THE SKIN MANIFESTATIONS OF COVID-19 IN CHILDREN (PART III)

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Dermatopathology of cutaneous COVID-19 infection in children

A systematic review demonstrated that skin lesions are present in only 0.25% of 2445 pediatric patients in 119 published studies (130). Besides, biopsies from skin lesions in children with confirmed or suspected COVID-19 have rarely been described in the literature. Most of the histopathological descriptions come from isolated cases or small series and some lesions have only been biopsied in adults. Since cutaneous lesions may be related to the direct effect of the virus and/or to the immune responses secondary to the infection, histological findings may reflect the direct cytopathic effect of the virus or secondary inflammatory responses.

Histology often follows usual patterns (table 1)

Table 1 – Table of histological appearances of COVID-19 associated rashes in children

Presentation	Histological appearance	Immunohistochemistry	Has the virus been present in the biopsied tissue
Chillblains (Figure 1) (15,16,39,44)	Moderate to dense superficial and deep perivascular lymphocytic infiltrate, exocytosis to the epidermis and acrosyringia, perieccrine accentuation, necrotic keratinocytes, mild vacuolar degeneration of the basal layer, papillary dermal oedema and spongiosis. Lymphocytic	T cell infiltrate with a predominance of CD4 over CD8 T lymphocytes. Scattered CD30+ cells are occasionally observed. Mature B cells represent a minor proportion of the infiltrate	Presence of cytoplasmic granular positivity for SARS-CoV-2 spike protein in endothelial cells in upper dermis and epithelial cells of the secretory portion of eccrine glands Round membrane-bound structures within the cytoplasm

	vasculitis fibrinoid necrosis, endothelialitis and thrombosis, red cell extravasation and dermal oedema		of endothelial cells showing an electro-lucent centre, and surrounded by tiny spikes in keeping with viral particles
Maculopapular eruptions (74, 131)	Superficial perivascular dermatitis with slight exocytosis, swollen thrombosed vessels with neutrophils, eosinophils and nuclear debris. Cuffs of lymphocytes surrounding blood vessels, focal acantholytic suprabasal clefts with dyskeratotic and ballooning herpes-like keratinocytes , groups of apoptotic keratinocytes in the epidermis(74).		
Erythema multiforme (20, 56)	Normal epidermis. Spongiosis and mild vacuolar interface damage and exocytosis of lymphocytes. A superficial and deep perivascular and perieccrine lymphocytic infiltrate reaching the adipose tissue. No eosinophils. Vascular ectasia and mild features of lymphocytic vasculitis, but fibrinoid necrosis and thrombosis were absent.	T cell infiltrate with a predominance of CD4 over CD8 T lymphocytes. Scattered CD30+ cells are occasionally observed. Mature B cells represent a minor proportion of the infiltrate	Positivity for SARS-CoV/SARS-CoV-2 spike protein was demonstrated in endothelial cells and epithelial cells of eccrine glands
Purpuric and livedoid patterns (Andina D, personal communication, 46, 135)	Dilated superficial dermal vessels lined by swollen endothelial cells and significant red cell extravasation around the vessels, multiple thrombi occluding most small-sized vessels of the superficial and mid-dermis, pauci-inflammatory thrombogenic vasculopathy, was demonstrated	IgM, C3, and fibrinogen within dermal vessel, C9 deposition, with deposition of C5b-9 and C4d in the cutaneous microvasculature	Cytoplasmic granular positivity for SARS-CoV/SARS-CoV-2 spike protein was detected in the cytoplasm of endothelial cells and epithelial cells of eccrine glands, COVID-19 spike glycoproteins in the cutaneous microvasculature

Urticarial rashes

As far as we are aware, no reports on histological features of urticarial rashes have been published in children. Histology in adults reveal perivascular infiltrates of lymphocytes, eosinophils and upper dermal edema (63) and vacuolar-type interface dermatitis with occasional necrotic keratinocytes without the presence of eosinophils, resembling erythema multiforme (131).

Vesicular exanthem

Biopsies from vesicular lesions in adults with COVID-19 have shown suprabasal intreapidermal unilocular vesicles with prominent non-ballooning acantholysis and eosinophilic dyskeratosis, with a striking “pomegranate-like” aspect. No nuclear atypia or large multinucleated cells were noted. No vasculitis was seen. Direct immunofluorescence and SARS-CoV-2 PCR tests performed on vesicles were reported to be negative (85). The findings described can mimic other acantholytic disorder like autoimmune or familial pemphigus or Grover’s transient acantholytic dermatosis (132) and it is important to rule out herpetic infection (133,134).

Purpuric and livedoid lesions

In a case series of adult patients with COVID-19 and purpuric skin lesions, a pauci-inflammatory thrombogenic vasculopathy, with deposition of C5b-9 and C4d and a co-localization of COVID-19 spike glycoproteins and C5b-9 and C4d in the cutaneous microvasculature was demonstrated (46).

Pityriasis rosea-like lesions

The histology of a digitate papulosquamous eruption reminiscent of pityriasis rosea in an adult patient revealed mild diffuse epidermal spongiosis, and spongiotic vesicles containing lymphocytes and Langerhans cells. Papillary dermis was slightly oedematous, and a mild lymphohistiocytic infiltrate was seen in the upper dermis (136).

Testing and management of children with COVID-19 skin disease

There is no test of high sensitivity and specificity for diagnosing COVID-19 featuring skin lesions in the paediatric population. Therefore, the epidemiologic context, the context of exposure to COVID-19, the personal history of flu signs, and the characteristics of cutaneous signs (acute signs, not very specific however) are key points that allow for a tentative diagnosis of COVID-19-related skin lesions in children.

Data published by the Chinese Novel Coronavirus Pneumonia Emergency Response Epidemiology Team showed that about 2% of the patients infected with COVID-19, or SARS-CoV-2 (out of 72,314 subjects) were children aged 0 to 9 years (137). The incubation period in children is usually about 2 days, with a range of 2-10 days. Children usually undergo more asymptomatic forms, less severe symptoms and better prognosis than adults (90,137,138). Because more than 90% of the children have asymptomatic, mild or moderate disease, the diagnosis of COVID-19 may be

overlooked. On the other hand, it may be necessary to characterize the cases of COVID-19 in children perfectly, for a better pandemic control.

Some indications for the proper testing and diagnosis of children with suspected COVID-19 is provided. Figure 2 shows an algorithm that can help clinicians to work-up children with skin rashes suspected of COVID-19 infection.

SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR)

The gold standard for confirmation of COVID-19 in subjects with clinical symptoms consists of testing samples taken from the respiratory tract to assess for the presence of nucleic acid targets specific to SARS–CoV-2. Nasopharyngeal swabs are the preferred choice for testing, although oropharyngeal swabs also are acceptable (Centers for Disease Control and Prevention. Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19). Accessed at www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html. on 05 June 2020). RT-PCR was shown to be very specific, but sensitivity is heterogeneous, thus negative results do not allow for excluding the infection. RT-PCR results varies over time, and testing is all the more positive as it is performed during the first days of symptoms (139).

RT-PCR testing is reported in the paediatric population who presented with COVID-19 related cutaneous signs (14-16,20,33,119,140). Among them, 68 had pseudo-chilblains, 4 had erythema multiforme, and one was a neonate with diffuse livedo associated with acute respiratory signs. Sixty-one among 69 underwent nasopharyngeal or oropharyngeal swabs for RT-PCR testing, and 59 (97 %) were negative. The 2 positive cases included a neonate with livedo (119), and a child with chilblains and associated erythema multiforme who had GI signs 2 days before occurrence of the chilblains (20).

The published data suggest that when skin manifestations are concomitant with general signs of viral infection, PCR might be positive and is thus recommended (however, with a low sensitivity), whereas when signs appear several days later, as is the case with pseudo-chilblains, testing is usually negative.

Search for other infectious agents

Among most of the adult patients diagnosed with COVID-19 with acute respiratory symptoms, the occurrence of concomitant respiratory viral infections (influenza viruses-A and -B, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Legionella pneumophila*, among others) has been reported in more than 50% cases (141). In children with isolated cutaneous signs, especially pseudo-chilblains, immunoassays for Parvovirus B19 were performed in 31 cases and they were either negative or in favour of an old infection (16,33). However, the associations with other infections were not looked for.

The published data suggest that there is no need to search for Parvovirus B19 antibodies by serologic immunoassays in children having COVID-19 related cutaneous signs.

Serologic immunoassays (COVID-19 IgM, IgG, IgA antibodies)

Various serological assays to determine antibodies against COVID-19, such as enzyme-linked immunosorbent assays, are currently available which provide information about the development of immunity against reinfection. With the available data, the utility of serologic assays for diagnosing acute COVID-19 infection seems limited. It has been shown that seroconversion occurs with a median time of 5-12 days for IgM antibodies and after 14 days for IgG and IgA (139,142). Cross-reactivity is also a potential problem(143). Cross-reactive antibody response has been shown between SARS-CoV-2 and SARS-CoV infection (144). Interestingly, SARS-CoV-2 CD4+ cells are detected in 40 to 60% of unexposed individuals. This result suggests that cross-reactive T cell recognition might exist between previous common cold coronavirus and SARS-CoV-2 (145).

We have very limited data on serologic assays in children with skin COVID manifestations, , but when performed they were negative for IgG and IgM in all cases (16,33,140). Only one patient showed positive IgA against COVID-19 (33). In an Italian series, specific serology against S1 domain of SARS-Cov-2 spike protein performed was positive in 6/19 cases for IgA, and in 1/19 for IgG (16).

The relevance of serologic assay in dermatologic conditions needs to be confirmed (146). The published data suggest that the presence of IgM and IgG by immunoassays has very low diagnostic relevance to cutaneous signs of COVID-19 in children. The observations related to presence of IgA antibody responses need to be further investigated.

Routine laboratory tests, inflammation markers and coagulation panels

Lab tests are necessary in presence of severe general symptoms of COVID-19 and in in case of cytokine storm syndrome and may require hospitalization. This is usually not the case for isolated skin lesions except when they are associated with general symptoms or persist beyond expected. Unwell patients may demonstrate decreased albumin (~75%), elevated C-reactive protein (~60%), elevated lactate dehydrogenase levels (~60%), and lymphopenia (~40%). No biomarker or combination of biomarkers currently exists that is sensitive/specific enough to establish a diagnosis of COVID-19, or to pragmatically predict its clinical course (138).

In most reported children with common COVID-19 related skin lesions who underwent routine lab tests, no significant abnormalities in serum chemistry were observed. The various coagulation markers were observed to be within the normal range in children except for D-dimer levels that were slightly raised in 3 cases, whereas most others had a value < 1000 ng/ml (14,15,33). Adult patients with acral cyanosis often have a hypercoagulable and disseminated intravascular coagulation (147).

In children with the severe disease PIMS, abnormalities in lab values have been extensively reported.

Markers of autoimmunity including ANA and cryoglobulins tested in 14 of the 69 published cases in children, showed no significant anomalies, except one child with COVID-19-related chilblains who had raised anti-cardiolipin IgG antibodies (33).

Interference of COVID-19 with chronic skin diseases in children

During the COVID-19 pandemic, follow-up for children affected by chronic diseases has been interrupted or moved to remote methods, especially in countries heavily

affected. Outdoor play, activities and even schooling in most cases has been interrupted.

A study to evaluate the influence of COVID-19 on the hospitalizations in a tertiary dermatology department in South West Poland, compared the number of hospitalized patients during COVID-19 pandemic with the same period in 2019 (148). Hospitalized children (2-18 years old) decreased from 81 (12.9%) in 2019 to 12 (6.8%) during the period of study, especially for patients with chronic inflammatory diseases (atopic dermatitis, lichen, eczema, psoriasis, urticaria, and pityriasis rubra pilaris) (148). Similar data have been reported in Italy (149,150). A study described the management of 6,890 patients with psoriasis, including 120 children, during pandemic in the major three reference centres for psoriasis in Sardinia, Italy; about 23% of patients were affected by severe psoriasis. The Italian drug agency (AIFA) declared an automatic renewal of the therapeutic plan of patients with rare diseases or under biologics treatment. However, the dermatologists found difficulties including limitations to face-to-face consultations for severe cases, high infection rate among dermatologists (40%, compared to the national average 7-8%), and cancellation of outpatient clinics (150).

Dermatological consultations in Konya (Turkey) during the pandemic were mainly carried out by teledermatology (72.8 % of consultations), which allegedly allowed for reducing the risk of disease transmission (151).

A task force of 37 expert paediatric dermatologists filled out a survey concerning the management of systemic immunosuppressive therapies for children during SARS-CoV-2 infection spread and developed educational contents for patients, caregivers and providers accessible online (152). Three main areas where analysed: (i) treatment initiation, (ii) treatment continuation and (iii) laboratory monitoring of systemic therapies. COVID-19 significantly affected the management of immunosuppressive medications (97 % of the respondents), depending on: the drug (87 %), the condition being treated (78 %), family/patient preferences (62 %) and risks of COVID-19 versus not treating skin disease (84 %). The management of specific immunosuppressive medications was analyzed based on different clinical circumstances: (i) asymptomatic patients (ii) upper respiratory tract infection (URI) with unknown COVID-19 status, (iii) confirmed exposure to COVID-19, and (iv) confirmed SARS-CoV-2 infection. Selected drugs were classified into systemic therapy (methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, systemic steroids, apremilast, JAK inhibitors) and biologic therapies (anti-TNFα, anti-IL17, anti-IL-12/23, anti-IL-23, dupilumab).

The majority of dermatologists agreed that in SARS-CoV-2-negative patients all treatment should be continued or adapted to the context (152). In patients with URI most drugs were temporary discontinued, except for systemic steroids that were also decreased in dosage (30 % of respondents); apremilast and dupilumab were mostly continued (46% and 68 %, respectively). In patients exposed to confirmed households and with confirmed COVID-19 infection, all the selected drugs were mostly discontinued or decreased in dose, including systemic steroids (24% and 19% of respondents, respectively), apremilast (30% and 24 %, respectively) and dupilumab (49% and 16%, respectively). In addition, the frequency of laboratory monitoring was also reduced. Notably, discontinuance of a biologic therapy could lead to failure after reintroduction and tapering of corticosteroids may need to be assessed for adrenal suppression, especially in case of infection when stress-dose steroids may be required. In conclusion, a final statement for the management of immunosuppressive medications was not achieved, and it was advised that the decisions regarding treatment were regularly discussed with the patients and their caregivers (152).

The European Task Force on Atopic Dermatitis (ETFAD) published a statement on SARS-CoV-2 and atopic dermatitis (153). They suggested continuing all ongoing medications to prevent disease worsening, to observe hygienic procedures and to moisturize their skin regularly. In addition, if systemic treatment should be stopped, it should be replaced by a topical therapy. Dupilumab is preferred over other medications, because it does not increase the risk of viral infection.

Another evaluation of the use of systemic drugs during COVID outbreak suggested that dupilumab, aprelimast, and acitretin are not associated with increased risk of infection and seem to be safe during COVID-19 pandemic (154). Other suggestions to optimize the care of patients with atopic dermatitis during the outbreak included encouraging the skin care (hygiene, moisturizing…), the access to telehealth, and follow published indications on systemic drugs in this setting (155).

Similar indications to the above mentioned have been advocated for the use of immune-suppressive medications in psoriasis, autoimmune bullous diseases, and atopic dermatitis (156-159). The treatment of autoimmune bullous diseases should be maintained due to the high rate of morbidity and mortality of this disease group (160). In patients infected with SARS-CoV-2, azathioprine, mycophenolate mofetil/sodium, cyclophosphamide, methotrexate and cyclosporine may be stopped, while topical corticosteroids, dapsone/sulphapyridine, low dose prednisone/prednisolone, doxycycline/tetracycline, colchicine and IVIG can be continued. Systemic corticosteroids should be tapered, and not suddenly interrupted. Regular update through WHO/CDC homepage and the European Academy of Dermatology and Venereology, which published specific recommendations on the website, are recommended (160).

COVID-19 pandemic means a psychosocial impact on health-care providers and patients with chronic skin disorders (161). Also, the quarantine may have negative effects on chronic inflammatory conditions. Immobilization, decrease of physical activity and lockdown induce higher caloric intake, obesity, and a negative impact on mood. All these factors worsen psoriasis and hidradenitis suppurativa and decrease adherence to treatment (162).

Teledermatology and telemedicine appear as an opportunity for continuing health care delivery (163-165).

Some suggestions on dermoscopy during pandemic COVID-19 have been proposed: (i) avoid dermoscopy in specific body sites: mucosa, hands, nails, face and eyes, (ii) patient and doctors should respect distancing in waiting room, wear mask, and wash or sanitize hands before and after the exam, (iii) the dermoscope should also be sanitized before and after each patient, (iv) the examined skin should also be sanitized before and after the exam, and (v) digital report should be encouraged instead of printed paper (166).

Recommendations for paediatric dermatologists attending children with suspected COVID-19 skin disease.

The following advice may continue to change over the following months. Only 1-5% of confirmed COVID-19 positive cases are children. Overall, children have milder disease and deaths in children are exceptional (167).

The initial evaluation, like in adults, should be carried out at the department where the patient is attended first (emergency room, inpatient room), to avoid unnecessary patient movements in the hospital and avoid contacts with patients in waiting areas. Dermatologists attending children with skin lesions suspected of COVID-19 should wear proper personal protective equipment, which may include mask, goggles, protective suites, head caps and gloves (168).

A thorough evaluation by an experienced paediatrician is highly recommended. Whereas most children with SARS-CoV-2 infection are expected to preserve a good general status and normal vital signs, a poor general status and tachycardia are early signs of shock in COVID-19 (94,95).

Severe gastrointestinal symptoms appear to me more frequent than respiratory symptoms in severely ill children and can indicate the possibility of PIMS (95). However, most patients with cutaneous lesions do not present with systemic symptoms or, if present, these are mild, and usually occur days to weeks before the appearance of the skin lesions (15).

If history and clinical examination suggest SARS-CoV-2 infection, it is recommended to test by PCR and follow-up household contacts according to the local health authority protocols. In children with mild symptoms, the likelihood of transmission of the infection beyond the first week after the onset of symptoms is very low, (169,170) so home lockdown for 10 days is recommended. If you need to see an infectious child then one should try to see them in a COVID-19 area, as late as possible during the day to allow clearning and caregivers with symptoms must not attend. Informative announcements in the dermatology clinics must clearly explain medical requirements, such as fever screening at the clinic entrance, questionnaires about presence of symptoms in the last two weeks or close contact with suspected or confirmed COVID-19 cases, using alcohol-based hand sanitizer, wearing surgical mask for children and caregivers and maintaining appropriate distancing. Proper cleaning and disinfecting of the office should be carried out after every suspected or confirmed child is attended. Surfaces should be cleaned and disinfected regularly, such as doorknobs, light switches, computer keyboards, phones and tools using during examination such as dermoscopes (171). Surfaces should be disinfected with 1% sodium hypochlorite solutions, and the electronic gadgets with the alcohol based disinfectant.

After an initial in-person evaluation, teledermatology is a good choice for follow-up of COVID-19 children until the skin lesions are completely solved (172).

All health professionals involved in the care of children should try to stay updated, in spite of the increasing number of articles appearing in the literature. Up until the 11th of June 2020, only 3 months after the WHO declared the pandemic, 38,903 articles about COVID-19 had been published in PubMed, with 1,502 references regarding the paediatric population.

Figures

Figure 1. Histopathology of chilblains in COVID-19. A, Low power view showing intense previscular and perieccrine infiltrates; B, Edema in the papillary dermis with both dermo-epidermal and perivascular infiltrates. C, D. Prominent lymphocytic vasculitis with vessel wall damage in dermal vessels.
Figure 2. Algorithm for diagnosis of COVID-19 in children with a skin eruption

Learning points

- The histopathology of COVID-19 related chilblains is similar to classic primary chilblains.
- Sensitivity and specificity of PCR and serology tests are not high in children, and epidemiologic data are important in the diagnosis of COVID-19 in children.
- More than 90 % of children have asymptomatic, mild or moderate COVID-19, and the diagnosis may thus be overlooked.
- COVID-19 may interfere with the course of chronic skin diseases and with the access of patients to specialized care. Teledermatology may partly overcome this latter problem.
- COVID-19 may interfere with the use of immunosuppressive drugs for skin diseases. The continuation of these drugs should be balanced with the risk of withdrawal and worsening of the skin condition.
- Dupilumab appears to be safe and not associated with increased risk of infection.

Questions and answers

1. **Which of the following is not a histologic feature of COVID-19 related chilblains?**
   A. Lymphcytic vasculitis
   B. Leukocytoclasis
   C. Endothelialitis
   D. Thrombosis
   E. Red cell extravasation

Answers to question 1
   A. Incorrect.
   B. Correct.
   C. Incorrect.
   D. Incorrect.
   E. Incorrect.

2. **What percentage of proven COVID-19 patients are children?**
   A. < 5 %
   B. 10-20 %
   C. 20-40 %
   D. 40-60 %
   E. 60-80 %

Answers to question 2
   A. Correct. Children are a minimal part of the COVID-19 proven patients. This figure is probably an underestimate, because many children remain asymptomatic and the detection of SARS-CoV-2 by PCR has a low sensitivity in this age
   B. Incorrect.
   C. Incorrect.
   D. Incorrect.
   E. Incorrect.

3. **What is the most agreed option for children with atopic dermatitis treated with immunosuppressive drugs and no symptoms of COVID-19?**
   A. Continue therapy
   B. Reduce dose to half
   C. Taper for 2 weeks and then discontinue therapy
   D. Discontinue therapy
   E. Increase dose

Answers to question 3
   A. Correct. The majority of dermatologists agree that in SARS-CoV-2-negative patients all treatments should be continued or adapted to the context.
   B. Incorrect.
   C. Incorrect.
   D. Incorrect.
   E. Incorrect.

4. **Which of the following is the preferred systemic treatment for severe atopic dermatitis during COVID-19 pandemic?**
   A. Cyclosporin
   B. Methotrexate
   C. Azathioprine
   D. Mycophenolate
   E. Dupilumab

Answers to question 4
   A. Incorrect.
   B. Incorrect.
   C. Incorrect.
   D. Incorrect.
   E. Correct. Though all the drugs in the list are acceptable, dupilumab is preferred over other medications, because it is the only one that does not increase the risk of viral infection.

5. In a child with chilblains suspected to be related to COVID-19, what of the following measures is correct?
   A. PCR is not necessary
   B. The patient should be quarantined for 2 weeks regardless of the PCR result
   C. The patient should be admitted to hospital
   D. If PCR is negative, the likelihood of transmission of the infection is very low
   E. A complete blood cell count, serum chemistry and coagulation studies should be obtained.

Answers to question 5
   A. Incorrect. PCR is recommended for any patient suspected to have COVID-19
   B. Incorrect. If PCR is negative, the patient should not be locked down
   C. Incorrect. The condition is mild, regardless of the PCR result, and the patient should not be admitted.
   D. Correct.

E. Incorrect. No further testing is recommended.

References

1. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol. 2020, 34 (5): e212-3.
2. Mazzotta F., Troccoli T. 2020. Acute acro-ischemia in the child at the time of COVID-19. Eur. J. Pediat. Dermatol. 30 (2): 71-74.
3. Cappel JA, Wetter DA. Clinical characteristics, etiologic associations, laboratory findings, treatment, and proposal of diagnostic criteria of pernio (chilblains) in a series of 104 patients at Mayo Clinic, 2000 to 2011. Mayo Clin Proc. 2014; 89:207-15.
4. Ozmen M, Kurtoglu V, Can G, Tarhan EF, Soysal D, Aslan SL. The capillaroscopic findings in idiopathic pernio: is it a microvascular disease?. Mod Rheumatol. 2013;23(5):897-903. doi:10.1007/s10165-012-0768-9
5. Hughes M, Rogers S, Lepri G, Bruni C, Matucci-Cerinic M. Further evidence that chilblains are a cutaneous manifestation of COVID-19 infection [published online ahead of print, 2020 May 27]. Br J Dermatol. 2020;10.1111/bjd.19243. doi:10.1111/bjd.19243
6. Kluger N, Scrivener JN. The use of Google Trends for acral symptoms during COVID-19 outbreak in France [published online ahead of print, 2020 May 2]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16572. doi:10.1111/jdv.16572
7. Alramthan A, Aldaraji W. Two cases of COVID-19 presenting with a clinical picture resembling chilblains: first report from the Middle East [published online ahead of print, 2020 Apr 17]. Clin Exp Dermatol. 2020;10.1111/ced.14243. doi:10.1111/ced.14243
8. Romaní J, Baselga E, Mitjà O, Riera-Martí N, Garbayo P, Vicente A, Casals M, et al. Chilblain and acral purpuric lesions in Spain during Covid confinement : Retrospective analysis of 12 cases. Actas Dermosifiliogr 2020; doi:10.1016/j.ad.2020.04.002
9. Piccolo V, Neri I, Filippeschi C, et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients [published online ahead of print, 2020 Apr 24]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16526. doi:10.1111/jdv.16526
10. Galván Casas C, Català A, Carretero Hernández G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases [published online ahead of print, 2020 Apr 29]. Br J Dermatol. 2020;10.1111/bjd.19163. doi:10.1111/bjd.19163 [https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3586683].
11. Zhang Y, Cao W, Xiao M, et al. Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia. Zhonghua Xue Ye Xue Za Zhi. 2020;41:E006.
12. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect. 2020;9(1): 687-90.
13. De Masson A, Bouaziz JD, Sulimovic L, et al. Chilblains are a common cutaneous finding during the COVID-19 pandemic: a retrospective nationwide study from France [published online ahead of print, 2020 May 4]. J Am Acad Dermatol. 2020;S0190-9622(20)30789-1.
14. Colonna C, Monzani NA, Rocchi A, Gianotti R, Boggio F, Gelmetti C. Chilblain-like lesions in children following suspected COVID-19 infection [published online ahead of print, 2020 May 6]. Pediatr Dermatol. 2020;10.1111/pde.14210. doi:10.1111/pde.14210

15. Andina D, Noguera-Morel L, Bascuas-Arribas M, et al. Chilblains in children in the setting of COVID-19 pandemic [published online ahead of print, 2020 May 9]. Pediatr Dermatol. 2020;10.1111/pde.14215. doi:10.1111/pde.14215
16. El Hachem M, Diociaiuti A, Concato C, et al. A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection [published online ahead of print, 2020 May 31]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16682. doi:10.1111/jdv.16682
17. Garcia-Lara G, Linares-González L, Ródenas-Herranz T, Ruiz-Villaverde R. Chilblain-like lesions in pediatrics dermatological outpatients during the COVID-19 outbreak [published online ahead of print, 2020 May 6]. Dermatol Ther. 2020;e13516. doi:10.1111/dth.13516
18. Recalcati S, Barbagallo T, Frasin LA, et al. Acral cutaneous lesions in the time of COVID-19 [published online ahead of print, 2020 Apr 24]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16533. doi:10.1111/jdv.16533
19. Freeman EE, McMahon DE, Lipoff JB, et al. Pernio-like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries [published online ahead of print, 2020 May 29]. J Am Acad Dermatol. 2020;S0190-9622(20)30984-1. doi:10.1016/j.jaad.2020.05.109
20. Torrelo A, Andina D, Santonja C, et al. Erythema multiforme-like lesions in children and COVID-19 [published online ahead of print, 2020 May 23]. Pediatr Dermatol. 2020;10.1111/pde.14246. doi:10.1111/pde.14246
21. Mazzotta F., Troccoli T. 2020. Erythema multiforme in time of COVID-19. Eur. J. Pediat. Dermatol. 30 (2): 88-89. DOI: 10.26326/2281-9649.30.2.2106.
22. Bouaziz JD, Duong T, Jachiet M, et al. Vascular skin symptoms in COVID-19: a french observational study [published online ahead of print, 2020 Apr 27]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16544. doi:10.1111/jdv.16544
23. Navarro L, Andina D, Noguera-Morel L, Hernández-Martín A, Colmenero I, Torrelo A. Dermoscopy features of COVID-19-related chilblains in children and adolescents. J Eur Acad Dermatol Venereol 2020, in press
24. Herman A, Peeters C, Verroken A, et al. Evaluation of Chilblains as a Manifestation of the COVID-19 Pandemic [published online ahead of print, 2020 Jun 25]. JAMA Dermatol. 2020;e202368. doi:10.1001/jamadermatol.2020.2368
25. Roca-Ginés J, Torres-Navarro I, Sánchez-Arráez J, et al. Assessment of Acute Acral Lesions in a Case Series of Children and Adolescents During the COVID-19 Pandemic [published online ahead of print, 2020 Jun 25]. JAMA Dermatol. 2020;e202340. doi:10.1001/jamadermatol.2020.2340
26. Tagarro A, Epalza C, Santos M, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain [published online ahead of print, 2020 Apr 8]. JAMA Pediatr. 2020;e201346. doi:10.1001/jamapediatrics.2020.1346
27. Suarez-Valle A, Fernandez-Nieto D, Diaz-Guimaraens B, Dominguez-Santas M, Carretero I, Perez-Garcia B. Acro-ischemia in hospitalized COVID-19 patients [published online ahead of print, 2020 May 7]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16592. doi:10.1111/jdv.16592
28. Ling Y, Xu SB, Lin YX, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl). 2020;133(9):1039-1043. doi:10.1097/CM9.0000000000000774
29. Chen ATC, Lescure FX, Helms J) (Chen ATC, Coura-Filho GB, Rehder MHH. Clinical Characteristics of Covid-19 in China. N Engl J Med. 2020;382.
30. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis. 2020;20(6):697-706
31. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, Anheim M, Meziani F. Neurologic in Severe SARS-CoV-2 Infection. The New England journal of medicine. 2020.

32. Hadjadj J, Yatim N, Barnabei L et al. Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients; ttps://www.medrxiv.org/content/10.1101/2020.04.19.20068015v1
33. Hubiche T, Cardot-Leccia N, Le Duff F, Giordana P, Chiaverini C, Seitz-Polski B, et al. Chilblains appear as a manifestation of SARS-CoV-2 infection and reveal features of type I interferonopathy and micro-vasculopathy (submitted)
34. Kolivras A, Dehavay F, Delplace D, et al. Coronavirus (COVID-19) infection-induced chilblains: A case report with histopathologic findings [published online ahead of print, 2020 Apr 18]. JAAD Case Rep. 2020;6(6):489-492. doi:10.1016/j.jdcr.2020.04.011
35. Li G, Ju J, Weyand CM, Goronzy JJ. Age-Associated Failure To Adjust Type I IFN Receptor Signaling Thresholds after T Cell Activation. J Immunol. 2015;195(3):865-874
36. Channappanavar R, Fehr AR, Zheng J et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. J Clin Invest. 2019;129(9):3625-3639.
37. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. Nat Rev Immunol. 2015;15(2):87-103
38. Giannis D, Ziogas I, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lesson from the past. J Clin Virol. 2020; 127: 104362
39. Fox SE, Akmatbekov A, Harbert JL et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med. 2020;S2213-2600(20)30243-5
40. Ackermann M, Verleden SE, Kuehnel et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in COVID-19. The New England journal of medicine. 2020 May 21
41. Zhang Y., Xiao M., Zhang S. et Al. 2020. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020;382(17):e38
42. Al-Samkari H, Karp Leaf RS, Dzik WH et al. COVID and coagulation: bleeding and Thombotic manifestation of SARS-CoV infection. Blood. 2020 Jun 3
43. Cardot-Leccia N, Hubiche T, Dellamonica J et al. Pericyte alteration sheds light on micro-vasculopathy in COVID-19 infection. Intensive Care Medicine (2020); DOI: 10.1007/s00134-020-06147-7
44. Colmenero I, Santonja C, Alonso-Riano M et al. SARS-COV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of 7 paediatric patients. Br J Dermatol 2020, accepted.
45. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, Li MD, Witkin A, Rodriguez- Lopez JM, Shepard JO, Little BP, (2020) Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis
46. Magro C, Mulvey AJ, Berlin D et al. AGRO, Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Translational Research ; 2020. In press
47. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Vol. 395, The Lancet. Lancet Publishing Group; 2020. p. 1417–8.
48. Perrotta F, Matera MG, Cazzola M, Bianco A. Severe respiratory SARS-CoV2 infection: Does ACE2 receptor matter? Vol. 168, Respiratory Medicine. W.B. Saunders Ltd; 2020. p. 105996.
49. Ziegler CGK, Allon SJ, Nyquist SK et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell. 2020 May 28;181(5):1016-1035.e19
50. He L, Mäe MA, Sun Y et al. Pericyte-specific vascular expression of SARS-CoV-2 receptor ACE2 – implications for microvascular inflammation and

hypercoagulopathy in COVID-19 patients. In press. https://www.biorxiv.org/content/10.1101/2020.05.11.088500v1
51. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004 Jun;203(2):631–7.
52. Hernandez C, Bruckner AL. Focus on "COVID Toes" [published online ahead of print, 2020 Jun 25]. JAMA Dermatol. 2020;10.1001/jamadermatol.2020.2062. doi:10.1001/jamadermatol.2020.2062
53. French LE, Prins C. Erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis. In: Bolognia JL, Jorizzo JL, Schaffer JV, editors. Dermatology. 3rd edn. Elsevier Saunders, Atlanta, Georgia, USA. 2012: p. 319–33
54. Siedner-Weintraub Y, Gross I, David A, Reif S, Molho-Pessach V. Paediatric Erythema Multiforme: Epidemiological, Clinical and Laboratory Characteristics. Acta Derm Venereol. 2017;97(4):489-492.
55. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. Int J Dermatol. 2012;51(8):889-902.
56. Jimenez-Cauhe J, Ortega-Quijano D, Carretero-Barrio I, et al. Erythema multiforme-like eruption in patients with COVID-19 infection: clinical and histological findings [published online ahead of print, 2020 May 9]. Clin Exp Dermatol. 2020;10.1111/ced.14281.
57. Janah H, Zinebi A, Elbenaye J. Atypical erythema multiforme palmar plaques lesions due to Sars-Cov-2 [published online ahead of print, 2020 May 9]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16623.
58. Labé P, Ly A, Sin C, et al. Erythema multiforme and Kawasaki disease associated with COVID-19 infection in children [published online ahead of print, 2020 May 26]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16666.
59. García-Gil MF, García García M, Monte Serrano J, Prieto-Torres L, Ara-Martín M. Acral purpuric lesions (Erythema multiforme type) associated with thrombotic vasculopathy in a child during the COVID-19 pandemic [published online ahead of print, 2020 May 20]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16644.
60. Imbalzano E, Casciaro M, Quartuccio S, et al. Association between urticaria and virus infections: A systematic review. *Allergy Asthma Proc.* 2016;37(1):18-22.
61. Sachdeva M, Gianotti R, Shah M, et al. Cutaneous manifestations of COVID-19: Report of three cases and a review of literature. *J Dermatol Sci.* 2020 May;98(2):75-81.
62. Fernandez-Nieto D, Ortega-Quijano D, Segurado-Miravalles G, et al. Comment on: Cutaneous manifestations in COVID-19: a first perspective. Safety concerns of clinical images and skin biopsies. *J Eur Acad Dermatol Venereol.* 2020 Jun;34(6):e252-e254.
63. Rodriguez-Jimenez P, Chicharro P, De Argila D, et al. Urticaria-like lesions in COVID-19 patients are not really urticaria. A case with clinicopathologic correlation. *J Eur Acad Dermatol Venereol.* 2020 May 9:10.1111/jdv.16618. doi: 10.1111/jdv.16618. Online ahead of print.
64. Gunawan C, Angela A, Widysanto A. Urticarial eruption in Coronavirus Disease 2019 (COVID-19) infection: a case report in Tangerang, Indonesia. *J Eur Acad Dermatol Venereol.* 2020 May 9:10.1111/jdv.16622. doi: 10.1111/jdv.16622. Online ahead of print.
65. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020 Feb 19. doi: 10.1111/all.14238. Online ahead of print.
66. Henry D, Ackerman M, Sancelme E, et al. Urticarial eruption in COVID-19 infection. *J Eur Acad Dermatol Venereol.* 2020 Jun;34(6):e244-e245.
67. Aktas H, Hamidi AA. Urticaria in a patient with COVID-19: Therapeutic and diagnostic difficulties. *Dermatol Ther.* 2020:e13610.

68. de Medeiros VLS, Silva LFT. Follow-up of skin lesions during the evolution of COVID-19: a case report. *Arch Dermatol Res.* 2020 May 14;1-4. doi: 10.1007/s00403-020-02091-0. Online ahead of print.
69. Naziroglu T, Sozen S, Ozkan P, et al. A case of COVID-19 pneumonia presenting with acute urticaria. *Dermatol Ther.* 2020 May 13:10.1111/dth.13575. doi: 10.1111/dth.13575. Online ahead of print.
70. van Damme C, Berlingin E, Saussez S, et al. Acute urticaria with pyrexia as the first manifestations of a COVID-19 infection. *J Eur Acad Dermatol Venereol.* 2020 Apr 24:10.1111/jdv.16523. doi: 10.1111/jdv.16523. Online ahead of print.
71. Estebanez A, Perez-Santiago L, Silva E, et al. Cutaneous manifestations in COVID-19: a new contribution. *J Eur Acad Dermatol Venereol.* 2020 Jun;34(6):e250-e251.
72. Hedou M, Carsuzaa F, Chary E, et al. Comment on "Cutaneous manifestations in COVID-19: a first perspective " by Recalcati S. *J Eur Acad Dermatol Venereol.* 2020 Apr 21;10.1111/jdv.16519. doi: 10.1111/jdv.16519. Online ahead of print.
73. Morey-Olive M, Espiau M, Mercadal-Hally M, et al. Cutaneous manifestations in the current pandemic of coronavirus infection disease (COVID 2019). *An Pediatr (Engl Ed).* 2020 PMID: 32341944.
74. Young S, Fernandez AP. Skin manifestations of COVID-19. *Cleve Clin J Med.* 2020 May 14. doi: 10.3949/ccjm.87a.ccc031. Online ahead of print.
75. de Masson A, Bouaziz JD, Sulimovic L, et al. Chilblains are a common cutaneous finding during the COVID-19 pandemic: a retrospective nationwide study from France [published online ahead of print, 2020 May 4]. J Am Acad Dermatol. 2020; S0190-9622(20)30789-1.
76. Gisondi P, PIaserico S, Bordin C, Alaibac M, Girolomoni G, Naldi L. Cutaneous manifestations of SARS-CoV-2 infection: a clinical update. J Eur Acad Dermatol Venereol. 2020 Jun 25. doi: 10.1111/jdv.16774)
77. Marzano AV, Genovese G, Fabbrocini G, et al. Varicella-like exanthema as a specific COVID-19-associated skin manifestation: multi-center case series of 22 patients. J Am Acad Dermatol 2020 Apr 16.
78. De Giorgi V, Recalcati S, Jia Z, Chong W, Ding R, Deng Y, Scarfi F, Venturi F, Trane L, Gori A, Silvestri F, Gao XH, Lotti T.Cutaneous manifestations related to coronavirus disease 2019 (COVID-19): A prospective study from China and Italy. J Am Acad Dermatol. 2020 May 19.
79. Fernandez-Nieto D, Ortega-Quijano D, Jimenez-Cauhe J, Burgos-Blasco P, de Perosanz-Lobo D, Suarez-Valle A, Cortes-Cuevas JL, Carretero I, Garcia Del Real CM, Fernandez-Guarino M. Clinical and histological characterization of vesicular COVID-19 rashes: A prospective study in a tertiary care hospital. Clin Exp Dermatol. 2020 May 8
80. Marzano AV, Genovese G, Response to “Reply to ‘Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients’: To consider varicella-like exanthem associated with COVID-19, virus varicella zoster and virus herpes simplex must be ruled out”, Journal of the American Academy of Dermatology (2020)
81. Tang K, Wang Y, Zhang H, Zheng Q, Fang R, Sun Q. Cutaneous manifestations of the Coronavirus Disease 2019 (COVID-19): A brief review. Dermatol Ther. 2020 May 7:e13528.
82. Gianotti R, Veraldi S, Recalcati S, et al. Cutaneous Clinico-pathological findings in three COVID-19-positive patients observed in the metropolitan area of Milan, Italy. Acta Derm Venereol. 2020;100(8): adv00124.
83. Genovese G, Colonna C, Marzano AV. Varicella-like exanthem associated with COVID-19 in an 8-year-old girl: a diagnostic clue? Pediatr Dermatol. 2020.
84. Wollina U, Karadağ AS, Rowland-Payne C, Chiriac A, Lotti T. Cutaneous signs in COVID-19 patients: A review.Dermatol Ther. 2020 May 10:e13549.

85. Mahé A, Birckel A, Merklen C, Lefèbvre P, Hannedouche C, Jost M, Droy-Dupré L. Histology of skin lesions establishes that the vesicular rash associated with COVID-19 is not “varicella-like” J Eur Acad Dermatol Venereol. 2020 Jun 5
86. Mahe A, Birckel E, Krieger S, et al. A distinctive skin rash associated with coronavirus disease 2019. J Eur Acad Dermatol Venereol: JEADV. 2020.
87. Schnabel A, Hedrich CM. Childhood Vasculitis. Front Pediatr. 2018; 6:421.
88. Makino N, Nakamura Y, Yashiro M, Kosami K, Matsubara Y, Ae R, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015-2016. Pediatr Int Off J Jpn Pediatr Soc. 2019; 61(4):397-403.
89. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association [Internet]. Vol. 135, Circulation; 2017. Disponible on: https://pubmed.ncbi.nlm.nih.gov/28356445/
90. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis. 2005;191(4):499-502.
91. Esper F, Weibel C, Ferguson D, Landry ML, Kahn JS. Evidence of a novel human coronavirus that is associated with respiratory tract disease in infants and young children. J Infect Dis. 2005; 191(4):492-8.
92. Chang L-Y, Lu C-Y, Shao P-L, Lee P-I, Lin M-T, Fan T-Y, et al. Viral infections associated with Kawasaki disease. J Formos Med Assoc Taiwan Yi Zhi. 2014; 113(3):148-54.
93. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020 Jun;145(6):e20200702. doi: 10.1542/peds.2020-0702.
94. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet Lond Engl. 2020; 395(10237):1607-8
95. Cabrero-Hernández M, García-Salido A, Leoz-Gordillo I, Alonso-Cadenas JA, Gochi-Valdovinos A, González Brabin A, De Lama Caro-Patón G, Nieto-Moro M, de-Azagra-Garde AM, Serrano-González A. Severe SARS-CoV-2 Infection in Children With Suspected Acute Abdomen: A Case Series From a Tertiary Hospital in Spain. Pediatr Infect Dis J. 2020 May 26. doi: 10.1097/INF.0000000000002777. Online ahead of print.
96. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet Lond Engl. 2020; 395(10239):1771-8.
97. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasakilike multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020; 369:2094.
98. Trouillet-Assant S, Viel S, Gaymard A, Pons S, Richard J-C, Perret M, et al. Type I IFN immunoprofiling in COVID-19 patients. J Allergy Clin Immunol. 2020 April 29; S0091-6749 (20)30578-9.
99. ECDC. Paediatric inflammatory multisystem syndrome and SARSCoV- 2 infection in children, 2020. https://www.ecdc.europa.eu/ sites/default/files/documents/covid-19-riskassessment-paediatricinflammatory- multisystem-syndrome-15-May-2020.pdf.
100. CDC. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19), 2020. https://emergency.cdc.gov/han/2020/han00432.asp.
101. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. Hosp Pediatr. 2020; 10(6):537-40.

102. Licciardi F, Pruccoli G, Denina M, Parodi E, Taglietto M, Rosati S, et al. SARS-CoV-2-Induced Kawasaki-Like Hyperinflammatory Syndrome: A Novel COVID Phenotype in Children. Pediatrics. 2020 May 21: e20201711.
103. Yancy CW. COVID-19 and African Americans. JAMA. 2020; 323 (19): 1891-1892.
104. Giudicessi JR, Roden DM, Wild A, Ackerman MJ. Genetic Susceptibility for COVID-19-associated Sudden Cardiac Death in African Americans. Heart Rhythm. 2020, May 5, S 1547. .
105. M Oualha, M Bendavid , L Berteloot, A Corsia, F Lesage, et al. Severe and Fatal Forms of COVID-19 in Children. Arch Pediatr. 2020.Jul; 27 (5): 235-238.
106. Grimaud M, Starck J, Levy M ,, Marais C, Chareyre J , et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Annal. Intensive Care 2020. 10:69
107. Li Y, Zheng Q, Zou L, Wu J, Guo L, Teng L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-γ as biomarkers for early recognition. Pediatr Rheumatol Online J. 2019;17(1):1.
108. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet Lond Engl. 2020; 395(10229):1033-4.
109. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet Lond Engl. 2020;395(10223):497-506.
110. Turnier JL, Anderson MS, Heizer HR, Jone P-N, Glodé MP, Dominguez SR. Concurrent Respiratory Viruses and Kawasaki Disease. Pediatrics. 2015; 136(3):609-614.
111. Shirato K, Imada Y, Kawase M, Nakagaki K, Matsuyama S, Taguchi F. Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. J Med Virol. 2014; 86(12):2146-53.
112. Ebihara T, Endo R, Ma X, Ishiguro N, Kikuta H. Lack of association between New Haven coronavirus and Kawasaki disease. J Infect Dis. 2005;192(2):351-2.
113. Schroeder AR, Wilson KM, Ralston SL. COVID-19 and Kawasaki Disease: Finding the Signal in the Noise. Hosp Pediatr. 2020; doi 10.1542/hpedS. 2020-000356.
114. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, et al. Recognition of a Kawasaki Disease Shock Syndrome Pediatrics. Pediatrics; 2009; 123:783-9.
115. Abrar-Ahmad Zulfiqar, Noël Lorenzo-Villalba, Patrick Hassler, Emmanuel Andrès. Immune thrombocytopenic purpura in a patient with Covid-19. N Engl J Med. 2020 Apr 15 : NEJMc2010472. Published online 2020 Apr 15. doi: 10.1056/NEJMc2010472
116. Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for Dengue. J Am Acad Dermatol 2020. DOI:10.1016/j.jaad.2020.03.036
117. Jimenez-Cauhe J, Ortega-Quijano D, Prieto-Barrios M, Moreno-Arrones OM, Fernandez-Nieto D. Reply to "COVID-19 can present with a rash and be mistaken for Dengue": Petechial rash in a patient with COVID-19 infection. J Am Acad Dermatol. 2020.
118. Olisova OY, Anpilogova EM, Shnakhova LM. Cutaneous manifestations in COVID-19: a skin rash in a child [published online ahead of print, 2020 May 30]. Dermatol Ther. 2020;e13712. doi:10.1111/dth.13712
119. Kamali Aghdam M, Jafari N, Eftekhari K. Novel coronavirus in a 15-day-old neonate with clinical signs of sepsis, a case report. Infect Dis (Lond) 2020 doi: 10.1080/23744235.2020.1747634
120. Kang JH. Febrile Illness with Skin Rashes. Infect Chemother. 2015;47(3):155-166.
121. Llamas-Velasco M, Muñoz-Hernández P, Lázaro-González J, Reolid-Pérez A, Abad-Santamaría B, Fraga J, Daudén-Tello E. Thrombotic occlusive vasculopathy

in skin biopsy from a livedoid lesion of a COVID-19 patient. Br J Dermatol. 2020 May 14. doi: 10.1111/bjd.19222. [Epub ahead of print] PubMed PMID: 32407552; PubMed Central PMCID: PMC7272899.
122. Diaz-Guimaraens B, Dominguez-Santas M, Suarez-Valle A, et al. Petechial skin rash associated with severe acute respiratory syndrome coronavirus 2 infection. JAMA Dermatol. 2020. https://doi.org/10. 1001/jamadermatol.2020.1741. [Epub ahead of print]
123. Herrero-Moyano M, Capusan TM, Andreu-Barasoain M, Alcántara-González J, Ruano-Del Salado M, Sánchez-Largo Uceda ME, Calzado-Villarreal L, Pérez-González Y. A clinicopathological study of 8 patients with COVID-19 pneumonia and a late-onset exanthema. J Eur Acad Dermatol Venereol. 2020 May 19. doi: 10.1111/jdv.16631. [Epub ahead of print] PubMed PMID: 32426864; PubMed Central PMCID:PMC7276824
124. Reymundo A, Fernáldez-Bernáldez A, Reolid A, Butrón B, Fernández-Rico P, Muñoz-Hernández P, De Argila D, Llamas-Velasco M. Clinical and histological characterization of late appearance maculopapular eruptions in association with the coronavirus disease 2019. A case series of seven patients. J Eur Acad Dermatol Venereol. 2020 Jun 4. doi: 10.1111/jdv.16707. [Epub ahead of print] PubMed PMID: 32495368
125. Delaleu J, Deniau B, Battistella M, de Masson A, Bensaid B, Jachiet M, Lazaridou I, Bagot M, Bouaziz JD; Saint-Louis CORE (COvid REsearch) group. Acute generalized exanthematous pustulosis induced by hydroxychloroquine prescribed for COVID-19. J Allergy Clin Immunol Pract. 2020 Jun 7. pii: S2213-2198(20)30587-0.doi: 10.1016/j.jaip.2020.05.046. [Epub ahead of print] PubMed PMID: 32525093
126. Ehsani AH, Nasimi M, Bigdelo Z. Pityriasis rosea as a cutaneous manifestation of COVID-19 infection. J Eur Acad Dermatol Venereol. 2020 doi: 10.1111/jdv.16579.
127. Dursun R, Temiz SA. The Clinics of HHV-6 infection in COVID-19 pandemic: Pityriasis rosea and Kawasaki disease [published online ahead of print, 2020 May 31]. Dermatol Ther. 2020;e13730. doi:10.1111/dth.13730
128. Tartari F, Spadotto A, Zengarini C, Zanoni R, Guglielmo A, Adorno A, Valzania C, Pileri A. Herpes zoster in COVID-19-positive patients. Int J Dermatol. 2020 Jun 12. doi: 10.1111/ijd.15001. [Epub ahead of print] PubMed PMID: 32530063.
129. Llamas-Velasco M, Rodríguez-Jiménez P, Chicharro P, De Argila D, Muñoz-Hernández P, Daudén E. Reply to "Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients": To consider varicella-like exanthem associated with COVID-19, virus varicella zoster and virus herpes simplex must be ruled out [published online ahead of print, 2020 May 19]. J Am Acad Dermatol. 2020;S0190-9622(20)30943-9. doi:10.1016/j.jaad.2020.04.180
130. Hoang A, et al., COVID-19 in 7780 pediatric patients: A systematic review, EClinicalMedicine (2020), https://doi.org/10.1016/j.eclinm.2020.100433
131. Kaya G, Kaya A, Saurat JH. Clinical and Histopathological Features and Potential Pathological Mechanisms of Skin Lesions in COVID-19: Review of the Literature. Dermatopathology (Basel). 2020;7(1):3-16.
132. Llamas-Velasco M, Chicharro P, Rodríguez-Jiménez P, Martos-Cabrera L, De Argila D, Fernández-Figueras M, Fraga J. Reply to "Clinical and histological characterization of vesicular COVID-19 rashes: a prospective study in a tertiary care hospital": Pseudoherpetic Grover disease seems to appear in patients with COVID-19 infection. Clin Exp Dermatol. 2020 May 21:10.1111/ced.14305. doi:10.1111/ced.14305.
133. Elsaie ML, Youssef EA, Nada HA. Herpes zoster might be an indicator for latent COVID 19 infection. Dermatol Ther. 2020 May 23:e13666. doi:10.1111/dth.13666.

134. Elsaie ML, Nada HA. Herpes Zoster (shingles) complicating the course of COVID19 infection. J Dermatolog Treat. 2020 Jun 16:1-7. doi:10.1080/09546634.2020.1782823.
135. Bosch-Amate X, Giavedoni P, Podlipnik S, Andreu-Febrer C, Sanz-Beltran J, Garcia-Herrera A, Alós L, Mascaró JM Jr. Retiform purpura as a dermatological sign of covid-19 coagulopathy. J Eur Acad Dermatol Venereol. 2020 Jun 3:10.1111/jdv.16689. doi: 10.1111/jdv.16689.
136. Sanchez A, Sohier P, Benghanem S, L'Honneur AS, Rozenberg F, Dupin N, Garel B. Digitate Papulosquamous Eruption Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection. JAMA Dermatol. 2020 Apr 30. doi:10.1001/jamadermatol.2020.1704.
137. Zhang Y. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. Chinese Journal of Epidemiology (by The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team). 2020.
138. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020 Apr 14 : 10.1111/apa.15270. doi: 10.1111/apa.15270 [Epub ahead of print]
139. Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-COV-2. JAMA. 2020 May 6. doi: 10.1001/jama.2020.8259
140. Cordoro KM, Reynolds SD, Wattier R, Mccalmont TH. Clustered cases of acral perniosis: clinical features, histopathology and relationship to COVID-19. Pediatr Dermatol 2020 May 12. doi: 10.1111/pde.14227. Online ahead of print.
141. Xing Q, Li G, Xing Y, Chen T, Li W, Ni W, et al. Precautions are needed for COVID-19 patients with coinfection of common respiratory pathogens. MedRxiv. doi: https://doi.org/10.1101/2020.02.29.20027698
142. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-19. Nature. 2020 May;581(7809):465-469. doi: 10.1038/s41586-020-2196-x. Epub 2020 Apr 1.
143. Patrick DM, Petric M, Skowronski DM, et al. An outbreak of human coronavirus OC43 infection and serological cross-reactivity with SARS coronavirus. Can J Infect Dis Med Microbiol. 2006;17:330-6.
144. Lv H, Wu NC, Tsang OT, Yuan M, Perera RAPM, Leung WS, et al. Cell Rep 2020 Jun 2;31(9):107725. doi: 10.1016/j.celrep.2020.107725. Epub 2020 May 18.
145. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell. 2020 May 20:S0092-8674(20)30610-3. doi: 10.1016/j.cell.2020.05.015.
146. Jääskeläinen AJ, Kekäläinen E, Kallio-Kokko H, Mannonen L, Kortela E, Vapalahti O, et al. Evaluation of commercial and automated SARS-CoV-2 IgG and IgA ELISAs using coronavirus disease (COVID-19) patient samples. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable
147. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020;135:2033-2040.
148. Bialynicki-Birula R, Siemasz I, Otlewska A, Matusiak L, Szepietowski JC. Influence of COVID-19 pandemic on hospitalizations at the tertiary dermatology department in south-west Poland. Dermatol Ther. 2020; doi:10.1111/dth.13738.
149. Patrizi A, Bardazzi F, Filippi F, Abbenante D, Piraccini BM. The covid-19 outbreak in Italy: preventive and protective measures adopted by the dermatology unit of bologna university hospital. Dermatol Ther. 2020; doi:10.1111/dth.13469.
150. Atzori L, Mugheddu C, Addis G, et al. Psoriasis health care in the time of the coronavirus pandemic: insights from dedicated centers in Sardinia (Italy) [published online ahead of print, 2020 Apr 15]. J Eur Acad Dermatol Venereol. 2020; doi:10.1111/jdv.16473.

151. Temiz SA, Dursun R, Daye M, Ataseven A. Evaluation of dermatology consultations in the era of COVID-19. Dermatol Ther. 2020; doi:10.1111/dth.13642.
152. Reynolds SD, Mathur AN, Chiu YE, et al. Systemic immunosuppressive therapy for inflammatory skin diseases in children: Expert consensus-based guidance for clinical decision-making during the COVID-19 pandemic. Pediatr Dermatol. 2020; doi:10.1111/pde.14202.
153. Wollenberg A, Flohr C, Simon D, et al. European Task Force on Atopic Dermatitis (ETFAD) statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2)-infection and atopic dermatitis. J Eur Acad Dermatol Venereol. 2020; doi:10.1111/jdv.16411.
154. Ricardo JW, Lipner SR. Considerations for Safety in the Use of Systemic Medications for Psoriasis and Atopic Dermatitis during the COVID-19 pandemic. Dermatol Ther. 2020; doi:10.1111/dth.13687.
155. Shah M, Sachdeva M, Alavi A, Shi VY, Hsiao JL. Optimizing Care for Atopic Dermatitis Patients During COVID-19 Pandemic. J Am Acad Dermatol. 2020; doi:10.1016/j.jaad.2020.05.027.
156. Mahil SK, Yiu ZZN, Mason KJ, et al. Global reporting of cases of COVID-19 in psoriasis and atopic dermatitis: an opportunity to inform care during a pandemic. Br J Dermatol. 2020; doi:10.1111/bjd.19161.
157. Abdollahimajd F, Shahidi-Dadras M, M Robati R, Dadkhahfar S. Management of Pemphigus in COVID-19 Pandemic Era; a Review Article. Arch Acad Emerg Med. 2020; 8:e51
158. Di Altobrando A, Patrizi A, Bardazzi F. Should SARS-CoV-2 influence immunosuppressive therapy for autoimmune blistering diseases? J Eur Acad Dermatol Venereol. 2020; doi:10.1111/jdv.16491.
159. Wang C, Rademaker M, Baker C, Foley P. COVID-19 and the use of immunomodulatory and biologic agents for severe cutaneous disease: An Australian/New Zealand consensus statement. Australas J Dermatol. 2020; doi:10.1111/ajd.13313.
160. Kasperkiewicz M, Schmidt E, Fairley JA, et al. Expert recommendations for the management of autoimmune bullous diseases during the COVID-19 pandemic. J Eur Acad Dermatol Venereol. 2020; doi:10.1111/jdv.16525.
161. Garcovich S, Bersani FS, Chiricozzi A, De Simone C. Mass quarantine measures in the time of COVID-19 pandemic: psychosocial implications for chronic skin conditions and a call for qualitative studies. J Eur Acad Dermatol Venereol. 2020; doi:10.1111/jdv.16535.
162. Marasca C, Ruggiero A, Napolitano M, Fabbrocini G, Megna M. May COVID-19 outbreaks lead to a worsening of skin chronic inflammatory conditions? Med Hypotheses. 2020;doi:10.1016/j.mehy.2020.109853.
163. Chen P, Zhang G, Zhan Y. Management strategies of autoimmune bullous diseases during the outbreak of 2019 Novel Coronavirus disease (COVID-19). J Dermatolog Treat. 2020;1-2. doi:10.1080/09546634.2020.1771261.
164. Brunasso AMG, Massone C. Teledermatologic monitoring for chronic cutaneous autoimmune diseases with smartworking during Covid-19 emergency in a tertiary center in Italy. Dermatol Ther. 2020;e13495. doi:10.1111/dth.13695.
165. Radi G, Simonetti O, Diotallevi F, et al. How Can I Take Care Of You? The Dermatologist Meets Patients' Needs During The Covid19 Pandemic. Dermatol Ther. 2020; doi:10.1111/dth.13740.
166. Jakhar D, Kaur I, Kaul S. Art of performing dermoscopy during the times of coronavirus disease (COVID-19): simple change in approach can save the day! J Eur Acad Dermatol Venereol. 2020; doi:10.1111/jdv.16412.
167. Devrim I, Byram N. Infection control practices in children during COVID-19 pandemic: Differences from adults. Am J inf control 2020;S0196-6553(20)30317-5

168. Chen Y, Pradhan S, Xue S. What are we doing in the dermatology outpatient department amidst the raging of the 2019 novel coronavirus?. J Am Acad Dermatol. 2020;82(4):1034. doi:10.1016/j.jaad.2020.02.030
169. Cheng HY, Jian SW, Liu DP, et al. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset [published online ahead of print, 2020 May 1]. JAMA Intern Med. 2020;e202020. doi:10.1001/jamainternmed.2020.2020
170. Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020;20(6):656-657. doi:10.1016/S1473-3099(20)30232-2
171. Fahmy DH, El-Amawy HS, El-Samongy MA, et al. COVID-19 and dermatology: a comprehensive guide for dermatologists [published online ahead of print, 2020 May 19]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16545. doi:10.1111/jdv.16545
172. Villani A, Scalvenzi M, Fabbrocini G. Teledermatology: a useful tool to fight COVID-19. J Dermatolog Treat. 2020;31(4):325. doi:10.1080/09546634.2020.1750557