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COVID-19 and implications for dermatological and allergological diseases

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Summary

COVID-19, caused by the coronavirus SARS-CoV-2, has become pandemic. A further level of complexity opens up as soon as we look at diseases whose pathogenesis and therapy involve different immunological signaling pathways, which are potentially affected by COVID-19. Medical treatments must often be reassessed and questioned in connection with this infection.

This article summarizes the current knowledge of COVID-19 in the light of major dermatological and allergological diseases. It identifies medical areas lacking sufficient data and draws conclusions for the management of our patients during the pandemic. We focus on common chronic inflammatory skin diseases with complex immunological pathogenesis: psoriasis, eczema including atopic dermatitis, type I allergies, autoimmune blistering and inflammatory connective tissue diseases, vasculitis, and skin cancers. Since several other inflammatory skin diseases display related or comparable immunological reactions, clustering of the various inflammatory dermatoses into different disease patterns may help with therapeutic decisions. Thus, following these patterns of skin inflammation, our review may supply treatment recommendations and thoughtful considerations for disease management even beyond the most frequent diseases discussed here.

Introduction

COVID-19, caused by the coronavirus SARS-CoV-2, has become pandemic. The impact of SARS-CoV-2 infection on the immune system and its modulation or suppression by pharmacological intervention has been dissected in detail with regards to clinical implications of the various cytokines and cellular functions affected [1]. A further level of complexity opens up as soon as we look at diseases whose pathogenesis and therapy involve different immunological signaling pathways, which are potentially affected by COVID-19. Medical treatments must often be reassessed and questioned in connection with this infection. However, there is still considerable uncertainty in this regard and we are currently in a phase of almost exponentially growing data on various diseases in the context of SARS-CoV-2 infections. The medical knowledge as well as the literature on COVID-19 and its treatment options is growing at an overwhelming pace [2–5].

This article focusses on common chronic inflammatory skin diseases with complex immunological pathogenesis: psoriasis, eczema including atopic dermatitis, type I allergies, autoimmune blistering and inflammatory connective tissue diseases, vasculitis, and skin cancers. Since several other inflammatory skin diseases display related or comparable immunological reactions, clustering of the various inflammatory dermatoses into six disease patterns was recently proposed [6]. Thus, following these patterns of skin inflammation, our review may supply treatment recommendations and thoughtful considerations for disease management even beyond the most frequent diseases discussed here (Table 1).

SARS-CoV-2 and psoriasis

Like other respiratory viral infections, SARS-CoV-2 infection may aggravate psoriasis [7]. Of practical relevance is the question whether antipsoriatic treatments increase the risk of infection with SARS-CoV-2 or aggravate the course of COVID-19 disease. Several aspects need to be considered in this discussion:

- Patients with untreated psoriasis and/or psoriatic arthritis (PsA) have a 1.5 fold increased risk of severe infections compared to control individuals [8–10] and therapeutic normalization of an intrinsically aberrant immune response may improve the host defense against infection.
- The immune response to SARS-CoV-2 is complex; elimination of the virus is associated with an innate and adaptive immune response involving T cells, NK cells, probably B cells and mediators such as IL-12, IL-15, interferon- α/β and $-\gamma$. In a small subgroup of patients with severe COVID-19 and persistent virus replication, a hyperinflammatory response may develop with overexpression of IL-6, TNF α , IL-17A and other cytokines that are also targets of psoriasis therapies [11]. In this situation, cytokine inhibition may be beneficial and/or have a preventive effect [12]. The JAK1/2 inhibitor baricitinib and cyclosporine may increase the risk of viral infections, but may also inhibit viral entry and replication, respectively [13, 14].
- Some risk factors for a more severe course of COVID-19 including arterial hypertension, type II diabetes, smoking

Table 1 Overview of dermatological and allergological diseases and the established or suspected effects of SARS-CoV-2 infection/COVID-19 on disease severity. Approved therapeutic compounds are listed as well as recommendations for continued use and novel introduction of systemic treatment.

Disease	Impact of COVID-19 or infection with SARS-CoV-2 on disease	Approved therapeutic compounds affecting immune responses	Recommendations for continued systemic therapy	Recommendations for novel introduction of systemic treatment
Psoriasis	Possible aggravation of disease	<ul style="list-style-type: none"> – infliximab, adalimumab, certolizumab, etanercept – ustekinumab, guselkumab, risankizumab, tildrakizumab – secukinumab, ixekizumab, brodalumab – cyclosporine – methotrexate – retinoids – fumaric acid esters 	Maintain immunomodulatory therapy without changes	No distinction is being made between labeled treatment options. Targeted therapy probably preferable over conventional systemic immune modulation
Eczema	Possible aggravation of disease	<ul style="list-style-type: none"> – dupilumab – cyclosporine – retinoids – GCS 	Maintain immunomodulatory therapy without changes	Retinoids and targeted therapy with dupilumab probably preferable over conventional systemic immune modulation
Allergic bronchial asthma, allergic rhinitis, anaphylaxis	Possible aggravation of disease	<ul style="list-style-type: none"> – dupilumab – mepolizumab, benralizumab, reslizumab – omalizumab – antihistamines – GCS 	Maintain immunomodulatory therapy without changes	New therapies may be started, since no specific risk has been identified
Autoimmune blistering dermatoses	Possible aggravation of disease	<ul style="list-style-type: none"> – rituximab – azathioprine – dapsone – GCS 	Maintain immunomodulatory therapy when needed to avoid uncontrolled flares	Postpone rituximab to delay B cell depletion during peak COVID-19 when possible and consider use of IVIG instead
Connective tissue disease	Possible aggravation of disease	<ul style="list-style-type: none"> – belimumab – hydroxychloroquine – chloroquine – azathioprine – GCS 	Maintain immunomodulatory therapy without changes	Introduce novel treatment regimen as needed
Vasculitis	Aggravation of disease, and new onset of disease	<ul style="list-style-type: none"> – rituximab – cyclophosphamide – intravenous immunoglobulins – azathioprine – GCS 	Use of immunosuppressants for vasculitis treatment should be even more restricted	Use of immunosuppressants for vasculitis treatment should be even more restricted. Postpone rituximab and cyclophosphamide to delay immunosuppression during peak COVID-19 when possible and consider use of IVIG instead
Skin cancer	Currently unclear	<ul style="list-style-type: none"> – ipilimumab – nivolumab – pembrolizumab – avelumab – cemiplimab 	Maintain immunomodulatory therapy without changes	Introduce novel treatment regimen as needed

Abbr.: GCS, glucocorticosteroids, IVIG, intravenous immunoglobulins.

and overweight are more common among psoriasis patients [15]. On the other hand, there is increasing evidence that successful treatment of psoriasis improves cardiovascular comorbidity [16].

- Most studies and registries have not demonstrated a significantly elevated risk of viral or respiratory tract infections in systemically treated patients with psoriasis [15].

In light of this complex discussion, national and international recommendations suggest not to delay the onset of appropriate systemic therapy and not to stop such therapy in patients without symptoms [17]. No significant differentiation is being made between labeled treatment options. As a precautionary measure in patients with typical symptoms of COVID-19, systemic therapy should not be started and an existing therapy paused until a possible SARS-CoV-2 infection has been excluded or resolved. Clinical evidence based on larger cohorts is only beginning to emerge. In one retrospective Italian study comparing patients with psoriasis on systemic therapy ($n = 1,193$) with the background population of Lombardy since March 2020, the authors reported a higher rate of symptomatic SARS-CoV-2 infection, self-quarantine ($n = 17$) and hospitalization ($n = 5$) for patients on biologics, but no increased risk of ICU admission or death [18]. In another Italian multicenter study, patients with psoriasis on biologics ($n = 5,206$) were followed between February 20th and April 1st 2020 [19]. There were no COVID-19-related deaths and the hospitalization rate was similar to that observed in the general population. Together with an earlier case series from New York City ($n = 86$) [20], these findings support the above recommendations and should reassure patients with psoriasis and their treating physicians.

SARS-CoV-2, atopic dermatitis and other types of eczema

Although respiratory and cutaneous viral infections may worsen or complicate atopic dermatitis and other types of eczema [21], data on effects of SARS-CoV-2 infection on eczema patients have not been published. Since T cells are centrally involved in the complex immuno-pathophysiology of eczema and associated diseases, SARS-CoV-2 infections may be of special concern in eczema patients with comorbid diseases such as asthma/chronic obstructive lung disease, eosinophilic esophagitis, or severe allergies [22]. SARS-CoV-2-induced lymphopenia may hamper antiviral immunity and currently serves as a biomarker and a possible target for intervention by stimulation of lymphocyte proliferation or prevention of apoptosis to reduce the risk of severe disease [22]. Prelimi-

nary data points towards a direct infection of T lymphocytes with SARS-CoV-2, which may also cause cytopathic effects on infected T cells [23].

Following the sanitary recommendations for more frequent hand washing and disinfection procedures during the pandemic, the prevalence of hand eczema is rising significantly, even among persons not previously affected [24, 25]. Basic topical treatment with emollients, as well as specific treatment with topical corticosteroids and calcineurin inhibitors should be initiated or continued according to current guidelines without any specific requirements, including UV-light therapies. Since exacerbations of the skin disease may negatively affect the patients' immunity, systemic treatment in eczema patients should be continued for all immune-modulating drugs including immuno-suppressive therapy, as consented and advised by the *European Task Force on Atopic Dermatitis* (ETFAD) [26].

If a patient on systemic treatment is diagnosed with COVID-19, interdisciplinary risk assessments are necessary on whether to continue or pause systemic treatment, preferably in tertiary care centers [27]. In atopic dermatitis, immune-modulating medication may also control the severity of asthma/chronic obstructive lung disease and other comorbid conditions. Hence, termination of a stable treatment regimen with immune-modulating drugs may not be beneficial [28]. However, in patients with exclusive skin disease such as hand eczema, pausing of immune-modulating therapies seems to be less problematic in case of COVID-19, since flare-ups of the skin disease may be acceptable during the critical time of the viral infection. Whenever immune-modulating therapy is stopped, patients need to be supplied with ample topical treatment and detailed instructions to control the skin disease for the following weeks. Close monitoring of comorbid diseases is important in these individuals. Targeting specific cytokines may even benefit patients with COVID-19, since therapeutic cytokine blockade without affecting viral clearance may inhibit hyper-inflammatory host responses [11].

If patients need to be started on systemic treatment for different types of eczema during the pandemic, exclusively anecdotal clinical data may support the following theoretical considerations. In general, conventional systemic immune-modulating drugs such as glucocorticoids, cyclosporine, azathioprine, or methotrexate affect the cellular immune response, mainly *via* inhibition of lymphocyte function and activation. Retinoids or type II immune response-directed therapies such as dupilumab affect the immune defense against viral infection to a lesser degree and may therefore be preferred [29]. Patients treated with dupilumab showed no increase in systemic infections, and occurrence of eczema herpeticum was significantly reduced in comparison to placebo treatment.

SARS-CoV-2 and type I allergies

IgE-mediated type I allergic diseases affect up to 25 % of the population and dealing with these common diseases during the pandemic is necessary. The following comments refer to allergic bronchial asthma, allergic rhinitis and anaphylaxis.

Diagnosis of a type I allergy should currently focus primarily on *in vitro* tests, if possible. Exceptions are drug and food intolerance reactions, as only few reliable *in vitro* tests are available. Skin prick tests and provocation tests with aerosols (e.g. rhinomanometry) should only be performed after a strict indication and with sufficient protection of the personnel. Gloves, protective goggles, gowns and FFP2/FFP3 respiratory masks should be worn to prevent the transmission of droplets and direct contact [30–32]. If this is not possible, the test should not be performed. To optimize the use of personal protective equipment in the event of inadequate supply, personnel should be assigned to specific tasks and procedures should be performed in specially designated areas.

Considerations for therapy of patients with type I allergic diseases

- Symptomatic topical antiallergic treatment, including topical corticosteroids, should be initiated or continued without restriction according to patient needs.
- Systemic antihistamines and leukotriene antagonists may be initiated or continued without restriction as needed. There is no evidence that this could adversely affect the susceptibility to infection or the course of SARS-CoV-2 infection.
- Systemic corticosteroid therapy, especially at a dose of more than 10 mg/d, should be avoided or used only after a very strict indication and if possible only for a short period.
- The treatment of allergic bronchial asthma, nasal polyps or rarely anaphylactic reactions with biologicals should be continued. New therapies may be started, since no specific risk has been identified in SARS-CoV-2 infected patients [33].
- Anaphylactic shock should be treated acutely with epinephrines according to the current guidelines.
- The indication for administration of high-dose corticosteroids should be strictly defined, especially since the efficacy of corticosteroids in anaphylaxis is not clear.
- Specific subcutaneous or sublingual immunotherapy can be continued in symptom-free and healthy patients, and the treatment regimen should not be interrupted. In case of symptoms such as fever, unclear cough or reduced general condition, immunotherapy should be suspended and continued at a later (symptom-free) time [34].
- In the case of interruption of subcutaneous immunotherapy (SCIT), the dose of SCIT should be adjusted according to the manufacturer's recommendations. Re-commencement of sublingual immunotherapy should be performed under medical supervision.

SARS-CoV-2 and autoimmune blistering dermatoses

Autoimmune blistering dermatoses (AIBD) are a heterogeneous group of potentially life-threatening disorders that characteristically present with blisters and erosions on the skin and/or mucous membranes near the outer skin surface [35–38]. Patients with AIBD likely belong to the COVID-19 risk group [39]. An increased risk is arguably due to the long-term use of corticosteroids, immunosuppressive adjuvants and rituximab [40]. In addition, the advanced age of patients with pemphigoid diseases, which accounts for two thirds of AIBDs in Europe and Northern America, is another major risk factor [36, 41]. Whether SARS-CoV-2 can enter through uncovered erosive skin lesions or oropharyngeal erosions can be debated.

The AIBD task force of the *European Academy of Dermatology and Venereology* (EADV) has provided patient information, in addition to general advice on SARS-CoV-2, on how to take immunosuppressive drugs and on general precautions [42]. Patient recommendations in German can be accessed *via* the websites of the *Deutsche Dermatologische Gesellschaft* [32] and the *Pemphigus und Pemphigoid Selbsthilfegruppe e.V.* [43]. These are in line with international expert recommendations and the *International Pemphigus and Pemphigoid Foundation* [44–46]. Some authors suggest to postpone rituximab to delay immunosuppression during peak COVID-19 and to use intravenous immunoglobulins (IVIG) instead [46]. The latter have shown promise in severe COVID-19 [35, 47]. Others propose to maintain immunomodulatory therapy when needed to avoid uncontrolled flares with high morbidity and mortality. In COVID-19 patients with AIBD, immunosuppressants may be interrupted, and prednisone equivalent > 10 mg/d reduced, while topical corticosteroids, prednisone (\leq 10 mg/d), dapsone (with normal hemoglobin levels), doxycycline/tetracycline, colchicine, and IVIG can be continued [45].

Several clinical studies for the treatment of COVID-19 are currently ongoing including the use of inhibitors of pro-inflammatory IL-6, IL-1 α , and JAK1/2. These mediators are, however, probably not centrally involved in the pathophysiology of AIBD [35, 36, 48]. In contrast, C5 activation has been identified as crucial for lesion formation in experimental bullous pemphigoid and mucous membrane pemphigoid [49–51]. Since inhibition of C5 may result in

immediate clinical improvement of severe COVID-19 [52], its blockade may alleviate both, COVID-19 and pemphigoid diseases. Overall, beneficial anti-inflammatory effects should be weighed up against the potentially detrimental effects of inhibiting antiviral immunity [53].

So far, seven Italian AIBD patients with COVID-19 have been published [54–56]. Of the four patients with bullous pemphigoid who had to be hospitalized due to severe COVID-19, three died, while one recovered [55]. In a survey by the AIBD task force of the EADV, 56 AIBD patients including 13 (23 %) fatal cases with COVID-19 were identified in 51 centers from 22 countries worldwide until April 30, 2020. While no centers from China or the USA were included, most cases were reported from Iran and France. To gather more information on potential risk factors, a registry for AIBD patients with COVID-19 has been launched by the AIBD task force of the EADV [57].

SARS-CoV-2 and inflammatory connective tissue disease (collagenoses)

Systemic autoimmune diseases such as lupus erythematosus (SLE) or systemic sclerosis (SSc) are associated with increased IL-6, TNF α , IL-17 and IL-23 that induce autoreactive T-cells and autoantibodies. Only few data are available on SLE and SSc, so far none on cutaneous LE, morphea or dermatomyositis [58].

Recently, the clinical course of COVID-19 in 17 SLE patients was reported [59]. All patients received long-term hydroxychloroquine (HCQ), 71 % prednisone below 10 mg/d and 41 % immunosuppressants. During COVID-19, a higher rate of dyspnea, headache and diarrhea was detected in SLE patients compared to a previously reported Chinese general population from the Wuhan area [33, 60]. The majority of patients (76 %) developed viral pneumonia, 65 % with respiratory failure and 29 % with acute respiratory distress syndrome. All patients were hospitalized, and two patients died during the 4-weeks observation period. None of the SLE patients showed clinical signs or deterioration of LE during COVID-19. In another study on 165 Italian SLE patients, clinical data on COVID-19 contact and infection were collected [61]. 77 % of patients were treated with HCQ, 25 % with mycophenolic acid and 7 % with other immunosuppressants. Twelve patients (7.2 %) developed COVID-19. Only one patient with confirmed infection and severe SLE had to be admitted to hospital with ICU treatment and non-invasive ventilation. Seven other SLE patients did not develop any symptoms of infection despite contact with COVID-19 patients. These early findings document the course of SARS-CoV-2 infection in SLE and suggest that long-term intake of HCQ does not prevent severe COVID-19, nor does standard

treatment affect the disease course. The relevance of HCQ is still much-debated [62–64] and respective trials have been stopped. Yet, the current shortage of the drug poses a serious hazard to SLE patients as a stable and effective treatment of the disease is recommended to minimize consequences of COVID-19.

A number of reports encompassing 201 COVID-19 patients described acro-ischemic lesions resembling chilblain LE [65]. In a larger retrospective case series with 132 patients from Spain (mean age 19.9 years), 41 % had close contact to a confirmed COVID-19 patient, 14.4 % were clinically diagnosed, but only two tested positive by PCR [66]. A chilblain-like pattern was found in 72 %, an erythema multiforme-like pattern in 28 % of the patients. All published patients had mild infectious disease and mostly developed cutaneous lesions up to three weeks after clinical symptoms suggestive of COVID-19. Cutaneous lesions may be induced by a SARS-CoV-2 infection-associated vasculopathy [67]. Only recently, relations to Kawasaki syndrome were described which is discussed in the next section on vascular changes.

A potentially high-risk group for developing severe COVID-19 are patients with systemic sclerosis and interstitial lung disease (SSc-ILD). A case report described a 57-year old female with SSc-ILD and SARS-CoV-2 infection [68]. Tocilizumab (anti-IL-6 receptor antibody) was initiated four weeks prior to SARS-CoV-2 infection, which presented with mild symptoms. Larger trials are underway to evaluate the risks and benefits of tocilizumab in COVID-19 [69].

SARS-CoV-2 and vascular changes and diseases

Many case reports and case series observed “vascular skin symptoms” in COVID-19 patients. A study from France considering 14 confirmed SARS-CoV-2 patients reported acral chilblain- and livedo-like lesions as well as purpura [70]. Case reports on at least clinically confirmed vasculitis of small vessels or immune-complex vasculitis are rare [71]. More (including histological) evidence exists on occlusive vasculopathies, especially on acral chilblain-like dermatoses, which appear to accumulate in patients with COVID-19 [72]. Histologically, they show occlusive vasculopathy rather than actual vasculitis. Livedo-like lesions and necrosis occurred in 6 % of the cases in one study and mostly affected elderly patients with severe disease [65, 72]. Another report from France described acral lesions in 142 of 277 patients; 75 % of these presented with chilblain-like lesions [73]. In children, acral lesions mimicking perniones have attracted attention during the pandemic as well [74, 75]. Thus, chilblain-like lesions could be a sign of pauci-symptomatic SARS-CoV-2 infection [70, 73].

Of particular note are the recent cases of SARS-CoV-2-associated Kawasaki disease. Previously, this disease has been suspected to be associated with yet unidentified infectious triggers that provoke an intense proinflammatory response in genetically predisposed patients [76, 77]. In a study from Bergamo, Italy, Kawasaki-like disease was found 30-fold more often in children after start of the COVID-19 pandemic than before. Affected children were relatively older, presented with a higher rate of cardiac involvement and macrophage activation syndrome resulting in arterial hypotension and peripheral hypoperfusion than children diagnosed with Kawasaki disease before the COVID-19 pandemic [78–80]. Interestingly, the majority of the Kawasaki patients were negative for SARS-CoV-2 nucleic acid testing but all except two were positive for IgG/IgM antibodies to SARS-CoV-2 [78, 79]. It was hypothesized that the mounting of an immune response against the virus rather than the initial infection itself had been responsible for Kawasaki disease, suggesting that it is a post-infectious, possibly immune complex-mediated inflammatory syndrome [78, 80]. Treatment with intravenous immunoglobulins and glucocorticoids led to disease control in most patients [78, 80].

During the COVID-19 pandemic, the use of immunosuppressants for vasculitis treatment should be even more restricted when there is no sufficient evidence for their efficacy as in most cases of IgA vasculitis or polyarteritis nodosa cutanea. However, they must not be stopped abruptly or prophylactically in ANCA-associated and other severe systemic vasculitides. During the peak of the pandemic, 162 Italian patients with previously diagnosed large vessel vasculitis (67 with Takayasu arteritis, 95 with giant cell arteritis) on treatment were surveyed [81]. Four patients had a microbiological diagnosis of SARS-CoV-2 infection, and two of them required hospitalization from which both fully recovered. Importantly, their vasculitis treatment was initiated before the SARS-CoV-2 outbreak (including tocilizumab [n = 53], methotrexate [n = 51], infliximab [n = 25]), and it was not stopped or reduced indicating that immunosuppression did not necessarily result in negative outcomes [81].

SARS-CoV-2 and skin cancer

The current COVID-19 pandemic also presents several challenges for the daily care of patients with skin cancer. The first challenge is to protect individuals with advanced disease (e.g. metastatic melanoma or carcinoma as well as late stage cutaneous lymphoma). These patients could be at above-average risk of SARS-CoV-2 infections due to systemic immunosuppression. This view is supported by publications, according to which cancer patients have a higher risk of SARS-CoV-2 infections as well as of more severe courses of COVID-19

[82–84]. However, these reports were hampered by small cohort sizes and limited clinical information. A more recent multi-center study revealed that patients with hematological malignancies, lung cancer or metastatic disease had the highest rates of severe events during COVID-19 and the highest death rate [85]. Detailed data assessing the risk of COVID-19 for patients with advanced skin cancer are not available yet. Therefore, individual decisions should be made adapted to the patient's current health situation. A second challenge is to maintain regular services for skin cancer patients because many fear to acquire a SARS-CoV-2 infection in the hospital and therefore cancel their appointments. At the same time, government regulations and supply shortages have transiently limited the access of patients to regular health services [86]. This has led to concerns of some patients that their urgently needed treatments are postponed during the pandemic. It is therefore important to balance the necessity of skin cancer treatment with the potential morbidity and mortality due to an infection with SARS-CoV-2 on an individual basis [87].

The *European Society for Medical Oncology* (ESMO) as well as several other oncology societies have published guidelines for cancer patient management during the COVID-19 pandemic [88, 89]. According to the ESMO guidelines, all cancer patients undergoing surgery, radiotherapy, chemotherapy, or immunotherapy should be regularly tested for SARS-CoV-2 infections before each treatment cycle. In the case of melanoma, patients with a new diagnosis of invasive primary cancer or with complications during targeted therapies or immunotherapies for inoperably advanced stage III or IV disease should be prioritized for regular visits and continuous treatment [88]. Especially patients treated with checkpoint inhibitors need to be carefully controlled for COVID-19 symptoms since some side effects such as autoimmune pneumonitis cannot easily be differentiated from progressive COVID-19 disease.

In Germany, a task force consisting of the *Deutsche Krebsforschungszentrum* (DKFZ), the *Deutsche Krebshilfe* and the *Deutsche Krebsgesellschaft* is continuously documenting the effects of the COVID-19 pandemic on the care of cancer patients. So far, there is no measurable shortage in the care of these patients. However, the large number of cancelled appointments could reduce the diagnosis of early cancer stages, which could perhaps later translate into an increased number of more advanced stages. It is therefore important to explain to patients that the fear of SARS-CoV-2 infection should not prevent them from potentially life-saving visits to the doctor.

Conclusions

Generally, patients who feel ill with typical respiratory symptoms should be advised to have an initial telephone or video

consultation, and for the time being no careless visits to the practice or hospital should be arranged. The medical knowledge as well as diagnostic and therapeutic recommendations on COVID-19 and its impact on dermatological and allergological diseases may change rapidly and need to be updated regularly. Since tremendous efforts are undertaken to improve our understanding and to consolidate optimal treatment regimens of COVID-19 patients, we encourage physicians to check regularly the homepages and recommendations of the different national and European societies for updates on patient management during the pandemic.

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References

- Schön MP, Berking C, Biedermann T et al. COVID-19 and immunological regulations – from basic and translational aspects to clinical implications. *J Dtsch Dermatol Ges* 2020 [in press].
- Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. 2020 May 15 [Online ahead of print].
- Goldman JD, Lye DCB, Hui DS et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med* 2020 May 27 [Online ahead of print].
- Phua J, Weng L, Ling L et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med* 2020; 8: 506–17.
- Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? *Lancet Infect Dis* 2020; 20: e102–7.
- Eyerich K, Eyerich S. Immune response patterns in non-communicable inflammatory skin diseases. *J Eur Acad Dermatol Venereol* 2018; 32: 692–703.
- Sbidian E, Madrange M, Viguier M et al. Respiratory virus infection triggers acute psoriasis flares across different clinical subtypes and genetic backgrounds. *Br J Dermatol* 2019; 181: 1304–6.
- Wakkee M, de Vries E, van den Haak P et al. Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. *J Am Acad Dermatol* 2011; 65: 1135–44.
- Takeshita J, Shin DB, Ogdie A et al. Risk of serious infection, opportunistic infection, and herpes zoster among patients with psoriasis in the United Kingdom. *J Invest Dermatol* 2018; 138: 1726–35.
- Haddad A, Li S, Thavaneswaran A et al. The incidence and predictors of infection in psoriasis and psoriatic arthritis: results from longitudinal observational cohorts. *J Rheumatol* 2016; 43: 362–6.
- Schett G, Sticherling M, Neurath MF. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat Rev Immunol* 2020; 20: 271–2.
- Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids. *Int Immunopharmacol* 2020; 84: 106560.
- Stebbing J, Phelan A, Griffin I et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 2020; 20: 400–2.
- Rudnicka L, Goldust M, Glowacka P et al. Cyclosporine therapy during the COVID-19 pandemic is not a reason for concern. *J Am Acad Dermatol* 2020 May 4 [Online ahead of print].
- Augustin M, Reich K, Glaeske G et al. Co-morbidity and age-related prevalence of psoriasis: Analysis of health insurance data in Germany. *Acta Derm Venereol* 2010; 90: 147–51.
- Yiu ZZN, Smith CH, Ashcroft DM et al. Risk of serious infection in patients with psoriasis receiving biologic therapies: a prospective cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Invest Dermatol* 2018; 138: 534–41.
- Deutsches Psoriasis Register (PsoBest): <https://www.psobest.de/en/the-registry/>; American Academy of Dermatology (AAD): <https://aad.org/>; International Psoriasis Council (IPC): <https://www.psoriasis-council.org/> [Last accessed May 31, 2020].
- Damiani G, Pacifico A, Bragazzi NL et al. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: real-life data from a large cohort during red-zone declaration. *Dermatol Ther* 2020 May 1; e13475 [Online ahead of print].
- Gisoni P, Facheris P, Dapavo P et al. The impact of the COVID-19 pandemic on patients with chronic plaque psoriasis being treated with biological therapy: the Northern Italy experience. *Br J Dermatol* 2020 Apr 28; [Online ahead of print].
- Haberman R, Axelrad J, Chen A et al. Covid-19 in immune-mediated inflammatory diseases – case series from New York. *N Engl J Med* 2020; 383(1): 85–8.
- Weidinger S, Beck LA, Bieber T et al. Atopic dermatitis. *Nat Rev Dis Primers* 2018; 4: 1.
- Azkar AK, Akdis M, Azkar D et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020 May 12 [Online ahead of print].
- Wang X, Xu W, Hu G et al. SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. *Cell Mol Immunol* 2020 Apr 7 [Online ahead of print].

- 24 Singh M, Pawar M, Bothra A et al. Overzealous hand hygiene during the COVID 19 pandemic causing an increased incidence of hand eczema among general population. *J Am Acad Dermatol* 2020; 83(1): e37–e41.
- 25 Elsner P, Schliemann S, Fartasch M. Dermatologische Empfehlungen zur Handhygiene in Schulen während der COVID-19-Pandemie. *J Dtsch Dermatol Ges* 2020 [in press].
- 26 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; 34(6): e241–2.
- 27 Vestergaard C, Thyssen JP, Barbarot S et al. Quality of care in atopic dermatitis – a position statement by the European Task Force on Atopic Dermatitis (ETFAD). *J Eur Acad Dermatol Venereol* 2020; 34: e136–8.
- 28 Buhl R, Förster-Ruhrmann U, Hamelmann E et al. Biologika und Covid-19. *Allergo J* 2020; 29: 60.
- 29 Ruzicka T, Lynde CW, Jemec GB et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; 158: 808–17.
- 30 <https://www.ecdc.europa.eu/en/publications-data/guidance-wearing-and-removing-personal-protective-equipment-healthcare-settings> [Last accessed May 31, 2020].
- 31 WHO. World Health Organization: rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages: interim guidance, 6 April 2020. 2020.
- 32 <https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-novel-coronavirus-disease-2019-covid-19-pandemic-increased> [Last accessed May 31, 2020].
- 33 Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–62.
- 34 Klimek L, Pfaar O, Worm M et al. [Allergen-Immuntherapie in Der Aktuelle Covid-19-Pandemie]. *Allergo J* 2020; 29: 17–25.
- 35 Schmidt E, Kasperkiewicz M, Joly P. Pemphigus. *Lancet* 2019; 394: 882–94.
- 36 Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet* 2013; 381: 320–32.
- 37 Didona D, Maglie R, Eming R et al. Pemphigus: current and future therapeutic strategies. *Front Immunol* 2019; 10: 1418.
- 38 Maglie R, Hertl M. Pharmacological advances in pemphigoid. *Curr Opin Pharmacol* 2019; 46: 34–43.
- 39 https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Risikogruppen.html [Last accessed June 7, 2020].
- 40 Eming R, Sticherling M, Hofmann SC et al. S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid. *J Dtsch Dermatol Ges* 2015; 13: 833–44.
- 41 Hübner F, Recke A, Zillikens D et al. Prevalence and age distribution of pemphigus and pemphigoid diseases in Germany. *J Invest Dermatol* 2016; 136: 2495–8.
- 42 <https://eadv.org/covid-19/task-force> [Last accessed May 31, 2020].
- 43 <http://www.pemphigus-pemphigoid-selbsthilfe.de> [Last accessed May 31, 2020].
- 44 <http://www.pemphigus.org> [Last accessed May 31, 2020].
- 45 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 Apr 25 [Online ahead of print].
- 46 Shakshouk H, Daneshpazhooh M, Murrell DF et al. Treatment considerations for patients with pemphigus during the COVID-19 pandemic. *J Am Acad Dermatol* 2020; 82: e235–6.
- 47 Cao W, Liu X, Bai T et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect Dis* 2020; 7: ofaa102.
- 48 Pollmann R, Schmidt T, Eming R et al. Pemphigus: a comprehensive review on pathogenesis, clinical presentation and novel therapeutic approaches. *Clin Rev Allergy Immunol* 2018; 54: 1–25.
- 49 Hefpe EN, Tofern S, Schulze FS et al. Experimental laminin 332 mucous membrane pemphigoid critically involves C5aR1 and reflects clinical and immunopathological characteristics of the human disease. *J Invest Dermatol* 2017; 137: 1709–18.
- 50 Karsten CM, Beckmann T, Holtsche MM et al. Tissue destruction in bullous pemphigoid can be complement independent and may be mitigated by C5aR2. *Front Immunol* 2018; 9: 488.
- 51 Liu Z, Giudice GJ, Swartz SJ et al. The role of complement in experimental bullous pemphigoid. *J Clin Invest* 1995; 95: 1539–44.
- 52 Risitano AM, Mastellos DC, Huber-Lang M et al. Complement as a target in COVID-19? *Nat Rev Immunol* 2020; 20: 343–4.
- 53 Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? *Lancet* 2020; 395: 1111.
- 54 Balestri R, Rech G, Girardelli CR. Occurrence of SARS-CoV-2 during mycophenolate mofetil treatment for pemphigus. *J Eur Acad Dermatol Venereol* 2020; in press.
- 55 Carugno A, Sena P, Raponi F et al. Bullous skin disease patients in a high-epidemic COVID-19 area, Bergamo, Italy. *Br J Dermatol* 2020 May 2 [Online ahead of print].
- 56 Di Altobrando A, Patrizi A, Bardazzi F. Should SARS-CoV-2 influence immunosuppressive therapy for autoimmune blistering diseases? *J Eur Acad Dermatol Venereol* 2020 Apr 17 [Online ahead of print].
- 57 <https://eadv.org/covid-19/further-reading> [Last accessed May 31, 2020].
- 58 Günther C, Aschoff R, Beissert S. Cutaneous autoimmune diseases during COVID-19 pandemic. *J Eur Acad Dermatol Venereol* 2020 Jun 13 [Online ahead of print].
- 59 Mathian A, Mahevas M, Rohmer J et al. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. *Ann Rheum Dis* 2020; 79: 837–9.
- 60 Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
- 61 Bozzalla Cassione E, Zanframundo G, Biglia A et al. COVID-19 infection in a northern-Italian cohort of systemic lupus erythematosus assessed by telemedicine. *Ann Rheum Dis* 2020 May 12 [Online ahead of print].

- 62 Sawalha AH, Manzi S. Coronavirus Disease-2019: implication for the care and management of patients with systemic lupus erythematosus. *Eur J Rheumatol* 2020 Apr 8 [Online ahead of print].
- 63 Sawalha AH. Patients with lupus are not protected from COVID-19. *Ann Rheum Dis* 2020 Apr 24 [Online ahead of print].
- 64 Goyal M. SLE patients are not immune to covid-19: importance of sending the right message across. *Ann Rheum Dis* 2020. PMID: 32327426.
- 65 Piccolo V, Neri I, Filippeschi C et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. *J Eur Acad Dermatol Venereol* 2020 Apr 24 [Online ahead of print].
- 66 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. *Clin Exp Dermatol* 2020 May 9 [Online ahead of print].
- 67 Sardu C, Gambardella J, Morelli MB et al. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. *J Clin Med* 2020; 9(5): 1417.
- 68 Mihai C, Dobrota R, Schröder M et al. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. *Ann Rheum Dis* 2020; 79: 668–9.
- 69 Alattar R, Ibrahim TBH, Shaar SH et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol* 2020 May 5 [Online ahead of print].
- 70 Bouaziz JD, Duong T, Jachiet M et al. Vascular skin symptoms in COVID-19: a french observational study. *J Eur Acad Dermatol Venereol* 2020 Apr 27 [Online ahead of print].
- 71 Vanegas Ramirez A, Efe D, Fischer M. Drug-induced vasculitis in a patient with COVID-19. *J Eur Acad Dermatol Venereol* 2020 May 7 [Online ahead of print].
- 72 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. *Br J Dermatol* 2020; 183(1): 71–7.
- 73 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. *J Am Acad Dermatol* 2020 May 4 [Online ahead of print].
- 74 Andina D, Noguera-Morel L, Bascuas-Arribas M et al. Chilblains in children in the setting of COVID-19 pandemic. *Pediatr Dermatol* 2020; 37(3): 406–11.
- 75 Cordoro KM, Reynolds SD, Wattier R et al. Clustered cases of acral pernio: clinical features, histopathology and relationship to COVID-19. *Pediatr Dermatol* 2020; 37(3): 419–23.
- 76 Shulman ST, Rowley AH. Kawasaki disease: insights into pathogenesis and approaches to treatment. *Nat Rev Rheumatol* 2015; 11: 475–82.
- 77 Sunderkötter C, Lamprecht P, Mahr A et al. Nomenclature of cutaneous vasculitides – German translation of the dermatologic addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *J Dtsch Dermatol Ges* 2018; 16: 1425–32.
- 78 Verdoni L, Mazza A, Gervasoni A et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020; 395(10239): 1771–8.
- 79 Riphagen S, Gomez X, Gonzalez-Martinez C et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; 395: 1607–8.
- 80 Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. *Lancet* 2020; 395(10239): 1741–3.
- 81 Tomelleri A, Sartorelli S, Campochiaro C et al. Impact of COVID-19 pandemic on patients with large-vessel vasculitis in Italy: a monocentric survey. *Ann Rheum Dis* 2020 Apr 28 [Online ahead of print].
- 82 Liang W, Guan W, Chen R et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; 21: 335–7.
- 83 Yu J, Ouyang W, Chua MLK et al. SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol* 2020 Mar 25 [Online ahead of print].
- 84 Zhang L, Zhu F, Xie L et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020; 31(7): 894–901.
- 85 Dai M, Liu D, Liu M et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov* 2020; 10(6): 783–91.
- 86 Al-Quteimat OM, Amer AM. The impact of the COVID-19 pandemic on cancer patients. *Am J Clin Oncol* 2020; 43: 452–5.
- 87 Schrag D, Hershman DL, Basch E. Oncology practice during the COVID-19 pandemic. *Jama* 2020 Apr 13 [Online ahead of print].
- 88 <http://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic> [Last accessed May 31, 2020].
- 89 <http://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19> [Last accessed May 31, 2020].