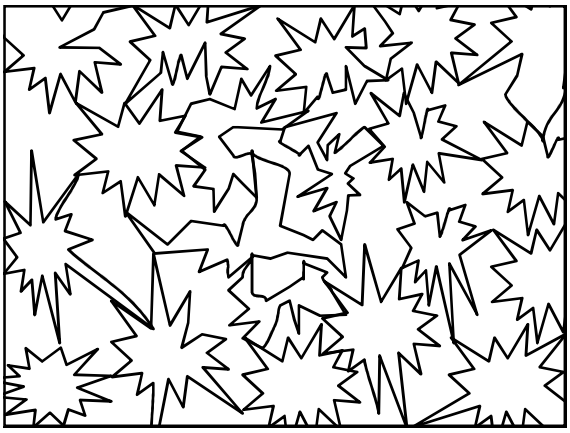


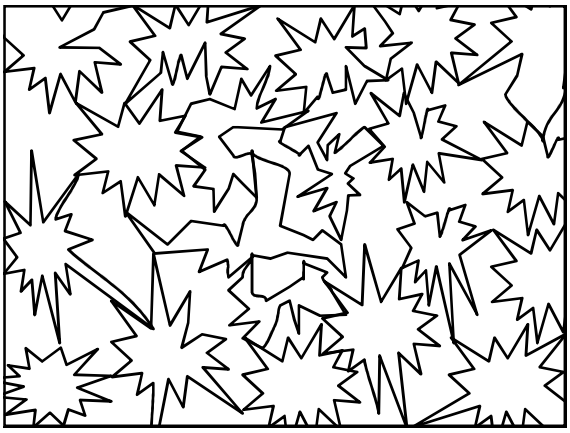
Retiform Purpura

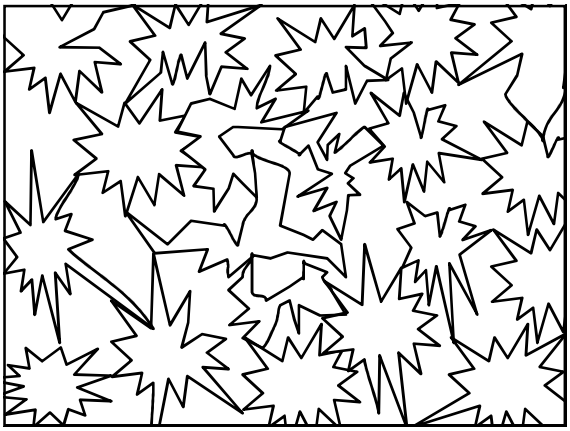


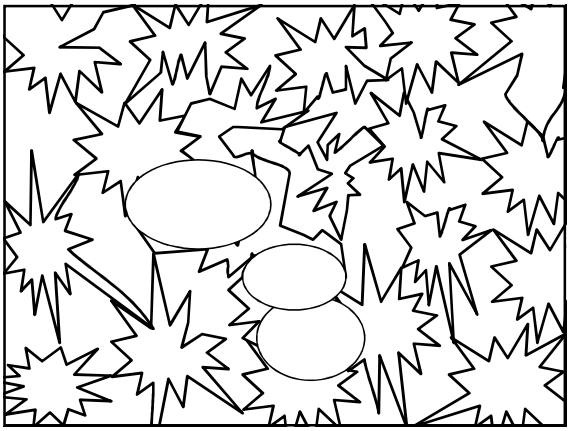
Retiform Purpura



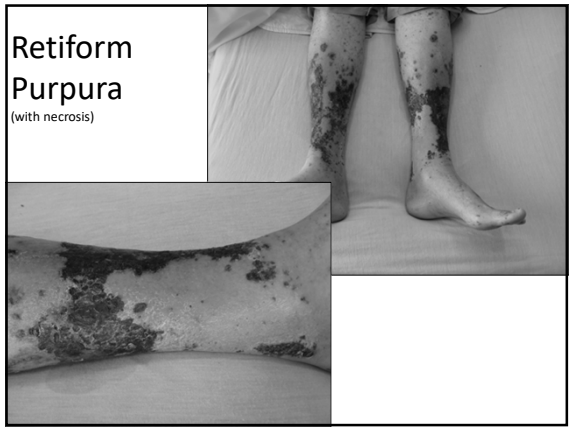


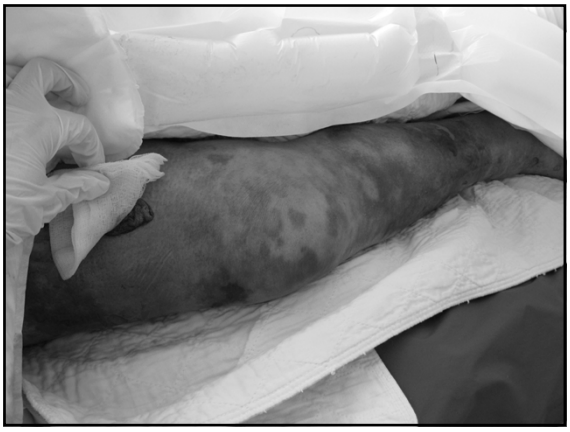


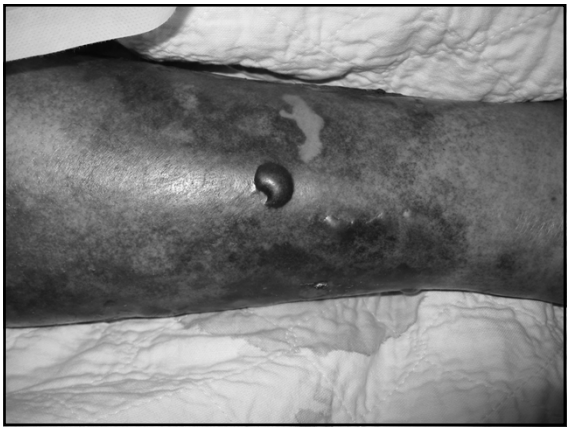


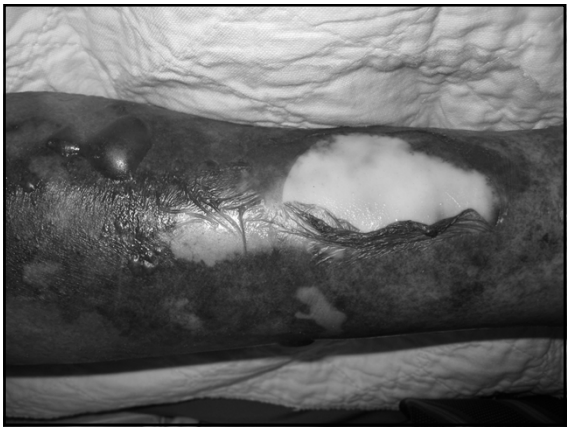


Retiform
Purpura
(with necrosis)





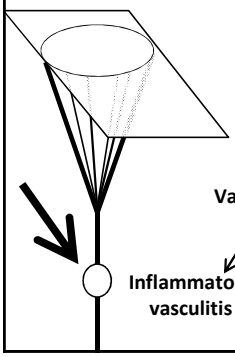




Case Details

- PMH: Systemic lupus, lupus nephritis
- Meds: Mycophenolate mofetil, prednisone
- ED presentation:
  - Vitals: **T104.6, P140s, SBPs 80s**
  - Unresponsive, rash on right leg
- Labs: BASELINES in parentheses after figures
  - **WBC 1.8** (4-9), **HCT 22.7** (24-37), **Plt 76** (150-350)
  - Na 142, K 4.3, Cl 112, HCO3 20, **BUN 79, Creatinine 2.7** (1.2)

Retiform Purpura:
Differential Diagnosis



Perforating Arteriole Occlusion

In-situ Thrombosis

Embolism

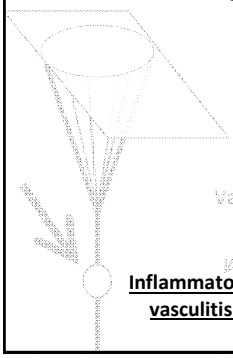
Vasculitis

Hypercoagulable state

Inflammatory vasculitis

Septic (vessel-invasive organism)

Retiform Purpura:
Differential Diagnosis



Perforating Arteriole Occlusion

In-situ Thrombosis

Embolism

Vasculitis

Hypercoagulable state

Inflammatory vasculitis

Septic (vessel-invasive organism)

Retiform Purpura: Select Differential Diagnosis	
Emboli	Cholesterol, Fat, Septic, Calciphylaxis, Amyloidosis, Nitrogen, Atrial myxoma, Ventilator Gas, Hyperoxaluria
Hypercoagulable states	APLAS, Sneddons, Cryos, AT III deficiency, Protein C/S def (especially with meningococcemia or coumadin), DVT, DIC, TTP
Inflammatory Vasculitis	PAN, Wegeners, Takayasu's, microscopic polyangitis, Rheumatoid vasculitis, livedoid vasculitis
Septic vasculitis (Angioinvasive pathogens)	Pseudomonas, Serratia, Aeromonas, Klebsiella, Vibrio, Moraxella, Morganella, E.coli, Staph aureus, Candida, Mucor, Aspergillus, Fusarium

Adapted from:
Gibbs MB, English, JC, Zirwas MJ. Livedo Reticularis: An Update. J Am Acad Dermatol 2005; 52: 1009-19

Please note:
(regarding retiform purpura)

- **Nothing on the differential is primary cutaneous**
- **Everything on the differential is bad**

Retiform Purpura: Select Differential Diagnosis

Emboli	Cholesterol, Fat, **Septic**, Calciphylaxis, Amyloidosis, Nitrogen, Atrial myxoma, Ventilator Gas, Hyperoxaluria
Hypercoagulable states	**APLAS**, Sneddons, Cryos, AT III deficiency, Protein C/S def (especially with meningococcemia or coumadin), DVT, **DIC, TTP**
Inflammatory Vasculitis	PAN, Wegeners, Takayasu's, microscopic polyangitis, Rheumatoid vasculitis, livedoid vasculitis
Septic vasculitis (Angioinvasive pathogens)	**Pseudomonas, Serratia, Aeromonas, Klebsiella, Vibrio, Moraxella, Morganella, E.coli, Staph aureus, Candida, Mucor, Aspergillus, Fusarium**

Differential:
Catastrophic APLAS ("thrombotic storm")
Thrombotic thrombocytopenic purpura
Systemic infection (Sepsis/DIC, emboli, vascular invasion)

Dermatologic Workup and Results

- Day 0:
  - Biopsies by derm and surgery
  - Later that night: Blood cultures stain for **GNR in 4/4 bottles**
- Day 1 post admission: Pathology preliminary results—
  - Neutrophilic inflammation in dermis and adipose with hemorrhage.
  - Deep biopsy has sparse GNR on Gram stain
- Day 2: blood and deep biopsy tissue—
  - ***Serratia marcescens***
- Day 3: Abd CT with contrast shows pan-enterocolitis

Diagnosis

Serratia marcescens sepsis with necrotic retiform purpura of a seeded limb

Retiform Purpura: Select Differential Diagnosis

Emboli	Cholesterol, Fat, Septic, Calciphylaxis, Amyloidosis, Nitrogen, Atrial myxoma, Ventilator Gas, Hyperoxaluria
Hypercoagulable states	APLAS, Sneddons, Cryos, AT III deficiency, Protein C/S def (especially with meningococcemia or coumadin), DVT, DIC, TTP, **COVID-19**
Inflammatory Vasculitis	PAN, Wegeners, Takayasu's, microscopic polyangitis, Rheumatoid vasculitis, livedoid vasculitis
Septic vasculitis (Angioinvasive pathogens)	Pseudomonas, Serratia, Aeromonas, Klebsiella, Vibrio, Moraxella, Morganella, E.coli, Staph aureus, Candida, Mucor, Aspergillus, Fusarium

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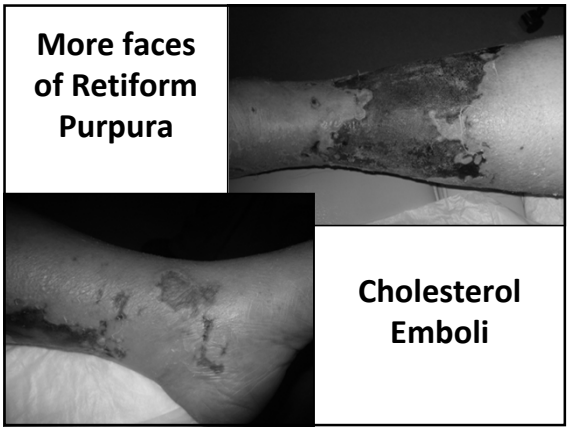
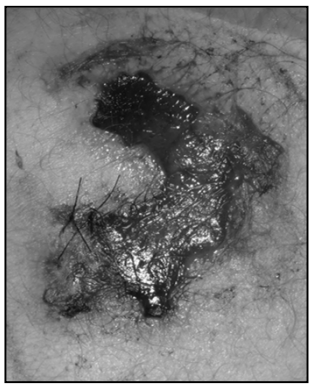
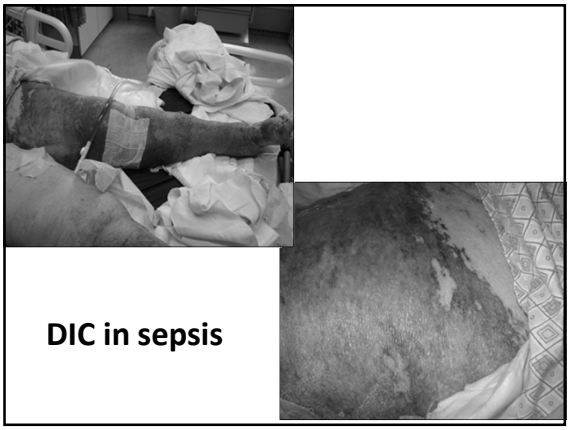
More faces of Retiform Purpura



Cholesterol Emboli

Ecthyma Gangrenosum





DIC in sepsis

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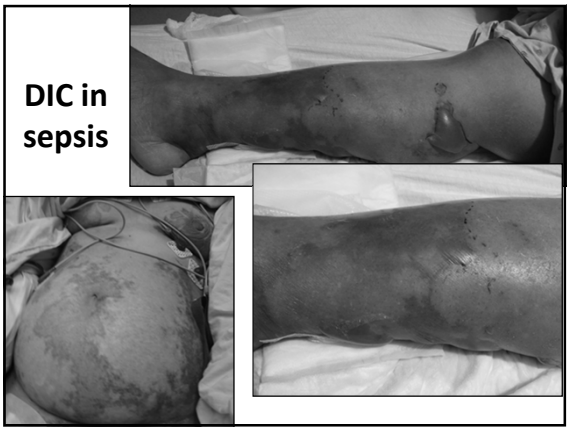
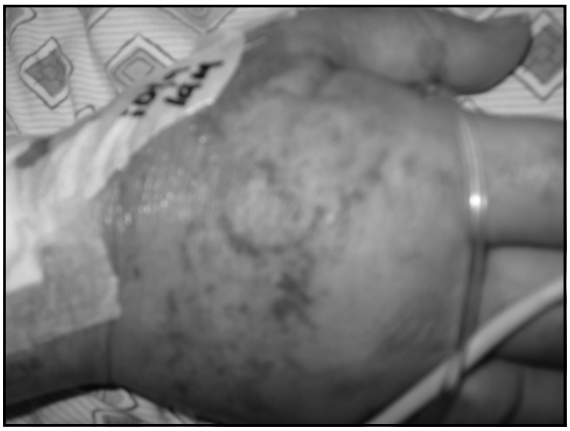


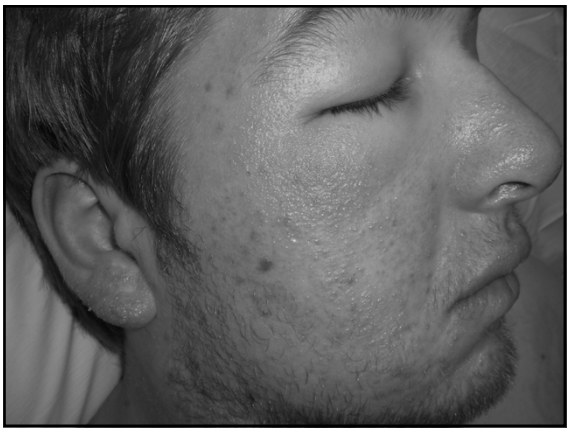


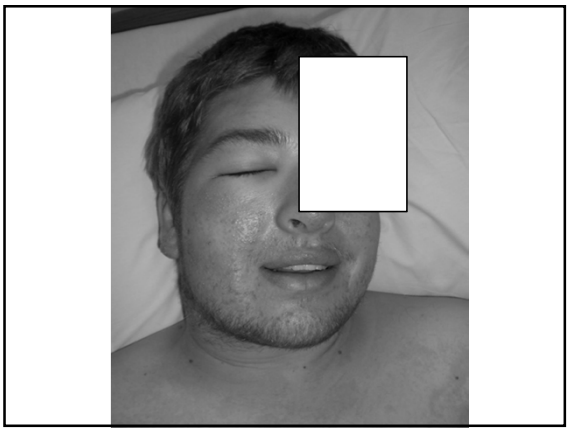
CASE KEY POINTS

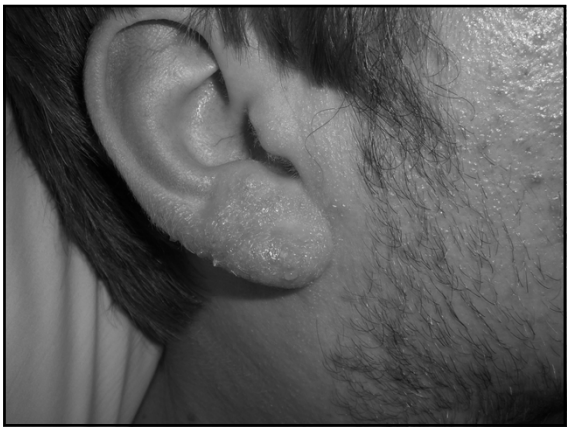
- **Recognize Retiform Purpura:**
  - **Well demarcated purpuric patches with jagged edges**
  - **Violaceous, dusky, white, black**
  - **Evidence of necrosis (bullae, ulcers, eschars)**
- **Early indicator of a systemic, generally malignant process**

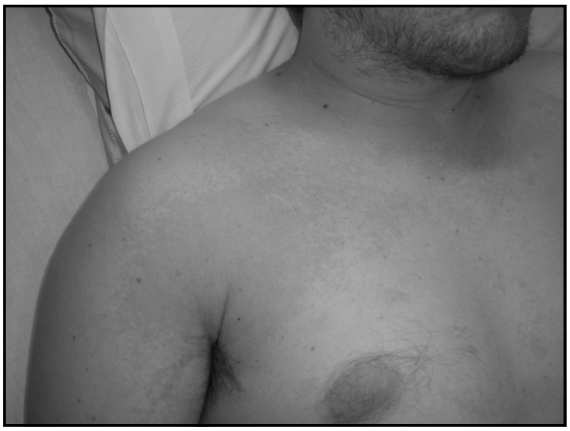
Case

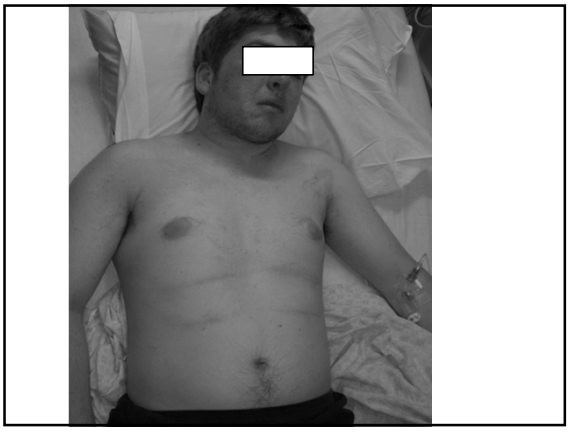
- Healthy 18 year-old male
- 1 day of worsening pruritic rash on face
- ED Diagnosis: impetigo
- Admitted to ED-Observation IV antibiotics
- Next AM: rash extended toward lip and eye
- Derm Consulted

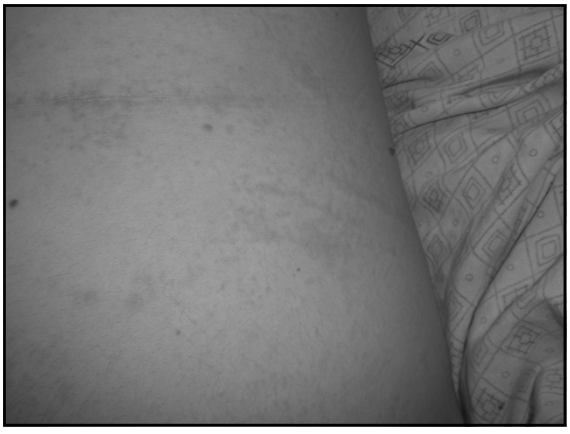


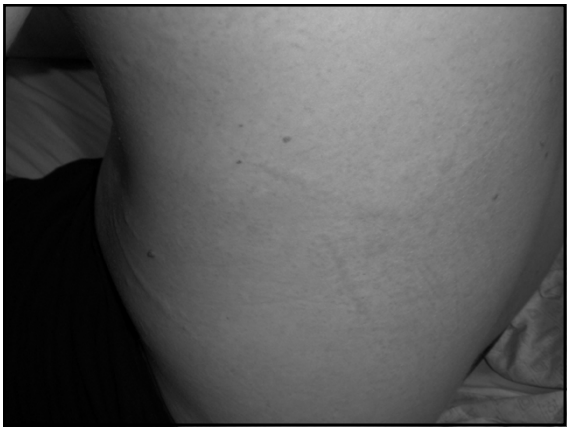




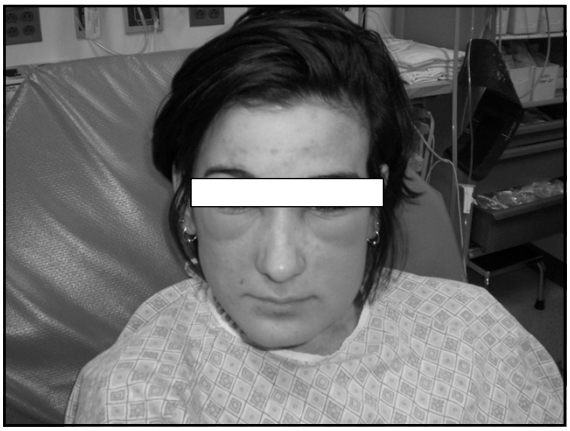


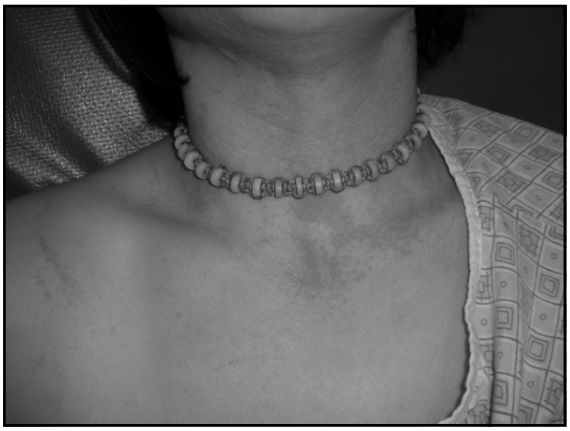






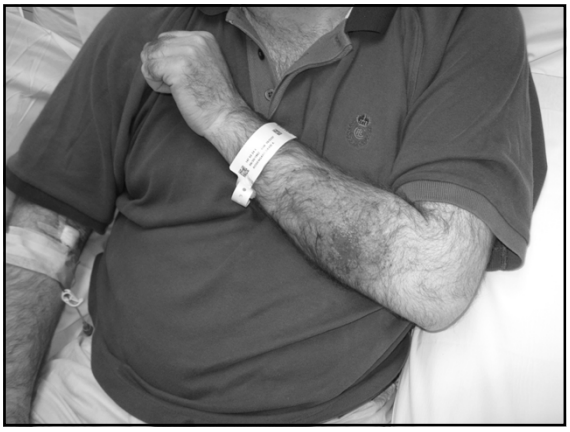
Meanwhile, 40 feet away…

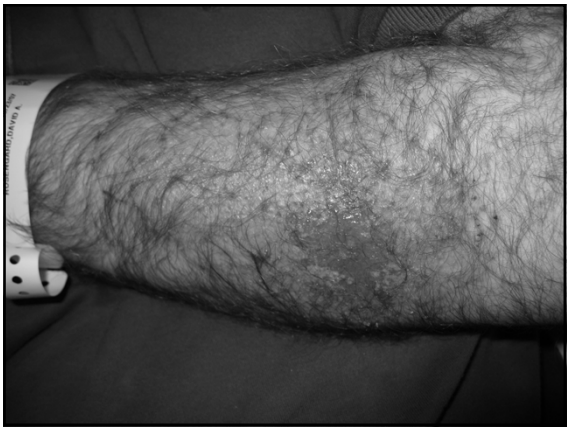


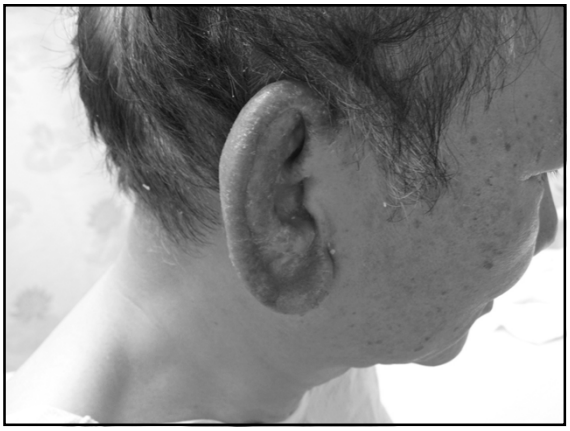


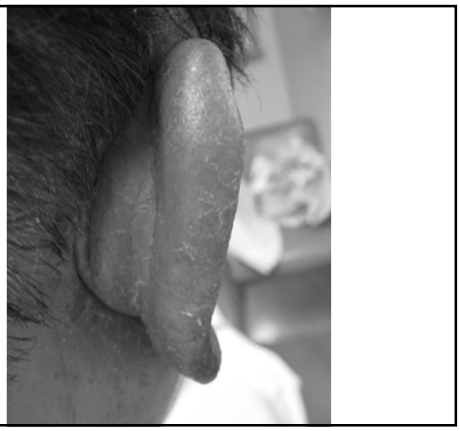
Allergic Contact Dermatitis (to poison ivy: toxin = urushiol)

- Type IV, T-cell mediated hypersensitivity
- Eczematous reaction pattern
  - Acute: vesicles, erythema, serous fluid
  - Subacute: erosions, erythema, serous fluid
  - Chronic: scaling, lichenification, dyspigmentation, prurigo nodules
- Other important physical exam features
  - Symptoms: Pruritic, non-tender
  - Lines/ geometric shapes









Take-Home Points

- Cellulitis is tender
- Recognize retiform purpura
- Triple antibiotic oint causes contact dermatitis

Thank you

- Richard Johnson
- Arturo Saavedra
- Anisa Mosam
- Ncoza Dlova
- My patients who allowed me to photograph them to benefit others

Key References

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