REVIEW ARTICLE

Dermatologists and SARS-CoV-2: the impact of the pandemic on daily practice

P. Gisondi,[1,*] S. Piaserico,[2] A. Conti,[3] L. Naldi[4,5]

[1]Department of Medicine, Section of Dermatology and Venereology, University of Verona, Verona, Italy
[2]Dermatology Unit, Department of Medicine, University of Padua, Padua, Italy
[3]Department of Surgical, Medical, Dental and Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, Dermatology Unit, University of Modena and Reggio Emilia, Modena, Italy
[4]Study Centre of the Italian Group for the Epidemiologic Research in Dermatology (GISED), Bergamo, Italy
[5]Department of Dermatology, San Bortolo Hospital, Vicenza, Italy
*Correspondence: P. Gisondi. E-mail: paolo.gisondi@univr.it

Abstract

Since the first case of 'pneumonia of unknown aetiology' was diagnosed at the Wuhan Jinyintan Hospital in China on 30 December 2019, what was recognized thereafter as 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2) has spread over the four continents, causing the respiratory manifestations of coronavirus disease-19 (COVID-19) and satisfying the epidemiological criteria for a label of 'pandemic'. The ongoing SARS-CoV-2 pandemic is having a huge impact on dermatological practice including the marked reduction of face-to-face consultations in favour of teledermatology, the uncertainties concerning the outcome of COVID-19 infection in patients with common inflammatory disorders such as psoriasis or atopic dermatitis receiving immunosuppressive/immunomodulating systemic therapies; the direct involvement of dermatologists in COVID-19 care for patient assistance and new research needs to be addressed. It is not known yet if skin lesions and derangement of the skin barrier could make it easier for SARS-CoV-2 to transmit via indirect contact; it remains to be defined if specific mucosal or skin lesions are associated with SARS-CoV-2 infection, although some unpublished observations indicate the occurrence of a transient varicelliform exanthema during the early phase of the infection. SARS-CoV-2 is a new pathogen for humans that is highly contagious, can spread quickly, and is capable of causing enormous health, economic and societal impacts in any setting. The consequences may continue long after the pandemic resolves, and new management modalities for dermatology may originate from the COVID-19 disaster. Learning from experience may help to cope with future major societal changes.
Received: 27 March 2020; Accepted: 8 April 2020

Conflicts of interest

Gisondi P has nothing to declare. Conti A has nothing to declare. Piaserico S has nothing to declare. Naldi L has nothing to declare.

Funding sources

None declared.

Introduction

Since the first case of 'pneumonia of unknown aetiology' was diagnosed at the Wuhan Jinyintan Hospital in China on 30 December 2019, what was recognized thereafter as 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2) has spread over the four continents, causing the respiratory manifestations of coronavirus disease-19 (COVID-19) and satisfying the epidemiological criteria for a label of 'pandemic', broadly defined as the uncontained spread of an infection in multiple regions.[1] As of 24 March 2020, more than 420 000 cases have been identified worldwide, and almost 19 000 deaths have occurred. After China, the area more severely affected nowadays is Europe, with Italy having the dubious record of the number of deaths.[2]

P. Gisondi and S. Piaserico equally contributed to the manuscript.

The SARS-CoV-2 pandemic

SARS-CoV-2 is a zoonotic single-stranded RNA virus of the Coronaviridae family, which has crossed species to infect humans, as previously occurred for the virus of the 'severe acute respiratory syndrome' (SARS), transmitted to humans from exotic animals in wet markets in China, and for the virus of the 'Middle East respiratory syndrome' (MERS), transmitted from camels in Saudi Arabia.[3] Phylogenetic analyses indicate that bats are the reservoir of SARS-CoV-2, with the intermediate host (if any) not identified yet. The virus enters the body through mucosal surfaces via droplets, aerosols or hand contact. Airborne spread, *per se*, is not a major route of transmission. Faecal shedding has been demonstrated in some patients, but oro-faecal transmission is not recognized as a relevant driver of infection.[4] Transmission of SARS-CoV-2 mainly occurs in households and other close settings. Nosocomial outbreaks have been reported.[5] Disease presentation can range from no symptoms to severe pneumonia and death (Table 1). The mean incubation period is 5–6 days (range 1–14 days), and the virus can be isolated from the nasopharynx 1–2 days prior to symptom onset. About 90% of people have mild disease and recover.[6] A small proportion has a severe or critical condition. The proportion of truly asymptomatic people remains to be determined. Transmission during an asymptomatic stage does not seem to play a relevant role in spreading the virus. Individuals at higher risk for severe disease include people aged over 60 years and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer.[3,6] The disease in children is unapparent or mild. To date, the management of infection has been largely supportive.[3,5,7] Case fatality rates, that is the proportion of deaths from the disease compared to the total number of people diagnosed during a certain period of time, varies, among the others, with location, intensity of transmission, demography of the population, health service organization and modalities adopted to identify cases. The estimates range from 0.3% in Germany to about 10% in Italy.[2]

SARS-CoV-2 is a new virus to humans, and no immunization exists in the population at large. Hence, the virus spreads with astonishing speed. The basic reproduction number (i.e. the number of cases one infected individual generates), R0, has been estimated to range between 1.4 and 3.9 according to the mitigating measures adopted, and the epidemic in the early phase in China was doubling every 6.4 days.[3,7,8] Some model predictions indicate that millions of people may be infected by the end of 2020. There is evidence that public health interventions can reduce and even interrupt transmission. These measures must fully incorporate immediate case detection and isolation, rigorous close contacts tracing with quarantine and direct population engagement (Table 2).[9–11] Contents of educational interventions should include social distancing measures and personal protection strategies such as hand hygiene.

The ongoing pandemic is having a huge impact on dermatological practice. We are making specific reference to Italy, but the situation is similar to what is happening in other countries (personal communications and[12]).

Table 1 Clinical manifestations of SARS-CoV-2 infection

Most common symptoms (in order of decreasing frequency)
Fever
Dry cough
Fatigue
Sputum production
Shortness of breath
Profound loss of smell and taste
Sore throat
Headache
Myalgia or arthralgia
Chills
Nausea or vomiting
Nasal congestion
Diarrhoea
Haemoptysis
Conjunctival congestion
Severe disease
Dyspnoea
Respiratory frequency $\geq$30/min
Blood oxygen saturation $\leq$93%
PaO_2/FiO_2 ratio <300
Lung infiltrates >50% of the lung field occurring rapidly (24–48 h)
Critical disease
Respiratory failure
Septic shock
Multiple organ dysfunction/failure

Table 2 Prevention methods during the SARS-CoV-2 pandemics

Insolation of cases and protection of healthcare workers
Quarantine for exposed people
Protective sequestration
Travel restrictions and border closure
Social distancing (e.g. school closure)
Personal protective equipment (gloves, masks†, hand sanitizers)
Handwashing
Environmental decontamination
Closing of live animal markets

†A mask should only be used by health workers, care takers and individuals with respiratory symptoms. Before touching the mask, hands should be cleaned and cleaned again after removal.

Shrinking of face-to-face consultations and new role for telemedicine

A significant reduction of outpatient dermatological visits both in public hospitals and in private practice offices is registered in most countries. In Italy, the reduction of dermatological consultations is approximately 80–90%. Such a marked reduction also applies to medical specialities other than dermatology. Most hospitals have postponed appointments for elective surgery and non-urgent visits to avoid people moving from home and to focus on COVID-19 management. In Italy, the reduction is also one of the consequences of the legislative decree of the Italian prime minister #IoRestoaCasa (translated: I stay at home) recommending the closure of any commercial activities all over Italy, except for pharmacies, groceries and other essential services.[13] Citizens are not allowed to leave their homes unless there is the need of going to work (such as in the case of health workers), for urgent health reasons or the purchase of necessary goods. Triage is made before any patient attends a health consultation looking for any respiratory symptom or fever. In case of symptoms, the patient is put in a separate area.

In this situation, remote working is boosted, and telemedicine – that is defined as 'the remote diagnosis and treatment of patients by means of telecommunications technology' – could be very appropriate.[14] By practicing teletriage, which prioritizes in-person clinic visits for patients with conditions associated with greater morbidity or mortality and uses telemedicine for the rest, the delivery of dermatologic care can be pursued during the pandemic.[15–19]

Uncertainties about biologic and targeted therapies

It remains unknown to what extent SARS-CoV-2 infection impacts chronic inflammatory skin diseases and their treatment. It would be reasonable for physicians to be alert to potentially harmful effects of the infection and to counsel all their patients on how to prevent transmission of the virus.[20] Given the available data on increased rates of selected infections associated with biologic therapies from clinical trials and registries, patients and physicians may be concerned about the continuation or starting of biologic therapies during the SARS-CoV-2 pandemic. No specific data are available. It is reasonable that for dermatological patients diagnosed with COVID-19, physicians consider discontinuation of immunosuppressant medications.[20] This is in accordance with established treatment guidelines for psoriasis for example (see the European Dermatology Forum and the American Academy of Dermatology guidelines[21]). The safety of initiating immunosuppressant medications during the pandemic is questionable.[22] The benefit-to-risk ratio of any immunosuppressive therapeutic intervention should be carefully weighted in dermatological patients on a case-to-case basis. Individuals over the age of 60 years and/or patients with comorbid conditions including cardiovascular diseases, diabetes, metabolic syndrome, chronic obstructive pulmonary disease, chronic kidney diseases and cancer have a higher risk of developing more serious infections.[20,23]

As of now, there is insufficient evidence to determine how SARS-CoV-2 infection will impact the clinical course of chronic inflammatory conditions such as psoriasis and to estimate potential risks associated with systemic treatment.[24] In COVID-19 patients, but also in SARS and MERS patients, inflammatory cytokines assume a double role: in the first place, they stimulate the activation of an effective immune response, while at a later time, in case of failure of the adaptive immunity (mainly Th1-polarized), they mediate the development of an exaggerated systemic inflammation.[25–27] This 'cytokine storm' is both ineffective towards the pathogen and detrimental for the body, eventually leading to acute respiratory distress syndrome (ARDS) and potentially to death.[28]

Several studies have demonstrated that interleukin (IL)-17 and tumour necrosis factor (TNF)-alpha elevation plays a key role in the development of the detrimental inflammatory response correlated with both coronavirus and non-coronavirus viral pneumonia.[29] In a model of immunosuppressed macaques infected with MERS-CoV, significantly higher levels of MERS-CoV replication in respiratory tissues and viral shedding were found. However, despite increased viral replication, pathologic changes in the lungs were significantly lower in immunosuppressed animals.[30] MERS-CoV virus itself caused little damage to the cells that it infected and the tissue damage might be attributed to the overactive inflammatory response. Therefore, it has been hypothesized that treatment for patients with symptomatic COVID-19 would benefit from additional therapy that lessens the inflammatory response, and not be based solely on therapies that are aimed at controlling virus replication. In this context, agents blocking TNF or IL17 pathways could have the potential to improve COVID-19's aberrant immune response and ARDS-related mortality.[31]

Based on these observations, two clinical trials investigating the use of ixekizumab or adalimumab associated with antiviral therapy are currently on going in China as a possible treatment for COVID-19.[32,33]

The exaggerated inflammatory responses (cytokine storm) and increased damage of tissues seen in SARS, MERS and COVID-19 might also be enhanced by patient's comorbidities, namely diabetes, or even by ageing *per se*. Older adults have elevated levels of pro-inflammatory cytokines, and the term 'inflamm-ageing' was coined to describe this phenomenon. This could partially explain the association between patient's older age and some comorbidities with a worse outcome.[34]

What about immunosuppressive therapies?

Intriguingly, during SARS outbreak in 2002 and MERS and COVID-19 (so far), no death was reported in transplanted patients or under immunosuppressive treatments, (e.g. cyclosporine, methotrexate, azathioprine) at any age.

In a recent letter, D'Antiga reported 3 immunosuppressed children in Bergamo, Italy, who were tested positive for SARS-CoV-2 but only had a mild disease without any pulmonary involvement.[35] Published data on SARS, MERS and SARS-CoV-2 seem to suggest that patients with drug-induced immunosuppression are not at particularly increased risk of severe pulmonary disease compared to the general population.

Dermatologists directly involved in COVID-19 care

The role of dermatologists during the pandemic may not be limited to their Dermatology clinics. In the areas of Italy severely affected by the coronavirus outbreak, extra beds have been created in Internal Medicine wards for COVID-19 patients; dermatologists, along with doctors from other medical subspecialties, have therefore been asked to provide assistance to COVID-19 patients in these departments due to the shortage of doctors. For those dermatologists who are now fighting in the front line against COVID-19, a number of challenges need to be faced on a daily basis, the most crucial one being personal protection. As of 20 March, 3.654 health workers were infected with COVID-19 in Italy, representing about 10% of the total number of positive patients,[36] and 17 physicians died due to SARS-CoV-2 infection.[37] Such appalling data underscore the importance of the availability of protective equipment like medical masks, gloves, eye protection and gowns for medical personnel dealing with infected patients. Shortage of medical masks for health workers due to 'panic shopping' from the population may jeopardize the safety of physicians dealing with COVID-19 patients.

A further area where dermatologists are involved is with damages to the skin from personal protective equipment of healthcare professionals and with procedures such as frequent hand washing. Clinical manifestations include acute and chronic irritant dermatitis, secondary infections and possible aggravation of pre-existing cutaneous disorders. Recommendations for preventing these adverse effects have been published.[38] Recommendations for preventing irritant hand dermatitis include avoiding harsh soaps because while these will clear any infectious agent from the skin, at the same time, they destroy the protective barrier that protects us from other pathogens. We need to compensate for the damage we are inflicting on our skin with frequent hand washing or alcohol-based hand sanitizers by putting moisturizer on damp skin.[38]

Research needs

There are several unaddressed issues of SARS-CoV-2 infection for dermatologists. First, dermatologists from Wuhan suggested that skin lesions and derangement of the skin barrier could make it easier for SARS-CoV-2 to transmit via indirect contact.[39] However, no clear evidence is currently available pointing to any modes of transmission other than inhaling droplets and aerosols, or contact with a contaminated surfaces followed by touching mouth, nose or eyes.[40] Secondly, it remains to be defined if specific mucosal or skin lesions are associated with SARS-CoV-2 infection. Recalcati S. analysed the cutaneous involvement in patients hospitalized of COVID-19 infection in the Lecco Hospital, Lombardy, Italy. In 18 out of 88 patients (20.4%), he found cutaneous manifestations either at the onset of and during the course of the infection, including erythematous rash (14 patients), widespread urticaria (3 patients) and chickenpox-like vesicles (1 patient). Trunk was the main involved region. Itching was low or absent and usually lesions healed in few days. Apparently, there was not any correlation with disease's severity.[41] From Thailand, Joob B *et al.*[42] reported a case presenting with a skin rash with petechiae associated with low platelet count, initially diagnosed as dengue, suggesting that also vascular lesions may be early signs of the infection. We observed a diffuse papular eruption in a woman with COVID-19 febrile infection, as reported in Fig. 1. Finally, data are currently lacking, as already discussed, concerning the outcome of COVID-19 infection in patients with inflammatory and malignant skin conditions. The course of COVID-19 in patients with immune-mediated diseases like psoriasis receiving different systemic therapies is completely unknown and may be of special interest to guide the future management of these patients and, more in general, to understand the role of immune response in COVID-19 outcome.[43]

Conclusions

COVID-19 is a new pathogen for humans that is highly contagious, can spread quickly, and is capable of causing enormous

(a)
(b)

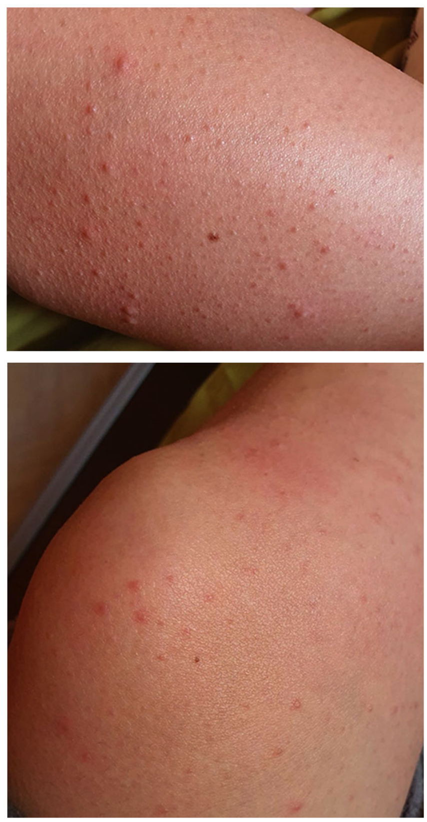

Figure 1 Diffuse papular eruption involving the lower limbs in a woman with confirmed febrile COVID-19 infection. (a) Details of lesions on the inner thigh and (b) knee area. Images kindly provided by Dr. Anna Di Landro

health, economic and societal impacts in any setting. Dermatological care is already deeply impacted by the pandemic. The consequences may continue long after the pandemic resolves, and new management modalities for dermatology may originate from the COVID-19 disaster. Learning from experience may help to cope with future major societal changes.[44]

Acknowledgement

The patients in this manuscript have given written informed consent to publication of their case details.

References

1 Callaway E. Time to use the p-word? Coronavirus enter dangerous new phase. *Nature* 2020; **579**: 12.
2 [WWW document]. URL https://www.ecdc.europa.eu/en/cases-2019-ncov-eueea (last accessed: 27 March 2020).
3 Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [WWW document]. URL https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (last accessed: 27 March 2020).
4 Wang W, Xu Y, Gao R *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; **323**(18): 1843–1844.
5 Del Rio C, Malani PN. 2019 novel coronavirus-important information for clinicians. *JAMA* 2020; **323**: 1039.
6 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**: 1054–1062.
7 Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet* 2020; **395**: 1225–1228.
8 Neher RA, Dyrdak R, Druelle V *et al*. Potential impact of seasonal forcing on a SARS-CoV-2 pandemic. *Swiss Med Wkly* 2020; **150**: w20224.
9 Hellewell J, Abbott S, Gimma A *et al*. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *Lancet Glob Health* 2020; **8**: e488–e496.
10 Flahault A. COVID-19 cacophony: is there any orchestra conductor? *Lancet* 2020; **395**: 1037.
11 Layne SP, Hyman JM, Morens DM, Taubenberger JK. New coronavirus outbreak: framing questions for pandemic prevention. *Sci Transl Med* 2020; **12**: eabb1469.
12 Heymann WR. The profound dermatological manifestations of COVID-19 [WWW document]. URL https://www.aad.org/dw/dw-insights-and-inquiries/2020-archive/march/dermatological-manifestations-covid-19 (last accessed: 27 March 2020).
13 Paterlini M. On the front lines of coronavirus: the Italian response to covid-19. *BMJ* 2020; **368**: m1065.
14 Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. *N Engl J Med* 2020; **382**: 1679–1681.
15 Chuchvara N, Patel R, Srivastava R, Reilly C, Rao BK. The growth of teledermatology: expanding to reach the underserved. *J Am Acad Dermatol* 2020; **82**: 1025–1033.
16 Leavitt ER, Kessler S, Pun S *et al*. Teledermatology as a tool to improve access to care for medically underserved populations: a retrospective descriptive study. *J Am Acad Dermatol* 2016; **75**: 1259–1261.
17 Chansky PB, Simpson CL, Lipoff JB. Implementation of a dermatology teletriage system to improve access in an underserved clinic: a retrospective study. *J Am Acad Dermatol* 2017; **77**: 975–977.
18 Nelson CA, Takeshita J, Wanat KA *et al*. Impact of store-and-forward (SAF) teledermatology on outpatient dermatologic care: a prospective study in an underserved urban primary care setting. *J Am Acad Dermatol* 2016; **74**: 484–490.e481.
19 Heffner VA, Lyon VB, Brousseau DC, Holland KE, Yen K. Storeand-forward teledermatology versus in-person visits: a comparison in pediatric teledermatology clinic. *J Am Acad Dermatol* 2009; **60**: 956–961.
20 International Psoriasis Council. Statement on the Coronavirus (COVID-19) Outbreak [WWW document] 11th March 2020. URL https://www.psoriasiscouncil.org/blog/Statement-on-COVID-19-and-Psoriasis.htm (last accessed: 27 March 2020).
21 American Academy of Dermatology. Guidance on the use of biologic agents during COVID-19 outbreak [WWW document]. URL https://www.aad.org/member/practice/managing/coronavirus (last accessed: 27 March 2020).
22 Conforti C, Giuffrida R, Dianzani C, Di Meo N, Zalaudek I. COVID-19 and psoriasis: is it time to limit treatment with immunosuppressants? A call for action. *Dermatol Ther* 2020; e13298.
23 Yang J, Zheng Y, Gou X *et al*. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis* 2020; **94**: 91–95.
24 Bashyam AM, Feldman SR. Should patients stop their biologic treatment during the COVID-19 pandemic. *J Dermatolog Treat* 2020; **31**: 317–318.
25 Josset L, Menachery VD, Gralinski LE *et al*. Cell host response to infection with novel human coronavirus EMC predicts potential antivirals and important differences with SARS coronavirus. *MBio* 2013; **4**: e00165-13.
26 Ryzhakov G, Lai CC, Blazek K *et al*. IL-17 boosts proinflammatory outcome of antiviral response in human cells. *J Immunol* 2011; **187**: 5357–5362.
27 Hussell T, Pennycook A, Openshaw PJ. Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunopathology. *Eur J Immunol* 2001; **31**: 2566–2573.
28 Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother* 2020. https://doi.org/10.1093/jac/dkaa114
29 Shi X, Zhou W, Huang H *et al*. Inhibition of the inflammatory cytokine tumor necrosis factor-alpha with etanercept provides protection against lethal H1N1 influenza infection in mice. *Crit Care* 2013; **17**: R301.
30 Prescott J, Falzarano D, de Wit E *et al*. Pathogenicity and Viral Shedding of MERS-CoV in Immunocompromised Rhesus Macaques. *Front Immunol.* 2018; **9**:205.
31 Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *Lancet* 2020; **395**: e35–e36.
32 [WWW document]. URL http://www.chictr.org.cn/showprojen.aspx?proj=50251 (last accessed: 27 March 2020).
33 [WWW document]. URL http://www.chictr.org.cn/showprojen.aspx?proj=49889 (last accessed: 27 March 2020).
34 Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. *Nat Rev Immunol* 2013; **13**: 875–887.
35 D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. *Liver Transpl* 2020; **26**: 832–834.
36 Istituto Superiore di Sanità. Integrated surveillance of COVID-19 in Italy [WWW document]. 20th March 2020 update. URL https://www.epicentro.iss.it/coronavirus/bollettino/Infografica_20marzo%20ENG.pdf (last accessed: 26 March 2020).
37 FNOMCeO. Elenco dei Medici caduti nel corso dell'epidemia di Covid-19 [WWW document]. URL https://portale.fnomceo.it/elenco-dei-medici-caduti-nel-corso-dellepidemia-di-covid-19/ (last accessed: 27 March 2020).
38 Yan Y, Chen H, Chen L *et al*. Consensus of Chinese experts on protection of skin and mucous membrane barrier for healthcare workers fighting against coronavirus disease. *Dermatol Ther* 2019; **2020**: e13310.
39 Tao J, Song Z, Yang L *et al*. Emergency management for preventing and controlling nosocomial infection of 2019 novel coronavirus: implications for the dermatology department. *Br J Dermatol* 2020; **182**(6): 1477–1478.
40 Adhikari SP, Meng S, Wu YJ *et al*. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease

(COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty* 2020; **9**: 29.
41 Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol* 2020; **34**: e212–e213.
42 Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for Dengue. *J Am Acad Dermatol* 2020; **82**: e177.
43 Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection–a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect* 2020; **9**: 727–732.
44 Jones DS. History in a crisis – lessons for Covid-19. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMp2004361