Key Clinical Cases in Dermatology

Adam D. Lipworth, MD

Director of the Lahey Skin Infection Program
Division Chair, Dermatology
Lahey Hospital & Medical Center

Assistant Professor, Part-time
Harvard Medical School

Beth Israel Lahey Health
Lahey Hospital & Medical Center

HARVARD MEDICAL SCHOOL | Postgraduate Medical Education

Adam Lipworth, MD

- University of Pennsylvania School of Medicine
- Internship in Internal Medicine @ MGH
- Residency: Harvard Combined Dermatology Program
- Dermatology Chair @ Lahey Hospital & Med Center
- Assistant Professor, Part-time @ HMS
- Director of the Lahey Skin Infection Program

Disclosures

- I have no financial disclosures
- Will discuss off-label use of medications

Objectives

Use case vignettes to help the participants:

- Review presentations of a rising epidemic disease
- Optimize management of simple cellulitis
- Recognize an easily overlooked, common, serious eruption
- Distinguish allergic contact dermatitis from infection (time-permitting)

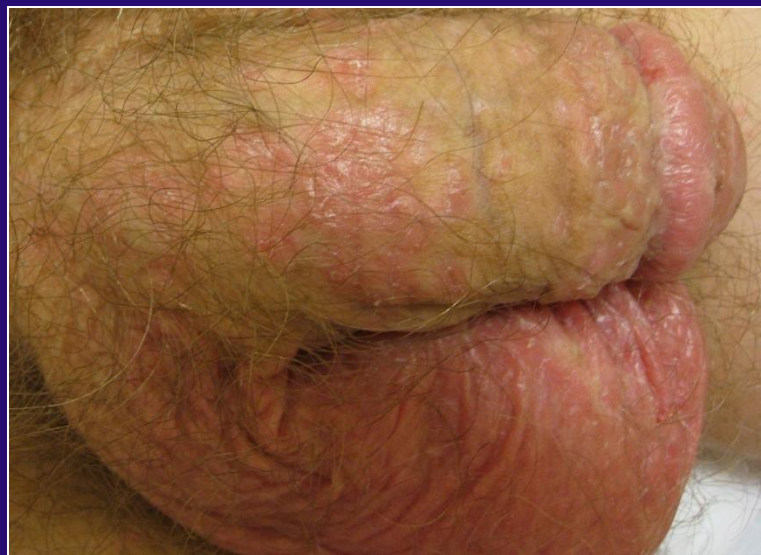
Case

- 49 yo M
- 5 weeks of pruritic rash
  - Whole cutaneous surface, *except* palms and soles
  - Tongue sores, eye discharge
  - Low grade fevers, myalgias, headaches, lethargy

- PMH: Bipolar disorder (stable off medication x several years)
- Meds: diphenhydramine, lorazepam, sildenafil

Diagnosis?

A. Syphilis
B. Psoriasis
C. Pityriasis rosea
D. Measles



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INITIAL WORKUP	
RPR	Negative
HIV ELISA	Negative
Skin Biopsy	Lichenoid and superficial and deep lymphohistiocytic infiltrates with plasma cells and granulomas

Does this change anyone's mind?

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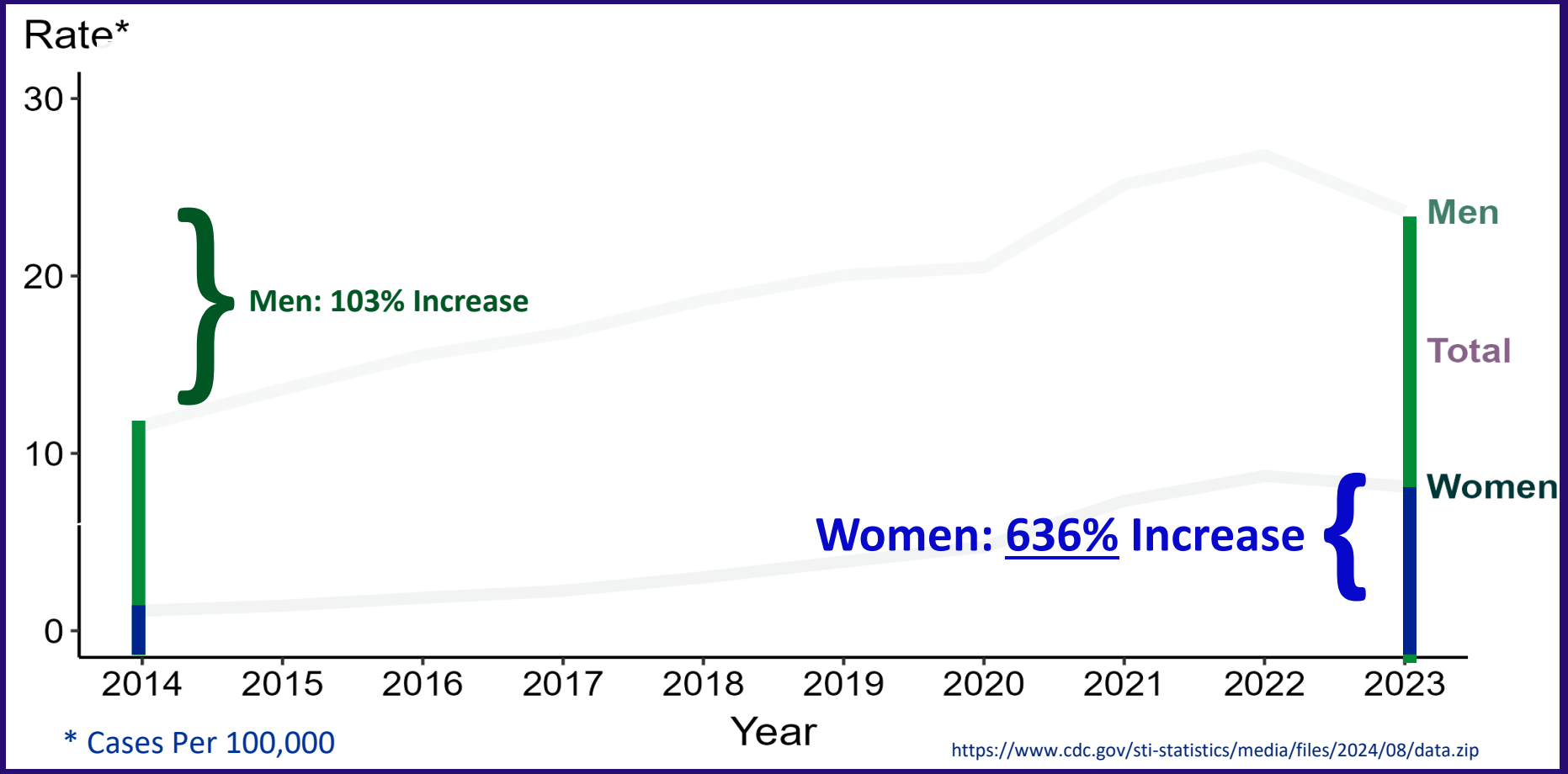
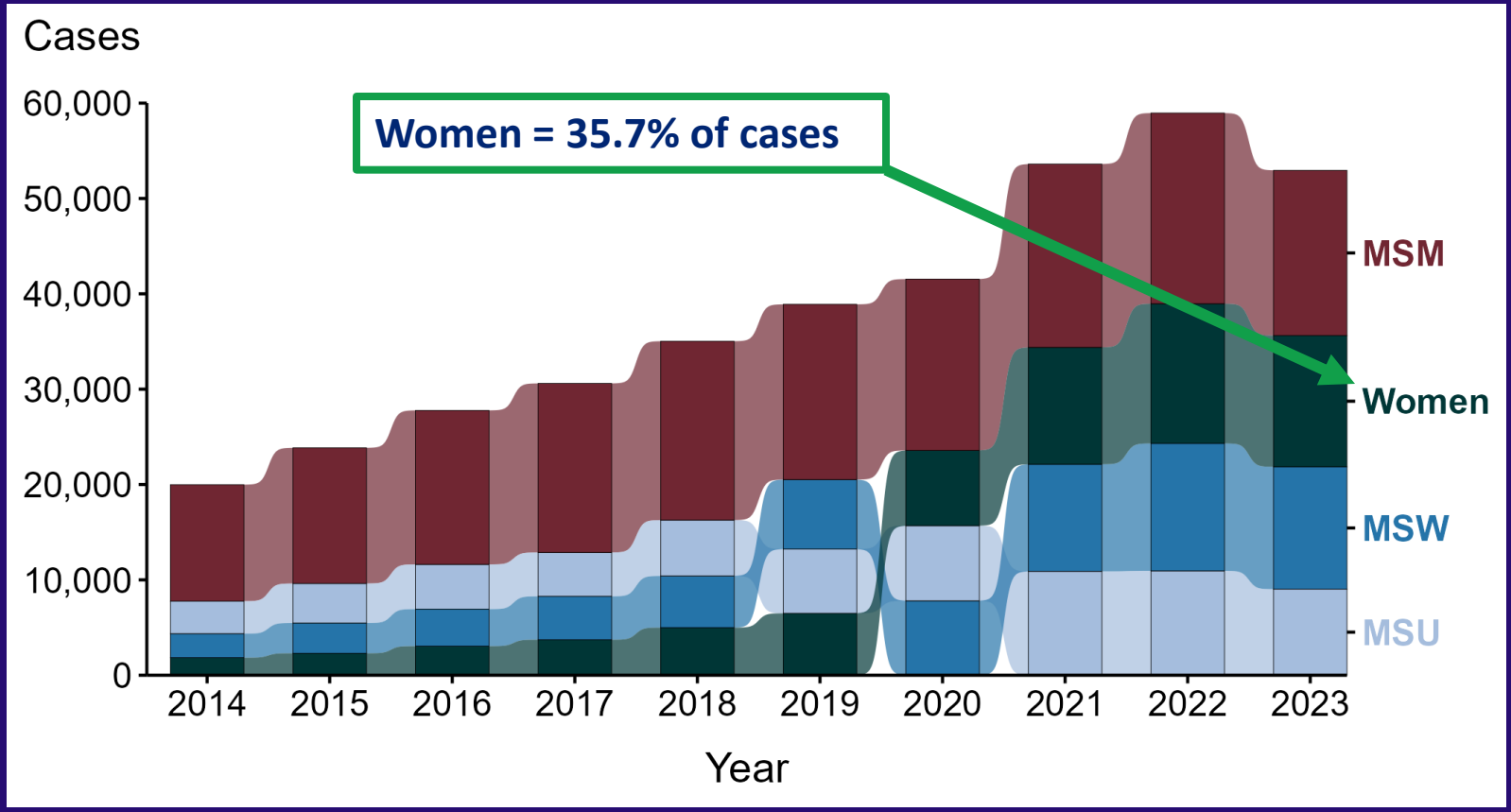
Why a false negative RPR?

But first, why revisit syphilis at all?

Primary and Secondary Syphilis — Rates of Reported Cases by Sex, United States, 2014–2023



Primary and Secondary Syphilis — Reported Cases by Sex and Sex of Sex Partners and Year, United States, 2014–2023

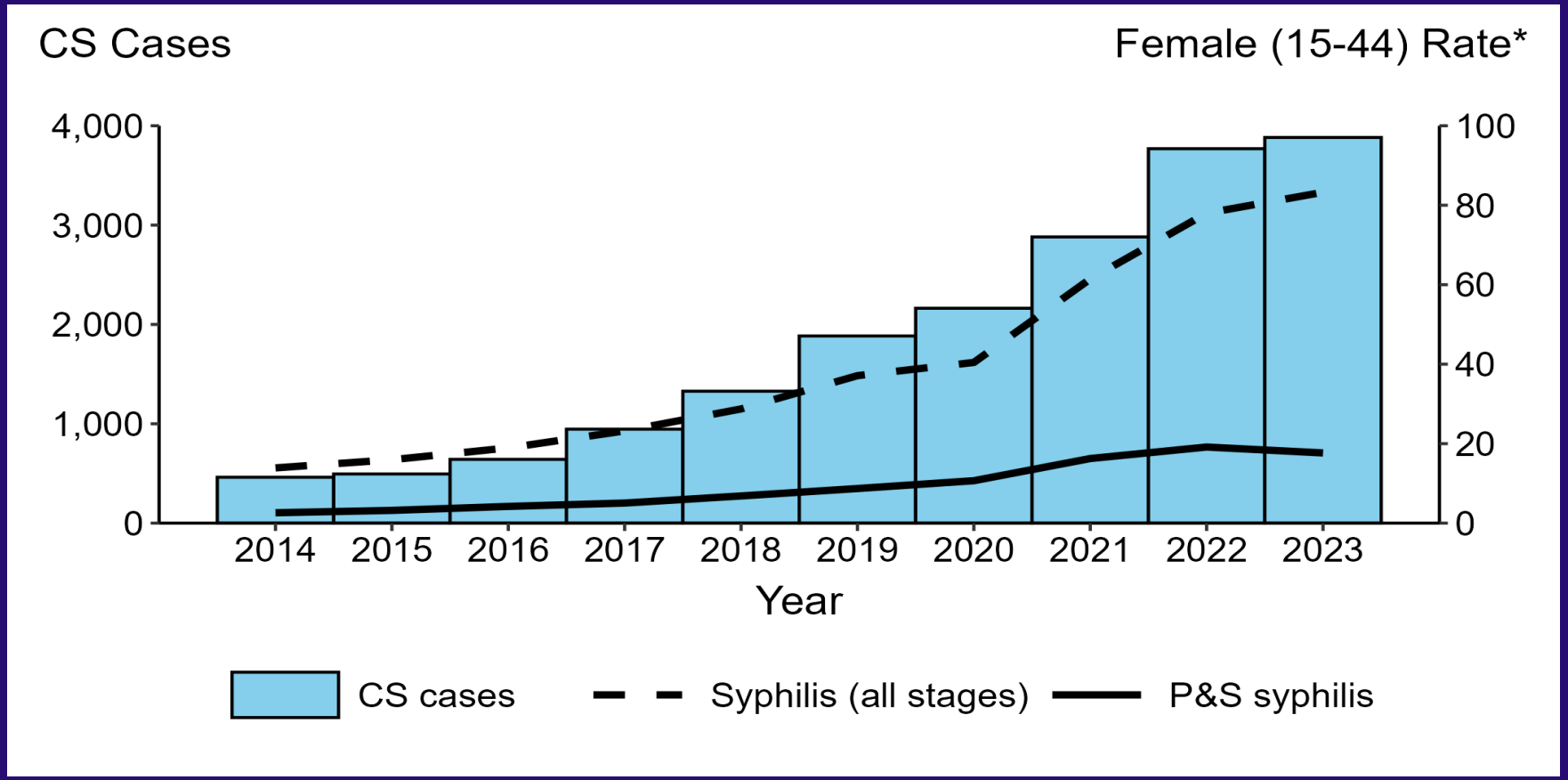


ACRONYMS: MSM = Men who have sex with men; MSU = Men with unknown sex of sex partners; MSW = Men who have sex with women only

https://www.cdc.gov/sti-statistics/media/files/2024/08/data.zip

Congenital Syphilis

Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis and Syphilis (All Stages) Among Women Aged 15–44 Years, United States, 2014–2023



* Per 100,000

ACRONYMS: CS = Congenital syphilis; P&S Syphilis = Primary and secondary syphilis

https://www.cdc.gov/sti-statistics/media/files/2024/08/data.zip

Syphilis

- We have an epidemic
- Rising fastest in women
- Congenital syphilis rising in parallel
- Diagnosis *can* be tricky

Diagnosis?

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Why a false negative RPR?

Prozone Phenomenon

- Non-treponemal tests (RPR, VDRL)
  - Treponeme incorporates and modifies host cardiolipin
  - Host produces antibodies to cardiolipin

Prozone Phenomenon

- Non-treponemal tests (RPR, VDRL)
  - Treponeme incorporates and modifies host cardiolipin
  - Host produces antibodies to cardiolipin
- Test mechanism
  - Patient serum + cardiolipin→ precipitation / flocculation
  - False positives from other sources of cardiolipin antibodies
  - False negatives:
    - Too early, too late, too immunosuppressed, or
    - **Prozone phenomenon: Notable antibody excess → *no* agglutination**

Prozone Phenomenon

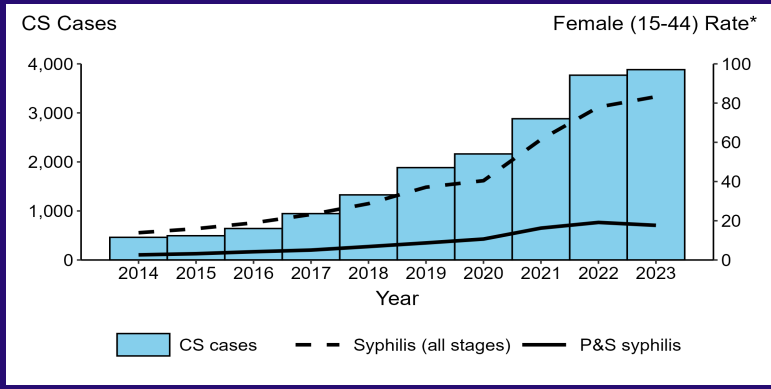
Prozone phenomenon: Notable antibody excess prevents agglutination

Fastest way to check if negative RPR is from Prozone Phenomenon?

- **Dilute the patient's serum and re-test RPR**
- **This patient: RPR Positive at a 1:16 dilution**

Risk factors for Prozone Phenomenon:

Neurosyphilis and **Pregnancy** **(CID 2014)**



Congenital Syphilis (by Year of Birth) and Syphilis Among Females Aged 15–44 Years, U.S., 2010–2019

https://www.cdc.gov/sti-statistics/media/files/2024/08/data.zip

Li-Li Liu, Li-Rong Lin, Man-Li Tong, Hui-Lin Zhang, Song-Jie Huang, Yu-Yan Chen, Xiao-Jing Guo, Ya Xi, Long Liu, Fu-Yi Chen, Ya-Feng Zhang, Qiao Zhang, Tian-Ci Yang, Incidence and Risk Factors for the Prozone Phenomenon in Serologic Testing for Syphilis in a Large Cohort, *Clinical Infectious Diseases*, Volume 59, Issue 3, 1 August 2014, Pages 384–389

Prozone Phenomenon

Prozone phenomenon: Notable antibody excess prevents agglutination

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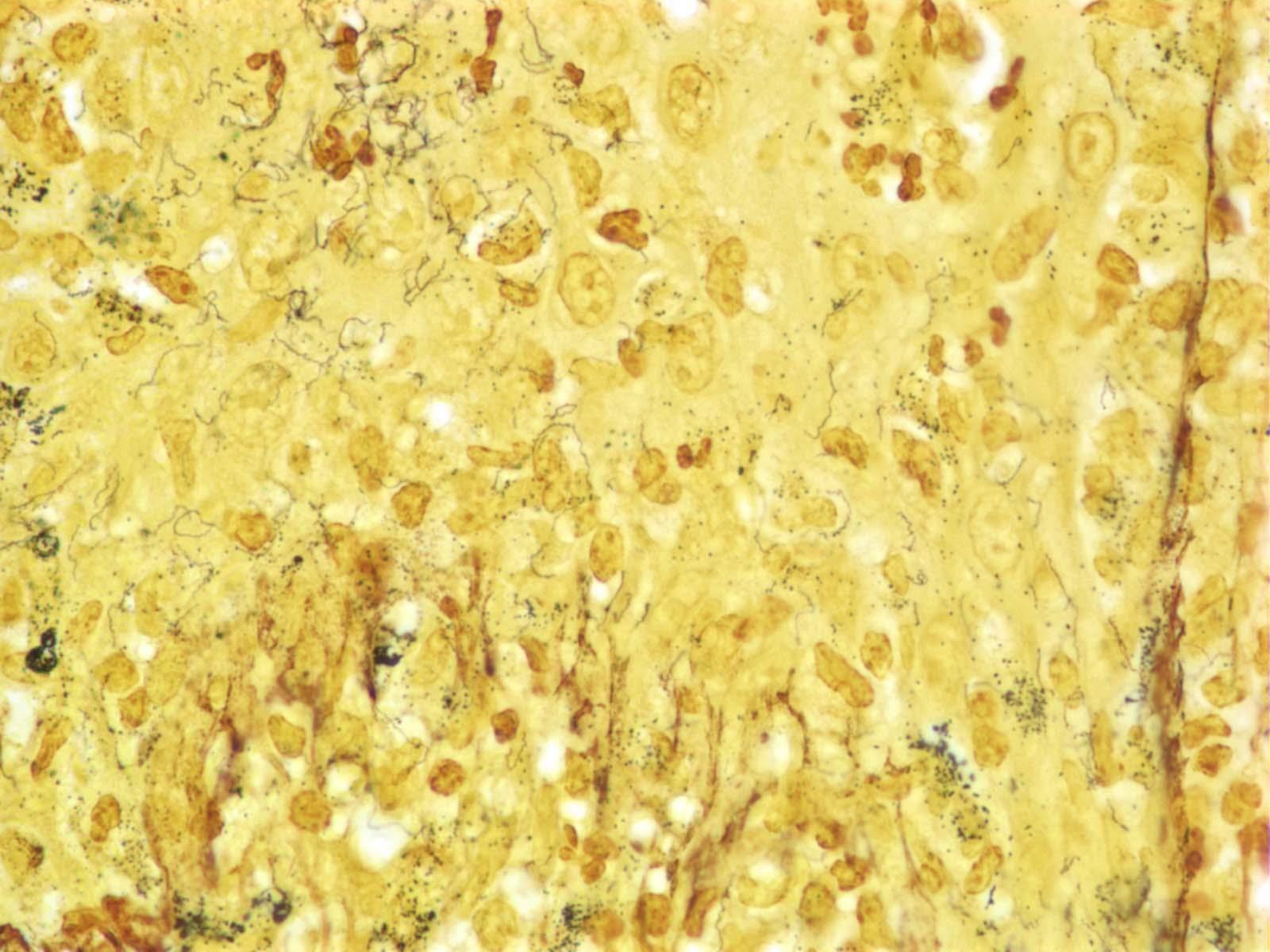
Alternative means to confirm a diagnosis of syphilis:

- Treponemal-specific antibodies: blood or tissue immunohistochemistry
- PCR from blood or tissue
- Darkfield microscopy: rare in United States
- Silver staining of tissue



Final syphilis pearl: Why did the papules *spare* the palms and soles?

- Classic Secondary Syphilis:
  - early macular phase: ham colored macules + adenopathy
  - late papular phase: pink papules with scale
  - +/- mucous patches, moth-eaten alopecia, condyloma lata, et al

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- Other variants (Syphilids)
  - Psoriasiform
  - Lichenoid
  - Follicular
  - Annular – “nickels & dimes”
  - Corymbose: central + satellites
  - Pustular
  - Ecthymatous: deep ulcers
  - Rupioid: “oyster shell”
  - Nodular
  - Lues maligna

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Syphilis Key Points

- Rates are rising, cases *are* being missed
- Presentations vary (of course)
- No test or testing algorithm is perfect

- Maintain a high index of suspicion & re-test if concerned

Case

- 54 yo F
- 5 days s/p excision of a BCC
- Progressive peri-incisional redness and pain
- Malaise
- Temp 100.5

Cellulitis

Which of the following characteristics is most SENSITIVE for cellulitis?

A. Tenderness
B. Fever
C. Leukocytosis
D. Pruritus
E. Malaise

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Management of Cellulitis

To cover MRSA or NOT to cover MRSA?

Management of Cellulitis

STEP 1: Cellulitis or NOT Cellulitis?

JAMA Dermatology | Original Investigation

Costs and Consequences Associated With Misdiagnosed Lower Extremity Cellulitis

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

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

Cellulitis misdiagnosis→

- 259 pts admitted from ED with cellulitis
  - 30% did not have cellulitis. 17% did not require admission
- Extrapolation to U.S.: 50,000-130,000 unnecessary admissions
- $195 million- $515 million avoidable healthcare $$s

Step 1: Cellulitis or NOT Cellulitis?

Tender? **If not, consider alternative**

If tender, then:

- Bilateral? Consider alternative
- Pruritic? Consider alternative
- Geometric? Consider alternative

Step 2: consider SEVERITY

- Assessment of severity
  - Ill-appearing patient
  - Severe co-morbidities
  - Evidence of deep infection

- Management of SEVERE cellulitis:
  - Admission/Observation, Debride if needed
  - Broad spectrum IV antibiotics: Cover GAS, MRSA, MSSA, et al.

Management of SIMPLE Cellulitis

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

But which one???

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*
- 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

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

OXFORD JOURNALS

Clinical Infectious Diseases

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,[3] 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[3]

[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

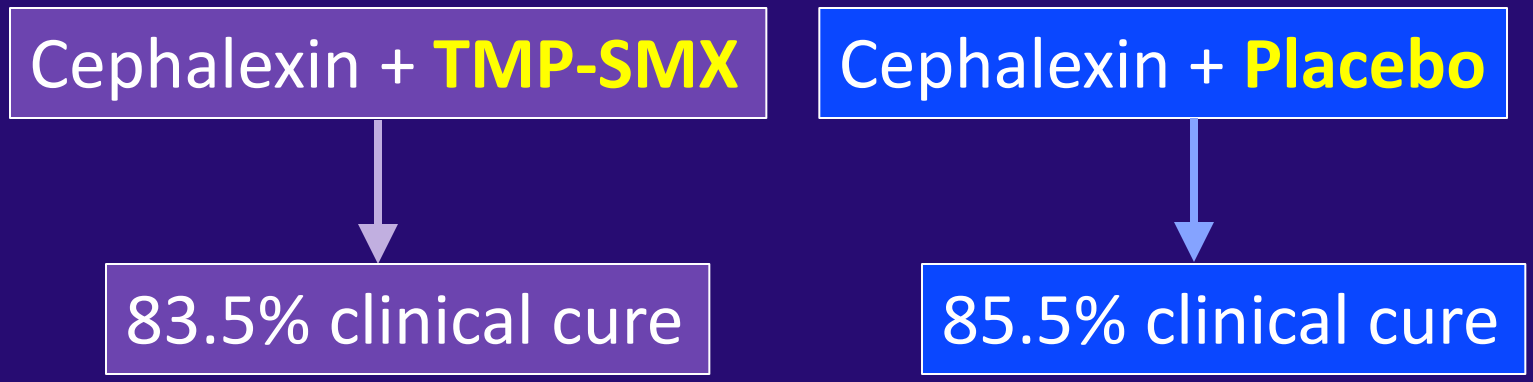
- 3 Boston Emergency Depts, 2007-11
- 153 Simple Cellulitis patients randomized

- 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



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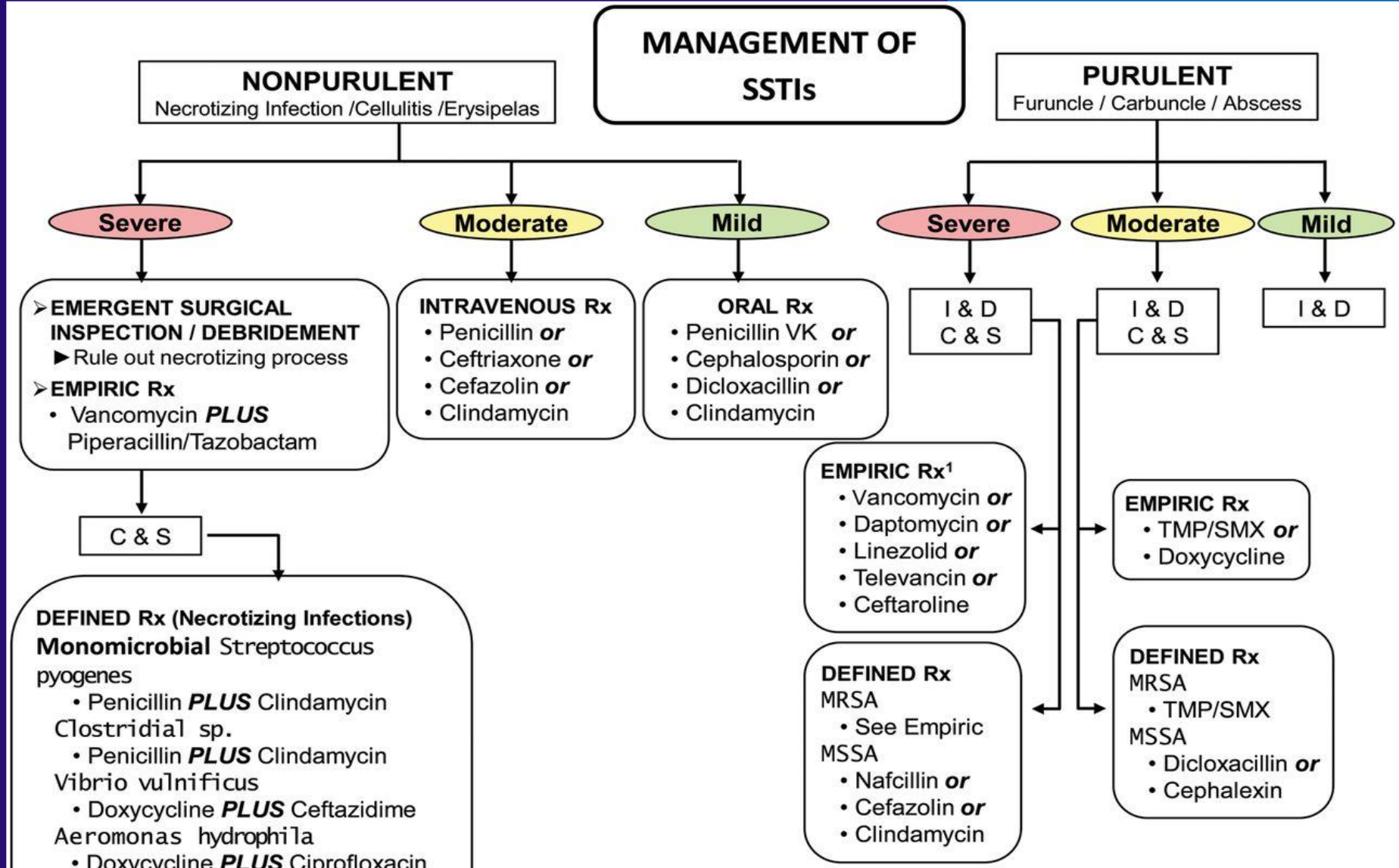
Moran GJ, Krishnadasan A, Mower WR, Abrahamian FM, LoVecchio F, Steele MT, Rothman RE, Karras DJ, Hoagland R, Pettibone S, Talan DA. Effect of Cephalexin Plus Trimethoprim-Sulfamethoxazole vs Cephalexin Alone on Clinical Cure of Uncomplicated CellulitisA Randomized Clinical Trial. *JAMA*. 2017;317(20):2088–2096.

June 2014

Clin Infect Dis, Volume 59, Issue 2, 15 July 2014, Pages e10–e52

IDSA GUIDELINE

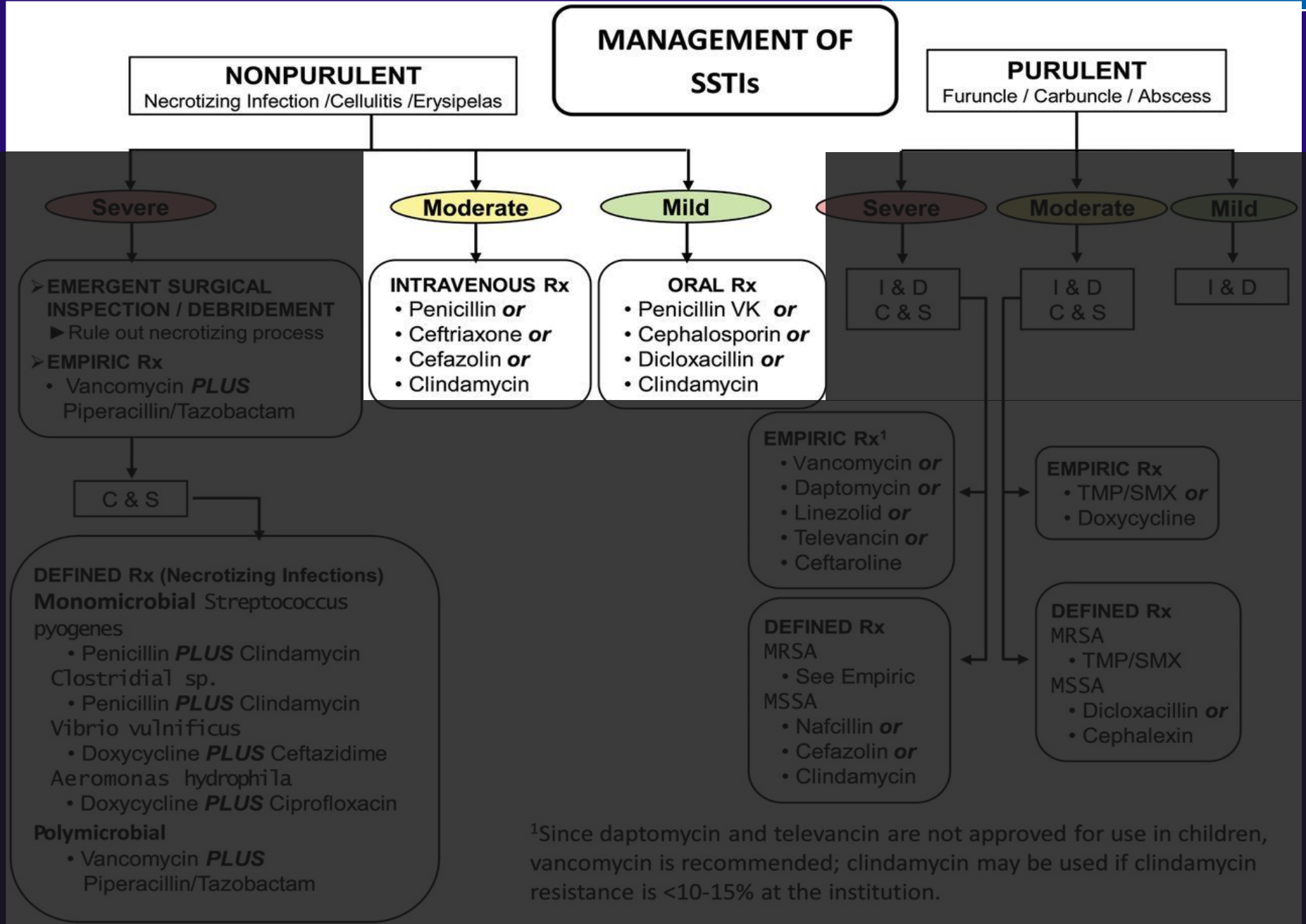


[1]Since daptomycin and televancin are not approved for use in children, vancomycin is recommended; clindamycin may be used if clindamycin resistance is <10-15% at the institution.

June 2014

Clin Infect Dis, Volume 59, Issue 2, 15 July 2014, Pages e10–e52

IDSA GUIDELINE



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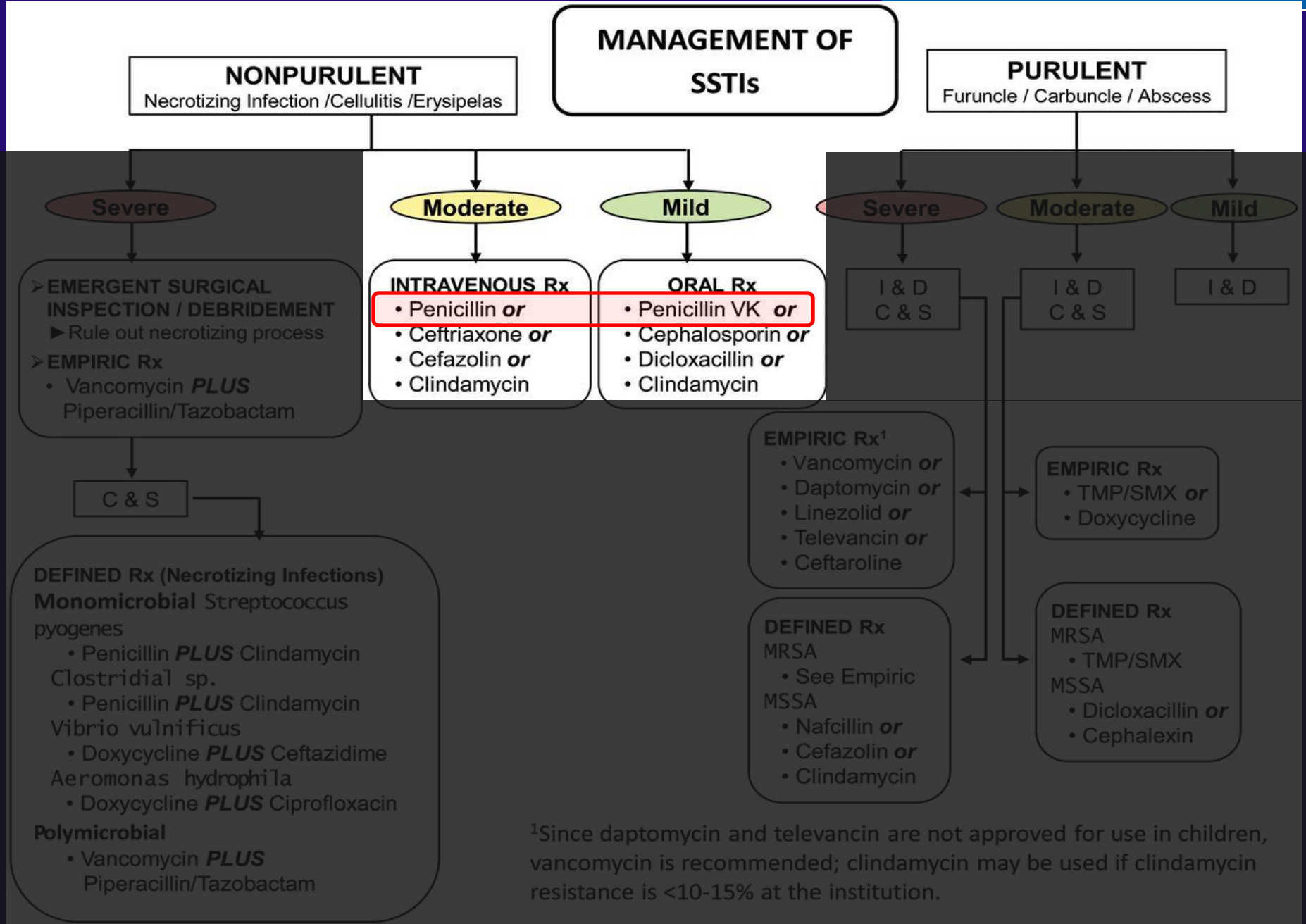


2014 IDSA Guidelines
Caution Regarding Penicillin for Cellulitis

- Assumes Strep is dominant, minimal MSSA/MRSA
- 5 pre-1996 studies of *culture* data
- One 2010 study using **serologies** & **β-lactam response** (Jeng et al)
  - Study Conclusions:
    - Serologies: "73% of non-culturable cellulitis caused by **βHS**"
    - β-lactam response rate: 95.6%
  - **BUT!**
    - **31% lost without serologies. Intention-to-test analysis → ~51% βHS+**
    - **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)

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
  - Strongly consider a **β-lactamase resistant β-lactam**

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

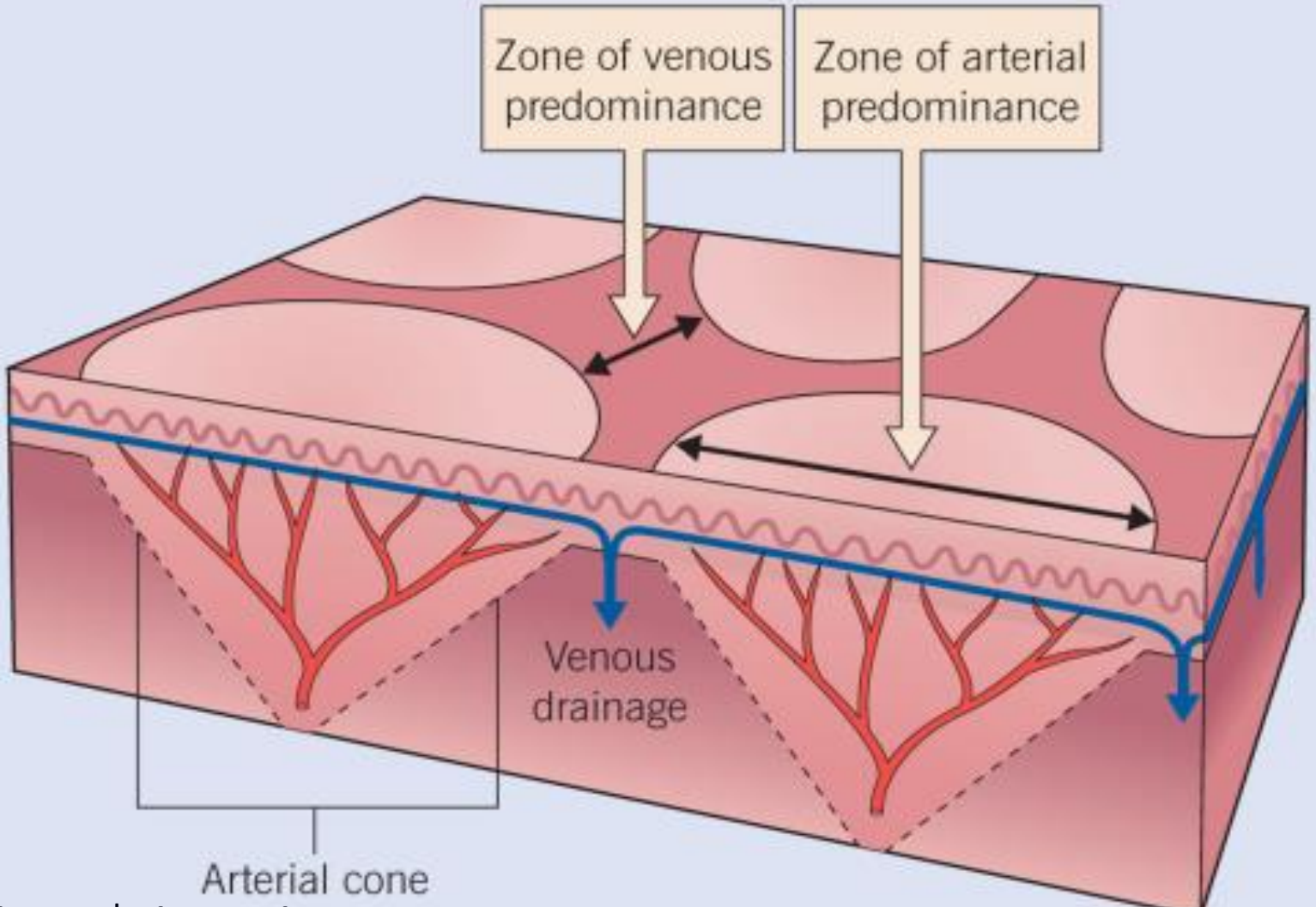
Hospital Day 1


MEDCOR

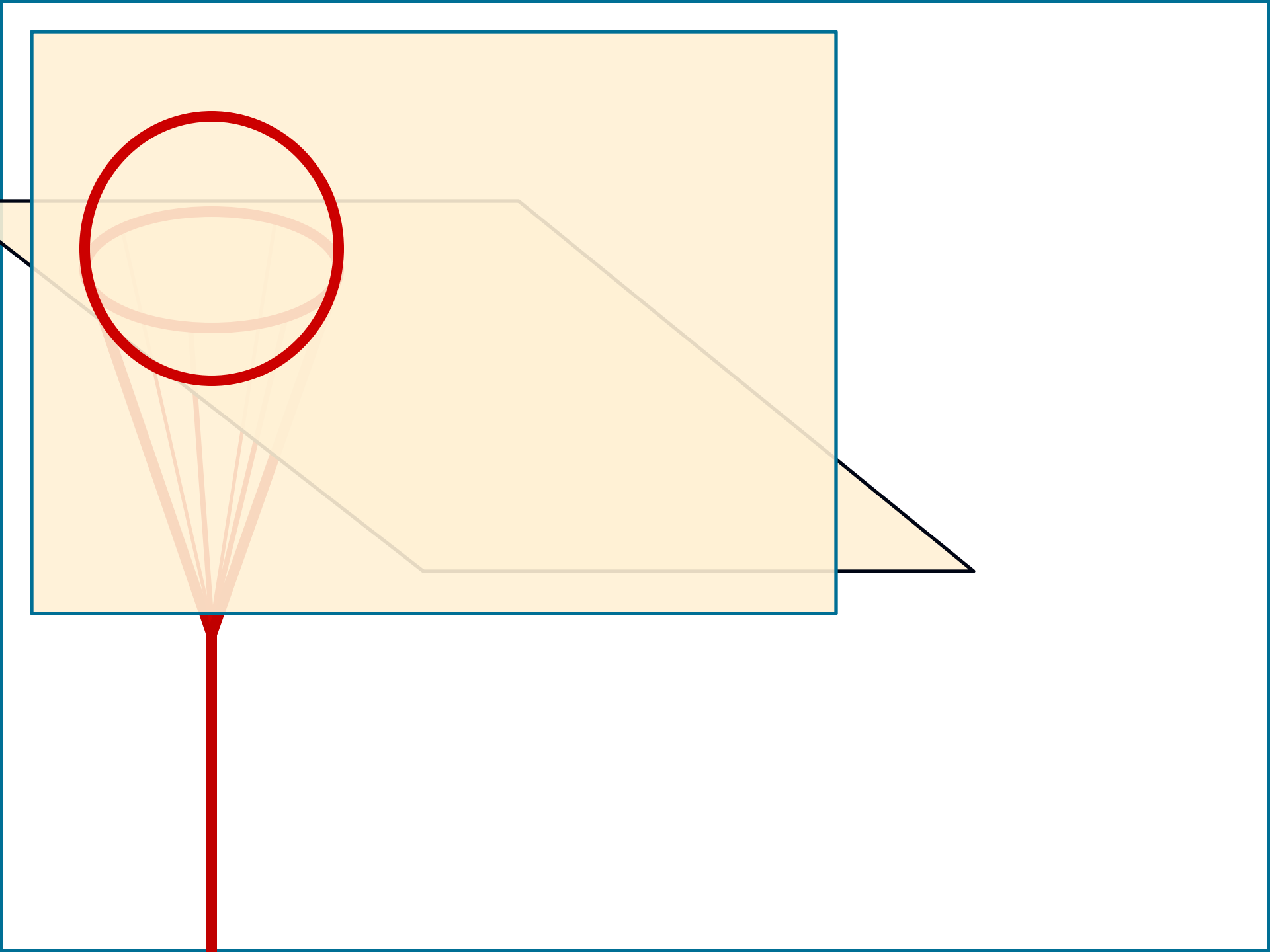
Hospital Day 3

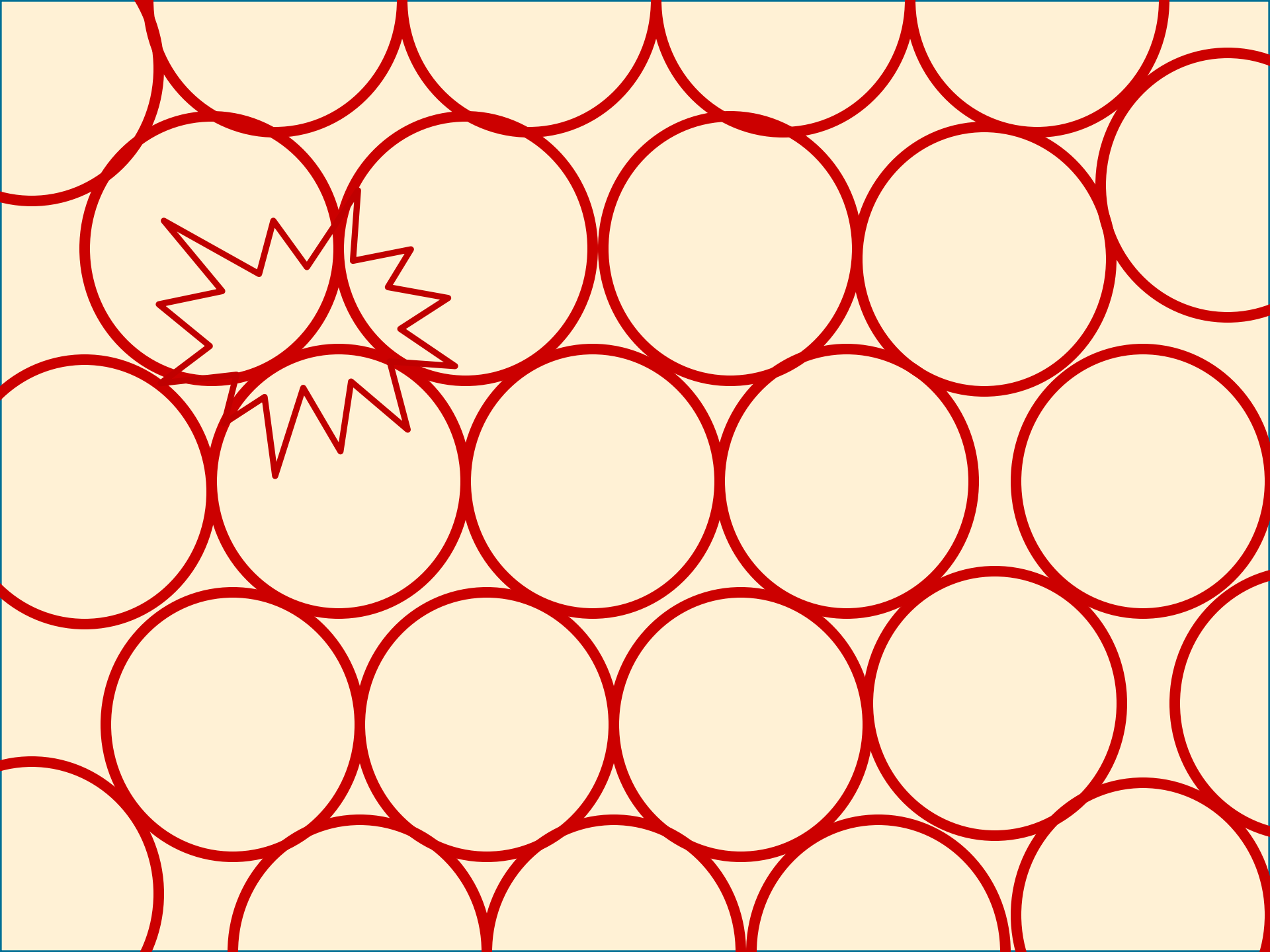
What can morphology tell us about pathophysiology?

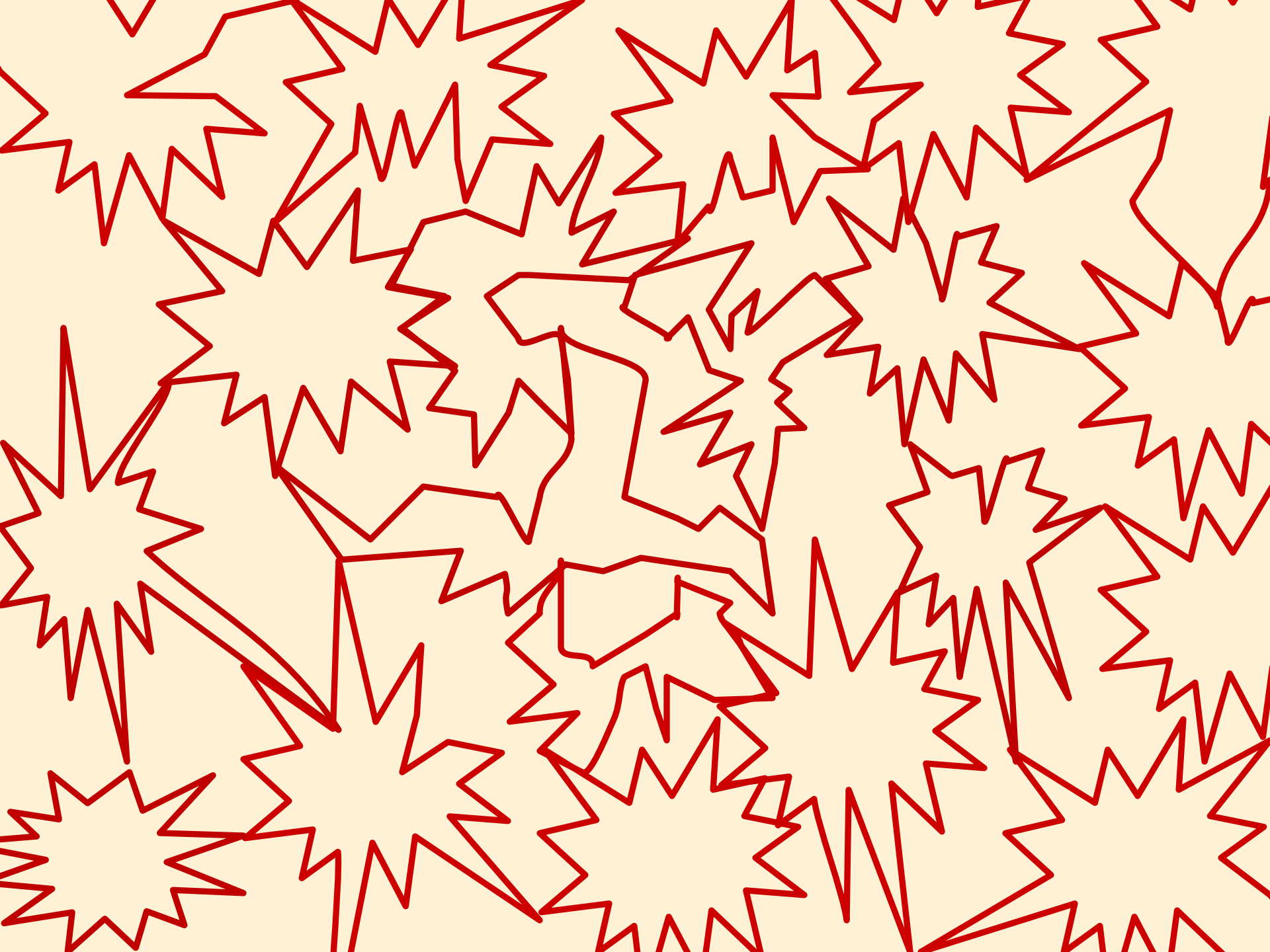
ANATOMICAL BASIS FOR THE DEVELOPMENT OF LIVEDO RETICULARIS

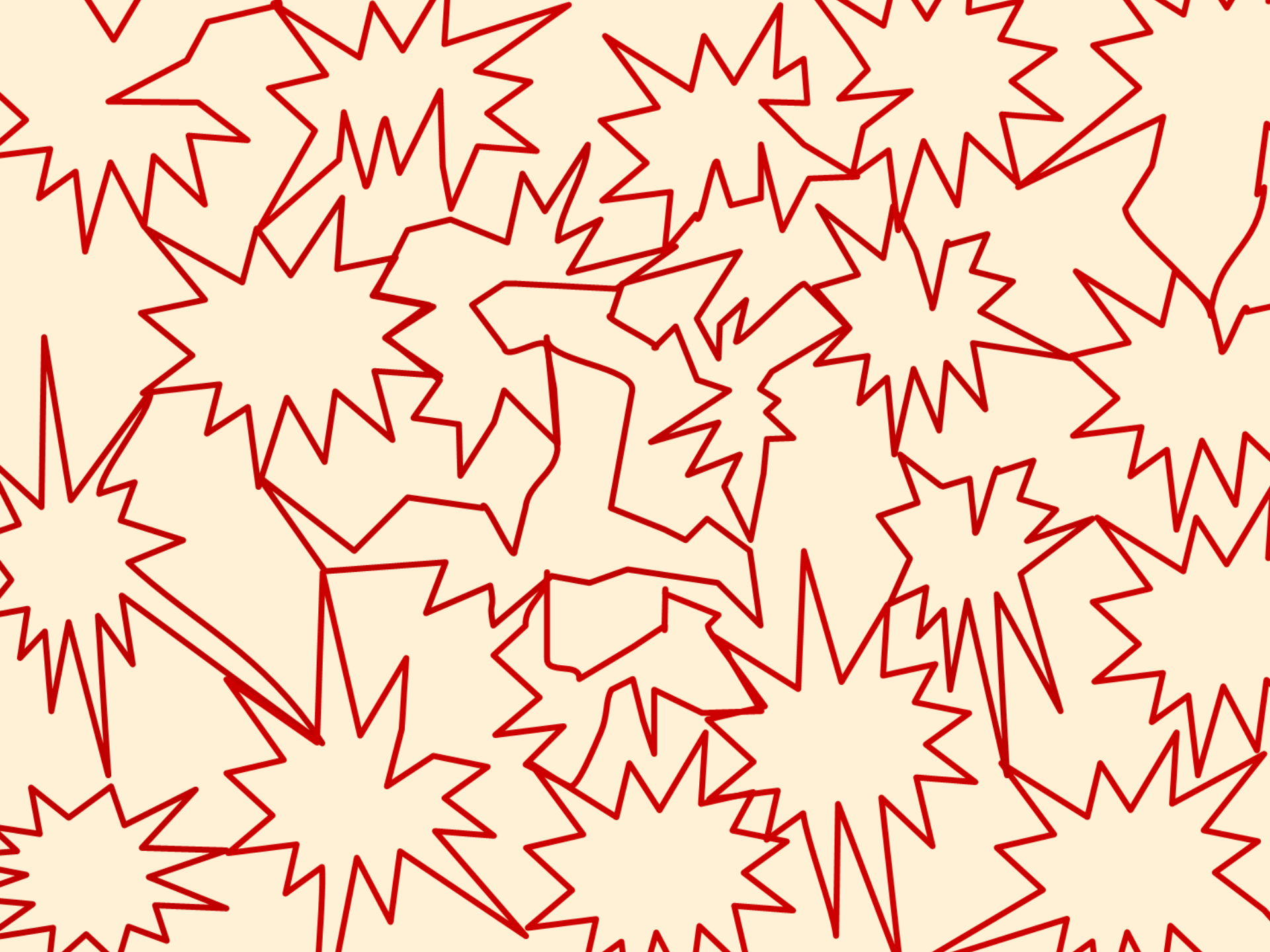


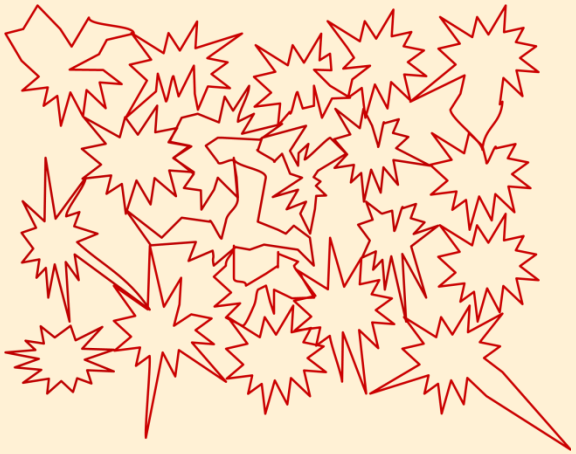
Dermatology, 2nd Edition. Eds Jean L Bolognia et al. Spain: Mosby Elsevier, 2008

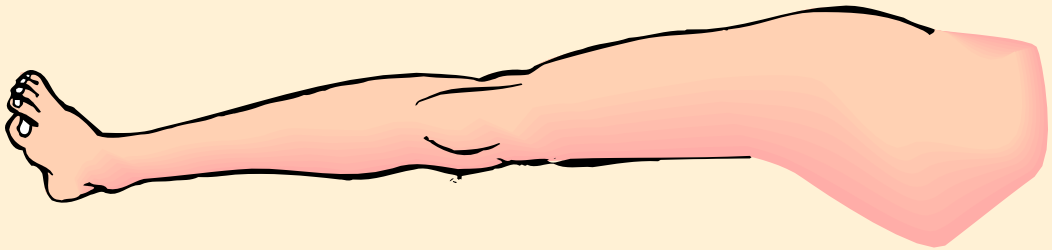










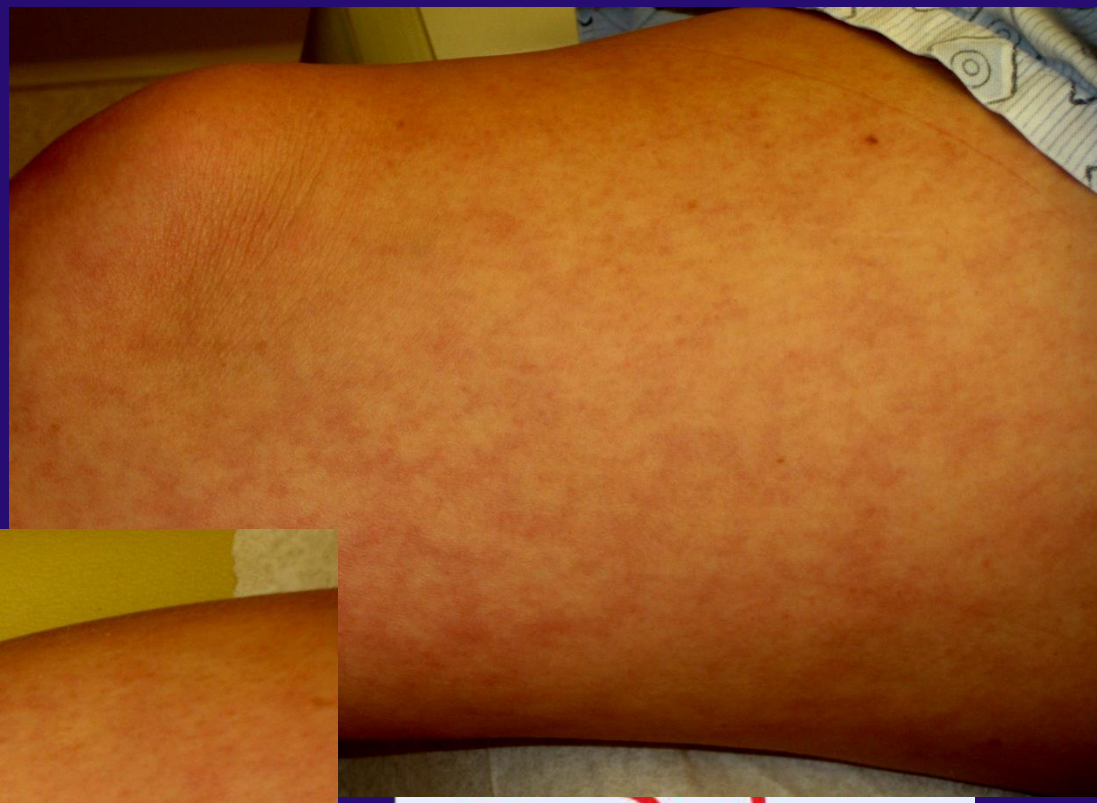


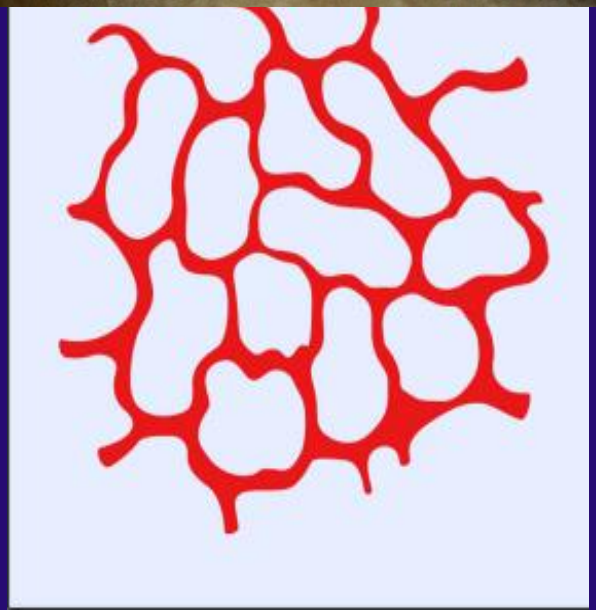
2 potential problems with this system

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



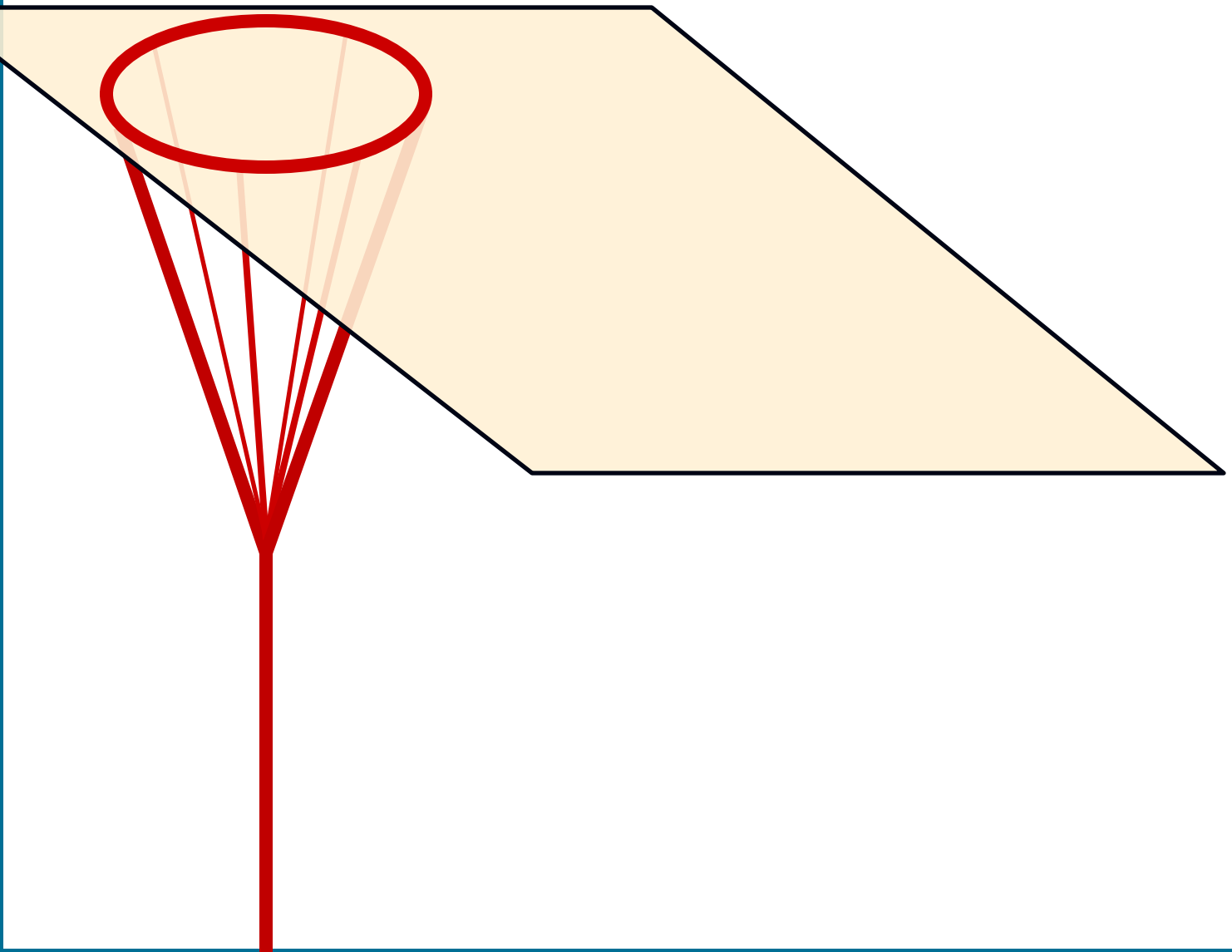


Problem 2:

Retiform Purpura

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

Retiform Purpura



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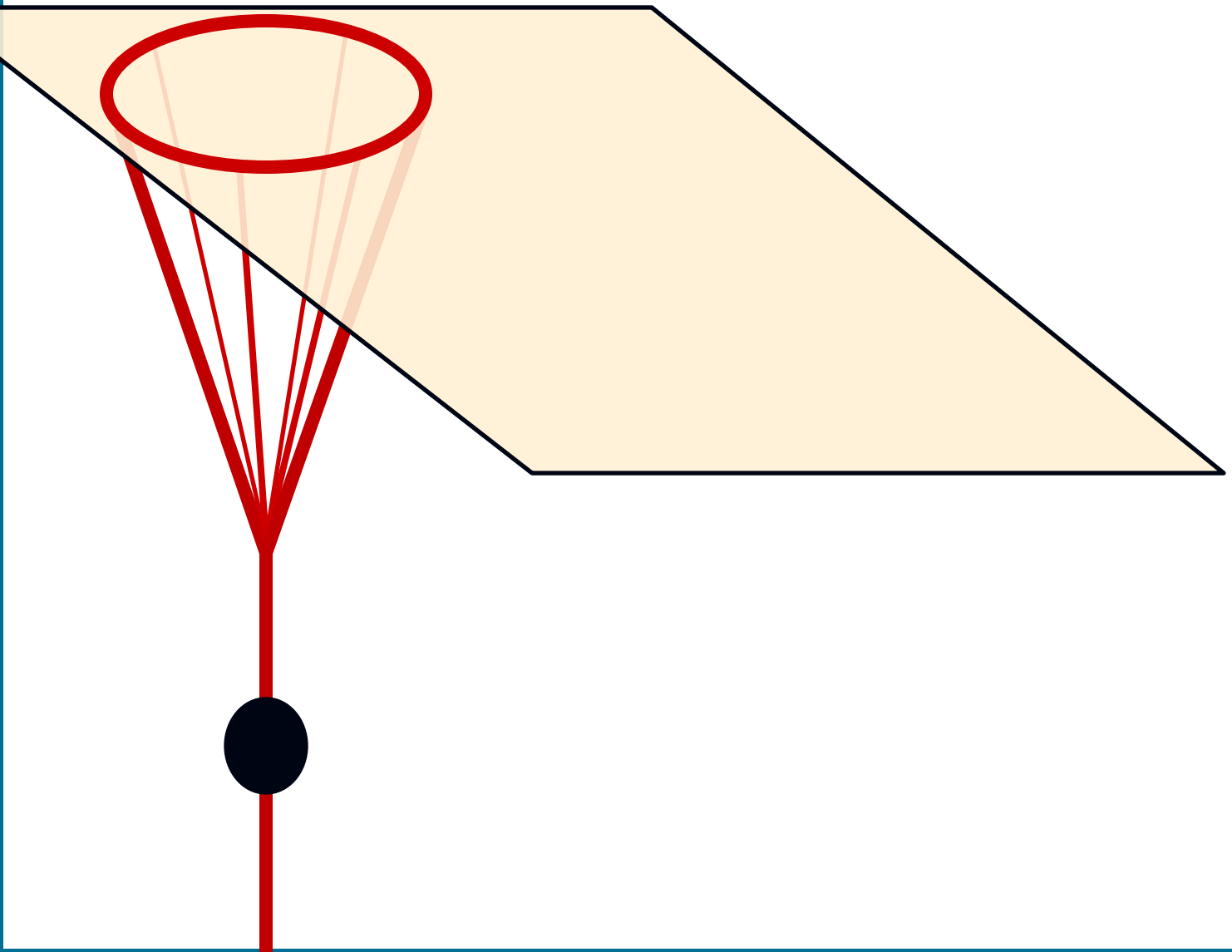

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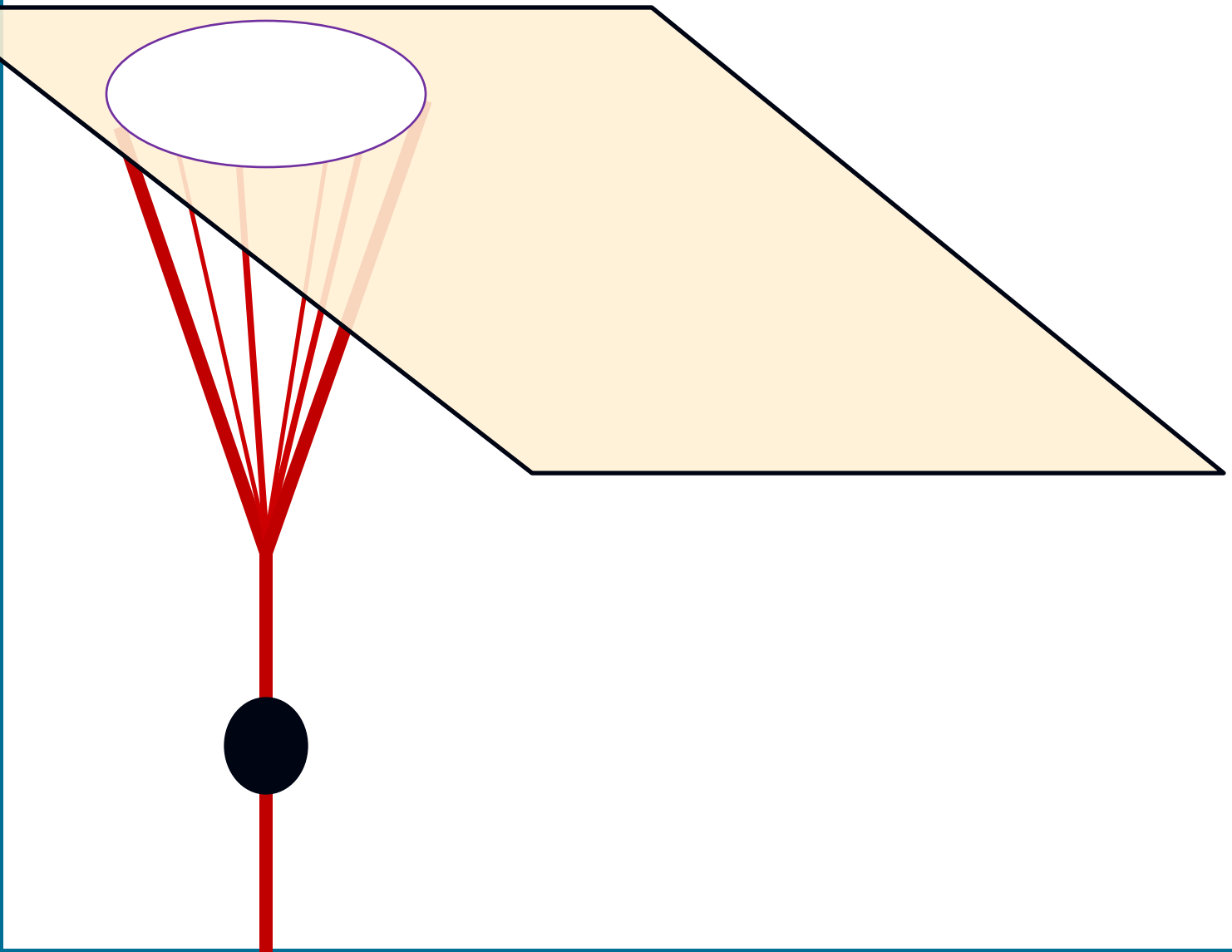

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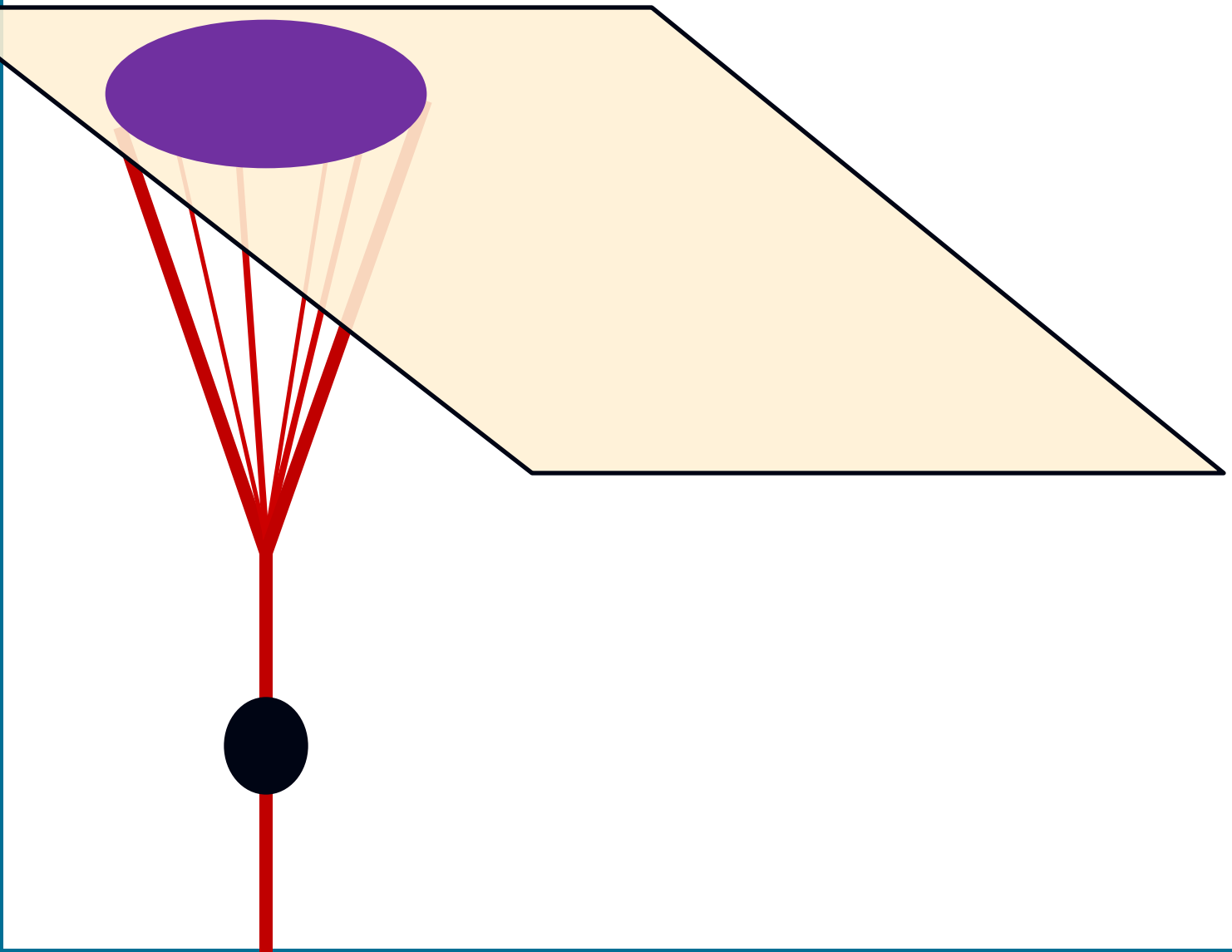

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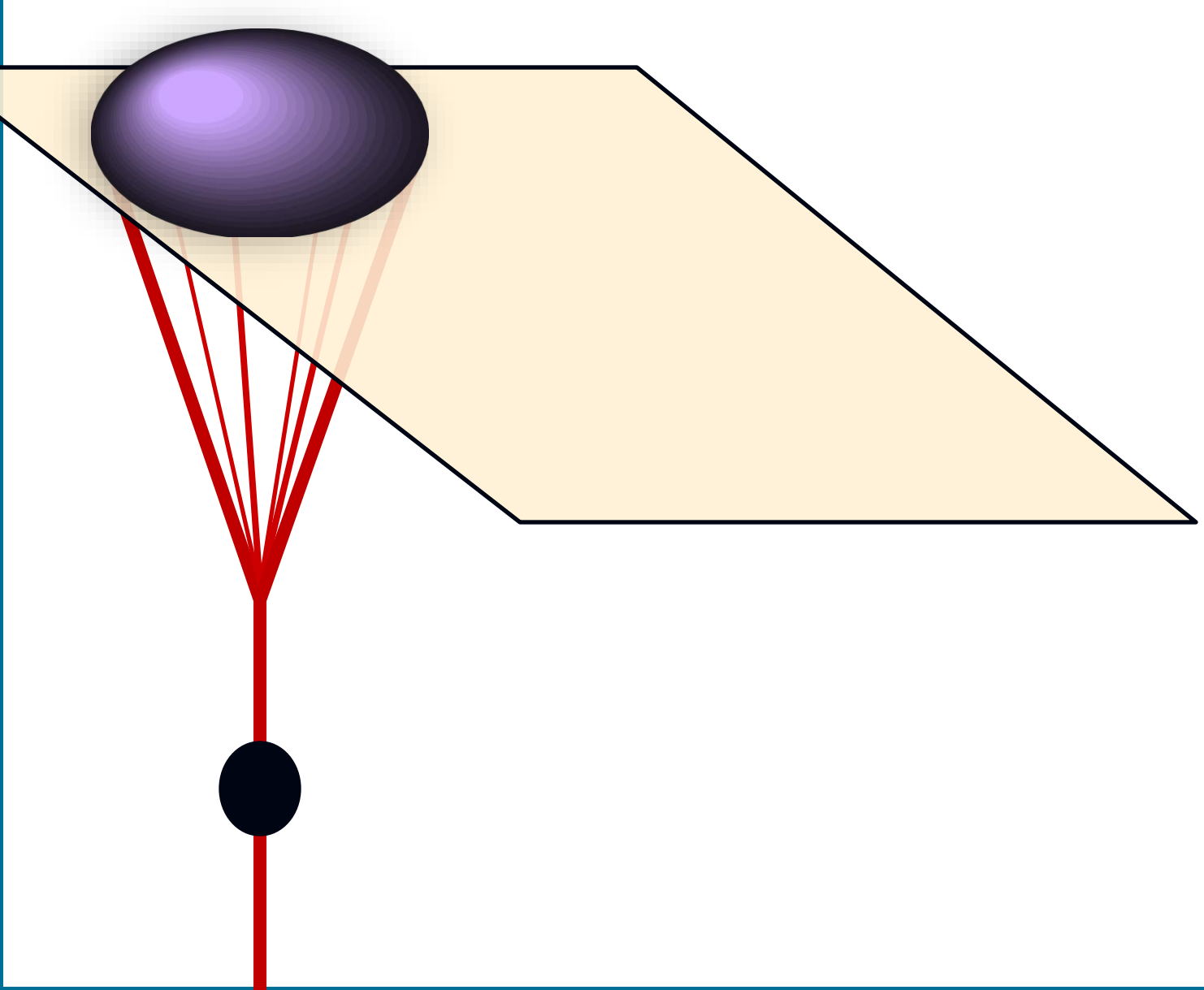

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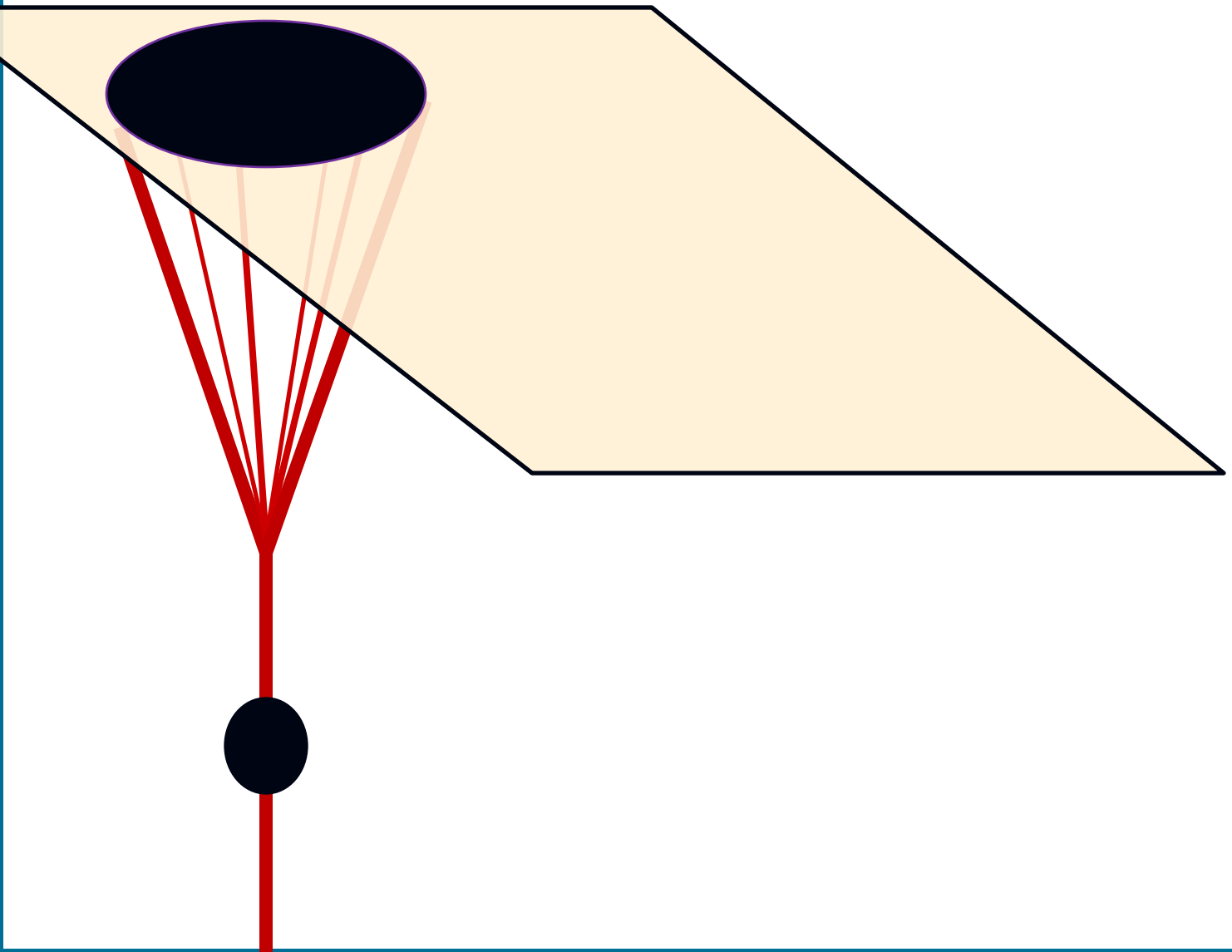
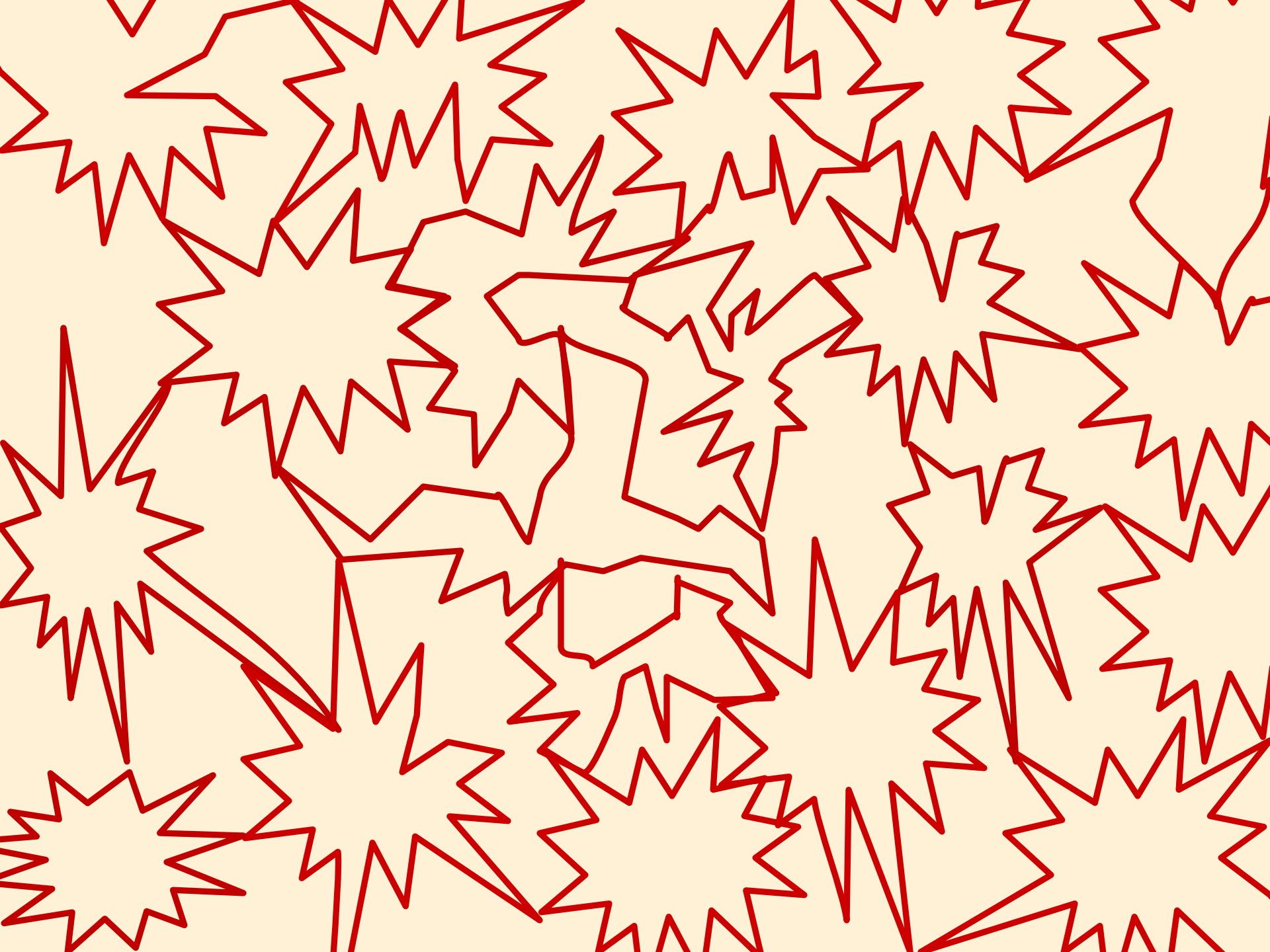
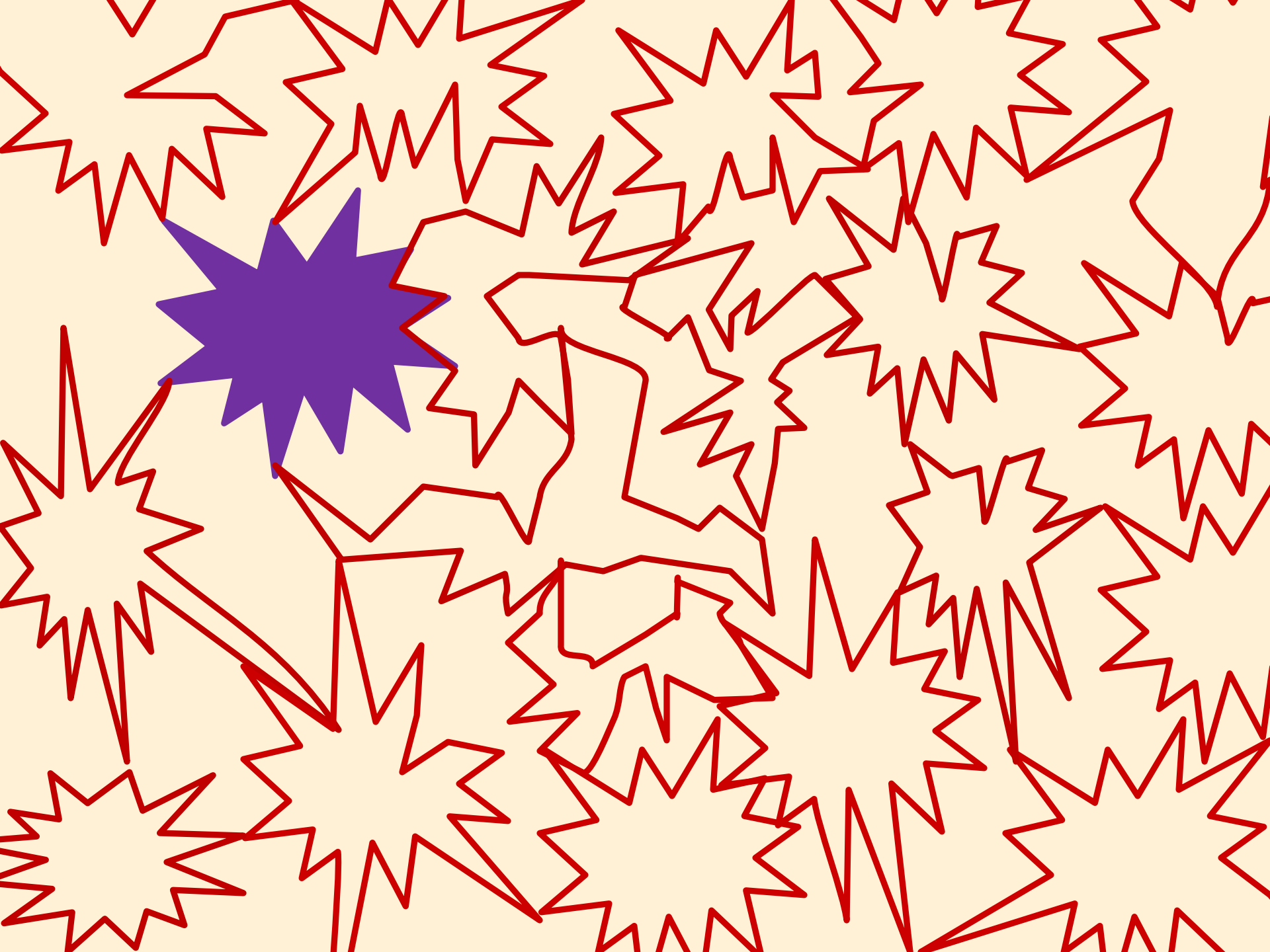
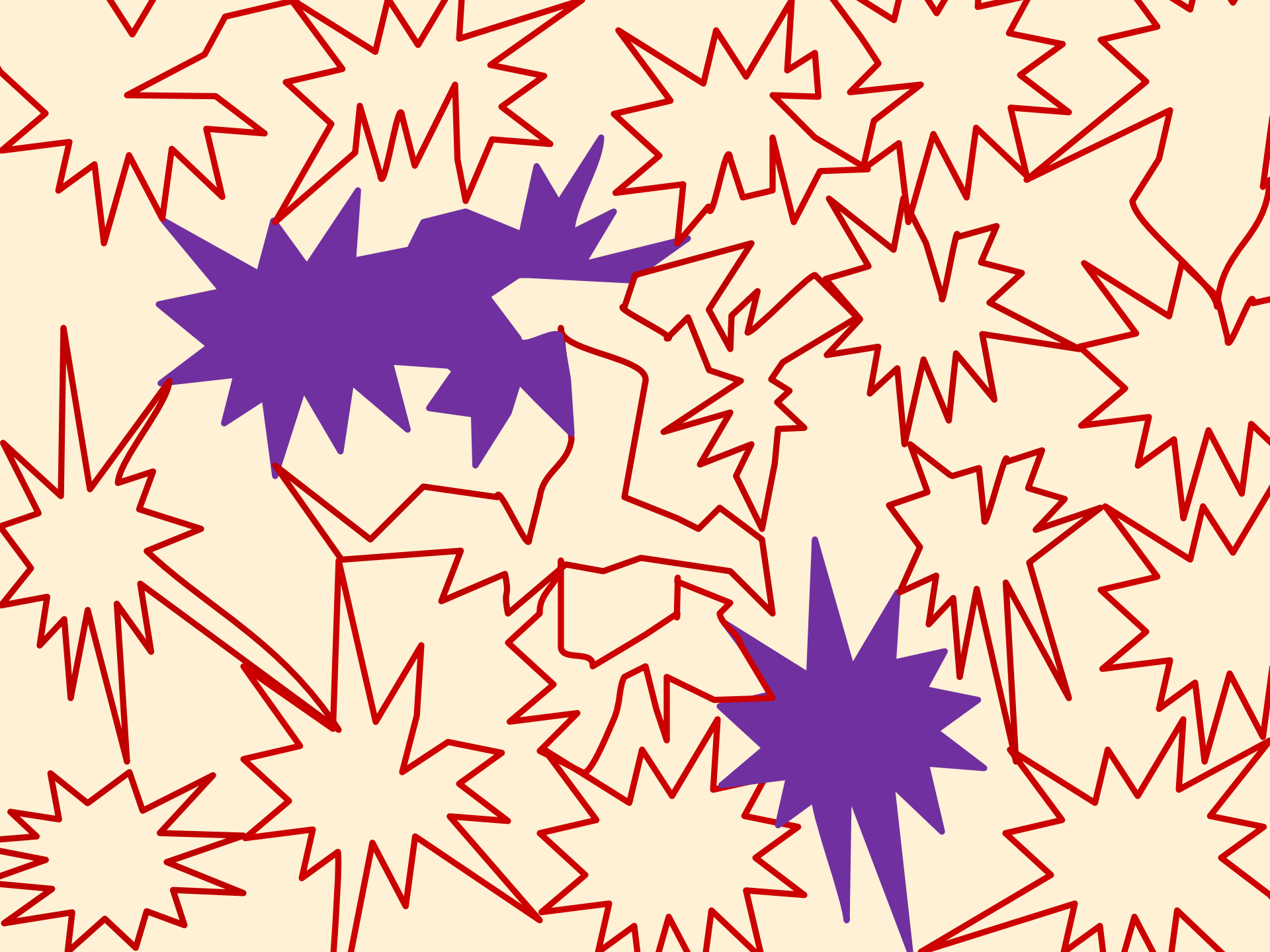
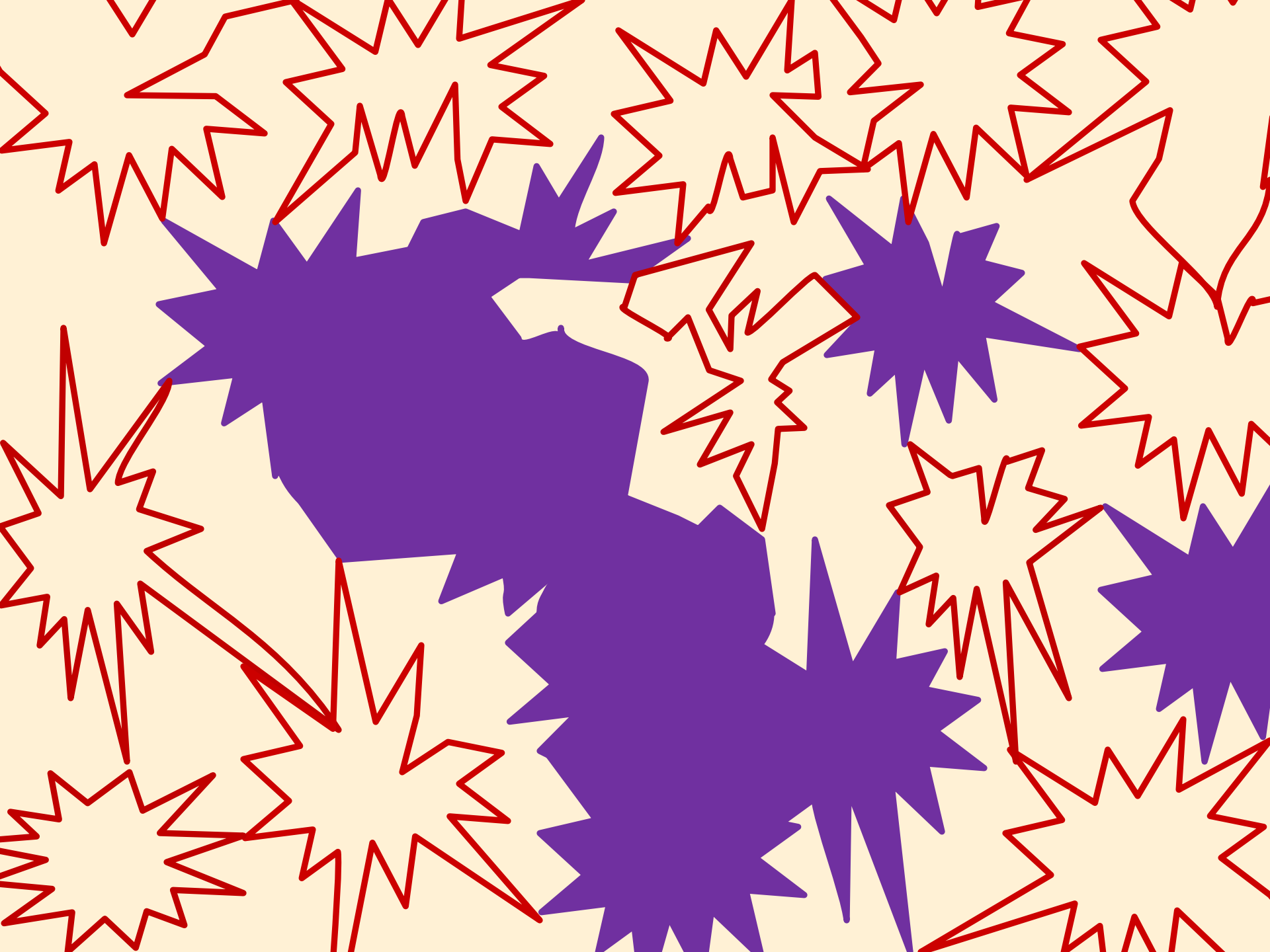










Retiform Purpura

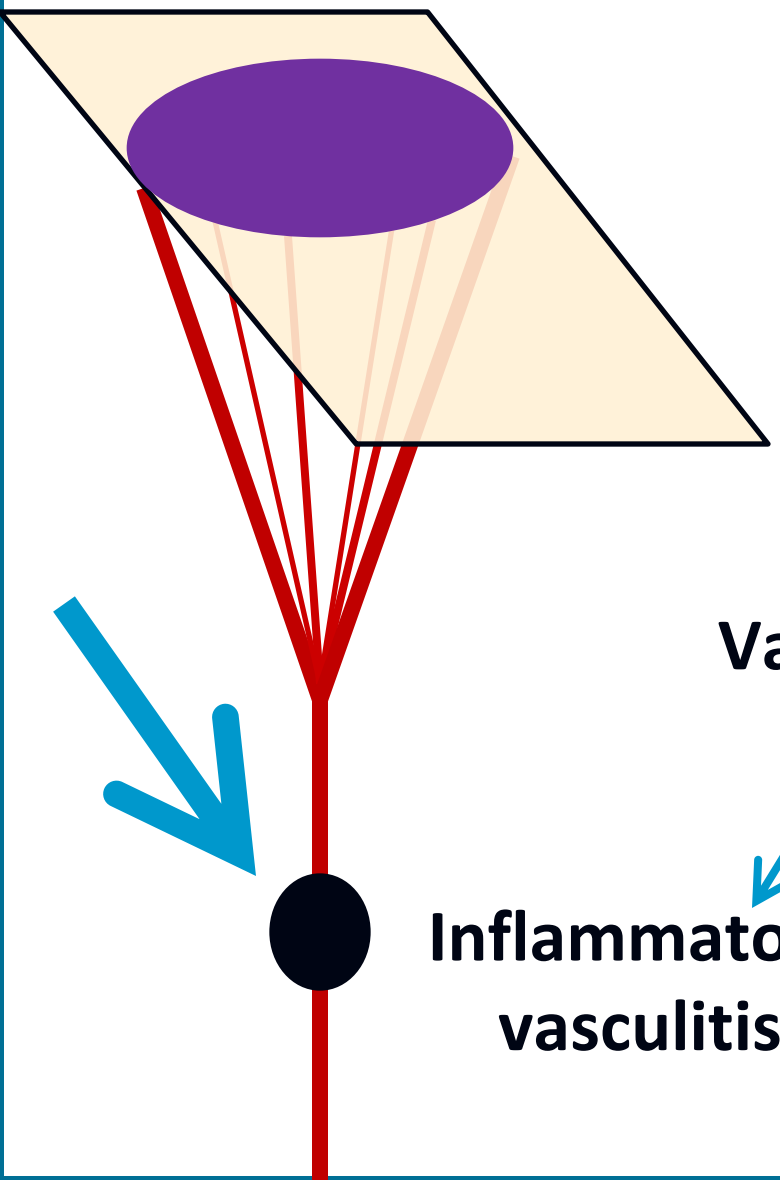
(with necrosis)

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

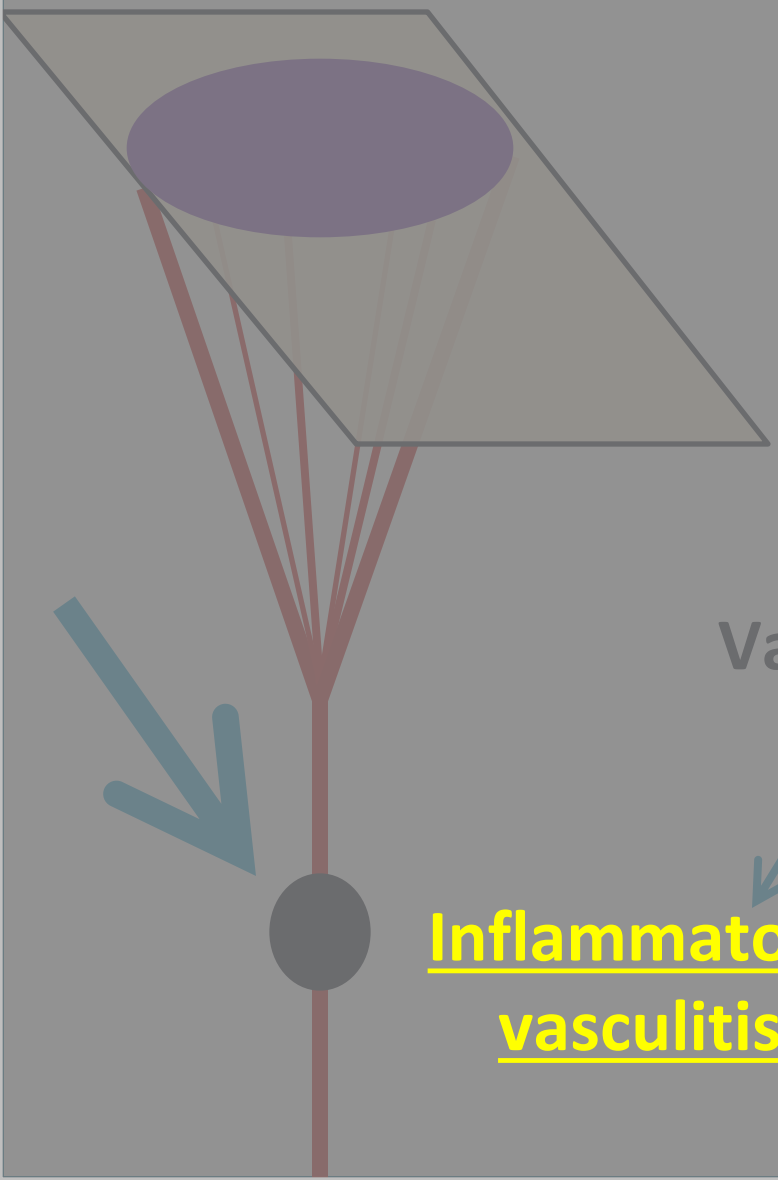
Vasculitis

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	Amniotic Fluid, Atrial Myxoma, Cholesterol, Fat, Nitrogen, Septic, Ventilator Gas
Hypercoagulable States	Amyloidosis, AT III Deficiency, Atrophie Blanche / Livedoid Vasculopathy, APLAS, Calciphylaxis, COVID-19, Cryoglobulinemia, DIC, DVT, Hyperoxaluria, Protein C/S Deficiency, Sneddons Dz, TTP, Xylazine
Inflammatory Vasculitis	Microscopic Polyangiitis, PAN, Rheumatoid Vasculitis, Takayasu's, Wegeners
Septic vasculitis (Angioinvasive pathogens)	GPC: S. aureus GNRs: Aeromonas, E.coli, Klebsiella, Moraxella, Morganella, Pseudomonas, Serratia, Vibrio Fungi: Aspergillus, Candida, Fusarium, Mucor

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	Amniotic Fluid, Atrial Myxoma, Cholesterol, Fat, Nitrogen, **Septic**, Ventilator Gas
Hypercoagulable States	Amyloidosis, AT III Deficiency, Atrophie Blanche / Livedoid Vasculopathy, **APLAS**, Calciphylaxis, COVID-19, Cryoglobulinemia, **DIC**, DVT, Hyperoxaluria, Protein C/S Deficiency, Sneddons Dz, **TTP**, Xylazine
Inflammatory Vasculitis	Microscopic Polyangiitis, PAN, Rheumatoid Vasculitis, Takayasu's, Wegeners
Septic vasculitis (Angioinvasive pathogens)	**GPC: S. aureus** **GNRs: Aeromonas, E.coli, Klebsiella, Moraxella, Morganella, Pseudomonas, Serratia, Vibrio** Fungi: Aspergillus, Candida, Fusarium, Mucor

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

More faces of Retiform Purpura

NURSE
SEL

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 sinister process**

Take-Home Points

- Consider prozone phenomenon in unexpected negative tests for syphilis (RPR, VDRL)
- Cellulitis is tender
- Recognize retiform purpura

Thank you

- Course organizers
- My patients who allowed me to photograph them to benefit others

Select References

- https://www.cdc.gov/sti-statistics/annual/summary.html
- 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 Cellulitis--A Randomized Clinical Trial. *JAMA.* 2017;317(20):2088–2096.
- 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
- 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)

Bonus Case
(Time Permitting)

- 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
- Other important physical exam features
  - Symptoms: Pruritic, non-tender
  - Lines/ geometric shapes