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Review

Recurrent or unusual infections in children – when to worry about inborn errors of immunity

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***Abstract*:** Recurrent infections are a common presenting feature in paediatrics and, while most times considered part of normal growing up, they are also a classical hallmark of inborn errors of immunity (IEI). We aimed to outline the value of currently used signs for IEI and the influence of the changing epidemiology of infectious diseases due to implementation of new vaccines and the effect of the COVID-19 pandemic on the assessment of children with recurrent infections. Warning signs for IEI have been developed, but the supporting evidence for their effectiveness is limited, and immune dysregulation is more commonly recognised as a feature for IEI, making reliable identification of children who should be screened for IEI on clinical grounds difficult. In addition, the epidemiology of infectious diseases is changing due to restrictions related to Covid-19 as well as immunisations, which may change the threshold to screen children for IEI. Treatments for IEI are evolving and are often more effective and less complicated when started early. Screening for IEI can be initiated by the non-immunologist and should be considered early to ensure optimal treatment outcomes.

Keywords: child, diagnostics, immunodeficiency, infection, pandemic, recurrent

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Introduction

Infection in childhood is extremely common and often self-limiting, whereas inborn errors of immunity (IEI) is neither. Children and young people (CYP) are expected to have a higher frequency of infection than adults, so it may be difficult to identify those with recurrent infections who merit further investigation from those who have a normal frequency of childhood infection. IEI may involve any part of the innate or adaptive immune system, and it may affect any organ system. Infection with unusual organisms, unusually severe infection or unusual frequency of infection are the traditional hallmarks of IEI. There are different susceptibilities to infection depending on the immunological defect; therefore, the pattern of infection may provide clues to the underlying immunological diagnosis.[1] We are increasingly recognising a wider phenotype of IEI. Extra-immune manifestations and associations are being reported regularly, with immune dysregulation and predisposition to malignancy now recognised as features of IEI.[2]

The reported overall prevalence of IEI varies significantly depending on the context and definition used. Individually, these are rare illnesses with the notable exception of IgA deficiency that is estimated to affect around 1 in 600 people, although this is often asymptomatic.[3] Once IgA deficiency is excluded, in the United States it is thought that 1 in 1200 people have IEI while France reports 4.4 cases of IEI per 100,000 people.[4] This variation may be due to differences in reporting and classification of disease, although ethnic and geographical variations in particular diseases are noted. A uniform approach to diagnosing and classifying IEI diagnosis is promoted and valuable in comparing studies, but new IEI are being identified every year.[5] The International

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Union of Immunological Societies (IUIS) regularly publish updated classifications of IEI to take into account these new discoveries.[6]

Treatment for IEI aims to minimise infection frequency, severity, and complications; to prevent complications of underlying disease; and to correct the immunodeficiency where possible. Severe combined immunodeficiency (SCID) is a medical emergency, while other IEI can be managed less urgently. A range of treatments may be deployed. Prophylaxis against infection and extra immunisations are directed against anticipated immunological weaknesses based on the underlying diagnosis or pattern of test results. Immunoglobulin replacement is available for those who do not produce functional immunoglobulins. Haematopoietic stem cell transplant (HSCT) aims to cure the immunological defect by inserting healthy haematopoietic progenitors into the host bone marrow that will in turn produce a functional immune system. However, HSCT is not without significant complications and risks, including treatment-related mortality. In addition, it does not cure disease manifestations in other organ systems, unless immune mediated. Therefore, even when theoretically effective for a particular IEI, it is not always appropriate. Specific treatments aimed at the molecular defect are being developed, such as the use of abatacept in lipopolysaccharide receptor beige-like anchor (LRBA) deficiency.[7] Gene therapy is a promising avenue of research with treatments aimed at single gene defects. There is a growing evidence base and it may replace HSCT for some conditions.[8]

Better outcomes are achieved when treatment is started early, and indeed with the advent of newborn screening for SCID, it is possible to identify and treat more children before they develop any infections or other complications. Newborn screening in California has resulted in a 94% post-HSCT survival rate.[9] Whereas in Europe where newborn screening was not routine, the post-HSCT survival was 66–90% depending on donor stem cell source.[10] However, there are no screening programmes for most IEI, and patients mostly first present to general practitioners, paediatricians, and respiratory and ENT (ear, nose and throat) teams. It is therefore important for all clinicians to be aware of what is normal, when to suspect IEI, and which initial investigations to perform depending on the clinical presentation.

We aimed in this review to outline the value of currently used signs for IEI and the influence of the changing epidemiology of infectious diseases due to implementation of new vaccines and the effect of the COVID-19 pandemic on the assessment of children with recurrent infections.

What is normal?

Expert opinion suggests that 6–10 self-limiting viral infections per year are within the normal range. More frequent infections can be expected in the winter, and an infection may last for 1–2 weeks. Therefore, it may seem like a normal child is unwell for most of the winter period. Young children with siblings, children attending day care and those exposed to smoking or living in deprived areas are known to have increased infection rates compared with those who do not have these risk factors.[11] Most of them will not have an IEI.

Warning signs

There have been several efforts to create checklists of red flags for IEI aimed at non-immunologists to assist in identifying CYP who may have IEI. The first of these was the Ten Warning Signs from the Jeffrey Modell Foundation (Box 1).[12] They recommend that IEI should be considered if a child has one or more of the Warning Signs. A separate set of warning signs has been published for adults.[12]

The Ten Warning Signs were evaluated in an Egyptian retrospective study of the notes of 92 patients with confirmed IEI based on World Health Organization (WHO) diagnostic criteria and 112 controls who had been referred to the same unit with suspected IEI but did not have a confirmed IEI diagnosis after thorough evaluation.[4] Children accounted for 45% of the cohort. They found that every patient with confirmed IEI had at least one of the Ten Warning Signs, whereas 72% of those without IEI had at least one warning sign. In their cohort, having at least one warning sign gave a sensitivity of 100%, specificity of 26%, positive predictive value (PPV) of 53% and negative predictive value (NPV) of 100%. When two warning signs were present, the sensitivity fell to 94%, specificity increased to 64%, PPV increased to 68% and NPV fell to 92%.

The most common warning signs in those without IEI were need for intravenous (IV) antibiotics

Box 1. The Ten Warning Signs of inborn errors of immunity (adapted from Jeffrey Modell Foundation).[12]

1. Four or more new ear infections within 1 year
2. Two or more serious sinus infections within 1 year
3. Two or more months on antibiotics with little effect
4. Two or more episodes of pneumonia within 1 year
5. Failure to thrive in an infant
6. Recurrent deep skin, or internal organ abscesses
7. Persistent oral candidiasis or fungal skin infections
8. Need for intravenous antibiotics to clear infections
9. Two or more deep seated infections, including septicaemia
10. A family history of IEI

IEI, inborn errors of immunity.

(53%), two episodes of pneumonia in 1 year (37%) and failure to thrive (33%). However, these signs were also very common in those with confirmed IEI. A family history of IEI was the strongest predictor of confirmed IEI, with a relative risk of 32 [95% confidence interval (CI), 2.8–332.2]. The need for IV antibiotics had a relative risk of 12 (95% CI, 3.6–41.7) and more than two deep-seated infections has a relative risk of 16 (95% CI, 1.8–141.2), whereas two or more episodes of pneumonia in 1 year was not statistically significant. Parental consanguinity and the death of a sibling had relative risks of 6 (95% CI, 2.6–14.3) and 5 (1.0–18.4) for IEI, respectively.[4]

A similar retrospective review focussed exclusively on CYP aged less than 21 years old who had been referred to a tertiary US immunology service with suspected IEI.[13] Seventy-four percent (105/141) of their cohort had one or more warning signs, of whom 19% (20/105) had an IEI.[13] In contrast, 32% (12/37) of those without a warning sign were ultimately diagnosed with IEI. While the rates of IEI diagnosis were not significantly different between those with and without warning signs, it should be noted that this is a population with a higher likelihood of IEI as they have been referred to a tertiary service for assessment.

Comparing a cohort of CYP referred to two UK tertiary immunology centres with confirmed IEI with a cohort of children who had severe, recurrent or unusual infections but did not have a confirmed IEI, the strongest predictor of IEI was a physician diagnosed IEI in a family member with a relative risk of 18.[14] In addition, failure to thrive was a strong predictor of T-cell immunodeficiency, and requirement for IV antibiotics was a strong predictor for a neutrophil immunodeficiency.

The Ten Warning Signs have served well in raising physician and wider societal awareness of IEI, including increased charitable fundraising for the benefit of this patient cohort. However, they are not particularly specific or sensitive at identifying IEI. Considering the growing understanding of the diversity of IEI presentations and underlying diagnoses, it has been suggested that speciality-specific warning signs should be developed. These would be tailored to highlight IEI that are likely to present to particular specialities, such as screening patients with non-cystic fibrosis (CF) bronchiectasis.[14] Indeed, a study of two UK tertiary paediatric respiratory units found that 36% of children with non-CF bronchiectasis had an underlying IEI.[15] Extensive and persistent warts and molluscum, and opportunistic infections such as disseminated BCG and persistent infections with other live-attenuated vaccines, have also been identified as hallmarks of specific IEI.[16–18] However, further work is required to determine the effectiveness of any given set of speciality-specific warning signs.

Immunodysregulatory phenomena do not feature in the Ten Warning Signs. However, they are common features of IEI, indeed diseases of immune dysregulation comprise one category in the IUIS classification.[19] This category includes familial haemophagocytic lymphohistiocytosis (HLH), autoimmune lymphoproliferative syndrome (ALPS) and regulatory T-cell disorders.[6] Allergies are immunological disorders and may be presenting features of IEI syndromes, such as DOCK-8. Atopic dermatitis is a feature of Wiskott Aldrich syndrome and autosomal dominant hyper IgE syndrome.[19] Autoimmunity is a common feature of IEI with a 120 times increased risk of autoimmune cytopaenia, 80 times increased risk of inflammatory bowel disease and 40 times increased risk of arthritis.[20] Therefore, the physician should also be alert to immunodysregulatory phenomena as potential features of IEI.

Some immunodeficiencies are recognised in the context of syndromes such as 22q11 deletion syndrome and Trisomy 21, with a.o. facial dysmorphic features and congenital cardiac abnormalities in which some patients have an immunodeficiency.[21] Patients with these conditions can present with recurrent or severe infections, but quite a few will initially be brought to the attention of the healthcare system due to congenital defects, failure to thrive or dysmorphic features. These patients will need an immunology workup to assess if in them immunodeficiency is a feature that requires management.

Is normal infection changing?

The Ten Warning Signs rely on exposure to pathogens leading to infection in order to expose an underlying IEI. There have been several developments recently, not least the Covid-19 pandemic that have affected CYP exposure to pathogens. Other developments, such as changing immunisation policies and coverage, have also had an impact.

Impact of immunisation

Immunisation is a significant modifier of childhood infection, with changes to national schedules made upon assessment of new data about the vaccines themselves, epidemiology of infection, economic analyses or response to outbreaks.[22,23] The examples of *Streptococcus pneumoniae* and *Neisseria meningitidis* infection illustrate well the influence of immunisation on the changing epidemiology of infection and what infection reveals about potential IEI.

In the United Kingdom, the pneumococcal conjugate vaccine has been offered to at-risk groups since 2001 and to all children under 2 years since 2006. A 7-valent vaccine (PCV7) was introduced in 2006 with a catch-up campaign that achieved good levels of coverage. This led to an 86% reduction in the incidence of invasive pneumococcal disease (IPD) in all ages by 2010.[24] However, there was an increase in infection by non-vaccine strains, leading to introduction of the 13-valent vaccine (PCV13) in the United Kingdom in 2010 without a catch-up campaign. The incidence of IPD decreased by 32% in all ages in 2013–2014 compared with 2008–2010. The incidence of IPD caused by the six additional strains covered by PCV13 fell by 69% in all age groups. Unsurprisingly, the largest fall was in children under 5 years old, being the group who received the PCV13 immunisation. However, while the overall incidence of IPD has fallen, there has been an increase in non-vaccine strains from 4.19 cases per 100,000 in 2008–2010 to 5.25 cases per 100,000 in 2013–2014, with the largest increase in incidence in children under 2 years old.[24]

Recurrent IPD should trigger screening for IEI as two or more deep-seated infections is a warning sign. A retrospective Danish study examined all cases of IPD in children aged less than 15 years that were registered with the Danish Streptococcus Pneumoniae Registry between 1980 and 2008.[25] They identified 2192 children who had IPD, of whom 54 had recurrent disease. Of these children, 32 had a known risk factor such as HSCT recipient or anatomical defect. The 22 children who had no known risk factor were offered an immunology assessment. Six children declined to participate in the study, and one had died. The remaining 15 children were screened, and 10 had an underlying immunodeficiency. Six had a complement deficiency, one had a toll-like receptor deficiency and three had a specific antibody deficiency. This illustrates a relatively high incidence of immunodeficiency in this cohort, with 45% of children with recurrent IPD and no other known risk factors having an underlying immunodeficiency.

Similar patterns were observed in France, where immunisation with PCV7 was introduced in 2006 and changed to PCV 13 in 2010.[26] A prospective study involving 28 paediatric centres across France identified 163 children with IPD between 2005 and 2011, of whom 17 (10.4%) had recurrent infection.[26] In total, 127 children had comprehensive immunological screening and 35 children had partial screening. Twenty-six children (16%) had abnormal immunological results, of whom 17 were subsequently diagnosed with IEI. Twelve children had an antibody deficiency, 3 children had a complement deficiency, 1 child had asplenia and 1 child had MyD88 deficiency. In this study, 10% of all children with IPD in an immunised population had an IEI.

The experience to screen for IEI with other vaccine preventable diseases is less clear. Invasive meningococcal disease (IMD) results from infection with one of six pathogenic serotypes of *Neisseria meningitidis* (A, B, C, W135, X and Y). The United Kingdom was the first country to introduce immunisation in 1999 by vaccinating toddlers and adolescents against *N. meningitidis* serotype C (MenC). The incidence of MenC fell dramatically with a fall of 90% in cases among immunised people and 66% in unimmunised people.[27] However, with the fall in MenC cases, serotypes B (MenB) and W (MenW) became more prevalent in the United Kingdom. Therefore, immunisation against MenB was introduced for infants in 2015, with the adolescent MenC booster replaced with MenACWY.[27]

A single-centre study in the North East of England assessed all referrals for suspected meningococcal infection between 1996 and 1999. In the survivors, 212 of the laboratory confirmed cases and 85 of the non-confirmed cases had complement screening through measurement of CH100/AP100. Only one case of complement deficiency (0.3%) was identified, in a child who also previously had IPD.[28]

Screening for IEI in adults is recommended after two invasive bacterial infections.[12] A multicentre French study looked retrospectively at young adults aged 18–40 who had an invasive infection with an encapsulated organism between 2010 and 2012, including pneumococcus, meningococcus, *Neisseria gonorrhoeae*, *Haemophilus influenzae* group or group A *Streptococcus*. They identified 38 patients with an invasive infection caused by an encapsulated bacterium over a 3-year period, for 36 of whom this was the first episode. IEI was diagnosed in seven (19%) patients of the first episode cohort. Seven patients in the study had IMD, of whom three had an IEI. Eleven patients had IPD, of whom two had an IEI. Overall, three patients had an antibody deficiency, two had complement deficiency and two had common variable immunodeficiency. Both patients with a previous episode had recurrent *Neisseria* sp. infection and were diagnosed with a complement deficiency.[29]

These studies indicate a significant risk of underlying IEI in children with recurrent IPD. However, in the era of pneumococcal immunisation, the overall incidence of IPD has fallen and has uncovered a population of children with IEI following one invasive infection. However, there is no data to support a similar phenomenon in IMD. Data from young adults, however, show a significant detection rate after one invasive infection with encapsulated bacteria, including IMD. Given that invasive infection with encapsulated bacteria can be devastating, it seems prudent to screen CYP after one invasive pneumococcal infection.

Effect of Covid-19 on 'normal infection rate'

The first reports of pneumonia of unknown cause were made to the WHO on 31 December 2019, and Covid-19 was declared a pandemic on 11 March 2020. The United Kingdom went into 'lockdown' on 23 March 2020 when schools closed, social distancing became mandatory, and wearing of face masks, and increased emphasis on cough and hand hygiene were implemented.[30] While these measures reduced the spread of Covid-19, they also had profound effects on the epidemiology of common childhood infections and presentations to services.

Attendance to Paediatric Emergency Departments (PEDs) had been rising over the years prior to the Covid-19 pandemic. However, one study of four PEDs in England showed that in 2020 attendance was reduced by 34% when compared with the preceding 3 years.[31] This reduction was significantly less marked in infants less than 30 days old, however, where the difference in attendance ranged from 12% reduction to 14% increase.[31] Reduction in ED attendance was most marked

for minor injuries and illnesses, but less so for severe disease.[32] Comparing the diagnoses made in two UK PEDs in 2020 with those in previous years showed a PED attendance rate reduction to 56.8% of the preceding 4 years, and a reduced inpatient admission rate to 59.4% of the preceding 4 years.[33] Eighty percent of the change was due to reduction in infections, while the remaining 20% was due to a decrease in accidental injury or ingestion, and non-specific symptoms. Infectious presentations overall were reduced by 58.9%, while the reduction in non-specific viral illnesses accounted for approximately 30% of the whole reduction in presentations.

Respiratory infection historically accounts for a large proportion of paediatric consultations in PEDs and primary care, as well as a significant proportion of antibiotic prescriptions in paediatrics. Seeing this in a local/regional context is however important as prescription rates are very variable between centres.[34] Children have been relatively spared from symptomatic Covid-19 infection, with less than 2% of UK cases occurring in CYP and relatively low admission rates.[35] Measures to reduce the spread of Covid-19 appear to have had a similar effect on other paediatric respiratory infections. English national data comparing the rates of paediatric infectious diagnoses in 2021 against the annual mean of previous 3 years demonstrated a particular reduction in the incidence of respiratory infection.[35] There was a 94% reduction in influenza, 80% reduction in bronchiolitis, 78% reduction in croup, 56% reduction in viral wheeze, 60% reduction in pneumonia, 66% reduction in upper respiratory tract infection and 74% reduction in otitis media. In addition, the rates of five of six invasive bacterial infections had also significantly decreased.[35] The incidence of sepsis fell by 33%, meningitis by 52%, septic arthritis by 35%, osteomyelitis by 26% and cellulitis by 43%. Pyelonephritis rates, however, remained stable.[35] These findings are supported by data across the world, such as a decline of 85.5% in otitis media in one Brazilian PED, reduction in Respiratory Syncytial Virus (RSV) in England and influenza in Australia.[36–39]

One UK centre assessed the results of all respiratory viral Polymerase Chain Reactions (PCRs) taken in their PED over the 5-year period to July 2021 in order to assess the effects of Covid-19 on the incidence of seasonal respiratory viral infection.[40] They found that the incidence of all pathogens was reduced during the first UK lockdown period from March to September 2020. However, there was a resurgence of rhinovirus and adenovirus when CYP returned to school in September 2020. The incidence of influenza remained low throughout, while there was no seasonal winter peak of respiratory syncytial virus in 2020/2021.

In England, the incidence of IPD was 0.7 cases per 100,000 children in 2020. However, in July–December 2021, when restrictions were lifted, and schools reopened, it was 1.96 cases per 100,000 in comparison with pre-pandemic levels of 1.43 cases per 100,000 per year in 2017–2019.[41]

Of note, the Covid-19 pandemic has also interrupted routine childhood immunisation. The WHO reported in May 2020 that 68 lower income countries had reduced or suspended immunisation programmes, while in the United Kingdom the immunisation rate for measles, mumps and rubella decreased by 20% at one point, although rates have recovered since.[42,43] Coverage of UK children with PCV13 fell from 94.5% in 2020 to 93.6% in July 2021. Measles, mumps and rubella immunisation coverage fell from 85.0% to 84.1% over the same period.[43] Therefore, there has been a small, but significant, decline in immunisation coverage.

Considering the general decrease in childhood infection seen in the Covid-19 pandemic, we may fail to identify CYP with warning signs of IEI given the reduced number of infections in their medical history due to decreased exposure, or onset of symptoms at an older age than previously expected in IEI. Therefore, other warning signs, such as family history, become more useful in determining the likelihood of IEI.

How does SARS-CoV-2 infection affect those with inborn errors of immunity?

IEI are a heterogeneous group of conditions and therefore SARS-CoV-2 may result in anything from an asymptomatic infection to death due to severe Covid-19 disease. A multicentre retrospective review of IEI patients who had Covid-19 and were reported to the IUIS included 649 previously undescribed patients.[44] The different types of IEI, along with the proportions requiring

Table 1. Patients with IEI and Covid-19 infection (after Bucciol *et al.*[44]).

Type of IEI	Number of patients	Intensive care admission	Case fatality rate
Primary antibody deficiencies	330 (51%)	14%	8%
Combined immunodeficiencies	94 (14%)	20%	13%
Immunodysregulatory disorder	62 (10%)	28%	15%
Autoinflammatory disorder	54 (8%)	4%	6%
Innate immune disorder	39 (6%)	62%	10%
Phagocyte disorder	34 (5%)	6%	6%
Complement deficiency	29 (4%)	0%	0%
Good syndrome	7 (1%)	75%	43%

IEI, inborn errors of immunity.

intensive care admission and case fatality rates, are summarised in Table 1.

The Combined Immunodeficiency group includes 17 patients with SCID, of whom 10 have undergone HSCT. Four of the 7 children with SCID who had not received HSCT died, whereas there were no deaths among the 10 children who had received HSCT. Fifteen patients had undergone HSCT or gene therapy for non-SCID conditions, of whom 3 (20%) died.

The immunoregulatory group included 27 with autoimmune polyendocrine syndrome type 1 (APS-1), 41% of whom required intensive care in contrast to 28% of the group overall. However, mortality remained the same at 15%. In this case, the antitype 1 interferon autoantibodies produced in APS-1 inhibited the initial type 1 interferon response to SARS-CoV-2 infection.[45] They noted a high proportion of intensive care admission in innate immune defects, which may be due to more studies assessing these illnesses in severely unwell Covid-19 patients.

Overall, they noted an intensive care admission rate of 16% and case fatality rate of 9%, as compared to a global morality rate of 2.1% (range, 0.5–18%). The differences may be explained by two factors. They comment that widespread screening for SARS-CoV-2 in the general population led to a lower mortality rate among the general population. A study of all Italian patients with IEI demonstrated a case fatality rate of 3.8% compared with 3% in the general population.[46] They also found that patients with IEI tend to accumulate co-morbidities earlier in life than immunocompetent people, suggesting that this leads to more severe infection in IEI patients than immunocompetent patients of the same age.

Their findings were similar to an earlier retrospective multicentre study of 94 patients. Eighteen patients (19.4%) required an intensive care admission. Nine patients died (9.6%), including 7 adults and 2 children.[47] They noted that every adult who died also had pre-existing co-morbidities. The children both died from intercurrent sepsis and HLH, and therefore, it is difficult to assess to what extent SARS-CoV-2 infection contributed to their deaths.

SARS-CoV-2 infection appears to be more severe in specific IEI, such as APS-1 and possibly innate immune defects. However, overall, the case fatality rate is only slightly increased compared to that of the general population.

Diagnostic approach to the child with suspected recurrent or unusual infection

Investigation of a child with suspected IEI need not rest exclusively within the realm of the

Table 2. ESID investigation protocols and clinical presentations [after De Vries and European Society for Immunodeficiencies (ESID) members[49]].

Investigation protocol	Clinical presentation
1. Antibody and complement protocol	Recurrent ENT infections Recurrent infection with encapsulated bacteria Angioedema
2. Combined immunodeficiency protocol	Failure to thrive in infancy Unusual infection, or unusually severe infection Recurrent infection with fungi, viruses, and intracellular bacteria
3. Neutrophil disorders protocol	Recurrent pyogenic infections
4. Choice of protocol guided by clinical presentation	Eponymous syndromes Autoimmune disease, chronic inflammatory disease, lymphoproliferation

ENT, ear, nose and throat; ESID, The European Society for Immunodeficiencies.

Immunologist. The European Society for Immunodeficiencies (ESID) published excellent guidance on the diagnosis of IEI aimed at non-immunologists in 2006, updated in 2011.[48,49] The ESID guidance is based on expert opinion and aims to increase awareness of IEI among all doctors, as well as providing guidance on initial investigations. ESID use the patient's clinical presentation to guide the clinician to one of three pathways: predominantly antibody and complement deficiencies; combined T- and B-cell disorders; and neutrophil disorders. Their pathways will move clinicians between the protocols depending on the initial results until a likely working diagnosis is reached. The clinical presentations are linked to their initial investigation protocol in Table 2. It should be emphasised that while this is the most likely immunological deficit, it is not necessarily the part of the immune system where the final diagnosis lies. In addition, many of these presentations, in particular respiratory tract infections and those associated with failure to thrive or developmental problems, can be caused by conditions other than IEI.

The tests looking for IEI requested depend on the presenting symptoms and severity as well as pathogens identified. Sometimes the infecting organism will provide a clue as to where the expected immunodeficiency lies, which is incorporated in the ESID guidance. Infection with encapsulated organisms such as pneumococcus and meningococcus may indicate a complement disorder or hyposplenism. Infection with *Staphylococcus aureus* or *Aspergillus* may indicate chronic granulomatous disease.[50]

For a full explanation of the full diagnostic protocols, we refer to the excellent paper of De Vries and European Society for Immunodeficiencies (ESID) members.[49] Initial testing for immunodeficiency will typically include measurement of Immunoglobulin A (IgA), Immunoglobulin G (IgG) and Immunoglobulin M (IgM); vaccine responses to common immunisations such as PCV13, tetanus and *Haemophilus influenzae* type B (protocol 1 and 2); and a full blood count (all protocols) with further analysis of lymphocyte subsets. A basic lymphocyte subset panel should include B cells (CD19), NK cells (CD16/56) and T cells (CD3), including Helper (CD4) and Cytotoxic (CD8) T cells (Protocol 2). It is important to assess total number of cells as well as percentages, and a contemporaneous full blood count is needed to help interpret the absolute lymphocyte numbers. A full blood count will also identify neutropenia, and a blood film may identify Howell-Jolly bodies associated with hyposplenism (protocol 3). Subsequent investigations will depend on the results, (ongoing) symptoms and family history. It is important to consider secondary causes of immunodeficiency, including

HIV as well, as they will affect ongoing management of the patient.

Vaccine responses should be interpreted in light of the vaccination history, including the interval between vaccination and testing. Haemophilus B-directed antibodies tend to decline more rapidly without this being of significant concern. It is also helpful to send serotype-specific pneumococcal responses rather than a total pneumococcal response as the CYP may have responded well to only a few serotypes in the PCV13, which will give an overall falsely reassuring impression. Suboptimal vaccine responses should be boosted and then rechecked 6–8 weeks later. In children with recurrent infections, replacement of vaccine serotype pneumococcal strains with non-vaccine pneumococcal strains after vaccination can result in an initial increase of infections after PCV13 booster vaccination.[51]

Functional testing may be required in some cases, such as neutrophil oxidative burst to identify defective phagolysosome activity seen in chronic granulomatous disease. Complement function testing, such as CH100/AP100, will help identify disorders in this pathway and indicate further direction of testing. Sending samples to the lab promptly to prevent falsely abnormal results is essential, and any abnormal result requires repeat testing for confirmation. Further lymphocyte subset analysis, lymphocyte proliferation assays and cell marker testing are available when a more detailed examination or testing for a specific disease is required, such as testing for the CD11 cell marker in leukocyte adhesion disorder. These tests are usually organised by specialist teams and are only available in selected specialist immunology laboratories.

Finally, genetic testing is becoming increasingly useful in the diagnosis of IEI. Specific immunodeficiency gene panels and whole exome or genome sequencing with targeted analysis of genes associated with immunodeficiency is now available through specialist clinicians. While a generalist is unlikely to be requesting this test, they are likely to see increasing numbers of children for whom an underlying genetic defect has been identified. These tests can be requested for patients with complex phenotypes, severe disease and those that have a positive family history of recurrent infections or early death.

Genetic testing is helpful in a range of clinical scenarios and may change management as well as confirming the diagnosis. It is useful when standard immunological testing demonstrates an abnormality and narrows down the differential diagnosis, but does not confirm the final diagnosis. An example of this is SCID, where the lymphocyte subset immunophenotype can narrow down likely genetic defect to a small number.[52] However, in this situation, chemotherapy regimens for HSCT will differ if the patient has a genetic defect causing radiosensitive SCID.[53] Genetic testing often represents a straightforward route to diagnosing radiosensitivity disorders.

In situations where there are clear abnormalities in immunology testing with an unclear diagnosis, for example, immune dysregulation, the immunologist may proceed with genetic testing as the next line of diagnostics. Genetic testing may also be useful for family counselling where a diagnosis has been made with standard immunological testing. Identification of the mutation will allow the geneticist to offer screening to relevant family members. Parents who are carriers may also wish to evaluate their reproductive options if they plan further children.

Genetic testing is not affected by the clinical condition of the patient or medication. Therefore, it may be useful in those on large doses of immunosuppressant medications that will interfere with functional testing. DNA may also be stored from patients without a diagnosis who are in extremis. The immunologist may then offer testing to the family at an appropriate time, even after the patient has died.

Conclusion

The major challenge is not identifying which tests to do, but who they should be performed on. IEI are a rare group of diseases, but one where late diagnosis leads to poorer outcomes. Warning signs for IEI have been developed and remain a useful, though imperfect, screening tool for clinicians. The changing epidemiology of infection and social context of the patient should be considered when assessing for warning signs of IEI. Treatments for IEI continue to advance and are more effective when started early. Screening for IEI should feature in the management of every child or young person with severe, unusual or

recurrent infection. When in doubt a specialist in infectious diseases and immunology should be consulted to guide diagnostics and management.

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Marieke Emonts: Conceptualization; Resources; Supervision; Writing – review & editing.

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