
In the name of god

In Memoriam

Living with Primary immune deficiency

N. Behniafard

Allergist and Clinical Immunologist

Yazd Shahid Sadoughi University of Medical Sciences

- *More than 400* ***inborn errors of immunity (IEI)***
- *PIDD →life-threatening disorders presenting in infancy to less severe disorders diagnosed in adulthood.*
- *the prevalence of these conditions is approximately* ***1-5/1000*** *.(Stiehmt's Immune Deficiencies,2014)*

PIDD present with:

- *Recurrent or chronic infections*

(a range of both common and opportunistic pathogens or a very narrow number of pathogens)

- *Failure to thrive*
- *Severe atopy*
- *Autoinflammatory diseases*
- *Autoimmune diseases*
- *Malignancies*

Accurate diagnosis is essential for:

- *proper patient management*
- *targeted pharmacotherapy and biologic use*
- *curative therapies such as BMT or gene therapy*

Clinical features suggestive of a primary immunodeficiency

- *Family history of immunodeficiency or unexplained early death (before age 30 years)*
- *Failure to thrive*
- *Need for intravenous antibiotics and/or hospitalization to clear infections*
- *Six or more ear or respiratory tract infections within one year*
- *Two or more serious sinus infections or pneumonias within one year*

Clinical features suggestive of a primary immunodeficiency

- *Four or more new ear infections within one year*
- *Two or more episodes of sepsis or meningitis in a lifetime*
- *Two or more months of antibiotics with little effect*
- *Recurrent or resistant oral or cutaneous candidiasis*
- *Recurrent deep skin or organ abscesses*

Clinical features suggestive of a primary immunodeficiency

- *Infection caused by an unusual microbial organism and/or in an unusual location*
- *Complications from a live vaccine (eg, rotavirus, varicella, and BCG vaccines)*
- *Chronic diarrhea*
- *Nonhealing wounds*
- *Extensive skin lesions*
- *Persistent lymphopenia (a count of <1500 cells/microL in patients over five years and <2500 cells/microL in younger children)*

Clinical features suggestive of a primary immunodeficiency

- *Unexplained autoimmunity or fevers*
- *Granulomas*
- *Hemophagocytic lymphohistiocytosis (HLH)*
- *Lymphoma in childhood*
- *Features typical of syndromic PIDs (eg, cartilage-hair hypoplasia, Chediak-Higashi syndrome, ataxia-telangiectasia)*

Measures to prevent initial infections

Isolation measures :

- *Specially in patients who might be candidates for HCT*
- *SCID* → *remaining at home or hospitalization in an isolation room?*
- *Some immunologist* → *if there are no other young children at home who may transmit infections and outside contacts can be avoided keeping at Home is better*

✓ *social situation of the family*

✓ *ease of access to the hospital*

✓ *clinic visits should be planned as to avoid the patient from sitting in busy waiting rooms*

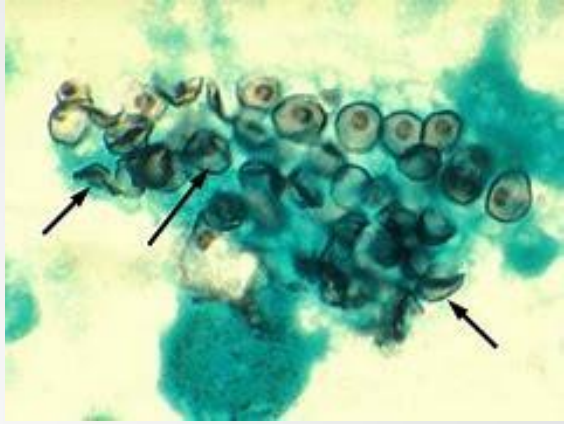
- ***Hospitalization*** *: the patient should be placed into a positive pressure room with high-efficiency particulate air (HEPA) filtration.*
- ***Staff:*** *Good hand washing and use of mask, gown, and gloves. the number of visitors should be minimized*

Measures to prevent initial infections

Caregiver counseling :

- *Good handwashing*
- *For patients with moderate to severe forms of PIDD, caregivers and parents who work, utilize public transportation are encouraged to change their clothing and wash hands prior to interacting with the patient.*
- *The number of guests/visitors to the home should be minimized.*
- *Those who are permitted to visit should have up-to-date vaccinations*

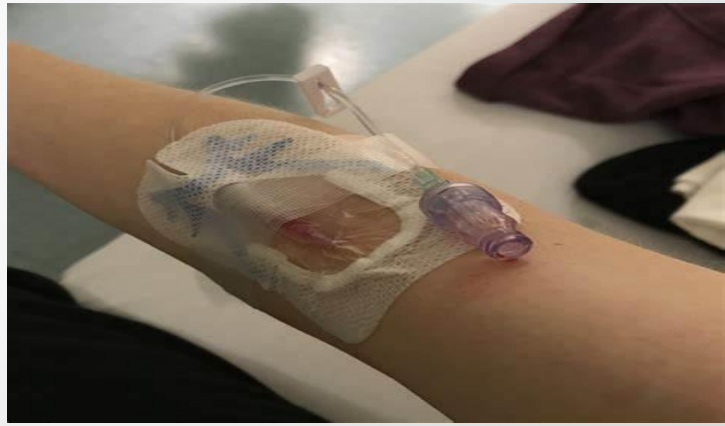
Measures to prevent initial infections



Prevention of Pneumocystis jirovecii pneumonia(Prophylaxis for PCP) :

- *moderate to severe T cell deficiency such as SCID,*
- *forms of CID*
- *in patients receiving potent immunosuppressive therapy*

Measures to prevent initial infections



Immune globulin replacement :

- *primary antibody deficiencies*
- *SCID and CID until B cell function is restored*

Ig can be replaced intravenously (IVIG) or subcutaneously (SCIg)

- *If replacement is needed urgently, IVIG is preferred*
- *Trough levels should be monitored. Recent meta-analyses suggest that maintaining higher trough levels (>1000 mg/dL) correlate with a reduced risk of pneumonia*
- *For SCIg replacement, the starting dose is often 100 to 200 mg/kg/dose and commonly is administered every seven days*.

Measures to prevent initial infections

Prophylactic antimicrobial therapy:

- *Few studies of the efficacy of prophylaxis in specific immune disorders have been performed, with some notable exceptions (eg, CGD)*
- *A survey of American immunologists with clinical focus in PIDD reported that, approximately 75 percent of practitioners administered prophylactic antibiotics to at least some of their patients with immunodeficiency*
- *There is no standardized approach to the use of prophylactic antimicrobials in PID.*

Measures to prevent initial infections

Prior to initiation of prophylactic antibiotics:

- *it is essential to screen symptomatic patients for active infections.*
- *Particular attention should be paid to screening for mycobacterial infection prior to azithromycin use, due to the high risk of resistance development with monotherapy.*
- *Baseline screening → on the adverse reaction profile of the considered antibiotic, which could include ECG when using QTc prolonging agents, as well as audiologic testing.*

Examples of prophylactic antibiotic regimens used in patients with immunodeficiency

Infection to be prevented	First-line regimen	Alternative regimens
Pneumocystis jirovecii	Sulfamethoxazole-trimethoprim: ■ Infants >4 weeks of age and children: 5 mg/kg/day orally in 2 divided doses, 3 days/week (based on TMP; maximum 160 mg per dose, 320 mg per day) ■ Adults and adolescents with normal renal function: 160 mg (based on TMP) daily or 3 days/week, or 80 mg (based on TMP) daily	Dapsone: ■ Infants and children: 2 mg/kg/dose orally once daily (maximum daily dose: 100 mg/day) ■ Adults: 100 mg once daily or 50 mg twice daily Atovaquone: ■ 1 to 3 months: 30 mg/kg orally once daily ■ 4 to 24 months: 45 mg/kg orally once daily ■ >24 months: 30 mg/kg orally once daily ■ Adolescents ≥13 years and adults: 1500 mg orally once daily Pentamidine: ■ Children <5 years: 9 mg/kg (maximum dose: 300 mg/dose) inhalation per nebulizer once every 4 weeks ■ Children >5 years, adolescents and adults: 300 mg inhalation per nebulizer once every 4 weeks
***Staphylococcus* spp, gram negative spp**	Sulfamethoxazole-trimethoprim: ■ Infants >4 weeks of age and children: 5 mg/kg/day orally in 2 divided doses (based on TMP; maximum 160 mg per dose, 320 mg per day) ■ Adolescents and adults: 160 mg (based on TMP) daily or twice daily	Amoxicillin:* ■ Children: 10 to 20 mg/kg per day as a single dose or divided twice daily (maximum dose 875 mg per day) ■ Adolescents and adults: 875 mg twice daily Ciprofloxacin:*¶ ■ Children: 10 mg/kg/dose twice daily (maximum dose 500 mg) ■ Adults: 500 mg twice daily Amoxicillin and clavulanate:* ■ Children: 20 mg/kg per day as a single dose or divided twice daily (maximum dose 875 mg per day, based on amoxicillin) ■ Adolescents and adults: 875 mg daily (based on amoxicillin)
***Mycoplasma* spp, *Streptococcus* spp**	Azithromycin: ■ Children: 5 to 10 mg/kg/dose orally 3 times weekly (maximum dose of 250 mg) ■ Adolescents and adults: 250 mg orally 3 times weekly	

Examples of prophylactic antibiotic regimens used in patients with immunodeficiency

Non-tuberculous mycobacteria	Azithromycin: ■ Children: 20 mg/kg/dose orally once weekly (maximum dose 1200 mg weekly but may be given as 600 mg twice per week if higher doses cause nausea) ■ Adolescents and adults: 1200 mg weekly but may be given as 600 mg twice per week if higher doses cause nausea	
***Aspergillus* spp**	Itraconazole: ■ Children: 5 mg/kg/day orally daily (maximum dose 200 mg) ■ Adolescents and adults: 200 mg orally daily	Voriconazole: $^{\Delta}$ ■ ≤50 kg: 8 mg/kg/dose orally twice daily (maximum dose 350 mg) ■ >50 kg: 4 mg/kg/dose orally twice daily (maximum dose 200 mg)
***Candida* spp**	Fluconazole: ■ Children: 6 mg/kg orally daily (maximum dose 400 mg) ■ Adolescents and adults: 400 mg orally once daily	
HSV/VZV	Acyclovir: ■ Children <40 kg: 600 mg/m^2/dose orally 4 times per day ■ Children >40 kg: 800 mg orally 4 times per day ■ Adults: 800 mg orally twice daily	
CMV	Valganciclovir: ■ Children 1 month to 16 years old: once daily oral dose (mg) = 7 × body surface area × creatinine clearance ■ Adolescents ≥17 years and adults with normal renal function: 900 mg orally once daily	

Measures to prevent initial infections

Antibiotic prophylaxis alone :

- *mild hypogammaglobulinemia,*
- *IgA deficiency,*
- *IgG subclass deficiency, who are not receiving immune globulin*

✓ *Patients with more severe Ab deficiencies receiving Ig may have an increased rate of bacterial infections chronically or at certain times of the year (during the winter) and may also benefit from antibiotic prophylaxis.*

✓ *A randomized trial in pts with primary Ab deficiency → Azithromycin prophylaxis significantly reduced the rate of pulmonary exacerbations and hospitalizations versus placebo, with no drug related adverse events or increase in macrolide-resistance bacterial species*

Measures to prevent initial infections

- *Influenzas' prophylaxis* → *during influenzas' season for high-risk immunodeficient patients and for patients in close contact with other persons with infuenza. (preventive antiviral therapy or in some instances, full treatment doses)*
- *herpesvirus family prophylaxis* → *in some patients with recurrent mucosal or skin herpes simplex outbreaks in the context of specific immunodeficiencies, including those with defects in NK cells or defects in toll-like receptor 3 signaling .*

Measures to prevent initial infections

- ✓ *Patients with CID with CMV infection* → *prolonged antiviral prophylaxis.*
- ✓ *Antifungal prophylaxis targeting Candida species* → *defects in the interleukin (IL)-12/23/Th17 pathway, or in the presence of anti-cytokine autoantibodies which occur in autoimmune polyendocrinopathy disorder type I.*
- ✓ *Prophylaxis against mycobacterial infections* → *MSMD, such as defects of the interferon gamma-IL-12 axis, NEMO deficiency*

Measures to prevent initial infections

Vaccination of patients, family members, caregivers :

- *PIDD patients can significantly benefit from herd immunity,*
- *Live vaccines are contraindicated in patients with moderate to severe forms of PIDD, but expert consensus recommends that healthy family members and close contacts receive all vaccines in order to provide secondary protection.*

Can immune-deficient patients receive a COVID-19 vaccines?

- *Immune deficient people can get mRNA and DNA vaccines. These vaccines aren't alive. Even though they contain genes, they are not going to cause disease*

Will a COVID-19 vaccine be as effective for an immune-deficient patients as it is for someone with a normally functioning immune system?

- *For many who have immunodeficiencies, the vaccine likely will be as effective as it is for the general population.*
- *"People with antibody deficiencies will likely have an incomplete response, which doesn't mean they shouldn't get it,"*

Clinical outcomes and features of COVID-19 in patients with primary immunodeficiencies in New York City

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- *the clinical impact of COVID-19 in PIDs varies from mild symptoms to death.*
- *The proportion of deaths in this series (25%) was greater than that in the general population with COVID-19 reported at New York City hospitals (10.2%),and similar to outcomes data reported in the kidney transplant population (28%).*
- *In this single-center experience(report of 16 PID patients), those who died had preexisting PID-associated autoimmune/inflammatory complications.*

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- *One study involved global research collaboration across 50 centers.(report of 94 PID patients)*
- *Data was collected from patients in the USA, UK, France, Spain, Italy, Germany, the Netherlands and Latin America.*
- *the rate of fatality from COVID-19 was no higher in this group than the general population*
- *certain forms of immune suppression, which reduce the function of IL-6, are protective against the pathological effects of the cytokine storm frequently observed in patients,*
- *56% of the patient cohort had a deficiency in their ability to produce antibodies, yet they had similar outcomes to the rest of the cohort.*

Measures to prevent initial infections

Travel recommendations :

- *to drink only bottled water,*
- *to avoid eating undercooked food.*
- *Medication prophylaxis may be indicated*
- *to have an emergency treatment plan.*
- *Ideally, local experts in PIDD should be identified in case of illness during travel*

Caution with blood products

Any cellular blood products given to these patients must be irradiated for preventing GVHD:

- *SCID*
- *Wiskott-Aldrich syndrome,*
- *NEMO deficiency,*
- *complete DiGeorge syndrome*

Leukocyte reduction is also highly recommended in order to minimize chances of transmission of CMV, which can cause significant disease in individuals who have an underlying T cell defect or have undergone BMT

Infectious diseases

- *culture and identify the pathogen and initiate antibiotics as rapidly as possible.*
- *prolonged antibiotic courses are often required in patients with PIDD(two to three times longer than standard recommendations)*
- *For example, rather than treating acute sinusitis with 10 days of antibiotics, some immunodeficient patients may require a 21-day course (or even up to 28 to 30 days), with careful observation in the initial weeks after treatment to make sure that symptoms do not reappear*

Infectious diseases

- ***increased risk of bacterial infections :*** *Patients with cellular, complement, or Ab defects*
- ***increased risk of fungal infections :***

✓ *CGD (Aspergillus),*

✓ *X-linked hyper IgM (Pneumocystis jirovecii, Cryptococcus),*

✓ *CMCC,*

✓ *CARD9 deficiency*

✓ *Pts with TNF autoantibodies*

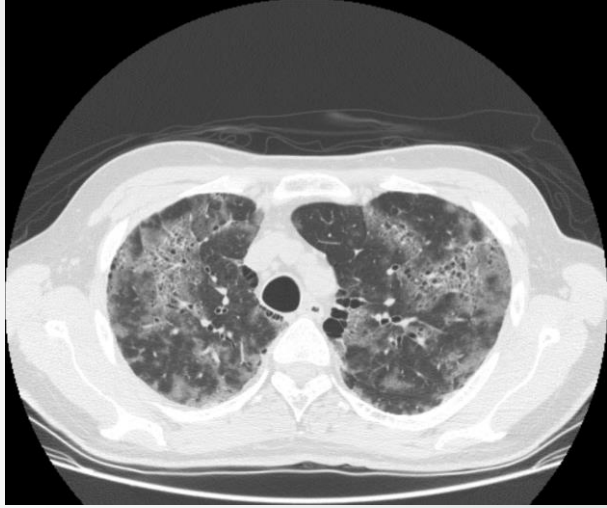
Infectious diseases

- *Chronic GI infections can occur in Pts with CVID and other antibody deficiency disorders, including enterovirus, giardia, C. jejuni, or salmonella, norovirus or cryptosporidium*
- *Severe and recurrent viral infections (Herpesviruses such as CMV, EBV, and varicella-zoster virus)are found in children with defects in T cells, NKcells, or innate pathogen signaling.*

Infectious diseases

- *Adenovirus infection can be similarly severe and warrants screening in the setting of GI or respiratory symptoms*
- *In some diseases characterized by susceptibility to HPV infection, the underlying genetic defect may not be restricted to the immune system, but also involve keratinocytes, as in the case of epidermodysplasia verruciformis but also in X-linked and JAK3 deficiency.*

Pulmonary diseases



pulmonary infections (acute and chronic infections)

- *The association of pneumonia with recurrent sinus infections*
- *pneumonias in varying locations of the lung*
- *The presence of unusual complications of pneumonia, such as pneumatoceles or cavitary lesions*
- *complicated pneumonia requiring inpatient hospitalization or surgical intervention*
- *Opportunistic/unusual pathogens*

Pulmonary diseases

Specific types of structural/functional lung abnormalities

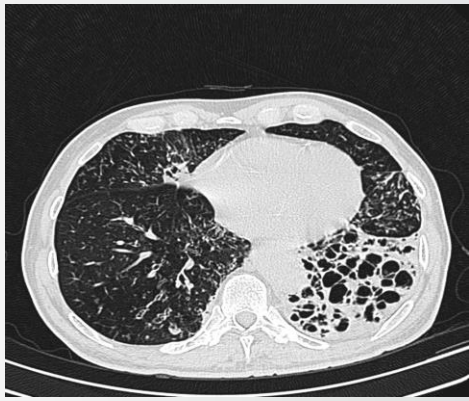
✓ ***Hilar and/or mediastinal adenopathy***

in the context of infection(eg, tuberculosis, histoplasmosis)

in the context of granulomatous lung involvement(CVID,CGD) related to infection or chronic inflammation

in the context of malignancy(AT,WAS,CVID)

Specific types of structural/functional lung abnormalities



✓ ***Obstructive lung diseases***

bronchiectasis and bronchiolitis obliterans

- ***Bronchiectasis****: signet ring sign and Tree in bud pattern in lung HRCT*

♠ *primary antibody deficiencies (XLA,CVID), CID (PI3KD syndrome)*

♠ *disorders of phagocyte dysfunction (CGD)*

- ***bronchiolitis obliterans****(SCID, AT, and CVID)*

♠ *reversible obstructive airways disease on spirometry plus ↓DLCO or hypoxemia on exertion is suggestive of BO*

Specific types of structural/functional lung abnormalities

✓ *Restrictive lung diseases*

- ♠ ***interstitial lung disease*** *(ILD)*

inflammatory and fibrotic infiltration of the respiratory interstitial granulomatous and lymphocytic interstitial lung disease (GLILD)

- ♠ ***organizing pneumonia (OP),***
- ♠ ***Granulomatous inflammation***
- ♠ ***Pulmonary alveolar proteinosis***

Screening for pulmonary complications :

- ***pulmonary functional testing :***

spirometry

measurement of lung volumes (eg, plethysmography)

DLCO

- ***Imaging :***

HRCT

MRI

MRI : pulmonary parenchymal abnormalities in patients with possible ILD and underlying radiation sensitivity, such as AT

There are no guidelines regarding the ideal timing or modality of screening imaging in absence of symptoms in different PIDDs

Gastrointestinal disorders

- *Manifestations include infection, autoimmune inflammation, malabsorption, granuloma formation, and lymphoproliferative disorders.*
- *These patients typically require aggressive, extended antibiotic and/or immune modulating therapy .*
- *Moreover, surgical intervention may be required to help manage obstruction due to abscesses, granulomas, or lymphoid hyperplasia*

Lymphoproliferative and malignant disease

- *Defects in DNA repair mechanisms are associated with high rates of malignancy :*

✓ *ataxia telangiectasia,*

✓ *Bloom syndrome,*

✓ *Artemis deficiency,*

- *In the presence of CID chronic infection with oncogenic viruses such as EBV or HPV can lead to malignancies.*

- *impaired cytotoxic T cell function could allow development of EBV-driven lymphoproliferative disease (EBV-LPD). In EBV-LPD, EBV-infected B cells may infiltrate secondary lymphatics as well as solid organs, and is usually associated with marked elevation of EBV viral load.*

Health Maintenance

- *Dental care*
- *audiologic care*
- *vision care*
- *screening for complications from infections, inflammatory disorders, and medications.*

Dental care

risks of dental disease(caries, periodontitis, and tooth loss) in some PIDD :

- ✓ *functional defects in neutrophils*
- ✓ *functional defects inTh17 CD4+ T cells*
- ✓ *defects in the receptor activator of NFK-B(essential for bone metabolism)*

Dental care

- ***Routine dental visits*** *:at least twice annually*
- *Antibiotic prophylaxis is generally not required for routine dental work for PIDD patients.*
- ***Brushing:*** *at least twice daily and preferably after every meal.*
- ***Flossing*** *: at least once per day.*
- ***Electric toothbrushes*** *are recommended.*
- *Sugary drinks should be avoided.*
- *high-dose fluoridated toothpaste : for patients susceptible to dental caries*
- *Avoidance of routine dental X-rays in ataxia telangiectasia, Artemis deficiency*

Audiologic care

All patients with PIDD should have baseline audiologic screening

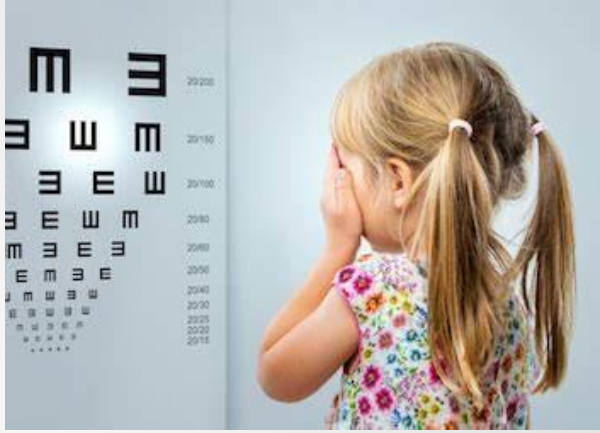
Hearing loss can be a potential risk due to infections or medication toxicities:

- *Cytomegalovirus →in patients with cellular immunodeficiency*
- *Aminoglycosides are known to be potential causes of ototoxicity,*
- *vancomycin and macrolides such as erythromycin and azithromycin are associated with lower risk of hearing loss, which is often described to be reversible.*
-

Audiologic care

- *Certain forms of PIDD also have intrinsic risk of hearing loss. ADA deficiency →elevated risk of SNHL after BMT.*
- *One study found that 38 % of a group of 47 children with either X-linked or AR agammaglobulinemia or CVID had hearing loss.*

Vision screening



All patients with PIDD should have baseline ophthalmologic examinations

- ***Infections :***

CMV, HSV1/2, and VZV can cause retinitis and/or uveitis.

Toxoplasmosis can similarly cause chorioretinitis.

Bacterial or fungal chorioretinitis may also occur in the setting of disseminated infection.

- ***Many autoinflammatory disorders are associated with uveitis:***

FMF

CANDLE syndrome

Blau syndrome

NOMID

TRAPS

- ***Diseases involving granulomatous inflammation****: CGD→ retinal disease*

Family and psychosocial support

Mental and emotional health :

- *Cognitive, neurologic, and developmental problems may also be specific associations with PIDDs, such as ADA deficiency, DiGeorge syndrome, .*
- *Patient support groups may be helpful, and neurologic, psychiatric, and social treatment and support should be sought early.*

Genetic testing and counseling

Benefits of determining the underlying genetic etiology:

- *Genotype-specific management in primary immunodeficiency*
  - *Genotype-specific counseling*

Thank you for your attention