

## Commentary

**COVID-19 hygiene measures: hand eczema and insights into ACE2 and integrins as key molecules for SARS-CoV-2 cutaneous transmission****Pietro Sollena<sup>1</sup>, MD, Simone Cappilli<sup>2</sup>, MD, Alfredo Piccerillo<sup>1,2</sup>, MD, Andrea Chiricozzi<sup>1,2</sup>, MD and Ketty Peris<sup>1,2</sup>, MD**<sup>1</sup>Dermatologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; and <sup>2</sup>Dermatologia, Università Cattolica del Sacro Cuore, Rome, Italy**Correspondence**

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Conflict of interest: Pietro Sollena reports personal fees for presentations during dermatologic meetings from Leo-Pharma, Novartis, Pierre Fabre, Sanofi, and Almirall, outside the submitted work. Simone Cappilli has no conflict of interest to report. Alfredo Piccerillo has no conflict of interest to report. Andrea Chiricozzi served as advisory board member and consultant, and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Biogen, Fresenius Kabi, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme, and UCB-Pharma, outside the submitted work. Ketty Peris reports personal fees for Advisory Board Meetings from Almirall, AbbVie, Biogen, Lilly, Celgene, Galderma, Leo Pharma, Novartis, Pierre Fabre, Sanofi, Sandoz, Sun Pharma, and Janssen, outside the submitted work.

Funding source: None.

doi: 10.1111/ijd.15208

The outbreak of coronavirus disease 2019 (COVID-19) has rapidly spread worldwide, since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is characterized by high contagious rate and rapid human-to-human transmission. Currently, respiratory droplets and direct contact are considered to be the main transmission routes.<sup>1</sup>

The World Health Organization (WHO) and other international politics and health institutions have developed regularly updated strategies and limitations to contain the rapid spread of the infection. One of the leading recommendations is to frequently wash the hands and use alcohol-based hand rubs, other than avoiding hand contact with eyes, nose, and mouth.

Since the COVID-19 outbreak, all healthcare workers (HCWs) revealed a highly significant increase of hand washing and disinfection frequency, even if not directly involved in the treatment of patients affected by SARS-CoV-2 infection. The HCWs' improved hygienic awareness was correlated with a higher prevalence of signs and symptoms associated with hand dermatitis (e.g., erythema, itching, and dryness), despite hand eczema itself was proportionately underreported.<sup>2</sup>

The risk of hand eczema among HCWs has been reported in a cross-sectional study showing dose-dependent positive correlation between number of daily hand washes and increased risk of eczema.<sup>3</sup> Recently, a telematic survey was conducted among

frontline HCWs in a COVID-19 hospital, reporting similar data on hand-skin damage associated with enhanced infection prevention measures, especially hand washing over 10 times per day.<sup>4</sup> HCWs were diagnosed to have either irritant or allergic contact dermatitis.<sup>3,4</sup>

Skin barrier damage, because of overzealous hand hygiene, has been suggested as a potential route of entry for SARS-CoV-2 virus.<sup>4</sup> This hypothesis is based on the mechanism of SARS-CoV-2 entry into cells that is primed by the interaction between the receptor-binding domain located in the viral spike protein (S protein) and the cellular angiotensin-converting enzyme 2 receptors (ACE2). ACE2 is expressed in the basal cell layer of the epidermis extending also to the basal cell layer of hair follicles, as well as in epithelia of the eccrine glands and smooth muscle surrounding the sebaceous glands.<sup>5,6</sup>

In addition to ACE2 interaction, the viral infection process might be facilitated and accelerated in alveolar epithelial cells by the binding of SARS-CoV-2 S protein to integrins.<sup>6</sup>

Thereby, a putative role of some integrins (such as  $\alpha V\beta 1$ ,  $\alpha V\beta 3$ ,  $\alpha V\beta 5$ ,  $\alpha V\beta 6$ ,  $\alpha V\beta 8$ ,  $\alpha 5\beta 1$ ,  $\alpha 8\beta 1$ , and  $\alpha 11\beta 3$ ) has been proposed as an alternative host-cell receptor of SARS-CoV-2 or acting in a supplemental role to ACE2 binding, facilitating endocytosis of virion particles.<sup>7</sup>

Integrins are a large family of heterodimeric transmembrane receptors, constituting  $\alpha\beta$  subunits, largely expressed on keratinocyte-cell surface acting as a physical link between dermal extracellular matrix and basal keratinocytes. Their function extends through the cell membrane in a bidirectional manner as a way of contributing to main physiologic cellular processes like proliferation, differentiation, migration, and apoptosis.<sup>7,8</sup>

The integrin-S protein interaction is likely caused by S protein mutation that leads to the presence of Arg-Gly-Asp (RGD) sequence at the interaction surface, constituting a further viral mechanism of cell entry.<sup>9</sup> Besides binding RGD sequence, other integrin-binding sites were found to be specifically expressed in SARS-CoV-2, and, in particular, a genetic alteration leading a change from a Leu-Asp-Val (LDV) to a Leu-Asp-Ile (LDI) motif seems to be significant for viral infection process. Orf1ab, a polyprotein found on gene sequences in SARS-CoV-2, contains many integrin-binding motifs implicated in cell adhesion, included RGD, LDV, and LDI, serving as binding sites for alpha/beta subfamilies of integrin.<sup>10</sup>

While most epithelial integrins are constitutively expressed in the skin, the expression of integrins, such as  $\alpha5\beta1$  and  $\alphaV\beta6$ , is induced during wound healing, proving level changes in other pathological conditions, like inflammatory disorders and cancers.<sup>8</sup> Moreover, an upregulation of integrin- $\alpha6$  and integrin- $\beta1$  was observed while treating an *in vitro* reconstituted skin equivalent model with oligosaccharides of hyaluronic acid, reproducing the wound healing process at sites of tissue injury.<sup>11</sup>

Since numerous alternative routes of transmission have been under investigation, including aerosols nebulization, fecal-oral, and sexual and intrauterine vertical transmission, the theoretical possibility that cutaneous erosions of hand eczema in a setting of excessive hand hygiene could contribute to the direct contact transmission of SARS-CoV-2 should not be excluded. Further observations are needed to confirm this hypothesis. As dermatologists, we believe that promotion of proper procedures to avoid hand eczema should be encouraged more. Up to date, the adoption of preventive measures is warranted and represents an actual key issue, since these general recommendations are addressed to the worldwide general population and

not only to HCWs. Therefore, we suggest the choice to wash hands by alcohol-based hand rubs, avoid detergent and soaps when dirt is not visible, and the regular use of lipid-rich moisturizers in order to prevent severe eczema and to heal cutaneous fissures and erosions.

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