INTRODUCTION

The characteristics of patients in the intensive care unit (ICU)—for example, the sedated patient—can cause dermatologic problems to go unnoticed, as the patient may be reliant on ICU staff to make note of the integumentary issue for them (1). Nevertheless, the emergence of skin problems affecting ICU patients can reach up to 10% of those admitted (2).

The definition of dermatologic disorders (DDs) refers to problems found in the skin, which, due to their magnitude, need treatment, or the fact that they may be indicators of potentially serious diseases, need a medical diagnosis. A definitive diagnosis may then be made by an intensivist and, in many cases, finalized by a dermatology consultant (Table 142.1). Due to the potential severity of its consequences, it is essential that this pathology be handled by a critical care specialist (3).

DDs that produce alterations in the normal structure of the skin can become severe due to the loss or deterioration in the cutaneous functions. The definition of DDs that will be used in this chapter is not that used in conventional studies of dermatology but follows a perspective based in intensive care medicine (Table 142.2).

LIFE-THREATENING DERMATOLOGIC DISORDERS

Some dermatologic diseases produce a loss of cutaneous functions due to an alteration in the stratum corneum, which protects us from physical, chemical, and microbiologic assault and also helps to maintain corporal temperature and homeostasis (4,5). The destruction of the stratum corneum, which provides the skin’s barrier function, produces a significant loss in fluids, causes disorders in thermoregulation, and favors infection. The term, acute skin failure, was born out of the need to define those dermatologic diseases that, owing to their severity and involvement of cutaneous tissue, can lead to multiple systemic complications which may be life threatening (6).

Skin failure has various causes—apart from the most common pathologies such as thermal injury, which are discussed elsewhere—and include cutaneous disorders (i.e., immunobul lous disorders, pustular psoriasis, erythroderma, etc.), drug reactions, and infectious disorders, which can produce systemic complications (7) (Table 142.3).

Specific Skin Diseases

Pemphigus

Pemphigus is a disease that produces severe blistering of the skin and mucous membranes. It is related to various factors that can condition an immunologic reaction against epidermal desmosomes. The disorder has been associated with drugs such as penicillamine and captopril, viruses—especially herpes virus (8), pregnancy, and malignancies such as lymphoma and other lymphoproliferative disorders (9). Pemphigus may also be related to other autoimmune diseases, such as rheumatoid arthritis, myasthenia gravis, and pernicious anemia (10). Pemphigus vulgaris is the most common form of this group of disorders.

It is characterized by the loss of intracellular adhesion (acantholysis) of the keratinocytes induced by the IgG immunoglobulins that act against the desmoglein 1 and 3 (Dsg1 and 3) markers that are responsible for the intercellular adhesion of the desmosomes (11).

In most patients, the lesions start in the oral mucous membranes, which represent the first indication of the disease. The blisters found in the oral mucous membranes are very fragile, easily bursting, and leaving very painful denuded areas. Later, flaccid bullae develop over large areas of the patient, especially the trunk, scalp, and flexor surfaces (Fig. 142.1). The epidermal fragility shows itself with the Nikolsky sign.

The diagnosis of pemphigus is based on three criteria: clinical signs, histologic examination, and immunologic studies. The routine histopathologic examination reveals a suprabasilar blister, acantholysis, and a mild superficial dermal inflammatory infiltration (Fig. 142.2). Direct immunofluorescence (IF), using the perilesional skin as a substrate, reveals IgG and C3 deposition in the intercellular spaces of the keratinocytes. Indirect IF confirms the existence of antibodies circulating in more than 90% of the patients with active illness, and the enzyme-linked immunosorbent assay (ELISA) detects antibodies against Dsg 1 and 3 (12).

Oral lesions will respond partially to topical or intralesional treatment with corticosteroids or other immunosuppressants (13,14). The standard treatment for pemphigus vulgaris includes the administration of oral prednisone at a dose of 70 to 90 mg daily; the dose is increased until control is achieved. The use of steroids with other immunosuppressants—for example, azathioprine—allows the steroid dosage to be reduced (15).

Another therapeutic option is the use of plasmapheresis, which acts by removing the pathogenic antibodies. However, due to the risk of infection, the administration of intravenous immunoglobulin, at a dose of 2 g/kg for 3 to 5 days, which decreases the concentrations of circulating pathogenic antibodies, is the treatment of choice (16). Alternative adjuvant treatments used with steroids, apart from azathioprine, are cyclophosphamide, mycophenolate mofetil, methotrexate, gold, and dapsone (17).

Rituximab has shown promising results in the treatment of moderate–severe or refractory pemphigus. However, additional evidence is required to confirm this finding. Topical therapies are also important to improve the healing of ulcers. Although topical corticosteroids have been widely used, other treatments including topical epidermal growth factor, tacrolimus, and pimecrolimus offer promising efficacy (18).
Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) includes a group of autoimmune bullous diseases characterized by subepithelial blistering, erosions, and scarring of mucous membranes and/or skin, which generally affects the elderly but can also affect young people and children. The natural course of the disease involves exacerbations and relapses, but it halts, even without treatment, in most patients after 5 years (19).

The typical lesions of MMP are tense blisters that can appear on normal or inflamed skin. The mucous membrane, particularly the oral and ocular mucous, is the most common area affected. The bullae are normally full of clear liquid and
do not scar. Unlike pemphigus vulgaris, the lesions are pruritic and, after their rupture, are not painful. The Nikolsky sign is negative (20). The clinical characteristics of the lesions, along with the histopathologic and immunologic findings, are diagnostic. Histologic study of the lesion shows a subepidermal blister with fibrinoid material and inflammatory cell infiltration in its interior, with a predominance of eosinophils. Direct IF will show deposits of IgG and C3 in the dermoepidermal junction, whereas indirect IF shows autoantibodies circulating in the serum of the patient against proteins of the basal membrane.

Systemic or topical corticosteroids are the mainstay of therapy for MMP. Localized MMP usually responds to topical corticoid treatment (21).

**Acute Generalized Pustular Psoriasis**

Acute generalized pustular psoriasis (von Zumbusch type) is an acute variant of the psoriasis that is characterized by widespread erythema and pustules. Precipitating factors have been detailed and include infection, pregnancy, hypocalcemia, lithium, and the withdrawal of steroids (22). The disorder is characterized by a high fever, followed by the sudden appearance of sterile pustules 2 to 3 mm in diameter. Skin pain and tenderness are also observed. These are initially noted in pre-existing psoriatic plaques but rapidly generalize to the trunk and extremities, including palms and soles, and are associated with generalized erythema (23).

The diagnosis is clinical, based on the previous history of psoriasis with the appearance of marked erythema and pinpoint pustules.

The recommended first-line therapy is acitretin, cyclosporine, and methotrexate. However, infliximab is a good alternative, especially in patients with extensive diseases. Topical therapy may be useful as an adjunct to systemic therapy. Triamcinolone ointment plus wet dressings reduces scaling, tenderness, pruritus, and discomfort, and helps to re-establish the barrier function of the skin (24).

**Erythroderma**

Erythroderma is defined as a cutaneous inflammation affecting more than 90% of the body surface area, with a loss of normal integumentary function. It is the clinical manifestation of diverse dermatologic or systemic diseases (Table 142.4). The most frequent causes are psoriasis, spongiotic dermatitis, drug reaction, and cutaneous T-cell lymphoma, although, on occasion, it is not possible to identify the underlying disease, and the disorder is classified as idiopathic erythroderma (25).

Laboratory findings are not particularly helpful in making the diagnosis of erythroderma. Clinical signs, together with a cutaneous biopsy, are what actually yield the data for the diagnosis.

The main objective is the control of systemic problems derived from the loss of cutaneous function. Parallel to this, it is necessary to investigate the disease responsible for erythroderma in order to establish a specific treatment regimen. In the case where the underlying disease is not known, we evaluate the use of corticosteroids and cyclosporine (26).

**Severe Drug Eruptions**

**Toxic Epidermal Necrolysis**

Toxic epidermal necrolysis (TEN), described by Lyell, is a dermatologic disease caused by an idiosyncratic reaction to drugs. Usually it starts with a nonspecific febrile picture, followed by mucocutaneous lesions, and later develops epidermal detachment, which affects more than 30% of the body’s surface area (27); the mortality rate ranges between 30% and 50%.

Certain medications, an altered immune response, and genetic susceptibility are predisposing factors to develop TEN. Sulfonamides are the drugs most frequently associated with TEN, followed by cephalosporins, quinolones, imidazoles, and anticonvulsants such as carbamazepine and phenytoin. Certain specific HLA genotypes have been implicated in TEN caused by carbamazepine and allopurinol, namely HLA-B1502. This association has been found mostly in the Han-Chinese, Thai, and Malaysian populations but not in Caucasian patients. Therefore, the FDA recommends genetic screening for patients of Asian ancestry before initiation of carbamazepine therapy (28).

The severity and prognosis of TEN is assessed based on the SCORTEN scale. This scoring system uses seven independent factors: age, malignancy, heart rate, percentage of epidermal detachment, serum urea, serum glucose, and serum bicarbonate. However, a potential limitation is that SCORTEN may underestimate mortality in patients with respiratory involvement (29).

The lesions start as erythematous macules, followed by flaccid blisters that are easily ruptured, producing necrosis and weeping from the epidermis; the Nikolsky sign is positive. The eroded surface usually comprises between 30% and 80% of the cutaneous surface. In most cases, there is mucous membrane involvement with painful erosions.
TEN lesions are characterized by a massive apoptosis of the epidermis that induces epidermal necrosis with the development of subepidermal blisters, with an underlying sparse mononuclear cell infiltration (30).

After making the diagnosis, the first therapeutic response is the rapid withdrawal of potentially culpable medications from the patient, along with general supportive therapy; the latter therapy usually requires a burn or ICU. The major goal of supportive care is resuscitation and cardiovascular stabilization.

Although corticosteroids have been used extensively, they have not demonstrated obvious beneficial effects and, in some series, result in an increase in mortality. Notwithstanding this lack of positive effect of steroids, severe TEN may be treated with cyclosporine at a dose of 3 to 5 mg/kg/d; this regimen has resulted in promising results. Other therapies, such as zinc, plasmapheresis, and immunoglobulins, although promising, require more study (31,32).

Stevens–Johnson Syndrome

Stevens–Johnson syndrome (SJS) is a mucocutaneous disease caused by a drug-induced reaction, sharing etiologic, histologic, and therapeutic characteristics with TEN. Classically, SJS was considered a severe variant of erythema multiforme. Today, however, these are considered to be two different entities (33).

The clinical presentation of SJS is the same as that of TEN but usually involves less than 10% of the total body surface area. The range of epidermal loss between 10% and 30% is called SJS–TEN overlap. The mucous membranes are involved, and a disseminated cutaneous eruption with discrete, dark-red maculae—sometimes with a necrotic center—fol­lowed by epidermal necrosis, is seen.

Therapy involves withdrawal of causal drugs, supportive measures, and the avoidance of steroids (34,35).

Infectious Dermatologic Disorders

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is a severe blistering disease caused by exfoliative exotoxin produced by Staphylococcus aureus. The exotoxin provokes subcorneal separation of the corneal stratum through interaction with desmoglein 1, essential for maintaining the integrity of the epidermis (36).

SSSS is produced in the context of staphylococcal septicaemia. The primary infection is usually not found cutaneously, but in the nasopharyngeal mucous membrane, in the urinary tract, or at the conjunctival level. Flaccid bullae form predominantly in the folds of the skin and around natural orifices. The blisters grow and break easily, leaving a wet erythematous base that gives the appearance of scalded skin (Fig. 142.3). At resolution, there is no scarring, and very rarely are the mucous membranes involved. The Nikolsky sign is positive.

The diagnosis is initially based on the clinical picture, with the presence of erythroderma, desquamation, and bullae. Microbiologic study, with the isolation of an exotoxin producing S. aureus, confirms the diagnosis. Histologic study reveals a subcorneal separation in the granular layer due to intraepidermal acantholysis. As with the isolation of S. aureus, the histologic study—showing no epidermal necrosis—permits the exclusion of TEN, as these two entities can be indistinguishable clinically.

The resolution of the cutaneous lesions is swift after the initiation of an adequate antibacterial regimen, often with beta-lactamase–resistant penicillin. Other therapies such as plasma exchange or intravenous immunoglobulin may be considered. As the cutaneous desquamation is superficial, usually there is no serious loss of fluids or electrolytes through the skin. If treatment is begun promptly, the mortality rate can be reduced in children, although in adults the prognosis is much worse (37,38).

Systemic Diseases Presenting as Dermatologic-Like Disorders

Some dermatologic alterations are not signs of a life-threatening cutaneous disorder. However, they are expressions of potentially serious systemic diseases. Sometimes these lesions are subtle and may pass unnoticed by the patient and/or his or her physician; however, their recognition may be the key to obtaining early diagnosis and treatment (Table 142.5).

Peripheral Vascular Disorder-Related Systemic Infection

In some infectious systemic diseases, an alteration to the blood vessels is produced, secondary to direct vascular damage or, on occasion, due to a hypersensitivity reaction whereby immune-complex deposits give rise to characteristic cutaneous lesions.

<table>
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<tr>
<th>TABLE 142.5</th>
<th>Dermatologic Disorders That Are Manifestations of a Systemic Disease</th>
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<tr>
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<td>Peripheral vascular disorder–related systemic infection</td>
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<td></td>
<td>Necrotic purpuric rash</td>
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<td>Erythema gangrenosum</td>
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<td>Septic microemboli</td>
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<td>Connective tissue disorders</td>
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<td>Scleroderma</td>
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<td>Systemic lupus erythematosus</td>
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<td>Dermatomyositis</td>
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<td>Cutaneous vasculitis</td>
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Purpura Fulminans

Purpura fulminans is a severe skin manifestation of disseminated intravascular coagulation associated with acute systemic infection. Although various bacterial infections have been associated with purpura such as *Haemophylus influenzae*, *S. aureus*, or *Streptococcus pneumoniae*, these lesions are highly specific of meningococcemia. *Neisseria meningitidis* targets human endothelial cells and this interaction triggers the vascular damages that characterize purpura fulminans (39). Generally, early recognition of these lesions helps in the diagnosis of this severe systemic disease.

Petechiae and ecchymoses are the most common lesions, usually localized on the trunk and the extremities (Fig. 142.4), although, occasionally, they may affect mucous membranes as well. In the most serious cases, these ecchymotic areas become necrotic, requiring amputation if the patient survives.

Histologic study of the lesions reveals endothelial damage with areas of thrombosis and hemorrhage in the vascular wall, and containing nuclear “dust” and neutrophils in, and around, the vessels. The Gram stain and culture of the skin lesion biopsy may show meningococci.

When diagnosing a patient with fever and hemorrhagic eruption, especially in the presence of meningeal signs, meningococcemia should be suspected. Early diagnosis is crucial for establishing a cause and administering life-saving treatment for an illness with high mortality that affects mainly young people (40).

Ecthyma Gangrenosum

Ecthyma gangrenosum (EG) is an infectious vascular occlusive disease normally associated with *Pseudomonas aeruginosa* bacteremia.

Normally, EG is seen in immunologically compromised patients, such as those with diabetes mellitus, neutropenia, hematologic malignancies, organ transplantation, AIDS, or other severe chronic diseases in immunocompetent patients (41). The lesions of EG are characterized by cutaneous macules or papules, with central vesicle, that progress into hemorrhagic bullae. These break, leaving ulcers with a black necrotic center, surrounded by narrow, pink to violaceous halos. Perhaps most important, these lesions appear on the extremities and buttocks.

Histologic studies always show invasion of the adventitial and medial layers of the small vessel walls by gram-negative bacilli, resulting in a necrotizing and hemorrhagic vasculitis. Cultures of blood and of the vesicular contents usually show *P. aeruginosa* as well.

Early treatment with intravenously administered antipseudomonal antibiotics is essential since EG manifests as a necrotizing soft-tissue lesion, which often requires surgical debridement (42).

Septic Microemboli

Septic microemboli result in the eponymic Janeway lesions and Osler nodules, often associated with bacterial endocarditis.

Janeway lesions are painless, irregular, and hemorrhagic macules that are found on the palms and soles (Fig. 142.5). Histologically, they show dermal neutrophilic microabscesses and vessel thrombosis without evidence of vasculitis. Gram stain of the tissue is usually positive for organisms (43).

Osler nodes are small, painful erythematous nodules—normally found in the pads of fingers or toes—that resolve without ulceration. Histologic evaluation shows endothelial swelling, inflammation, and thrombosis, with obliteration of the superficial arteriolar lumina. Only very few biopsies of Osler’s node have obtained positive cultures for the pathogenic organism. Peripheral stigmata provide an excellent clue for the diagnosis of infective endocarditis (44).

Connective Tissue Disorders

Connective tissue diseases—such as scleroderma, lupus erythematosus, and dermatomyositis—are autoimmune disorders of unknown origin, which can affect various organs and show characteristic skin damage that can assist in making the diagnosis. These three diseases sometimes require admission to ICU, either because of their impact on vital organs or due to the secondary infectious complications related to the immunosuppressive treatment.

Scleroderma, a disorder characterized by widespread disruption of the microcirculation with intense fibrosis of the blood vessels, manifests with integumentary lesions with symmetrical fibrosis that usually affects the distal extremities and is often limited to the fingers and face, although a widespread...
form may affect the distal and proximal extremities and, often, the trunk and face (45).

Systemic lupus erythematosus (SLE) affects the skin, kidneys, lungs, central nervous system, and joints. The skin is a target organ that is affected by the disease in a variety of ways. About 80% of the patients have some cutaneous manifestation in the course of the SLE. In the skin, a characteristic “butterfly” blush (erythema over the malar eminences of the face and bridge of the nose) is seen. When especially severe, acute cutaneous lupus erythematosus produces vesiculobullous skin lesions (46).

Dermatomyositis is an inflammatory, degenerative myopathy of striated muscle with characteristic cutaneous manifestations. The integument presents a heliotropic rash, which may or may not be accompanied by periorbital edema and violet Gottron papules on the extensor surfaces of the joints; these are pathognomonic of the disease (47).

Cutaneous Vasculitis

Vasculitis includes a varied group of diseases with different degrees of systemic manifestations, and common characteristic of inflammation and necrosis of the blood vessels. The skin and subcutaneous tissues are frequently affected and often show the initial manifestation of vasculitis. Although the impact of the systemic vasculitis on the integument does not result in great risk, per se, its importance lies in the fact that it is suggestive of the type of vasculitis with which the patient is presenting and may assist in the generation of an appropriate differential diagnoses list.

Cutaneous manifestations of vasculitis include urticaria, purpura, papules, ulcer, livido reticularis, nodules, and digital gangrene. Vasculitis affecting small vessels is noted as palpable purpura, above all on the lower extremities (Fig. 142.6). On the other hand, nodules are typical lesions of vasculitis affecting small vessels as palmar eruption, purpura, and bridge of the nose (48). The classification of primitive vasculitis, which was originally based on the size of the vessel affected, currently also involves immunologic markers from the 2012 Chapell Hill Consensus Conference Nomenclature of Vasculitides (49).

The systemic vasculitis presenting as skin lesions that most often require ICU admission are polyarteritis nodosa, microscopic polyangiitis, granulomatosis with polyangiitis (Wegner’s), and eosinophilic granulomatosis with polyangiitis (Churg–Strauss).

Dermatologic Disorders during ICU Stay

ICUs are characterized by the use of invasive monitoring techniques and therapeutic procedures that, sometimes, represent an assault on the anatomic barrier of the patient. The critically ill patient’s skin is also affected by a series of local factors such as immobility, humidity, and maceration, as well as more general factors such as diabetes mellitus and the use of corticosteroids that may compound dermatologic problems. The skin is in continuous contact with pathogens, and the alteration of its protective function and characteristics allows bacterial, viral, and fungal agents to more easily penetrate this barrier. On the other hand, ICU patients often receive many drugs that may result in cutaneous drug reactions.

The most common dermatologic problems in the ICU as a result of polypharmacy and a patient’s prolonged length of stay are noted in Table 142.6. Although these dermatopathies do not usually increase patient mortality, they may require specific treatment.

Cutaneous Infection

Bacterial Infection

Superficial bacterial infections are usually produced by *S. aureus* and *Streptococci pyogenes*. The most frequent form of infection is impetigo (Fig. 142.7). This is an infection of the superficial layers of the epidermis that exists in two clinical varieties, bullous impetigo—caused exclusively by *S. aureus*, a producer of an exotoxin—and impetigo contagiosa. Impetigo contagiosa or nonbullous impetigo is the most common form and can be caused by both streptococci and staphylococci.

It is characterized by discrete thin-walled vesicles that rapidly become pustular and then rupture. The exudates dry to form loosely stratified golden yellow crusts, which usually appear on exposed areas of the body such as the face, nose,

![Image](image_url)

**FIGURE 142.6** Palpable purpura affecting the lower legs in leukocytoclastic angiitis. (Courtesy of J.M. Casanova, MD, www.dermatoweb.net.)

<table>
<thead>
<tr>
<th>TABLE 142.6 Dermatologic Disorders Developed during ICU Stay</th>
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<td><strong>Cutaneous infection</strong></td>
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<td><strong>Bacterial infection</strong></td>
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<td>- Bullous impetigo</td>
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<td>- Impetigo contagiosa</td>
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<tr>
<td><strong>Viral infection</strong></td>
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<tr>
<td>- Herpes simplex virus type 1 (HSV-1) and 2</td>
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<tr>
<td>- Perioral/genital herpes</td>
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<td>- Eczema herpeticum</td>
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<tr>
<td>- Varicella-zoster virus 3 (VZV)</td>
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<tr>
<td>- Chickenpox (varicella)</td>
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<td>- Shingles (zoster)</td>
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<td><strong>Fungal infection (Candida species)</strong></td>
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<td><strong>Reactions to intensive therapy</strong></td>
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<tr>
<td>- Morphalliform reactions</td>
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<tr>
<td>- Urticaria and angioedema</td>
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<tr>
<td>- Contact dermatitis</td>
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<td>- Skin necrosis induced by drugs</td>
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and extremities (50). In ICU patients, these lesions usually appear on areas of skin damaged by pressure, wounds, or trauma. For bacteriologic diagnosis, a culture of the lesion is required, as the exanthem resultant from *S. aureus* and group A streptococci are clinically indistinguishable. In the last two decades, *S. aureus* has eclipsed *S. pyogenes* as being the most common cause of nonbullous impetigo.

Although the therapeutic options include diverse oral and topical antimicrobials, as well as disinfectants, one should note that topical antibiotic treatment with mupirocin or fusidic acid is at least as effective as oral antibiotics, without the side effects of the latter (51).

**Viral Infection**

The herpes virus family, of which there are eight human serotypes, may produce significant skin lesions. In critically ill patients, viral skin lesions are almost always due to herpes virus types 1 and 2, and the varicella-zoster virus (VZV) 3 (52).

**Herpes Simplex Virus Types 1 (HSV-1) and 2 (HSV-2).** Skin eruptions caused by HSV-1/2 are common dermatoses usually localized around the lips (HSV-1) or on the genitalia (HSV-2).

HSV-1 is the most common of these virus types, affecting the perioral area and lips, although occasionally it can affect other areas of the body. This presents as painful skin lesions around the lips, accompanied by a burning sensation and the formation of small vesicles grouped in bunches on an erythematous base. These vesicles become umbilicated and rupture quickly, forming a scab that heals after 7 to 10 days, without a scar. The reactivation of the labial herpes is aided by diverse factors such as hormonal alterations, febrile processes, or stressful situations frequent in the intensive care environment. The association of perioral herpes with bacterial infection is typical, especially that caused by *S. pneumoniae*. This demonstrates the phenomenon of the virus reactivation behaving as an indicator of underlying gram-positive bacterial infection (53,54). Reactivation is also a frequent complication associated with immunosuppression (55), organ transplantation (56), dermatoses (57), and burn patients (58).

Although the diagnosis is fundamentally clinical, the Tzanck test can show the presence of multinucleated giant cells, and direct IF and polymerase chain reaction (PCR) techniques confirm the diagnosis.

Topical treatment, started as soon as possible after diagnosis, with 5% acyclovir or 1% penciclovir applied five times a day, is effective in reducing the duration and severity of the symptoms. Recently, the use of antiviral and anti-inflammatory combined therapy (5% acyclovir/1% hydrocortisone) has been shown to be more effective than antiviral treatment alone (59).

A serious variant of a skin infection by HSV is eczema herpeticum or Kaposi varicelliform eruption (KVE) (60). This emerges in patients with previous dermopathy, generally atopic dermatitis. It is characterized by vesicular lesions in areas of dermatitis that grow into large erosive areas covered in honey-like crusts. The microscopic finding of a Tzanck for multinucleated giant cells can confirm a herpes virus infection. This is accompanied by signs of systemic implications, and requires systemic treatment with acyclovir (10 mg/kg every 8 hours). Sometimes an immunosuppressant treatment must be applied (systemic corticosteroids, cyclophosphamide, azathioprine, and cyclosporine) to control the severity of the primary dermatosis (60).

**Varicella-Zoster Virus 3.** VZV 3 causes chickenpox (varicella) and shingles (zoster). Varicella is the most common form of the initial presentation of VZV. This is a contagious disease, generally benign and typically seen during infancy. It is rare among adults, but when present, is associated with severe complications such as varicella pneumonia, the most common complication occurring in 15% to 50% of cases with 10% to 35% mortality (61,62).

The skin rash is quite characteristic: each spot starts as a 2- to 4-mm-diameter red papule, developing an irregular outline (rose petal) as a small vesicle appears. The vesicle quickly develops into a pustule, which becomes umbilicated and results in a pruritic scab in less than a day. One will observe multiple lesions in different evolutionary periods with this disorder (Fig. 142.8), as opposed to the lesions of smallpox, which develop in uniform “crops.”

**Figure 142.7** Subcorneal bullae followed by an exudative erosive lesion in impetigo.

**Figure 142.8** Adult with varicella. The rash is in different stages of evolution, with some vesicles, macules, and papules.
Varicella pneumonia normally emerges within 1 to 6 days of the skin rash. The typical skin lesions, with respiratory symptoms and radiologic findings of interstitial pneumonitis (Fig. 142.9), are suggestive of the diagnosis (63).

Optimal treatment is intravenous acyclovir at a dose of 10 mg/kg every 8 hours. Use of corticosteroids has demonstrated a significant improvement in oxygenation and shortening of the duration of mechanical ventilation in preliminary studies (64).

Herpes Zoster. Herpes zoster is an acute radiculitis accompanied by a vesicular eruption grouped over an erythematous base localized in the corresponding dermatome on the affected ganglion (65). It is produced by a reactivation of the VZV that is latent in the ganglions of the nerve roots (66). The thoracic and trigeminal nerves are the most frequently affected dermatomes.

Initially, a prodrome of hyperesthesia, dysesthesias, itching, or pruritus throughout the affected dermatome presents; later, the typical lesions appear with a maculopapular rash that evolves into vesicles grouped in bunches, distributed along the affected dermatome. The most common chronic complication of this acute radiculitis is postherpetic neuralgia, which can be debilitating.

Famciclovir, valganciclovir, and acyclovir are effective treatments for herpes zoster (67); in the most severe cases, intravenous agents are used. The use of corticosteroids to help with pain is of doubtful utility; gabapentin and the tricyclic antidepressants are recommended for postherpetic neuralgia (68).

Fungal Infection (Candida Species)
Cutaneous candidiasis is a superficial infection that emerges in damp and macerated areas of skin, usually in the folds of the axillae and the submammary area (69). Cutaneous candidiasis is a frequent problem in long-stay critically ill patients who have most often received broad-spectrum antibiotic therapy and have very limited mobility.

The infection is characterized by intense shiny erythema with scarce whitish exudates and satellite papules and pustules (Fig. 142.10). Diverse factors assist in the candidal infection’s initiation and progression. On the one hand, maintaining hygiene is important but, on the other hand, drying the skin of critically ill patients with limited movement—in some cases, with the added complication of obesity which involves deeper and more numerous skin folds—helps the emergence of mucosal candidiasis (71). The diagnosis can be supported by potassium hydroxide (KOH) examination of skin scrapings.

Therapeutic measures include hygiene, the avoidance of abrasion, and topical treatment with potassium permanganate, followed by topical clotrimazole or nystatin.

Neutropenia and immunosuppression are risk factors in disseminated candidiasis, which may be seen as papules and pustules that extend over the entire body surface area. In these cases, systemic antifungal treatment—such as amphotericin B, fluconazole, voriconazole, or echinocandin—is advisable (72).

Dermatologic Reactions to Therapy in the ICU
ICU patients require multiple drug therapies, many of which are capable of inducing adverse reactions (73). Cutaneous involvement is the adverse reaction most frequently attributed to such drugs. It is estimated that rashes caused by drug reactions occur in 10% of ICU patients (Table 142.7). Because the drugs have an antigenic potential determined by their physicochemical properties, there may be one of a number of immune reactions: Type I hypersensitivity reaction is defined as a fast-developing immunologic reaction that occurs in individuals having been previously sensitized by an antigen–antibody interaction. Urticaria and angioedema are the chemical expressions for these types of hypersensitivity reactions, with a morbilliform rash that is of unclear cause. Contact dermatitis is produced by a type IV hypersensitivity reaction through lymphocytes in skin that has been previously sensitized. In some cases, contact dermatitis is due to the direct irritative action of the external agent. However, secondary cutaneous necrosis to drugs is not an immunologic problem, but is attributed to direct toxicity of the exposed agent.

Morbilliform Reactions
A morbilliform rash is the most common form of secondary rash caused by drugs, representing 40% of all drug reactions. It is characterized by erythematous macules and papules,
generally symmetrically distributed, which can become confluent (Fig. 142.11). The rash usually begins on the trunk and in pressure-prone areas, subsequently extending to the extremities, and may include the mucous membranes, palms, and soles, although it does not usually affect the face.

The morbilliform reaction usually appears about a week after starting the causative medication, and may last 1 to 2 weeks. The drugs most often associated with this rash are penicillin and its derivatives, sulfonamides, anticonvulsants, and allopurinol, although further exposure to the drug does not always cause a reappearance of the damage.

Identifying and discontinuing the causative drug are the most important steps in patient management. Symptomatic treatment and glucocorticoids may be helpful (74).

Urticaria and Angioedema

In approximately half of all cases, urticaria is accompanied by angioedema that consists of edema of the deep dermis, the subcutaneous tissue, and the mucous membranes, including the respiratory and intestinal tract. Multiple drugs are implicated in the emergence of urticaria/angioedema such as penicillin and other beta lactams, as well as nonsteroidal anti-inflammatory drugs that produce a type I urticarial eruption mediated by IgE (75).

Urticaria is a skin lesion characterized by the emergence of wheals, defined as a confined elevation of the skin, erythematous or pale in the center, surrounded by an erythematous halo of variable size.

Drug-induced urticaria produces a sudden benign and transitory eruption that normally disappears in less than 24 hours, and is characterized by the emergence of multiple erythematous papules and edema in any part of the body's surface. It is normally pruritic, affecting mostly the scalp, palms, and soles. The lesions of angioedema have a variable coloration, from off-white to erythematous, are normally not painful, and usually last less than 24 hours. They are localized in areas where the dermis is the thinnest, such as the face, and respiratory, gastrointestinal, and genitourinary mucous membranes. When it affects the oropharynx, it can produce acute compromise of the respiratory tract, creating a life-threatening situation that may require an urgent tracheostomy (76). Normally, angioedema accompanies the urticaria, although it may appear isolated as in cases of angioedema secondary to angiotensin-converting enzyme inhibitors or angioedema secondary to a deficit of C1 inhibitor (77,78).

Treatment includes antihistamines (chlorpheniramine, 0.1 mg/kg), corticosteroids (methylprednisolone, 1 to 2 mg/kg), and, in case of respiratory tract compromise, epinephrine.

Angioedema due to C1 inhibitor deficiency, whether hereditary or acquired, is characterized by recurring episodes of peripheral angioedema associated with abdominal pain with variable clinical expression (79). The diagnosis is made through the evaluation of C4, which is decreased—the first indicator of the disease. It is necessary to note that episodes of hereditary angioedema do not respond to normal treatment with epinephrine, antihistamines, and corticosteroids. The optimum treatment is the administration of concentrated C1 inhibitor (80).

Contact Dermatitis

Contact dermatitis is an eczematous disease attributed to an inflammatory reaction of the skin to external agents, irritants, or allergens. Irritative contact dermatitis is due to the direct action of a substance that provokes an inflammatory skin reaction without the intervention of an immunologic mechanism. Most cases of irritative dermatitis in the ICU are associated with hygienic body soap, iodine-based antiseptics, chlorhexidine (81), and the auto-adhesive electrodes of continuous electrocardiographic monitoring (Fig. 142.12). Allergic contact

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### Table 142.7 Drugs Most Commonly Associated with Acute Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Penicillin and other beta-lactams</th>
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<tbody>
<tr>
<td>Natural and semisynthetic penicillins</td>
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<tr>
<td>Cephalosporins</td>
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<td>Monobactams</td>
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<td>Carbapenems</td>
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<th>Nonsteroidal anti-inflammatories</th>
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<tr>
<td>Salicylates</td>
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<tr>
<td>Indolacetic acids (indomethacin)</td>
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<tr>
<td>Aylacetic (diclofenac)</td>
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<tr>
<td>Propionic acid (ibuprofen)</td>
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<td>Pyrazolones (metamizole)</td>
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<td>Oxicams (piroxicam)</td>
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<table>
<thead>
<tr>
<th>Non-beta-lactam antibiotics</th>
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<td>Tetracyclines</td>
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<tr>
<td>Sulfonamides</td>
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<tr>
<td>Levofloxacin</td>
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<td>Azithromycin</td>
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<td>Erythromycin</td>
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<tr>
<th>Anticonvulsants</th>
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<td>Phenytoin</td>
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<tr>
<td>Carbamazepine</td>
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<td>Pentobarbital</td>
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<td>Lamotrigine</td>
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<th>Antihypertensives</th>
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<tr>
<td>Angiotensin-converting enzyme inhibitors (ACEI)</td>
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<tr>
<td>Angiotensin II receptor antagonist (ARA II)</td>
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<tr>
<td>Thiazides</td>
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<tr>
<td>Diltiazem</td>
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<table>
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<tr>
<th>Other</th>
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<tbody>
<tr>
<td>Contrast agents</td>
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<tr>
<td>Anthral (acyclovir)</td>
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<tr>
<td>Antifungals (amphotericin B)</td>
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<tr>
<td>Steroids</td>
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dermatitis (ACD) is a delayed hypersensitivity reaction that is produced in skin previously sensitized to an allergen (82). Differentiation should be made between contact dermatitis and other eczematous disorders such as atopic dermatitis (83). Typically, patients with contact dermatitis have an eczematous reaction with papules or vesicles over erythematous plaques and localized edema in areas exposed to the exogenous substance; intense pruritus is the most frequent symptom (84). The treatment includes, first, withdrawal of the agent responsible, and symptomatic treatment with topical antihistamines and corticosteroids (85).

**Skin Necrosis Induced by Drugs**

Oral anticoagulants and intravenous vasopressor drugs can produce skin necrosis through alteration of blood circulation. Skin necrosis secondary to oral anticoagulants usually appears early, and is produced in areas rich in adipose tissue, such as the breast, buttocks, and thighs (86). It is characterized by pain and paresthesias, followed by erythema and purpuric lesions that quickly progress to extensive ecchymotic areas that are well circumscribed and blue–black in color with cutaneous ischemia. These alterations generate a state of initial transitory hypercoagulability that provokes local thrombosis of the veins of the dermis and the subcutaneous cell tissue.

Skin necrosis can also appear as a complication of the infusion of vasopressor drugs, requiring, in some cases, amputation of the affected extremity. Classically, it is related to the use of high doses of dopamine and norepinephrine. The existence of disseminated intravascular coagulation and hypovolemia are risk factors for the development of gangrene related to vasopressors (89,90). Vasopressin, useful in the treatment of catecholamine-resistant vasodilatory shock, may also provoke cutaneous ischemia, due to its vasoconstrictor action on the arteriolar level (91). The ischemic skin lesions are normally localized in the distal area of the extremities and the trunk. When the administration of vasopressin is by a peripheral vein, it may provoke local cutaneous ischemia if it infiltrates into the subcutaneous tissue. To avoid the potential for ischemic lesions, administration of vasopressin should be by central venous catheter, and careful monitoring of the extremities to detect ischemic changes should be carried out (92). Terlipressin, a vasopressin agonist, is used in the treatment of variceal bleeding and hepatorenal syndrome. Terlipressin has a lower incidence of severe ischemic complications than vasopressin. However, it can produce serious complications such as skin necrosis (93). The application of topical nitroglycerin, in addition to decreasing the dose of the vasopressor, may improve the symptoms and signs of ischemia (94).

**DERMATOLOGIC DISORDERS IN SPECIFIC SITUATIONS**

### Graft versus Host Disease

The allogenic transplant of hematopoietic stem cells is a procedure used to treat various malignant diseases, above all those of hematologic origin. Graft versus host disease (GVHD) is the most important complication in stem cell transplantation and occurs because of the introduction of immunologically competing cells into an immunodepressed host. It is the main cause of morbidity and death in transplant patients. Historically, acute GVHD has been defined by the onset of GVHD signs and symptoms within the first 100 days of transplant, whereas chronic GVHD occurs afterwards. However, evolving transplant practices have altered the typical onset of acute and chronic disease manifestations. GVHD has been recently reclassified based primarily on clinical manifestations and histologic findings. The diagnosis and staging guidelines included new disease classifications, including an “overlap syndrome,” with features of both acute and chronic GVHD, and “late acute GVHD” which is characterized by persistent, recurrent, or late-onset acute GVHD occurring more than 100 days after transplant (95).

Acute GVHD usually occurs between days 10 and 40 following the transplant. Its main manifestations are in the skin, liver, and gastrointestinal tract, secondary to damage to the epithelial cells of these areas. The skin is the most commonly affected organ in patients. This involvement begins with pain or itching, followed by a maculopapular rash resembling measles. The early injuries can be folliculocentric blanching erythematous macules or papules, which are suggestive of GVHD, accompanied by very painful mouth ulcers. If not serious, the injuries can resolve spontaneously or after increasing the immunosuppressant treatment.

Chronic GVHD often appears in patients who have previously suffered the acute form of GVHD. Other risk factors are advanced age of the donor, high level of histo-incompatibility, and previous total body irradiation. Chronic GVHD is characterized by its effect on the skin, oral mucous membranes, eyes, and salivary glands. Chronic cutaneous GVHD may present with many different sclerotic and nonsclerotic manifestations. Diagnostic manifestations include poikiloderma, lichen planus-like eruption, deep sclerotic features, and morphea-like or liquen sclerosus-like lesions. Cutaneous biopsy confirms the diagnosis.

Treatment must be directed toward preventing GVHD by depleting lymphocytes in the graft donor and using immunosuppressants such as cyclosporin combined with methotrexate and corticosteroids (96). If, in spite of this treatment, the patient develops GVHD, an augmented dose of systemic steroids, cyclosporine, and azathioprine may be attempted to gain control. If it persists, photochemotherapy with psoralen
and UV-A irradiation has been shown to be beneficial (97). Thalidomide and extracorporeal photopheresis have also been shown to be effective (98).

**Acquired Immunodeficiency Syndrome**

Infection with the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome are related to many integumentary and mucous membrane manifestations. This damage is due to disrupted immunologic function, and may often be the first sign of the disease or a mark of its progress.

The severity and extent of the skin disorders related to HIV depend on the degree of immunodeficiency. During the asymptomatic phase of the infection, the main cutaneous manifestations are seborrheic dermatitis, psoriasis, xeroderma, and pruritic papular rashes. As the infection advances and the immunologic response diminishes, these skin diseases tend to become more chronic and severe, and opportunist infections appear, along with other more unusual disorders such as oral hairy leukoplakia, chronic herpes simplex, cryptococcosis, Kaposi sarcoma, etc. (Fig. 142.13).

The variety of integumentary disorders during the course of the infection is a consequence of the progressive immunodeficiency and of the underlying disease (99). The adoption of combined antiretroviral therapy in the treatment of HIV infection has changed the course of the disease, reducing the levels of viral proliferation and allowing a partial reconstitution of immunity (100).

**Prior Dermatologic Disorders**

Skin disorders are frequent in the general population. Patients with chronic skin disorders may require admission to the ICU for a life-threatening disease that has nothing to do with the skin, but we must also take the latter into account, along with other comorbidities, such as atrial fibrillation, diabetes mellitus, hypertension, and so forth, as some skin disorders may require specific care.

The diagnosis of a previous DD is optimally made with the clinical history, although sometimes, because of the severity of illness or sedation, the patient cannot assist with the history and the definitive diagnosis must be verified with a dermatologist consultant.

**Key Points**

- Acute skin failure, which must be included in multiple organ dysfunction syndrome, involves different pathologies that can lead to multiple systemic complications which may be life-threatening.
- In critical patients, a careful exploration of their skin can help in the diagnostic of severe systemic disorders.
- Collaboration with dermatologists is essential to achieve an accurate diagnosis and treatment of dermatologic problems in critical patients.

**References**


