2 Signs and symptoms of infections and differential diagnosis from noninfectious conditions

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Lower respiratory tract

Infection of the lung is one of the most frequent infections seen in cancer patients, or at least it is one of the most frequently diagnosed on radiography or computed tomography (CT) scan. Aspiration of oropharyngeal bacteria is the usual mechanism by which patients acquire lung infection, and the hematogenous route is more exceptional. Lung infection is favored by local obstruction, for example, a tumor mass caused by lung cancer or, less frequently, metastatic cancer.

In patients with alteration of cell-mediated immunity, the most frequent etiologic agents are *Pneumocystis carinii*, *Mycobacterium tuberculosis*, and viruses, especially cytomegalovirus (CMV). In patients with altered humoral immunity, encapsulated bacteria are major sources of infection: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*. In patients who are neutropenic, either because of the underlying illness (leukemia) or because of chemotherapy, gram-negative bacteria and fungi are the main etiologies.

Signs and symptoms

Cough, fever, dyspnea, and sputum production are the major symptoms and signs suggesting the presence of lung infection. Alteration in mental status, rales, pleuritic pain, and hypoxemia may be present. The characteristic pattern of dry cough and orthopnea—patients breath well when supine but are dyspneic when sitting or even unable to speak one whole sentence without interruption—suggests *Pneumocystis carinii* pneumonia. Onset of cough and fever in the neutropenic patient, even in a nonhospital setting, suggests pneumonia with either gram-positive or gram-negative organisms, and prompt treatment should be directed against both, pending culture results. Persistance or recurrence of fever in the presence of x-ray evidence of pneumonia in the neutropenic patient suggests fungi: *Aspergillus* spp., *Mucor* spp., and less frequently *Candida* spp. [1]. *Aspergillus* spp. should be particularly suspected if the hospital or ward undergoes reconstruction [2]. Adult respiratory distress syndrome (ARDS), especially when associated with viridans streptococci, has been described in neutropenic patients [3–5].

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Diagnostic procedures

Chest radiography will usually confirm clinically suspected pneumonia and show more or less typical radiographic patterns: focal lesions, interstitial lesions, and atelectasis. In a review of the role of chest radiography in febrile neutropenic patients, pulmonary disease could be found in 30 percent of febrile episodes despite the presence of a normal chest radiogram [6]. The radiogram may appear normal in deeply neutropenic patients, especially when the granulocyte count is under 100/μl, because these patients are unable to produce an inflammatory reaction that would be visible on chest radiography.

Some radiographic signs have been described as being more or less specific for definite etiologic agents. The radiographic air crescent representing air interposed between a radiodense parenchymal lung lesion and the surrounding normal lung is most frequently seen in angioinvasive aspergillosis [7], less commonly in pulmonary mycetomas caused by other fungi, such as mucormycosis [8], and also in infection caused by *S. aureus* [9]. Patients who have normal chest radiograms or radiograms interpreted as demonstrating nonspecific changes may have infiltrates detected only by chest CT scans [10].

Sputum examination

The only proof of infection is isolation of the etiologic agent. Obtaining a valuable sample for microbiological examination is essential for distinguishing infectious from noninfectious conditions, for sensitivity testing, and for allowing correct treatment. Demonstration of tissue involvement is essential to prove invasive fungal disease. But even though every effort should be made to establish a definitive diagnosis, invasive procedures are often contraindicated in the presence of marrow aplasia. Gram stain and sputum culture are of less diagnostic value in neutropenic than in non-neutropenic patients, because there will not be sufficient polymorphonuclear leukocytes to validate the sputum specimen. Other immunocompromised patients fail to produce sputum at all, for example, patients with *Pneumocystis carinii* pneumonia. For *Aspergillus* there tends to be a consensus that if in the presence of a radiographic finding suggestive of invasive *Aspergillus* infection an *Aspergillus* spp. is isolated in the sputum, the probability of infection is very high [11].

Invasive procedures include transtracheal aspiration (TTA), bronchoscopy associated with bronchoalveolar lavage (BAL) and bronchial brushing, and transbronchial transpleural or open lung biopsy. All procedures have their adepts, and probably each center has the best results with the procedure the center is most used to and performs most often. It also depends on the kind of patient. For example, TTA is most useful for recovering anaerobic bacteria, but these infections are not common in the setting of cancer patients. Bronchoalveolar lavage and bronchial brushing are most useful for the diagnosis of *P. carinii* pneumonia. This technique is thus very useful in AIDS patients. Refinements of the BAL technique to avoid possible contamination by oropharyngeal bacterial flora have been described by Wimberly et al. [12] and others [13].

Quantitative bacteriology on samples obtained by bronchoscopy has also been attempted for greater diagnostic accuracy [14]. Obtaining a correct sputum sample for microbiological analysis is not only important to establish a diagnosis of infection but also to differentiate between infection and tumor invasion or radiation pneumonitis. For this differential diagnosis, biopsy, together with a negative microbiology exam, is the procedure of choice.

None of the procedures is 100 percent diagnostic, and often a combination of more than one only gives an approximate guess. More than one diagnosis may also coexist: a patient can have a mixed infection (e.g., *P. carinii* and CMV), superinfection, or a combination of a noninfectious process with an infection. Blood cultures are occasionally helpful in establishing the diagnosis.

Noninfectious causes mimicking lung infection in cancer patients are mainly neoplastic lung disease causing obstruction and secondary bacterial infection (lesions from lung cancer or from metastatic cancer, leukemic infiltrates, invasion of the mediastinal lymph nodes), pulmonary emboli, congestive heart failure, radiation pneumonitis, pulmonary hemorrhage, drug-induced pneumonitis (many cytostatic agents, including methotrexate, bleomycin, busulfan), and leukoagglutinin reactions during or in the 24 hours following blood transfusions. Leukoagglutinin reactions are rarer today because of the use of red blood cells rather than whole blood, containing leukocytes, and because of the use of filters [15].

As in the case of infectious causes, fever and dyspnea may be the only symptoms and signs present in the noninfectious conditions, and often consideration of the clinical setting will provide the clue to diagnosis: Previous radiation therapy, drugs administered, fever pattern according to the time schedule the drugs are administered, dissociation of fever and pulse rate, clotting abnormalities, and epidemiological patterns of *Legionella* or *Aspergillus* infections in the hospital.

Sinus infections

Pain, often unilateral, involving the frontal, temporal, or occipital area; dysesthesias over the face; and occasionally nasal discharge suggest sinusitis or spread of an ear, nose, and throat (ENT) tumor. The paucity of signs and symptoms often delays diagnosis and treatment. Sinusitis may mimick tumor or may accompany tumor or proton beam therapy [16]. Radiography or CT scan may differentiate between infection and tumor; aspiration or biopsy of the sinus will establish the definitive diagnosis, and in the case of sinusitis may demonstrate the etiologic agent. Gram-positive bacteria, including *S. pneumoniae* and *S. aureus*, gram-negative bacteria, and anaerobic bacteria may be the cause. If, however, after antibiotic treatment the symptoms do not improve, fungal infection should be strongly suspected; aspirated material will be positive by the potassium hydroxyde wet mount method if a sufficient fungal load is present. Cultures will be positive for *Aspergillus* spp. or *Mucor* spp., the most frequent fungi. *Alternaria* spp. have been isolated in six cases of localized sinonasal infection in a series of 1186 patients who underwent bone marrow transplantation [17,18].

Skin

Skin infections should be easy to diagnose because they are easily seen and are readily accesible for diagnostic procedures [19]. They can be divided into localized or regional infections, hematogenous infections, and infections around an implanted device. Localized infections include, especially in neutropenic patients, carbuncles, cellulitis, and abscesses. Clinical clues are often only pain and redness; the typical fluctuation, even in the presence of an abscess, is missing in those patients not able to produce an inflammatory local reaction. Other types of lesions are hemorrhagic or vesicular, or resemble subcutaneous nodules. Localized skin infections are rarely misdiagnosed; thrombophlebitis is a differential diagnosis of cellulitis. Particularly frequent are abscesses of the perianal region, which should be looked for systematically to avoid their resulting in life-threatening bacteremia.

Etiologic agents of localized infections include *S. aureus* and coagulase-negative staphylococci, gram-negative bacteria, or mixed gram-negative and anaerobic infections (especially in the perianal region), and also fungi and Herpes simplex virus. Skin infections as a manifestation of disseminated infection are often the long expected clue to make a correct diagnosis of an obscure fever in cancer patients. Sometimes the diagnosis is easy: Varicella or Herpes-zoster infection in patients with lymphomas are easy to recognize and can be treated effectively. Ecthyma gangrenosum is a lesion that is necrotic and ulcerates in its center, while ecchymotic in the periphery. It is classically a sign of *Pseudomonas aeruginosa* infection, but necrotizing skin lesions have also been described with other pathogens, including other gram-negative organisms. *Aeromonas hydrophila*, marine vibrios, *Nocardia* spp., and fungi have been described [19–21]. Cutaneous septic emboli of bacteria, and also of *Candida* spp., *Cryptococcus*, *Mucor* spp., and *Aspergillus* spp., have been reported [22–24].

Bacterial, mycobacterial, and fungal cultures, as well as histological examination of aspiration material or punch biopsy material, should actively be undertaken and will distinguish those maculopapular lesions from the true ecthyma gangrenosum lesions and also from pyoderma gangrenosum, a noninfectious lesion [25], and from Sweet's syndrome [26].

Skin infections presenting as abscesses, furuncles, nodules, or papules due to *Mycobacterium haemophilum*, accompanied sometimes by septic arthritis, osteomyelitis, pneumonia, or bacteremia, have recently been described in patients with lymphoma, after bone marrow transplantation for aplastic anemia or for acute myelocytic leukemia, as well as in renal transplant patients and patients with AIDS [27]. When acid-fast bacilli are observed in a sample recovered from a cancer patient with skin infection, special culture media and incubation at 30°C for 4 weeks should be utilized [28].

Punctures of the skin, and venous and arterial access devices

In the neutropenic patient venipunctures or punctures associated with invasive procedures can result in localized or disseminated infection. Short-term peripheral

intraarterial and intravenous catheters, as well as insertion of foreign bodies, such as Ommaya reservoirs for the treatment of meningeal infection or carcinomatosis, may also cause localized or generalized infection. For repeated courses of chemotherapy, administration of blood products, antibiotics, or parenteral nutrition, semipermanent venous access lines are now commonly used. Two types are currently available: tunneled silicone catheters exiting the skin (Hickman type) and totally implantable, subcutaneous infusion ports. Hickman-type catheters may result in exit-site infection, which is defined as erythema, induration, pain, or purulent discharge at the exit site or within 2 cm of the skin exit site. Erythema, tenderness, or induration along the subcutaneous tract of the catheter on a length greater than 2 cm defines tunnel infection [29]. Port pocket infection is defined as induration, erythema, and tenderness around the port with a culture-positive material aspirate from the port pocket [30]. Atypical mycobacterial infections have been described as exit-site infections around devices [31,32].

In granulocytopenic patients inflammatory signs may be discrete. All localized infections may be associated with bacteremia or fungemia. Site infection can sometimes be easily managed with local care and topical antibiotics. Catheter-associated bacteremia or fungemia can often be treated with antibiotics without removal of the catheter [33,34]. If, however, tunnel infection or port pocket infection is present, if there is evidence of systemic emboli, or if fever persists in spite of appropriate antibiotic treatment, removal is mandatory [34]. In a nonrandomized series comparing Hickman-type devices with ports, the incidence of infections per device day was 12 times greater with catheters than with ports, and the difference was 21-fold for bacteremia and fungemia [30].

Gastrointestinal tract and intraabdominal infections

Apart from the presence of a gastrointestinal or intraabdominal cancer itself, chemotherapy is the main factor predisposing cancer patients to develop infections. Intensive cytostatic treatment produces mucositis and ulceration of the gastrointestinal mucosa that allows invasion by microorganisms. Neutropenia favors infection with bacteria present in the mouth or gut, and alteration of cell-mediated immunity favors infection with CMV and *Salmonella* nontyphi. Both favor infections with parasites, especially the hyperinfection syndrome due to invading *Strongyloides* infection.

Mouth and pharynx

Stomatitis and pharyngitis may be noninfectious, due to chemotherapy, or infectious, due to the resident streptococcal or anaerobic flora, or to HSV. They may also first be noninfectious and then become infectious after colonization by resident bacteria or hospital flora. Symptoms of stomatitis, pharyngitis, and gingival infection are pain and difficulties with chewing and swallowing. If inspection of the oral cavity shows white plaques, *Candida* infection is suspected. Less frequent

manifestations of *Candida* infection are erythematous lesions on the dorsal surface of the tongue, called *acute atrophic candidiasis*, and involvement of the angles of the mouth (*perleche* or *angular cheilitis*). One should note, however, that true *Candida* infection is difficult to differentiate from *Candida* colonization: Biopsy, rarely performed, would prove tissue invasion.

Infectious mucositis in granulocytopenic patients may be caused by anaerobes, streptococci, and hospital-acquired gram-negative bacilli. A clinical presentation of necrotizing gingivitis is a more reliable diagnosis than a culture result, which may mean only colonization. Herpes simplex virus is another agent of mucositis and should be isolated by microbiological techniques, since successful treatment is now possible.

Esophagus

Candida oesophagitis is a common finding in neutropenic patients or in patients with altered cell immunity. It often accompanies or follows oral thrush. It should be suspected if pain on swallowing, retrosternal burning pain, or meallic taste or impression of food stop at the end of the esophagus or, less commonly, gastrointestinal bleeding is present. To confirm the diagnosis we prefer endoscopy to classical radiography of the esophagus, because it enables one to obtain a biopsy specimen at the same time and because radiographic specificity is lower. The endoscopic appearance of white plaques usually provides sufficent evidence to start antifungal treatment; culture is not useful because it does not distinguish between invasion and colonization; only biopsy proves fungal invasion. *Candida* infection may also present as ulcers or vesicles and must be distinguished from HSV infection or, more rarely, CMV, bacteria, or noninfectious causes such as reflux [35].

Stomach, small intestine, and colon

Gastric infection is rarely diagnosed in cancer patients but should be suspected in cases of nausea, vomiting, epigastric pain, and bleeding, especially when patients are receiving chemotherapy or corticosteroids. Endoscopy or radiologic exams may reveal an ulcer, and biopsy may show evidence of either CMV infection or gastric candidiasis [36–39]. Radiography shows a bull's-eye appearance, and the differential diagnosis is submucosal metastasis or lymphoma [39].

Small intestine and colon infection is suspected in patients with diarrhea, abdominal pain, small bowel or colon ulceration, or focal or diffuse colitis on radiography or endoscopy, which may lead to massive gastrointestinal bleeding and/or perforation. CMV is a major cause of small bowel and colon infection [36], but the role of *Candida* spp. is less well established. The 'usual' enteric pathogens should be considered: *Giardia lamblia*, especially in patients with dysgammaglobulinemias, *Salmonella* spp. in patients with alterations of cellular immunity, and *Cryptosporidium* [40]. Diarrhea and pseudomembraneous colitis may also be due to *Clostridium difficile* following chemotherapy [41–43]. *Strongyloides stercoralis*, usually causing mild or inapparent symptoms in the immunocompetent host, in the

immunocompromised host may lead to the hyperinfection syndrome, which is life threatening and consists of intestinal obstruction, gastrointestinal bleeding, and diffuse peritonitis [44,45]. The clinical presentation is one of acute surgical abdomen, due to perforation of the bowel by the parasite and subsequent bacterial infection, causing peritonitis and septicemia.

To prevent this life-threatening syndrome, examination of concentrated stool, especially in patients who have traveled to endemic areas or with a history of blood eosinophilia, should be performed prior to the administration of chemotherapy and corticosteroids. Acute abdominal pain should raise the suspicion also of appendicitis and of another entity mimicking appendicitis, neutropenic enterocolitis, an infection caused by *Clostridium septicum*, occurring in patients with neoplastic disease. Mucosal ulcerations of the gut seem to be the portal of entry. It also follows cytotoxic drug therapy for leukemia and lymphoma, and progresses rapidly to peritonitis, septicemia, and shock [46].

Another clinical entity causing intraabdominal infection should be mentioned, hepatosplenic candidiasis, also called chronic disseminated candidiasis [47,48]. It occurs most frequently in leukemic patients following prolonged neutropenia, which suggests that the gastrointestinal tract is the site of entry via the portal circulation. The clinical presentation is essentially fever without any detectable focus of origin, and sometimes abdominal or pleuritic pain, not responding to broad-spectrum antibiotics. The fever persists or recurs even when the patient recovers from neutropenia. Alkaline phosphatase is elevated, and the other liver function tests may be normal or abnormal. Ultrasonography, CT scan, or magnetic resonance imaging (MRI) showing multiple lesions in the liver and spleen suggest the diagnosis. Confirmation of the diagnosis should be obtained by liver biopsy before treatment is initiated with prolonged amphotericin B in high doses with or without flucytosine, or with liposomal amphotericin B. Biopsy will rule out other diagnoses, such as disseminated tuberculosis [49].

Central nervous system

Neutropenia as well as alteration of cell-related immunity predispose to central nervous system (CNS) infection. Symptoms and signs may be very subtle, and one should not let them worsen until obtundation and agitation occur. The subtle signs are sudden-onset or progressive headache and/or slightly modified mental status. Sometimes focal neurological signs may be present. Even if symptoms and signs are subtle, due to a diminished inflammatory response by immunosuppression, diagnostic procedures should be started immediately. They consist of CT scan or MRI and lumbar puncture. If lumbar puncture is performed before CT scan or MRI, papilloedema should be excluded on fundoscopic examination. Computed tomography scan or MRI will exclude mass lesions such as brain abscess, toxoplasmosis, or noninfectious causes, such as solid tumor or metastasis. Cerebral spinal fluid (CSF) examination will confirm or exclude meningitis or show leukemic meningitis with the presence of blast cells.

Which kind of meningitis do we expect in immunocompromised patients? Encapsulated bacteria (*S. pneumoniae, Neisseria meningitidis, H. influenzae, S. aureus*) are possible, especially in myeloma patients or in patients who have undergone splenectomy. *Staphylococcus aureus* and gram-negative bacilli (Enterobacteriaceae and *Pseudomonas* spp.) are frequent in neutropenic patients and cause meningitis by either the hematogenous route or by superinfection of surgical wounds. Cerebrospinal fluid shunt infections or infections resulting from implantation of devices, such as an Ommaya reservoir, are caused mainly by coagulase-negative staphylococci and *S. aureus*, but corynebacteria and gram-negative bacilli may be encountered [50,51]. *Listeria monocytogenes* is an important pathogen in patients with deficiencies of T-lymphocyte functions [52]. Cerebrospinal fluid findings are extremely variable: In a series of 78 patients white blood cell counts ranged from 6 to 12,000 cells/mm^3, and differential counts varied from 99 percent polymorphonuclear leukocytes to 98 percent mononuclear cells. Glucose levels may be low or normal, and the organism, a gram-positive rod, may not be seen on Gram stain and should not be mistaken on culture for a diphtheroid [53].

Fungal CNS infections occur in patients with a decrease of cell-mediated immunity. *Cryptococcus neoformans*, although less frequent than in AIDS patients, has been isolated in some cancer centers, quite often among patients with CNS disease [52,54,55]. Cerebrospinal fluid examination may show normal glucose and proteins, and only a slight pleocytosis. India ink examination may or may not show budding yeasts, and cultures are usually positive. The best diagnostic procedure, however, is the detection of cryptococcal antigen in CSF and in serum, which is positive in nearly all cases of cryptococcal infection. Other fungi that cause more rare CNS infections are *Aspergillus* spp. and *Mucor* spp. [56], which may both cause the rhinocerebral syndrome with infiltration of the brain from the sinus, causing proptosis and cellulitis around the eye, progressing to ophthalmoplegia and coma. The CNS infection is often associated with lung infection. Biopsy is needed to confirm the diagnosis.

Only one parasite causing CNS disease in cancer patients will be mentioned: *Toxoplasma gondii*. Excluding AIDS patients, who are much more frequently infected, 120 published cases of toxoplasmosis have been reviewed by Ruskin in 1989 [57], the majority of them occuring in patients with lymphoma and leukemia, and 65 presenting as a major neurologic syndrome. The ultimate diagnostic procedure is brain biopsy. Computed tomography scan or MRI may, however, as in AIDS patients, suggest the diagnosis strongly enough to allow a therapeutic trial, and only if there is no improvement will biopsy be undertaken [58]. Clinical presentation includes patients with headache, lethargy, confusion, fever, or seizures. Serology is rarely helpful in the immunocompromised patient, and CT scan and MRI suggest the diagnosis by showing enhancing lesions, typically the ring-enhancing lesions [58,59].

One would expect an increased incidence of viral diseases, especially of the genus Herpes in cancer patients with diminished T-cell function, but there is no evidence in the medical literature to firmly support this hypothesis. This may only be due to inadequate diagnostic methods at present.

Sepsis without a focus of origin

One of the greatest challenges to the oncology patient is isolated fever without microbiological or even clinical evidence of infection. We admit as a rule that fever in the neutropenic patient must be considered as having an infectious origin, unless proven otherwise, and be treated with antibiotics. A vigorous attempt should be made to establish the infectious focus and to document the microbiological etiology. Organ-oriented signs and symptoms that have been described and analyzed earlier must be carefully looked for, and diagnostic procedures that look most promising in a given situation should be undertaken. Common infections, such as urinary tract infections, should not be forgotten, and rare infections, such as babesiosis [57,60], must be kept in mind.

Fever can be due to noninfectious causes. We have already mentioned, in the differential diagnosis of lung infection emboli, atypical pulmonary edema, leukoagglutinin reactions, radiation pneumonitis, and drug-induced pneumonitis. Drug fever without pneumonitis is also frequent. Transfusion of blood products, hematomas, noninfectious infarcts of the spleen, graft-versus-host disease after bone marrow transplantation, and neoplasms themselves, especially Hodgkin's lymphoma, acute leukemias, hepatoma, and hypernephroma, can also cause fever, but these diagnoses must be accepted only if infections are ruled out. Recent studies seem to show a decline in the incidence of documented infections, probably due to the administration of prophylactic absorbable antibiotics, mostly quinolones, and perhaps also due to quicker empirical antibiotic treatment in the case of fever [61]. The latest published EORTC study [62] analyzing 858 febrile episodes in 677 patients found 29.5 percent of episodes were microbiologically documented infections (83 percent being bacteremias), 27.5 percent were clinically documented infections, and 43 percent were unexplained fevers. Some infections may not be recognized until autopsy. Many patients with or without documented infection respond to antibiotics.

Can laboratory parameters distinguish between fever of infectious and noninfectious origin? The best proof of an infection remains a positive blood culture, and the sooner the blood cultures detect the bacteria or the fungi, the sooner an appropriate treatment can be started. Some microorganisms only rarely grow in blood, such as *Aspergillus* spp., while others may have a fastidious growth, and blood cultures may become positive only after several days of incubation. The newer blood culture systems, such as lysis centrifugation, yield an earlier growth and detect more fungi than conventional broth systems [63]. Other systems, such as the infrared nonradiometric resin system (Bactec 660), or a system based on colorimetric detection, known as the BacT/Alert Microbial Detection System, may detect bacteremia and fungemia earlier.

Viral cultures should also be undertaken. They quite often yield positive results, especially for CMV, when using newer techniques, such as the shell vial assay and the polymerase chain reaction (PCR) [64,65]. PCR is a promising new tool, which, however, still yields too many false-positive results [66,67].

Because bacterial sepsis is accompanied by metabolic changes, referred to as

acute-phase responses, that are mediated by cytokines, the serum concentrations of tumor necrosis factor, interleukin-1 beta, interleukin-6, serum amyloid A (SAA), and C-reactive protein (CRP) have been measured in children with cancer who had fever and neutropenia to determine if these parameters could differentiate between bacterial infection and fever due to other causes. None of these variables correlated with documented bacterial etiology; they were not helpful for clinical decisions, neither on admission of a neutropenic child with fever nor after 2 days. The sensitivity of CRP determination proved to be poor [68,69].

A retrospective study [70] found CRP determination to be more helpful because it showed a statistically significant difference in patients with septicemia compared with patients without positive blood cultures. A significant difference was also found between CRP levels in patients with major infections and those in patients with minor infections. No difference was found between patients with microbiologically versus those with clinically documented infections. The authors concluded, however, that a prospective epidemiological study is needed before concluding that CRP is really helpful for predicting and diagnosing infection.

Bacterial serology using antigens for *S. aureus, S. pneumoniae, H. influenzae, Moraxella catarrhalis*, and Enterobacteriaceae, in a prospective study of 91 episodes of fever in neutropenic children with cancer, seemed helpful according to the investigators [71]. They found, however, that there may exist cross-reactions between *S. aureus* and *S. viridans*; the study also was not designed to rule out false-positive or false-negative antibody reactions. Even if bacterial serology becomes a promising tool in the future, this author believes that, for the moment, it does little to help the clinician make an appropriate decision when faced with a febrile neutropenic patient.

Fungal serology has also not made tremendous progress in recent years, especially in those infections in which it is most needed, *Aspergillus* spp. and *Candida* spp. infections. One remarkable exception is antigen detection of *Cryptococcus neoformans* (see earlier). Detection of anti-*Candida* antibodies or antigens, detection of *Candida* metabolites and cell-well components, and amplification of *Candida* DNA by PCR reaction are being investigated in several laboratories, but no system has yet been standardized enough to allow regular clinical use [72,73].

Fungal infections are probably the most frequent cause of fever of unknown origin in cancer patients [74]. In autopsy studies demonstrating candidiasis, the fungi were isolated when the patients were still alive by blood cultures in less than 50 percent of cases [75]. The role of fungi in infections of cancer patients has probably become even more important because of the widespread use of catheters. The significance of catheter-associated fungemia has not been clarified. Earlier investigators suggested that removal of the catheter is sufficient [76]. This may be true in some cases, but it is equally true that it is very difficult to distinguish between those patients who will have tissue invasion after fungemia and those who will not [75]. Probably all immunocompromised patients who have catheter-associated fungemia should be treated by systemic antifungal antibiotics to avoid serious complications, either clinically patent, such as endophthalmitis, endocarditis, or arthritis, or occult, which are discovered only at autopsy [77].

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