The 10 warning signs: a time for a change?

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Purpose of review
It is 20 years since the 10 Warning Signs of primary immunodeficiency (PID) were first published and with over 180 PIDs now identified it is timely to evaluate their effectiveness, given the broadening clinical spectrum of PID.

Recent findings
Two recent studies have sought to define the features that best identify patients with PID and compare these with the 10 Warning Signs. They suggest the 10 Warning Signs discriminate poorly between those with and without PID, and that other features identify about one-third of patients with PID in whom none of the 10 Warning Signs was present. Recent literature describes the diverse presenting features that may assist in more accurately identifying those with PID.

Summary
Further development and refinement of early warning signs in light of the growing knowledge of how PIDs manifest clinically may allow relatively simple yet effective guidelines targeted at different groups to better detect PID.

Keywords
autoimmunity, diagnosis, guidelines, infection, primary immunodeficiency

INTRODUCTION

The 10 Warning Signs of primary immunodeficiency [1,2] (PID) were first published by the Jeffrey Modell Foundation (JMF) in 1993 [3], based on an expert consensus meeting. Internationally recognized, they have contributed greatly to increased diagnosis [3] and awareness of PID including leveraging government funding to obtain a 40-fold return in donated media and advertising [4] and are promoted directly to physicians [5]. Despite their widespread promotion, until recently, there were few published data evaluating their effectiveness. Two recent studies [6,7▪▪] suggested limitations in their ability to identify children with PID, informing a review [8] suggesting refinements and development if we are to better detect PID in the future.

With over 180 identified PIDs, the spectrum of clinical manifestations has broadened; PIDs may present with cutaneous [9,10,11▪▪], gastrointestinal [12] or autoimmune [13–15] manifestations, or a single episode of invasive infection may herald a potentially life-threatening PID [16]. The existing Warning Signs may not cover these clinical presentations, yet early diagnosis and treatment of PID remain critically important.

This review will evaluate the findings of recent studies of the 10 Warning Signs and explore possible signs for the various clinicians who may encounter patients with undiagnosed PID.

THE 10 WARNING SIGNS

Separate 10 Warning Signs exist for children [2] and adults [1] (Table 1) [1,2]. The presence of two or more of the warning signs should trigger investigation for PID. Early warning signs have to strike a difficult balance between being too sensitive, resulting in unnecessary investigations and patient anxiety, or too specific, leading to missed or delayed diagnoses. Any tool designed to identify potential PID patients is likely to overidentify, but until recently, there have been few published data evaluating this.

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KEY POINTS

- PID can present with diverse clinical features, including cutaneous, gastrointestinal and autoimmune manifestations.
- Early identification and management of PID are vital to minimize complications and improve outcomes.
- The existing 10 Warning Signs of PID do not identify some patients with PID.
- Targeted warning signs for different groups may improve the early diagnosis of PID by focusing on those clinical manifestations most relevant to a clinician's specialty.
- Diagnosis and management of PID require early consultation with and/or referral to PID experts.

CLINICAL FEATURES OF PRIMARY IMMUNODEFICIENCY AND EVALUATION OF THE 10 WARNING SIGNS

Two recent studies have sought to find which clinical features best define paediatric patients with PID. MacGinnitie *et al.* [7▪▪] reviewed the charts of patients evaluated for PID at a paediatric hospital allergy and immunology clinic, the decision to assess for PID being made by the treating physician. Importantly, this study focused on the signs present at initial evaluation excluding patients with known PID. Of 141 children initially evaluated, 32 (23%) were ultimately diagnosed with PID, and half of those required some form of treatment. The vast majority had antibody deficiencies (30 of 32), with one case each of congenital neutropaenia and 22q11.2 deletion syndrome.

One hundred and five children met at least one of the 10 Warning Signs; however, the rate of PID diagnosis did not differ between the Warning Sign-positive and negative groups (19 and 32%, respectively). The specificity of the presence of at least one Warning Sign for the diagnosis of PID was unsurprisingly low at 23%, with a sensitivity of 63%; over one-third of patients diagnosed with PID did not meet any of the Warning Signs.

The study by Subbarayan *et al.* [6] included a very different cohort of paediatric patients; their patients were 430 children with known PID and a comparator group of 133 children with severe, unusual or recurrent infections in whom an underlying PID was not identified. The clinical services seeing these children included a quaternary PID service for paediatric bone marrow transplantation in the United Kingdom, explaining why more severe PIDs were seen: T-cell defects (56%), antibody deficiencies (21%), phagocyte defects (17%) and complement deficiencies (5%). The strongest predictor of PID was a history of physician-diagnosed PID in a family member, which was 18 times more common in those with PID than those without. Other discriminatory signs were the use of IV antibiotics in identifying children with neutrophil PID, and failure to thrive in children with T-cell PID. In combination, those three warning signs identified 96% of children with neutrophil and complement PID, 86% of T-cell PID but less than 60% of antibody PID. Ninety-five percent of children in this cohort were initially referred from hospital paediatricians, with only 5% referred from primary care. This led to the reasonable conclusion that additional efforts should be made to educate hospital-based paediatricians, in addition to targeting those families of

Table 1. The 10 Warning Signs of primary immunodeficiency

10 Warning Signs of PID for children	10 Warning Signs of PID for adults
Four or more new ear infections within 1 year	Two or more new ear infections within 1 year
Two or more serious sinus infections within 1 year	Two or more new sinus infections within 1 year in the absence of allergy
Two or more months on antibiotics with little effect	One pneumonia per year for more than 1 year
Two or more pneumonias within 1 year	Chronic diarrhoea with weight loss
Failure of an infant to gain weight or grow normally	Recurrent viral infections (colds, herpes, warts and condyloma)
Recurrent, deep skin or organ abscesses	Recurrent need for intravenous antibiotics to clear infections
Persistent thrush in mouth or fungal infection on skin	Recurrent, deep abscesses of the skin or internal organs
Need for intravenous antibiotics to clear infections	Persistent thrush or fungal infection on skin or elsewhere
Two or more deep-seated infections including septicemia	Infection with normally harmless tuberculosis-like bacteria
A family history of PID	A family history of PID

PID, primary immunodeficiency. 'These warning signs were developed by the Jeffrey Modell Foundation Medical Advisory Board. Consultation with Primary Immunodeficiency experts is strongly suggested. © 2009 Jeffrey Modell Foundation'. Adapted from [2] and [1].

children with PID to receive genetic counselling and promote screening of subsequent children after birth.

These studies provide useful and complementary information when evaluating the 10 Warning Signs. Not unexpectedly, the Warning Signs appear to be less sensitive in those patients with less severe PID. Are there signs, other than the 10 Warning Signs, that are leading to referral and diagnosis? It is of note than none of the 10 Warning Signs was present in the more than one-third of children with PID from MacGinnitie's study [7▪▪], whereas in the UK cohort, waiting for the appearance of two or more Warning Signs would have delayed diagnosis in 38% of patients with potentially life-threatening PID [8]. Thus, some other clinical or laboratory finding raised the possibility of PID in the mind of the treating clinician.

The utility of any screening programme or diagnostic guidelines will vary according to the population of patients to which they are applied. These studies clearly demonstrate that the 10 Warning Signs are not a comprehensive diagnostic or referral tool, and that the importance of particular clinical and laboratory features are likely to be weighted differently by primary care physicians, general paediatricians and physicians, subspecialty clinicians and immunologists.

Given our growing knowledge of how an increasing number of PIDs may be manifest clinically, perhaps a move away from a single set of Warning Signs for all PIDs and physicians is needed. Rather than a paradigm shift, perhaps 'paradigm evolution' towards Warning Signs for specific patient and physician groups would help?

DEVELOPMENT AND REFINEMENT OF THE 10 WARNING SIGNS

Recently software has been developed that links medical coding data with the Warning Signs to identify patients with possible PID [3]. This novel approach offers another pathway to the diagnosis of PID but is ultimately reliant on the ability of the Warning Signs to correctly identify those with PID; the limitation of this is highlighted by the finding that only 63% of those with diagnosed PID met at least one of the Warning Signs in a study evaluating the software [3].

First, it is important to define the purpose and target audience for any refined guidelines. Given the diversity and complexity of PID manifestations, undiagnosed PID patients present to many different generalists and specialist practitioners. Warning Signs must ensure that patients with possible PID receive appropriate referral and investigation in an even more timely manner. In this model, a distinction emerges between warning signs appropriate for the general population, those with a family history of PID, primary care physicians and community-based and hospital-based specialty practitioners.

Comprehensive guidelines to assist non-immunologists in evaluating patients with possible PID have been developed [17] and updated [18▪] by the European Society for Immunodeficiencies (ESID). The initial protocol outlines the infectious hallmarks of PID together with aspects of family history and 40 other pointers to PID. The ESID guidelines group different clinical presentations of PID, associated immune defects, likely pathogens and other distinguishing features, and outline a suggested diagnostic protocol with non-PID differential diagnoses. The 2011 update [18▪] adds physical examination findings and common laboratory parameters to the list of signs of potential PID and detail on pathogenesis. These guidelines provide an excellent reference resource for physicians and paediatricians and the content is broadly appropriately targeted to its readers; however, the level of detail especially in the 2011 update is perhaps too great for all but nonimmunologists with a particular interest in PID. Different clinicians will encounter different presentations of PID according to their area of practice. Thus, the development of warning signs targeted at different groups could provide a simpler yet effective approach. In the second part of this review, we propose a possible series of warning signs, although recognizing that they will need evaluation and discussion.

WARNING SIGNS FOR THE NEONATAL PHYSICIAN

Many life-threatening PIDs present in early infancy and haematopoietic stem cell transplantation (HSCT) is curative in many cases [19]. To have the best chance of success, patients must be diagnosed early before serious infective damage has occurred. Therefore, a distinct set of warning signs for the neonatologist or physician seeing young infants is vital to minimize harm from a delayed diagnosis of PID. A combination of the features of cellular PID relevant to the primary care physician suggested by a 2009 workshop of HSCT experts [20] and the warning signs of PID in the first year of life proposed by Carneiro-Sampaio *et al.* [21▪] are as follows:

1) oral thrush, chronic diarrhoea or failure to thrive in the first months of life
2) recurrent infections with bacterial pathogens, opportunistic organisms and viruses

3) pneumonitis that does not clear
4) extensive skin lesions, such as rashes with erythroderma or eczema that do not resolve with therapy
5) delayed umbilical cord detachment (more than 30 days)
6) hepatosplenomegaly, lymphadenopathy
7) congenital heart defects, particularly conotruncal anomalies
8) family history of PID or deaths in infancy
9) laboratory findings of lymphopaenia (lymphocyte count <3400 cells/μl), other cytopaenias or leukocytosis without infection, immunoglobulin M (IgM) less than 0.2 g/l, IgA less than 0.05 g/l or hypocalcaemia.
10) absence of thymic shadow on radiograph

WARNING SIGNS FOR DERMATOLOGISTS

Cutaneous manifestations are characteristic of many PIDs. Over one-third of children with PID had skin manifestations among their presenting clinical features [11▪▪]. Most common were bacterial skin infections, a clinical presentation not only seen by a dermatologist. However, other relatively frequent manifestations of PID include molluscum contagiosum and warts, eczema, erythroderma and alopecia, which may be more likely to be seen in a dermatology clinic.

The challenge, of course, is to identify which of these patients should be further evaluated. In the neonatal period, generalized erythroderma should raise the possibility of Omenn syndrome [11▪▪]. Eczema in association with recurrent cutaneous viral infections or abscesses may trigger a referral to evaluate for *DOCK8* deficiency [10] or autosomal-dominant hyper-IgE syndrome (AD-HIES) [22], respectively, whereas the presence of petechiae or a history of bleeding may prompt assessment of platelet number and volume for suspected Wiskott–Aldrich syndrome. In a patient with cystic acne, an associated sterile arthritis, pyoderma gangrenosum or pathergy may herald the pyogenic arthritis, pyoderma gangrenosum and acne syndrome [23].

WARNING SIGNS FOR GASTROENTEROLOGISTS

Gastrointestinal symptoms are common in PID. Chronic diarrhoea with or without malabsorption may be associated with antibody deficiency disorders [12], although the presence of diarrhoea alone is unlikely to identify those patients most at risk of PID. Similarly, although chronic granulomatous disease (CGD) may present with gastrointestinal manifestations indistinguishable from inflammatory bowel disease (IBD), screening 191 children with IBD revealed no CGD cases or carriers [24▪▪,25].

A staged system of warning signs may be more appropriate in this context. Measurement of serum immunoglobulins could be recommended in patients with chronic diarrhoea in whom no cause is immediately apparent or those with a history of sinopulmonary or cutaneous infection. In patients presenting with IBD, selected subgroups could be investigated to exclude CGD, such as children under 5 years of age, those with a personal or family history of infections including cervical lymphadenitis or abscesses, presence of perianal disease [26], or histopathological findings such as eosinophilic inflammation and characteristic large macrophages [12,27] or reduced CD68-positive cells [28].

WARNING SIGNS FOR RESPIRATORY PHYSICIANS AND OTOLARYNGOLOGISTS

Respiratory tract infection and damage are a feature of many PIDs; however, respiratory tract infections are common and usually not associated with PID. The presence of pneumatocoeles in a patient with eczema, eosinophilia and elevated IgE strongly suggests AD-HIES [29]. Both the clinical syndrome of 'mulch pneumonitis', an inflammatory reaction to *Aspergillus* spores [30], and *Aspergillus* pneumonia [31,32] should prompt investigation for CGD, as should other fungal pneumonias extending across tissue planes [33].

Bronchiectasis is a common manifestation of antibody deficiency and should be suspected in children with a chronic moist cough between viral infections, treatment-refractory asthma, non-resolving pertussis-like illness or haemoptysis; and in adults with a persistent productive cough, particularly when associated with young age of onset, no history of smoking, expectoration of large volumes of purulent sputum or haemoptysis [34]. Screening for hypogammaglobulinaemia is recommended for all patients with non-cystic fibrosis bronchiectasis [34]; the incidence of clinically significant antibody deficiency in patients with bronchiectasis has not been well established, but recent expert guidelines suggest antibody deficiency contributes to at least 5% of bronchiectasis and PID was identified as the cause of bronchiectasis in 29% of children from a tertiary referral centre [35]. Defining the features that identify those most at risk of an underlying PID represents a challenge for future study.

Sinusitis and otitis are frequently seen in patients with antibody deficiency and included as Warning Signs of PID; however, a recent study [36]

found no difference in antibody responses to pneumococcal conjugate vaccine in otitis-prone children compared with healthy controls; a thorough immune evaluation may be better limited to only those with infections at multiple sites or other features of PID [37]. Screening for immunodeficiency is not recommended with isolated episodes of acute bacterial rhinosinusitis [38] but may be warranted in adults with chronic rhinosinusitis refractory to medical therapy and requiring surgical management in which 11.6% were found to have specific antibody deficiency in a recent retrospective study [39]. The important role of the otolaryngologist in diagnosing PID has been highlighted [40▪], but further study is required to identify which patients with recurrent otitis and sinusitis require evaluation for possible PID.

WARNING SIGNS FOR MICROBIOLOGISTS/INFECTIOUS DISEASES PHYSICIANS

Despite an expanding spectrum of PID presentations, the hallmark of PID remains increased susceptibility to infection. Most are due to common pathogens; however, infection with certain less common microbes makes certain PIDs much more likely. Awareness of these 'warning sign' organisms provides an additional opportunity to diagnose PIDs.

Routine screening for complement deficiency in children with one episode of meningococcal disease is not supported by existing data from northern European children if caused by the serotypes most prevalent in that population; only one of 296 children investigated in the United Kingdom with group B or C infection was found to have a complement deficiency and that child had a history of recurrent invasive infection with encapsulated organisms [41]. However, if a less common *Neisseria meningitidis* serotype (such as W135 or Y in the United Kingdom) is isolated or there is recurrent infection or a family history of meningococcal disease, further investigation is warranted.

In determining whether invasive pneumococcal disease (IPD) may be a harbinger of PID, numerous factors need to be considered. Although IPD is a typical feature of some Toll-like receptor (TLR) signaling defects [16], routine screening of TLR function in 50 children with IPD did not detect any cases of PID [42]. However, it is noteworthy that only one of these patients had meningitis (the most commonly described manifestation of IPD in patients with confirmed IRAK4 and MyD88 defects [16]), and only four had received pneumococcal conjugate vaccine (PCV). There has been a significant shift in the epidemiology of IPD since the introduction of PCV [43]. Therefore, the likelihood of identifying PID might be increased by selecting those patients with IPD in whom *Streptococcus pneumoniae* has been isolated from cerebrospinal fluid or in whom vaccination against the infecting serotype is offered in that population.

Viral encephalitis is most frequently caused by primary Herpes simplex virus-1 (HSV-1) infection, although it remains uncommon with an estimated incidence of one in 250 000 per year [44▪]. Otherwise healthy and immunocompetent children may have a single episode of Herpes simplex encephalitis (HSE); however given the rarity of HSE and increasing identification of PID characterized by an isolated susceptibility to encephalitis but not other forms of HSV-1 infection, a possible defect in the TLR3 pathway (including TLR3, UNC93B, TRIF and TRAF3 [44▪]) should be considered in these patients, particularly if there is any family history of HSE.

Invasive *Aspergillus* infection or the isolation of *Burkholderia cepacia* in blood cultures should raise the possibility of CGD. Although recent series have reported a low frequency of *Burkholderia* infection in patients with CGD [45,46], it remains an uncommon infection in immunocompetent patients without underlying lung disease and so is a very useful 'warning sign'. Similarly, infections with other unusual bacterial species such as *Chromobacterium, Francisella* and *Granulibacter* and fungi including *Paecilomyces, Aspergillus nidulans* and *Neosartorya* are rarely seen in groups other than CGD [32], whereas *Giardia lamblia* is a frequent cause of infective diarrhoea in patients with common variable immunodeficiency [12].

WARNING SIGNS FOR OTHER SPECIALTIES

Autoimmunity is emerging as an increasingly common manifestation of PID. Chronic mucocutaneous candidiasis (CMC) in association with hypoparathyroidism and adrenal failure characterises autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia syndrome [47], whereas hypothyroidism may be seen with gain-of-function STAT1 mutations [48]. In patients with clinical features of CMC, simple biochemical screening (calcium, sodium, glucose and thyroid-stimulating hormone) may be sufficient in the first instance. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome is a potentially fatal PID that presents more often with noninfective diarrhoea, dermatitis, diabetes and thyroiditis than recurrent infection [14]. A relatively high prevalence of PID (15%) in paediatric patients with

autoimmune disorders highlights the need to identify warning signs for the rheumatologist, particularly as none of those patients had recurrent infections or a family history strongly suggestive of PID [49].

CONCLUSION

The 10 Warning Signs of PID were devised to raise awareness and improve diagnosis of PID at a time when the understanding of the spectrum of immune defects and possible clinical presentations was relatively limited compared with what is known today. They have been undoubtedly successful in the promotion of PID awareness particularly through the work of the JMF; however, it is difficult to objectively measure the clinical utility of any early warning signs when studying a cohort of patients already referred to an immunology service.

We propose that an evolution of the Warning Signs with versions tailored to different target audiences might better meet the needs of patients and physicians to further improve identification of possible PID. A succinct set of specialty-specific warning signs may be helpful in day-to-day practice, not to diagnose PID but rather to prompt the clinician to consider it as a possibility. These tailored warning signs require expert debate that can be informed by currently available data and should include a plan to evaluate their utility and identify where gaps in knowledge exist to direct future research. The warning signs should promote the early identification and urgent referral to an immunologist of patients with potentially life-threatening PID, whereas in other instances, it may be appropriate to incorporate an initial laboratory evaluation by nonimmunologists. The point at which a patient with possible PID should be referred to an immunologist will vary depending on the experience of the clinicians involved, but ultimately the diagnosis or exclusion of PID is best determined by an experienced immunologist, and therefore appropriate early consultation should be encouraged as part of any new warning signs that are developed.

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Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 671–672).

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