Psoriasis

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Psoriasis is an immune-mediated, genetic disease manifesting in the skin or joints or both. A diverse team of clinicians with a range of expertise is often needed to treat the disease. Psoriasis provides many challenges including high prevalence, chronicity, disfiguration, disability, and associated comorbidity. Understanding the role of immune function in psoriasis and the interplay between the innate and adaptive immune system has helped to manage this complex disease, which affects patients far beyond the skin. In this Seminar, we highlight the clinical diversity of psoriasis and associated comorbid diseases. We describe recent developments in psoriasis epidemiology, pathogenesis, and genetics to better understand present trends in psoriasis management. Our key objective is to raise awareness of the complexity of this multifaceted disease, the potential of state-of-the-art therapeutic approaches, and the need for early diagnosis and comprehensive management of patients with psoriasis.

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Disease burden and epidemiology

Psoriasis is a common skin disorder that is associated with both a physical and psychological burden. As with other dermatoses, visible disfiguration can trigger a negative reaction in others, which can cause much of the readily measurable psychological burden of the disease. In a comparison with a selection of other chronic disorders including cancer, myocardial infarction, and congestive heart failure, only depression and chronic lung disease impaired psychological quality of life more than psoriasis.[1] The high physical burden of disease is not so well understood by scientists, but might be related to symptoms such as itching or burning sensations.[1] Symptoms regularly reported by patients include pain, itch, and bleeding.[2] Disease burden is further increased by several comorbid diseases, which include metabolic syndrome and cardiovascular diseases that result from the syndrome. In 2013, after consideration of a psoriasis burden of disease report, the Executive Board of WHO recommended to the 67th World Health Assembly a resolution that requests the Director-General to raise awareness of psoriasis as a major global health problem.[3]

Psoriasis prevalence is also an important consideration for WHO. In Europe and North America, psoriasis prevalence is about 2%.[4] Prevalence increases are roughly linear over the lifecourse, from 0·12% at age 1 year to 1·2% at age 18 years.[5] About 70–80% of patients have mild psoriasis that can be controlled using topical therapies alone.[6] Climate, sun exposure, and ethnicity are thought to affect psoriasis prevalence; however, results from a recent study showed weak correlation between latitude and psoriasis prevalence, which suggests that other factors, or combinations of factors, might be involved.[7] The ultraviolet (UV) index is a useful variable in psoriasis diagnosis and treatment, since cutaneous psoriasis and psoriatic arthritis worsen in winter and improve in summer.[8]

Individuals with psoriasis are at an increased risk of developing other chronic and serious health diseases. These comorbid diseases include psoriatic arthritis, metabolic syndrome or components of the syndrome, cardiovascular disorders, and several other diseases such as anxiety and depression, non-alcoholic fatty liver disease, Crohn's disease, and lymphoma.[9,10]

Clinical manifestations of psoriasis

Psoriasis is a multifarious disease that is equally prevalent in both sexes, although results from a recent study have shown that on average men have more severe forms of the disease than do women.[11] Five types of psoriasis have been reported: plaque psoriasis (also known as psoriasis vulgaris); guttate (droplet) or eruptive psoriasis, which is characterised by scaly teardrop-shaped spots; inverse psoriasis, also called intertriginous or flexural psoriasis that is usually found in folds of skin; pustular psoriasis, which can either take the form of palmoplantar pustulosis (pustular psoriasis of the palms and soles), or generalised pustular psoriasis (a rare and serious form of psoriasis); and erythrodermic psoriasis, which is a rare but very serious complication of psoriasis.

Plaque-type psoriasis

Chronic plaque psoriasis (psoriasis vulgaris) is the most common form of the disease, and accounts for about 90% of cases. Typical lesions are monomorphic, sharply demarcated erythematous plaques covered by silvery lamellar scales (figure 1A). Plaques can be few (figure 1B), they can extend over larger areas (figure 1C), and they can also present as erythroderma affecting the entire body surface (figure 1D). Erythroderma is a potentially life-threatening disease, and any form of psoriasis can become erythrodermic.

Search strategy and selection criteria

We searched PubMed using the terms "psoriasis", "epidemiology", "pathogenesis", "genetics", "psoriasis susceptibility loci", "therapy", "guidelines", and "comorbidity". Our search covered articles published in English, German, and French published between 1974 and May 13, 2015. We identified additional reports from the reference list of seminal reviews.

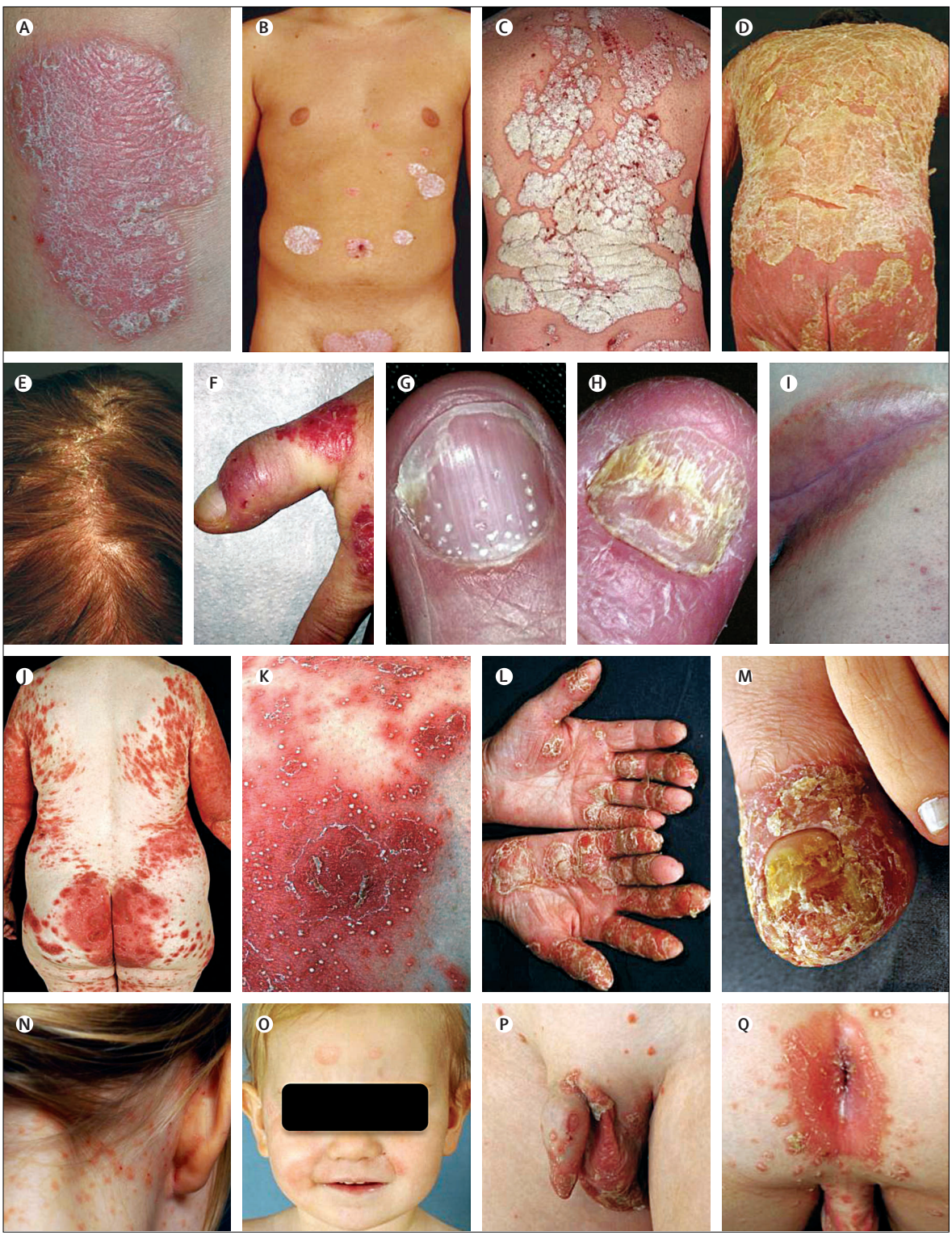

Figure 1: **Clinical manifestations of psoriasis**
Typical erythematous plaques with silvery scales (A) can be scattered (B, psoriasis nummularis), cover larger areas of the skin (C, psoriasis geographica) or affect the entire body surface (D, erythrodermic psoriasis). Scalp involvement might be accompanied by non-scarring alopecia (E). Psoriatic arthritis affects up to 30% of all patients (F, thumb interphalangeal joint). Nail changes are frequent and range from pitting and yellow or brown discolouration (G) to complete dystrophy (H). Psoriasis inversa occurs in intertriginous areas and is usually devoid of scales (I). Pustular psoriasis might occur in a generalised form (J, K) or localised (L, palmoplantar type and M, acrodermatitis continua suppurativa type). In children, the onset as guttate psoriasis might follow streptococcal infection of the upper respiratory tract (N) and affect any site of the body (O,P,Q).

Psoriasis can affect any skin site; however, typical locations (predilection sites) include the extensor surfaces of forearms and shins, peri-umbilical, peri-anal, and retro-auricular regions and scalp. Psoriasis of the scalp develops in 75–90% of patients with psoriasis,[12] and non-scarring alopecia is not uncommon (figure 1E).[13]

Nail psoriasis (psoriasis of the fingernail or toenail) occurs in about 50% of patients with psoriasis at diagnosis with a lifetime incidence of 80–90%.[14] Furthermore, up to 90% of patients with psoriatic arthritis (figure 1F) show nail involvement.[15,16] Mild psoriatic nail changes include pitting and discolouration in the form of yellow or brown patches underneath the nail plate (figure 1G). The nail plates thicken and crumble and end-stage nail psoriasis results in complete dystrophy of the nails (figure 1H), which can be debilitating.[14]

Inverse psoriasis is a site-specific variant of psoriasis that occurs in flexural (curved or bent) and intertriginous areas (figure 1I) and is usually devoid of scales because of the friction and moisture at these sites. Sebopsoriasis results when psoriasis and seborrhoeic dermatitis occur simultaneously and typically occurs on the face, scalp, and presternal skin.

Pustular psoriasis

Pustular psoriasis is characterised by white coalescing pustules (blisters of non-infectious pus). Variants of pustular psoriasis have been distinguished clinically. Generalised pustular psoriasis is often present in patients with existing or previous psoriasis vulgaris, but can also develop in people without a history of psoriasis.[17] Genetic analyses have identified interleukin-36RN mutations and a caspase recruitment domain family member (CARD14) gain-of-function mutation as important predisposing factors of psoriasis variants. Most cases of generalised pustular psoriasis alone are caused by recessive mutations of interleukin 36RN, but very few cases of generalised pustular psoriasis with psoriasis vulgaris have recessive interleukin-36RN mutations, which suggests that generalised pustular psoriasis alone is genetically different than when combined with psoriasis vulgaris. Identification of recessive interleukin-36RN mutations leads to early diagnosis of generalised pustular psoriasis, and a CARD14 gain-of-function mutation is a predisposing factor for generalised pustular psoriasis with psoriasis vulgaris.[17,18] Generalised pustular psoriasis is characterised by disseminated dark erythematous patches with conspicuous sterile pustules, which coalesce to form large lakes of pus (figure 1J, K). Skin lesions can progress rapidly and the disease is potentially life-threatening. Localised forms of pustular psoriasis include psoriasis pustulosa palmoplantaris (figure 1L) and acrodermatitis continua suppurativa (figure 1M), the former affects the palms of the hand and soles of the feet, the latter typically affects the tips of fingers or toes or both with nail involvement. Paradoxically, tumour necrosis factor (TNF) inhibitor agents that are effective therapies for treating psoriasis have also been associated with the onset of pustular psoriasiform eruptions, mostly located on palms and soles.[19,20]

Childhood psoriasis

The onset of psoriasis in children often occurs as guttate (droplet) psoriasis (figure 1N), a disease that is often preceded by a streptococcal infection of the upper respiratory tract. Antigenic similarities between streptococcal proteins and keratinocyte antigens might explain the trigger by streptococcal infections.[21] A third of children with guttate psoriasis go on to develop plaque psoriasis in later life.[22] Psoriasis is common in children and prevalence ranges between 0·5% and 2·0% in different studies.[23] A recent large psoriasis survey revealed a prevalence of 0·71% in German children and adolescents aged 0–18 years, with a roughly linear increase with age.[5] Psoriasis affects children at skin sites that are uncommon in adults such as the face (figure 1O), which needs particularly careful management.[24] Moreover, a full body examination including the genito-anal region is advisable (figure 1P, Q).

Trigger factors

Psoriasis can be provoked by non-specific triggers such as mild trauma (scratching, piercings, and tattoos), sunburn, or chemical irritants. Systemic drugs such as β blockers, lithium, antimalarials, and non-steroidal anti-inflammatory agents can exacerbate the disease.[25] Psoriasis can be triggered or substantially aggravated by occupational risk factors impairing the skin barrier function. In such cases, in particular with palmoplantar psoriasis, the patient's work environment should be assessed and adequate protective measures put in place.[26] HIV infection might also be a trigger of psoriasis, because the prevalence of psoriasis in HIV-infected patients is the same or slightly higher than in the general population, and HIV-infected patients with pre-existing psoriasis often have a flare of lesions that are difficult to treat.[27]

Diagnosis and differential diagnosis

Diagnosis is usually made on clinical findings; skin biopsy is rarely used to diagnose psoriasis. The Psoriasis Area and Severity Index (PASI) score has been used to quantify disease severity of erythema, infiltration or thickness, scaling and the extent of lesions in patients with widespread disease.[28] More recently, easier-to-use scores, such as the psoriasis global assessment (PGA) or lattice system-physician's global assessment (LS-PGA) have been developed for routine clinical practice.[29]

Clinical diagnosis of inverse psoriasis can be difficult, owing to secondary alterations such as friction. A full body examination, in particular the genito-anal, peri-umbilical, and retro-auricular areas, scalp, and nails, should be checked for psoriasis.

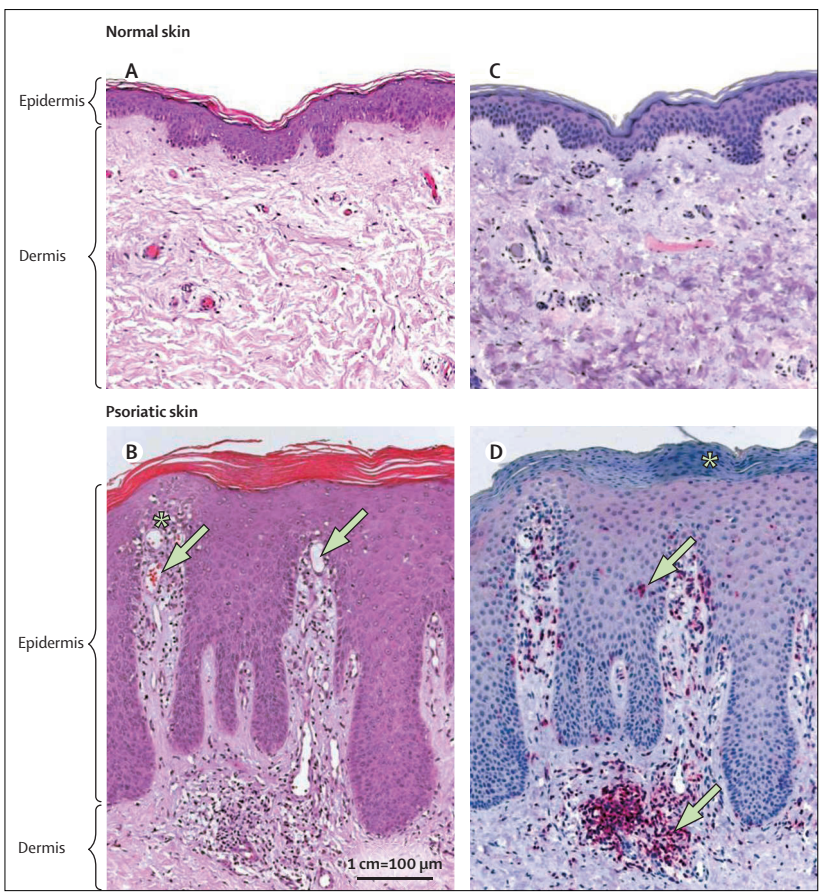

Figure 2: **Histopathological features of psoriasis**
Within the typical plaque, psoriatic epidermis shows marked epidermal acanthosis, hyperkeratosis, and elongation of rete ridges (A, normal skin and B, lesional psoriatic skin; stained with haematoxylin and eosin). Dilated and contorted dermal blood vessels reach into the tips of the dermal papillae (B, arrows). A mixed inflammatory infiltrate with neutrophils accumulating within the epidermis is noted (B, asterisk). By contrast with normal skin (C), immunohistochemical detection of CD3 reveals many T cells in the dermis and epidermis of lesional psoriatic skin (D, arrows). Cell nuclei present in the cornified layer of the epidermis are also characteristic for lesional psoriatic skin (D, asterisk).

The patient's history should include details of family members with the disease, and potential trigger factors such as present infections or new medications. The patient should be informed of the chronic nature of the disease, that psoriasis can be triggered by infections, and that the disease is not contagious. The physician should enquire about joint involvement because up to 30% of patients with psoriasis develop psoriatic arthritis.[30]

Psoriasis screening instruments such as the psoriatic arthritis screening and evaluation (PASE) questionnaire, Toronto psoriatic arthritis screening (ToPAS) questionnaire, and psoriasis epidemiology screening tool (PEST) can be used to aid diagnosis. The sensitivity of PASE, ToPAS, and PEST were reported to be similar (74·5%, 76·6%, and 76·6%, respectively) in a recent head-to-head comparison study in patients with psoriasis.[31] In cases of severe psoriasis, screening for metabolic, cardiovascular, and mental health disorders is mandatory.[32]

Psoriasis shows characteristic histopathological changes in almost every cutaneous cell type (figure 2A–D). By contrast with normal skin (figure 2A, B), psoriatic hallmark features include epidermal acanthosis (thickening of viable layers), hyperkeratosis (thickened cornified layer), and parakeratosis (cell nuclei present in the cornified layer; asterisk in figure 2D). Epidermal rete ridges (thickenings that extend down between dermal papillae) are markedly elongated. In the dermis, dilated and contorted blood vessels reach into the tips of the dermal papillae (arrows in figure 2C). An inflammatory infiltrate containing T-lymphocytes is notable within the dermis and epidermis (figure 2B, D), and an increased number of macrophages, mast cells, and neutrophilic granulocytes. These cells accumulate within the epidermis (asterisk in figure 2B) forming so-called pustules of Kogoj or subcorneal microabscesses, also referred to as Munro's microabscesses.

The most common differential diagnoses of psoriasis include tinea capitis and tinea corporis, seborrheic dermatitis (scalp, face, and chest involvement) and eczema of several causes (atopic dermatitis, allergic, or irritant contact dermatitis). Less common differential diagnoses include lichen planus (mucosal involvement, scarring alopecia, and severe itch), pityriasis rosea (usually self-limiting within a few weeks), pityriasis rubra pilaris, secondary syphilis (especially in cases of guttate psoriasis), and cutaneous lymphoma.

Pathogenesis

Involvement of the immune system in psoriasis is now widely accepted.[33,34] Genome-wide scans for psoriasis-associated genes have identified predominantly immune-related genes,[35,36] providing a mechanistic link between genetics and immunity. Psoriatic skin lesions originate as a result of dysregulated interactions of innate and adaptive components of the immune system with resident cutaneous cell types.

Research into the immunopathogenesis of psoriasis has resulted in several highly specific therapies that target components of the immune system. To understand how these therapies act against psoriasis, information is needed about the complex pathophysiology of the disease (figure 3). We focus here on the central mechanisms of the disease: cross-talk between innate and adaptive immunity and the central role of TNFα; the interleukin-23/T helper cell 17 (Th17) axis; and the effect of immune reactions on other cells in the skin.

Cross-talk between innate and adaptive immunity

Psoriasis is mainly a dendritic cell and T-cell-mediated disease with complex feedback loops from antigen-presenting cells, neutrophilic granulocytes, keratinocytes, vascular endothelial cells, and the cutaneous nervous system. Cross-talk between the innate and the adaptive immune system mediated by cytokines including TNFα, interferon γ, and interleukin 1 is a major research focus.[36]

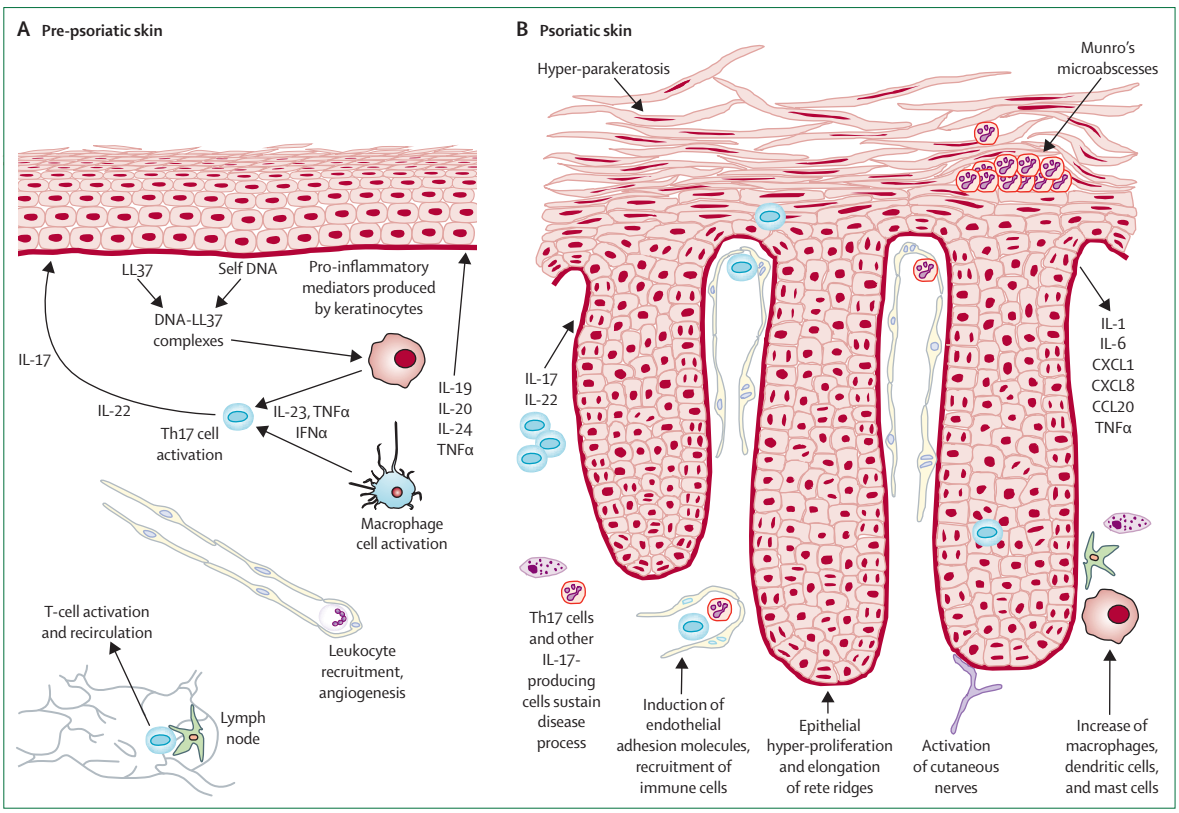

Figure 3: **Immune pathogenesis of psoriasis**
The complex interplay of cutaneous cell types, which is dependent on macrophages, dendritic cells, T cells, and other cells of the immune system, involves many cytokines and chemokines that orchestrate the pathological changes in pre-psoriatic skin. Differentiation of Th1 and Th17 cells is stimulated by dendritic cells through IL-23 (A). Pathogenic cells of the adaptive (T cells) and innate immune system (macrophages, mast cells, granulocytes) produce several mediators that induce and maintain psoriatic hallmark features in both dermis (eg, endothelial cells) and epidermis (keratinocytes). In turn, the latter cell types facilitate the inflammatory response through their mediators (B). IL=interleukin. TNF=tumour necrosis factor. IFN=interferon.

Complexes of host DNA and the epidermis-produced antimicrobial peptide LL-37 (cathelicidin) are thought to stimulate dermal plasmacytoid dendritic cells to produce interferon α.[37] On exacerbation or onset of psoriasis, activated dendritic cells produce, among other mediators, TNFα and interleukin 23. TNFα is a pro-inflammatory cytokine that amplifies inflammation through several distinct pathways. TNFα is produced by a broad range of cell types including macrophages, lymphocytes, keratinocytes, and endothelial cells, and exerts its activities on several different cell types.[38] TNFα induces secondary mediators and adhesion molecules, all of which have been implicated in psoriatic disease. The clinical success of TNF-blocking agents is therefore not surprising.

Interleukin-23/Th17 axis

Interest is rising in the interleukin-23/Th17 axis in psoriasis, which has resulted in several novel targeted therapies.[39] Th17 cells are a subset of T-lymphocytes expressing interleukin 17, distinct from the classical Th17 cells[40] that play a predominant part in the pathogenesis of psoriasis[41] and other inflammatory disorders.[42,43] Expansion and survival of these T cells depends on myeloid cell-produced interleukin 23, which drives the differentiation of Th17 cells.[44] Interleukin 23 acts mainly on memory T cells, because naive T cells do not express the interleukin-23 receptor.[45] Other cytokines, such as interleukin 9, might support Th17-related inflammation.[46] Once activated, Th17 cells produce several mediators such as interleukin 17A, 17F, and 22, which induce keratinocyte proliferation and other hallmark features of psoriasis. In psoriatic skin, interleukin 17 is produced by CD4+ T cells, epidermal CD8+ T cells, neutrophils, mast cells, and macrophages, which might explain the broad and rapid clinical efficacy of specifically targeting interleukin 17.[47–50]

Effect on resident T cells of the skin

Complex dysregulation of almost every cutaneous cell type, which includes proliferation and cytokine production by epidermal keratinocytes, is affected by the TNFα pathway and interleukin-23/Th17 axis pathway. Furthermore, antimicrobial peptides, cytokines and chemokines secreted by keratinocytes act as chemoattractants for infiltrating immune cells.[51] Thus, a

positive feedback loop exists between cells of the immune system and resident epithelial cells in psoriasis. Vascular endothelial cells are also closely linked to psoriatic disease because the inflammatory milieu leads to induction and activation of a range of pro-angiogenic factors.[52,53] Regulatory T cells affect the vascular endothelial growth factor (VEGF)-related angiogenic microenvironment[54] and contribute to hallmark features of psoriasis such as epidermal hyperplasia.[55] Severe and early-onset forms of psoriasis might be associated with a single nucleotide polymorphism in the gene that encodes VEGF.[56] Moreover, the TNFα-governed pro-inflammatory environment in psoriatic skin induces endothelial adhesion molecules, which facilitate the recruitment of circulating leucocytes in psoriatic skin.[57] Therapies targeting vascular functions or leukocyte recruitment are a promising strategy to treat psoriasis.[58,59]

Feedback loops with cells of the immune system and other cell types such as nerve fibres are also likely to contribute to psoriatic pathophysiological abnormalities.[60,61] Psoriasis is no longer thought of as a disorder that affects only the skin, but is instead seen as a systemic inflammatory disorder.[62]

Genetics and pharmacogenetics

Results from population studies suggest a higher incidence of psoriasis in first-degree and second-degree relatives of patients than in the general population.[63] Furthermore, concordance rates in monozygotic twins are up to three times higher than in dizygotic twins.[63] Genetic factors are also likely to have an effect on disease severity because, on average, patients with an early onset of the disease (type I psoriasis) have a more severe course and a positive family history, whereas patients with late onset (type II psoriasis) tend to have milder forms of the disease and often have a negative family history.[64]

Many putative susceptibility loci have been described for psoriasis. Genome-wide linkage analyses have shown reproducibly of the association of psoriasis with a locus on chromosome 6p, with HLA-Cw6 being the most likely susceptibility allele in psoriasis susceptibility locus 1 (PSORS1), accounting for up to 50% of disease heritability.[65,66] Furthermore, roughly 40 additional loci are thought to be associated with psoriasis. Corresponding genes to these loci are involved in the pathogenesis pathways that play a central part in the adaptive and the innate immune system.[36,67,68] Variations in the genes that encode the interleukin-23 receptor and in the untranslated region of interleukin 12B suggest there is a general role of T cells and a specific role of Th17 lymphocytes in psoriasis pathogenesis and as indicators of psoriasis risk.[69,70] Analyses of transcribed genes in lesional psoriatic skin[71] show that T cells and dendritic cells are also key players in psoriatic inflammation.

Studies of the genetics of the disease have helped to better understand and re-classify clinical manifestations of psoriasis and the association of psoriasis with other important diseases. PSORS1 is strongly associated with guttate psoriasis but not with palmoplantar pustulosis.[72] Moreover, generalised pustular psoriasis has been linked to interleukin-36 receptor antagonist deficiency[18] and mutations or variants of CARD14.[17] Many genes, including interleukin 23R, are associated with psoriasis and psoriatic arthritis.[73,74] The gene *CDKAL1* is associated with psoriasis and comorbid diseases such as type II diabetes mellitus and Crohn's disease.[75]

Pharmacogenetic research is rapidly progressing in the specialty of psoriasis. Pharmacogenetic studies identify variations in the genome that can be associated with a clinical response, or with adverse effects of a given drug. Pharmacogenetics and conventional anti-psoriatic therapies have been reviewed recently.[76] An association between clinical outcome and two single nucleotide polymorphisms in the gene that encodes TNFAIP3, a protein belonging to the TNFα signalling pathway, has been described.[77] Furthermore, the HLA-Cw6 allele is associated with a faster and higher clinical response to ustekinumab, a biologic that blocks the interleukin-12/interleukin-23 pathway.[78]

Comorbid disease

Several important diseases occur more often in patients with psoriasis than expected based on their respective prevalence in the general population. Comorbid diseases of psoriasis include psoriatic arthritis, Crohn's disease, cancer, depression, non-alcoholic fatty liver disease, metabolic syndrome (or components of it), and cardiovascular disorders,[9,79] all of which contribute substantially to morbidity and mortality in patients with psoriasis. Comorbid disease needs to be treated, therefore the number of drugs taken by patients with psoriasis is substantially higher than in the general population.[80] Moreover, and similar to other chronic inflammatory diseases, life expectancy of patients with psoriasis is substantially reduced, with cardiovascular diseases contributing most.[81]

Association of comorbid disease with psoriasis might be due to similarities in the genetic basis of these diseases, although this association is still under debate.[82] For example, whether lymphoma and skin cancer are related to mechanisms involved in psoriasis itself, or to the treatment of psoriasis, is not yet known.[83] Furthermore, increased cardiovascular mortality has long been attributed to cumulating cardiovascular risk factors in patients with psoriasis.[84] However, only patients with severe psoriasis exhibit an increased cardiovascular risk and the reason for this is also not clear.[85–87] Three recent epidemiological meta-analyses identified an increased risk for cardiovascular mortality (relative risk: 1·39,[88] 1·37,[89] and 1·2[90]) and stroke (relative risk: 1·56,[88] 1·59,[89] and 1·21,[90]) in patients with psoriasis.

Although an association between severe psoriasis and increased cardiovascular mortality has been shown, this association does not provide evidence for causality.

The so-called psoriatic march has been proposed to explain the increase in cardiovascular mortality of patients with severe psoriasis.[9,32] According to this concept, psoriasis is a state of systemic inflammation, because many inflammation biomarkers are detected in the blood of patients with psoriasis and are associated with disease activity.[91] Systemic inflammation induces insulin resistance—ie, a reduction in the signalling of the insulin receptor on binding of its ligand. Insulin resistance in endothelial cells results in a reduction in the release of vasodilating factors such as nitric oxide. The resulting vascular stiffness is known as endothelial dysfunction, which is associated with the expression of adhesion molecules and provides the basis for the formation of atherosclerotic plaques. Depending on their localisation, diseases that result from atherosclerotic plaques comprise myocardial infarction or stroke, both of which are known to be associated with psoriasis. Several groups have independently published evidence in favour of this hypothesis.[92–94] Clinical signs and symptoms of psoriasis can be effectively treated using the insulin-sensitising drug glucagon-like peptide-1, which suggests insulin resistance is a central phenomenon in inflammation.[95]

Although the pathophysiological evidence is compelling, an increased cardiovascular mortality risk in association with psoriasis could not be verified in a recent review of published work[96] and in a Dutch cohort study.[97] Potential pitfalls in the interpretation of observational studies to establish the association between psoriasis and comorbidity have been published.[98]

Management and prevention

In recent years, several high-quality evidence-based guidelines have been developed for the treatment of psoriasis such as the German S3 guidelines,[99] North American guidelines,[100] and International European guidelines.[101] The German S3 guidelines were the first to include topical therapies, phototherapy, and conventional and biological systemic therapies.

Conventional therapies

Topical therapies such as glucocorticosteroids, vitamin D derivatives, or combinations of both are usually sufficient to manage mild disease (table 1). Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are used for difficult-to-treat sites, such as the intertriginous areas or the face. Potent or very potent corticosteroids are superior to vitamin D3 analogues for scalp treatment, which is also difficult to treat. Results from a recent meta-analysis[104] showed that a combination of corticosteroids and vitamin D3 was the most effective treatment for the scalp.

Practicability (time needed to apply treatment), convenience, and adverse effects such as skin irritation limit the use of topical drugs. A combination of phototherapy and systemic therapy is needed for patients with moderate-to-severe disease (table 1). Established phototherapies include the widely used narrow-band UVB and—to a lesser extent—photochemotherapy such as PUVA (psoralen plus UVA). Phototherapy and photochemotherapy are very effective treatments, but time consuming, and usually only used for short-term control of the disease. The carcinogenic potential of PUVA further limits its long-term use.

	Efficacy*	Level of evidence	Comment
Glucocorticosteroids[99]†	60%	1	Skin atrophy if used long-term
Vitamin D derivatives[99]†	45%	1	Safest long-term topical treatment
Calcineurin inhibitors[99]†	30%	2/3	Reserved for localised sites such as face and intertriginous areas
Ultraviolet B exposure[99]	70%	2	Time consuming; cumulative dose might cause adverse effects
Psoralen plus ultraviolet A exposure[99]	90%	2	Time consuming; cumulative dose might cause adverse effects (including malignancies)
Acitretin[99]	15%	2	Avoid in young women; not recommended as low-dose monotherapy
Ciclosporin[99]	45%	1	Often used for a few months only (nephrotoxicity)
Methotrexate[99]	50%	2	Effective also in psoriatic arthritis
Fumaric acid esters[99]	50%	2	Oral drug, available only in Germany
Apremilast[102]	30%	1	Innovative oral drug, effective also in psoriatic arthritis
Adalimumab[99]	70%	1	Most widely used biological for this indication
Etanercept[99]	50%	1	Regarded as suitable also for intermittent use
Infliximab[99]	80%	1	Very fast onset of action; recommended for generalised pustular psoriasis (off-label)
Ustekinumab[99]	70%	1	Only four injections per year during long-term treatment
Secukinumab[103]	80%	1	Patients often achieve complete clearance of skin symptoms

*Estimated proportion of patients who achieved at least a 75% reduction in their Psoriasis Area and Severity Index score from baseline to end of short-term therapy. †Topical therapeutic, which as monotherapy is shown to treat mild psoriasis only.

Table 1: **Anti-psoriatic therapies**

Established systemic drugs for the treatment of psoriasis include methotrexate, ciclosporin, acitretin, and in some countries fumaric acid esters. Perhaps with the exception of fumaric acid esters, these conventional systemic drugs exhibit drug–drug interactions and cumulative organ toxicities. However, with appropriate monitoring, all except cyclosporin A, which is usually applied in the short term, can be used for the maintenance therapy of psoriasis. Additionally, the oral phosphodiesterase 4 inhibitor apremilast has been approved in USA and Europe.

Biologics

In the past decade, several biologics have been developed and approved for the treatment of psoriasis (table 1). With the exception of etanercept, which is a fusion protein, the approved biologics are monoclonal antibodies. TNFα inhibitors etanercept, adalimumab, and infliximab are approved for the treatment of psoriasis and psoriatic arthritis, and golimumab has been approved for psoriatic arthritis. Ustekinumab, a drug that blocks interleukin 12 and 23, is also approved for both indications. Ustekinumab interferes with the development of Th17 lymphocytes, which are important effector cells in psoriatic inflammation. Secukinumab was approved as the first biological blocking IL-17A, a key effector cytokine produced by TH17 and other cells. Biological efficacy for short-term therapy seems to be better than that for conventional systemic drugs, although this has so far been proven in only a few head-to-head clinical studies.[105] Biologics are used for long-term treatment because there is no evidence of cumulative toxicity or drug–drug interactions. Furthermore, biologics have a good safety profile with only a small increase in opportunistic infections. TNFα inhibitors are generally used after phototherapy and when conventional systemic therapies have either have failed, were not tolerated, or were contraindicated. This second-line use is in part because of the high direct costs for drugs, which are in the order of ten-times higher than for conventional systemic drugs.

Changing treatment frameworks

Four recent developments have begun to change the way psoriasis is treated: redefinition of disease severity, definition of treatment goals, integration of comorbid diseases into psoriasis management, and the quest to reduce medical risks of patients with psoriasis.

Clinical manifestation patterns could substantially affect the subjective classification of disease severity, which is not adequately reflected by the PASI score—eg, in cases of predominant nail or scalp psoriasis. Experts have suggested that the definition of moderate-to-severe psoriasis should be broadened to facilitate access to systemic treatments for a larger group of patients.[106] A change to the definition of moderate-to-severe psoriasis is important because manifestations of moderate-to-severe psoriasis such as nail psoriasis are particularly bothersome, topical therapies are often ineffective, and the evidence for biological and conventional systemic drug efficacy is improving.[107]

The present goal in psoriasis treatment, according to a European consensus statement, is to reduce cutaneous signs and symptoms by at least 75% as measured by the PASI score, and to guarantee a good quality of life, as measured by a dermatology life quality index score of 5 or less.[106] Critics have identified weaknesses in this concept. For example, patient groups that have reached the treatment goal of a 75% reduction could still have a high PASI score. The need to assess the status of the patient and to evaluate treatment responses in an objective and standardised way is now widely accepted and forms part of a larger trend in dermatology towards comprehensive assessment.[108]

As mentioned, comorbidity is common in patients with psoriasis, which necessitates a comprehensive management approach (table 2). The management approach should include screening for the most important comorbid diseases and involve structured cooperation with staff from other relevant disciplines if comorbid disease is identified.[115,116] Early detection of psoriatic arthritis is of particular practical relevance. Dermatologists could diagnose psoriatic arthritis early using validated questionnaires, because most patients develop psoriasis (of the skin) many years before their first joint symptoms.[117,118]

Increased mortality as a result of comorbid cardiovascular disease has been documented in patients with severe psoriasis.[15] Therefore, whether systemic treatments for psoriasis or psoriatic arthritis also reduce cardiovascular comorbidity is of much interest. For example, long-term systemic anti-inflammatory treatment could be used to treat psoriasis and decrease the risks of atherosclerosis, which is fuelled by systemic inflammation.[32,119,120] Data from retrospective analyses and small prospective studies [92,93,121,122] suggest that this might indeed be the case. However, conclusive data from registries and clinical trials is not yet available.

Unresolved questions, new developments, and unmet medical needs

Substantial progress has been made to understand the complex pathogenesis of psoriasis and to facilitate the development of more effective, targeted therapies. However, despite these advances more research is needed in several areas.[123]

Psoriasis has no known cure but many therapies can reduce or nearly stop symptoms. A treatment to which all patients respond adequately, and a reliable test that predicts individual responses before starting treatments, is not yet available.[124] The identification of biomarkers would help to tailor individualised treatment algorithms,[125] but retrospective pharmacogenetic studies using single nucleotide polymorphisms to predict

	Odds ratio* (95% CI)	Suggested screening†[115,116]
Diabetes mellitus‡	1·76 (1·59–1·96)[109]	Fasting blood glucose
Arterial hypertension‡	1·58 (1·42–1·76)[110]	Two consecutive blood pressure measurements
Obesity‡	1·66 (1·46–1·89)[111]	Body-mass index; waist circumference
Dyslipidaemia‡	1·5 (1·4–1·7)[112]	Fasting blood lipids
Cardiovascular disease	Myocardial infarction: 1·32 (1·13–1·55) Stroke: 1·26 (1·12–1·41)[113]	Screening for components of the metabolic syndrome
Non-alcoholic fatty liver disease	1·7 (1·1–2·6)[114]	Transaminases‡
Psoriatic arthritis	About 25% of psoriasis patients[115]	Screening questionnaire (eg, ToPAS, PASE, PEST); ask about, or look for, tender or swollen joints; ask about inflammatory back pain¶

*The odds of having that comorbid disease in patients with psoriasis as compared with the general population. †Recommendations for dermatologists (recommendations in the respective guidelines might vary). ‡Components of the metabolic syndrome. §Non-alcoholic fatty liver disease cannot be ruled out on the basis of laboratory tests alone. ¶Typically at night, eases with physical activity.

Table 2: **Comorbid disease and screening recommendations**

treatment responses have not yet been translated into clinical use. Furthermore, loss of biological efficacy might be caused by anti-drug antibodies, but research into the generation and effect of anti-drug antibodies on the treatment course remains a challenge.[126] There is a substantial unmet need in the treatment of patients with mild-to-moderate disease, particularly those with psoriasis in difficult-to-treat locations. Treatment options available today are either time consuming, inconvenient to apply, or do not lead to complete lesion resolution.[127,128] In view of the paucity of approved therapies and absence of clinical trials, the treatment of children with psoriasis is also an area of unmet medical need.[23,129]

Many genetic loci associated with psoriasis have been identified, but little is known about functions of the actual disease-related variants of these genes and how they are involved in the complex pathophysiological abnormalities that occur in psoriasis.[35] Also unclear is how pathogenic signalling pathways interact with one another and how newly identified microRNAs affect the disease process.[130] Besides the interleukin-23/Th17 axis, other inflammatory cell types and resident T cells of the skin are likely to have a pivotal role in the psoriatic disease process. For example, keratinocytes amplify the activity of Th17 cells.[131]

Research into the pathogenesis of psoriasis has been hampered by the absence of appropriate animal models. However, genetic modifications and immunological manipulations in rodents have resulted in hyperproliferative inflammatory skin disorders to study pathophysiological aspects that are relevant to psoriasis.[132] Animal models might also provide insight into the contribution of intrinsic pathways of resident cutaneous cells, such as was recently shown for TNF-dependent keratinocyte functions in hyperplastic epidermis.[133]

Associations of other systemic disorders with psoriasis have been known for almost two decades,[79] but the comorbidity of patients with psoriasis, such as cardiovascular disease, metabolic syndrome, and psychological or psychiatric diseases in particular, has only recently become a focus in psoriasis research.[32] Furthermore, the pathogenic relation of psoriasis with other auto-inflammatory and auto-immune diseases still remains to be elucidated.

More research is needed into environmental triggers, disease burden, and the effect of psoriasis on health-care resources.[134] The immense socioeconomic effect of psoriasis is now a focus[134] and substantial improvements are needed in patient-centred care. Patient registries and large population studies will hopefully provide insight into these areas.[135]

Evidence is accumulating that insulin resistance is a key mechanism that links inflammation with atherosclerosis.[32,119,136] Similarly, insulin resistance helps to understand the epidermal changes in psoriasis.[137] To establish whether targeting insulin resistance is an effective approach to treat cutaneous signs and symptoms of psoriasis,[95] and reduce the cardiovascular risk of the patient, will be an important area of study.

Conclusion

Psoriasis is a systemic inflammatory disorder that involves complex pathogenic interactions between the innate and adaptive immune system that can be targeted by innovative biological therapies. The treatment framework is changing from short-term intervention of acute rashes toward long-term management, taking into consideration both the skin symptoms and comorbid diseases. The quest to reduce medical risks of patients with psoriasis through comprehensive treatment and early identification of psoriatic arthritis are areas that practising physicians can make a difference for the better of their patients. Other challenges include the identification of mechanistic links between psoriasis and comorbid diseases, personalised treatment approaches, unmet needs of available treatments, and the prevention of psoriatic arthritis or even psoriasis.

Contributors

Both authors jointly reviewed the published work, interpreted the data, wrote the report, and prepared the figures.

Declaration of interests
W-HB has received honoraria as a speaker or adviser for Abbvie, Biogen Idec, Covagen, Galderma, Janssen, Leo, Lilly, MSD, Novartis, Pantec Biosolutions, Pfizer, Celgene and UCB. MPS has received honoraria as a speaker or adviser for Abbvie, Biogen Idec, Janssen, Leo, Lilly, MSD, Novartis, Pfizer, and Celgene. MPS has received research funding from AbbVie and Biogen Idec and serves as an adviser of the Deutsche Psoriasis Bund, a patient self-help organisation. Neither author has had, within the past 3 years, stocks, shares, or equity in a relevant company, nor a contract of employment or named position on a company board.

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