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Le Immunodeficienze nell'Anziano

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Primary immunodeficiency diseases (PIDs) are a genetically heterogeneous group of disorders that affect distinct components of the innate and adaptive immune system, such as neutrophils, macrophages, dendritic cells, complement proteins, natural killer cells, and T and B lymphocytes.

Secondary immunodeficiency diseases are immune system disfunction depending on many conditions which primarily impair function of other organ systems. As with primary immune deficiency, secondary immune dysfunction leads to an increased incidence of infection and malignancy, and the occurrence of autoimmune disease.

The acquired immune deficiency syndrome (AIDS) is an important example of secondary immune deficiency, which constitutes an entire discipline by itself

Conditions associated with secondary immune deficiency

Immunosoppressive therapy

Microbial infection

Malignancy

Disorders of biochemical homeostasis

Autoimmune disease

Trauma

Environmental exposure

Other

Immunosoppressive therapy
Cytotoxic chemotherapy for malignancy
Treatment of autoimmune disease
Bone marrow ablation prior to transplantation
Treatment or prophylaxis of graft vs host disease following bone marrow transpl.
Treatment of rejection following solid organ transplantation

Microbial infection
Viral infection
HIV, AIDS
Measles
Herpes viruses
Bacterial infection (superantigens)
Mycobacterial infection
Parasitic infestation

Disorders of biochemical homeostasis
Diabetes mellitus
Renal insufficency/dialysis
Hepatic insufficiency/chirrosis
Malnutrition

Malignancy
Hodgkin's disease
Chronic lymphocytic leukemia
Multiple myeloma
Solid tumors

Autoimmune disease
Systemic lupus erythematosus
Rheumatoid arthritis

Trauma
Burns

Environmental exposure
Radiation
Ionizing
Ultraviolet
Toxic chemicals

Other
Pregnancy
Stress

IMMUNOSUPPRESSIVE THERAPY

Drugs are administered with the express intent of suppressing immune system function in order to treat autoimmune diseases, to treat or prevent graft-versus-host disease following bone marrow transplantation, and to treat or prevent rejection of solid organ grafts.

In many of these cases, an increased rate of infection and malignancy (predominantly hematologic) exists due to the underlying disease process, and is exacerbated as an almost inevitable consequence of treatment with these drugs.

The degree of immune deficiency is dependent upon the condition being treated, the doses of single agents, and drug combinations that are frequently synergistic.

Laboratory studies of immune function are often used to monitor therapy.

The spectrum of infections may include common pathogens, opportunistic infections, and sometimes normal flora.

Infectious morbidity must be reduced through appropriate anticipatory or prophylactic measures.

Some drugs are used in the treatment of malignancy in order to selectively target mitotically active cells. Bone marrow cells and lymphocytes are also affected because these cells normally undergo high rates of cell division throughout life. In these settings, a decrease in immune system function is inevitable and prophylaxis may be appropriate.

A variety of medications used for many different purposes have been shown to have some "immunomodulatory" activity with respect to in vitro and in vivo lymphocyte function. In some cases, a decrease in function is apparent, but its relation to a clinically significant impairment of host defense may not be evident.

Many of these drugs are used in various combinations with each other, often making it difficult to determine the precise interaction of each with the human immune system, and with the disorder being treated, which may independently be associated with immunologic abnormalities.

Glucocorticoids are routinely used for their antiinflammatory and immunosuppressive properties.

They bind to the intracellular glucocorticoid receptor after passively diffusing across the cellular membrane. Binding of the drug to the receptor results in translocation of the complex to the nucleus where it can interact directly with specific DNA sequences (glucocorticoid responsive elements, or GREs), and other transcription factors. These interactions may be associated with increased or decreased transcription of downstream genes

Some genes that are "activated" may encode molecules that themselves are inhibitory for transcription of other genes important in inflammation and immunity.

Glucocorticoid administration also results in reductions in all circulating leukocytes with the exception of neutrophils. Neutrophils "demarginate" (detach from endothelial cells) and are found in increased numbers in the blood. However, the detachment of neutrophils from vessel walls diminishes the ability of these cells to exit the circulation and enter sites of infection and tissue injury. The bactericidal capacity of both neutrophils and monocytes is also impaired.

The effect upon the immune system varies with the dose of corticosteroid.

At low or moderate doses (<2 mg/kg per day prednisone equivalent in children, <40 mg/day in adults), T lymphocytes may be slightly reduced in the circulation, CD4-positive more than CD8-positive T cells. Cutaneous anergy also occurs primarily due to the failure of inflammatory cells to be recruited to the site of the reaction.

There are isolated case reports of impaired immunoglobulin function with long term therapy, although this is not believed to be common. Higher doses of prednisone (>2 mg/kg per day in children, >40 mg/day in adults) lead to greater suppression of lymphocyte activation and suppression of antibody production by B cells.

The increased susceptibility to infections with corticosteroids is enhanced among older individuals with functional limitations.

Common viral (mainly herpesviruses), bacterial (Staphylococcus aureus and others), and fungal (mainly Candida) pathogens are encountered with greater frequency in a dose-dependent manner during therapy with glucocorticoids. The major opportunistic infection encountered is Pneumocystis carinii (jiroveci) pneumonia (PCP). Other protozoan or helminthic infections are unusual, except in areas of the world where they are endemic (eg, P. falciparum).

Methotrexate — Methotrexate acts via inhibition of dihydrofolate reductase, thereby impeding synthesis of nucleotides and certain amino acids, resulting in retardation of cell division.

With high dose therapy (>20 mg/kg, used in cancer chemotherapy), there may be profound bone marrow suppression, leading to hemorrhage and sepsis. Primary and secondary cellular and humoral immune responses are depressed

The risk of infection in patients receiving low-dose methotrexate as used in rheumatoid arthritis and other rheumatic diseases has not been well established.

Lymphocyte subsets, the CD4/CD8 ratio, and in vitro T cell mitogen responses appear to be unaffected.

Decreases in serum immunoglobulins and in vitro antibody synthesis have been reported, but these findings have not been consistently observed.

In one summary of several large studies, 121 infectious events were noted among more than 1700 patient-years of methotrexate at lower doses of 20 mg/square meter per week. Approximately one-half of patients were receiving concomitant therapy with glucocorticoids. The infections ranged from mild to moderate viral and bacterial respiratory tract infections, as well as herpes zoster, urinary tract infections, cellulitis, and one case of P. carinii pneumonia.

There are numerous isolated reports of opportunistic infections in patients receiving low-dose methotrexate for rheumatoid arthritis and other inflammatory disorders. These include pneumonia caused by Pneumocystis carinii (jiroveci) pneumonia (PCP), cytomegalovirus, and Cryptococcus, and disseminated infections with herpes zoster, and Nocardia. Many of these patients were also receiving glucocorticoids.

There are several reports of solid tumors occurring in patients treated with methotrexate; however, there is no evidence in larger series that the relative risk is increased.

A higher rate of Epstein-Barr virus-associated lymphoproliferative disease is associated with methotrexate treatment. In some cases, lymphoproliferation resolves after drug withdrawal. However, many situations in which methotrexate is used (eg, rheumatoid arthritis, transplantation) are independently associated with an increased risk of lymphoproliferation.

Cyclosporine and tacrolimus — Cyclosporine is a natural fungal product with potent immunosuppressive actions. It binds to a series of intracellular proteins known as cyclophilins (a subset of a larger family of molecules called immunophilins), which leads to the interruption of a lymphocyte signaling pathway involving the calcium-dependent phosphatase calcineurin. The activity of calcineurin is required for the formation of a transcription activator known as NF-AT (nuclear factor of activated T cells). NF-AT, in turn, is important for the transcription of a number of genes including those for the cytokines GM-CSF, IL-2, IL-3, IL-4, IL-5, IL-8, IL-13, TNF, IFNg, and surface molecules such as CD40L (CD154).

Cyclosporine may also affect the activity of additional transcription factors and affect antigen-presenting function and cytokine secretion by B cells, monocytes/macrophages, and dendritic cells.

Tacrolimus (FK-506) is a fungal macrolide that also inhibits calcineurin, although it binds to FK-binding proteins, which are immunophilins distinct from the cyclosporine-binding cyclophilins.

Rapamycin is a related drug that interacts with FK-binding proteins, although it does not inhibit calcineurin. The mechanism of immune suppression is unknown. Rapamycin has a synergistic effect with cyclosporine.

Neither cyclosporine nor tacrolimus are associated with significant lymphopenia or leukopenia.
Therapy with cyclosporine predisposes to viral and bacterial pneumonias, and fungal sepsis.
Tacrolimus therapy may pose a greater risk for fungal sepsis, although data are limited.
In the lung transplant study noted above, the incidence of bacterial pneumonia was higher with cyclosporine (0.92 vs 0.33 episodes/100 patient days), while the incidence of fungal sepsis was higher with tacrolimus (0.49 versus 0.10 episodes/100 patient days).
Viral pneumonia, predominantly due to CMV, was found equally in both groups.

Rituximab — Rituximab may occasionally cause hypogammaglobulinemia associated with infections when given repeatedly or combined with other chemotherapeutic agents

· One retrospective study reviewed 97 patients who received rituximab and several chemotherapy regimens for treatment of various B cell malignancies. Twenty percent (19 patients) were found to have one or more infectious complications (predominantly sinopulmonary bacterial infections not associated with neutropenia). Of these 19 patients, 15 had measurement of serum immunoglobulins, and all were hypogammaglobulinemic (14, 6, and 13 had low IgG, IgA, and low IgM, respectively). The combination of fludarabine with rituximab was an independent predictor of the occurrence of these infections. Some patients received one or two doses of gamma globulin, which did appear to reduce the frequency and severity of these infectious complications. None were given conventional, prolonged, replacement therapy with gamma globulin.

· Another retrospective study examined 14 patients who received rituximab as adjuvant therapy after hematologic recovery following autologous bone marrow transplantation for B cell lymphoma . Six patients (43 percent) were found to have hypogammaglobulinemia and reduced switched (IgD-) memory B cells. Bacterial infections were observed in only one of these individuals and responded well to gamma globulin replacement.

Rituximab has also been associated with reactivation of latent hepatitis B infection.

Azathioprine, 6-mercaptopurine, and mycophenolate — Azathioprine and mycophenolic acid inhibit the biosynthesis of nucleotides required for DNA replication in dividing cells. Azathioprine is a prodrug that is quickly converted to 6-mercaptopurine (6-MP) after administration.
These drugs can lead to both inhibition of neoplastic growth and to immune suppression, since lymphocyte proliferation is an important component of most specific immune responses. In addition, some drug metabolites may interfere with other processes important in immune activation, such as antigen recognition, lymphocyte adhesion, and cell-mediated cytotoxicity. These drugs can also cause bone marrow suppression, leading to neutropenia and a further reduction in host defenses.

Observed infectious complications with azathioprine and mycophenolate span the spectrum of common pathogens, as well as opportunistic infections and malignancy. In one comparison of prednisone (1 mg/kg every other day) plus azathioprine (1.5 mg/kg per day) versus prednisone plus placebo in the treatment of acute graft-versus-host disease, the incidence of certain infectious complications was significantly higher in the group treated with azathioprine. These included disseminated varicella zoster (24 versus 11 percent), bacteremia (11 versus 6 percent), and interstitial pneumonia (14 versus 5 percent). Mortality due to infection was also higher in the azathioprine group (29 versus 10 percent), most of which was due to disseminated zoster.

Alkylating agents — Alkylating agents, such as cyclophosphamide, chlorambucil, and melphalan, act principally by chemically modifying nucleotides, leading to DNA breakage and errors in DNA replication and transcription.
This mechanism interferes with cell division, and leads to inhibition of lymphocyte proliferation with mitogenic stimuli and bone marrow suppression.

With cyclophosphamide, for example, lymphocyte counts are consistently suppressed by 40 to 80 percent, with T and B cells being equally affected.

The effect on primary antibody responses and cutaneous delayed hypersensitivity are variable and depend upon dose and antigen. The breadth of immune suppression is similar to that observed with azathioprine

There is a significant incidence of serious infection in patients treated with alkylating agents (ranging from 4 to 15 percent).
The risk of bacterial infection is highest in those who become neutropenic or who are also treated with steroids, while herpes zoster may be directly activated by the alkylating agent.

One study, for example, evaluated 75 patients with a variety of vasculitides and connective tissue diseases who received 451 intravenous pulses of cyclophosphamide (500 mg/m2, mean dose 764 mg); all patients were also treated with corticosteroids. Thirty infections occurred in 21 patients (28 percent), seven of which were severe. All patients were also treated with prednisolone, which could have contributed to the infectious risk.

The infections included sepsis (Salmonella, S. aureus, meningococcus), pneumonia, viral upper respiratory tract infections, herpes zoster, soft tissue infections, and gastroenteritis.

The overall risk of herpes zoster with alkylating agent therapy for vasculitis and other rheumatic diseases has ranged from 8 to 33 percent.

MICROBIAL INFECTIONS — Many human pathogens have evolved sophisticated means for surviving attack by the immune systems of their hosts.

In most cases, these mechanisms selectively affect host response to the invader and are not generally immunosuppressive. A clear exception is the profound immune suppression resulting from HIV infection.

Herpesviruses — Herpesvirus infections are regularly associated with transient depression of cell-mediated immunity manifested by decreased in vitro proliferation with mitogens, and reduced interferon-gamma production in response to mitogens during the acute phase of the illness.

These phenomena are most profound and long-lived with cytomegalovirus, but secondary superinfection is unusual.

Measles — Other than HIV, measles (morbillivirus) is the only viral agent implicated in significant global immune suppression, leading to severe, and sometimes fatal, superinfection.

The most frequent infectious complications of measles are pneumonia, gastroenteritis, otitis media, gingivostomatitis, and laryngotracheobronchitis.

Pathogens included common viral agents such as herpes simplex, cytomegalovirus, parainfluenza, adenovirus, coxsackie, and respiratory syncytial virus.

Bacteria included community-acquired organisms such as Staphylococcus aureus and Streptococcus pneumoniae, as well as nosocomial pathogens such as Klebsiella, Pseudomonas, and Acinetobacter. Mycobacterium tuberculosis and Candida albicans were also found.

Immune alterations induced by measles include T cell lymphopenia with depletion of T-dependent areas of lymph nodes and spleen, cutaneous anergy, diminished in vitro T cell proliferation with mitogens or alloantigens, and diminished antibody production.

These effects are caused by direct infection of T cells by measles virus and by infection of dendritic cells, impairing their important antigen presenting/accessory function in T cell activation. A diminished number of circulating T cells indicates the potential for significant immune compromise and is associated with doubling of the fatality rate.

Malnutrition is an important independent risk factor for severe immune compromise, superinfection, and death from measles infection.

Bacterial infections — Infection by bacteria is not generally associated with significant secondary immune suppression. One exception may be in bacteria that produce "superantigen" toxins (eg, staphylococci, streptococci).
Superantigens can bind simultaneously to MHC class II antigens and to the non-antigen-binding region of T cell receptors, thereby stimulating large numbers (up to 20 percent) of T cells. These T cells then produce large amounts of inflammatory cytokines, which lead to a syndrome resembling septic shock with multisystem organ failure (eg, staphylococcal toxic shock syndrome). Following interaction with superantigens, circulating T cells first increase, then decrease.
Animal studies have shown that some T cells enter a state of anergy and cannot be further activated.
The clinical importance of these phenomena for secondary infection has not been determined.

Mycobacterial infections — Mycobacteria establish chronic infections and replicate within phagocytic cells (monocytes and macrophages). Several secreted and surface mycobacterial products inhibit the ability of the infected cell to kill the invader and also prevent normal cooperation with other cells in immune responses. This may lead to some increase in the risk of secondary infection.

Parasite infestation — Apart from HIV infection, the immune suppression resulting from protozoan infestation tends to be more pronounced than that found with other classes of microbes.
As an example, cell-mediated immunity is generally suppressed in malaria.
This leads to susceptibility to infections by other microbes, delayed graft rejection, and to a higher rate of various malignancies.

Malaria infection is one aspect of the marked association of Epstein-Barr virus (EBV) infection with Burkitt's lymphoma that is observed in Africa, but not in Europe or Americ. Although the seroprevalence of EBV in western countries is significant, malaria is uncommon.
Plasmodia inhibit the ability of cytotoxic T cells to maintain EBV transformed B cells under control, leading to lymphomas.

Trypanosomiasis is associated with diminished antibody responses, cutaneous anergy, and diminished in vitro T cell mitogen responses.

Delayed graft rejection and impaired humoral immunity have also been found in infestations with helminths, such as Trichinella and schistosomes.

Some of the possible mechanisms underlying the immune suppression occurring during parasitic infection include:

- Alteration in macrophage function
- The induction of suppressor T cells
- Production of immunosuppressive factors by the parasites themselves, which may promote the first two mechanisms or may affect other aspects of immune function

A decreased capacity for antigen presentation and microbicidal activity have been demonstrated in macrophages in malaria, trypanosomiasis, and leishmaniasis. Leishmaniasis is also associated with diminished macrophage expression of MHC class II and interleukin-1 production, while the function of normal T cells may be suppressed when cultured together in malaria and trypanosomiasis.

Suppressor T cells have been implicated in the immune dysfunction in many parasitic diseases, but a detailed description of their phenotype and function is lacking.
Similarly, many studies have demonstrated the presence of factors in parasite culture fluids that may nonspecifically suppress lymphocyte proliferation or may activate B cells polyclonally, leading to autoantibody production.
The chemical characteristics and function of any of these factors has not yet been determined.

MALIGNANCY — A variety of immunologic abnormalities have been observed in patients with malignancy.

In many instances, it is difficult to ascertain whether the immune "defect" led to failure of immune tumor surveillance, or if it arose as a "paraneoplastic process."

The most consistent immunologic abnormalities have been found in association with hematologic malignancies.

Hodgkin lymphoma — Hodgkin lymphoma has been associated with impaired delayed-type hypersensitivity (DTH) to recall antigens and to new contact sensitizers such as dinitrochlorobenzene, and with decreased in vitro responses to T cell mitogens.

These deficiencies are greatest in patients with metastatic disease or a large tumor burden.

Humoral immunity and neutrophil function appear to be intact, and serum immunoglobulin concentrations are usually normal, even during therapy.

Immunization prior to therapy elicits normal antibody responses to proteins and polysaccharides, with the exception of meningococcal vaccine.

Antibody responses may be impaired by treatment.

The interaction of therapy with any preexisting immune abnormality makes it extremely difficult to establish the pathophysiology underlying the types of infections encountered in these patients.
Many receive treatment with a combination of splenectomy, chemotherapy, and radiation.

Herpes zoster and varicella often precede therapy, while bacteremia with pneumococci and other organisms occurs with a mortality that may be as high as 20 percent.

The risk is greatest in patients undergoing splenectomy and treated with a combination of chemotherapy and radiation therapy.

Depressed cellular immunity may persist for up to 10 years following successful therapy. This supports the existence of altered immunity independent of or existing prior to the malignancy itself.

However, fixed abnormalities related to treatment, or a combination of the two, may also be responsible.

Chronic lymphocytic leukemia — Clinically significant hypogammaglobulinemia is found in 60 percent of patients with chronic lymphocytic leukemia (CLL) and is a major cause of morbidity.

The degree of antibody deficiency correlates with the tumor burden; there is also a poor response to new antigen exposure by either natural infection or vaccination.

An increased propensity to infection in CLL may also be related to the development of autoantibodies.

Autoantibodies reactive to B cells are found, as well as autoantibodies produced by the malignant clone itself.

Approximately 20 percent of CLL B cells have "natural" antibody activity and show polyspecific reactivity to self antigens such as DNA and cytoskeletal proteins.

Additional factors predisposing to infection in CLL may include diminished complement activity, poor natural killer cell function, and diminished antibody-dependent cellular cytotoxicity (ADCC).

The principal pathogens include Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae.

Recurrences of herpes zoster are also common, and opportunistic infections are observed following the use of immunosuppressive chemotherapy.

The enhanced incidence of infection causes significant morbidity and mortality. A survey of deaths in patients with CLL showed that documented or suspected infection was the cause in 57 percent of individuals. In the 21 cases in which an organism was identified, 5 (24 percent) were cases of gram-positive (mainly S. pneumoniae) infection; 8 (38 percent) were gram-negative (mainly Pseudomonas); and 3 (14 percent) were fungal. The remaining patients had infection due to anaerobic bacteria, Mycoplasma tuberculosis, and viruses.

The hypogammaglobulinemia of CLL is treated with regular intravenous infusions of gamma globulin.

Multiple myeloma — Multiple myeloma (MM) arises from a malignant transformation of a B cell that permits it to differentiate into an antibody-producing cell independent of the stimuli normally required for this process.

A number of immunologic abnormalities may be found at diagnosis, possibly resulting in infection as the presenting symptom:

· The number of CD4 positive T cells is decreased, CD8 suppressor cells may be increased, and the CD4/CD8 ratio is frequently less than one. These findings are not specific, and may be observed in other plasma cell dyscrasias and hematologic malignancies.

· Although the level of serum immunoglobulin is often increased by virtue of the M (monoclonal) component, the ability to produce effective antibody responses is reduced.

These patients have hypogammaglobulinemia if the contribution of the M component is not considered.

This may be associated with a decrease in circulating B cells which bear the same immunoglobulin light chain isotype as the myeloma.

· Poorly characterized deficits in complement activation and in neutrophil function contribute to the increased risk of infection with S. pneumoniae and other encapsulated organisms.

Chemotherapy for MM is associated with additional risk of gram-negative sepsis and opportunistic infections. In one survey of fatalities in MM, documented or suspected infection was responsible for 42 percent. Of the 22 cases in which an organism was identified, 9 (41 percent) had gram-positive infection; 6 (28 percent) gram-negative (mainly E. coli) infection; and 2 (9 percent) fungal disease. The remaining patients had infections due to anaerobic bacteria, M. tuberculosis, or viruses, or polymicrobial infection.

Pneumococcal vaccine is recommended at diagnosis, with penicillin prophylaxis if the response is inadequate.

Prophylaxis with intravenous immune globulin (IGIV) has been studied with promising results. A controlled trial randomized 82 patients with plateau-phase MM to monthly IGIV (0.4 g/kg) or placebo. The IGIV group had significantly fewer serious infections (19 in 449 patient-months versus 38 in 470 patient-months). The use of IGIV should be considered in patients who have poor antibody production, hypogammaglobulinemia, or an increased incidence of infections caused by encapsulated bacteria or common viral pathogens.

Solid tumors — A variety of solid tumors have been associated with impaired recall DTH and decreased in vitro T cell proliferation to mitogens.

Some studies have implicated tumor-associated "suppressive factors," since tumor culture supernatants may inhibit the in vitro function of normal lymphocytes. Increased in vitro suppressor lymphocyte activity has been described in breast and lung cancers, gastric cancer, and osteogenic sarcoma . Diminished autocytotoxic and allocytotoxic activity of tumor-infiltrating lymphocytes from cancers involving the skin, breast, gastrointestinal tract, and central nervous system has also been reported.

Diminished skin and in vitro T cell activity has been associated with decreased peripheral T lymphocyte counts which may be progressive with the spread of malignancy. This has been observed in a variety of tumors originating in the skin, breast, head and neck, pelvis, and colon. B cell numbers and antibody responses are relatively spared in most cancers.

Despite these cellular immune abnormalities documented by in vivo and in vitro testing, clinically significant immune deficiency associated with solid tumors is generally encountered only after the administration of chemotherapy.

Blood cell counts and some parameters of immune function are commonly monitored during such therapy. These may include lymphocyte subsets, delayed hypersensitivity reactions, mitogen responses, immunoglobulin levels, and antibody responses to immunization.

DISORDERS OF BIOCHEMICAL HOMEOSTASIS — Disease processes that lead to chronic imbalances in hormones, nutrients, and toxic metabolic waste products in body fluids may have profound effects on the function of one or more components of the immune system. There are a great many diagnostic entities that may be grouped under this broad heading. It may be that many have as yet unknown effects on immune function.

Diabetes mellitus — Neutrophil dysfunction underlies much of the predisposition to fungal infections found in patients with diabetes.
The decreased neutrophil function is directly related to the level of hyperglycemia. In addition, poor peripheral circulation leads to skin ulceration, and diminished delivery of neutrophils to sites of microbial entry.
Some characteristic infectious complications of diabetes include disseminated candidiasis, rhinopulmonary mucormycosis, and malignant otitis due to P. aeruginosa.

Cirrhosis — Reduced hepatic metabolism in cirrhosis leads to high levels of endogenous glucocorticoids, which may partly explain the immune dysfunction associated with liver disease. In addition, shunting of portal blood reduces the ability of hepatic Kupffer cells to clear opsonized particles, and hypocomplementemia reduces serum opsonic activity. The most common infectious complications of severe cirrhosis are sepsis, and bacterial peritonitis.

Dialysis and uremia — The mechanism of immune suppression in hemodialysis is unknown.
Patients receiving hemodialysis display reduced T cell function in vitro and in vivo (cutaneous anergy), diminished antibody production, and compromised neutrophil and dendritic function.
Compromised neutrophil function may be due in part to the use of bioincompatible dialysis membranes, resulting in impaired adherence and attenuated responses to phagocytic stimuli.
Low expression and/or function of IgG Fc receptors has also been noted.
Some of these immune defects may be partly explained by the presence of high endogenous glucocorticoid levels.

Patients undergoing chronic peritoneal dialysis do not display systemic immune defects.
However, peritoneal neutrophil function is depressed as a result of the removal of opsonic factors (immunoglobulin and complement) with the dialysate, as well as directly suppressive effects of the dialysate itself.

These features, together with the presence of an indwelling foreign body, explains the susceptibility to bacterial peritonitis observed in these patients.

Malnutrition — Most studies on nutritionally-determined immune suppression have focused on protein-energy malnutrition. This is associated with a spectrum of immune defects including cutaneous anergy, diminished T cell mitogen responses, and decreased phagocytic cell function [2]. Additional abnormalities include the following:

· The number of circulating T cells declines, while the percentage of natural killer cells rises.

· Serum immunoglobulin is normal or increased; however, specific antibody responses are impaired.

· Primary and secondary lymphoid organs are relatively depleted of cells, and lymphoid follicles are sparse.

An acute lowering of food intake may also severely affect immune function. One recent study, for example, found depression of circulating lymphocytes and interleukin-2 production following mitogen stimulation after a fast of only seven days

A similar spectrum of defects and increased susceptibility to infection have also been linked to restricted nutritional deficiencies of zinc, iron, folate, pyridoxine and vit A
Immune function returns to normal when proper nutritional balance is restored.
Malnutrition predisposes to a greater incidence of clinically apparent infection, and increased morbidity and mortality due to infection with the pathogens prevalent in a given area.
It is estimated that worldwide, for example, malnutrition leads to a 10 and 30 fold increased mortality from pneumonia and gastroenteritis, respectively.

AUTOIMMUNE DISEASE — Autoimmune disease and immune deficiency are frequent concurrent abnormalities, and it is often an issue of definition whether one is secondary to the other. Since the mechanisms initiating pathologic autoimmunity remain incompletely understood, it may be best not to attempt to establish causality and simply to describe the association.

As with microbial infection, more or less subtle changes in immune function have been described in virtually all autoimmune diseases.

However, a link between these abnormalities and diminished host defense is less apparent. Nevertheless, the importance of secondary infection related to immune dysfunction is prominent in systemic lupus erythematosus.

Rheumatoid arthritis — There are no consistent abnormalities of circulating T cell function observed in rheumatoid arthritis. A few studies have reported subtle alterations in immune host defense, such as decreased numbers of circulating cytotoxic T cells specific for the Epstein-Barr virus. A similar observation has been made in other inflammatory arthropathies. There does not, however, appear to be a significant global defect in cytotoxic T cell function. Other aspects of immune function also appear to be intact. As an example, recent studies have observed intact DTH responses in rheumatoid arthritis, as well as normal antibody production with influenza vaccination.

Systemic lupus erythematosus — Infection is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE), and is the main cause of death in 33 percent of patients.
Frequent pathogens span the microbial spectrum and include S. aureus, E. coli, P. aeruginosa, S. enteritidis, S. pneumoniae, N. meningitidis, L. monocytogenes, M. tuberculosis, herpes zoster, C. albicans, C. neoformans, P. carinii, and T. gondii

Observed immune defect(s) are not solely dependent upon the use of immunosuppressive therapies.

Furthermore, immune impairment is not universal; there is great heterogeneity among patients with SLE. Defects in virtually every component of specific and nonspecific immune defense have been recorded in SLE.

These include:

- T cell (especially CD4+) lymphopenia
- Decreased production of cytokines, such as interleukin-2 (IL-2) and gamma-interferon (IFN-gamma)
- Significantly reduced DTH responses, as well as decreased in vitro T cell responses to mitogens and antigens
- A characteristic increase in the number of circulating T cells with the phenotype TCRalpha/beta+CD4-CD8-. The significance of this cell population for autoimmunity or immune deficiency is not known.
- Polyclonal B cell activation and hypergammaglobulinemia. However, significant hypogammaglobulinemia, as well as dysgammaglobulinemias such as IgA and/or IgG subclass deficiency and common variable immunodeficiency are also observed
- Diminished numbers of natural killer cells and impaired NK cytotoxicity.
- Variable antibody response to immunization, which may depend on the particular antigen used.

Cell-mediated immune responses in vivo and in vitro are more consistently suppressed

- Diminished capacity for phagocytosis, antigen presentation, cytokine production, and clearance of immune complexes among macrophages. Autoantibodies to IgG Fc receptors may play a role in this setting.
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Deficiency of the neutrophil number (neutropenia) and function (decreased phagocytosis).

These may result from autoantibodies to adhesion molecules, which may lead to increased clearance from the circulation, and to chronic partial activation resulting in subsequent impaired response to a physiologic stimulus.

Much of the depressed T cell function in SLE may be due to autoantibodies, usually of the IgM class, that react with T cells.

This may result in the loss of suppressor activity that has been observed in SLE, and lead to the inability to control additional autoantibody production by B cells. This mechanism, however, remains speculative.

Certain genetic deficiencies of complement are associated with SLE or lupus-like syndromes. Autoantibodies to complement receptor 1 (the major complement opsonic receptor) have also been found in patients with SLE.

Functional asplenia associated with sepsis has also been reported.

TRAUMA — Trauma is associated with subsequent defects in host defense that are generally proportional to the extent of tissue injury.
The mechanism initiating the cascade of immune effects is thought to be the massive release of inflammatory cytokines (interleukin-1, tumor necrosis factor) due to widespread activation of monocytes and macrophages by the products of cellular necrosis.

Burns — Burn trauma tends to result in a relatively greater immune suppression than mechanical trauma, when the extent of injury is similar.
The reason for this is not known. In addition to depression of specific immune activation and effector mechanisms, burns also disrupt a relatively large area of nonspecific defense (the skin). This also greatly increases the risk of infection by providing microbes ready access to the interior of the body.

Nephrotic syndrome — Decreased levels of numerous serum factors leads to depressed immunity in patients with the nephrotic syndrome:

· Losses of immunoglobulin and complement lead to increased bacterial infections.

Loss of vitamin D and other nutrients and serum factors may also lead to depressed cellular immunity.

· Patients are also frequently treated with immunosuppressive drugs, such as glucocorticoids, leading to further decreased resistance to infection.

· Hypogammaglobulinemia in some cases can be quite severe with total IgG less than 200 mg/dL, thereby leading to an increased risk of infection, particularly peritonitis. As an example, in one retrospective series of 351 children with nephrotic syndrome, 24 episodes of peritonitis occurred in 19 patients (5 percent). One-half were caused by pneumococci, and 24 percent by E. coli.

As a result, some clinicians recommend administration of pneumococcal vaccine to adults with hypogammaglobulinemia, and to all children older than two years with nephrotic syndrome.

Intravenous immunoglobulin is frequently administered to patients with the lowest IgG levels (less than 200 mg/dL).

Intestinal lymphangiectasia — Intestinal lymphangiectasia is abnormal dilatation of intestinal mucosal lymphatic channels leading to loss of lymph with immunoglobulins and lymphocytes into the gut. The disorder may be congenital, or may arise secondarily to processes which obstruct lymph drainage of the gut or raise central venous pressure. Congenital forms may also be associated with pulmonary chylothorax and lymphedema.

Hypogammaglobulinemia and lymphopenia are not usually severe, but some patients have an increased rate of infections. There is evidence for a functional T cell defect as well, possibly related to nutritional losses.
Somewhat selective loss of CD4 T cells with inversion of the CD4/CD8 ratio has been reported.

Patients with recurrent infections and low serum IgG may benefit from gamma globulin infusions; however, relatively large doses may be required due to ongoing intestinal loss.

Allogeneic blood transfusion — Blood transfusion from major-histocompatibility-unrelated donors increases the rate of postoperative infection by 30 percent or more. As an example, in a retrospective study of almost 10,000 consecutive hip fracture patients undergoing surgical repair, allogeneic blood transfusion was associated with a significant increase in the risk of serious postoperative bacterial infection (5.2 versus 3.7 percent with no transfusion).

There was a significant dose-response relationship between the adjusted hazard ratios for these two complications and the number of units of allogeneic blood transfused. The mechanism of susceptibility is unknown, but the effect is not seen with leukocyte-depleted blood in animal studies.

One estimate of excess mortality due to infection resulting from blood transfusion-induced immune suppression is 125 deaths/million units. In animal models, blood transfusion also leads to accelerated tumor growth and increased mortality. This may be important in the occurrence and recurrence of malignancy in humans.

Blood transfusion increases mortality by 9 percent in patients with colorectal cancer

Aging — There are many potential confounding factors in studies of immune system function in aged humans. These include acute or chronic illnesses, use of a large number of medications, nutritional status, and age-related changes in other body systems.
The immune deficiency of old age is relatively mild, and severe opportunistic infections such as P. carinii pneumonia, or disseminated fungal infections, are not common.
Reactivation of tuberculosis and varicella infection are two frequent features of age-associated decline in immunity.

Non-specific defense mechanisms such as mucus secretion are decreased in the elderly.

Generalized loss of tissue elasticity/contractility and decreased autonomic function also contribute to increased bacterial infections of the respiratory and urinary tracts.

Phagocytic cell function, including mobilization in response to inflammatory mediators, phagocytosis, and intracellular killing, may all be decreased in aged individuals. This leads to decreased leukocytosis during infection, and a diminished ability to kill invading microbes.

A defect in cytokine production by these cells is also suggested by the attenuated febrile response in the elderly.

In adolescence, the thymus begins involution which continues gradually through middle age. The number of immature T cells in the peripheral circulation increases with age, reflecting the impairment of the thymic maturational environment. T cells from aged animals and humans consistently show depressed responsiveness to mitogens, alloantigens, and specific foreign antigens. Decreased or absent response to skin DTH testing is common. About 1 in 10 people infected with M. tuberculosis under the age of 55 are anergic, while above age 55 the number rises to 1 in 3. In aged skin, the number of Langerhans cells may be reduced by as much as one-half.The number of circulating B cells does not change with age. However, the titer of specific antibodies falls, and the amount of autoantibodies rises correspondingly. This decline in foreign antigen response appears to result principally from deficient T cell help, since the response of B cells to nonspecific stimuli such as mitogens or anti-Ig antibody is well-preserved. Elderly subjects do not respond to vaccination as consistently as do younger people. Their responses also wane more rapidly. These phenomena may indicate a need for revision of immunization schedules for older people.Circulating autoimmune T cells and autoantibody levels increase with age. The reason for this is unknown. It is generally thought to reflect progressive dysregulation of lymphocyte development and function with age. There is no clear evidence that these autoreactive elements are responsible for much pathology. Many forms of cancer are common in older people and age alone is the single most important risk factor for any form of neoplasm. Increased malignancy in the elderly is most often attributed, at least in part, to declining immune system surveillance against neoplastic cells.
However, this has not been clearly demonstrated.

Stress — Major life stresses such as bereavement, as well as less catastrophic stresses such as examinations in medical school, have been associated with increased rates of respiratory tract infection, reactivation of herpesvirus infections, and increased incidence of cancer. Similar findings occur in humans and animals during and after space flight. While the space environment may play a role, this is thought to be most likely the result of a relatively extreme occupational psychological stress, with possible implications for more down-to-earth highly stressful occupations.

Laboratory studies have consistently shown reduced natural killer cell activity and depressed lymphocyte mitogen responses in stressed individuals.
The discipline of psychoneuroimmunology is devoted to the study of these phenomena, although well-defined mechanisms of neural regulation of immunity are yet to be described. Increased production of corticotropin-releasing factor and sympathetic autonomic activity have been suggested to play a role.

It is unlikely that emotional stress alone, however severe, will commonly cause an increased incidence or severity of infection sufficient to prompt investigation of immune function.

The degree to which stress contributes to the public health burden of infectious disease and malignancy remains a subject of debate.

Laboratory evaluation of the immune system

Immune deficiency most frequently comes to clinical attention because of an increase in the incidence or severity of infectious illness beyond what is considered "normal." These diseases may also present clinically with symptoms arising from the dysfunction of organ systems or cells not directly related to the immune system. The laboratory evaluation of suspected immune deficiency is guided by the particular circumstances of the patient's presentation, such as the age of onset of disease, the nature of the infections (viral, bacterial, fungal, opportunistic), and any associated nonimmunologic symptoms and signs.

Definitive diagnosis frequently requires specialized molecular methods that are not generally available in reference laboratories.

CELLULAR IMMUNITY — Specific cellular immunity is mediated by T cells, and defects affecting these lymphocytes underlie the most severe immune deficiencies.

Because antibody production requires intact T cell function, most T cell defects lead to combined (cellular and humoral) immune deficiency.

Any child presenting with recurrent or severe viral and/or bacterial illnesses or opportunistic infections in the first year of life requires evaluation of T cell number and function. Similar considerations apply to adults with these types of infections.

In the pediatric age group, most cases are due to congenital immune deficiency.

In older children and adults, the major causes are HIV infection and iatrogenic immune suppression due to therapy for autoimmune disease, malignancy, or transplantation.

Occasionally, mild forms of primary combined immune deficiency escape diagnosis until adulthood.

Complete blood count with differential and blood smear — The complete blood count (CBC) with differential and blood smear must be performed in all cases. Normal ranges for cell populations in adults are well established, and the normal ranges for lymphocytes in children are also available

In many diseases, cell populations are initially normal, and then decline over time. Thus, normal results in the past cannot be relied upon as a reflection of the current state.

The CBC establishes the presence or absence of lymphopenia, and any associated gross hematologic abnormalities, some of which may greatly assist in diagnosis. Sequential CBCs can also be used to monitor the courses of various disorders. However, a single finding of lymphopenia should be interpreted with caution, since transient lymphopenia is frequently found in a variety of common infectious illnesses.

On the other hand, significant lymphopenia should not be ignored, since lymphopenia may be the first indication of SCID. It is also critical to note that normal lymphocyte counts in infants are much higher than in older children and adults.

In an infant with any significant infection and a total lymphocyte count <3,000 cells/cubic mm, flow cytometry (see below) should be performed.

In the absence of other indicators of immune dysfunction, there should at the very least be subsequent measurement of the lymphocyte count to document normalization.

Persistent lymphopenia requires further investigation of immune function.

HUMORAL IMMUNITY — Panhypogammaglobulinemia is a hallmark of most forms of severe combined immune deficiency. In other combined immune deficiencies, as well as in several predominantly humoral immune deficiencies, there are characteristic alterations in the profile of immunoglobulin (Ig) isotypes that may aid in diagnosis.
Clinically, antibody deficiency most frequently results in recurrent and severe sinopulmonary infections with encapsulated bacterial strains.

Measurement of serum immunoglobulins — Routine measurement of IgG, IgA, and IgM is useful in all cases of suspected antibody deficiency, and in children older than one year of age measurement of IgG subclasses may be considered but is controversial.

Measurement of IgE should also be performed since serum levels may be altered in characteristic patterns that may aid in diagnosis.

Measurement of serum IgD is not useful for the diagnosis of immune deficiency.

Medical therapy of immune deficiency

The predominant clinical consequence of immune deficiency is an increased frequency and severity of infection. A better understanding of the molecular pathophysiology of many of these disorders has recently been realized. In addition, a number of new medical therapies have provided dramatic improvements in life expectancy and in the quality of life for immune deficient and immune suppressed subjects.

IMMUNE GLOBULIN REPLACEMENT — Human immunoglobulin was first administered in the treatment of an immune deficiency by Dr. Bruton in 1952. His patient, an eight year-old boy with X-linked agammaglobulinemia, received intramuscular injections. He responded with a decreased incidence of infections and lived into his fourth decade when he died from pneumonia. Intramuscular immunoglobulin clearly provided some protection from bacterial infection, at the cost of frequent painful injections.

Preparations of human immunoglobulin for intravenous administration (IGIV) became available in the United States in 1981.

Intravenous infusion provided the advantages of less frequent and higher dosing with greater efficacy and less discomfort.

SPECIAL IMMUNE SERUM GLOBULINS — Serum from donors having high titers of antibodies directed against particular infectious organisms may be pooled to prepare special lots of immune globulin with standardized amounts of antibody activity against the pathogen in question.
Only cytomegalovirus immune globulin and varicella-zoster immune globulin are commonly used in the management of immune deficiency disorders.

Cytomegalovirus immune serum globulin — CytoGam (MedImmune, Inc., Gaithersburg, MD) is a gamma globulin preparation using pooled serum from donors with high titers of cytomegalovirus (CMV) antibody. It has been used principally for the prophylaxis of CMV infection

PROPHYLACTIC ANTIBIOTICS — Standard regimens of antibacterial prophylaxis applied in the care of immune deficient patients are identical to those derived from a series of immunocompetent patients with recurrent otitis media. A general principal is the use of approximately one-half of a therapeutic dose:

For adults — amoxicillin (500 mg daily or 250 to 500 mg BID) or trimethoprim-sulfamethoxazole (160 mg as trimethoprim daily or 80 to 160 mg BID); azithromycin 500 mg/kg q wk.

If these options are not effective, clarithromycin 500 mg per day or amoxicillin-clavulanate 875 mg or 1000 mg per day in a single dose can be used.