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Walter J. Hamlin Professor and Chair, Dept. of Dermatology
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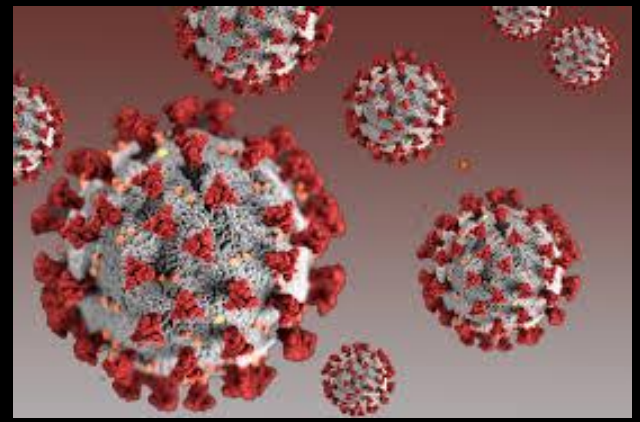


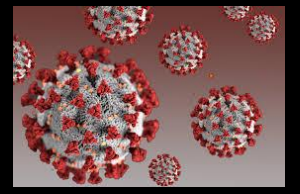
Pediatric Perspectives of COVID-19
May 19, 2020

NORTHWESTERN UNIVERSITY

NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

What do we know about pediatric COVID-19 infection?

In general, children handle SARS-CoV-2 well



Original reports from China

- Only 1.3% of >72,000 were < 20 years old with rare ICU admissions/deaths

CDC report Apr 6

- 1.7% of almost 150,000 known US COVID-19 cases in children
- Of 2572 known pediatric cases: 15 ICU admissions with 3 deaths

- In China: up to 35% of children had asymptomatic disease
- Same viral persistence (about a month, longest in stool)

Zimmermann and Curtis. Pedi Infect Dis J June 2020;39:469

Theories about lower severity in children

- Stronger innate immune responses, higher T/B cell numbers, NK cells
  -- Strong helper T cell responses in milder COVID-19 cases

Crotty and Sette. Cell 2020

- Lower prevalence of co-morbidities associated with more severe disease
- Frequency of other coronavirus infections: immunity may cross-react
- Higher mucosal colonization by viruses and bacteria
- Usually infected from an adult: 2nd or 3rd generation virus may be less pathogenic
- Perhaps fewer mucosal ACE2 receptors

Zimmermann and Curtis. Pedi Infect Dis J June 2020;39:469

COVID-19 is not always mild in children

Consortium of 46 N. American PICUs (March 14- Apr 3)

- 48 children admitted with median age 13 years (4-17 years)
- 83% had significant preexisting comorbidities
- 73% presented with respiratory symptoms
- 38% required invasive ventilation (2% ECMO)
- Hydroxychloroquine was most commonly used agent
- Outcome: 31% still hospitalized and 4% died
- If discharged: Median length of hospitalization 7 days; in PICU 5 days

Shekerdemian et al. JAMA Pediatrics May 11 2020 [Epub]

Multisystem Inflammatory Syndrome in Children (MIS-C)

Formerly called Pediatric Multi-System Inflammatory Syndrome (PMIS)

- Late April: Royal College Pediatric and Child Health: First PMIS/MIS-C Definition

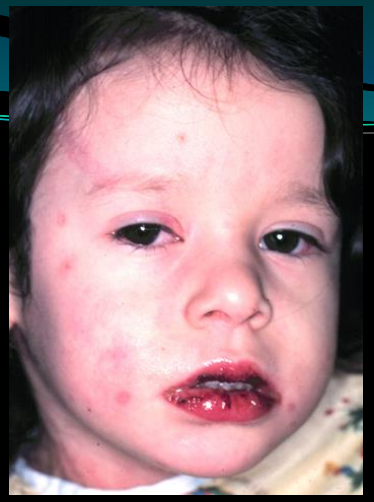
- May 4: NYC Dept of Health Alert on PMIS/MIS-C
  - 15 patients 2-15 yrs Apr 17 – May 1 with fever, often shock, GI, rash
  - <50% with respiratory symptoms; only 4 PCR+, but 6 serology+
  - >50% required support for hypotension; 33% required ventilation

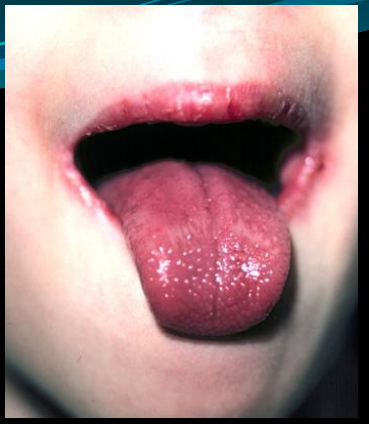
- May 13: NYC Dept of Health Advisory
  - >100 children in NY with 3 deaths + other states + >50 cases in Europe

Resembled “Kasawaki Disease” (classic or atypical)

Kawasaki Disease

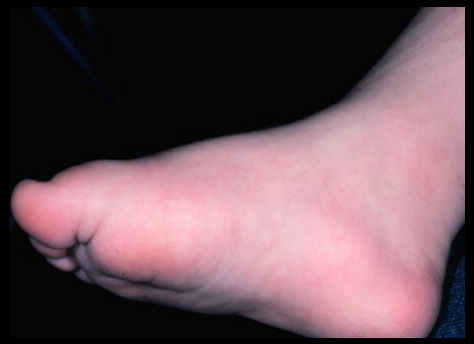
1:1000 in Japan; 1:6000 in US; 1:12,000 UK

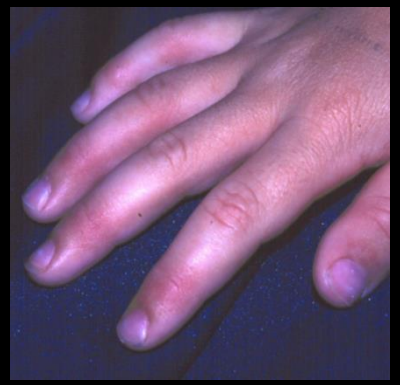


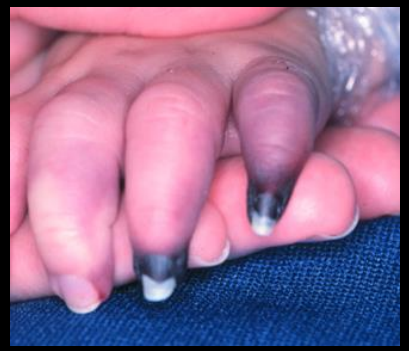


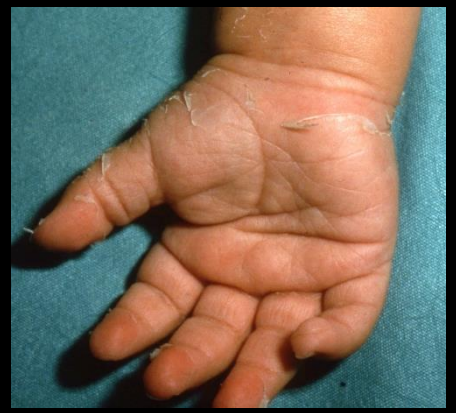
- High fever for 5+ days PLUS
- At least 4 of these 5 features:
  - Bilateral conjunctival injection
  - Oral mucosal erythema, fissuring
  - Peripheral edema, erythema; later desquamation
  - Cervical lymphadenopathy (at least 1.5 cm)
  - Polymorphous rash (often EM-like)

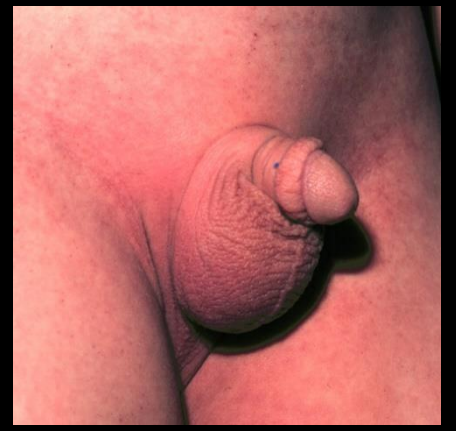
"Atypical/incomplete": Fever + 2-3 features





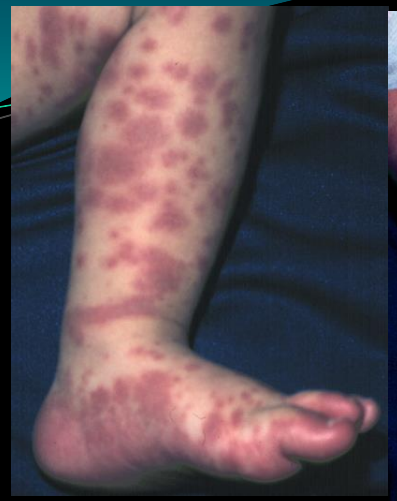
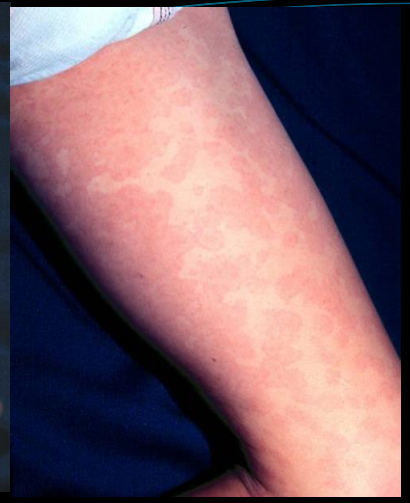
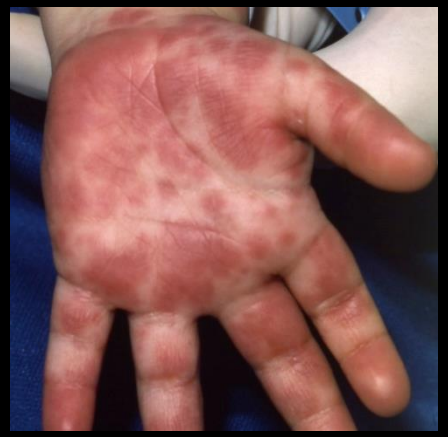
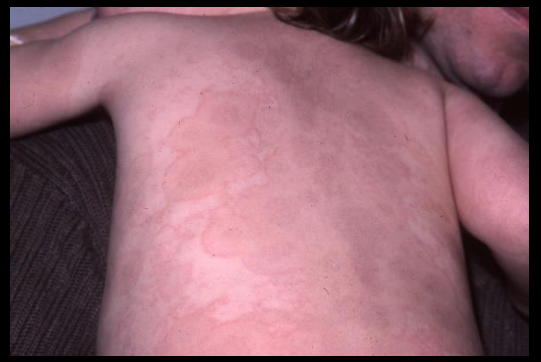
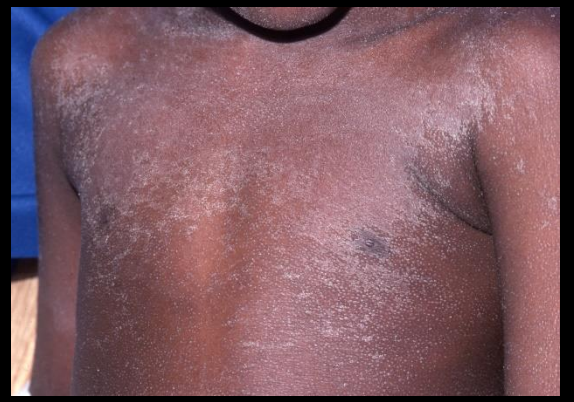
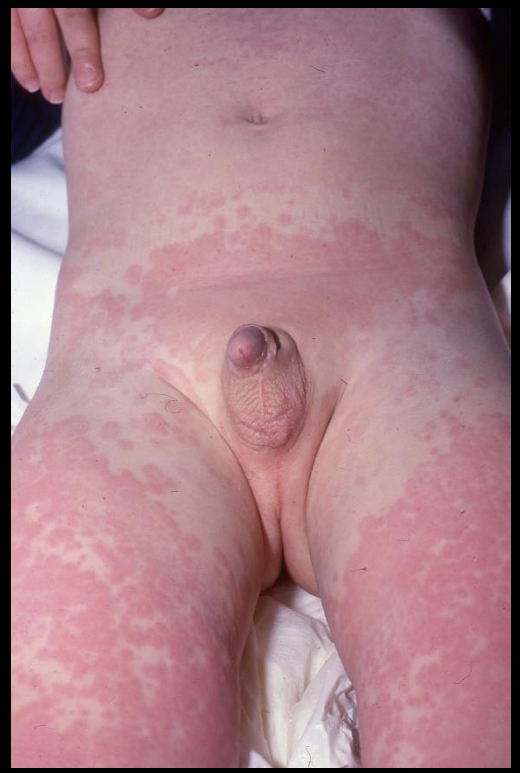
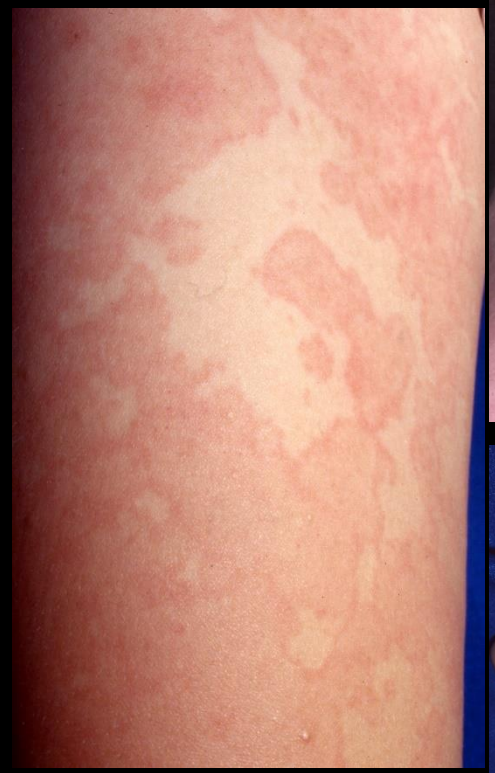
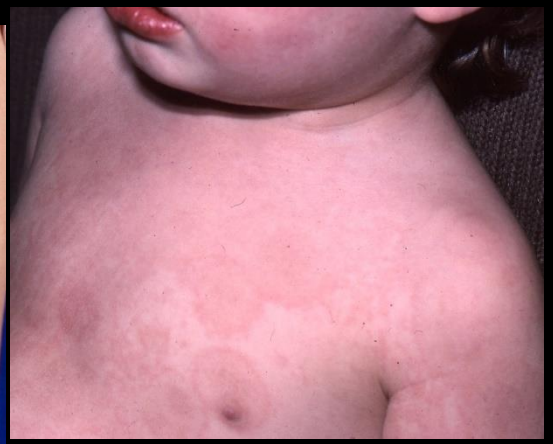
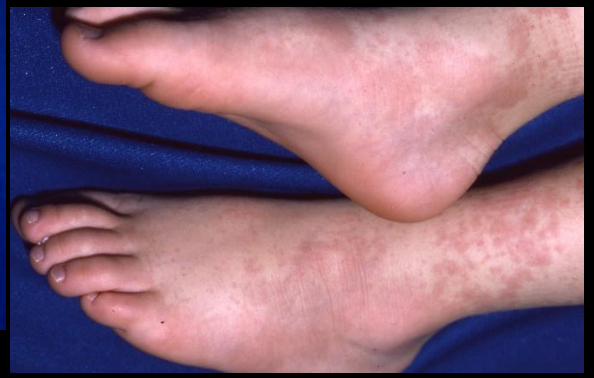
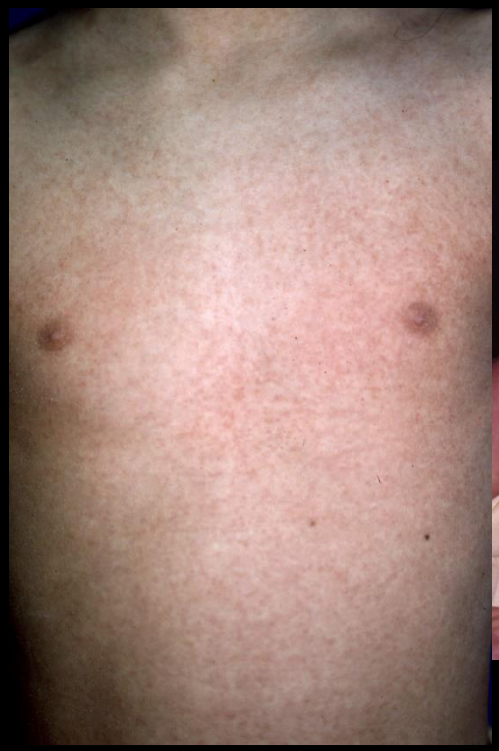
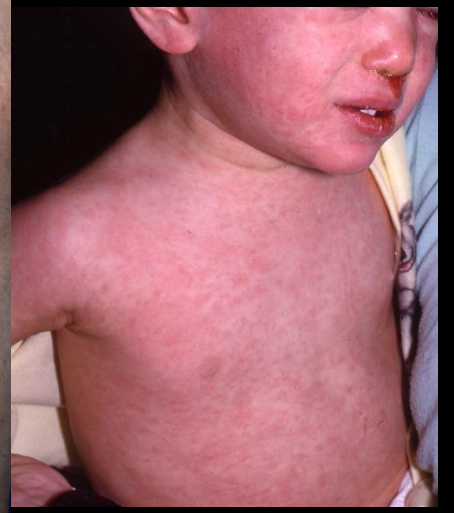






- Vasculitis of medium vessels – later coronary aneurysm

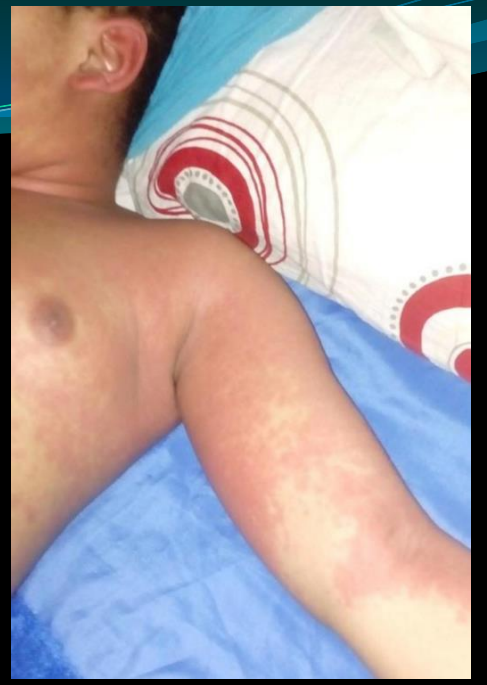
Polymorphous rash (often EM-like > scarlatiniform)

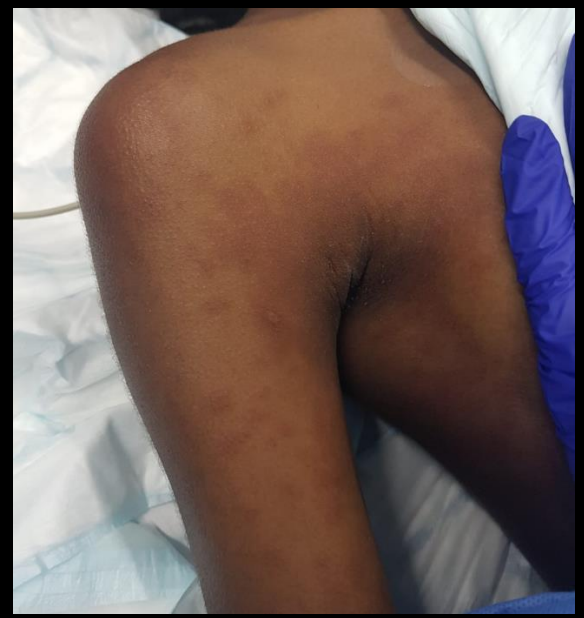












Riphagen series (UK)… May 7th

- Cluster of 8 children with hyperinflammatory shock “resembling atypical KD, KD shock syndrome, or toxic shock”
- 8 Afro-Caribbean; mean 8.9 yo; M:F 1.7
- Temp >39^{o}C for ≥4 days
- 7 with GI sxs (diarrhea, vomiting, pain)
- 5 with non-exudative conjunctivitis
- 4 with “rash”
  - Per author: “All edematous; some red sore mouths; some sandpapery. No post-inflammatory desquamation”
- All with myocardial dysfunction and 7 needed ventilation (not for respiratory support)
- Treated with IVIG + ASA/heparin cases 5-8 + steroids (5/8)
- One patient died of ischemic infarction
- 2 PCR+; most others exposed to COVID-19

Riphagen et al. Lancet May 7 2020 [Epub]





Courtesy of Dr. Shelley Riphagen, UK

Bergamo series

- Comparison study of experience Jan, 2015 to Feb 17, 2020 with pediatric Kawasaki disease (n=19) vs. Feb 18 to Apr 20, 2020 with PMIS/MIS-C (n=10; how many are KD?)

- KD: Mean 3.0 yo, M:F 1:0.6 (0.3 per month)
  PMIS/MIS-C: Mean 7.5 yo, M:F 2.3:1, 50% with "classic"; 50% "atypical" (10 per month)

- Classic group:
  - ✓ Fever
  - ✓ Bilateral conjunctival injection
  - ✓ Peripheral edema, erythema
  - ✓ Polymorphous rash
  - ✓ Oral erythema (80%)
  - ✓ Cervical adenopathy (20%)

- Incomplete group:
  - ✓ Fever
  - ✓ Bilateral conjunctival injection
  - ✓ Polymorphous rash (80%)
  - ✓ Oral erythema (60%)

60% with "shock" and/or macrophage activation syndrome (40% with classic and 60% with incomplete)

Small aneurysms 20%; all with myocardial dysfunction

2 (incomplete) with +PCR; 8 with +serology

50% with known COVID contact

Verdoni et al. Lancet May 13 2020 [Epub]

Patients in the US

- NYC: Highly variable; only some with KD-like features; all with fever, conjunctivitis

8 yo boy with flu-like illness and
then cardiovascular collapse
+COVID serology [ABC7 news, NY)

- None at Lurie Children's (but curve has followed surge by >1 month)
  3 at U of Chicago "All African-American boys; mild abdominal pain, no respiratory symptoms or cough; conjunctivitis; dry, cracking lipd; only 1 of 3 had an urticarial/EM-like rash. All with hypotension and high inflammatory markers; All responded to IVIG, aspirin, systemic steroids"

Thanks to Sarah Stein, U of C, May 16, 2020

COVID-19 Shock vs. KD Shock

COVID-19 MIS-C 2020	Kawasaki Disease
• Almost all ≥5 yo • Blacks at highest risk (not in Japan or China)	• 80% of patients <5 yo • Asians at highest risk
• Severe abdominal pain, GI symptoms	• Some GI complaints, not common
• Myocarditis/ myocardial dysfunction • NT-proBNP and troponin markedly increased • Coronary aneurysms small, unusual	• Myocardial function normal - mildly reduced • Markers normal or mildly increased • 25-60% with coronary aneurysms
• Very high ferritin, CRP; Low platelets, albumin • Platelet counts normalize with recovery • Lymphopenia, no leukocytosis	• Acute phase reactants, but less severe • Marked thrombocytosis days 10-14 • Leukocytosis, no lymphopenia
• Treatment with ASA and IVIG (plus steroids)	• Treatment with ASA and IVIG

CDC Definition of MIS-C (May 14): Very broad

- < 21 years with fever, lab evidence of inflammation, severe illness requiring hospitalization with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
  - ≥38ºC fever (or subjective) for ≥24 h
  - Evidence of inflammation: High CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, PMNs; low lymphocytes, low albumin

- AND No alternative plausible diagnoses

- AND +SARS-CoV-2 infection by PCR, serology or antigen test; or COVID-19 exposure within 4 weeks before symptom onset

Could KD result from a Coronavirus?

- Likely inflammation in response to virus in a susceptible child

  ….but not a coronavirus

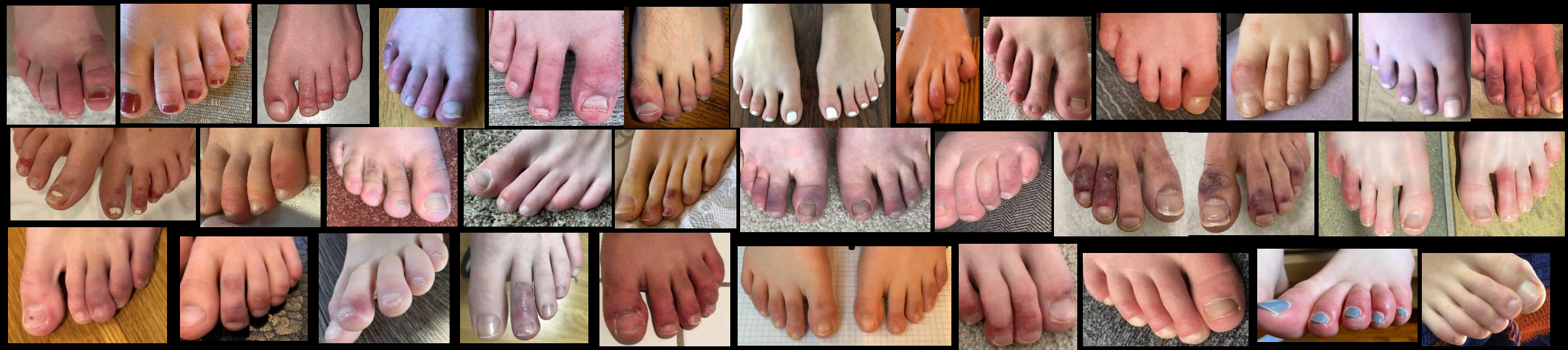
- High throughput RNA sequencing data from many KD tissues did not identify coronavirus sequences in the tissues, even in the tissues with viral inclusions and virus-like particles
- Virus-like particles in KD tissue is not big enough in diameter to derive from a coronavirus (large viruses)
- Likely a new virus that is not currently recognized based on sequences
  - Using identified short regions of protein homology to find sequences that would encode them

Input courtesy of Dr. Anne Rowley, Lurie Children's, Chicago

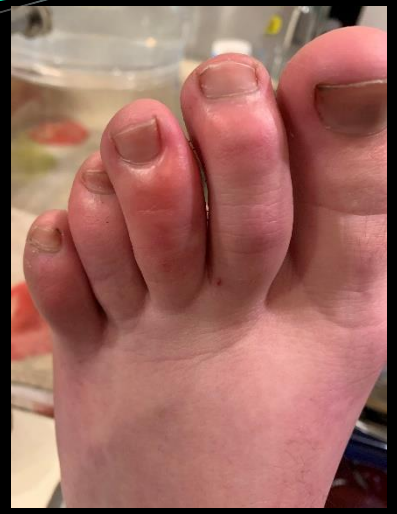
“COVID toes” (pseudochilblains)

First cases from Wuhan (early Feb): COVID signs (fever, cough, dyspnea) + acrocyanosis, which progressed to bullae, ulcers, necrosis in association with coagulopathy (d-dimers, high PTT, fibrogen degradation products); high risk

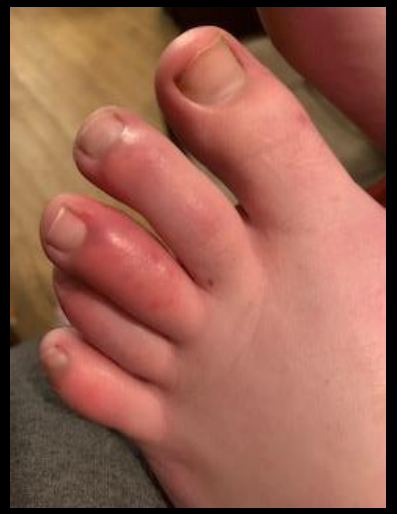
- Europe, Middle East, US: Benign pattern of “pseudo-chilblains”
- Large numbers cannot be explained by colder US spring (warm sites too), some other infection, detection bias



Progression from bright red to dusky purple is not uncommon/ blisters, erosions



15 yo boy Apr 3



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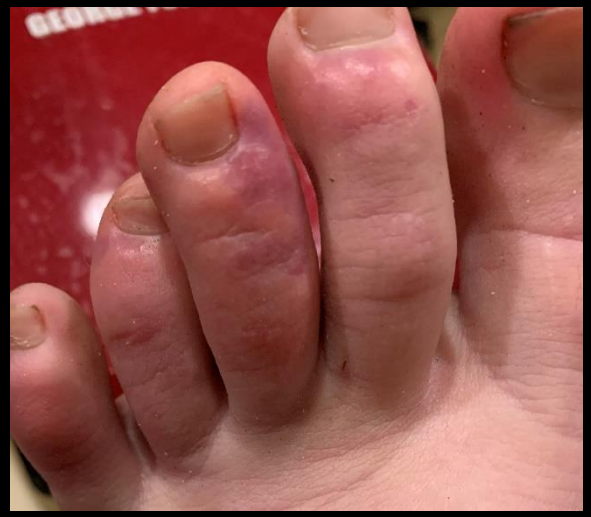

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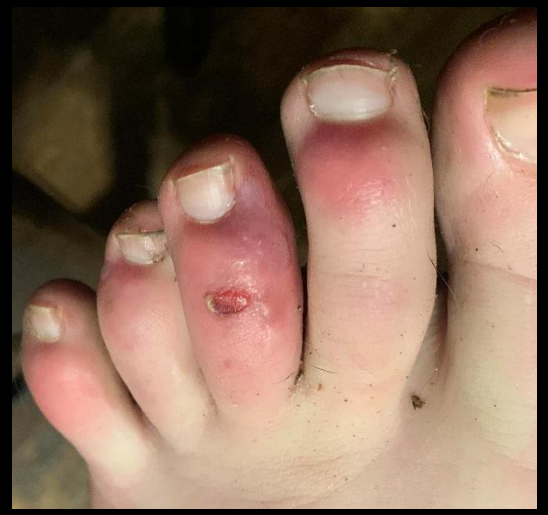

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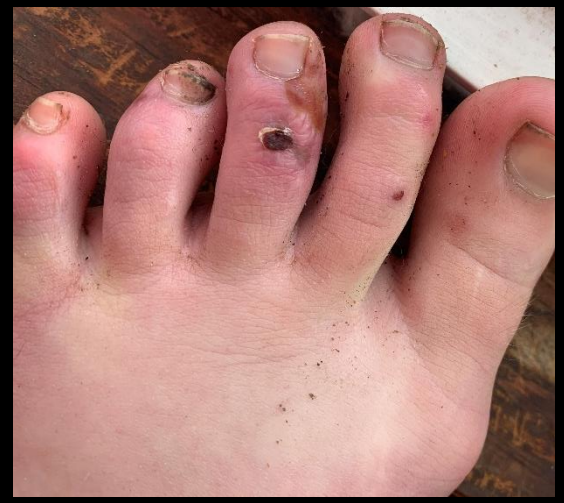
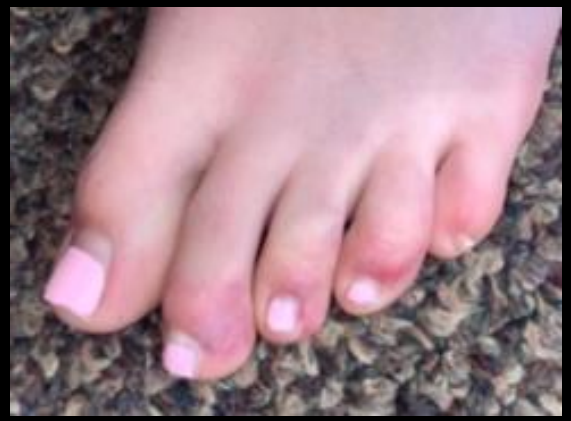


Apr 21

16 yo girl Apr 24



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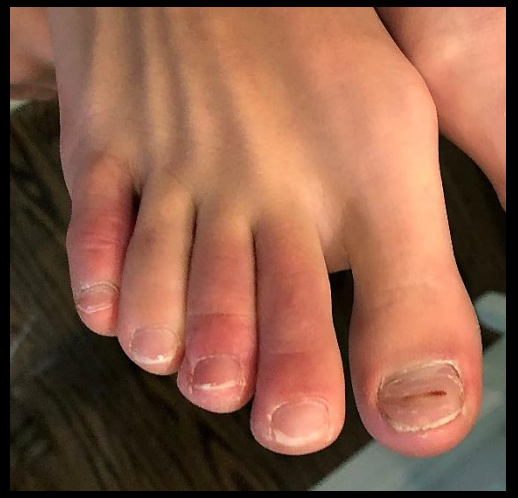
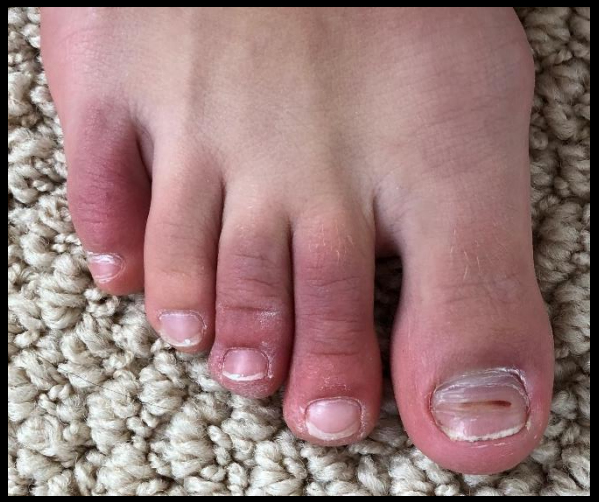
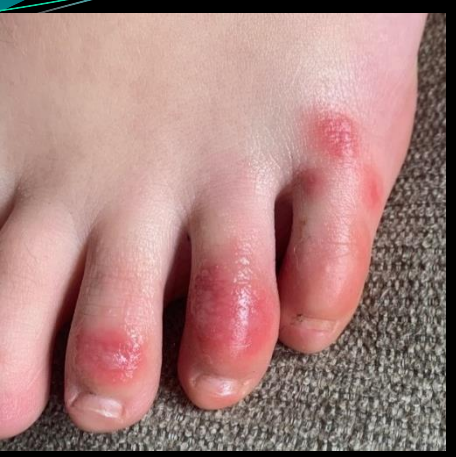
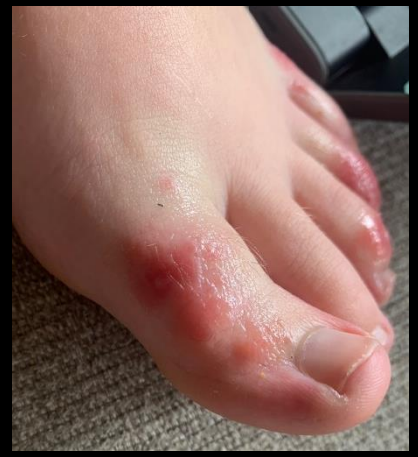


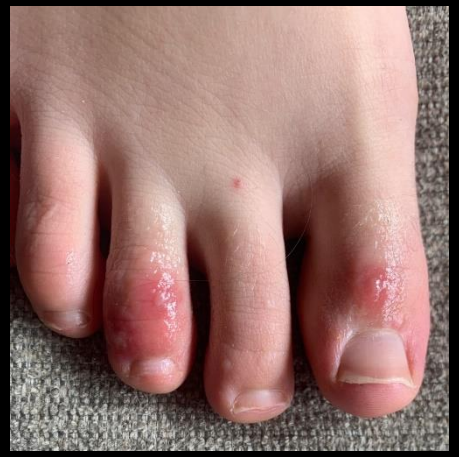


12 yo girl progression of a few days

Persistence for months is not rare; recurrences after improvement







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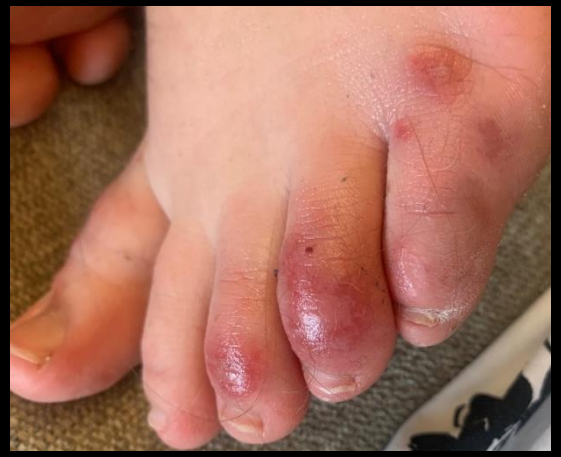

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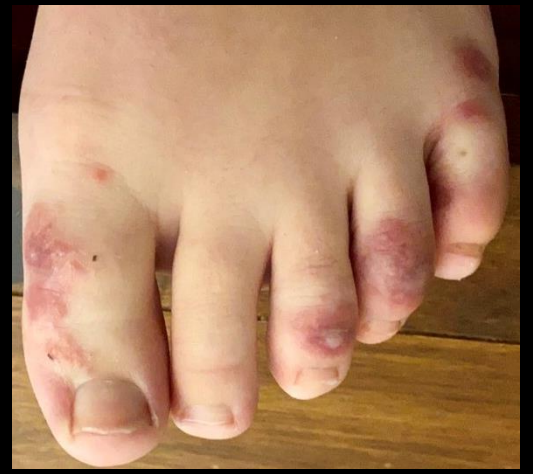

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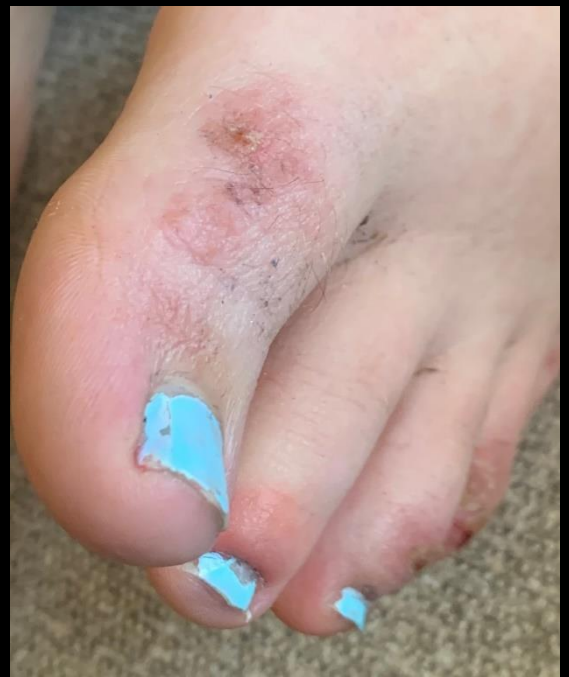

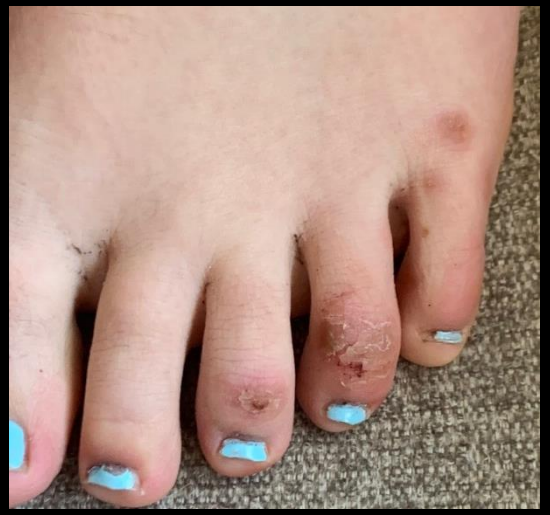

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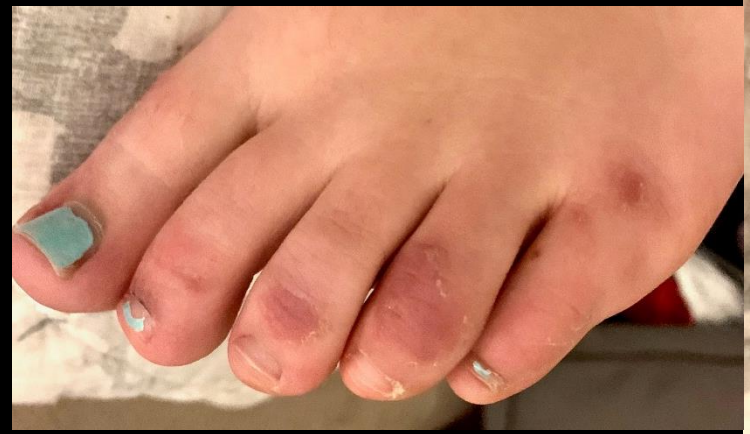
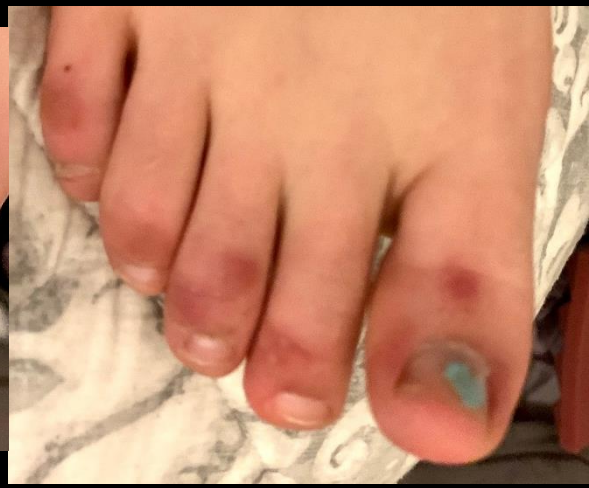
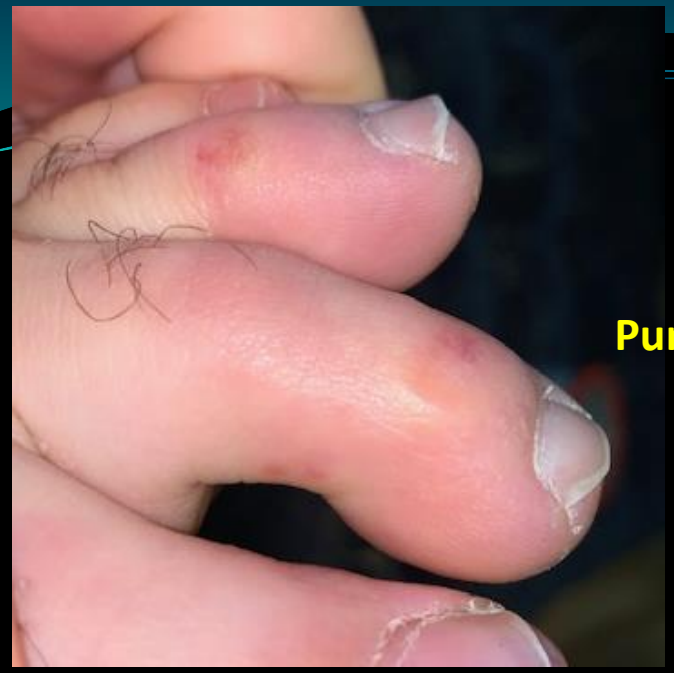


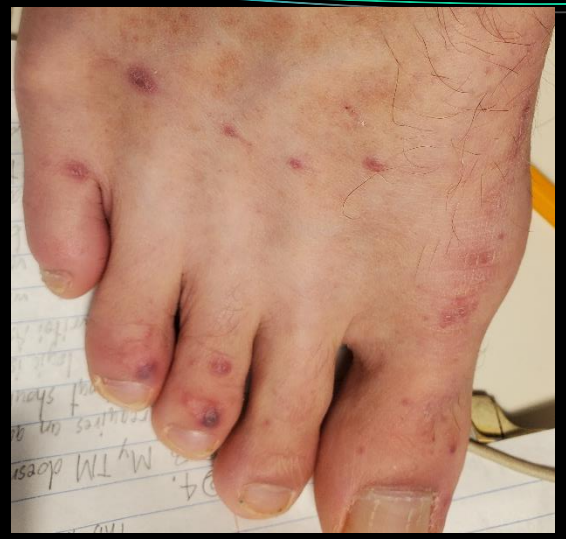


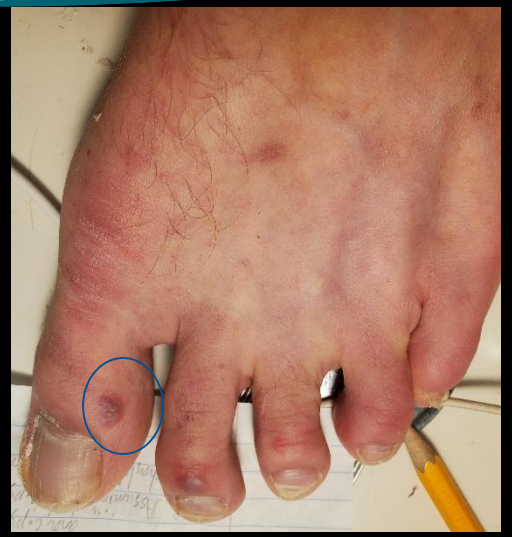
May 14

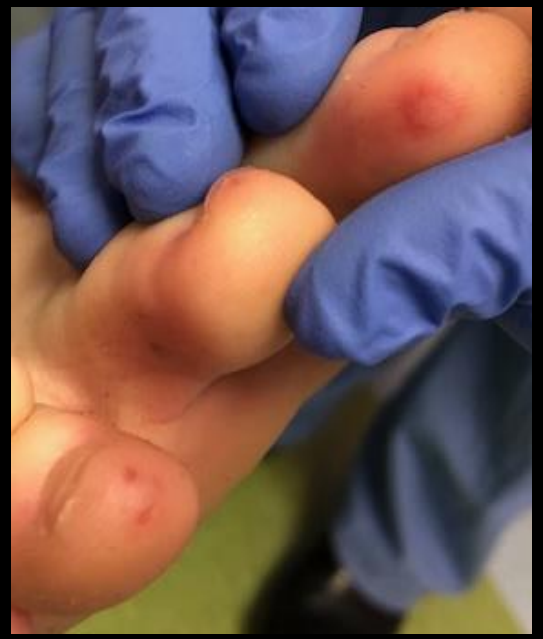


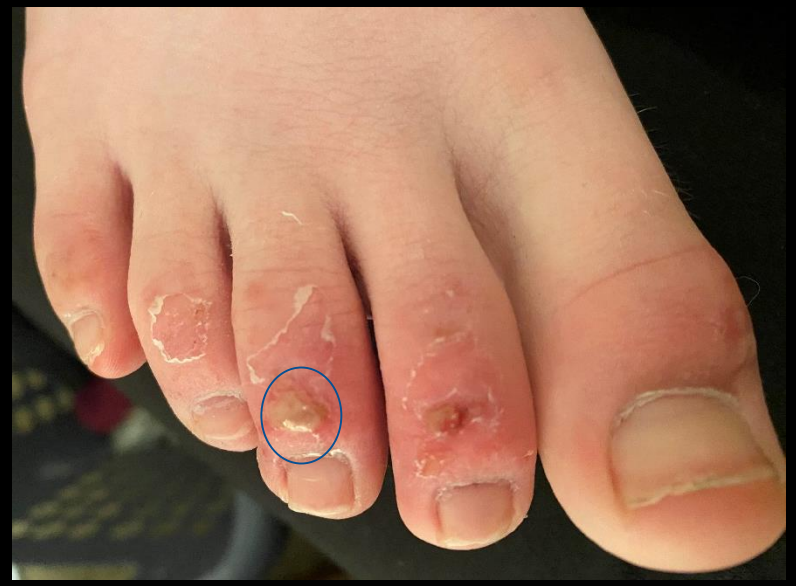
Purpuric macules

Hemorrhagic vesicles

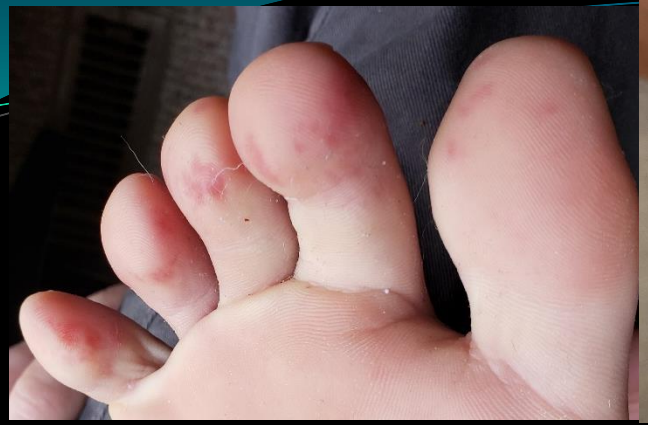
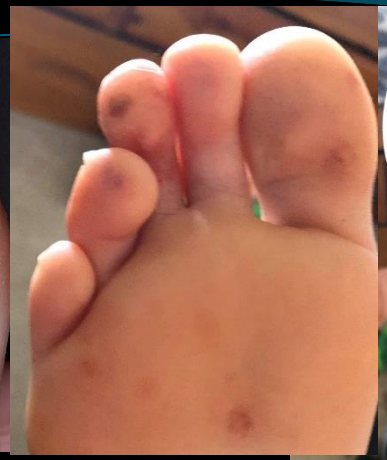
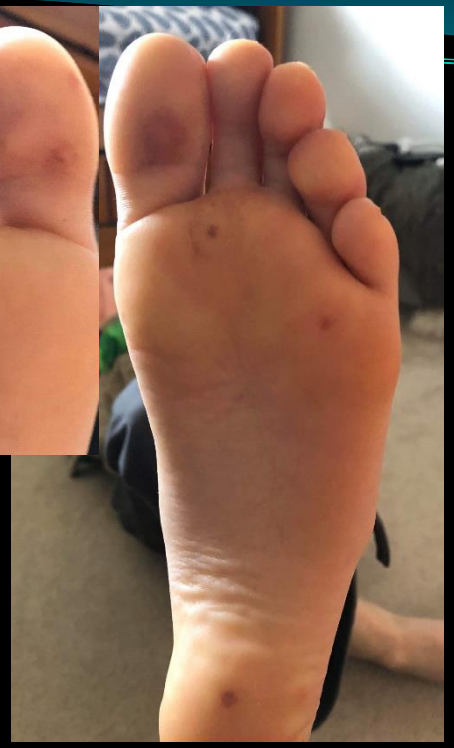
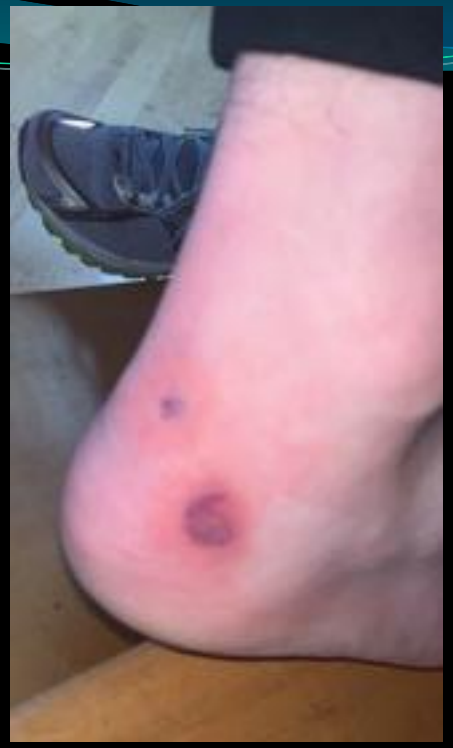
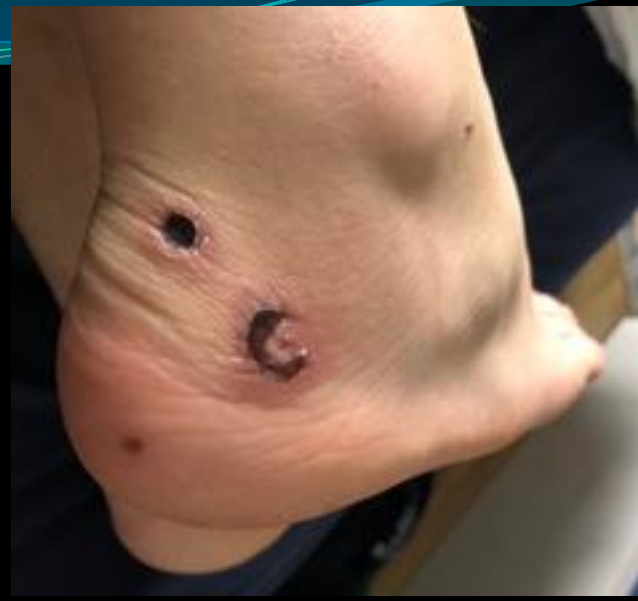
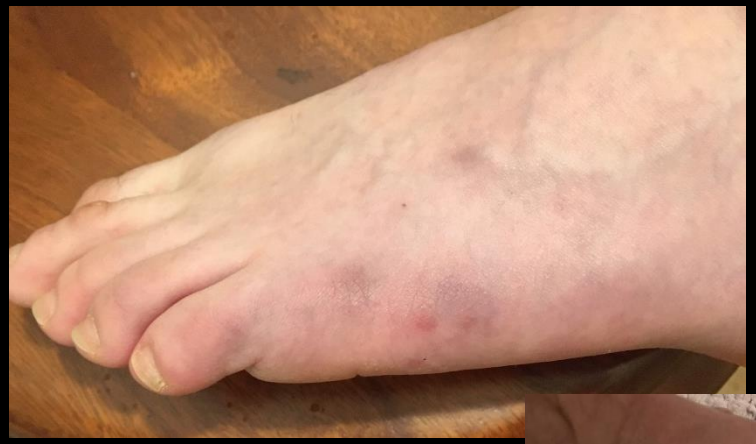






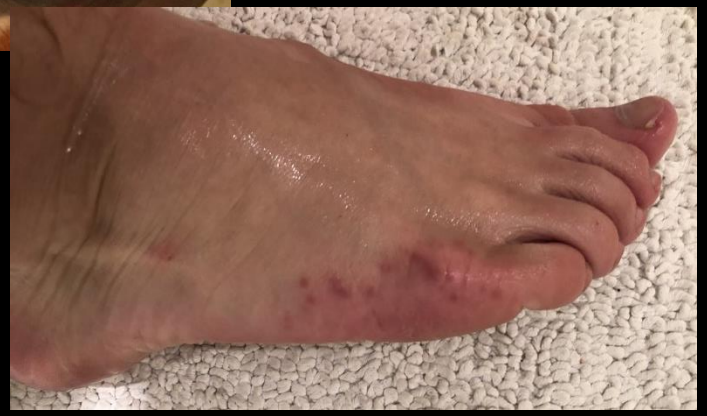
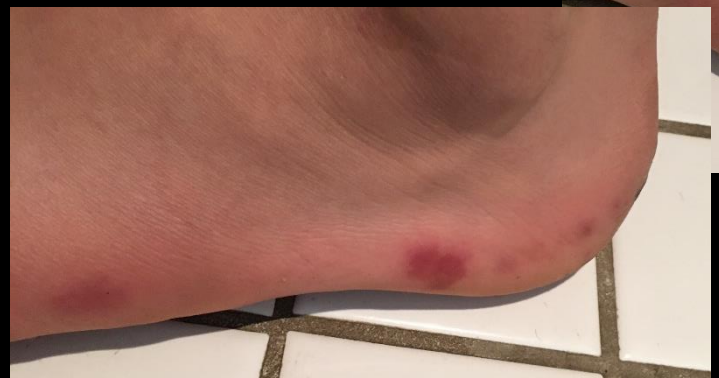
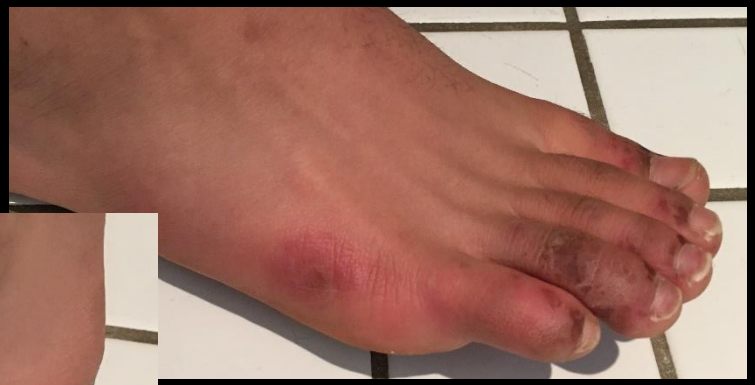


Pustules

Plantar surface, heels, lateral aspects

Infrequent on fingers (n=2)

"COVID toes"

Growing PeDRA registry (up to 112 cases)

https://pedraresearch.org/2020/04/20/covid-acral-ischemia-perniosis-in-children/

AAD registry: 28% pediatric cases (per Esther Freeman); low due to PeDRA's?
https://www.aad.org/member/practice/coronavirus/registry

81 patients <25 years old: clinical data and photographs from my "practice" (largely telederm) Apr 17 to May 13

- **64 children with "COVID toes" (5-17 years): Mean, 13.3 yrs; Median 14 yrs**
- **Male: Female 1.8:1**
- **Tops of toes only: 54 (84%); mean number of affected toes = 8.4**
- **Asymptomatic 22 (34%); pain only (28%); itch only (20%); itch+pain 11 (17%)**

Thanks to Sean Rangwani, FSM-NU M1, for helping to pull data together

"COVID toes"

- Only 8 (12%) children had systemic features that are linked to COVID-19 at presentation, including fever, cough, headache, sore throat (56 did not)
- 15 (23%) children had these viral signs in previous 3 wks (49 did not)
  - In entire cohort (n=81), 12% had nothing at presentation, but 31% had some signs of COVID-19 in the previous 3 wks
- 12 (19%) cases had already resolved but 27/45 (60%) had lasted more than 14 days already
- Few had known (2/ 3%) or possible (12/ 19%) COVID-19 exposure (including indirectly through parents)

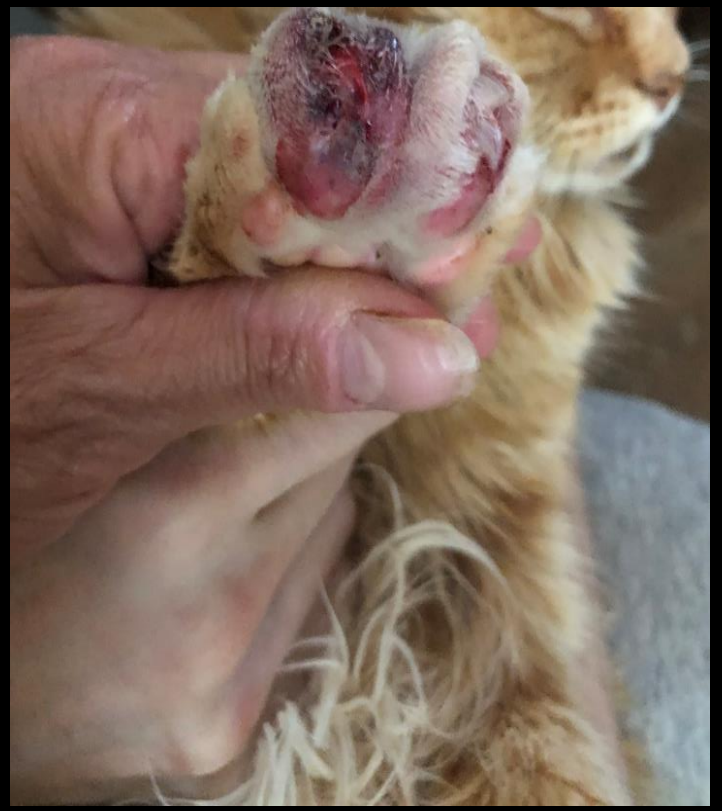
- Running around house barefoot?: Most do (but no control group)

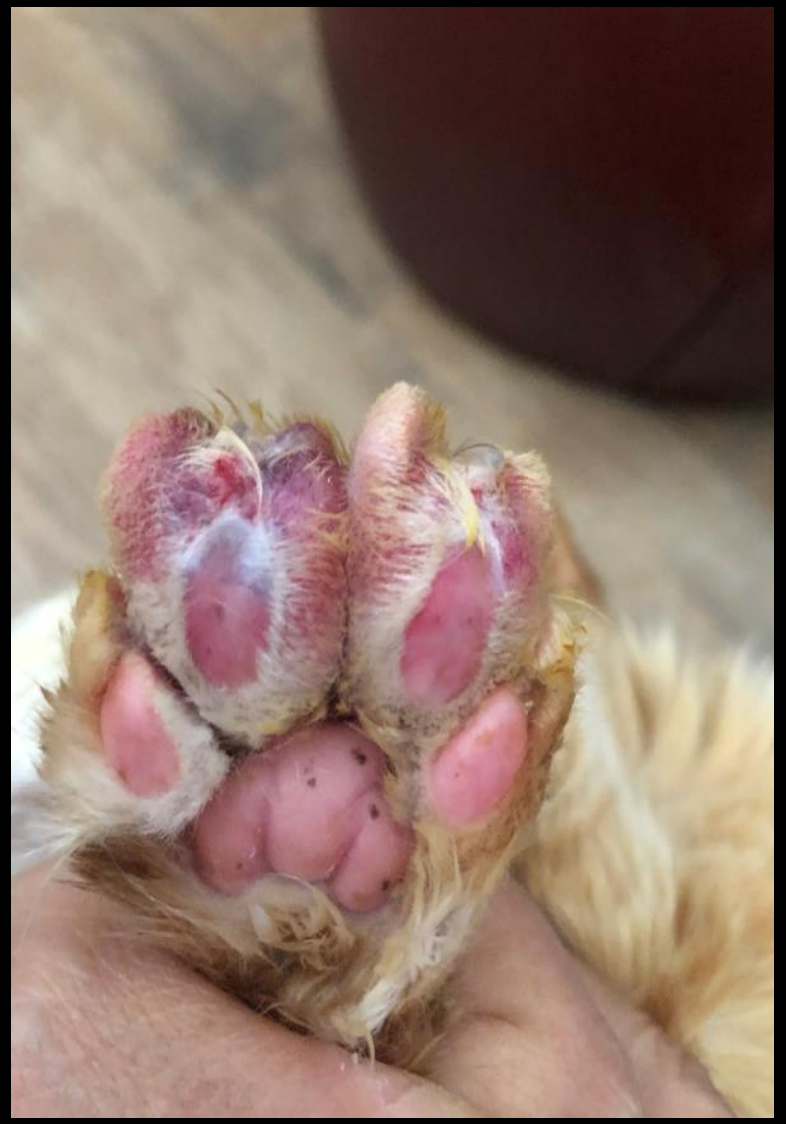
“COVID paws” – Two week history of paw pain and inflammation

“Does not feel well”

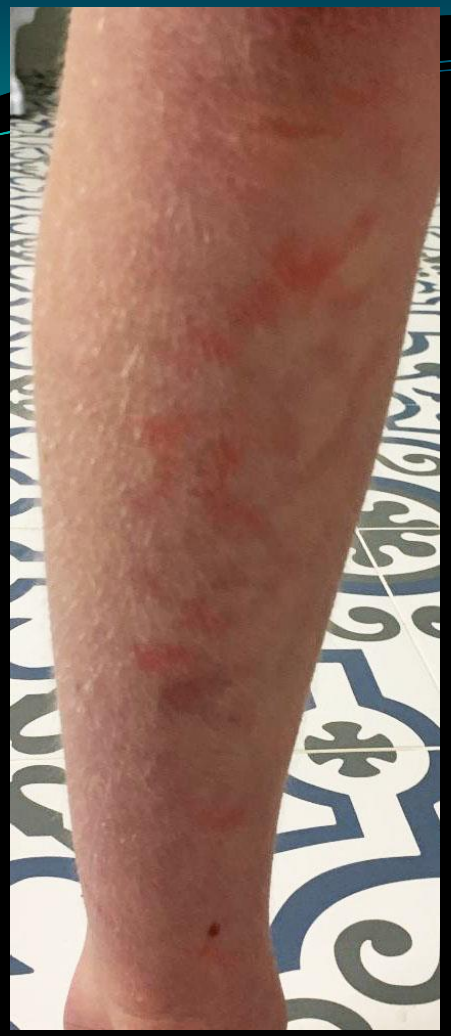
Evaluation yielded no underlying issue

Unresponsive to antibiotics or soaking

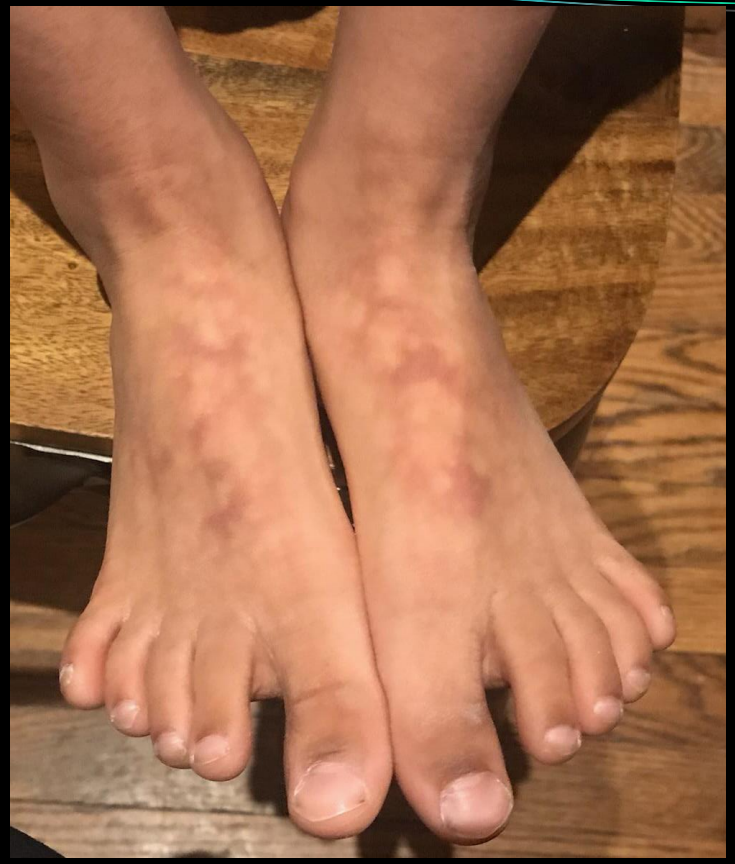




Livedo



8 yo girl
Livedo on legs
Lasted 2 days
Otherwise well
Both parents + IgM/IgG Ab

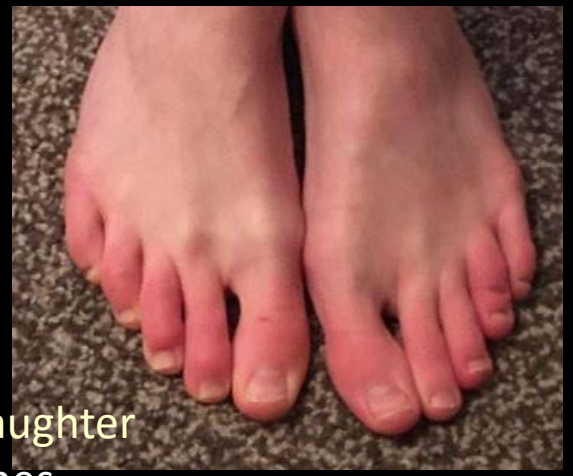


9 yo girl
Livedo on feet and ankles
Otherwise well

13 yo boy
Livedo on legs
Lasted 3 days; then fever, leg pain
Atomoxetine/ADHD 2 days before
11 yo sister developed similar rash in next few wks

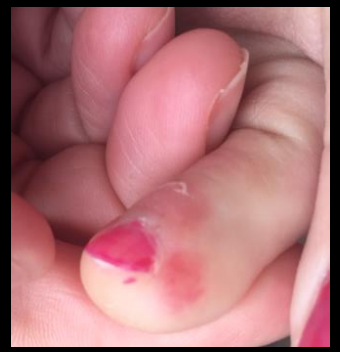
None had concurrent COVID toes

Catching COVID toes?

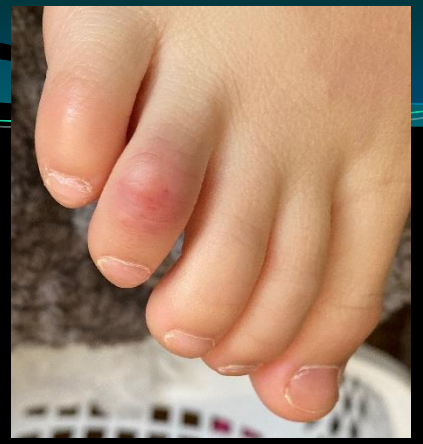


11 yo daughter
Headaches
Swollen, painful toes
x 10 d in March

In mid-April, mother (cough); Husband is exposure through work but COVID-



11 yo girl - sister

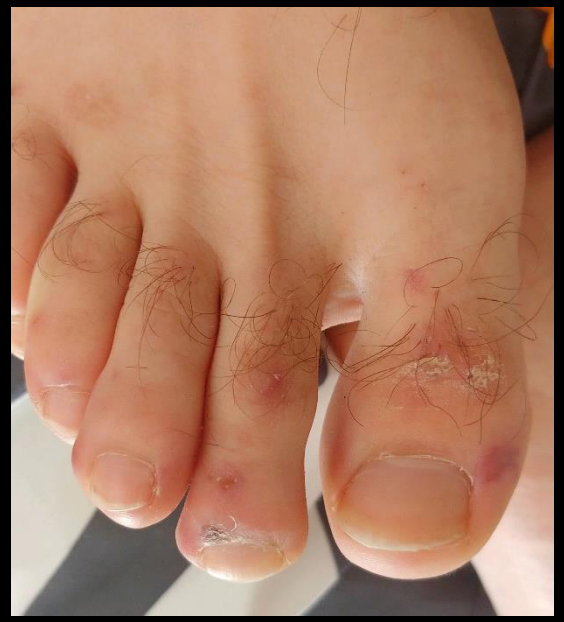


10 yo brother
2 days later

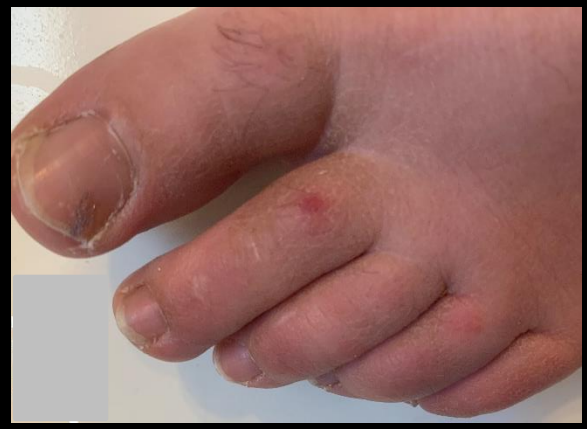
Mom – bad cough, fever, chills Feb: COVID-

Grandma COVID+ in nursing home, but no contact since before dx

4 yo sister with high fever but COVID- 1 wk before



Boyfriend (sides, bottom too) on March 29



Proband - Last saw boyfriend 3/29
Her toes (swollen, itchy) 4/13
Better 1 wk later, recurred 4/28

Male friend last in contact 3/29 and developed late April

Clusters recently reported

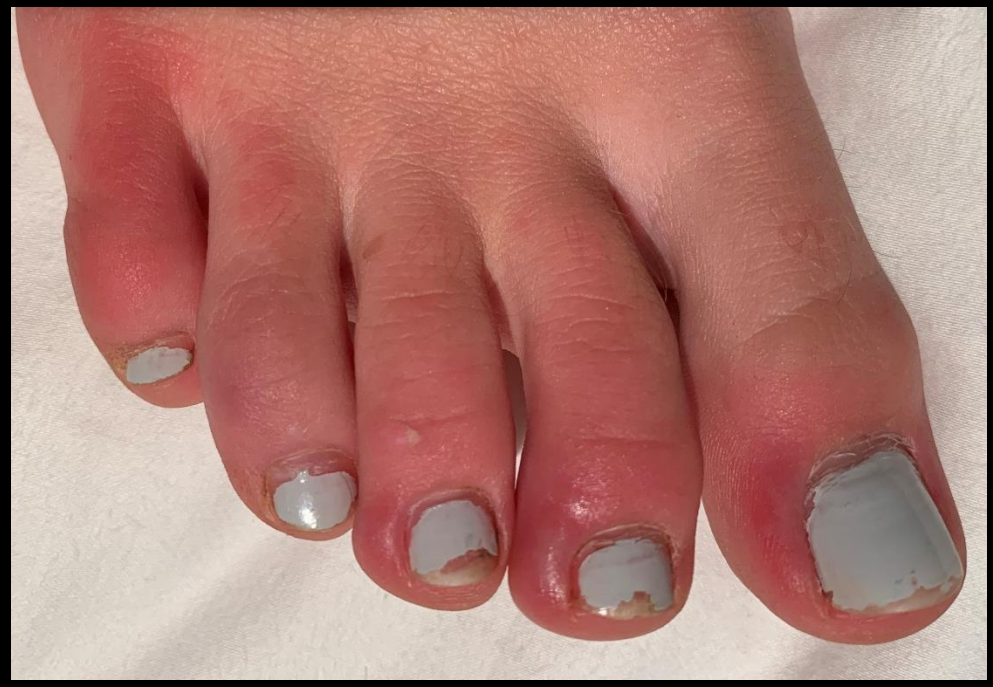
- 2 families, each with 3 children (12-17 yo) with purpuric acral lesions who presented in April
  - "COVID toes/feet", livedo
- Viral symptoms (not cough) 1 week before in some sibs
- No known COVID-19 contact
- Biopsies resembled pernio
- PCR testing negative

Cordoro et al. Pediatr Dermatol May 12 2020 {Epub]

- Testing to date: 7 negative PCR's; 1 positive PCR

4 negative antibody test

Only COVID PCR+ 12 yo girl



Itchy and painful, red, swollen toes with blistering

4 days later: Fatigue and Temperature 99.6°F

5 days later: Headache; PCR testing for COVID +

Largest case series in children from Spain

- 22 children (6-17 years; median 12 yo; M:F 1.44)
- All had foot involvement (only 3 on fingers); few on fingers (periungual)
- Pruritus (41%) or mild pain (32%)
- 1 - brother with “COVID toes”; 1 - confirmed COVID+ household contact
- Normal labs (d-dimer up in 1)
- COVID PCR + in 1/19 (5%); no known exposure, mild GI symptoms 2 days before
- Treatment oral analgesics (pain) and antihistamines (itch) for most
- Clear/near clear 3-5 wks after onset

Andina et al. Pediatr Dermatol May 9 2020 {Epub]

4 patients with chilblains also had EM-like lesions: Biopsies not typical of EM and IHC vs spike protein was + in endothelial and eccrine gland cells

Torrelo et al. Pediatr Dermatol – in press

How are we evaluating "COVID toes"?

- **Generally <u>not doing</u> evaluation: not major issue and "sheltering in"**
  - **A few scattered biopsies in children: all like pernio/ inflammatory without thrombi or immune complex vasculitis**

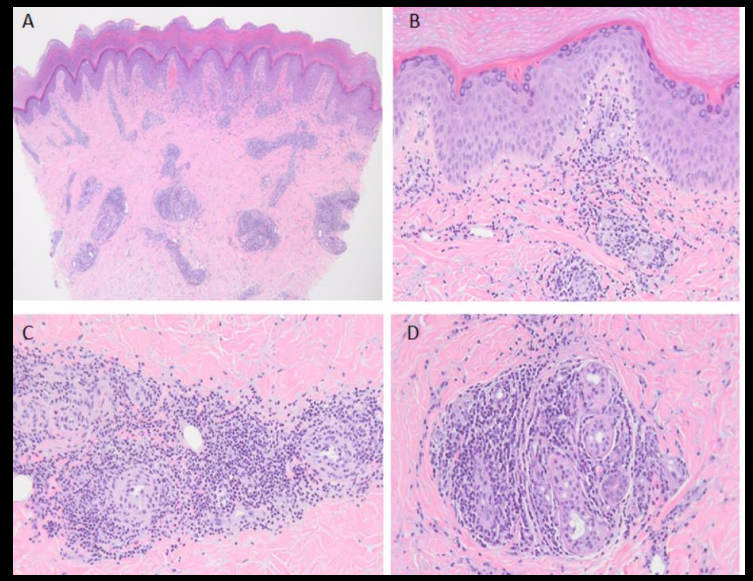
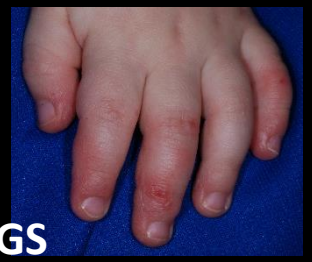
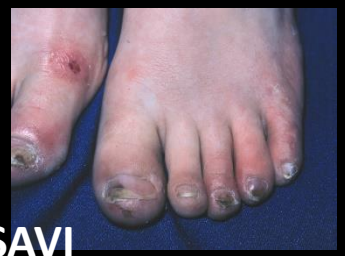


Image from Cordoro et al. Pediatr Dermatol May 12 2020 [Epub]

- **PeDRA list of labs to consider if severe:**
- CBC/differential
- CRP, ESR
- PT, PTT
- Anti-phospholipid antibodies/ ANA/ complements (C3/C4/CH50)
- Interferons; TNF
- Cryoglobulins/fibrinogens
- D-dimer and fibrinogen
- Sample for later testing



AGS



SAVI

How are we treating “COVID toes”?

- Depends on symptoms and severity
  - Often no treatment (does it matter to keep the toes warm?)
  - Topical steroids for pruritus; NSAIDs for pain
  - Topical nifedipine has been used
  - Anti-coagulants if evidence of coagulopathy
  - Have not heard of oral hydroxychloroquine or compounded JAK inhibitor use
- Unclear whether to quarantine and “track”: Most are at home and isolated, except for family

….Thanks for your attention and register your patients!