

2022 MGH/HMS Internal Medicine
Comprehensive Review and Update

Dermatology Update for the Internist
(Instructive Cases You Never Saw in Medical School)

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June 6, 2022

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Disclosures

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

Learning Objectives

- Identify implications of key COVID-19 skin manifestations
- Review presentations of another rising epidemic disease
- Recognize an easily overlooked, common, serious eruption
- Distinguish between allergic contact dermatitis and infection

Note: Cellulitis and purulent skin and soft tissue infections to be covered by Dr. Sandra Nelson on Wednesday

Case

Your patient develops this rash 8 days after her first mRNA COVID vaccine, at the injection site. How do you manage, and do you advise her to get the second dose?

- A. Prednisone; No second dose
- B. No treatment; No second dose
- C. Prednisone; Encourage second dose
- D. No treatment; Encourage second dose



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- D. No treatment; Encourage second dose**

Dx: Large delayed local skin reaction



COVID mRNA Vaccine Skin Reactions

	Eruption	Timing after dose 1	Timing after dose 2	Contraindication to next dose?
Immediate	Urticaria, Angioedema	<4 hours	N/A	YES

Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases, Devon E. McMahon, BA, Erin Amerson, MD, Misha Rosenbach, MD, Jules B. Lipoff, MD, Danna Moustafa, BS, Anisha Tyagi, BA, Seemal R. Desai, MD, Lars E. French, MD, Henry W. Lim, MD, Bruce H. Thiers, MD, George J. Hruza, MD, MBA, Kimberly G. Blumenthal, MD, MSc, Lindy P. Fox, MD, Esther E. Freeman, MD, PhD. Journal of the American Academy of Dermatology

COVID mRNA Vaccine Skin Reactions

	Eruption	Timing after dose 1	Timing after dose 2	Contraindication to next dose?
Immediate	Urticaria, Angioedema	<4 hours	N/A	YES
NOT-Immediate	Local reaction	Days 1-5	Days 1-4	<u>NO</u>
	Delayed large local reaction	Day 7-11	Day 2-5	
	Urticaria	Day 3-8	Day 2-5	
	Morbilliform	Day 3-7	Day 2-4	
	Erythromelalgia	Day 7-13	Day 1-4	

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Days 1-5 Day 7-11	Days 1-4 Day 2-5	<u>NO</u>
Day 3-8	Day 2-5	
Day 3-7	Day 2-4	
Day 7-13	Day 1-4	

***Delayed large local reaction =
58% of all Moderna skin reactions,
16% of Pfizer reactions**

Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases, Devon E. McMahon, BA, Erin Amerson, MD, Misha Rosenbach, MD, Jules B. Lipoff, MD, Danna Moustafa, BS, Anisha Tyagi, BA, Seemal R. Desai, MD, Lars E. French, MD, Henry W. Lim, MD, Bruce H. Thiers, MD, George J. Hruza, MD, MBA, Kimberly G. Blumenthal, MD, MSc, Lindy P. Fox, MD, Esther E. Freeman, MD, PhD. Journal of the American Academy of Dermatology

COVID mRNA Vaccine Skin Reactions



Timing after dose 1	Timing after dose 2	Contraindication to next dose?
<4 hours (urticaria)	N/A	YES
Days 1-5 Day 7-11 >4 hours Day 2-3 Day 3-7 Day 7-13	Days 1-4 Day 2-5 Day 2-5 Day 2-4 Day 1-4	<u>NO</u>

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True/False

A patient develops a cough and this widespread urticarial eruption at the same time, and tests positive for COVID-19.

T/F: The rash is an excellent prognostic sign.

- A. True
- B. False



True/False

A patient develops a cough and this widespread urticarial eruption at the same time, and tests positive for COVID-19.

T/F: The rash is an excellent prognostic sign.

A. True

B. False Urticaria not an independent predictor of mortality/survival



COVID-19 Acute Eruptions

COVID Toes

(AKA chilblains, pseudo-chilblains, perniosis)

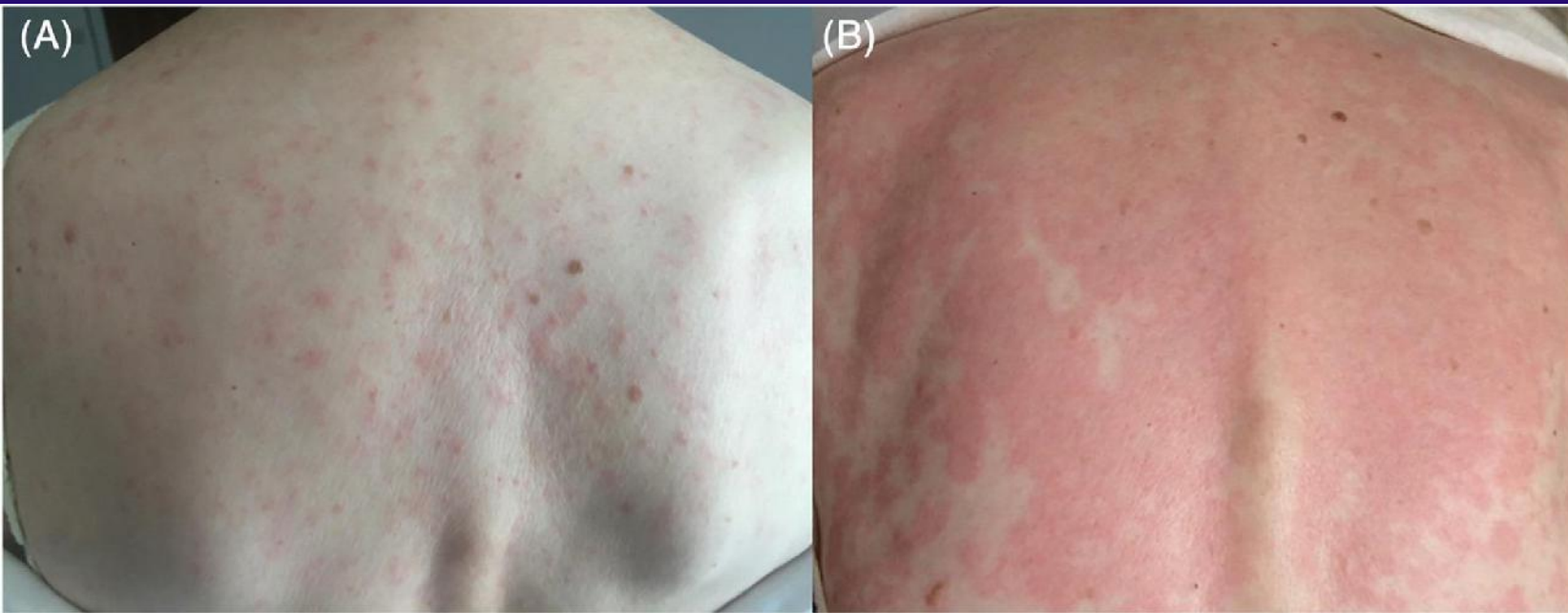


Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A, Moreno-Arrones OM, Saceda-Corralo D, Arana-Raja A, Ortega-Quijano D. Characterization of acute acral skin lesions in nonhospitalized patients: A case series of 132 patients during the COVID-19 outbreak. *J Am Acad Dermatol.* 2020 Jul;83(1):e61-e63.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

COVID-19 Acute Eruptions

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)

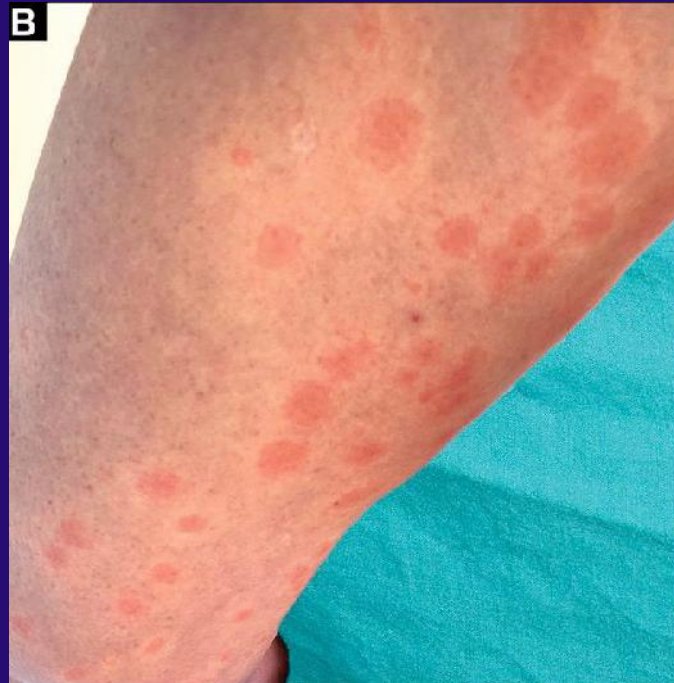
COVID-19 Acute Eruptions

COVID Toes

Maculopapular

Urticarial

AKA Hives



Skin manifestations of COVID-19.
Sarah Young, Anthony P. Fernandez Cleveland
Clinic Journal of Medicine May
2020, DOI: 10.3949/ccjm.87a.ccc031

COVID-19 Acute Eruptions

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, DOI: (10.1111/pde.14201)

COVID-19 Acute Eruptions

COVID Toes

Maculopapular

Urticarial

Vesicular

Vaso-occlusive



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,

ie, livedo racemosa, livedo reticularis, purpura, and retiform purpura

Skin manifestations of COVID-19. Sarah Young, Anthony P. Fernandez Cleveland Clinic Journal of Medicine May 2020,



COVID-19 Acute Eruptions

	% of all rashes
COVID Toes	41%
Maculopapular	28%
Urticarial	12.5%
Vesicular	10.5%
Vaso-occlusive (retiform purpura)	4.5%



COVID Toes

Fernandez-Nieto D, et al, J Am Acad Dermatol. 2020 Jul;83(1):e61-e63..



Retiform Purpura

Young, S et al, Cleveland Clinic Journal of Medicine May 2020

COVID-19 Acute Eruptions

Vasculopathy

% of all
rashes

COVID Toes

41%

Mild,
70% **Late** or **Isolated** sign

Severe,
72% **Early** sign

Vaso-occlusive

4.5%

(retiform purpura)



COVID Toes

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Retiform Purpura

Young, S et al, Cleveland Clinic Journal of Medicine May 2020

COVID-19 Acute Eruptions

Vasculopathy

% of all
Prognosis
rashes

COVID Toes

GOOD
11%

Mild,
70% **Late or Isolated**

Severe,
72% **Early sign**

Vaso-occlusive

POOR
4.5%

(retiform purpura)



COVID Toes

Fernandez-Nieto D, et al, J Am Acad Dermatol. 2020 Jul;83(1):e61-e63..



Retiform Purpura

Young, S et al, Cleveland Clinic Journal of Medicine May 2020

COVID-19 Acute Eruptions

Vasculopathy

COVID Toes

Mild,
70% Late or Isolated

Severe,
72% Early sign

Vaso-occlusive (retiform purpura)

Prognosis

GOOD

POOR

Timing

LATE

EARLY



COVID Toes

Fernandez-Nieto D, et al, J Am Acad Dermatol. 2020 Jul;83(1):e61-e63..



Retiform Purpura

Young, S et al, Cleveland Clinic Journal of Medicine May 2020

COVID-19 Acute Eruptions

Vasculopathy

COVID Toes

Prognosis

Timing

GOOD

LATE

Vaso-occlusive
(retiform purpura)

POOR

EARLY

No Known

Maculopapular

Urticarial

Vesicular



COVID Toes
12.5%
Fernandez-Nieto D, et al, J Am Acad Dermatol. 2020 Jul;83(1):e113-63



Retiform Purpura
Young, S et al, Cleveland Clinic Journal of Medicine May 2020

COVID-19 and the skin

Key Points

- Cutaneous vasculopathy can inform prognosis:
 - COVID Toes: Good
 - Retiform purpura: Bad
- Do not over-interpret *other* rashes: no known prognostic value (maculopapular, urticarial vesicular)
- Delayed vaccine reactions should *not* preclude future vaccination

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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- B. Psoriasis
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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?



Diagnosis? (round 2)

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

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?

Diagnosis? (round 2)

A. Syphilis!

B. Psoriasis

C. Pityriasis rosea

D. Measles

INITIAL WORKUP	
RPR	Negative
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Diagnosis? (round 2)

A. Syphilis!

B. Psoriasis

C. Pityriasis rosea

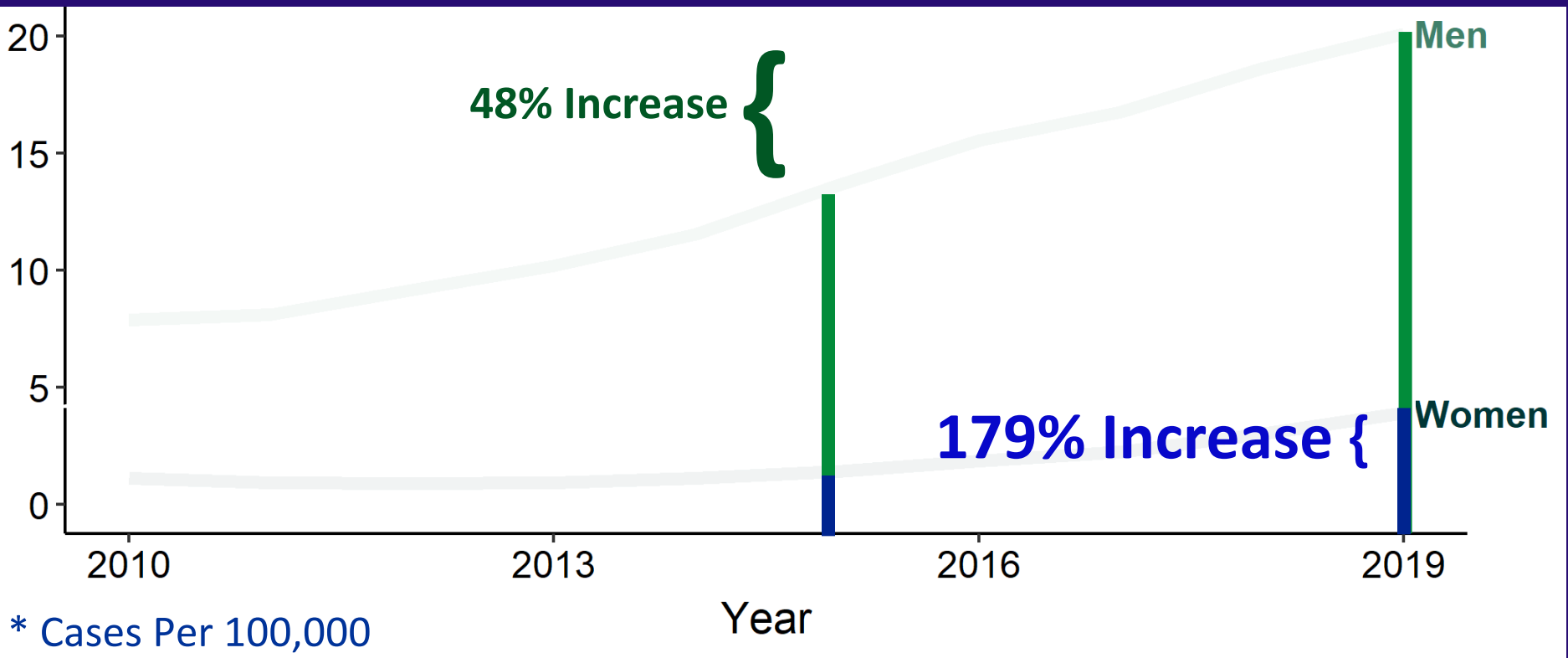
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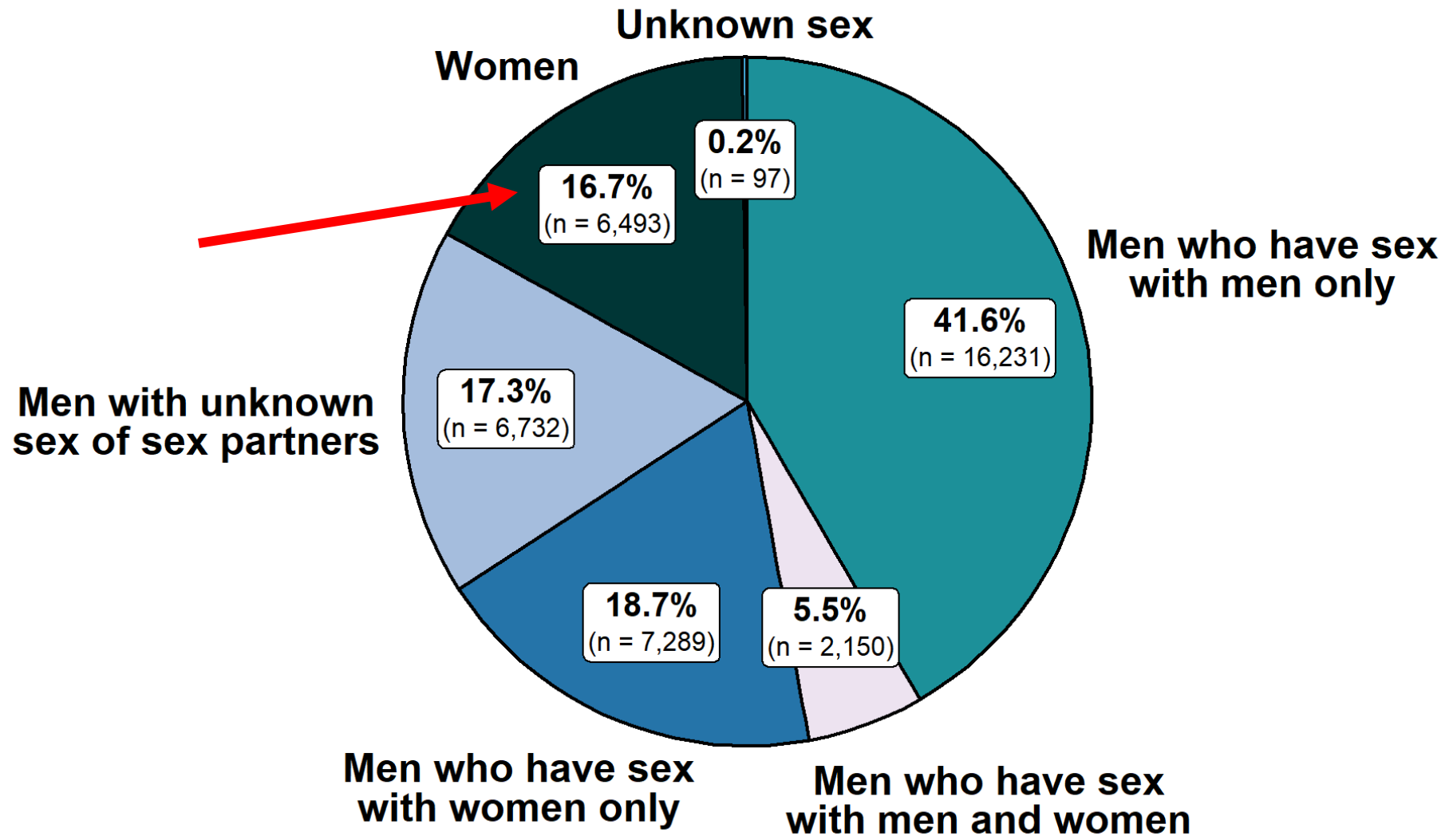
Why a false negative RPR?

But first, why revisit syphilis at all?

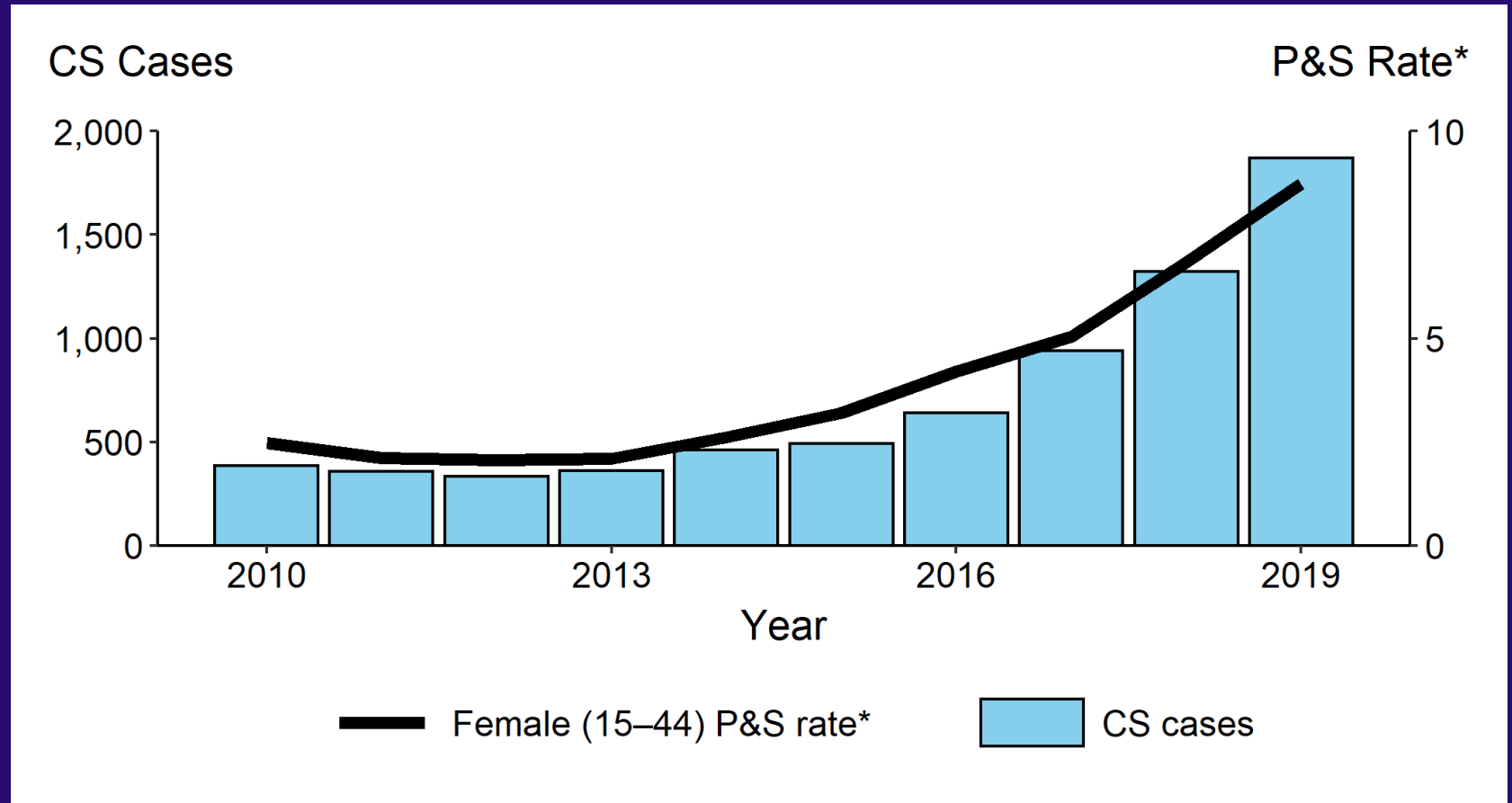
Primary and Secondary Syphilis — Rates of Reported Cases by Sex, United States, 2010–2019



Primary and Secondary Syphilis — Rates of Reported Cases by Sex, United States, 2010–2019



Congenital Syphilis (by Year of Birth) and Syphilis Among Females Aged 15–44 Years, United States, 2010–2019



* Per 100,000

www.cdc.gov/std/statistics/2019/data.zip

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

Syphilis

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



Diagnosis?

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

INITIAL WORKUP	
RPR	Negative
HIV ELISA	Negative
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Why a false negative RPR?

Prozone Phenomenon

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

Prozone Phenomenon

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

Prozone Phenomenon

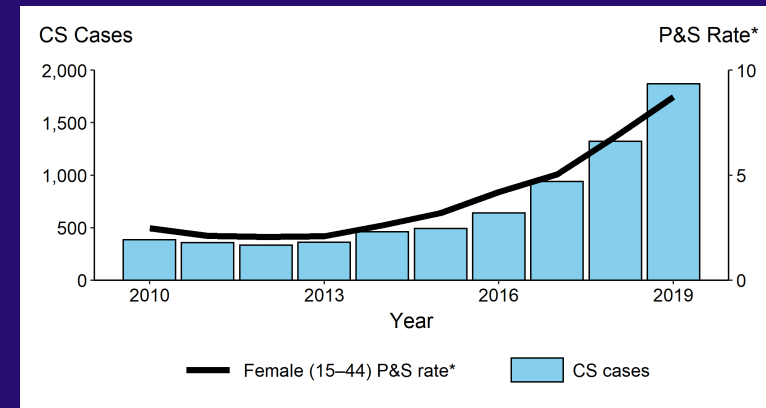
Prozone phenomenon: Notable antibody excess prevents agglutination

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
www.cdc.gov/std/statistics/2019/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

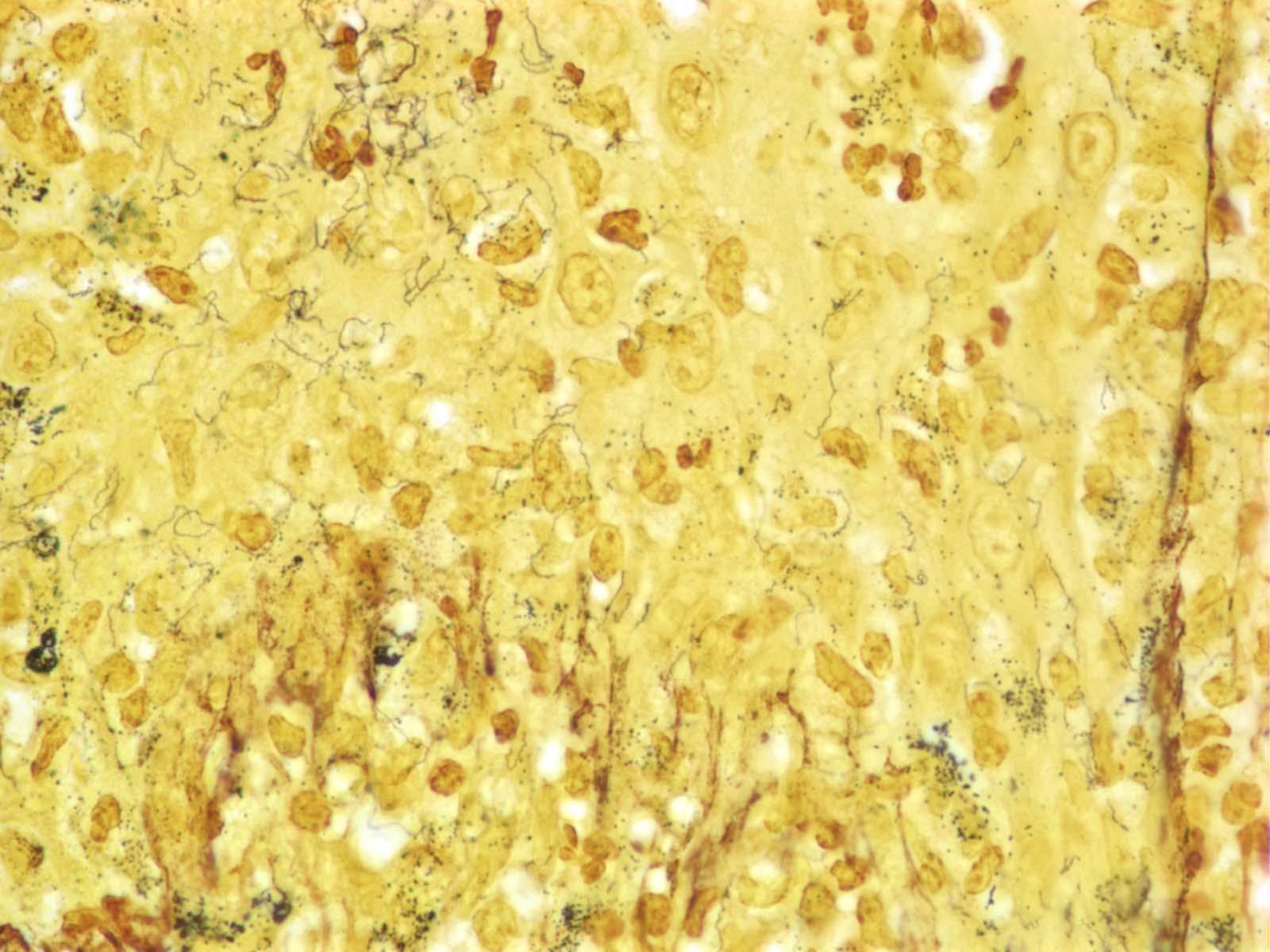
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Alternative means to confirm a diagnosis of syphilis:

- 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
 - Rupoid: “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