COMPASS

Coordinating care and improving outcomes in patients with pustular psoriasis

NEUTROPHILIC DERMATOSES: AN OVERVIEW

CONTENTS

ABBREVIATIONS

ACH	acrodermatitis continua of Hallopeau
AGEP	acute generalised exanthematous pustulosis
APIS3	adapter protein complex 1 subunit sigma 3 gene
APP	annular pustular psoriasis
CARD14	caspase recruitment domain-containing protein 14 gene
EED	erythema elevatum diutinum
ERASPEN	European Rare and Severe Psoriasis Expert Network
GPP	generalised pustular psoriasis
HS	hidradenitis suppurativa
IBD	inflammatory bowel disease
IgA	immunoglobulin A
IL-1	interleukin-1
IL1RN	IL-1 receptor antagonist gene
IL-17	interleukin-17
IL-36	interleukin-36
IL36RN	IL-36 receptor antagonist gene
NDs	neutrophilic dermatoses
NEH	neutrophilic eccrine hidradenitis
NU	neutrophilic urticaria
NUD	neutrophilic urticarial dermatosis
PAPA	PG, acne, and pyogenic arthritis
PASH	PG, acne, and hidradenitis suppurativa
PAPASH	PG, acne, pyogenic arthritis, and hidradenitis suppurativa
PG	pyoderma gangrenosum
PPP	palmoplantar pustulosis
PPPP	palmoplantar pustular psoriasis
PV	psoriasis vulgaris
QOL	quality of life
SERPINA3	serine protease inhibitor gene family A, member 3
SPD	subcorneal pustular dermatosis
SS	Sweet syndrome
TNF	tumour necrosis factor
TNFAIP3	TNFα-induced protein 3
TNIP1	TNFAIP3-interacting protein 1 gene
WBC	white blood cell

NEUTROPHILIC DERMATOSES: AN OVERVIEW

NEUTROPHILIC DERMATOSES: INTRODUCTION

Neutrophilic dermatoses (NDs) are a clinically heterogenous group of rare conditions characterised by the sterile accumulation of neutrophils in the skin. The mechanisms underlying NDs are not fully understood, but NDs may be viewed as a spectrum of autoinflammatory disorders, with several gene alterations identified and a central role for the interleukin-1 (IL-1) pathway.[1,2]

NDs are frequently associated with systemic conditions, including inflammatory bowel diseases (IBD), rheumatologic disorders, haematological malignancies, vasculitides (as a primary or secondary process), and inherited monogenic autoinflammatory diseases.[3,4] Extracutaneous manifestations of NDs may affect a wide range of organs and body systems.[3]

NDs are broadly classified by the depth of neutrophil infiltration in the skin: primarily **epidermal** or **dermal**.[4] Over time, the list of conditions recognised as NDs has expanded, with transitional forms and overlapping conditions posing a challenge for diagnosis and management.[4] Due to the rarity of most NDs, reliable epidemiological data are lacking.

EPIDERMAL NEUTROPHILIC DERMATOSES: PUSTULAR PSORIASIS

Pustular psoriasis has historically been grouped with plaque psoriasis (psoriasis vulgaris [PV]) but is now recognised as a distinct condition based on clinical, genetic, and immunological features.

As a first step towards an international consensus, the European Rare and Severe Psoriasis Expert Network (ERASPEN) defined three clinical phenotypes of generalised or localised pustular psoriasis, namely **generalised pustular psoriasis (GPP)** and pustular psoriasis that is localised to the palmoplantar surfaces (**palmoplantar pustulosis**, PPP) or the digits and nail apparatus (**acrodermatitis continua of Hallopeau** [ACH]).[5]

GENERALISED PUSTULAR PSORIASIS

GPP (also known as von Zumbusch variant) is characterised by primary, sterile pustules on non-acral skin, where the extent ranges from widespread discrete lesions to confluent forms (sometimes described as 'lakes of pus').[5,6] Mortality may occur in GPP due to sepsis, cardiac failure, or acute respiratory distress syndrome.[7] Defined as either a persistent or acute relapsing-

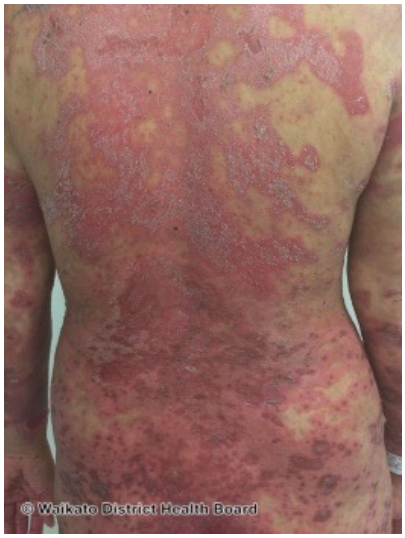
Pustular psoriasis: defining features[5]

Generalised pustular psoriasis	Non-acral skin (widespread)
	Persistent (>3 months) or relapsing (>1 episode)
	With or without systemic inflammation[1]
	With or without PV
Palmoplantar pustulosis	Palms and/or soles
	Persistent (>3 months)
	With or without PV
Acrodermatitis continua of Hallopeau	Nail apparatus
	Persistent (>3 months)
	With or without PV

[1] *Systemic inflammation was defined as fever >38°C and leucocytosis (WBC >12 × 10^9/L). PV, psoriasis vulgaris.*

remitting condition, GPP is further classified by the presence or absence of systemic inflammation and/or PV.[5] An analysis of 863 patients with pustular psoriasis found that concurrent PV was significantly less common in patients with PPP (16%) than those with ACH (46%) or GPP (54%).[8] Although GPP can be triggered by provocative factors (e.g., infection, pregnancy, hypocalcaemia associated with hypoparathyroidism, or medications), this does not form part of the diagnostic criteria.[5,6] The main differential of GPP is acute generalised exanthematous pustulosis (AGEP), which resembles GPP (and shares immunological and genetic features) but is most commonly a drug reaction.[9] This may be difficult to distinguish from medication-induced GPP flares.[6]

GPP is an autoinflammatory pustular neutrophilic disease that predominantly involves the innate immune system.[10] GPP lesions show sustained activation of the pro-inflammatory cytokines IL-1 and IL-36, leading to neutrophil infiltration and pustule formation.[11,12] Mutations in IL36 *receptor antagonist gene* are associated with more severe GPP clinical features – low prevalence of PV, early age of onset, severe inflammation and high recurrence rate.[8,13,14]



Generalised pustular psoriasis. ©Waikato District Health Board. Source 🖹. *Used with permission from* **DermNet New Zealand**. *Licensed under* **CC BY-NC-ND 3.0 NZ.**

PUSTULAR PSORIASIS VARIANTS THAT OVERLAP WITH GPP

Several uncommon forms of pustular psoriasis overlap with GPP. These include:

- **Pustular psoriasis of pregnancy**, also known as "impetigo herpetiformis", which most frequently occurs during the third trimester of pregnancy and can be life-threatening.[12] Although it resolves rapidly after delivery, it is associated with increased rates of pregnancy complications and typically recurs with subsequent pregnancies.[12] *IL36RN* mutations have been identified in some cases.[5]

- **Juvenile pustular psoriasis**, which is rare, may present similarly to adult GPP but an annular form is more common.[6] Precipitating factors include infection, vaccination, and corticosteroid withdrawal.[12]

- **Annular pustular psoriasis (APP)** is a chronically recurring form that may be classified as a subtype of GPP. However, it is generally much milder than GPP, with discrete lesions and a favourable prognosis.[6] Characteristics of APP include erythematous polycyclic lesions with sterile pustules on the lesion circumference. When present, systemic symptoms are usually much milder than in GPP.[6] A history of PV is uncommon but features of APP and GPP may overlap in the same patient.[7] In children, APP is the most frequent form of pustular psoriasis.[7] In adults, the onset of APP is typically in middle age and the condition is more common in women than men.[7]

PALMOPLANTAR PUSTULOSIS

PPP is a chronic localised form of pustular psoriasis characterised by primary, persistent sterile pustules on the palms of the hands and/or soles of the feet. PPP lesions are often painful and pruritic, and impaired quality of life (QOL) is common.[15]

Consensus is lacking over whether PPP and palmoplantar pustular psoriasis (PPPP) are the same condition; the latter term is used by some authors for cases with concomitant PV lesions (24–84%) and/or a family history of psoriasis,[15] whereas the European consensus is that PPP includes these cases.[5]

Prevalence estimates for PPP range from 0.01–0.12%, with a strong female predominance (65–94%), and a typical onset in middle age.[15] Female sex, early-onset disease, and current or former smoking status are associated with increased disease severity.[16]

Research has identified a role for IL-17 and IL-36 pathways in PPP, and some microbiome studies challenge the traditional concept of sterile pustules.[15] Triggering factors include smoking, infections (including tonsillitis and dental infections), dental metal allergy, and anti-tumour necrosis factor (TNF) agents, while comorbidities include thyroid disease, metabolic syndrome, psoriatic arthritis and depression.[15]

Treatment of PPP is challenging, with no standard treatment but various options, including topical and systemic treatments, phototherapy, and targeted therapies.[15,17] In patients with moderate-to-severe PPP, phototherapy combined with acitretin may be effective.[17]

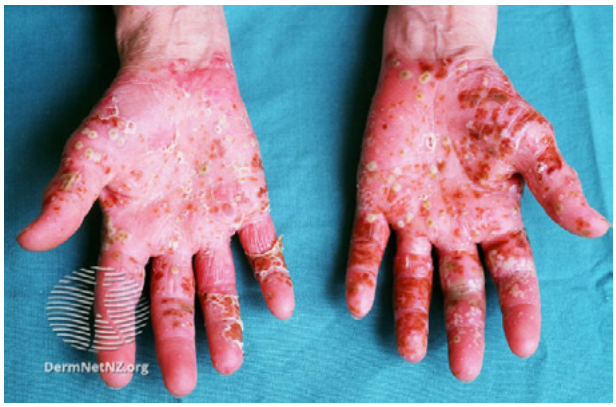
ACRODERMATITIS CONTINUA OF HALLOPEAU

ACH is another chronic localised form in which primary, persistent sterile pustules affect the nail apparatus, and often the distal fingers or toes.[5] Involvement of the nail apparatus is required for diagnosis.[5]

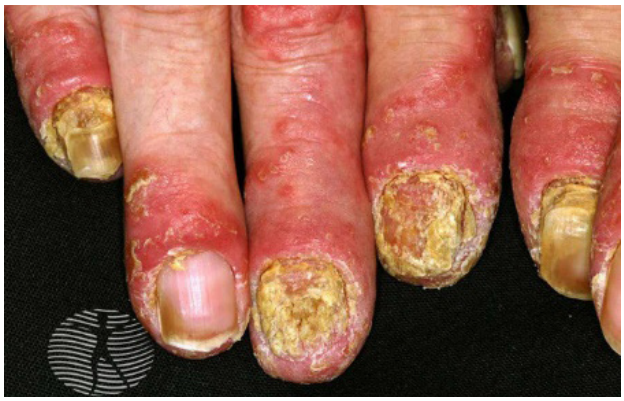
A painful and frequently disabling condition, ACH may develop following localised trauma or infection involving a single digit.[7] Middle-aged women are most commonly affected, although this is based on limited evidence.[7,18] ACH is associated with mutations in the *IL36RN*, *CARD14*, and *AP1S3* genes.[18]

Typically, ACH remains unilateral and localised to a limited number of digits for years,[18] but in some cases it may become generalised and overlap with GPP over time.[5] In severe cases, osteolysis may occur.[18]

Differential diagnoses for ACH include bacterial, fungal or viral paronychia, herpetic whitlow, secondary infection of contact dermatitis, dyshidrotic eczema, or a paraneoplastic process.[18] ACH has a chronic relapsing course, with intermittent episodes of acute pustulation, and is often refractory to treatment,[7] but biologics have shown promise.[18]

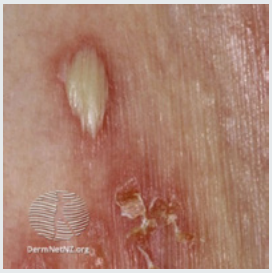


Palmoplantar pustulosis. ©DermNet New Zealand. Source. Used with permission from **DermNet New Zealand.**



Acrodermatitis continua of Hallopeau. ©Professor Raimo Suhonen. Source. Used with permission from **DermNet New Zealand.**

Typical features of PPP and ACH[18]	
Palmoplantar pustulosis	**Acrodermatitis continua of Hallopeau**
Rarely follows trauma	Often follows trauma
Does not always affect the nail; usually non-suppurative	Always affects the nail; suppurative nail involvement is a defining feature
Commonly bilateral	Commonly unilateral
Symmetrical distribution	Irregular distribution
No soft tissue sclerosis or osteolysis	Soft tissue sclerosis or osteolysis may occur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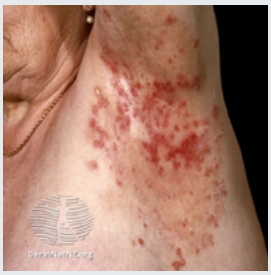
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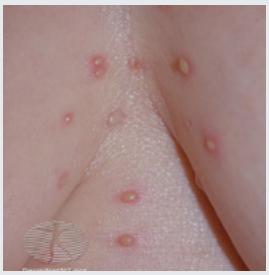
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Subcorneal pustular dermatosis. A and B: ©Professor Raimo Suhonen. C. ©DermNet New Zealand. Source. Used with permission from **DermNet New Zealand.**

OTHER EPIDERMAL NDS

Other epidermal NDs with unusual or atypical presentations include subcorneal pustular dermatosis (SPD or Sneddon–Wilkinson disease), which has an unclear relationship to GPP, amicrobial pustulosis of the folds, and a group of immunoglobulin A (IgA) neutrophilic dermatoses.[4]

SPD is most common in middle-aged women and presents with numerous large (several millimetres in diameter), sterile, flaccid pustules on normal or mildly erythematous skin.[6] Pustules are often symmetrically distributed on the trunk, especially axillary, inguinal and submammary areas, while systemic manifestations are rare.[4] SPD is chronic and commonly relapsing.[4]

DERMAL NDS

SWEET SYNDROME

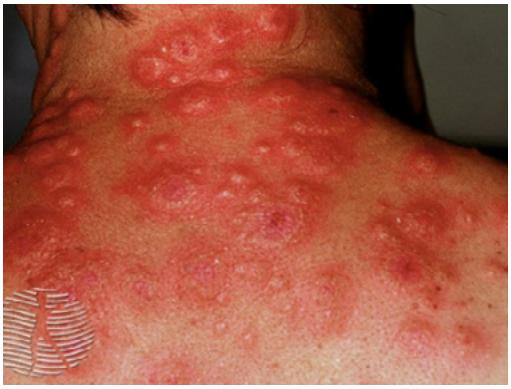
Sweet syndrome (SS), also known as acute febrile neutrophilic dermatosis, is more common in women than men and has a typical age of onset of 47–57 years.[19]

SS is characterised by abrupt onset of fever, peripheral neutrophilia, painful erythematous-to-violaceous nodules or plaques with a dermal neutrophilic infiltrate, absence of infection, and responsiveness to corticosteroids.[1,20] The classic subtype describes SS that is idiopathic or associated with infection, vaccination, inflammatory disorders (most commonly IBD), or pregnancy. Other SS subtypes are associated with malignancy or medications.[19] Since 2019, SS has been reported after infection with coronavirus disease 2019 (Covid-19) and as a rare reaction to Covid-19 vaccination.[21]

Diagnostic criteria for Sweet syndrome[19]	
Major criteria (both are required)	**Minor criteria (two are required)**
Abrupt onset of typical cutaneous lesions	Preceded by an associated infection or vaccination; presence of an associated malignancy or inflammatory disorder; associated with pregnancy or drug exposure
Histopathology consistent with Sweet syndrome	Fever and constitutional signs and symptoms
	Leucocytosis
	Excellent response to systemic corticosteroids

Less common presentations include cellulitis-like plaques over large surface areas, and subcutaneous SS.[4] SS that presents as a multisystem disease carries a risk of mortality.[19]

SS is a diagnosis of exclusion, with the differential diagnosis including infectious, inflammatory, and neoplastic diseases.[19]



Sweet syndrome. ©DermNet New Zealand. Source.
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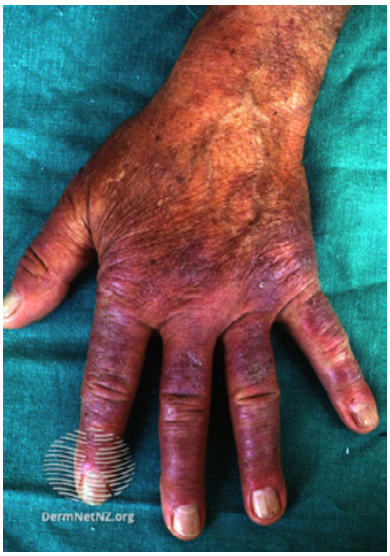
ERYTHEMA ELEVATUM DIUTINUM

Erythema elevatum diutinum (EED) is a chronic inflammatory dermatosis with brownish-red, elevated plaques distributed symmetrically over the interphalangeal joints, elbows, ankles, and knees; the trunk is characteristically spared.[3] Most cases begin in middle age, but onset can occur from infancy to the elderly, with no familial association or sex predisposition.[3] EED may be associated with a range of underlying conditions, most commonly IgA gammopathy, with other associations including Crohn's disease, ulcerative colitis, rheumatoid arthritis, haematological malignancies and infections, among others.[3]



Erythema elevatum diutinum. ©DermNet New Zealand.
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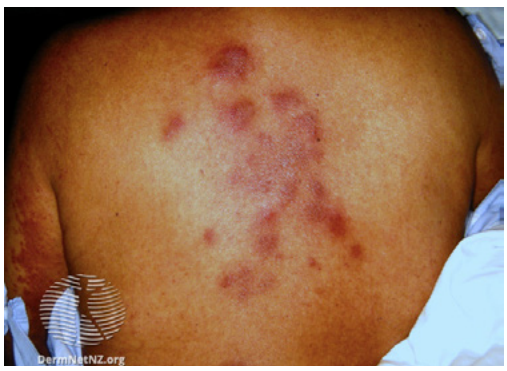
NEUTROPHILIC ECCRINE HIDRADENITIS

Neutrophilic eccrine hidradenitis (NEH) is clinically similar to SS and most commonly occurs in patients receiving chemotherapy for acute myeloid leukaemia,[3] although other medications have been implicated (including paracetamol, adalimumab, antiretrovirals, azathioprine, carbamazepine, and growth factors).[19]

NEH is characterised by erythematous, oedematous papules or plaques, most often on the trunk, with robust neutrophilic infiltrate of the eccrine gland secretory coils and epithelial necrosis.[19] Differential diagnosis includes SS and infection. The clinical presentation varies; diagnosis depends on the histopathology, with the key feature being eccrine glands showing degenerative vacuolar changes.[19] NEH may also occur in children as a benign, self-limited eruption, often in summer, with another variant in children being idiopathic plantar hidradenitis of NEH.[19]

Spontaneous resolution of NEH occurs after stopping chemotherapy. Systemic corticosteroids may be used to reduce pain or fever and dapsone may prevent recurrence.[19]

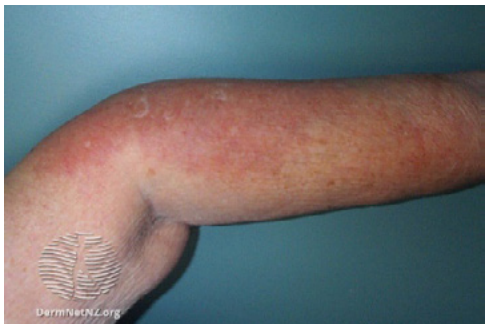


Neutrophilic eccrine hidradenitis. ©DermNet New Zealand. Source . Used with permission from **DermNet New Zealand**.

NEUTROPHILIC URTICARIAL DERMATOSIS

Neutrophilic urticarial dermatosis (NUD) was proposed as a new entity only in 2009; since then over 120 patients have been reported in the literature.[4] NUD characteristically occurs with either an immune-mediated or autoinflammatory disorder and must primarily be differentiated from neutrophilic urticaria (NU), which does not have these associations.[4] The most common associated conditions are adult-onset Still disease, systemic lupus erythematosus, Schnitzler syndrome, and cryopyrin-associated periodic syndrome.[4] Aberrant activation of the innate immune system is implicated in the pathophysiology, with a likely role of the IL-1 pathway.[4]

NUD lesions are chronic and recurrent, with eruptions of pale-to-red macules or slightly raised papules or plaques (up to 2 cm in diameter), which generally disappear spontaneously within 24–48 hours.[4] Lesions may be single or confluent and are usually on the trunk, arms, and legs, accompanied by a burning sensation, mild pain, or (less commonly) pruritus.[4] Systemic manifestations depend on the underlying disorder, although fever and arthralgia can occur in the absence of an underlying condition.[4]



Neutrophilic urticarial dermatosis. ©DermNet New Zealand. Source . Used with permission from **DermNet New Zealand.**

The differential diagnosis for NUD includes chronic spontaneous urticaria, urticarial vasculitis, neutrophilic urticaria, SS, and palisaded neutrophilic granulomatous dermatitis.[4] Where applicable, management of NUD should follow guidelines for the associated systemic disease. However, standard immunosuppressive therapies may be ineffective, and these patients may benefit from dapsone or colchicine, or IL-1 antagonists.[4]

DEEP NDS: DERMAL AND SUBCUTANEOUS

Severe forms of neutrophilic infiltration may extend into the deep dermis, subcutis, muscular fascia, or even into the muscle. It is very important to distinguish these mixed dermal and deep NDs from severe forms of bacterial cellulitis and necrotising fasciitis.[4]

Deep NDs include **pyoderma gangrenosum** (PG) and **hidradenitis suppurativa** (HS). PG may also occur in combination with HS or other inflammatory disorders; these rare syndromes include **PAPA** (PG, acne, and pyogenic arthritis), **PASH** (PG, acne, and hidradenitis suppurativa) and **PAPASH** (PG, acne, pyogenic arthritis, and HS).[22] Neutrophilic panniculitis and aseptic skin abscesses are other examples of deep NDs.[3]

PYODERMA GANGRENOSUM

The age-standardised prevalence of PG was 5.8 cases per 100,000 adults in the US, based on a large population-based sample.[23] Nearly 70% of cases occurred in people aged ≥50 years and the female-to-male ratio was >1.8 across all age groups.[23]

PG presents with painful ulcers that are debilitating and potentially life threatening.[1,21] The classical presentation is ulcers with violaceous, undermined borders and an overhanging epidermal edge, typically on the lower legs.[1,24] Over half of cases have associated medical conditions, especially IBD, arthritis and haematological malignancies.[21,24] The ulcerative presentation is one of five recognised clinical subtypes.[24]

Genital PG and postoperative PG are uncommon variants. Postoperative PG most commonly occurs within 2 weeks after breast or abdominal surgery;[24] early recognition is important to reduce morbidity and unnecessary debridement.[25]

HOW DEEP IS "DEEP"?

The primary classification of NDs is **epidermal** or **dermal**, whereas the distinction between **dermal versus deep NDs** is not clear-cut. For example, **Sweet syndrome** can be deep (subcutaneous) and **pyoderma gangrenosum** can be superficial.

Subtypes of PG and their associated medical conditions[24]

Clinical subtype	Associated medical conditions
Ulcerative	Inflammatory bowel diseases Rheumatoid arthritis Monoclonal gammopathies
Bullous	Haematological malignancies
Vegetative	–
Pustular	Inflammatory bowel diseases
Peristomal	Occurs near surgical stoma

Diagnosis of PG can be challenging. Until recently viewed as a diagnosis of exclusion,[1] Weiss et al. have usefully compared three existing diagnostic frameworks, including the Su criteria (2004), Delphi consensus criteria for ulcerative PG (2018) and the PARACELSUS scoring system (2019).[21]

Differential diagnoses of PG include vasculitides, thrombophilic conditions, infections (including bacterial cellulitis, herpes simplex virus and varicella zoster virus), malignancies, other inflammatory conditions (including SS, Behçet disease and cutaneous Crohn's disease), arthropod bite, factitious ulcer, and drug reactions.[24] Colonoscopy should be strongly considered and age-appropriate cancer screening is recommended for all patients. For patients aged ≥65 years, low threshold for referral to haematology and oncology for consideration of a bone marrow biopsy is recommended..[24]

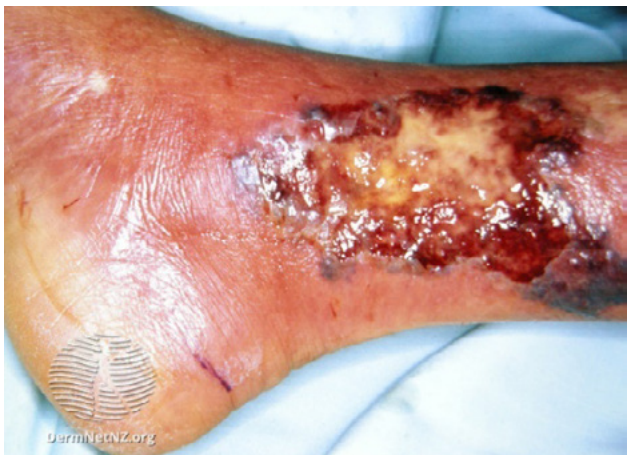
PG can be difficult to treat.[1] Treatment aims to halt the neutrophilic inflammation and heal the ulcer, which requires an individualised, multimodal approach involving wound care, local therapy, and systemic treatment.[24] Systemic treatment may include high-dose corticosteroids, mycophenolate mofetil, ciclosporin, TNF-α inhibitors, and IL-1β inhibition.[1]

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa (HS, also known as acne inversa) is a chronic, inflammatory disease of the hair follicles that presents with recurrent inflamed nodules that may progress to painful abscesses, sinus tract formation, and scarring.[26,27] The reported prevalence of HS varies widely but in the European–US population it ranges between 0.7 and 1.2%,[28] typically diagnosed in young adults and more commonly in women. The reverse is true in Asian populations (gender differences in smoking prevalence may be a confounding factor).[29] Approximately 70–75% of patients with HS are smokers.[26]

The pathogenesis of HS is complex and remains partly understood. Previously considered a disorder of primary follicular occlusion, HS is increasingly viewed as a multifactorial, polygenic, autoinflammatory disease.[29,] Neutrophil infiltration is characteristic and contributes to inflammation and immune dysregulation. Alterations in the skin microbiome are also involved.[29]

Delayed diagnosis is common in HS, with a mean reported delay of 7.2 years. This is a particular problem given the highly detrimental effects of HS on QOL, including suicide risk.[28] Diagnosis is based on clinical findings, including typical HS lesions, predilection for intertriginous sites, and recurrence.[26]



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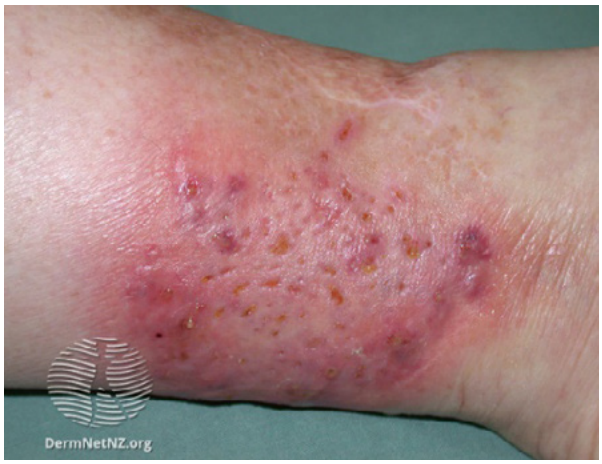

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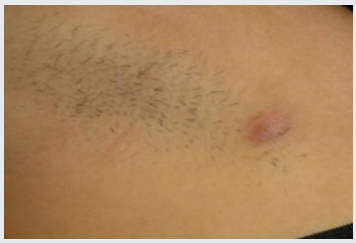
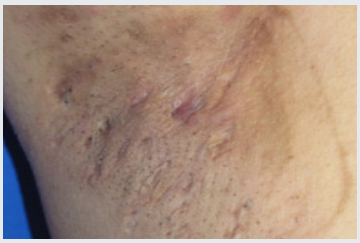
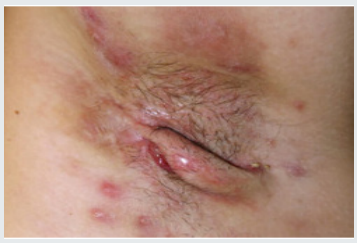
Pyoderma gangrenosum. ©*DermNet New Zealand. A. Source. B. Source. Used with permission from* **DermNet New Zealand.**



Hurley Stage I



Hurley Stage II



Hurley Stage III

Hidradenitis suppurativa of the axilla. ©DermNet New Zealand. Source 🗎. Used with permission from **DermNet New Zealand.**

US guidelines recommend routine screening for HS comorbidities, including smoking, diabetes, metabolic syndrome, depression/anxiety, follicular occlusion tetrad (HS, acne conglobata, dissecting cellulitis of the scalp and pilonidal sinus), and squamous cell carcinoma of HS-affected skin.[26]

The Hurley clinical staging system is used to classify the disease severity:[33]

- Stage I: single or multiple abscess formation, with no sinus tracts or scarring
- Stage II: recurrent abscesses with sinus tracts and scarring, single or multiple lesions
- Stage III: diffuse involvement or multiple interconnected sinus tracts and abscesses across the entire area

Management is often complex and may involve medical, surgical or laser treatment, with a need to address pain, medical and psychological comorbidities.[26,33] The Australasian consensus statement on the management of HS can be accessed here: **https://dermnetnz.org/topics/hidradenitis-suppurativa-guidelines.**

SUMMARY

NDs are a heterogenous group of rare, chronic or relapsing, non-infectious, autoinflammatory disorders characterised by sterile neutrophilic infiltration of the epidermis, dermis and/or subcutaneous tissues. Diagnosis and clinical management can be challenging due to the presence of overlapping conditions and transitional forms, a lack of reliable epidemiological data, and the absence of standard treatment guidelines. Nevertheless, accurate and timely diagnosis is needed to ensure the best outcomes for individuals living with conditions that are commonly painful and debilitating, associated with severely detrimental effects on QOL, and are potentially life-threatening, as in cases of severe GPP and PG. Some forms of SS and PG closely resemble severe infections, so it is especially important to recognise these variants to prevent patient harm from ineffective treatment and unnecessary surgery. Furthermore, NDs are frequently associated with benign or malignant systemic conditions that require treatment, notably IBD, rheumatologic disorders, and haematological malignancies. Advances in understanding the complex pathophysiology of NDs, including identification of gene mutations and the role of an autoinflammatory immune cascade, have highlighted the potential for targeted biological therapies in this challenging spectrum of disorders.

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ACKNOWLEDGEMENT We acknowledge Dr Jane Li (Melbourne Skin & Dermatology) for reviewing and for her input on this resource material. This resource was supported by an independent educational grant from the Boehringer Ingelheim. Boehringer Ingelheim had no influence or involvement in the development of the content or the selection of expert reviewer. Produced by In Vivo Academy Limited, PO Box 187, Strawberry Hills, NSW 2012, Australia. info@invivoacademy.org