The Approach to Children with Recurrent Infections

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ABSTRACT

Recurrent and chronic infections in children are one of the most common reasons for physicians' visits that make a diagnostic challenge to pediatricians. Although the majority of referred children with recurrent infections are normal, underlying causes of recurrent infection such as atopy, anatomical and functional defects, and primary or secondary immunodeficiency must be considered in evaluation of children with this complaint.

Although primary immunodeficiency diseases (PIDs) were originally felt to be rare, it has become clear that they are much more common than routinely appreciated. Early and accurate detection of PIDs in children is essential to institute early lifesaving care and optimized treatments.

Therefore in the approach to children with recurrent infections, careful medical history taking and physical examination with more attention to warning PIDs signs and symptoms are essential to distinguish those children with underlying PIDs from those who are normal or having other underlying disorders. If indicated, appropriate laboratory studies including simple screening and advanced tests must be performed.

Keywords: Approach; Diagnosis; Primary immunodeficiency diseases; Recurrent infections

INTRODUCTION

Recurrent and chronic infections in children are common reason for physicians’ visits, which make a diagnostic challenge to pediatricians.

Different risk factors and underlying disorders result in this problem. The main causes of recurrent and chronic infections are atopic disorders, anatomical and functional defects, secondary immunodeficiency, and primary immunodeficiency diseases (PIDs), which need to be considered in evaluation of children with history of recurrent infections.¹,²

Although PIDs were originally thought to be rare, they are much more common than previously estimated, while recurrent infections are the major manifestations of these hereditary disorders.³ Early
diagnosis of immunodeficient children is essential to institute early lifesaving care and optimized treatments; Therefore in the approach to children with recurrent infections, attention to medical history and physical examination considering warning signs and symptoms of PIDs are critical to differentiate those children with underlying disorders from healthy individuals. In the evaluation process, appropriate laboratory studies including simple screening and advanced tests must be performed if indicated.1,2

This article provides a guideline for approach to children with recurrent infections. Moreover, important warning signs and symptoms which suggest underlying PIDs and an appropriate laboratory studies are discussed.

Definition of Recurrent Infection
During the first 5 years of life, children even with a normal immune system can experience 6-8 respiratory tract infections per year particularly during the autumn and winter seasons.4-6 Day care centers attendance and exposed to smokers are common environmental risk factors, which may increase number of respiratory infections up to 10-12 episodes per year in children.4 Sometimes even up to 15 infections per year can still be within the normal range. Furthermore, it is difficult for pediatricians to count an accurate frequency of infections to consider the term of recurrent infection. In defining of recurrent infections, rather than number of infections, the nature and pattern of infections such as severity, long lasting of infection, resistant to treatment, unusual microorganism causing infection and unusual complications are important.

This definition will provide a more reliable guide to identify the child who needs further evaluation. For example, increased number of otitis media after the age of 2 years that is associated with mastoiditis or failure to thrive should raise the suspicion of an underlying immune disorder. However, it should be noted that sometimes a single infection with an unusual germ or pattern is enough to warrant physician to perform appropriate immunologic evaluations of the patient.

Major Causes of Recurrent Infections
Recurrent infections can be caused by different risk factors and underlying disorders including allergy, anatomical and functional abnormalities, and primary and secondary immune deficiencies. Occurrence of infections in one organ system suggests the existence of underlying diseases such as allergy, anatomical or functional abnormalities in the affected organ, while defects in immune system render patients susceptible to a variety of infections in different organs. However, most children with a history of recurrent infection are healthy. Young children in especial conditions can have up to 15 episodes of infection per year; even with a healthy immune system.7-9 Therefore it is important to distinguish these healthy children from children with underlying disorders. In our unpublished study, among 260 studied children with recurrent infection history, 123 children were healthy (47.3%), 81 patient had allergy (31.1%), 29 patients had anatomical and functional abnormalities (11.1%) and 27 patient were affected by primary immunodeficiency (10.5%) (Figure1). The main causes of recurrent infections are described in the following sections.

Allergy
Atopy affects 15-20% of children and causes chronic inflammation of the airways that facilitates the adherence of pathogens to the respiratory epithelium and development of respiratory infections.10,11 Allergy should be considered in all children with a history of recurrent infections and attention must be paid to abnormal seasonal patterns of infection and a family history of allergy or asthma in those children. Although distinguishing between sinusitis caused by allergic rhinitis/asthma and possible immunodeficiency is a difficult diagnostic challenge, documentation of bacterial infection with appropriate cultures is very helpful in these cases.

Anatomical and Functional Abnormalities
Abnormal lung anatomy may predispose children to recurrent respiratory tract infections; these associated anatomical defects include gastro-esophageal reflux, tracheobronchial foreign bodies, cystic fibrosis, immotile cilia disease, and congenital heart disease. Some or all of these conditions should be investigated in patients being evaluated for immunodeficiency. Gastro-esophageal reflux disorder (GERD) is the major cause of recurrent aspiration in children. GERD is manifested as epigastric discomfort, regurgitation, and vomiting contributing to respiratory tract infections by triggering inflammation in these upper passages. GERD may also cause asthma symptoms and aspiration pneumonia which facilitate the opportunity of higher rate of infections.12
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An estimated incidence of GERD in asthmatic patients may range from 34% to 89%.\textsuperscript{13,14} Bronchoconstriction induced by reflux usually occurs at night when the esophageal acid clearance is delayed. Rhinosinusitis, stridor, and croup may manifest secondary to inflammatory changes and swelling within the airway exposed to gastric reflux.\textsuperscript{15,16}

Tracheobronchial foreign bodies are most commonly aspirated during the toddler years when children are ambulatory and may be out of parental view. It has been reported that up to 50% of patients with foreign body aspirations do not have a contributing history available. The clinical presentation of acute airway obstruction associated with a foreign body aspiration is a brief period of choking, gagging, or wheezing. The resulting symptoms may mimic intermittent tracheobronchitis, recurrent pneumonia, or asthma.\textsuperscript{17}

Cystic fibrosis is an inherited disease of the glands that causes severe lung damage, nutritional deficiencies and pancreatic insufficiency. Affected children present with signs and symptoms in respiratory system (persistent cough, wheezing, repeated sinus and lung infections) and/or the digestive system (greasy stools, poor weight gain or growth, and distended abdomen due to constipation).\textsuperscript{18,19} The lungs are usually colonized with \textit{Staphylococcus aureus} and \textit{Pseudomonas aeruginosa}. In these cases progressive lung involvement is manifested by chronic productive cough, recurrent pulmonary infections, lung abscesses, bronchiectasis, cysts, cor pulmonale and acute or chronic respiratory failure.

**Secondary Immunodeficiencies**

Immunodeficiency may be overture for cause of recurrent infections, secondary or acquired factors are the most probable reasons. Secondary immunodeficiency diseases leading recurrent to infections affect 200,000-1,000,000 people in the US. Secondary immunodeficiencies occur when the immune system damage is caused by an environmental factor such as malnutrition, infectious diseases (particularly Human immunodeficiency virus and other viral diseases, such as congenital rubella, Epstein Barr virus and cytomegalovirus infections), immunosuppressive therapies, radiation, malignancies and other infiltrative diseases (such as leukemia, lymphomas, multiple myeloma and metastatic cancer), protein-losing disorders, and trauma.\textsuperscript{20,21} Protein-calorie malnutrition and deficiencies of vitamins and trace elements, particularly vitamin A, zinc and

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**Figure 1.** Study of 260 children with history of recurrent infection; 123 children were healthy, 81 patients had Allergy, 29 patients had anatomical and functional abnormalities and 27 patients were affected with primary immunodeficiency (unpublished data).
selenium are the commonest cause of secondary immune deficiencies.22 Loss of immunoglobulin also can result from a number of conditions including nephrotic syndrome, protein-losing enteropathy and intestinal lymphangiectasia.20

The following causes of secondary immunodeficiency are ones for which there are not any prevalence information: Burns, sickle cell disease, asplenia, and uremia. Different types of primary and secondary immunodeficiency were classified based on the known origins and mechanisms of defects.5 Therefore this classification is useful for acquaintance and approach to the patient who is suspected to have defect on immune system.

Primary Immunodeficiencies

PIDs are challenging condition in primary care settings where clinicians often encounter patients with a history of recurrent infection. Immunodeficiency should be suspected when recurrent infections are complicated, multi-located, and resistant to treatment or caused by unusual organisms. PIDs render an affected individual susceptible to a variety of infectious diseases. Early diagnosis and adequate therapy are the keys for survival and a better quality of life in patients with PIDs, while delay in diagnosis and/or inadequate management may lead to permanent organ damage.23

The overall frequency of PIDs has been estimated about 1:10,000–1:200,000 individuals.24 Up to now, more than 180 PIDs have been phenotypically described; single-gene defects have been identified in several PIDs.25

Unfortunately, failure to recognize these conditions is still a major problem for clinicians around the world and diagnosis of patients with PIDs is associated with a considerable delay.26 One major problem is that general practitioners and pediatricians especially in developing countries are not well aware of PIDs.27-32 Since the general practitioners and pediatricians are most often the first physicians who visit a patient with immunodeficiency, they should be familiar with these important disorders. With advances in diagnosis and treatment, these disorders have been better understood and more successfully treated, yet their prognosis depends on early recognition of the disorder and initiation of the appropriate management. Infections in immunodeficient patients usually occur with pathogens that are prevalent in the community but are of unusual severity, frequency, and duration and may tend to respond poorly to treatment. Severe immunodeficiency is also associated with infections caused by low-grade or opportunistic organisms that are rarely pathogenic for immunocompetent individuals.33-37 Attention should be paid to warning signs and symptoms in taking medical history and physical examination to distinguish patients with PIDs from those with intact immune system. It should be mentioned that in addition to the nature of infection, other factors such as age of onset of disease, site of infection, the type of microorganisms involved, and family history are helpful in the diagnosis of PIDs. The following steps can be of great use in the initial assessment of suspected PID patient:

Consider the Age of the Patient

Based on type of PIDs, the onset of disease varies. Therefore, the age of patient at the onset of disease is helpful in the differential diagnosis of PIDs. Some of more severe PIDs present during neonatal period. These include severe combined immunodeficiency disease (SCID), Omenn syndrome, leukocyte adhesion deficiency (LAD) type I, IL-1 receptor-associated kinase-4 (IRAK4) deficiency, DiGeorge syndrome, and severe congenital neutropenia (SCN).

In the neonatal period, existent of lymphopenia is suggestive of SCID. Also, erythroderma associated with massive lymphadenopathy and hepatosplenomegaly during infancy is highly suggestive of Omenn syndrome. Delayed separation of the umbilical cord beyond 6–8 weeks of age in neonates, omphalitis and poor wound healing are suggestive of LAD type I and IRAK4. Hypocalcaemia during infancy which is associated with facial dysmorphism and cardiac defects suggest DiGeorge syndrome.

Severe forms of B-cell deficiencies such as X-linked agammaglobulinemia (XLA) present during 6 months to 5 years.38,39 Presentation of antibody deficiency occurs beyond 7-9 months, once the acquired maternal IgG decreases below the protective serum levels.40,41 Defects in phagocyte function, such as chronic granulomatous disease (CGD), may present in infancy, or later.42,43 After 5 years of age, antibody deficiencies such as common variable immunodeficiency (CVID) and specific antibody deficiency are more frequent.44,45
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Pay Attention to the Pattern of Infection and the Affected Organ or System

Attention to the site of infections and their complications are very helpful, when physicians take past medical history. Occurrence of infection in one organ suggests existence of underlying diseases such as allergy, and anatomical or functional abnormalities in affected organ, while presence of infections in different organ sites indicates systemic immune dysfunction. For example, isolated recurrent respiratory infections could be due to anatomical or functional abnormalities in respiratory tract including cystic fibrosis, GERD, oropharyngeal aspiration, mucociliary dysfunction, and allergy; while children with PIDs are susceptible to multi-organ involved infections, such as upper and lower respiratory tract (otitis media, mastoiditis, sinusitis, and pneumonia), gastrointestinal tract (chronic diarrhea and enteropathy), central nervous system (meningitis and encephalitis), skin (cellulites, impetigo and recurrent abscesses), and septicemia.

In addition, the sites of infection may provide insights into the type of immunodeficiency. For example, patients with recurrent mucosal infections in respiratory and gastrointestinal tract may suggest primary antibody deficiency (PAD) or a lack of opsonization of the complement components. In contrast, recurrent stomatitis or gingivitis, and skin infections are observed more frequently in phagocytic defects, including neutropenia. 46-48

Take a Detailed Family History

Among all described PID, autosomal recessive (AR) is the most common pattern of inheritance, because of the high frequency of parental consanguinity in patients with PIDs. High rate of parental consanguinity in Iran and other Middle East countries makes PIDs (especially autosomal recessive forms) more prevalent in this region than those in the Western countries. 63-66

Indeed, many defective genes that underlie PIDs were first described in the patients originated from this region.

Therefore in evaluation of children with suspected PIDs, taking a careful family history is important and helpful. History of recurrent infection in male relatives or unexplained deaths due to possible infectious causes in infancy or early childhood on the maternal side of the family raises the possibility of X-linked immunodeficiency. Death due to severe infection during infancy in the relatives of suspected PIDs patients is highly suggestive of SCID and should be consider seriously.

Perform a Systematic Physical Assessment

Although a normal examination does not rule out the diagnosis of PID, it should be considered as an important step in the evaluation of children with a history of recurrent infections since significant abnormal findings in physical examination can raise the suspicion of underlying immunodeficiency (Table 1). In the examination, the initial attention should be paid to the general appearance of the patient. Patients with immunodeficiency may not appear ill; however, patients with more severe form of PID are chronically ill and usually present with failure to thrive. In children with a history of recurrent infection who are suspected of immunodeficiency, the physician should be able to answer the following questions after performing a careful physical examination:

a. Does the Child Appear Normal?

Some of facial abnormalities are characteristic for especial immunodeficiency; therefore the association of abnormal faces with recurrent infection could raise the suspicion of PID. 4

In DiGeorge syndrome, indicator facial abnormalities include hypo plastic mandible, high-arched palate, shortened philtrum, small mouth, and low-set posteriorly rotated ears.

Also, abnormal hair in the presence of short-limbed dwarfism in children with recurrent infection is highly suggestive of cartilage-hair hypoplasia. 67 Ectodermal dysplasia, conical teeth, fine sparse hair, and frontal bossing are characteristic features of children with defects in NF-κB regulation (NEMO). 68

Also, abnormal hair in the presence of short-limbed dwarfism in children with recurrent infection is highly suggestive of cartilage-hair hypoplasia. 67 Ectodermal dysplasia, conical teeth, fine sparse hair, and frontal bossing are characteristic features of children with defects in NF-κB regulation (NEMO). 68 Characteristic facies and microcephaly in association with growth retardation, and cognitive impairment are seen in patients with Nijmegen breakage syndrome (NBS), DNA ligase I and IV deficiencies. 69-71
Table 1. Important considerations on physical exam of patients with recurrent infections

<table>
<thead>
<tr>
<th>Physical points</th>
<th>Immunodeficiency</th>
</tr>
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<tbody>
<tr>
<td><strong>General feature</strong></td>
<td></td>
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<tr>
<td>Failure to thrive</td>
<td>T-cell defects</td>
</tr>
<tr>
<td>Dysmorphic Face</td>
<td>DiGeorge anomaly</td>
</tr>
<tr>
<td>Dysmorphic Extremities</td>
<td>Cartilage-hair hypoplasia</td>
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<tr>
<td>Ectodermal dysplasia</td>
<td>NEMO</td>
</tr>
<tr>
<td><strong>Skin/oral mucosa</strong></td>
<td></td>
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<tr>
<td>Infection: Candidiasis</td>
<td>T-cell defect</td>
</tr>
<tr>
<td>Eczema</td>
<td>Hyper IgE syndrome, Wiskott–Aldrich syndrome</td>
</tr>
<tr>
<td>Petechiae</td>
<td>Wiskott–Aldrich syndrome</td>
</tr>
<tr>
<td><strong>Conjunctivae</strong></td>
<td></td>
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<tr>
<td>Infection</td>
<td>B-cell defects</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>Ataxia telangiectasia</td>
</tr>
<tr>
<td><strong>Tympanic membrane of the ear</strong></td>
<td></td>
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<tr>
<td>Scarring</td>
<td>B-cell defects</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>DiGeorge anomaly</td>
</tr>
<tr>
<td><strong>Lymphoid tissues</strong></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>X-linked agammaglobulinemia, CD40L deficiency, CD40 deficiency, Severe combined immunodeficiency</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>Common variable immunodeficiency, AID deficiency, UNG deficiency</td>
</tr>
<tr>
<td><strong>Chest exam</strong></td>
<td></td>
</tr>
<tr>
<td>Bronchiectasis (rales, rhonchi, digital clubbing)</td>
<td>B-cell defects</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
</tr>
<tr>
<td>Lupus-like disease</td>
<td>Complement defect</td>
</tr>
<tr>
<td>Infectious arthritis</td>
<td>X-linked agammaglobulinemia</td>
</tr>
<tr>
<td>Spondyloepiphyseal dysplasia</td>
<td>Cartilage hair syndrome</td>
</tr>
</tbody>
</table>

Hypertelorism, epicanthal folds, and flat nasal bridge and developmental delay occur in approximately 70% of patients with immunodeficiency centromeric instability facial dysmorphism syndrome (ICF). Coarse faces and/or asymmetric features, delayed shedding of primary teeth, hyper extensible joints, and scoliosis are seen in patients with autosomal dominant form of HIES. Coarse facial appearance with puffy eyelids, brachycephaly, broad nasal tip, long upper lip, an everted lower lip, low hair line, and a short webbed neck have been reported in patients with LAD type II.

Early onset of recurrent infections in the first 6 months of life is frequently accompanied by growth failure and delayed maturation especially in T-cell impairment diseases. In all children with failure to thrive and recurrent infections especially with chronic diarrhea, immunodeficiency should also be suspected.

b. **Is There Any Skin or Mucosal Defect?**

Some of skin and oral mucosal lesions can raise the suspicion of different types of immunodeficiency disorders. For example, perianal ulceration, poor wound healing, severe gingivo-stomatitis, dental erosions and skin infections in the newborn period associated with leukocytosis is suggestive of LAD. Chronic periodontitis is also commonly seen in patients with neutrophil abnormalities.

Bacterial skin and deep tissue infections are also common findings in congenital neutropenic disorders. Primary antibody deficiency may be presented by Pyoderma. Skin and mucosal candidiasis is highly suggestive of disorders such as SCID, chronic mucocutaneous candidiasis or CARD9 deficiency, autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED), immunodysregulation polyendocrinopathy enteropathy or X-linked (IPEX) and even HIES. Occurrence of...
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lupus-like malar rash in the absences or low-titer of antinuclear antibodies (ANA) strongly suggest defect in the early components of the classical complement pathway. Eczema is seen in some PIDs including: Wiskott–Aldrich syndrome (WAS) (associated with petechiae), HIES (associated with staphylococcal pneumatoceles) and CGD (associated with thoracic or abdominal abscesses).

Telangiectasia of the skin is a part of clinical picture of patients with ataxia telangiectasia (AT) that characterized with cerebellar ataxia and recurrent respiratory infections. Telangiectasia of the skin is a part of clinical picture of patients with ataxia telangiectasia (AT) that characterized with cerebellar ataxia and recurrent respiratory infections.

Oculocutaneous hypopigmentation can be observed in children with Chédiak–Higashi syndrome, Griscelli syndrome type II, Hermansky–Pudlak syndrome type II, and p14 deficiencies.

c. Does the Patient Suffer from Complications of Ear, Nose or Throat?

Ear, nose, and throat (ENT) are common sites of infection in patients with PID. Sino-pulmonary infections (otitis media, sinusitis, bronchitis, and pneumonia) are the most frequent clinical manifestations of patients with PID, and the increased frequency of these infections can alert a practitioner to consider immunodeficiency. In children older than 6 months, recurrent bacterial ENT infections and its complications particularly with polysaccharide organisms, may suggest humoral immunodeficiency.

In our previous study, evaluation of 103 patients with history of recurrent or chronic ENT infections, showed that 17 (16.5%) patients had defect in antibody-mediated immunity. In addition, several studies have showed that a high proportion of patients, especially children with recurrent infections, have abnormalities in the humoral immune system. General practitioners, family physicians, and ENT specialists should be alert for any underlying immunodeficiencies in patients with recurrent or chronic ENT infections who refractory to the conventional treatments.

Complement deficiency may present with later sinopulmonary infection in childhood.

d. Is There Any Problem in the Respiratory and/or Cardiovascular System?

Patients with recurrent respiratory infections should be carefully evaluated for a possible underlying disorder. Cystic fibrosis, anatomical disorder and foreign body aspiration are some common reasons for persistent infectious involvement of respiratory system. Respiratory problems such as wheeze, productive cough, and recurrent infections are the most common presenting features of PIDs.

Children presenting with interstitial pneumonia caused by Pneumocystis jiroveci should be considered to have HIV infection, SCID, CD40 ligand deficiency or other combined immunodeficiencies. Fungal pneumonias particularly in the case of fulminant pneumonitis is suggestive of CGD. Staphylococcal lung infection associated with pneumatocele formation and eczema should raise the suspicion of HIES. Recurrent lower respiratory infections may be caused by neutrophil defects such as cyclic neutopenia, SCN or CGD.

The most common complications of pneumonia include pleurisy, bronchiectatic changes, and empyema. Therefore, examination of the lung for detection of related signs of these complications is important in evaluation of children with a history of recurrent respiratory infection. The presence of bronchiectasis and digital clubbing is an important indicator of significant lung disease in PID patients necessitating a careful workup.

In the study on 40 bronchiectatic patients, 37.5% were diagnosed to have defects in antibody mediated immunity including 5 (12.5%) patients with immunoglobulin class deficiency (two with CVID and three with IgA deficiency), 3 (7.5%) with IgG subclass deficiency, and 7 (17.5%) patients had specific antibody deficiency (SAD) against polysaccharide antigens.

Respiratory insufficiency and cor pulmonale as a result of end-stage lung disease are the major causes of morbidity in these PAD patients. Such complications is highly due to the diagnostic delay in spite of the existence of chronic respiratory symptoms and morbidity.

Physical findings of pulmonary hypertension and right heart failure presenting with elevated jugular vein pressure may be noted in PID patients with chronic lung disease resulting from repeated infections in the immune deficient host.

e. Is There Any Gastrointestinal Complication?

Gastrointestinal complication in patients with PIDs includes infectious diarrhea, villous atrophy, atrophic
gastritis, nodular lymphoid hyperplasia, inflammatory bowel disease (IBD), and other enteropathies. Diarrhea is usually more severe and persistent in PIDs patients leading to malabsorption.

Infectious diarrhea resulting in malabsorption and failure to thrive is a characteristic of T cell defects like HIV infection or SCID. Cellular immunodeficiencies can also be presented by persistent enteritis caused by Cryptosporidium parvum. Older males with sclerosing cholangitis may suffer from Cryptosporidium parvum infection in a background of CD40 ligand deficiency.

Schwachman–Diamond syndrome should be ruled out in patients with co-occurrence of neutropenia and exocrine pancreatic insufficiency.

Staphylococcus aureus and fungal pathogens can form abscess in various organs particularly liver in CGD patients. Pyloric obstruction due to granulomatous lesions can be a presenting feature of the CGD patients. The coincidence of eczema, endocrinopathy and persistent diarrhea in a male child should raise the suspicion toward IPEX syndrome.

f. Is There Any Neurodevelopmental Abnormality?

Neurodevelopmental disorders and delay may be associated with special PIDs. Late walking, broad-based gait and stumbling with elevated serum alpha fetoprotein in the first or second year of life which progress to late onset recurrent infections are suggestive of AT. Ataxia in addition to immune dysfunction may present in Griscelli syndrome, which diverse with AT by seizures, oculomotor and reflex abnormalities, and absence of telangiectasia. Patients affected by combined immunodeficiency or antibody defects may show spastic diplegia with dysarthria especially in purine nucleotide phosphorylase-deficient SCID. Flaccid paralysis after live poliomyelitis vaccination has been observed in cellular and humoral deficiencies.

Cognitive impairment, late neurological deterioration, nystagmus, central and peripheral neuropathies are the neurological findings in Chediak-Higashi syndrome.

Enteroviral meningo-encephalitis is highly suggestive for antibody deficiency, particularly in XLA.

g. Is There Any Abnormality in the Musculoskeletal System?

Arthralgia and monoarticular/oligoarticular arthritis in children with XLA, SCID, and AT are at increased risk of lymphoid malignancies. Also, patients with either CGD or CVID may have enlarged lymphoid tissue and lymphoid hyperplasia.

Characteristic skeletal findings in HIES are craniosynostosis, hyperextensible joints, hypodense and fragile bones leading to pathological fractures, delayed development, and scoliosis. Other immunodeficient patients suffering from cartilage hair hypoplasia syndrome, Schwachman–Diamond syndrome and adenosine deaminase deficiency also may have skeletal abnormalities.

h. Is There Any Abnormal Finding in the Lymphoreticular System?

The examination of the lymphatic system for the presence, absence or hyperplasia of lymphoid tissue is an important aspect of the physical examination in a patient suspected of immune deficiency.

Tonsillar tissue, adenoid and cervical lymph nodes are typically very small or absent in XLA, SCID, and hyper-IgM syndrome due to mutation in CD40 ligand or CD40 genes. In contrast, individual with hyper-IgM syndrome due to mutations of the Activation-Induced Cytidine Deaminase (AID) and uracil-DNA glycosylases (UDG) genes develop lymphoid hyperplasia. Also, patients with either CGD or CVID may have enlarged lymphoid tissue and even hepatosplenomegaly. Abscesses of the lymph nodes suggest a phagocyte defect such as in CGD.

Lymphoreticular malignancies are more observed in PID patients comparing to normal population. Lymphoma in association with EBV infection has been reported in XLP and WAS. Patients with defects of DNA repairing such as Nijmegen breakage syndrome and AT are at increased risk of lymphoid malignancies. Patients with autoimmune lymphoproliferative syndrome may suffer from Non-Hodgkin’s lymphoma. Lymphoreticular malignancy
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is also reported in some CVID patients. Cryptosporidial infection associated hepatoma is described in CD40 ligand deficiency.  

Mylodysplasia should raise suspicion of XLP and defects of DNA repairing like Nijmegen breakage syndrome. Patients affected by autoimmune lymphoproliferative syndrome are usually presented with hepatosplenomegaly and lymphadenopathy and may also suffer from cytopenia in association with human herpes virus infection.

i. Is There Any Abnormal Finding in the Hematological Investigations?

Although complete blood count (CBC) is a simple routine test in the primary evaluation of many patients, its results can be very beneficial alongside an accurate history taking and clinical examination. Children with recurrent infection who have shown lymphopenia in their CBC should be reinvestigated. The presence of lymphopenia in an infant at two or more separate times should raise the suspicion of SCID. However, the diagnosis of SCID cannot be excluded by normal lymphocyte count. Erythrophagocytosis, especially if is recurrent, can indicate the possibility of an underlying PID such as XLP, Griscelli syndrome, Chediak Higashi syndrome and familial hemophagocytic lymphohistiocytic syndromes. Low neutrophil count can be caused by some PIDs. Recurrent neutropenia every 3 to 4 weeks in association with fever, infection and mouth ulcers is characteristic of cyclic neutropenia. Patients affected by XLA and CD40 ligand deficiency may also have neutropenia. Autoimmune cytopenia can be the finding of some PIDs. In all male patients with thrombocytopenia, WAS should be rule out. Immune thrombocytopenia and hemolytic anemia have been reported in 8% of CVID patients. Autoimmune cytopenia also can be a presenting feature of DiGeorge and IPEX syndromes.

j. Is There Any Important Finding in the Microbiological Investigations?

In the evaluation of children with a history of recurrent infection, it is critical to document the type of microorganisms and its response to treatment carefully (Table 2). Information about the type of responsible pathogen for the infectious complication can raise suspicion of probability and the type of immunodeficiency. Although individually infection with encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae type b usually suggests an antibody or complement deficiency, the occurrence of these infections together with viral, fungal, mycobacterial, Pneumocystis jiroveci, and cryptosporidium strongly suggest a T-cell deficiency. Infection caused by disseminated mycobacterial infections is suggestive of a T-cell defect (e.g., SCID) or a group of disorders, named Mendelian susceptibility to mycobacterial diseases (MSMD). A history of skin infections with Staphylococcus aureus, lymphadenitis or recurrent abscesses caused by low-virulence gram-negative organisms and infection with aspergillus or other fungal organisms suggest a phagocytic dysfunction (e.g., CGD). An aspergilloma in a pneumatocele is suggestive of hyper IgE syndrome (HIES). Development of a fulminant infectious mononucleosis after infection with Epstein-Barr virus offers X-linked lymphoproliferative disease (XLP).

Congenital immune deficiencies affecting the late complement components (C5, C6, C7, and C8), also have hallmark presentation by Neisseria organisms infection. However, infection caused by atypical mycobacterium which is associated with non-typhoid Salmonella or severe herpes virus infection probably results from a defect in IFN-γ/IL-12 cytokine pathway. Herpes simplex encephalitis suggests a defect in Toll-like receptor 3.

Which Patient Needs to be Evaluated for Immunodeficiency?

Since infection is a common finding in many children, it is difficult to decide who needs further immunologic evaluation. High clinical suspicion is the key to on-time diagnosis and proper management until efficient screening is established for immunodeficiency disorders. Medical history, physical examination and family history should be also considered jointly with the pattern of infections in order to gain a better understanding of the patients’ probable underlying condition. Based on recommendation of European Society for Immunodeficiencies (ESID) the most common warning signs for children and adults are shown in table 3. While helpful algorithms have been established for the use of specialists and non-specialists alike, its most vital point is to consider the probability of an underlying immunodeficiency condition.
Table 2. Pathogens and their probable associated underlying Immune deficiencies (adapted from reference number (160))

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Deficiency</th>
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<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Mycoplasma/Ureaplasma</td>
<td>Antibody deficiencies</td>
</tr>
<tr>
<td>Neisseria meningitides</td>
<td>Deficiencies of alternative or terminal complement pathways components</td>
</tr>
<tr>
<td>Nocardiia sp</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Salmonella sp</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td><em>Serratia marcesens</em></td>
<td>Macrophage activation disorders</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (severe)</td>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td><em>Streptococcal sepsis</em></td>
<td>IRAK4 deficiency</td>
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<td></td>
<td>NEMO deficiency</td>
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<td>MyD88 deficiency</td>
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<td>Asplenia</td>
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<td>Complement deficiencies</td>
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<td>Antibody deficiencies</td>
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<td>Macrophage activation disorders</td>
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<td>Chronic granulomatous disease</td>
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<td><strong>Atypical mycobacteria</strong></td>
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<td></td>
<td>Macrophage activation disorders</td>
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<td></td>
<td>Chronic granulomatous disease</td>
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<tr>
<td><strong>Viruses</strong></td>
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<tr>
<td>Cytomegalovirus(CMV)/</td>
<td>X-lined lymphoproliferative disease</td>
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<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Familial hemophagocytic lymphohistiocytosis</td>
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<td>Serious T cell deficiencies</td>
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<tr>
<td>Herpes simplex virus (HSV)</td>
<td>UNC-93B and TLR3 deficiencies</td>
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<tr>
<td></td>
<td>(STAT1, Caspase 8, and NEMO deficiencies)</td>
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<tr>
<td>Influenza (severe)</td>
<td>TLR3 deficiency</td>
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<td></td>
<td>Ig CSR deficiencies</td>
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<td></td>
<td>Hyper IgE syndrome</td>
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<tr>
<td>HHV8</td>
<td>Severe T cell deficiencies</td>
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<td></td>
<td>Wiskott–Aldrich syndrome</td>
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<tr>
<td>Varicella</td>
<td>Most significant T and NK cell deficiencies</td>
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<tr>
<td>Papilloma virus</td>
<td>Warts, hypogammaglobulinemia</td>
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<td>infections, myelokathexis syndrome</td>
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<td></td>
<td>Epidermodysplasia verruciforms</td>
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<td>Severe infection with common</td>
<td>Severe combined immunodeficiency</td>
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<td>respiratory viruses</td>
<td>Other serious T cell deficiencies</td>
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<td><strong>Fungi</strong></td>
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<td>Candida</td>
<td>Chronic granulomatous disease</td>
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<td></td>
<td>Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy</td>
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<td>Histoplasmosis</td>
<td>Macrophage activation deficiencies</td>
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<tr>
<td>Low pathogenicity fungi</td>
<td>Chronic granulomatous disease</td>
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<tr>
<td><strong>Parasite</strong></td>
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<td>Cryptosporidida</td>
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<td>Giardia</td>
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<td>Pneumocystis jiroveci</td>
<td>Severe T cell deficiencies</td>
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<td>NEMO deficiency</td>
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<tr>
<td>Toxoplasmosis Severe T cell deficiencies</td>
<td>Ig CSR deficiencies</td>
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</table>
Table 3. Warning signs for children and adults with the primary immunodeficiency diseases

A. 10 warning signs of PID for children
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 pneumonias within 1 year.
5) Failure of an infant to gain weight or grow normally.
6) Recurrent, deep skin or organ abscesses.
7) Persistent thrush in mouth or fungal infection on skin.
8) Need for intravenous antibiotics to clear infections.
9) Two or more deep-seated infections including sepsis.
10) A family history of PID.

B. 6 warning signs of PID for adults
1) Four or more infections requiring antibiotics within one year (otitis, bronchitis, sinusitis, pneumonia)
2) Recurring infections or infection requiring prolonged antibiotic therapy
3) Two or more severe bacterial infections (osteomyelitis, meningitis, sepsis, cellulitis)
4) Two or more radiologically proven pneumonia within 3 years
5) Infection with unusual localization or unusual pathogen
6) PID in the family

Figure 2. Diagnostic testing algorithm for recurrent infections
Table 4. Initial laboratory screening for immunodeficiencies

**Screening tests of B cells Deficiency**
- CBC including granulocytes with differential, lymphocytes, platelets (with size if available) and hemoglobin
- Quantitative serum immunoglobulins—IgG, IgA, IgM +/− IgE
- Lymphocyte subset analysis by flow cytometry for B cells (CD19+, CD20+)
- Specific antibody production to vaccine (Tetanus/diphtheria, Pneumococcal and meningococcal, *Haemophilus influenzae B*)
- Isohemagglutinins (IgM antibodies to A and B blood group antigens)

**Screening tests of T cells Deficiency**
- CBC including granulocytes with differential, lymphocytes, platelets (with size if available) and hemoglobin
- Chest x-ray for verification of thymus shadow in newborns
- Lymphocyte subset analysis by flow cytometry for quantitation of total T cells (CD3+, CD2+) and T cell subsets (CD4+, CD8+)
- Delayed-type hypersensitivity skin tests (Mumps, Candida, Tetanus and fungal antigens only in older children and adults)

**Other screening tests**
- Evaluation of CD16+, CD56+ lymphocyte subsets for screening of NK cells deficiency
- Evaluation of HLA-DR for screening of MHC class II deficiency
- Evaluation of Dihydrorhodamine for screening of CGD
- Evaluation of CH50 and AP50 for screening of complement deficiency
- Sweat test to exclude cystic fibrosis
- Nasal mucosa biopsy to rule out immotile cilia syndrome

CBC= complete blood count; CGD= chronic granulomatous disease; HLA= human leukocyte antigen ; MHC= major histocompatibility complex.

Table 5. Advanced and comprehensive laboratory evaluation for immunodeficiencies

**Advanced Tests of B Cells Deficiency**
- IgG subclasses (IgG1, IgG2, IgG3 and IgG4 )
- In vitro IgG synthesis by stimulation of PBL or purified B cells cultured (in the presence of anti-CD40 and IL-4, lymphokines)
- Biopsies from rectal mucosa and lymph nodes
- Molecular and mutation analysis (e.g., Btk, µ heavy chain)

**Advanced Tests of T Cells Deficiency**
- In vitro proliferation of T-lymphocytes to mitogens (PHA, ConA), allogeneic cells (MLC), and specific antigens (candida, tetanus toxoid)
- Production of cytokines by activated T-lymphocytes
- Expression of activation markers (e.g., CD40L, CD69) and lymphokine receptors (e.g., IL-2Rγc, IFN-γR) after mitogenic stimulation
- Enumeration of MHC-I and MHC-II expressing lymphocytes
- Enzyme assays (ADA, PNP)
- Biopsies from skin, lymph node, thymus
- Lymphocyte-mediated cytotoxicity—NK and ADCC activity
- Signal transduction studies
- Chromosome analysis (probe for 22q11)
- Molecular and mutation analysis (e.g., CD40L, γc chain, Jak3, ZAP-70)

**Advanced Tests of Phagocytic System Deficiency**
- Absolute neutrophil count (serially to rule out cyclic neutropenia)
Approach to the Children with Recurrent Infections

WBC turnover
Anti-neutrophil antibody
Biopsy from bone marrow
Assessment of chemotaxis, adhesion in vivo and in vitro
CD11/CD18 assessment by flow cytometry
NBT slide test; metabolic burst by flow cytometry
Chemiluminescence
Bacterial assays
Enzyme assays (MPO, G6PD, Glutathione peroxidase, NADPH oxidase)
Mutation analysis (e.g., gp91phox; p22phox; p47phox; p67phox; β integrin)

Advanced Tests of Complement Deficiencies
Analysis of quantity and function of C components
Chemotactic activity of complement split products (C3a, C5a)

Laboratory Investigations (Figure 2)

Choosing the proper immunological test in the primary (Table 4) and advanced (Table 5) investigations should be decided regarding medical history, family history and physical examination. Therefore, the proper investigation can be chosen by using the diagnostic algorithm.148

In evaluation of humoral immunity, qualitative (immunoglobulins and subclass serum levels) and quantitative (response to vaccination against protein and polysaccharides antigens) surveys should be performed.141,149 Furthermore qualitative (lymphocyte proliferation after stimulation with specific antigen or mitogen) and quantitative (flow cytometry of special CD markers) evaluation is critical issues in the assessment of cellular immune system.150

However, additional investigations such as measurement of recent thymic emigrants, the measurement of cell surface markers such as CD40 ligand, class-switched memory B lymphocytes, and lymphocyte receptor spectratyping may be required. Genetic studies are also available in the diagnostic setting of many hereditary disorders that can be also used to evaluate family members of the patient.

In conclusion, it is recommended to consider any individual with the presentation of recurrent and chronic infections as immunodeficient. Instead of searching for reasons to evaluate a child further, the physicians should find enough reasons not to use more advanced investigations.

PRACTICAL QUESTIONS

Q1. Which one of the following is a reason for susceptibility to infection in children with an underlying non-immune chronic disease?

A. Cardiovascular disorders
B. Impaired clearance of secretions
C. Barrier failure
D. Chronic kidney disease
E. All of the above

Answer: The correct answer is E:

Children affected by chronic disorders are more prone to infections. It is reported that individuals with chronic diseases such as cardiovascular defects, impaired clearance of secretions, barrier failure, and those who are infected by resistant organism have a less protective immune system.151 Patients with chronic kidney disease are also reported to experience more frequent and severe episodes of infection. In addition, they may show an impaired response against pneumococcal capsular polysaccharide vaccination.152 Foreign bodies can also provide colonization site for some organisms. Moreover, those who have a foreign component as a therapeutic devise such as artificial valves and shunts or need CV lines are at increased risk for infections. Although the foreign body in these patients is a common site of infection, they may also be affected by an underlying disease which resulted in the use of these procedures.151
Q2. All following features should lead to suspicion of an immunodeficiency, except:
A. A history of hospitalization due to an episode of pneumonia
B. Recurrent abscesses at the same site
C. Failure to thrive
D. Complications from a live vaccine
E. Impaired response to vaccination

Answer: The correct answer is A:
Children who experience at least two episodes of severe pneumonias or sinus infections should be evaluated for the probability of an immunodeficiency disorder. Recurrent abscesses at the same site, failure to thrive, and autoimmunity without a well-known etiology should also raise suspicion of such disorders. Impaired response against properly administrated vaccines and complications due to their administration especially those who contain live viruses are highly suggestive of immunodeficiency.151,153,154

Q3. Certain immunodeficiencies commonly present with special infections. Which one of "signature" organisms is related to type of immunodeficiencies sinisterly?
A. Pneumocystis jiroveci pneumonia in SCID
B. Pseudomonas sepsis in neutropenia.
C. Aspergillus abscesses in HIGM
D. Enteroviral meningoencephalitis in XLA
E. Staphylococcal lung cysts in hyperimmunoglobulin E syndrome

Answer: The correct answer is C:
Patients with an underlying immunodeficiency are more prone to infection by specific pathogens. Pneumonia caused by *Pneumocystis jiroveci* (carinii) is a common finding in primary or secondary T cell immunodeficiencies including severe combined immune deficiency (SCID), HIV or those who receive immunosuppressive agents.155
Patients who are affected by neutropenia are at increased risk of pseudomonas infections. However, this increase in susceptibility is not reported in HIGM patients. Chronic granulomatous disease (CGD) patients may experience soft tissue infections or abscesses as a result of aspergillus infections.156
Although XLA patients are more prone to enteroviral meningoencephalitis, the use of IVIG is reported to be beneficial in the prevention of this condition.157 Individuals with hyperimmunoglobulin E syndrome may suffer from recurrent infections such as pneumonia, lung cysts, abscesses, and skin infections as a result of staphylococcus.158

Q4. Which following options can be evaluated for screening of suspected cases to B cell abnormality?
A. CBC, serum immunoglobulins, CD19+, CD20+, Specific antibody production
B. CBC, serum immunoglobulins, Chest x-ray, CD3+, CD2+, Delayed-type hypersensitivity skin tests
C. CBC, serum immunoglobulins, MHC class II, CD16+, CD56+, Isohemagglutinin titers
D. CBC, serum immunoglobulins, CD19+, CD20+, IgG subclasses
E. CBC, serum immunoglobulins, CD19+, CD20+, biopsies of skin and lymph nodes

Answer: The correct answer is A.
Initial Laboratory Screening for Immune Deficiencies are as follow: CBC including granulocytes with differential, lymphocytes, platelets (with size if available), hemoglobin, Quantitative serum immunoglobulins-IgG, IgA, IgM ±IgE , Lymphocyte subset analysis by flow cytometry for B cells (CD19+, CD20+), Specific antibody production to vaccine responses, Tetanus/diphtheria (IgG1), Pneumococcal and meningococcal polysaccharides (IgG2), Common viral respiratory pathogens (IgG1 and IgG3), Influenza A & B, Respiratory syncytial virus, Parainfluenza, Other vaccines-hepatitis B, influenza, MMR, polio (killed vaccine), Isohemagglutinins (IgM antibodies to A and B blood group antigens), B-cell quantitation by flow cytometry. IgG subclasses is the advanced and comprehensive laboratory evaluation of immune deficiency.1,148,150,159

REFERENCES
Approach to the Children with Recurrent Infections


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A. Aghamohammadi, et al.


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