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The role of bacterial skin infections in atopic dermatitis: expert statement and review from the International Eczema Council Skin Infection Group

Short title: The role of bacterial skin infections in atopic dermatitis

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What's already known about this topic?

- Patients with atopic dermatitis (AD) have an increased risk of recurrent skin infections causing significant morbidity.
- *Staphylococcus aureus* (*S. aureus*) colonizes lesional skin of most AD subjects and is the most common organism to cause infectious complications.
- AD subjects who are colonized with *S. aureus* have more severe disease, higher type 2 immune serum biomarkers, greater physiological barrier disruption and greater allergen sensitization.
- The abnormal host skin barrier, cutaneous innate and adaptive immune mechanisms, and trauma from scratching all contribute to the increased risk of skin infection

What does this study add?

- Based on the latest evidence and expert consensus discussions, this article defines the clinical features of bacterial infection in AD, including secondary viral and fungal infections, as well as infection in different ethnic skin types.
- We present our current understanding of the host and bacterial factors that influence microbial colonization and virulence in AD.

Abstract

Patients with atopic dermatitis (AD) have an increased risk of bacterial skin infections that cause significant morbidity and, if untreated, may become systemic. *Staphylococcus aureus* (*S. aureus*) colonizes the skin of most AD subjects and is the most common organism to cause infections. Overt bacterial infection is easily recognised by the appearance of weeping lesions, honey-coloured crusts, and pustules. However, the wide variability in clinical presentation of bacterial infection in AD and the inherent features of AD – cutaneous erythema and warmth, oozing associated with oedema, and regional lymphadenopathy – overlap with those of infection, making clinical diagnosis challenging.

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Furthermore, some features may be masked because of anatomical site- and skin-type-specific features, and the high frequency of *S. aureus* colonization in AD makes positive skin swab culture of suspected infection unreliable as a diagnostic tool. The host mechanisms and microbial virulence factors that underlie *S. aureus* colonization and infection in AD are incompletely understood. The aim of this article is to present the latest evidence from animal and human studies, including recent microbiome research, to define the clinical features of bacterial infections in AD, and to summarize our current understanding of the host and bacterial factors that influence microbial colonization and virulence.

Introduction

Patients with atopic dermatitis (AD; also known as 'atopic eczema') have an increased risk of recurrent skin infections.[1–4] *Staphylococcus aureus* (*S. aureus*) is the most common infectious organism, although beta-hemolytic streptococci may also be involved.[5–8]

The mechanisms underlying bacterial infection in AD are multifactorial and include both host and bacterial factors. The reduced skin barrier, cutaneous innate and adaptive immune abnormalities and trauma from scratching all contribute to the increased risk of skin infection.[9–13] The host skin microbiota may play a role in protecting against *S.aureus* colonization and infection in AD subjects.[14–17] Bacterial virulence factors, such as the superantigens, proteases and cytolytic phenol-soluble modulins (PSMs) secreted by *S. aureus,* cause skin inflammation and may also contribute to bacterial persistence and/or epithelial penetration and infection.[12,18,19]

The complex interaction between bacteria and host results in wide variability in the clinical presentation of infection in AD and can make the diagnosis challenging. Cutaneous infection may be associated with concomitant AD flares and the classic signs of infection (erythema, oozing and crusting, and increased cutaneous warmth) are masked by similar clinical features of AD itself. Increases in erythema in individuals with

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darker skin types are more difficult to appreciate, making diagnosis yet more challenging. Pustules are an uncommon sign of bacterial infection in AD, but if present can allow the diagnosis to be made with greater certainty. Diagnosis and management decisions are further complicated by the fact that the main causative organism, *S. aureus*, commonly colonizes even non-lesional, clinically unaffected AD skin, thus limiting the usefulness of bacterial cultures in identifying the causative organism.

Untreated bacterial skin infection in AD may become systemic and lead to life-threatening complications including sepsis, endocarditis and bone and joint infections.[20–22] Despite the significant morbidity caused by bacterial skin infection in AD, there is a lack of consensus on how to define and treat associated bacterial colonization and infection. Although there are many diagnostic criteria for AD itself, there are no validated diagnostic criteria for infected AD.[23]

The International Eczema Council (IEC), a group of approximately 100 experts in AD worldwide, has recently initiated a taskforce to define the role of bacterial skin infections and their management in AD through consensus statements in an effort to provide level D evidence. It is hoped that input from clinical experts will contribute to better defining the wide-ranging clinical presentations of *S. aureus* infection in AD and, more importantly, better identify those who may benefit from existing or novel antimicrobial treatments. Based on a systematic search of the literature, including terms for AD as well as 'infection', 'bacteria', 'staphylococcus aureus' and 'microbiome' (detailed search strategy available on request), this narrative review defines the clinical features of bacterial infection in AD and our current understanding of the host and bacterial factors that influence microbial colonization and virulence.

Clinical features of bacterial skin infection in AD

The typical clinical signs of overt bacterial skin infection in AD are well recognised. More specific signs of *S. aureus* infection in AD lesions include weeping, honey-coloured crusts, and pustules, both interfollicular and follicular-based (folliculitis) (Fig. 1a-b).[6,24] Pustules are an uncommon feature of infection in AD, but may be associated with significant pruritus and even pain (Fig. 1c). [25] By contrast, β-hemolytic streptococcal infection may present with well-defined, bright red erythema, thick-walled pustules and heavy crusting (Fig. 1d).[7,26] In severe cases, cutaneous bacterial infection may cause

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abscesses (especially with methicillin-resistant *S. aureus*/ MRSA infection), fever and lymphadenopathy. A complication in diagnosing infection in AD is the common association with a disease flare. Features of flared AD (increased erythema, oedema, papulation, oozing, and excoriation) can mask and/or resemble signs of infection.

Concomitant viral infection

Several non-bacterial infections can occur concomitantly with bacterial skin infection and can resemble bacterial infections, requiring consideration in the differential diagnosis. For instance, eczema herpeticum (EH) is caused by the local spread of herpes simplex virus (HSV) that favours AD lesional skin and is commonly observed in the context of an AD flare.[27] Early in the course of EH the characteristic skin lesions are superficial clusters of dome-shaped vesicles and/or small, round, punched-out erosions (Fig. 2a-b).[27] As the disease progresses, lesions may become superficially infected with *S. aureus* and may develop an impetiginized scale (Fig. 2c-d).[12] EH typically arises in involved AD skin, most frequently the face, neck, upper trunk, and antecubital/popliteal areas with AD, and is often accompanied by fever, malaise and lymphadenopathy.[28,29] Moderate-to-severe AD, filaggrin (*FLG*) loss-of-function mutation, a history of *S. aureus* skin infection, greater allergen sensitization, and type 2 immunity are important risk factors for EH.[30–32] Staphylococcal alpha-toxin and reductions in the tight junction protein, called claudin-1, results in greater epidermal spread of HSV *in vitro*.[33,34] This infection can spread rapidly and, in severe cases, may lead to keratoconjunctivitis and encephalitis.

Concomitant fungal colonization

Fungal colonization can also complicate the AD clinical picture. For instance, *Malassezia* colonization is thought to drive inflammation in AD in a subset of patients who typically have dermatitis in the areas with a high density of sebaceous glands (e.g., head, neck, and upper chest and back) (Fig. 3). This seborrheic distribution overlaps with, but is distinct from, the distribution of allergic contact dermatitis or airborne allergy, which typically involves the upper face, eyelids and periorbital regions, anterior neck, postauricular area, and exposed areas on the arms. *Malassezia* is a commensal yeast.

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Although it is not more abundant on AD skin[35], AD patients are more frequently sensitised to *Malassezia*.[36–38] In some patients, sensitization to yeast antigens induces autoreactivity to human proteins via molecular mimicry, leading to sustained skin inflammation.[39,40] Cross-reactivity between *Malassezia*-specific IgE and *Candida albicans* has also been shown.[41] A systematic review of the 8 published randomised, controlled trials evaluating the benefit of antifungal therapy found that 5 trials demonstrated a benefit from antifungal drugs and 3 trials found no benefit compared to placebo or standard therapy.[38]

Bacterial skin infection in different ethnic skin types

There is wide variation in the clinical manifestation of AD in different ethnic groups. This may be a result of underlying genetic variation, which influences AD susceptibility and clinical presentation, inadequate early intervention because of masking of erythema in dark skin and differences in both treatment response and environmental exposures.[42] In dark skinned individuals, perifollicular accentuation is often present and erythema appears violaceous and often muted (Fig. 4a-f).[43–45] This can lead to poor recognition of inflammation, underestimation of disease severity and inadequate intervention. AD patients of African descent often have extensor disease rather than the characteristic flexural lesions.[45] Importantly, *S. aureus* strain differences, including variability in the presence of superantigen genes, has been shown between European American, African American and Mexican American AD patients.[46]

Methicillin-resistant S. aureus (MRSA)

As in healthy subjects who are MRSA colonised, AD patients often suffer from recurrent infections and disease flares that are resistant to standard treatment regimens (Fig. 5). The prevalence of MRSA skin colonisation varies significantly with geographic location and study setting in both healthy and disease populations. It is therefore difficult to accurately compare the prevalence of MRSA colonisation between AD and healthy cohorts. In the United States, for example, there is significant state-wide variation, with MRSA colonisation varying between 0.3-13% in AD subjects.[47–50] In another study, 4-19% of children with AD from the United Kingdom and Ireland were found to be colonised with MRSA.[51,52] The reported prevalence of MRSA colonisation in AD subjects in Sri

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Lanka is 8% and in Korea 3-14%.[53–56] A meta-analysis of MRSA colonisation in the general population reported a prevalence of 0.2-7% worldwide.[57] The authors describe significant study heterogeneity. In a sub-group analysis that excluded subjects with prior health care contact MRSA colonization prevalence was found to be very low (0.2%).

Although some studies suggest MRSA colonisation rates are higher in AD subjects than in the general population, other studies have found much lower rates. For instance, a cross-sectional study of 200 patients with AD in Canada found MRSA in only one subject.[58] Similarly, children with AD from San Diego were found to have a lower rate of community-acquired MRSA colonization compared to the general outpatient paediatric population.[59] Further research is needed to understand the significance of MRSA in AD.

S. aureus colonization in AD

Most subjects with AD are colonised by *S. aureus*. A recent meta-analysis found that the pooled prevalence of *S. aureus* colonization of lesional AD skin is 70%, of non-lesional AD skin is 39% and of the nares 62%.[60] However, the prevalence varies greatly across studies (from 22-99% in lesional skin and 3-79% in non-lesional skin).[60–64] Most patients colonized by *S. aureus* do not exhibit overt signs of infection and 10% of healthy individuals carry *S. aureus*.[63,65]

S. aureus colonization can be associated with three main clinical scenarios in AD: (1) stable/baseline AD without clinical evidence of overt infection; (2) AD flare without clinical evidence of overt infection; and (3) overtly infected AD with the classical symptoms as described above. Although antimicrobial therapy is clearly essential for patients with overtly infected AD, the clinical significance, recognition and management of *S. aureus* colonization without clinical evidence of infectious disease is not fully understood. Some studies show that patients with AD improve with topical and systemic antibiotic treatments, even without overt signs of secondary infection.[66–71] Other studies, however, have found no clinical benefit of antibiotic treatment over corticosteroid therapy alone.[64,72] A 2010 Cochrane review found no support for routine topical or systemic anti-staphylococcal interventions in AD that is not clinically infected, although the studies were generally short-term and of poor quality.[73]

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It is likely that the density of *S. aureus* is more relevant than simply the presence of the bacteria. *S. aureus* colonisation density correlates with the severity of AD.[74–77] Leyden and Kligman used an early method of quantitative bacteriology to compare the effects of topical and systemic antibiotics on *S. aureus* in AD.[78] The detergent scrub technique was used on AD lesions to obtain bacterial samples, which were incubated before the *S. aureus* density was measured. They found that appreciable clinical improvement with antibiotic therapy occurred only in patients whose AD lesions were infected by *S. aureus* at a density of greater than 10^6 CFU/cm^2.[62,69] Similarly, microbiome studies of paediatric AD patients show that the relative abundance of *S. aureus* is associated with disease flares and correlates with severity.[79–82]

In addition to bacterial abundance, there are several additional factors that determine whether *S. aureus* successfully colonizes the skin in AD and whether this results in clinically relevant infection. Pirofski *et al*. described the "damage-response framework" (DRF) approach to microbial pathogenesis.[83,84] The basic tenets of this concept are that host and microbe interact to create a spectrum of possible states, ranging from commensalism and colonization to disease. Disease results from damage to the host, which can come from the host response, the microbe or both. The DRF defines infection as the acquisition of a microbe, but it does not necessarily mean the microbe is causing disease. Infection results in disease when the host-microbe interaction produces sufficient damage to become clinically apparent.[85] This approach is a framework that advances thinking beyond the classic microbe-centric Koch's postulates that dominated microbiological thought for more than a century. It may be a useful approach for understanding the *S. aureus*-host interaction in AD and the range of clinical scenarios that can arise (Fig. 6). We have some understanding of the various bacterial and host factors that contribute during *S. aureus* infection in AD. However, the key questions to be answered are: i) Which of these factors lead to worsening inflammation in AD? and ii) Can a threshold of host damage resulting from the *S. aureus*-host interaction be defined, beyond which antibiotics prove beneficial? If the key host and microbial factors that determine these outcomes are identified, then targeting of these specific factors with novel immunotherapies or selective antimicrobial therapies may become a reality.[14,86]

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Host factors associated with S. aureus colonization

Adults with AD who are colonized with *S. aureus* have more severe disease, greater T helper type 2 (Th2) immune deviation, allergen sensitization and barrier dysfunction than non-colonized AD patients.[87] Some studies have found that filaggrin mutations are associated with *S. aureus* colonization in AD, but others have not.[87–89] The increased susceptibility to *S. aureus* colonization and infection in AD is multifactorial and driven by skin barrier abnormalities as well as innate and adaptive immune responses (Fig. 7).

The impaired skin barrier

The impaired skin barrier in AD, characterized by reduced very long chain epidermal lipids, defective tight junctions, differentiation protein deficiency, including from *FLG* loss-of-function mutations, enhanced protease activity, and increased skin surface pH, provides a favourable environment for *S. aureus* colonization.[90–93] The deposition of stratum corneum (SC) fibronectin, to which *S. aureus* adheres, is increased in AD.[26,94,95] *S. aureus* clumping factor B (ClfB) binds to loricrin and cytokeratin 10 and promotes adhesion of *S. aureus* to the SC in AD.[96] Anti-microbial peptides (AMPs) such as β-defensins and cathelicidins are also reduced in AD lesions.[97]

Type 2 inflammation

Type 2 inflammatory pathways, in which the cytokines IL-4 and IL-13 play a major role, drive inflammation in AD. Th2 cytokines reduce expression of important skin barrier proteins, filaggrin, loricrin and involucrin.[98,99] The expression of fibronectin is increased by IL-4 and may facilitate *S. aureus* adherence in AD.[100] The failure to mount an appropriate AMP response in AD may also be due to the suppressive effects of IL-4 and IL-13, and may enhance *S. aureus* colonization further.[12,13,101]

A recent pooled analysis of seven randomized, placebo-controlled dupilumab trials in adults with moderate-to-severe AD found that bacterial skin infections were significantly less common in the dupilumab groups than the placebo group.[102] Similarly a meta-analysis of data from eight dupilumab trials found that patients treated with dupilumab had a lower risk of skin infection than those treated with placebo.[103] The reduced rate of

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skin infection with dupilumab supports the role of a Th2 driven host skin barrier defect in infection in AD, which after treatment may become a less favourable environment for bacteria. This shift may be mediated by inhibition of type 2 inflammatory cytokines, reduced scratching, or microbiome changes induced by dupilumab. Dupilumab treatment results in increased microbial diversity and decreased *S. aureus* abundance in AD.[104]

The skin microbiome

Microbial diversity is reduced in AD and inversely correlates with disease severity.[79,80,82] Skin commensal microbes, including coagulase negative staphylococci (CoNS), may aid skin homeostasis and provide protection against *S. aureus*. Thus, the diminution of commensal skin microbiota with flares may promote *S. aureus* colonization and infection in AD. During flares of paediatric AD, both *S. epidermidis* and *S. aureus* are increased, suggesting a compensatory role for *S. epidermidis*.[79] This skin commensal promotes AMP expression by cultured keratinocytes via TLR2 signalling.[105] Furthermore, *S. epidermidis* produces PSMγ and PSMδ, which enhance AMP effects and inhibit growth of *S. aureus* and *Group A Streptococcus in vitro.*[106] Cutaneous application of antimicrobial CoNS strains to adults with AD decreased colonization by *S. aureus* within 24 hours of a single application.[14] In addition to inhibiting *S. aureus* colonization, CoNS also reduce *S. aureus*-driven skin inflammation. CoNS from healthy skin produce auto-inducing peptides that inhibit the *S. aureus* accessory gene regulatory (agr) quorum sensing system, leading to reduced expression of the *S. aureus* virulence factor PSMα *in vitro* and reduced *S. aureus*-induced skin barrier damage in mice.[16] *C. acnes* supresses growth of MRSA in mice skin through glycerol fermentation, leading to short-chain fatty acid production and reduced bacterial intracellular pH.[15] Treatment with the gram-negative *Roseomonas mucosa*, collected from healthy human skin, inhibits the growth of *S. aureus in vitro* and results in reduced inner ear thickness in a mouse model of AD.[107] In human studies, spraying *R. mucosa* onto lesional AD skin of the antecubital area improved AD severity and reduced the need for topical corticosteroids.[17] MRSA colonisation is associated with reduced microbial diversity when compared with MSSA colonisation of AD lesional skin and greater decreases in relative abundance of skin commensal bacteria, including *Cutibacterium*, *Streptococcus* and *Corynebacterium.*[48]

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Further research is needed to understand the interactions between *S. aureus* and commensal organisms, and how these organisms relate to host immune responses.

S. aureus factors promoting colonization and virulence

S. aureus exacerbates AD by secreting virulence factors that affect the epidermis (leading to inflammation and skin barrier disruption) as well as factors that hamper innate and adaptive immune responses (Fig. 7). Staphylococcal superantigens activate polyclonal T cell responses without prior antigen processing and by activating epithelial cells via CD40.[108–110] Several of the staphylococcal enterotoxins can also act as allergens to stimulate SE-specific IgE production.[111] Staphylococcal enterotoxin B increases the expression of IL-31, which is well known to cause pruritus in AD.[112] IL-31 also suppresses filaggrin and AMP expression, resulting in increased *S. aureus* colonisation.[113,114] Superantigen producing strains are found in over 80% of *S. aureus* isolates from patients with AD.[115] MRSA produces higher levels of superantigen enterotoxins than methicillin-sensitive *S. aureus* (MSSA).[116]

Additional toxins, including the staphylococcal PSMs, including δ-toxin and α-toxin, may additionally enhance the virulence of *S. aureus* in AD. δ-toxin is a potent inducer of mast cell degranulation *in vitro* and in mouse models of AD.[117] Alpha-toxin treatment of AD skin causes keratinocyte death, which is enhanced by IL-4 and IL-13.[118] Recent studies have shown that alpha toxin activates keratinocyte IL-1α and IL-36α production, which stimulates γδT-cells, innate lymphoid cell (ILC)-3-mediated IL-17 release, and neutrophil recruitment.[119,120] Filaggrin protects keratinocytes by mediating the secretion of sphingomyelinase, an enzyme that reduces the number of alpha-toxin binding sites on the keratinocyte surface.[121] *S. aureus* growth and virulence factor production are reduced in the presence of filaggrin breakdown products.[122] These studies suggest that *S. aureus*-produced mediators potentiate *S. aureus* effects in AD and filaggrin-deficient epidermis may be particularly susceptible to *S. aureus.* Staphylococcal protein A (SpA) activates pro-inflammatory pathways via tumour necrosis factor receptor 1 on keratinocytes.[123] *S. aureus* lipoteichoic acid and lipoproteins activate toll-like receptor 2 (TLR2) and TLR6 to exacerbate AD and stimulate thymic stromal lymphopoietin (TSLP) release from

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keratinocytes. TSLP activates dendritic cells and ILC-2, leading to further production of type 2 cytokines.[12,124] *S. aureus* proteases are required for penetration of the bacteria into the deeper layers of the skin and the induction of Th2 cytokine production.[125] *S. aureus* also stimulates keratinocytes to increase their endogenous protease activity.[126] Whole genome sequencing of *S. aureus* has recently revealed higher levels of antimicrobial resistance genes in *S. aureus* isolates from children with AD compared with those from healthy control children, suggesting additional potential *S. aureus* virulence mechanisms in AD.[52,127]

Conclusion

Bacterial infection in AD is common and causes significant morbidity. Overt bacterial infection is easily recognised. However, less overt infection manifesting may be more difficult to diagnose, especially given the greater risk of infection with flares (themselves associated with increased erythema and oozing), as well as the limited value of culture, given the high rates of colonisation. Although we have some understanding of how *S. aureus* colonizes the skin and causes inflammation in AD, many questions related to this complex relationship remain unanswered. Further research is needed to better define features that distinguish infection from colonization. Future work of the International Eczema Council, through expert consensus statements, aims to provide guidance regarding the practical use of antimicrobial therapy in atopic dermatitis. Improving our understanding of *S. aureus* virulence mechanisms and downstream host immune mediators of *S. aureus*-driven inflammatory pathways may help identify novel therapeutic targets for infection in AD.

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Figure Legends

Figure 1: Clinical features of bacterial skin infection in AD

Clinical features of *S. aureus* infection in AD lesions include weeping, honey-coloured crusts (a), folliculitis (b), and pustulation (c). β-hemolytic streptococcal infection may present with well-defined bright red erythema (d).

Figure 2: Clinical features of eczema herpeticum

Early EH lesions are superficial clusters of dome-shaped vesicles and/or small, round, punched-out erosions (a-b). As the disease progresses, the lesions commonly become superficially infected with *S. aureus* and may have the characteristic impetiginized scale (c-d).

Figure 3: *Malassezia* colonization in AD

Malassezia colonization may drive inflammation in AD in patients who have head and neck dermatitis.

Figure 4: Atopic dermatitis in different ethnic skin types

In dark skinned individuals perifollicular accentuation is often present in AD and erythema appears violaceous (a-f)

Figure 5: MRSA infection in AD

MRSA infection in AD may cause recurrent flares that are resistant to standard treatment regimens

Figure 6: Hypothetical damage-response framework (DRF) for *Staphylococcus aureus* in AD.

Adapted from Casadevall and Pirofski.[80] Different host-*S. aureus* interactions result in different damage response relationships. Curves A and B represent the damage response relationships of *S. aureus* with two different hosts or those of a single host with two different *S. aureus* strains. The outcome for the host depends on the strength of the host response to *S. aureus* or the virulence of *S. aureus*. During intermediate host

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responses both interactions (A and B) do not cause clinical evidence of infection, since the amount of damage incurred by the host is insufficient (1). However, in the setting of weak or strong responses both interactions cause an AD flare (2) and interaction B causes overtly infected AD (3). The position of the curve is determined by multiple host and *S. aureus* factors.

Figure 7: Possible mechanisms of *S. aureus* colonisation and virulence in AD. *S. aureus* colonisation is increased in AD skin. This may be due to epidermal barrier dysfunction, reduced levels of antimicrobial peptides (AMP), reduced microbial diversity, and increased fibrinogen and fibronectin. Host- and *S. aureus*-produced proteases allow the bacteria to penetrate into the deeper layers of the skin. *Staphylococcal* enterotoxins (SE) stimulate polyclonal T cell responses, SE-specific IgE responses and IL-31 expression. Alpha toxin can cause keratinocyte death and can activate keratinocyte IL-1α and IL-36α production to stimulate γδT-cells, ILC-3-mediated IL-17 release and neutrophil (Neut) recruitment. Delta toxin causes mast cell (MC) degranulation. Staphylococcal protein A (SpA) activates pro-inflammatory pathways via tumour necrosis factor receptor 1 (TNFR1) on keratinocytes. *S. aureus* lipoteichoic acid (LTA) and lipoproteins activate toll-like receptor (TLR)-2 and TLR6 to produce thymic stromal lymphopoietin (TSLP), which activates dendritic cells (DC) and ILC-2 leading to production of Th2 cytokines.

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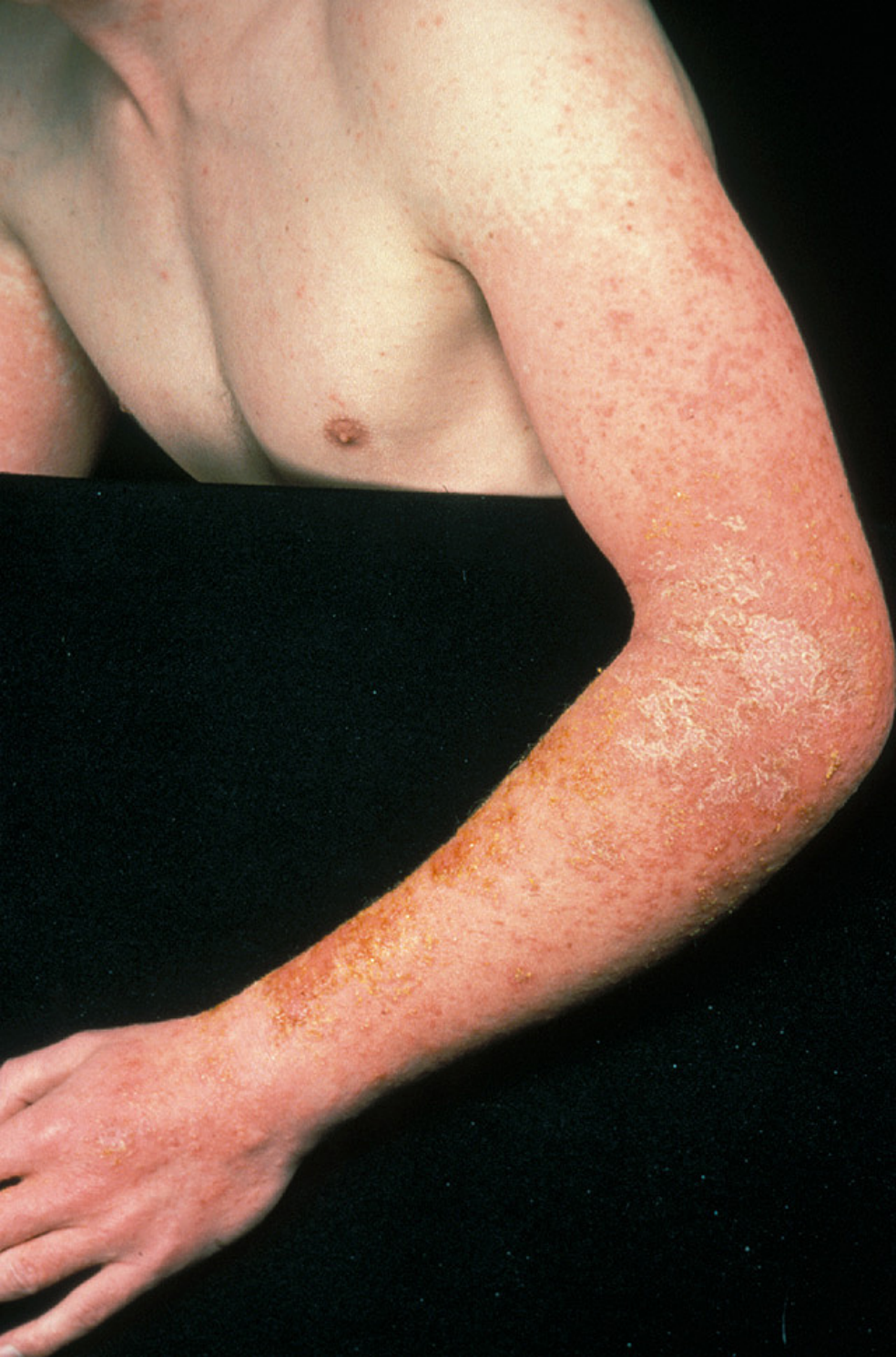
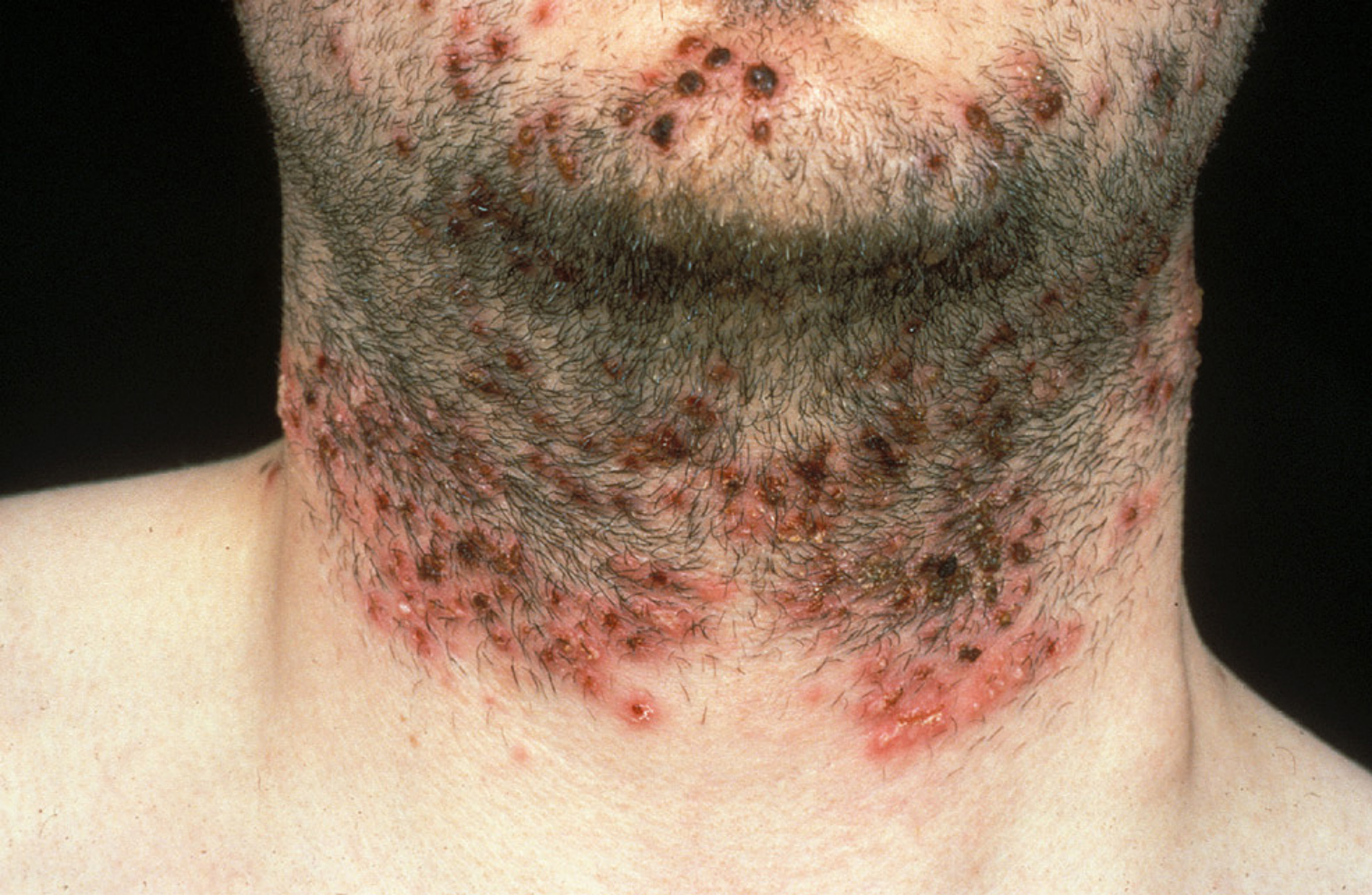
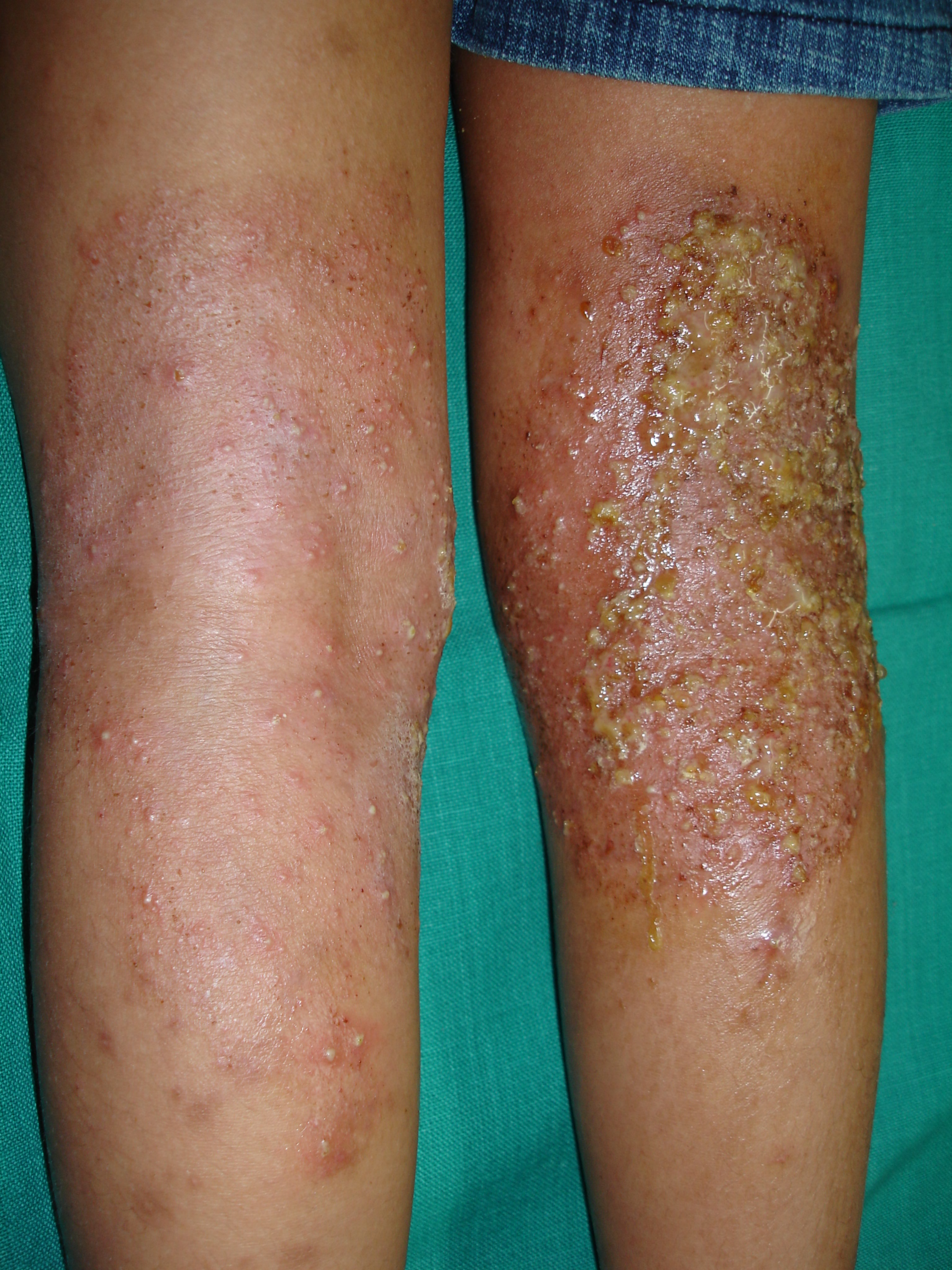
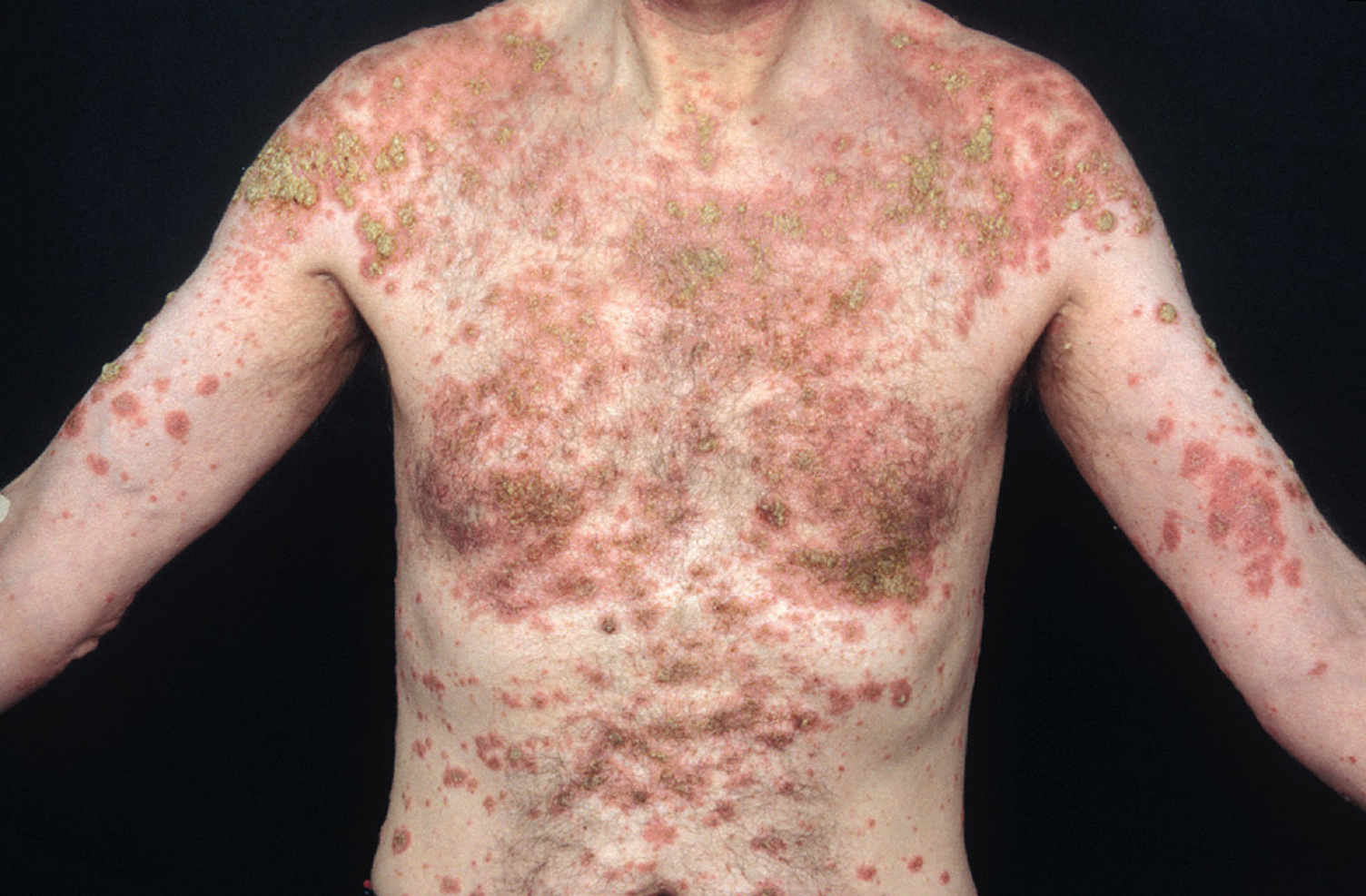
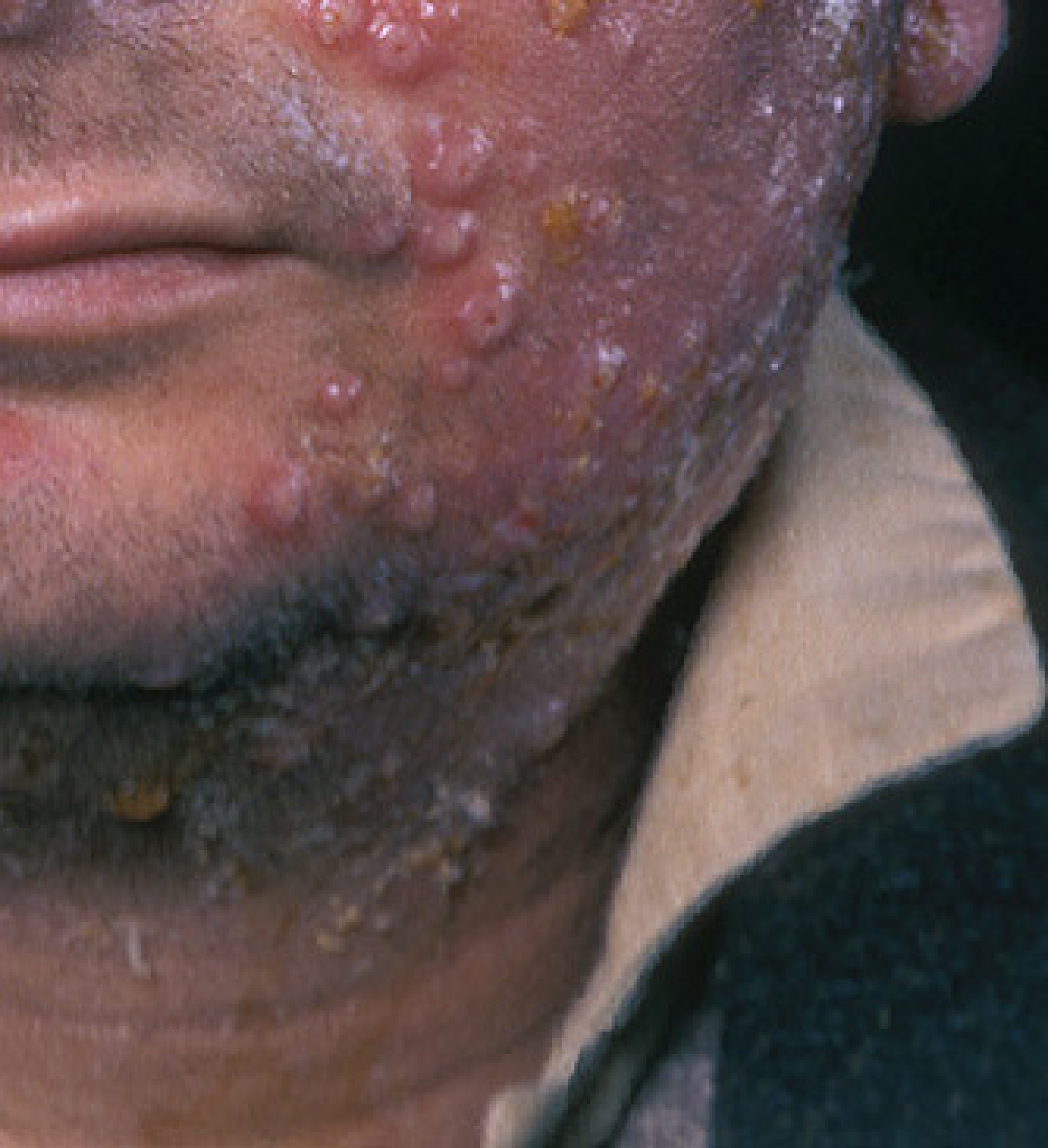
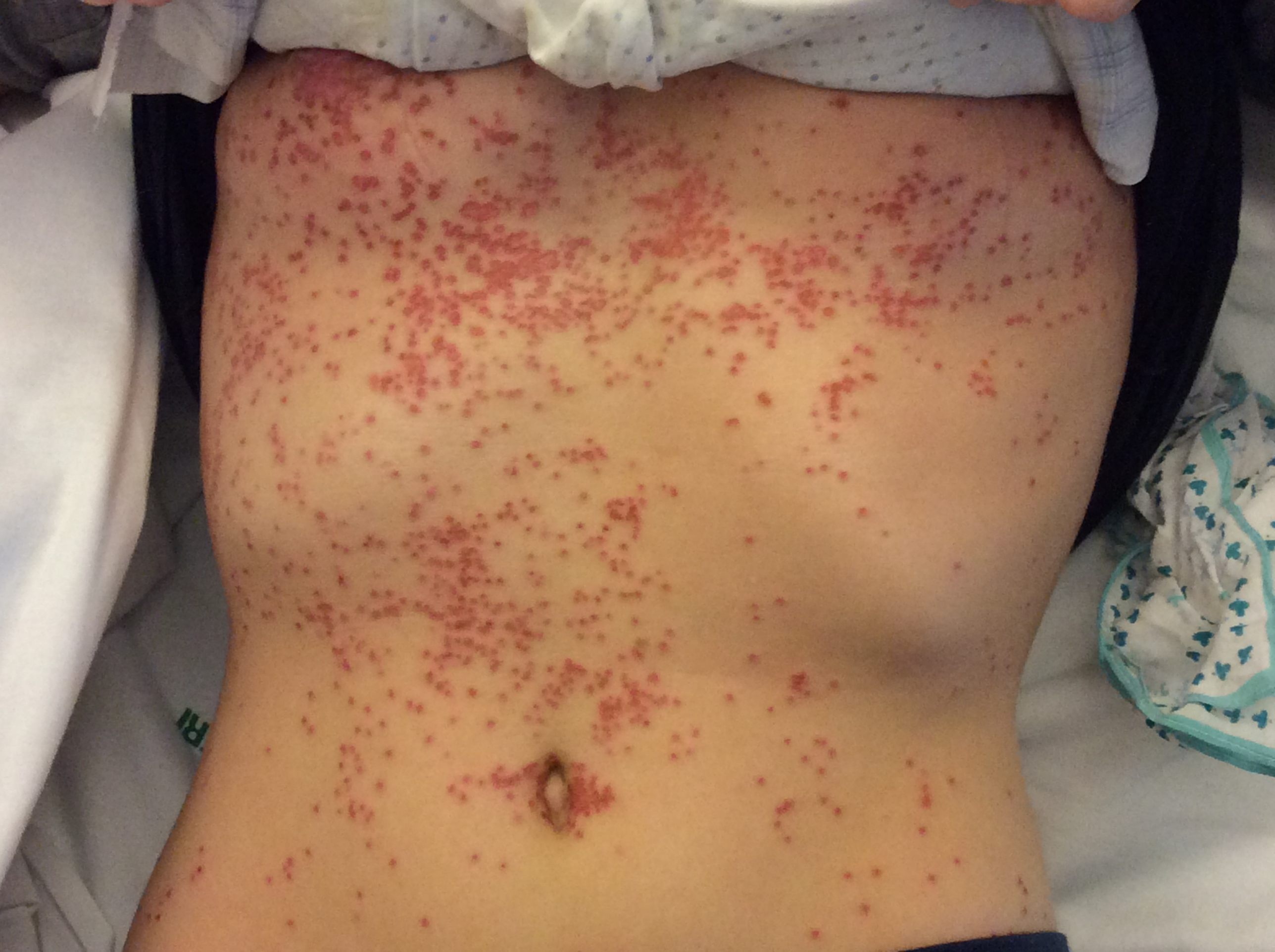


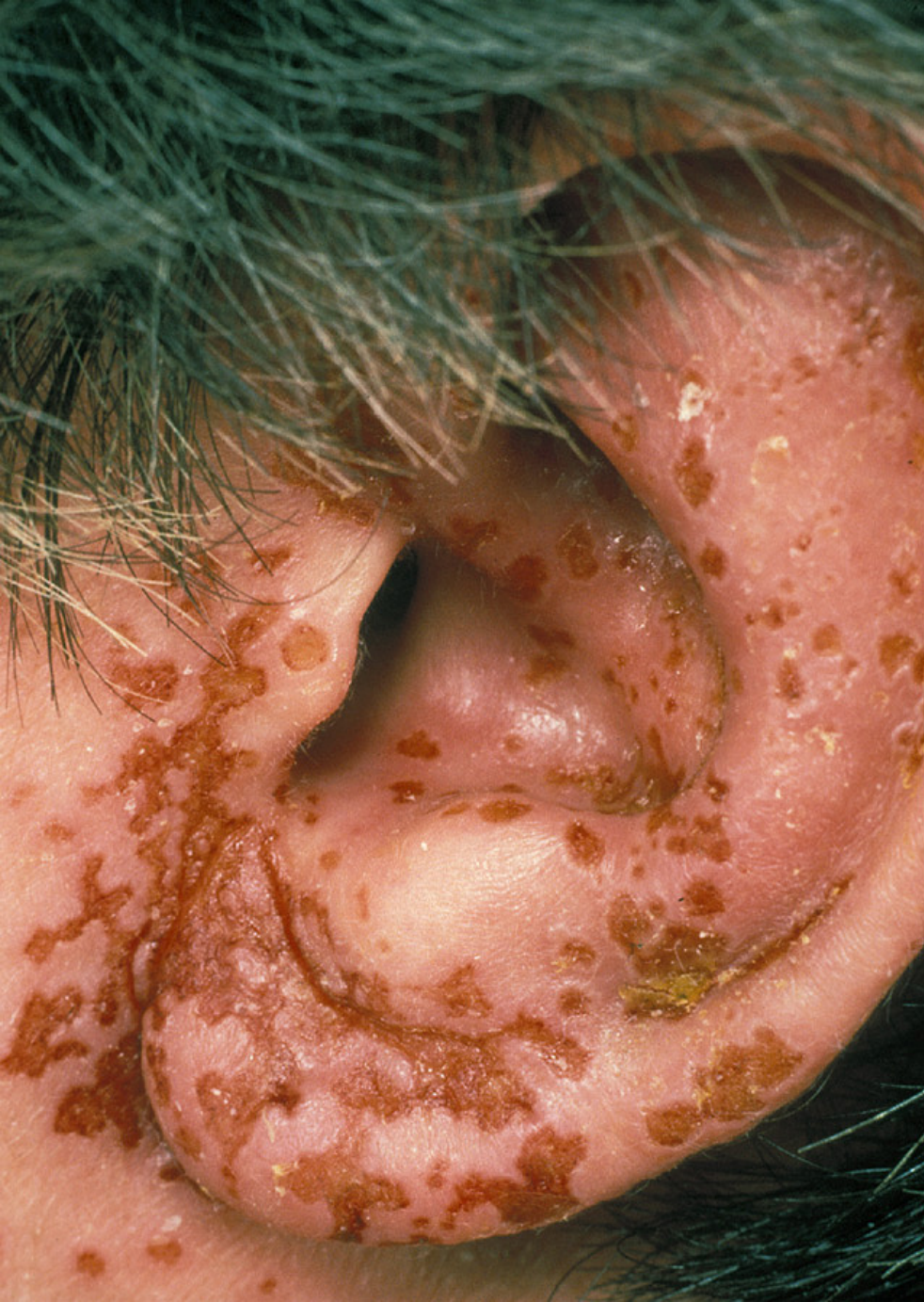


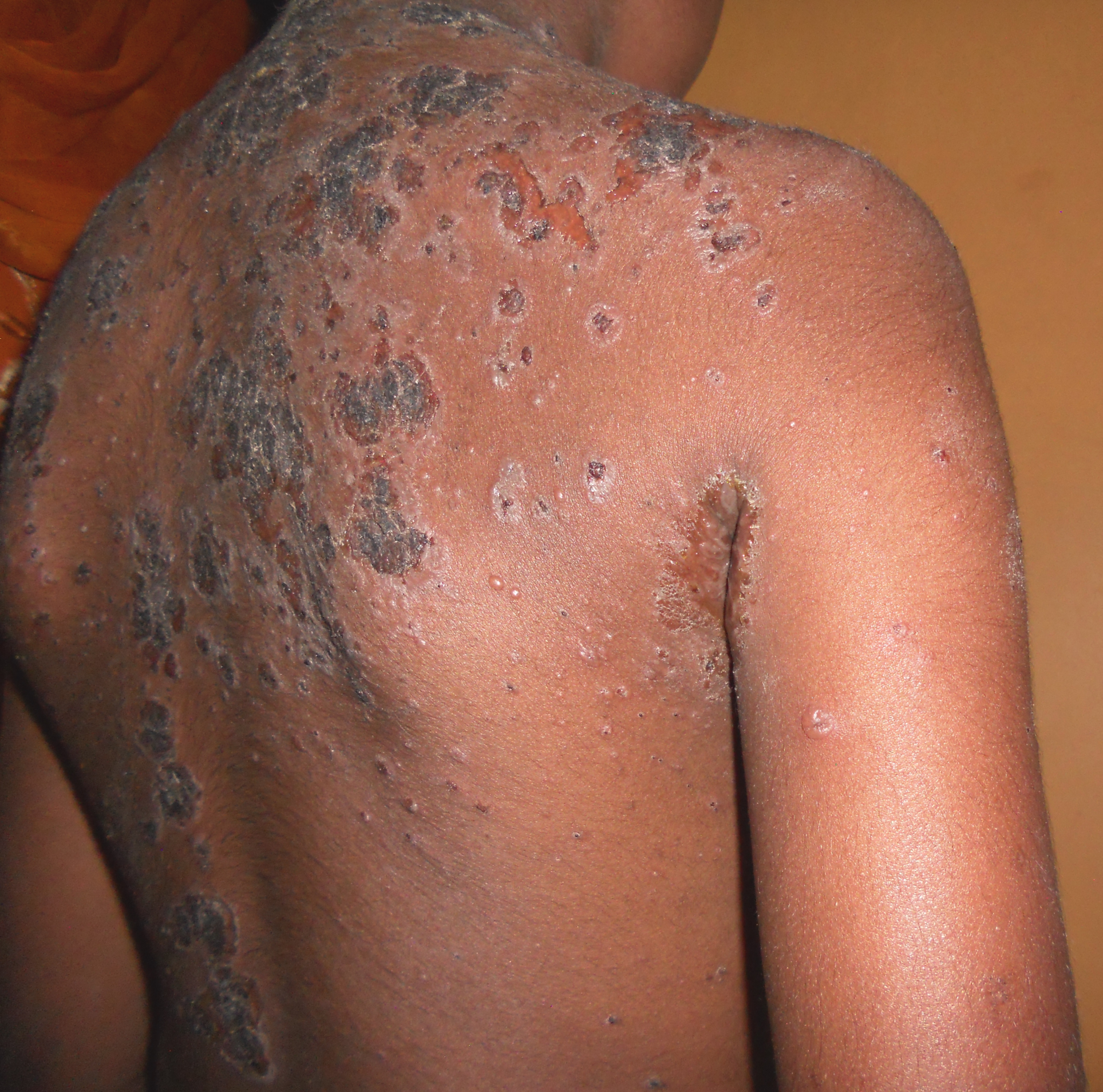


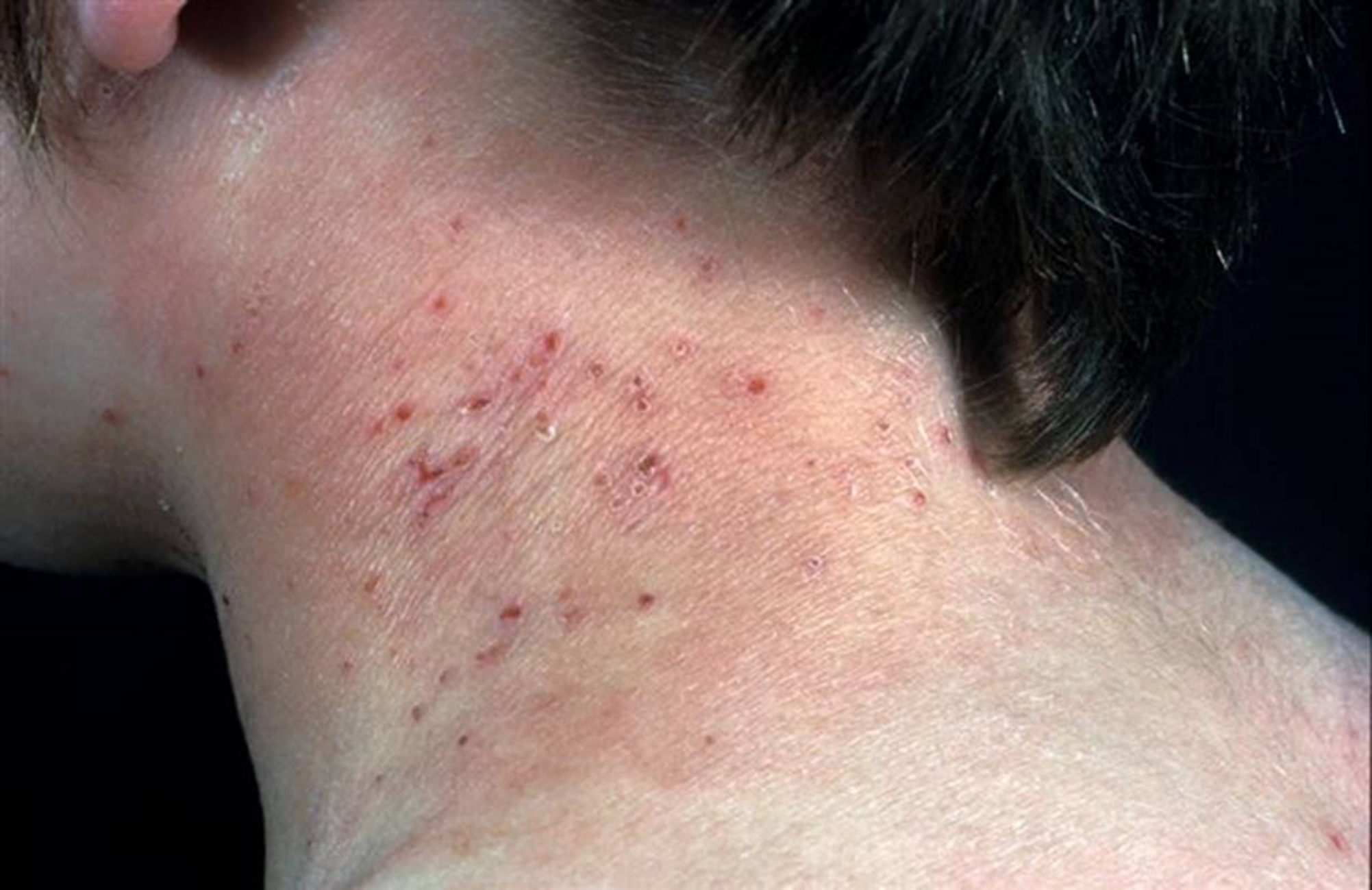


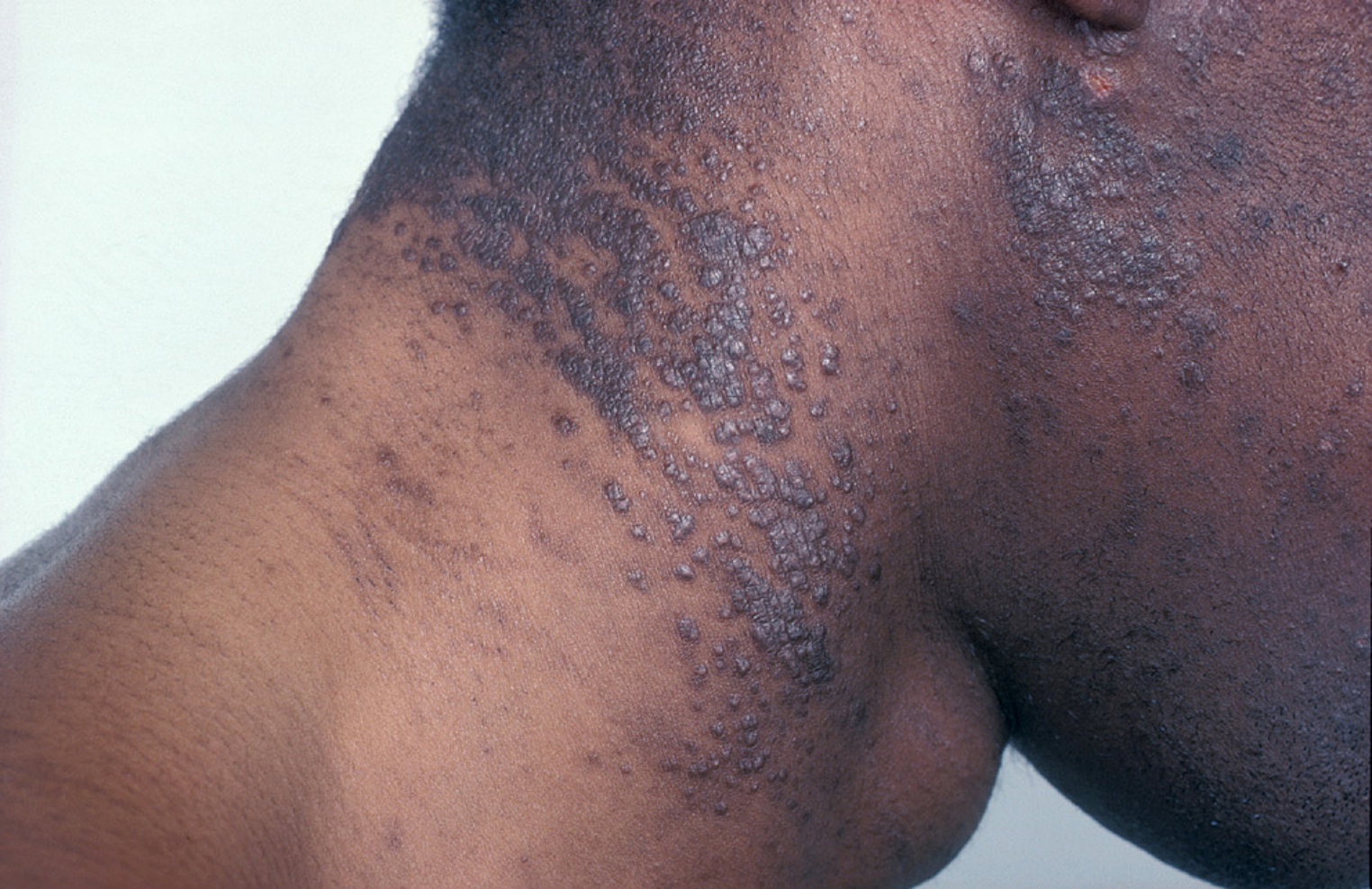


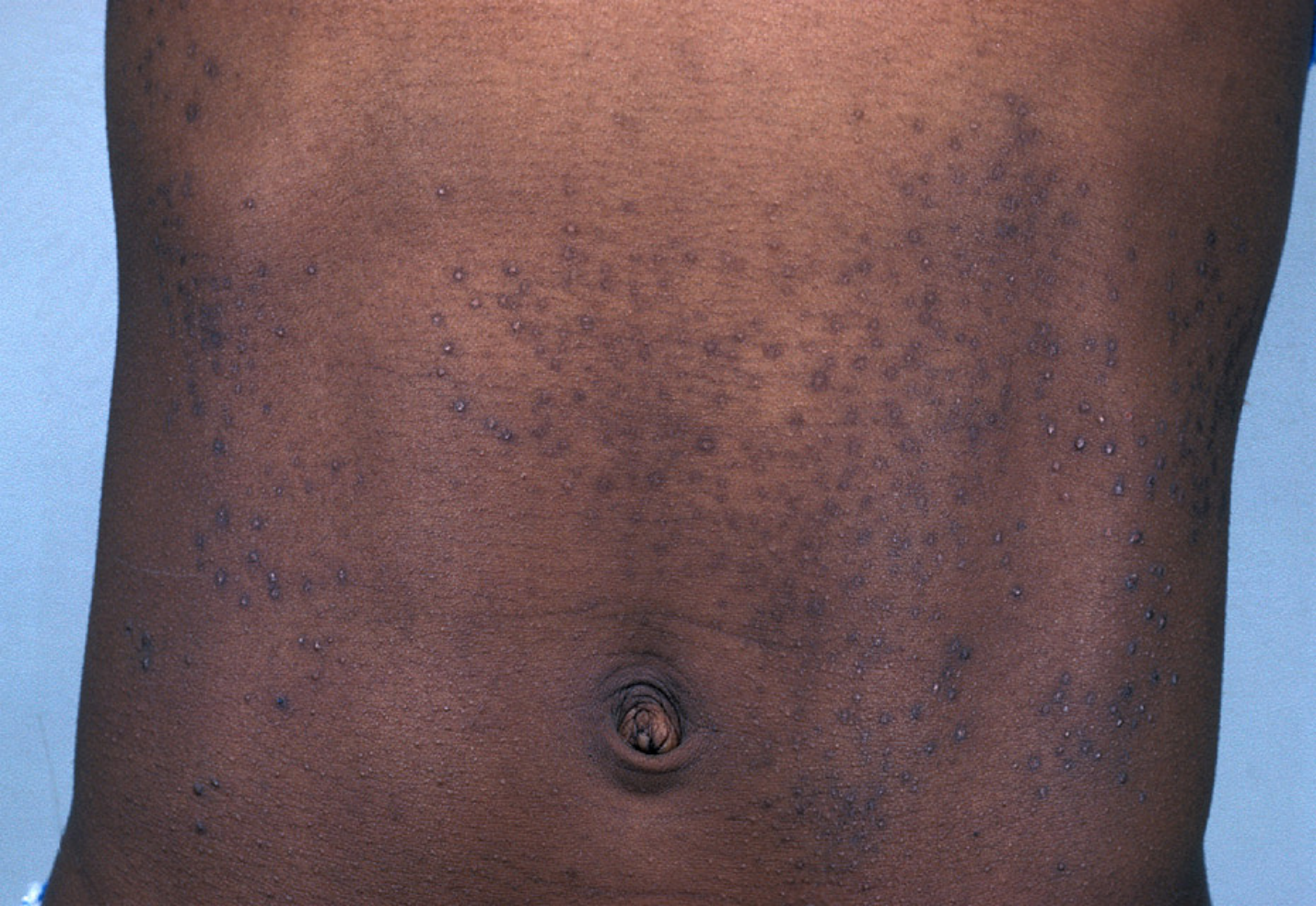


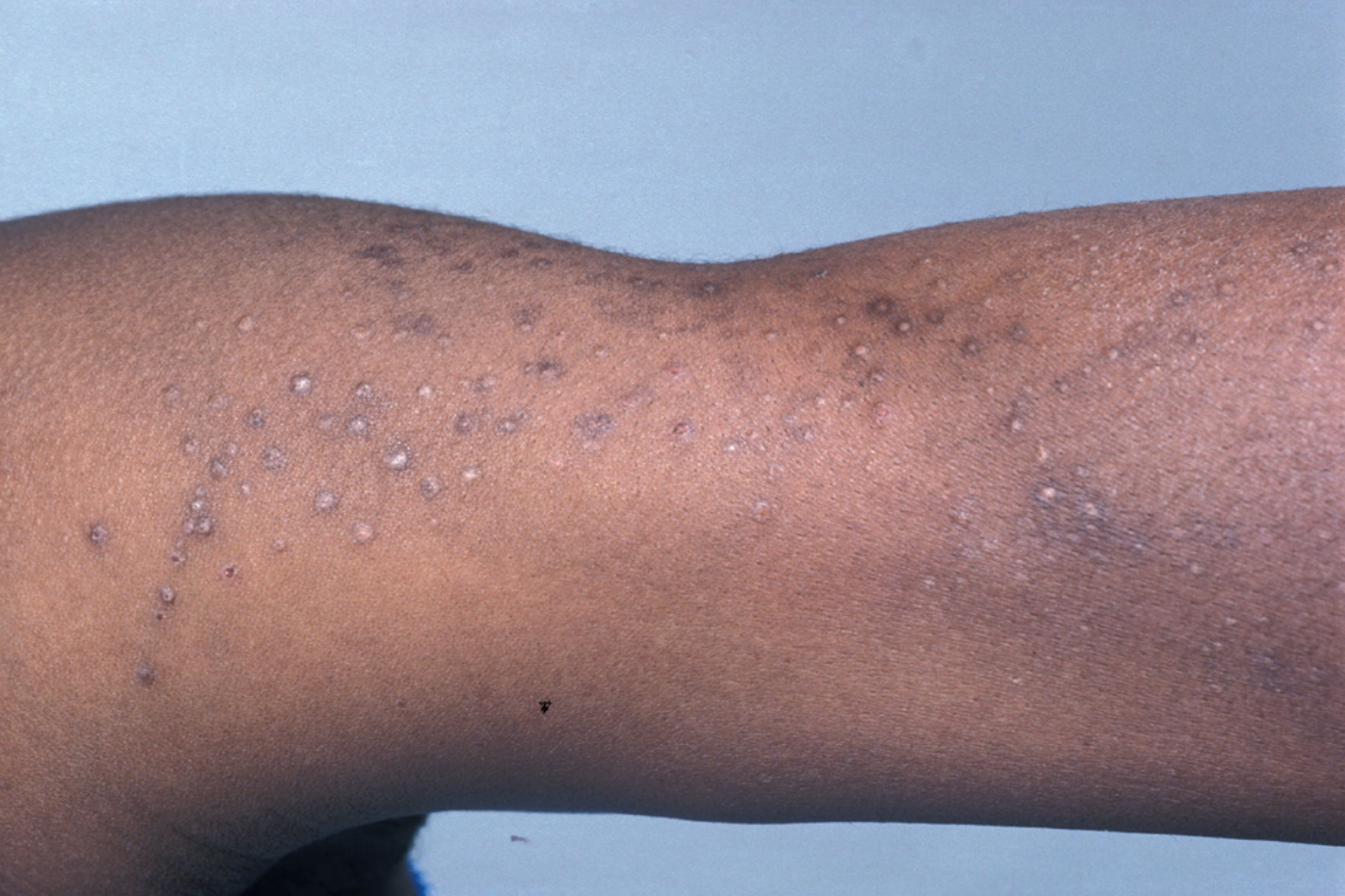


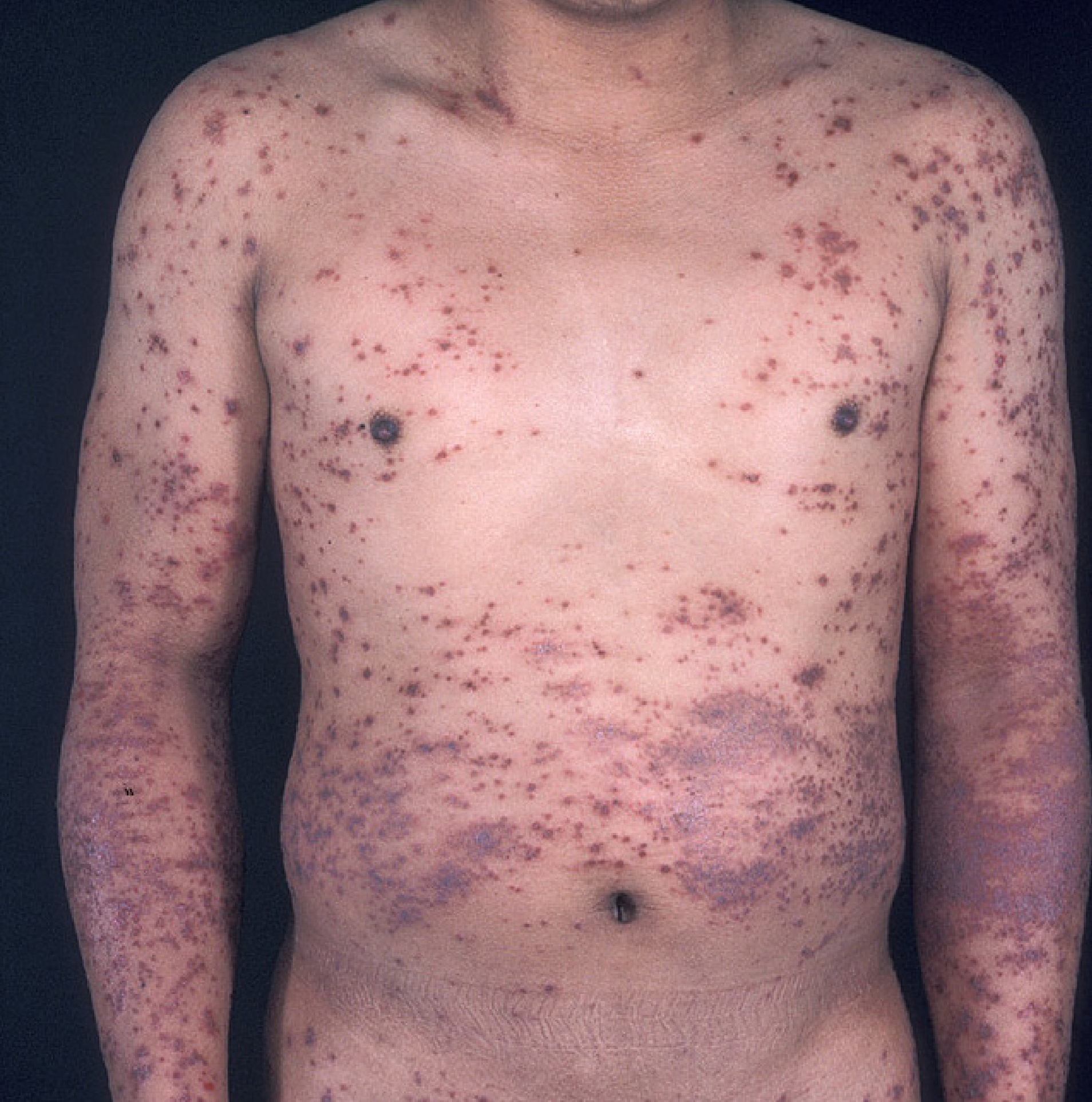


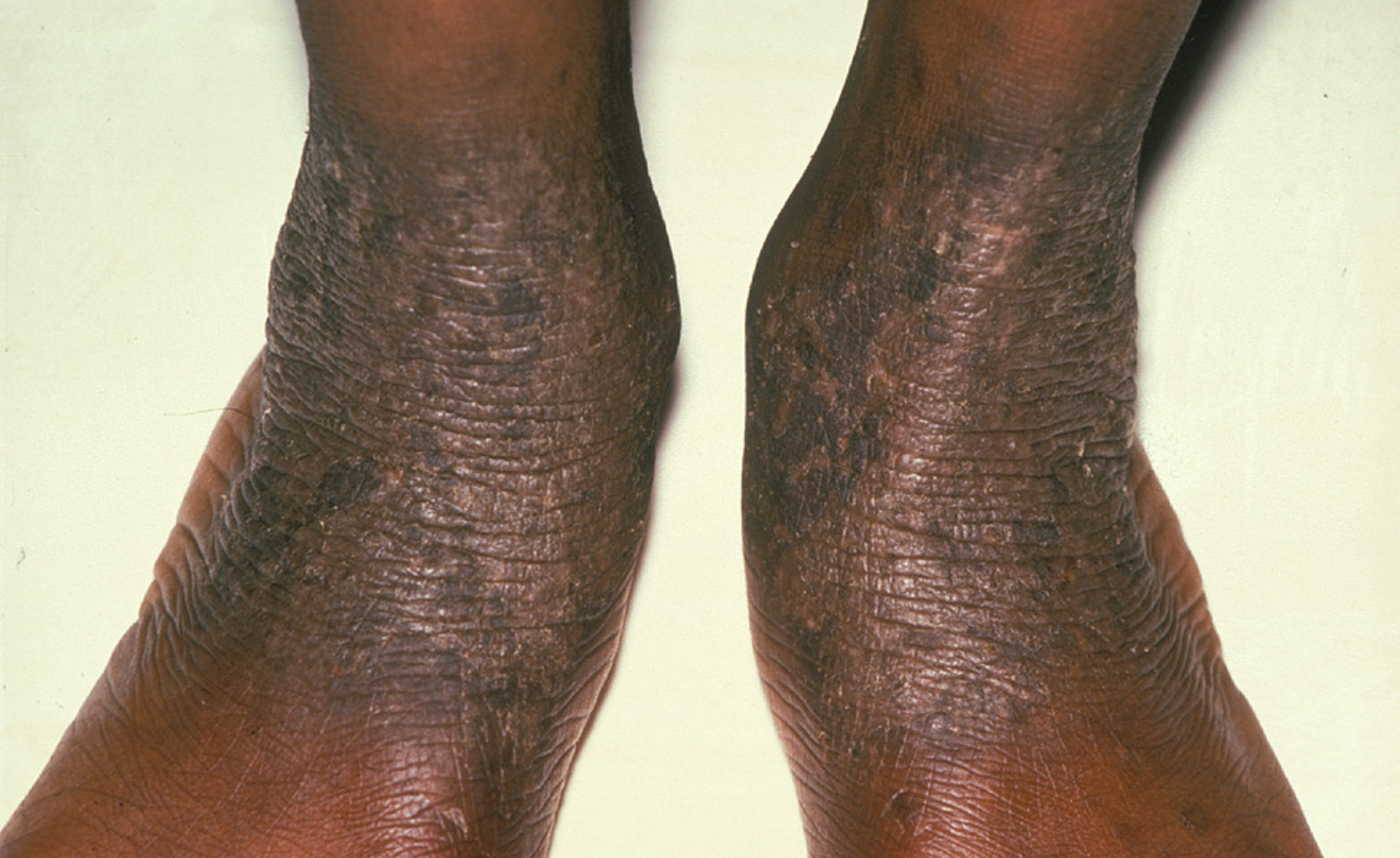


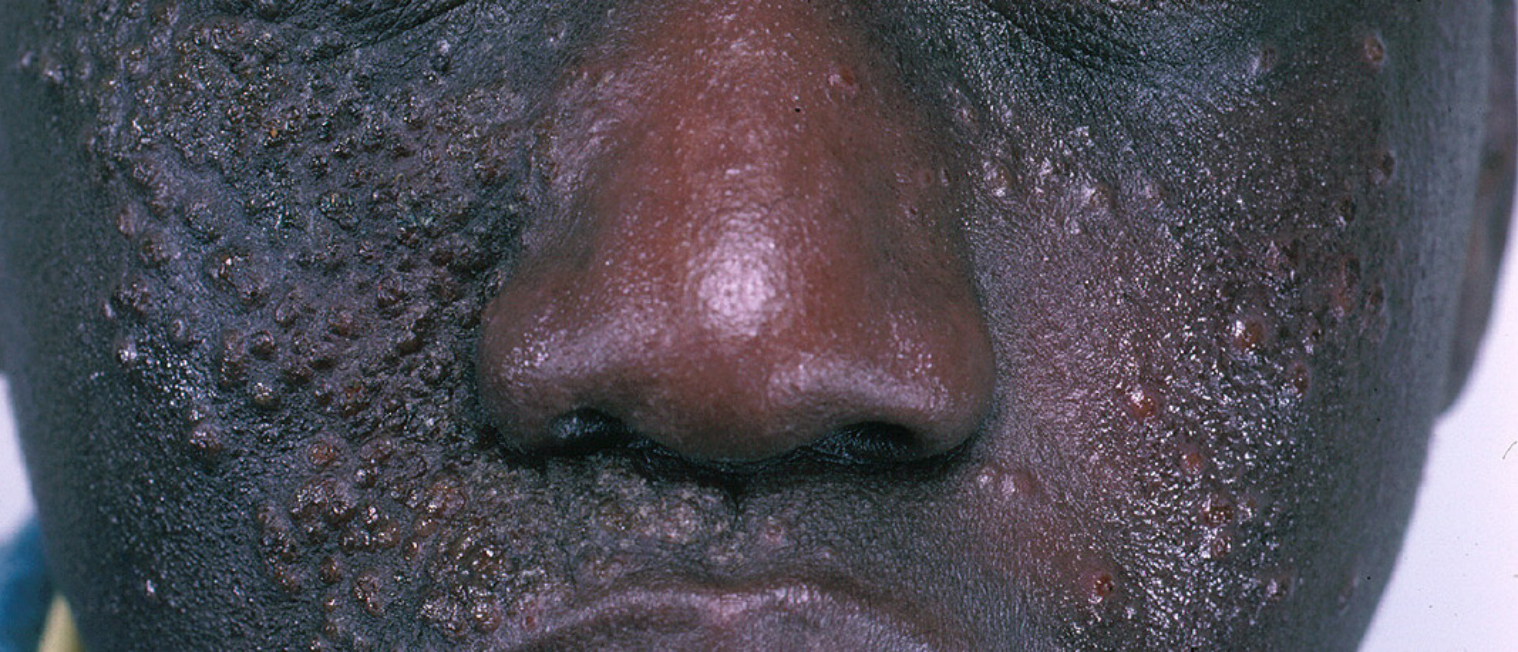


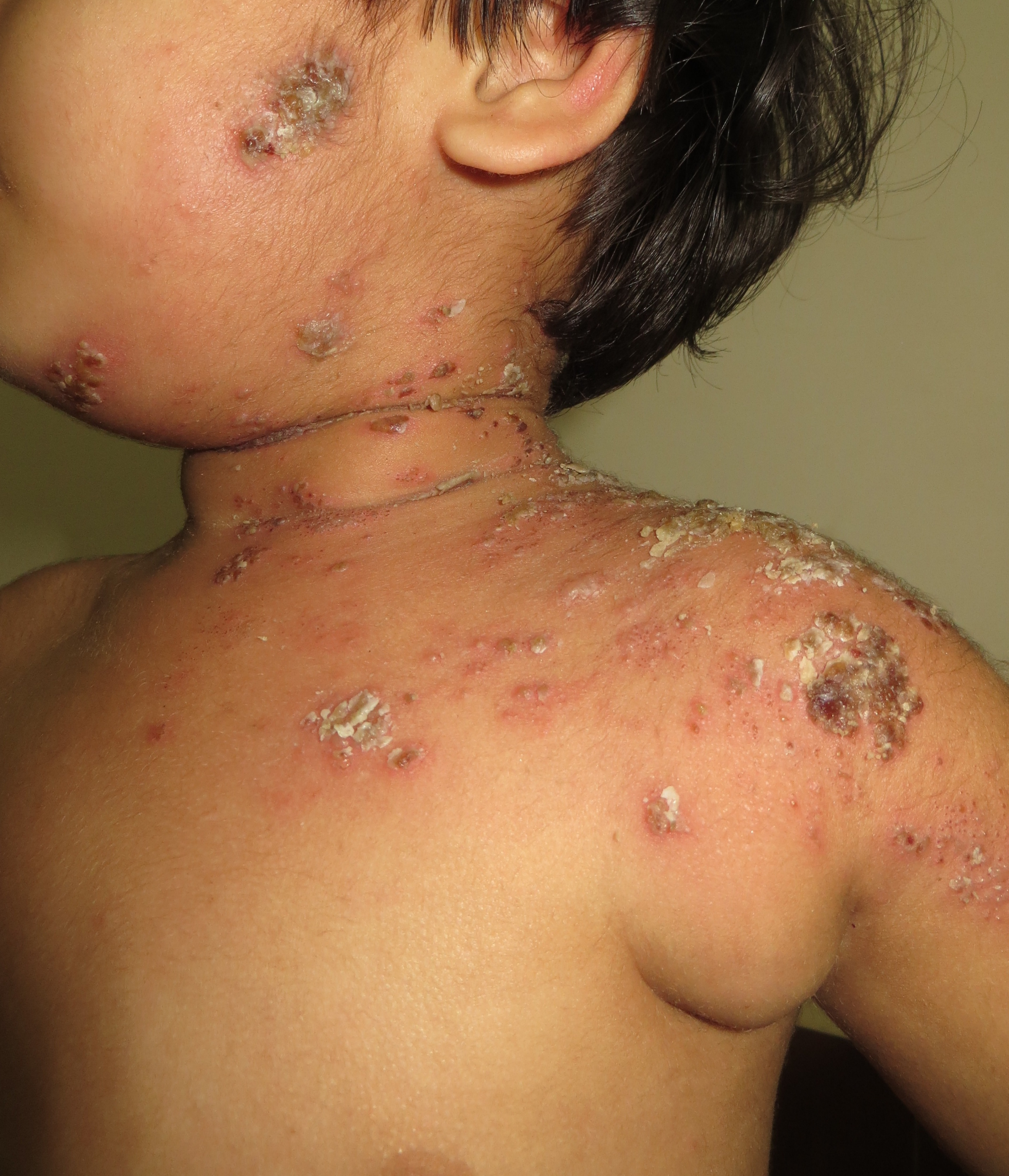


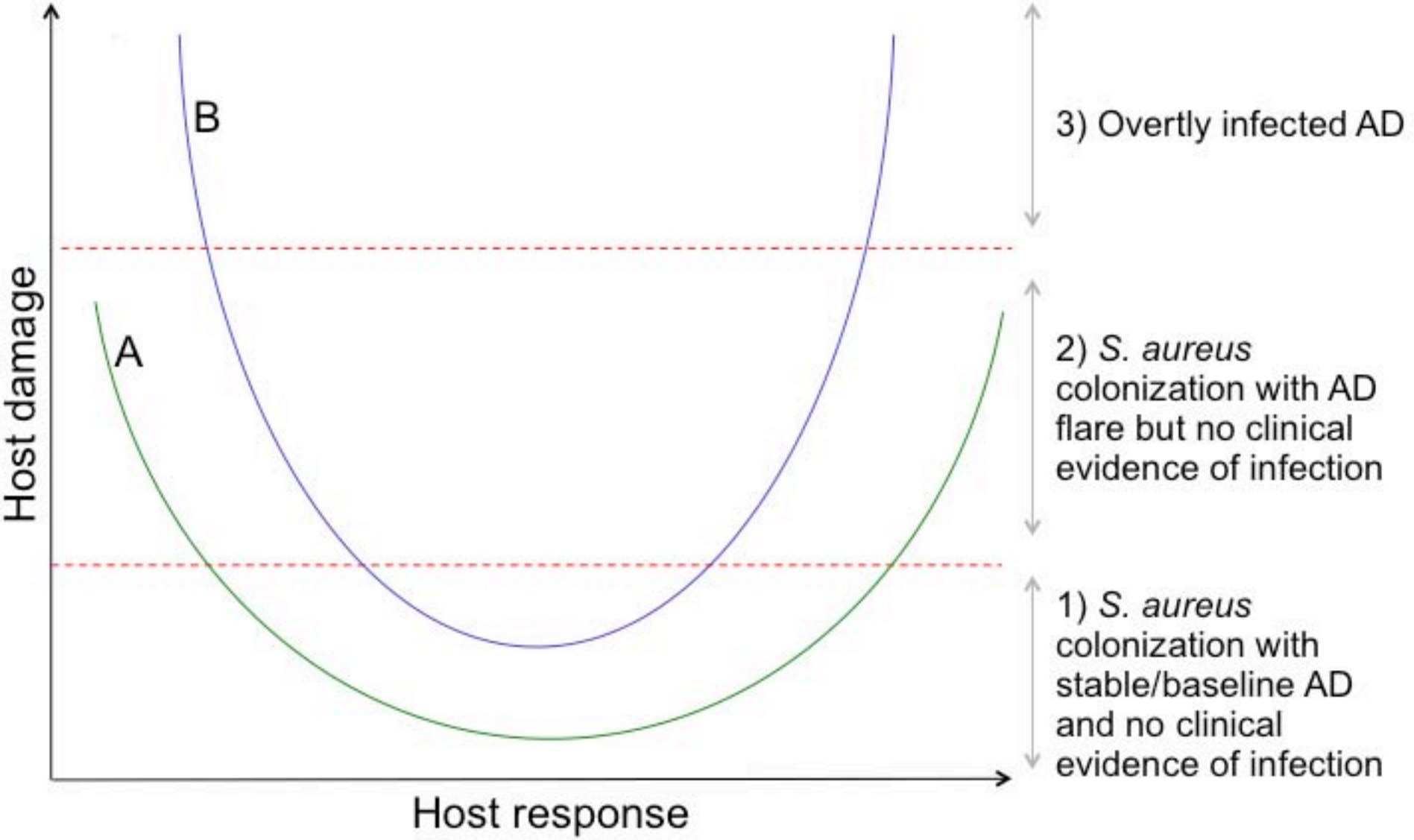


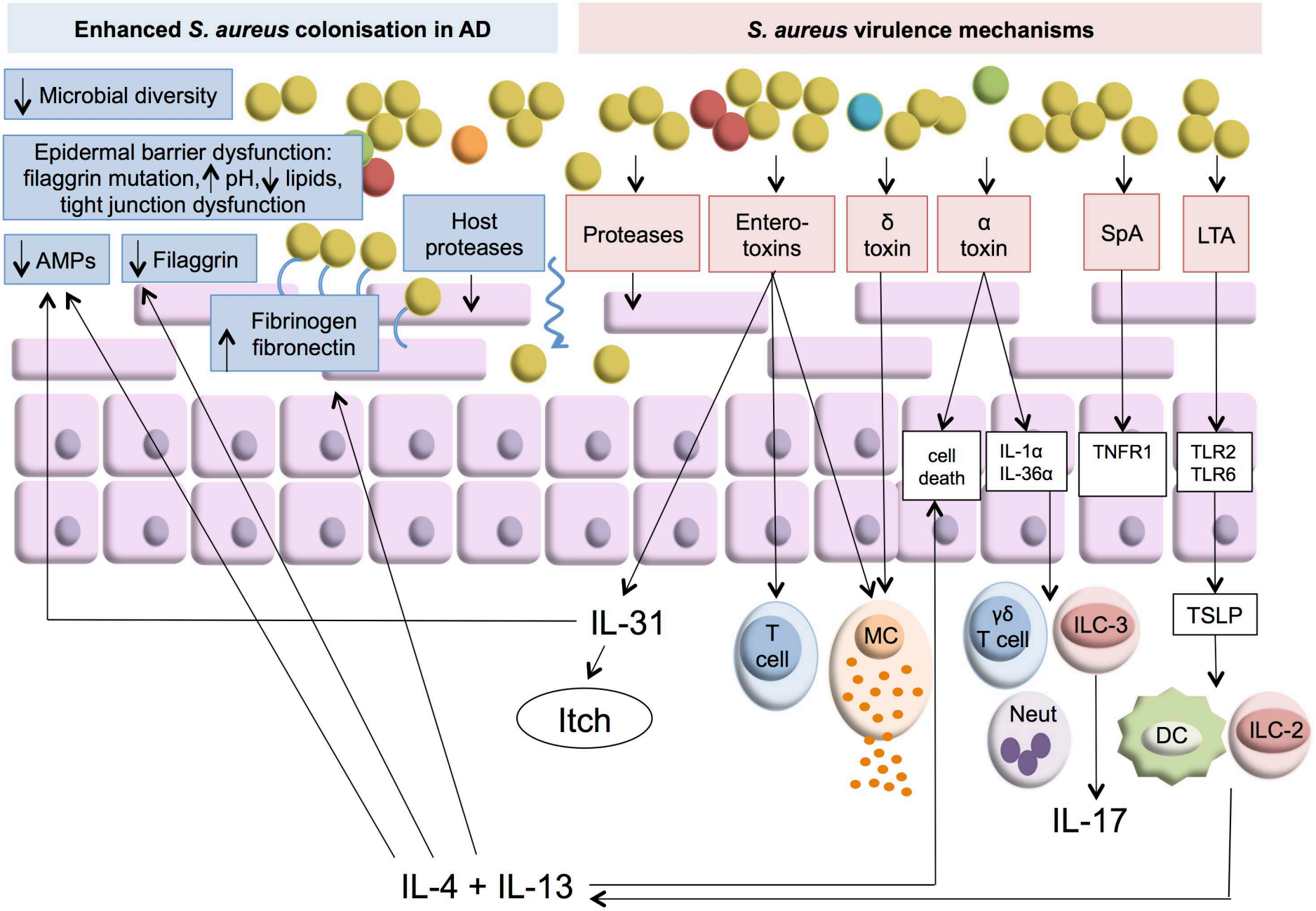









B
A
Host damage
Host response
3) Overtly infected AD
2) S. aureus colonization with AD flare but no clinical evidence of infection
1) S. aureus colonization with stable/baseline AD and no clinical evidence of infection


Enhanced S. aureus colonisation in AD
S. aureus virulence mechanisms
↓ Microbial diversity
Epidermal barrier dysfunction: filaggrin mutation, ↑ pH, ↓ lipids, tight junction dysfunction
↓ AMPs
↓ Filaggrin
↑ Fibrinogen fibronectin
Host proteases
Proteases
Entero-toxins
δ toxin
α toxin
SpA
LTA
cell death
IL-1α IL-36α
TNFR1
TLR2 TLR6
IL-31
Itch
T cell
MC
γδ T cell
ILC-3
TSLP
Neut
DC
ILC-2
IL-17
IL-4 + IL-13