FMDA
Florida Society for Post-Acute and Long-Term Care Medicine

Healing Challenges Associated with COVID-19 Skin and Long-Haulers

Presenter

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Vice President of Clinical Affairs
AMT/Restorix Health

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OBJECTIVES

At the end of this presentation participants should be able to:

1. Recognize that COVID-19 causes multiple and varied skin manifestations;
2. Relate some of the COVID-19 skin disruptions to other skin manifestations that look similar to, but are NOT COVID-19 skin issues;
3. Discuss COVID-19 disease potential effects on unavoidable wounds and delayed wound healing outcomes.

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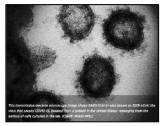
COVID-19 EPIDEMIC

- COVID-19 pandemic caused by SARS-CoV-2
  - Primarily triggers respiratory tract infections
  - Affects upper or lower respiratory tracts
  - Spreads same way other coronaviruses do
  - Mainly through person-to-person contact
  - Infections range from mild, moderate to severe to deadly outcomes



- Originally thought to be only respiratory disease
- Current research demonstrates significant extrapulmonary involvement
- **New variants** appear to cause less pulmonary involvement for most people

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CYTOKINE STORM & COVID-19

- Cytokines are part of immune system
- Causes acute hyperinflammatory response
- Immune cells spread beyond infected body parts
- Inflammatory response to infection
  - Attacks healthy tissues
  - Causes blood clots
    - Coagulopathy
    - Creates decreased blood flow to organs
- Skin is largest organ
- Blood flow and inflammatory processes often manifest on skin and mucous membranes

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PRIMARY SYMPTOMS OF COVID-19

- Fever (low, high, none)
- Coughing
- Shortness of breath
- Trouble breathing
- Fatigue
- Chills
- Body/muscle aches
- Headache
- Sore throat
- Loss of smell or taste
- Nausea
- Diarrhea
- Asymptomatic

Silent symptoms of COVID-19 include skin and mucocutaneous symptoms

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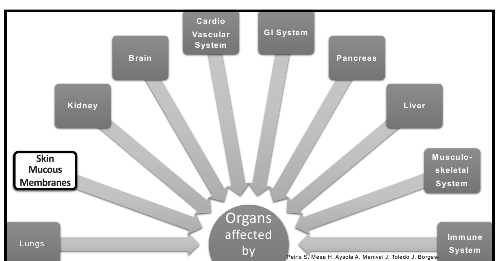

Young S, Fernandez AP. Skin manifestations of COVID-19. In COVID-19 Curbside Consultants. Cleveland Clinic. Posted May 7, 2020 https://www.ccjm.org/content/early/2020/05/12/ccjm.87a.ccc03

Peiris S, Mesa H, Aysola A, Manivel J, Toledo J, Borges-Sa M, et al. (2021) Pathological findings in organs and tissues of patients with COVID-19: A systematic review. PLoS ONE 16(4): e0250708

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LONG COVID NOMENCLATURE

- Post-acute sequelae of SARS-CoV-2 (PASC)-new formal name
- Post-COVID Syndrome (PCS)
- Long COVID
- COVID Long Haulers

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POST-ACUTE SEQUELAE OF SARS-COV2 INFECTION

- Described by WHO as persistence of symptoms or new symptoms more than 30 days post-SARS-CoV-2 infection
- CDC: 4 or more weeks after infection
- British NIH and Care Excellence (NICE): 12-weeks during or after infection; not explained by alternative diagnosis
- These longer effects of COVID-19 are actively being investigated and defined
- Clinical definition and understanding of underlying mechanisms of Long COVID are still in flux

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POST-ACUTE SEQUELAE OF SARS-COV2 INFECTION

- Lingering symptoms may persist months and in some cases years after the acute infection
- ICD-10 CM code for "post COVID-19 condition, unspecified"=U09.9
- Deployment of an ICD-10-CM code in US took nearly 2 years **after patients began describing their symptoms**
- Countries around the world are all dealing with Post COVID in their populations

Pfaff ER, Madlock-Brown C, Baratta JM, et al. Coding Long COVID: Characterizing a new disease through an ICD-10 lens. Preprint. *medRxiv*. 2022;2022.04.18.22273968. Published 2022 Sep 2. doi:10.1101/2022.04.18.22273968

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POST-ACUTE SEQUELAE OF COIVID: FACTS OVERVIEW

- Legacy of acute SARS-CoV-2 infection, affecting over 10-69% of patients with different signs and symptoms across a wide range of organs and systems.
- Most frequent manifestations of PASC, compromised lung functions, neurocognitive alterations; alterations of cardiovascular functions and increased risk of acute cardiac events; and fatigue.
- SARS-CoV-2 virus seeds and persists in different organs and tissues.
- Pathogenesis of PASC is multifactorial and includes:
  - Virus seeding and persistence in different organs; activation and response to unrelated viruses (e.g., EBV); autoimmunity; uncontrolled inflammation.
- Biomarkers of clinical PASC include levels of IgG, cytokines, chemokines, PTX3, and interferons.

- Mantovani, A., Morrone, M.C., Patrono, C. *et al.* Long Covid: where we stand and challenges ahead. *Cell Death Differ* **29**, 1891–1900 (2022).
- Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185(5):881-895.e20. doi:10.1016/j.cell.2022.01.014

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POTENTIAL CONTRIBUTORS TO PASC SYMPTOMS

Include consequences from acute SARS-CoV-2:

- Injury to one or multiple organs,
- Persistent reservoirs of SARS-CoV-2 in certain tissues,
- Re-activation of neurotrophic pathogens such as herpesviruses under conditions of COVID-19 immune dysregulation,
- SARS-CoV-2 interactions with host microbiome/virome communities,
- Clotting/coagulation issues,
- Dysfunctional brainstem/vagus nerve signaling,
- Ongoing activity of primed immune cells,
- Autoimmunity due to molecular mimicry between pathogen and host proteins.

The individualized nature of PASC symptoms suggests that different therapeutic approaches may be required to best manage care for specific patients with the diagnosis.

Edward Galaid, MD, RSFH Medical Director of Occupational Medicine. Roper St. Francis Healthcare. Management of Post-Acute Sequelae of SARS CoV-Infections. https://www.youtube.com/watch?v=pw7AgO6GDUg YouTube Accessed 10/30/22

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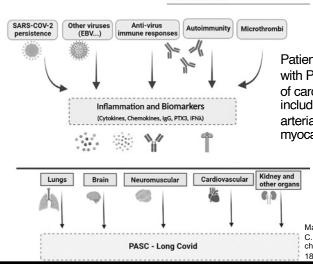
A. Mantovani et al.



Patients/residents with PASC have an elevated risk of cardiovascular complications, including pulmonary embolism, arterial and venous thromboses, myocardial infarction, and stroke.

Mantovani, A., Morrone, M.C., Patrono, C. *et al.* Long Covid: where we stand and challenges ahead. *Cell Death Differ* **29**, 1891–1900 (2022).

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LONG COVID = POST-ACUTE SEQUELAE OF SARS-COV-2 (PASC)

- Research indicated an ongoing, sustained inflammatory response following mild, moderate, and severe SARS-CoV-2 infections
- *"We can show that the macrophages from people with mild COVID-19 exhibit an altered inflammatory and metabolic expression for three to five months post-infection,"*
- *"Even though the majority of these people did not have any persistent symptoms, their immune system was more sensitive than that of their healthy counterparts."*

Hetsouphanh, C., Darley, D.R., Wilson, D.B. *et al.* Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol* **23**, 210–216 (2022).

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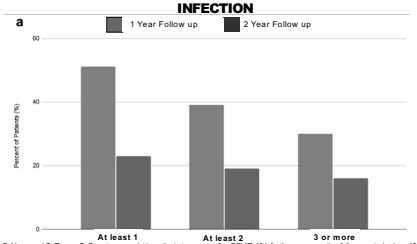
TOTAL NUMBER OF PERSISTENT SYMPTOMS AFTER COVID-19 INFECTION



Millet C, Narvaneni S, Roman S. Symptoms persist in patients two years after COVID-19 infection: a prospective follow-up study. June 16, 2022. Clin Microbiology and Infection/ European Society of Clinical Microbiology and Infectious Diseases. Accessed 10/28/22

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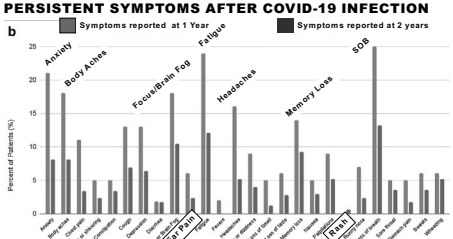
PERSISTENT SYMPTOMS AFTER COVID-19 INFECTION



Millet C, Narvaneni S, Roman S. Symptoms persist in patients two years after COVID-19 infection: a prospective follow-up study. June 16, 2022. Clin Microbiology and Infection/ European Society of Clinical Microbiology and Infectious Diseases. Accessed 10/28/22

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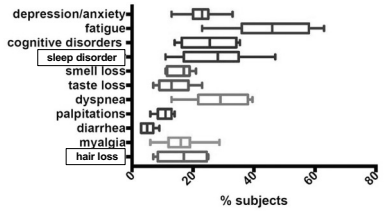
FREQUENCY OF MOST COMMON SYMPTOMS 4-WEEKS OR MORE AFTER ACUTE COVID-19 INFECTION



Mantovani, A., Morrone, M.C., Patrono, C. *et al.* Long Covid: where we stand and challenges ahead. *Cell Death Differ* **29**, 1891–1900 (2022).

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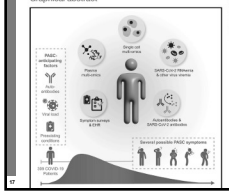
Cell

Article

Multiple early factors anticipate post-acute COVID-19 sequelae

Graphical abstract



Authors

Yapeng Su, Dan Yuan, Daniel G. Chen, ..., Mark M. Davis, Jason D. Goldman, James R. Heath

- Longitudinal multi-omics associate PASC with autoantibodies, viremia, and comorbidities
- Reactivation of latent viruses during initial infection may contribute to PASC
- Subclinical auto-antibodies negatively correlate with anti-SARS-CoV-2 antibodies
- Gastrointestinal PASC uniquely present with post-acute expansion of cytotoxic T cells

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COVID-19
Skin Manifestations

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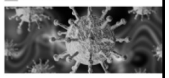
INITIAL COVID SKIN MANIFESTATIONS RECOGNITION IN HEALTHCARE

COVID-19 DERMATOLOGY REGISTRY



- April 2020 International League of Dermatological Societies and American Academy of Dermatology established international registry for COVID-19 dermatological manifestations
- At the same time, clinicians in LTC facilities reporting skin manifestations that looked like pressure injuries, but were NOT related to pressure
- Also, anecdotally, residents with wounds that HAD been improving began to stall or get worse after surviving COVID-19
- April 2020 the journey to learn about COVID skin manifestations began

https://www.aad.org/member/practice/coronavirus/registry

Mantovani, A., Morrone, M.C., Patrono, C. *et al.* Long Covid: where we stand and challenges ahead. *Cell Death Differ* **29**, 1891–1900 (2022).

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WHY IS KNOWLEDGE REGARDING COVID-19 SKIN SYMPTOMS IMPORTANT?

- Early detection of skin and mucosal symptoms can assist with early diagnosis of COVID-19

Urticaria=hive-type rash

Psuedo-chilblain Acral Lesion

Mucocutaneous

Livedoid/Necrotic lesions

Attribution: British Journal of Dermatology

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HOW DOES SARS-COV-2 VIRUS INFECT THE SKIN?

Direct Infection of Endothelial Cells	**Indirect** Infection of Endothelial Cells
• Small blood vessels in skin are targets for SARS-CoV-2 • Lymphocyte skin infiltration in patients with COVID-19 • Evidence that virus enters skin through blood vessels after systemic infection	• Superficial layers of skin prevent viral entry with normal conditions • Skin disruptions (e.g., wounds) • May allow contamination of underlying tissues

Khezri, Mohammad Rafi; Ghasemnejad-Berenji, Morteza PhD; Jafari, Reza PhD Skin Tissue: A Place for SARS-CoV-2 to Multiply and Transmit?, Advances in Skin & Wound Care: October 2021 - Volume 34 - Issue 10 - p 513-514

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SARS-CoV-2 VARIANTS SURVIVAL ON SKIN

- Researchers found different variants of virus survive on skin of cadavers for differing durations:
- Original version of SARS-CoV-2 survives for 8.6 hours
- Alpha variant survives for 19.6 hours
- Beta variant survives for 19.1 hours
- Gamma variant survives for 11 hours
- Delta variant survives for 16.8 hours
- Omicron variant again outlasts the other variants, surviving for 21.1 hours

Differences in environmental stability among SARS-CoV-2 variants of concern: Omicron has higher stability. Hirose R, Itoh, Y, Ikegaya H, Miyazaki H, et.al. bioRxiv 2022.01.18.476607; doi: https://doi.org/10.1101/2022.01.18.476607 Accessed 3/11/22

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CLASSIFICATION OF HISTOPATHOLOGICAL FINDING IN THE SKIN OF COVID-19 CASES

• Endothelial Injury	Endotheliitis
• Coagulopathy associated abnormalities	Petechiae Dermal necrosis Dermo-hypodermal/superficial thrombi Deep dermis thrombi
• Vasculitis	Livedo Purpura Subcutaneous lymphocytic vasculitis Lymphocytic infiltration of vessels
• Possible cytopathic effects	Intranuclear viral inclusions Multinucleated cells Intraepidermal vesicle Dyskeratosis Necrotic keratinocytes

Pathological findings in organs and tissues of patients with COVID-19: A systematic review
Crossref DOI link: https://doi.org/10.1371/JOURNAL.PONE.0250708; 4/28/21. Accessed 3/11/22

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NON-SPECIFIC FINDINGS ASSOCIATED WITH SKIN INFLAMMATION (DERMATITIS)

- Exocytosis
- Spongiosis
- Acantholysis
- Vesicles
- Suprabasal clefts
- Dermal edema
- Vascular ectasia
- Dermal mucin
- Dermal eosinophils
- Superficial dermal inflammatory infiltrates
- Perivascular deep inflammation
- Peri-eccrine inflammation
- Lymphocytic panniculitis
- Parakeratosis

Pathological findings in organs and tissues of patients with COVID-19: A systematic review
Crossref DOI link: https://doi.org/10.1371/JOURNAL.PONE.0250708; 4/28/21. Accessed 3/11/22

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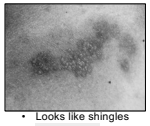
SKIN RASHES PREDICTIVE SYMPTOM OF COVID-19

- Virus causes wide variety of skin symptoms
- These skin changes may have diagnostic value for SARS-CoV-2 infections
- Support studies suggest that skin rash may be predictive symptom of COVID-19 infection

In nine percent of cases, dermatologists identified outbreaks of small blisters, commonly itchy, that appeared on the trunk of the body



- Looks like shingles
- **Is COVID-19**

Bataille V, Visconti A, Rossi N, Murray B et. al. Diagnostic value of skin manifestations of SARS-CoV-2 infection.
Young S, Fernandez AP. Skin manifestations of COVID-19. In COVID-19 Curbside Consultants. Cleveland Clinic. Posted May 7, 2020.

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WHAT IS THE DIAGNOSTIC VALUE OF NEW SKIN RASHES IN SARS-COV-2 INFECTION?

- Study. 336,847 UK users of the COVID Symptom Study app
- Results:
  - 8.8% (~30,000 patients) positive SARS-CoV-2 viral swab, reported a skin eruption
- Skin symptoms first: **15% – 17%**
- Skin symptoms during illness: **47%**
- Skin symptoms after illness: **35% – 39%**
- Skin symptoms only: **21%**
- This site has a large library of high-quality photos: https://covidskinsigns.com

Attribution:
• British Association of Dermatologists

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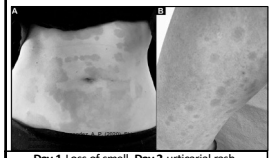
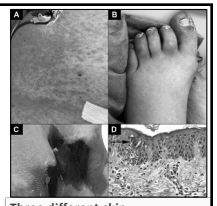
COVID-19 Cutaneous Manifestations



Day 1-Loss of smell, **Day 2**-urticarial rash, **Day 3**-onset of fever



Three different skin manifestations in same patient.

Galván Casas, C., Catalá, A., Carretero Hernández, G., Rodríguez-Jiménez, P., Fernández-Nieto, D., Rodríguez-Villa Lario, A., ... & García-Gavín, J. (2020). Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. British Journal of Dermatology, 183(1), 71-77.

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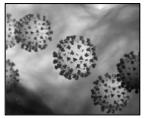
True Incidence of COVID-19 Related Skin Injuries Currently Unknown



- Many of the skin changes mimic known dermatologic disorders including pressure injuries, Kennedy Terminal Ulcer, and arterial insufficiency wounds

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COVID-19 Skin Manifestations

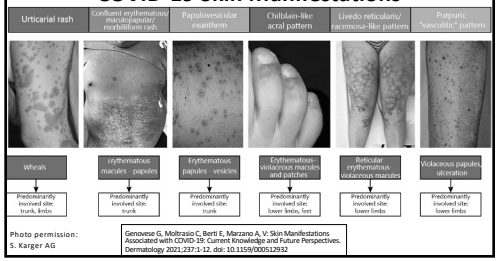

Photo permission: S. Karger AG

Genovese G, Moltrasio C, Berti E, Marzano A, V: Skin Manifestations Associated with COVID-19: Current Knowledge and Future Perspectives. Dermatology 2021;237:1-12. doi: 10.1159/000512932

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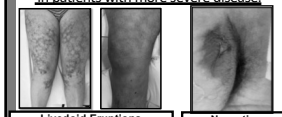
COVID-19 Cutaneous Manifestations

- Report categorized skin findings in patients with suspected and confirmed COVID-19
- Livedoid and necrotic eruptions, which were noted in patients with more severe disease.



Livedoid Eruptions
Light Skin Skin of Color

Necrotic Eruptions

Galván Casas, C., Catala, A. C. H. G., Carretero Hernández, G., Rodríguez-Jiménez, P., Fernández-Nieto, D., Rodríguez-Villa Lario, A., ... & García-Gavín, J. (2020). Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. British Journal of Dermatology, 183(1), 71-77.

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CHILBLAIN-LIKE SYMPTOMS (COVID TOES)

Older Toes Younger Toes

- Acral lesions
- Affect hands and/or feet
- Red-purple discolored skin-light skin
- Darker skin tones in skin of color
- Can be painful and itchy
- Sometimes small blisters or pustules
- Appear late in disease
- Seen more often in children & young adults
- Reported in older adults too – same process?
- Appear to be result of hypercoagulation
- May lead to gangrene/amputations

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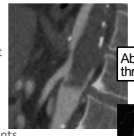
ACUTE LIMB ISCHEMIA AND COVID-19

- SARS-CoV-2 causes proinflammatory status (cytokine storm) with endothelial involvement
- Venous and arterial thrombosis
- Causing major vascular events such as acute arterial ischemia
- Anatomopathology of resected arterial segments
  - Inflammatory infiltrates & endothelial proliferations throughout arterial walls of aorta & femoropopliteal arteries
  - Resulted in amputation



Abdominal aortic thrombosis

Femoropopliteal thrombosis

Gonzalez CE, Gimenez G A, Rodriguez LL, Castro RJG, Martinez A, et al. Acute peripheral arterial thrombosis in COVID-19. Role of endothelial inflammation. Br J Surg. 2020 Sep;107(10):e444-e445.

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ACUTE LIMB ISCHEMIA AND COVID-19

- Seen in patients with severe disease who experienced significant lung damage and fibrosis
- Initial presentation may be in form of:
  - Chilblains
  - Bullae
  - Acral cyanosis
  - Bruising
  - Blood blisters
  - Dry gangrene
  - Life-threatening acute limb ischemia
- Any delay in diagnosis and/or treatment may lead to increased morbidity, including limb loss

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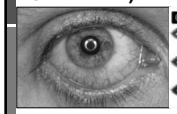
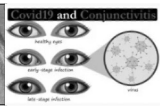
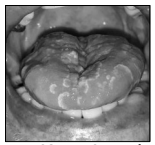
MUCOCUTANEOUS SYMPTOMS (EYES, TONGUE, GENITALIA) REPORTED





- COVID-19 Eye
- Secondary symptom in 3-15% of cases
- Self-limiting
- No ocular long-lasting complications reported



- COVID-19 Mouth

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MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) AND ADULTS (MIS-A)

- Like MIS in children (MIS-C), MIS-A associated with COVID-19
- Don't know the exact causes MIS-A
- Appears the condition develops due to a dysfunctional immune response after having COVID-19
- Unclear why some people develop MIS-A and others don't
- Differences in immune system and genetics between individuals may play a role
- COVID-19 causes high levels of inflammation in the body
- This is often accompanied by respiratory distress
- MIS-A is different in that it doesn't always happen with respiratory symptoms
- Organ systems outside of lungs are often affected
- Care should be given in the hospital setting

Skin Manifestation Child with Multisystem Inflammatory Syndrome in Children MIS-C

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SYMPTOMS OF MULTISYSTEM INFLAMMATORY SYNDROME IN ADULTS (MIS-A)

Primary Clinical Criteria
- Severe cardiac illness
- Rash and mucocutaneous symptoms

Secondary Clinical Criteria
- New-onset neurologic signs and symptoms
- Shock or hypotension not attributable to medical therapy
- Abdominal pain, vomiting diarrhea
- Thrombocytopenia (platelets <150,000/mL)

https://www.cdc.gov/mis/mis-a.html

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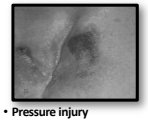
DIFFERENTIAL DIAGNOSIS

Deep Tissue Pressure Injury

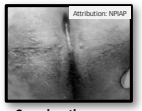


- Pressure injury
- Usually avoidable
- Deep: Bone/Muscle interface

Kennedy Terminal Ulcer Skin Failure

- Organ failure
- Unavoidable
- Superficial/Deep

COVID Skin Damage



- Coagulopathy
- Unavoidable
- Superficial

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OMICRON VARIANT SKIN SYMPTOMS

- Overall symptoms described as milder than earlier variants
- Symptoms similar to those of common cold in some people
- Omicron skin manifestations include:
  - Rashes
  - Dry lips
  - Grey/blue-tinged lips or nailbeds

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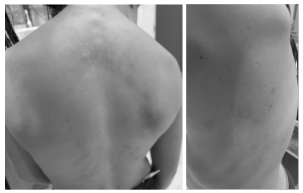
COVIC-19 RASH 1ST SYMPTOM IN 15 Y/0 JANUARY 2022 PCR POSITIVE FOR COVID-19 PROBABLY OMICRON VARIANT



- Skin manifestations reported with Omicron variant
- Similar to previous variants but fewer reports.

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SKIN & MUCOUS MEMBRANE SYMPTOMS REPORTED WITH OMICRON VARIANT

- Chilblain-acral lesions-fingers/toes
- Chapped or sore lips
- Xerostomia (dry mouth)
- Oral lesions
- COVID tongue
- Dry skin
- Other rash-like symptoms

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DOCUMENTATION BY PROVIDERS AND WOUND SPECIALISTS FOR COVID SKIN/WOUND HEALING ISSUES

Dr. Vycki Nalls, PhD, GNP-BC, ACHPN, CWS

- *"Wound healing: secondary effects from COVID-19 due to hypoxia, poor nutritional intake, and debility.*
- *Delayed wound healing expected due to these effects, and it would not be a surprise if the wound does not heal or declines further given patient's declining status."*

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ICD-10 DOCUMENTATION FOR DR. NALLS' PATIENT

- **L89.150 Pressure ulcer of sacral region, unstageable (HCC 158)**
  - Unstageable pressure injury to sacrum, with delayed wound healing due to co-morbid conditions of hypoxia, poor nutrition, debility, and overall decline from COVID-19 infection.
- **U07.1 COVID-19**
  - COVID positive patient with decline for aggressive management.
- **D68.8 Other specified coagulation defects (HCC 48)**
  - Coagulopathy due to COVID-19.

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ICD-10 CODES FOR COVID-DERMATOLOGIC MANIFESTATIONS

- **Use U07.1** as first diagnosis for patients with confirmed COVID-19.
- Add an additional diagnosis for pneumonia or other conditions, or symptoms.
- **D68.8** - is a specific ICD-10 code to indicate a diagnosis of other specified coagulation defect. COVID toes/fingers (acral lesions)
- **L99** - specifies a diagnosis of other disorders of skin and subcutaneous tissue in diseases classified elsewhere (rashes).

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COVID LONG-HAULERS AND THE SKIN

- Persistent morbidity noted in all systems of the body including skin
- **Urticarial and morbilliform** eruptions - short duration
- **Papulosquamous** eruptions, particularly **pernio** - longer-lasting
- American Academy of Dermatology data revealed previously unreported subset of patients who experience long-hauler symptoms in dermatology-dominant COVID-19
- Finding raises questions about persistent inflammation: even in patients who initially experienced relatively mild COVID-19
- More studies are needed to understand the long-hauler **dermatologic manifestations**

Carfì A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; **324**: 603–05.
10. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; **5**: 1265–73.

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LESSONS FROM PRACTICE-COVID SKIN MANIFESTATIONS

- Patients with COVID-19 may present with unusual skin manifestations, including urticarial rashes, vesicular lesions, and chilblains on fingers or toes
- These skin and mucous membrane manifestations may be the first sign of COVID-19 disease
- Most cutaneous manifestations of COVID-19 are self-resolving.
- Where treatment is appropriate, medium or high-potency topical corticosteroids, oral antihistamines, or systemic corticosteroids are usually sufficient for symptomatic relief
- Coinciding drug therapy reactions are a possible confounding factor for cutaneous manifestations of COVID-19

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OPEN QUESTIONS REGARDING PASC AND COVID SKIN MANIFESTATIONS

- Occurrence, mechanism, and significance of SARS-CoV-2 persistence in different organs?
- Mechanisms, targets, and significance of autommune reactions?
- Role of other viruses?
- Impact of host genetics and microbiome?
- Actual impact of vaccination in people who get breakthrough infections and its duration?
- Occurrence and severity of PASC after infection with future variants?
- Preventive and therapeutic approaches?

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QUESTIONS
Comments

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Thank You!

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