

Managing Infection in Cancer Patients and Other Immunocompromised Children

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ABSTRACT

Children on immunosuppressive therapy for cancer or organ transplantation are very similar to those with primary immunodeficiency in that all are highly predisposed to infection with all types of pathogens—ie, bacteria, viruses, fungi, and parasites—and are highly likely to experience the reactivation of microbial agents, particularly viruses, while they are immunosuppressed. For this reason, early recognition and treatment are critical for optimal chances of survival and minimal morbidity. The selection of initial empiric therapy for these patients when febrile is based on the type of immune suppression (eg, neutropenia and cellular immunity) and other predisposing factors such as the presence of central venous lines (CVLs). Much of our clinical approach to prophylactic and definitive antimicrobial therapy for children with cancer and suspected infection comes from our experiences in managing children with primary immunodeficiency. For this reason, the present review examines aspects of management of all patients with primary or acquired immunodeficiency. Consistent infections in all of these patients include bacteremia in those with CVLs, *Pneumocystis jirovecii* pneumonia, primary and reactivation infection with herpes group viruses, and opportunistic fungi.

Some infections in well-defined groups of immunosuppressed hosts are frequent enough to warrant prophylactic therapy; in most cases, the duration of such therapy is well defined. Excessive continuation is likely to lead to colonization and infection with antibiotic-resistant organisms. When antimicro-

bial therapy is used for defined infections, the use of the highest dosages considered safe and longer durations are warranted.

INTRODUCTION

Oncology patients, both children and adults, have a very high incidence of infection, resulting from the immunodeficiency that is iatrogenically introduced during their management (Table 1).^{1,2} This circumstance is an unavoidable consequence of advances in cancer treatment that have resulted in greatly increased survival and overall cure. Chemotherapeutic regimens for cancer patients, directed at inhibiting tumor replication, are toxic to all elements in bone marrow, including immunologically competent white blood cells. In addition, patients with a variety of diseases are kept alive for longer periods of time using extraordinary supportive measures that offer a much greater chance for eventual colonization with multiresistant or unusual microorganisms as well as eventual overt infectious disease. The infectious agents that cause such infections are often opportunistic organisms. For each medical intervention in these fragile patients, the physician must calculate risk-benefit factors and anticipate adverse events.³ Some common complications involve local factors related to diagnostic or therapeutic procedures and to the placement of indwelling catheters, cannulae, or other foreign bodies. Such factors set the stage for colonization with opportunistic pathogens, which may then account for significant morbidity and mortality.

Most patients with diseases that result in secondary immunodeficiency receive blood or blood products during the course of their therapy. The transmission of infectious diseases to these patients represents a significant risk, particularly for patients who receive multiple transfusions (Table 2).⁴ Potential blood donors are not screened for many of these agents. Hepatitis is the best-understood and most carefully monitored disease, whereas recent literature⁵ incriminates cytomegalovirus as an agent that is increasingly likely to cause severe illness. Blood donors are often asymptomatic for infectious agents

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Table 1. Iatrogenic Predisposition to Infection

Local factors; mucosal and skin lesions
Drugs (eg, cyclophosphamide)
Procedures (intravenous administration, cutdown, bone marrow biopsy)
Surgical wounds
Urinary catheters
Intravascular devices (intravenous, intraarterial, central venous pressure, Swan-Ganz catheters, etc)
Respiratory support (ventilator, intermittent positive pressure breathing, etc)
Transfusion-transmitted disease
Splenectomy
Hospital-acquired resistant bacteria (caused by inadequate handwashing)

at the time of phlebotomy. When the recipient of blood products is immunocompromised, additional care should be taken in screening donors and providing follow-up medical examination of donors as a routine aspect of the recipient's care. Additional problems of transfusion therapy are pulmonary edema from volume overload, hemolytic reactions, and other incompletely understood febrile reactions.

Table 2. Infections Transmitted by Blood Transfusions**Bacterial**

Bacterial sepsis
Endotoxemia
Brucellosis
Syphilis
Salmonellosis

Viral

Cytomegalovirus
Epstein-Barr virus
Hepatitis A, B, and C viruses (now rare)
Measles virus
Rubella virus
Colorado tick fever virus
Human immunodeficiency virus (now rare)

Other

Toxoplasmosis
Babesiosis
Malaria
Leptospirosis
Filariasis
Trypanosomiasis
Chagas disease
Creutzfeldt-Jakob variant (not established)

Table 3. Primary Immunodeficiency Syndromes in Order of Frequency

	Usual Age at Diagnosis	Gender
Transient hypogammaglobulinemia of infancy	6-12 months	Both
Selective immunoglobulin A deficiency	4-16 years	Both
Common variable hypogammaglobulinemia	All ages	Both
Chronic mucocutaneous candidiasis	1-2 years	Both
Cyclic neutropenia	All ages	Both
X-linked hypogammaglobulinemia (Bruton type)	6-12 months	Male
Ataxia telangiectasia	3-5 years	Both
Chronic granulomatous disease	2 years	Primarily male
Severe combined immunodeficiency	9 months	Both
Wiskott-Aldrich syndrome	1-2 years	Male
Thymic hypoplasia (DiGeorge syndrome)	3 months	Both
Complement deficiencies	All ages	Both

PRIMARY IMMUNODEFICIENCY

Determining the incidence of primary immunodeficiency syndromes is difficult because many of the more severe forms may result in early infant death before a diagnosis. One British study estimated that 1 in 50 child deaths was a result of immune dysfunction.⁶ Realistically, primary care physicians only occasionally encounter the more severe defects. More common deficiencies, such as transient hypogammaglobulinemia of infancy and selective immunoglobulin A (IgA) deficiency, are familiar to clinicians.

Most primary immunodeficiency syndromes present during infancy or early childhood, with the most notable exceptions being common variable hypogammaglobulinemia, cyclic neutropenia, and complement deficiencies that may not become clinically apparent until later in life. The deficiencies of the latter components of complement components 5-8 are not seen until adolescence or early adulthood with the presentation of recurrent meningococcal and gonococcal disease. Immunodeficiency syndromes and their usual age at diagnosis are summarized in Table 3.

The approach to therapy varies according to the specific defects demonstrated (Table 4). The most

Table 4. Therapeutic Approaches to Immunodeficiency Syndromes

Syndrome	Therapy
T cell deficiency	
DiGeorge syndrome (thymic aplasia)	Bone marrow transplantation
Nezelof syndrome (thymic hypoplasia)	Antimicrobial therapy, bone marrow transplantation
Wiskott-Aldrich syndrome	Bone marrow transplantation
Ataxia telangiectasia	Fresh plasma, antibiotics
Chronic mucocutaneous candidiasis	Ketoconazole, fluconazole suppressive therapy
B cell deficiency	
Hypogammaglobulinemia	Intravenous immunoglobulin replacement
Selective immunoglobulin A deficiency	Antibiotics
Complement deficiencies	Antibiotics, fresh plasma, meningococcal vaccine
T and B cell deficiency	
Severe combined immunodeficiency	Bone marrow transplantation
Phagocytosis	
Hyperimmunoglobulin E, Job syndrome	Antibiotics
Chronic granulomatous disease	Antibiotics, interferon, bone marrow transplantation
Neutropenia	Antibiotics, granulocyte colony stimulating factor, granulocyte transfusions

difficult deficiencies to manage are those with T lymphocyte or combined T and B lymphocyte abnormality, for which bone marrow transplantation usually represents definitive therapy. Selective B lymphocyte deficiencies with hypogammaglobulinemia are treated with immunoglobulin replacement and are best managed by primary care physicians. Intravenous preparations of human serum Ig are readily available for therapy, generally given at a dosage of 400 mg/kg monthly. These treatments should be used only for patients with documented hypogammaglobulinemia accompanied by recurrent clinical infection or with demonstrated inability to produce specific antibodies following antigenic challenge (eg, tetanus). The physiologic hypogammaglobulinemia, apparent at 3-6 months of age, does not require supplemental Ig and must be distinguished from the transient hypogammaglobulinemia seen in infancy. The latter deficiency represents a delay in normal antibody synthesis after maternal IgG is no longer at protective levels; these infants

Table 5. Most Common Causes of Secondary Immunodeficiency in Children

Acquired immunodeficiency syndrome	Splenectomy
Sickle cell disease	Poor nutrition
Leukemia	Other malignancies
Nephrotic syndrome	Autoimmune disease
Down syndrome	Immunosuppressive chemotherapy

occasionally require Ig supplementation until approximately 18 months of age.

Defects in neutrophil function must be followed closely and treated with antibiotics, especially during acute infectious episodes. Thus, close communication between patient or parent and physician becomes the most important aspect of management.

SECONDARY IMMUNODEFICIENCY

The suppression of immunologic function with resulting increased susceptibility to infection may result from a number of primary diseases (Table 5). This circumstance is more common in adults than in children because of the higher incidence of malignancy and the greater use of immunosuppressive chemotherapy for a variety of diseases. Acquired immunodeficiency syndrome is the most common predisposing factor in children.

More than 2% of all hospitalized children demonstrate secondary immunodeficiency.⁶ Recognition and treatment of these host defense abnormalities have therefore become a very important aspect of hospital practice. Secondary deficiency is actually much more common than primary immunologic disorders, even in infants and children, and is usually managed by primary care physicians with consultative support.

The recognition of associations between specific infectious processes and primary disease offers important guidance to diagnosis and treatment (Table 6). All of these should be well understood by physicians caring for pediatric patients.

Neutropenia

Congenital neutropenias may present either in childhood or during the adult years and include benign neutropenia and variants thereof, cyclic neutropenia, and infantile genetic agranulocytosis.⁷ These syndromes are secondary to the inadequate production of granulocytes. Although a large spectrum of clinical consequences has been described, most patients do not experience a significantly

Table 6. Unusual Pathogens and Disease Entities Associated With Secondary Immunodeficiency

Leukemia	Disseminated chickenpox <i>Pneumocystis jirovecii</i> pneumonia Herpes simplex <i>Candida</i> sp. sepsis Ecthyma gangrenosum (<i>Pseudomonas</i> , <i>Aeromonas</i> spp.) <i>Aspergillus</i> sp. pneumonia
Sickle cell disease	Pneumococcal meningitis, bacteremia and pneumonia <i>Salmonella</i> sp. osteomyelitis
Nephrotic syndrome	Pneumococcal peritonitis Disseminated chickenpox
Down syndrome	Pneumococcal pneumonia Hepatitis
Splenectomy	Pneumococcal sepsis
Diabetes	Malignant otitis externa (<i>Pseudomonas</i> sp.) Phycomycosis (mucormycosis) Listeriosis

increased propensity for infection. Inadequate production of neutrophil precursors may also be a consequence of nutritional deficiencies, including vitamin B₁₂ and folate, or secondary to infectious processes such as typhoid fever, infectious mononucleosis, and viral hepatitis. More common than congenital neutropenias are neutropenic states secondary to the use of cytotoxic drugs in cancer therapy, autoimmune disease, and the excessive destruction of granulocytes (either as inherited disorders, because of hypersplenism, or a result of artificial heart valves or hemodialysis).

More recently described⁷ is an autoimmune process in which antibodies, directed at neutrophils, produce profound neutropenia. These autoantibodies are often seen in conjunction with autoimmune states such as lupus erythematosus and Felty syndrome. In such cases, infectious diseases are difficult to manage and account for observed high mortality. Granulocyte transfusions are of no benefit because antineutrophil antibodies destroy donor cells.

The clinical approach for patients with neutropenia secondary to immunosuppressive chemotherapy consists of careful monitoring for infectious episodes and early institution of antimicrobial therapy. Once acute infection is documented, these patients must be treated for longer periods because eradicating bacteria without the help of the host's granulocyte killing capacity is extremely difficult.

Table 7. Susceptibility Staging for Neutropenia Secondary to Immunosuppressive Chemotherapy

Absolute Neutrophil Count/mm ³	Predisposition to Bacterial Infection
>1000	Little
500-1000	Mild
<500	Moderate (50%)
<100 anticipated >7 days	Severe (100%)

Normal neutrophil counts are generally in the range of 2,000-5,000/mm³, with variations by age, gender, and race. Although neutropenia is defined as an absolute neutrophil count of <1,500/mm³, increased infection is not observed until a neutrophil count is <1,000/mm³. The absolute neutrophil count is an important objective parameter for making clinical decisions about immunosuppressed patients with fever (Table 7). Offering antibiotics to febrile patients with a neutrophil count of <500/mm³ pending results of culture has become a fairly standard protocol.

During periods of anticipated transient neutropenia, such as during induction therapy for cancer, patients may benefit from granulocyte transfusions. Such transfusions may be impractical unless the period of neutropenia is ≤6 weeks, but under these defined conditions benefits from such transfusions have been demonstrated.⁸

Neutropenia and Fever

The most common clinical circumstance in which the physician must make decisions for the immunocompromised host involves fever in the neutropenic patient. In pediatrics, this individual is most likely a child with leukemia who is neutropenic secondary to chemotherapy administered during treatment of the oncologic process. Such patients are not only neutropenic, but their remaining granulocytes function poorly in mechanisms of phagocytosis and bacterial killing, unlike other neutropenic states (eg, congenital neutropenia) in which remaining neutrophils function normally. This function problem accounts for the increased susceptibility of neutropenic cancer patients over those with neutropenia of other etiologies. More common pathogens causing infection in childhood leukemia are listed in Table 8.⁹

The best indicator of susceptibility to systemic bacterial disease is the absolute neutrophil count. A count of <500/mm³ in a febrile patient dictates empiric antimicrobial therapy¹⁰ (Table 9). If therapy is not instituted and blood cultures are obtained daily for 5 days, 50%-80% will eventually demonstrate

Table 8. Documented Etiology of Infection in Childhood Leukemia

Bacterial	75%
<i>Staphylococcus epidermidis</i>	50%
<i>Staphylococcus aureus</i>	15%
<i>Escherichia coli</i>	3%
<i>Pseudomonas aeruginosa</i>	2%
<i>Klebsiella/Enterobacter</i> sp.	1%
Others	4%
Viral	20%
Varicella-zoster virus	7%
Herpes simplex virus	5%
Cytomegalovirus	5%
Others	3%
Fungal	5%
<i>Candida albicans</i>	4%
Others	1%

bacteremia. If antibiotics are not started until a positive culture is obtained, mortality is more than 80%.

Low-risk patients may receive initial oral or intravenous empirical antibiotics in a clinic or hospital setting (Tables 10 and 11).^{11,12} Ciprofloxacin plus amoxicillin-clavulanate in combination is currently recommended for oral empirical treatment.⁹

Diagnostic evaluation should include cultures of blood, urine, and any other areas of suspicion, with

Table 9. Initial Management of the High-Risk Febrile Neutropenic Patient

Intravenous Monotherapy (preferred)
•cefepime
•meropenem or imipenem cilastatin
•piperacillin-tazobactam
If <i>S aureus</i> or <i>S epidermidis</i> highly suspected
•add vancomycin
Penicillin-allergic patients
•cephalosporins except immediate-type reaction, then use ciprofloxacin plus clindamycin or aztreonam plus vancomycin
If gram-negative status is highly suspected
•add aminoglycoside
•other combinations with aminoglycoside
○ ticarcillin
○ ticarcillin/clavulanic acid
○ azlocillin
○ mezlocillin
○ piperacillin

Reassess after 3 days (see Tables 10 and 11)

Table 10. Continued Management of the Neutropenic Patient After 3 Days of Intravenous Antibiotics

Afebrile and etiology identified

Adjust to most appropriate management.

Afebrile and etiology not identified

Low risk

Oral antibiotics: ciprofloxacin plus amoxicillin-clavulanate
ANC >500/mm³ at day 7: stop

Intermediate risk (ANC <500/mm³ at day 7)

Clinically well: stop antibiotics when afebrile 5 days.

High risk (unstable or ANC <100/mm³)

Continue same intravenous antibiotic(s).

ANC, absolute neutrophil count.

chest x-ray and lumbar puncture to be performed if central nervous system infection cannot be ruled out clinically. Baseline liver enzymes, renal function studies, and serum electrolytes should also be obtained prior to beginning antimicrobial therapy. The selection of antibiotics must obviously provide coverage for the most likely pathogens, yet be particularly directed at the most difficult-to-treat organisms. In most settings, *Pseudomonas aeruginosa* represents the most resistant potential organism.

Presently no clinical evidence demonstrates that one particular combination from the list in Table 9 is more efficacious than another. Monotherapy is preferred unless *Staphylococcus aureus* is a major consideration.

Finally, the duration of recommended therapy is different from that for routine infections; treat-

Table 11. Management of Patients With Persistent Fever (5-7 Days)

Reassess

Options for management

1. Continue initial antibiotics.
Stop vancomycin if stable.
2. Change antibiotics for progressive disease.
3. Add IV fluconazole or liposomal amphotericin B.

Duration of therapy

Day 7: Afebrile and ANC >500/mm³

Stop antibiotics.

Day 7: Afebrile and ANC <500/mm³

Continue oral or IV antibiotics for 14 days and then reassess.

Day 7: Febrile

Continue IV antibiotics until afebrile 5 days.

IV, intravenous; ANC, absolute neutrophil count.

Table 12. Treatment of Candidemia in Neutropenic Patients**Stable Patients**

Fluconazole 12 mg/kg/d IV divided twice a day

Unstable Patients

Liposomal amphotericin B 3-5 mg/kg/d IV divided every 24 hours
and

Fluconazole 12 mg/kg/d IV divided twice a day
When stable, fluconazole

Empirical Therapy (including other fungi)

Fungus unlikely: fluconazole

Fungus likely: liposomal amphotericin B, voriconazole, posaconazole, micafungin, or caspofungin (all acceptable alternatives)

IV, intravenous.

ment courses depend on the period of fever and granulocytopenia. If a patient shows a return of peripheral neutrophils after 3 days of therapy, then intravenous antibiotics could be discontinued and treatment changed to oral therapy, particularly if cultures are negative and the patient is afebrile. On the other hand, if fever and granulocytopenia persist, antibiotics are usually continued even after what would normally be considered adequate therapy (Table 11).

Candidemia

The recovery of *Candida* sp. from the blood of immunosuppressed patients has become common-

place and usually results from 2 predisposing factors: long-term, broad-spectrum antibiotics and the presence of intravascular access lines. In almost all cases, medically placed catheters or other offending foreign bodies should be removed to help eradicate this fungus. Limiting the number of broad-spectrum antimicrobial agents used must also be considered. Table 12 summarizes the management of candidemia. Fluconazole or liposomal amphotericin B, in relatively low doses and of short duration, is usually effective in treating this infection. In the immunologically normal host with candidemia, the removal of the intravascular line is often the only necessary step.

PROPHYLAXIS

Some infections in a well-defined group of immunosuppressed hosts are frequent enough to warrant prophylactic therapy (Table 13).

CUTANEOUS ANERGY

Transient defects in cell-mediated immunity are commonly encountered during the course of acute or chronic illnesses (Table 14). For a variable period of time, patients may fail to demonstrate positive delayed hypersensitivity to intradermal skin testing.¹³ This lack of reaction presents an enigma to clinicians using a skin test to diagnose a patient's primary illness. To differentiate global cutaneous anergy, a battery of skin tests might be applied along with the test antigen. A positive skin test to a recall antigen such as tetanus or candida along with a negative skin test to the pathogen in question would reassure the

Table 13. Prophylaxis for the Immunocompromised Host

Underlying Disease	Infectious Agent	Prophylactic Regimen
Leukemia Primary immunodeficiency Severe combined immunodeficiency DiGeorge syndrome Nezelof syndrome	<i>Pneumocystis jirovecii</i>	Trimethoprim/sulfamethoxazole (TMP/SMX) 5 mg TMP/25 mg SMX per kg per day orally, divided every 24 hours or 3 times weekly
Asplenia Splenectomy Sickle cell disease	<i>Streptococcus pneumoniae</i>	Conjugate pneumococcal vaccine at age 2, 4, 6, and 12-15 months; pneumococcal polysaccharide vaccine at 2 years and 5 years later PLUS
Congenital complement deficiencies (C2, C3, C3b inhibitor, C5)		Benzathine penicillin G 1.2×10^6 U intramuscularly every 3 weeks (>60 lb); 600,000 U (<60 lb) every 3 weeks or Penicillin V 250 mg orally twice a day (>60 lb); 125 mg orally twice a day (<60 lb)
Chronic granulomatous disease	<i>Staphylococcus aureus</i>	TMP/SMX (for immune augmentation) 4 mg TMP/20 mg SMX per kg per day orally, divided every 12 hours

Table 14. Causes of Cutaneous Anergy

Primary Immunodeficiency
Secondary Immunodeficiency
Acquired immunodeficiency syndrome
Malignancy
Immunosuppressive therapy
Autoimmune disease
Surgery (recent)
Trauma
Burns
Poor nutritional status
Advanced age
Acute disease process
Infectious Diseases
Bacterial
Viral
Fungal
Rickettsial
Chronic Diseases
Sarcoidosis
Rheumatoid
Renal
Alcoholism
Cirrhosis
Diabetes

physician that this patient can respond to specific antigens, allowing the physician to interpret the negative specific skin test as evidence against disease. However, this reactivity is not absolute—particularly when skin testing for tuberculosis—because antigen-specific nonreactivity has been observed.

The phytohemagglutination (PHA) skin test is probably the most sensitive test for evaluating anergy; the question of infection would be more rapidly resolved with this mitogen in the initial skin test battery. Placing other skin tests first would create a delay of 2 days while reading these tests before the PHA skin test can be applied as a second step in the diagnostic work-up.

Physicians should monitor patients with diseases known to be associated with cellular immunodeficiency and be alert that such patients are highly predisposed to viral and fungal infectious processes. The degree of cellular immunosuppression can be roughly determined by quantitating T lymphocyte CD4 subpopulations. This testing for clinical management helps direct early and aggressive use of antifungal or antituberculous medication for severely immunosuppressed individuals, often prior to receiving final culture results. With the use of a

Table 15. Cellular Immunosuppression and Susceptibility Staging of Patients

Degree of Immunosuppression	CD4 Cells/mm ³
Severe	
Age (years)	
<1	<700
1-2	<500
2-6	<250
>6	<100
Moderate	
Age (years)	
<1	700-1,200
1-2	500-750
2-6	250-500
>6	100-250
Mild	
Age (years)	
<1	1,200-1,750
1-2	750-1,000
2-6	500-750
>6	250-500

staging system (Table 15), patients can be categorized into those who have mild suppression of cellular immunity and those who are severely immunosuppressed. The latter group of patients is at extremely high risk of infection with opportunistic pathogens, particularly fungi and herpes group viruses.

TRANSPLANT RECIPIENTS

Patients who have recently undergone transplantation, either bone marrow or solid organs, represent a population with moderate to severe immunodeficiency and a high risk for opportunistic infections. Many infections are caused by reactivated pathogens present in the host or donor organs at the time of transplant. Etiology varies with timing before or after transplantation and is consistent enough to use timing in relation to transplant in the initial approach to a differential diagnosis (Figure).⁵ The reactivation of herpes group viruses, particularly cytomegalovirus, is so common in these patients that obtaining serologic data prior to transplant to determine previous infection with these potential pathogens for both recipient and donor is critical. Prophylactic antiviral and antibacterial therapy is often warranted.

CONCLUSIONS

Infection in immunocompromised patients offers a particular clinical challenge because the patho-

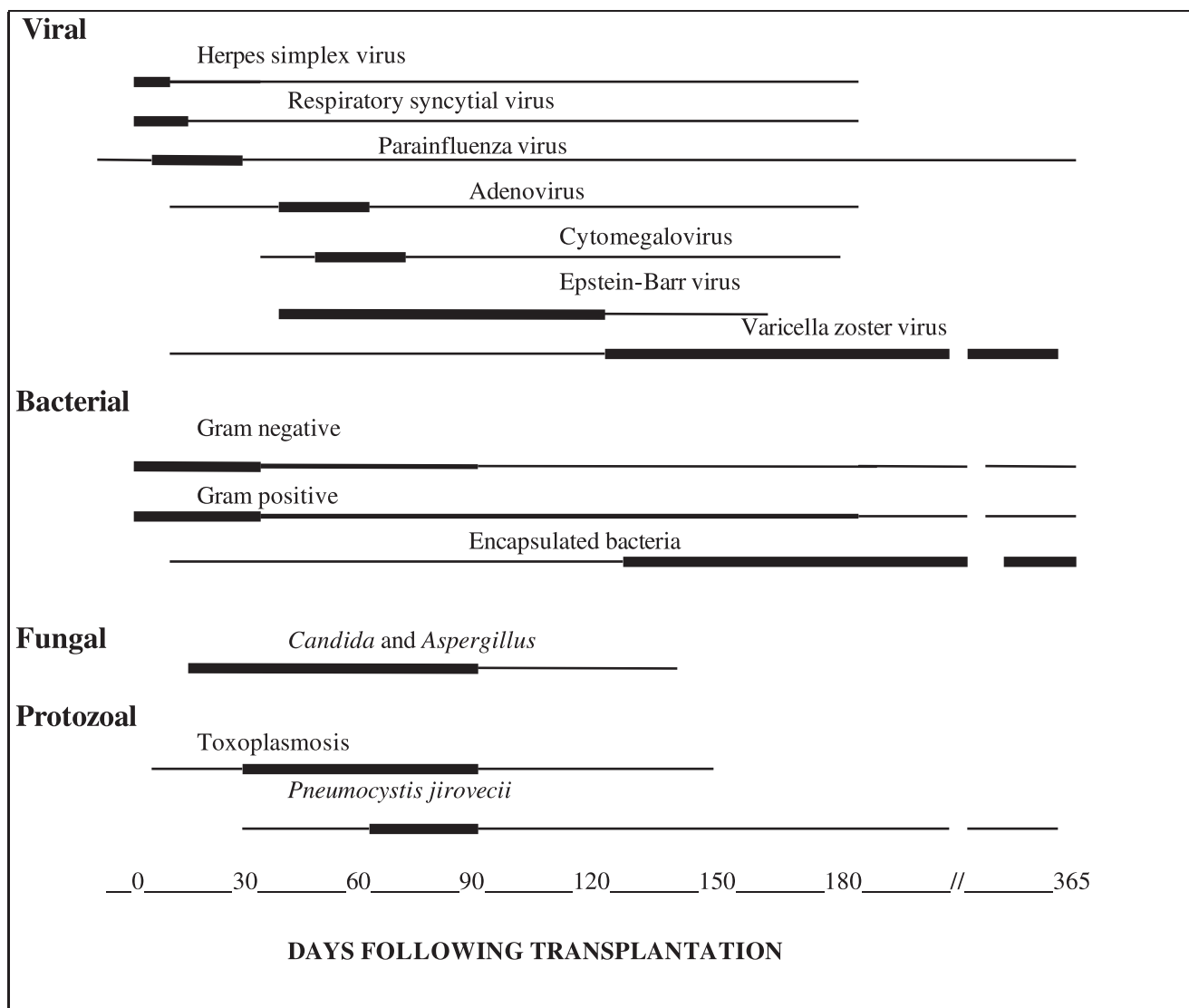


Figure. Timetable for infection following transplantation.

gens are often unusual, and appropriate treatment must begin early in the course of the illness. These patients also must receive the highest tolerated dosages of antimicrobial agents and for maximum durations. Prophylactic antibiotics should also be given based on the pathogens likely to reactivate during the time of more severe immunosuppression.

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