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Infectious Disease Complications in Cancer Patients

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Abstract

Critically ill cancer patients requiring intensive care unit (ICU) stay are vulnerable to infection due to a variety of factors, including local tumor effects, complex cancer treatments, disruption of physical barriers, neutropenia, humoral and/or cellular dysfunction, asplenia, and presence of foreign devices. Recognizing that cancer patients can have multiple immune defects concurrently is critical since it will affect diagnostic and therapeutic decision-making. This chapter describes common infectious complications that critical care teams may encounter while caring for cancer patients.

Keywords

infection; cancer; immunocompromised; neutropenia; sepsis; critical care

FEVER & NEUTROPENIA (F&N)

Febrile, neutropenic patients, particularly those with severe neutropenia >7 days, are at risk for progression to sepsis.[1] The model that is widely used to identify neutropenic patients at low versus (vs) high risk for complications is the Multinational Association for Supportive Care in Cancer risk score. The rate of septic shock associated with F&N ranges between 3.2% and 13.4% across centers.[2] With heightened recognition and improved supportive care, survival of neutropenic patients with severe sepsis or septic shock may be improving over time.[3] One challenge is distinguishing non-infectious mimics such as adrenal insufficiency and the cytokine release storm associated with receipt of chimeric antigen receptor T cells.[4]

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Diagnosis and Management

It is important to remember that neutropenic patients have attenuated signs and symptoms of infection. A thorough history and physical exam, including inspection of catheter sites, perirectal region, and the skin, are the bedrock of diagnostic evaluation. Initial evaluation also includes chest imaging for patients with respiratory symptoms, at least 2 sets of blood cultures (peripheral and catheter), and cultures of other sites as defined by the clinical presentation.[1] Prompt institution of empiric broad-spectrum antimicrobials (e.g., cefepime, piperacillin/tazobactam, carbapenem) is merited to prevent progression to sepsis. Upfront vancomycin use is not necessary unless there is suspected central venous catheter (CVC) infection, skin and soft tissue infection (SSTI), severe pneumonia, or hemodynamic instability. Modifications to the initial antibiotic regimen should be guided by clinical and microbiologic data. Patients who remain hemodynamically unstable despite standard F&N therapy should have their antimicrobial regimen broadened to include coverage for possible resistant bacteria and/or fungi.

CATHETER-RELATED BLOODSTREAM INFECTIONS (CRBSI)

CVC currently account for ~25% of all bloodstream infections (BSI) among oncology patients.[5] The most common etiologies include Gram-positive (GP) organisms such as coagulase-negative staphylococci (CoNS), *Staphylococcus aureus*, and *Enterococcus faecium* but with Gram-negative (GN) bacteria such as *Escherichia coli*, *Klebsiella* sp., and *Pseudomonas aeruginosa* also playing an important role. Recently, data suggest an epidemiological shift among oncology patients towards a GN predominance and may be attributable to infection prevention strategies primarily targeting GP organisms, including chlorhexidine for insertion site cleaning and use of antimicrobial-impregnated CVC.[5]

Pathogenesis

The most common source of catheter-related bloodstream infections (CRBSIs) is colonization of the catheter by the patient's own skin flora or contamination of the catheter hub during line insertion or manipulation. Less commonly, CRBSI are due to hematogenous seeding of the device from another site or rarely, due to contamination of the infusate. As colonizing organisms can establish themselves in the catheter's biofilm within 48–72 hours after insertion, they can be difficult to eradicate and can cause recurrent infection.

Diagnosis and Management

CRBSI are defined when simultaneously drawn blood cultures reveal a 3-fold greater number of colonies of the same organism from the CVC than the peripherally drawn culture; or when the CVC-drawn culture turns positive for the same organism at least 2 hours earlier than the peripherally drawn culture; or when the same organism is cultured from blood and the catheter tip.[6] Once the CVC is determined to be the source, management varies by pathogen. Vancomycin is typically used as empiric therapy for GP bacteria. Empiric therapy for GN pathogens relies on the local antibiogram and severity of disease and should include anti-pseudomonal coverage for neutropenic patients.

For CoNS BSI, CVC removal and antibiotic treatment for 5–7 days are recommended for patients with short-term CVC.[6] For those with long-term CVC, catheter retention may be appropriate if clinically stable and without evidence of persistent or relapsed bacteremia. While the usual antibiotic course is 10–14 days, some experts suggest that 5–7 days is adequate for uncomplicated cases.[7]

In contrast to CoNS, *S. aureus* BSI are often associated with complications (e.g., septic phlebitis, endocarditis).[8] Diagnostic workup includes echocardiography. A minimum 14-day treatment course is recommended for patients with *S. aureus* CRBSI with a longer duration (4–6 weeks) if there is evidence for metastatic sites of infection.[6] Due to high relapse rates, early CVC removal is strongly recommended for patients with both short- and long-term CVC.

For candidemia, initial empiric therapy is an echinocandin, and the minimum duration of treatment without metastatic complications is 2 weeks after blood culture clearance.[9] For non-neutropenic patients, early CVC removal is recommended since the source is usually catheter-related. For neutropenic patients and those with mucosal barrier injury, it is more difficult to determine the role of the gastrointestinal (GI) tract versus the CVC as the primary source of candidemia. An individualized approach is suggested when considering CVC removal in these patients. One exception is *Candida parapsilosis* for which CVC removal should always be performed.

In patients with GN CRBSI associated with persistent bacteremia or severe sepsis, the CVC should be removed.[6] In a study of 300 cancer patients, CVC removal within 2 days of onset of GN CRBSI was associated with improved microbiologic response and decreased mortality.[10] Notably, these findings were not observed for GN BSI that did not meet criteria for CRBSI or for CRBSI associated with mucosal barrier injury. Antibiotic de-escalation is recommended once culture and susceptibility results are available, and treatment duration is usually 7–14 days.[6]

RESPIRATORY INFECTIONS

Pneumonia remains a major cause of morbidity and mortality in critically ill cancer patients. The challenge for clinicians is that the differential diagnosis for pulmonary infiltrates in oncologic patients includes not just lower respiratory tract infections but also non-infectious causes (e.g., cancer progression, diffuse alveolar hemorrhage, drug or radiation toxicity, malignant airway obstruction, pulmonary edema, venous thromboembolic disease) with presenting signs and symptoms ranging from mild dyspnea to rapidly progressive respiratory failure.[11] In many instances, there can be more than one lung-related problem going on at the same time.

Pathogenesis and Host Factors

The pathogenesis of cancer-associated pneumonia has been well described.[12] Host susceptibility factors for pneumonia include general debility, malignancy-related catabolism, pre-existing lung disease, functional or anatomic defects, epithelial barrier disruption, and

immune system derangements.[12] Neutropenia is the most significant risk factor.[13] Other immune system derangements are associated with infections by specific pathogens (Table 1).

Diagnosis and Management

Computed tomography (CT) chest imaging is more sensitive than plain radiography in the detection and characterization of pneumonia, and the description of the radiologic pattern of lung infiltration may focus the differential diagnosis to likely etiologic agents.[12–14] However, CT patterns are non-specific, particularly in neutropenic patients, and cannot be solely relied upon for diagnosis.[12]

In patients from whom high-quality sputum samples cannot be obtained, flexible bronchoscopy with bronchoalveolar lavage (BAL) is the diagnostic procedure of choice.[12] The pace and severity of pneumonia may determine whether there is time to wait for response to initial therapy or whether to pursue a diagnostic procedure immediately. Molecular diagnostics for the rapid identification of respiratory pathogens including not only bacteria but also mycobacteria, fungi, and viruses have been a major advance in recent years.[15] The evidence for using procalcitonin-guided algorithms for critically ill cancer patients with bacterial pneumonia is limited. The selection of appropriate therapy, dose, duration, and monitoring should be personalized to the cancer patient based on etiologic cause, risk for multidrug-resistant (MDR) pathogens, and other factors.

Microbiologic Spectrum

Bacterial pneumonias—Bacteria remain the most common etiologic agents for pneumonia in cancer patients. The type of bacterial pneumonia depends on the underlying immune deficit and its duration, as well as whether the infection is community-acquired or nosocomial.[14]

Recent studies suggest that community-acquired pneumonia (CAP) in immunocompromised patients generally involves the same pathogens seen in immunocompetent hosts.[16,17] Certain epidemiologic exposures or risk factors raise the likelihood of infection with a particular pathogen (Table 1). *P. aeruginosa* deserves special mention since it is known to cause serious infections in neutropenic patients.[13] Additionally, secondary bacterial pneumonias following influenza or other respiratory viral infections occur frequently with *S. aureus* and *Streptococcus pneumoniae* being the most commonly isolated organisms, followed by *Haemophilus influenzae* and *Streptococcus pyogenes*.

Etiologic agents for hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) include the ESKAPE pathogens (i.e., *E. faecium*, *S. aureus*, *Klebsiella* sp., *Acinetobacter* sp., *P. aeruginosa*, and *Enterobacter* sp.) and are frequently MDR (Table 1).[18] Additional pathogens to be considered are *Citrobacter* sp., *E. coli*, *Proteus* sp., *Serratia marcescens*, and *Stenotrophomonas maltophilia*. Because MDR rates will vary by hospital, ICU, and other factors, the need for routine surveillance is emphasized.

A spotlight on some notable pathogens follows. *S. maltophilia* colonization and infection in patients with cancer has been increasingly reported. HAP/VAP due to this organism tend to occur in patients with extended ICU stay, tracheostomy, prolonged (>7 days) mechanical

ventilation, or exposure to broad-spectrum antibiotics.[19] In general, the clinical and radiographic presentation is similar to that seen with other infectious causes of HAP/VAP, but a syndrome of rapidly progressive and fatal hemorrhagic pneumonia due to *S. maltophilia* has been described in patients with hematologic malignancies (HM) and hematopoietic stem cell transplantation (HSCT) recipients.[20] Trimethoprim-sulfamethoxazole is the most reliable *in vitro* agent, but emerging resistance has been reported.[19]

HAP caused by *Legionella* sp. can occur at centers where the organism is present in the hospital water supply or where there is ongoing construction.[18] Although *L. pneumophila* serotype 1 is the most commonly recognized species, several non-*pneumophila Legionella* types (*L. jordanis*, *L. micdadei*) can cause pulmonary infections in severely immunocompromised hosts.[21,22]

Nocardia sp. is well recognized to cause focal or systemic infection in patients with impaired cell-mediated immunity. Common infecting species include *N. abscessus*, *N. cyriacigeorgica*, *N. farcinica*, and *N. nova*.[23] The lung is the primary site of infection in the majority of cases, but a search for sites of dissemination, including the brain, should be pursued since it will impact treatment duration.[24] Because *Nocardia* sp. can have markedly different susceptibility patterns, it is important to send out the recovered isolate for formal identification and sensitivity testing to guide therapy.

Mycobacterial infections—Pulmonary tuberculosis (TB) usually represents reactivation of latent infection. Patients with HM, particularly foreign-born individuals, and patients with head and neck cancer have disproportionately higher TB rates compared to the general United States (US) population.[25] Thus, TB should be considered in these patients with pulmonary infiltrates. Atypical mycobacterial pulmonary infections have also been described in cancer patients, who are typically older, have solid tumors, and have underlying lung disease.[26]

Fungal infections—*Pneumocystis jirovecii* has long been recognized to be an important opportunistic and potentially life-threatening pulmonary pathogen in cancer patients.[27] Risk factors include prolonged corticosteroid use, receipt of immunosuppressive therapy affecting cell-mediated immunity, and HSCT. High suspicion should be raised in patients presenting with fever, dry cough, hypoxemia at rest or exertion, and diffuse, bilateral interstitial infiltrates. Bronchoscopy should be pursued for diagnosis. The serum (1,3)-ß-D-glucan (BDG) is an adjunctive diagnostic test and cannot be used solely to diagnose *P. jirovecii* pneumonitis (PJP) since it is non-specific, but a negative BDG result essentially rules out PJP due to its excellent negative predictive value.[28]

Prolonged and severe neutropenia is a risk factor for invasive pulmonary aspergillosis, which is mitigated by mold-active azole prophylaxis in the highest-risk patient groups (e.g., acute leukemia, allogeneic HSCT).[29,30] Breakthrough mucormycosis infections in patients already taking voriconazole and have new pulmonary findings should be entertained.[31] The differential diagnosis for lung nodules should also include *Cryptococcus* sp., endemic fungi (*Blastomyces*, *Coccidioides*, *Histoplasma*), *Fusarium* sp., and *Geotrichum* sp.;

epidemiological clues may provide guidance as to their likelihood (Table 1).[14] Dematiaceous molds, such as *Alternaria* sp. and *Cladosporium* sp., are increasingly implicated as causes of lung infections in leukemic and transplant patients and pose therapeutic challenges due to variable susceptibilities to the available antifungal agents.

Viral infections—Respiratory viruses are frequent agents of CAP and have seasonal variation (Table 1).[32] Clinical presentation can range from asymptomatic shedding to acute respiratory distress, and providers should be vigilant for signs and symptoms of pulmonary bacterial superinfection.

Cytomegalovirus (CMV) pneumonitis, usually with concomitant viremia, can occur in allogeneic HSCT recipients and patients with HM who have received chemotherapeutic drugs such as alemtuzumab, rituximab, and fludarabine.[33] To a far lesser extent, patients with solid tumors can also reactivate CMV if exposed to T-cell suppressing therapy like high-dose corticosteroids.[34] Definitive diagnosis requires the presence of CMV inclusion bodies and/or CMV viral antigens in lung tissue.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that has resulted in a worldwide pandemic in 2020, with pneumonia being the most frequent serious manifestation of infection. Cancer patients with SARS-CoV-2 have a higher risk for severe events including ICU admission, invasive ventilation, and death compared to SARS-CoV-2-infected patients without cancer.[35]

Parasitic infections—*Strongyloides stercoralis* is an intestinal nematode that can cause hyperinfection and disseminated disease in highly immunocompromised patients.[36] Suspicion should be raised in individuals who have previously resided in tropical and subtropical endemic regions (e.g., immigrants, military personnel). The migration of filariform larvae during auto-infection can facilitate bacterial translocation from the GI tract, leading to pneumonia, meningitis, or sepsis. Acute respiratory distress syndrome (ARDS) can occur during severe disease along with multiorgan failure. Mortality is high even with treatment.

GI INFECTIONS

Infections in Solid Tumors

Solid tumor patients usually present with infections that result as a sequelae of tumor obstruction (e.g., cholangitis, intraabdominal abscesses) or in some cases, complications from GI surgery. Management of these infections often requires antibiotic therapy in combination with source control (e.g., percutaneous drainage, surgical washout).

Neutropenic Enterocolitis (NEC)

NEC or typhlitis is a life-threatening chemotherapy-associated complication that occurs most commonly among those with acute leukemia but has also been observed among other HM patients and those receiving high-dose chemotherapy for solid tumors.[37] The pathogenesis is thought to involve a combination of mucosal injury from cytotoxic drugs, profound neutropenia, and impaired host defenses leading to inflammatory, hemorrhagic,

and/or necrotizing involvement of the lower intestinal tract. The incidence ranges from 0.8%-26%. A recent study of critically ill patients with NEC reports ICU and hospital mortality rates of 32% and 39%, respectively.[38]

Common features include fever, diarrhea, abdominal pain, mucositis, nausea, and vomiting, but GI bleeding or obstruction can also be seen.[37] The diagnostic criteria include neutropenia, bowel wall thickening on CT imaging, and exclusion of other diagnoses such as *Clostridioides difficile*. Management of NEC includes bowel rest, nasogastric suction, intravenous (IV) fluids, nutritional and blood product support, as well as broad-spectrum antimicrobial therapy. Surgical intervention is reserved for those with bowel perforation, persistent GI bleeding despite correction of coagulopathies and thrombocytopenia, or clinical deterioration despite optimal medical management.

Hepatosplenic Candidiasis (HC)

HC is primarily observed among patients with acute leukemia, but it is seen less frequently now in the era of antifungal prophylaxis. This condition is thought to result from bloodstream invasion of *Candida* sp. from the GI tract with the portal system receiving the largest inoculum.[39] The clinical presentation includes high persistent fevers accompanied by right upper quadrant pain, nausea, and vomiting in a previously neutropenic patient who has recently experienced count recovery. An elevated serum alkaline phosphatase can be seen, and abdominal CT or magnetic resonance imaging (MRI) typically shows multiple hypodense lesions in the liver, spleen, and sometimes the kidneys. Due to emerging fluconazole resistance, initial therapy should include an echinocandin for several weeks followed by stepdown therapy to an oral azole after evidence of clinical improvement.[9] Treatment continues until there is radiographic resolution.

Infectious Diarrhea

Cancer patients are at increased risk for *C. difficile* infection (CDI) due to frequent and prolonged hospitalizations, immunosuppression, and exposure to factors that alter the gut microbiota. At the same time, the diagnosis of CDI is challenging since diarrhea is a frequent complication of chemotherapy, transplant-related GI complications, and novel immunotherapies. Additionally, the nucleic acid amplification tests (NAAT) that are commonly used for CDI diagnosis do not distinguish between colonization and true infection. Hospital-onset CDI rates have been reported to be higher at cancer centers and may in part be driven by the increased frequency of testing in the context of a high prevalence of diarrhea.[40,41] First-line treatment is oral vancomycin or fidaxomicin.[42] Among patients with fulminant CDI, oral vancomycin combined with IV metronidazole is recommended. If ileus is present, vancomycin can also be administered per rectum. Surgical indications include bowel perforation, septic shock, and associated organ failure.

Community-acquired diarrhea due to *Salmonella, Shigella, Yersinia*, and *Campylobacter* is uncommon in cancer patients. On the other hand, norovirus is an important cause of viral gastroenteritis and has been associated with outbreaks in hematology/transplant units and with reported mortality up to 25% in allogeneic HSCT recipients.[43] Supportive care is the mainstay of treatment. Colitis due to adenovirus can be life-threatening among patients with

impaired cellular immunity. Cidofovir is the only antiviral option and may be considered in severely ill patients although close monitoring is needed due to risk of nephrotoxicity.[44] CMV colitis has been described in allogeneic HSCT recipients and is managed with IV ganciclovir with transition to oral valganciclovir as the colitis resolves.[45] Foscarnet is an alternative if there is concern for ganciclovir-related myelosuppression but careful monitoring of renal function and electrolytes is needed.

CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS

A relatively small subset of cancer patients is at risk for CNS infections. Patients with primary or secondary brain tumors who have had neurosurgical procedures, including placement of shunts or Ommaya reservoirs, are at risk due to barrier disruption, decreased cellular immunity from corticosteroids, and poor wound healing following corticosteroid and radiation therapy.[46] Patients with deficient humoral immunity or with functional or anatomic asplenia are at risk for meningitis due to encapsulated bacteria (e.g., *S. pneumoniae*, *H. influenzae*), and those with T-cell defects are vulnerable to opportunistic infections encompassing a wide variety of bacterial, fungal, viral, and parasitic pathogens. For patients anticipating receipt of cytotoxic chemotherapy or HSCT, the risk for CNS infections in the current era is probably lessened by screening and/or antimicrobial prophylaxis.

Diagnostic Approach

While CT is faster, MRI of the brain can better distinguish among tumor, infection, and radiation effects.[46] After ruling out increased intracranial pressure, lumbar puncture should ideally be performed. While limitations exist, rapid diagnostics can improve the ability to identify the etiologic agent. One example is the US Food and Drug Administration (FDA)-approved multiplex NAAT that detects 14 bacterial, viral, and fungal pathogens of community-acquired meningitis and encephalitis.[47]

Clinical Presentation

Meningitis/Encephalitis—Meningitis is classically associated with the sudden onset of fever, headache, and nuchal rigidity, whereas encephalitis is distinguished by abnormalities of brain function.[46] The distinction between the two can be frequently blurred since patients can have features of both (meningoencephalitis). Seizures are common with encephalitis and can be detected by electroencephalography.

The CSF inflammatory response can be muted in cancer patients.[48] One study showed that the majority of infections occurred in patients with prior neurosurgery and not surprisingly, bacteria typically associated with device-related infections, including CoNS, *S. aureus*, *Propionibacterium acnes*, and *Corynebacterium jeikeium*, were well represented in this series.[48] In contrast, agents usually associated with community-acquired meningitis were uncommon. Nevertheless, the data do not negate the fact that meningitis is a medical emergency and warrants timely empiric antibiotics in cancer patients suspected to have this diagnosis. Empiric antibacterial regimens for community- and healthcare-associated meningitis are extensively reviewed elsewhere.[49,50] One key consideration is to include an

antibiotic with activity against *Listeria* as part of the empiric regimen for meningitis in immunosuppressed patients. For recent neurosurgical patients, IV vancomycin should be combined with a 3rd- or 4th generation cephalosporin (e.g., ceftazidime, cefepime) or a carbapenem.

Viruses are common agents of infectious encephalitis. In one recent study, causes of viral encephalitis in allogeneic HSCT recipients included human herpesvirus 6 (HHV6), Epstein-Barr virus, herpes simplex virus (HSV), JC virus, varicella zoster virus (VZV), CMV, and adenovirus.[51] Certain exam or imaging features may point to a diagnosis. Flaccid paralysis during the summer may suggest the possibility of West Nile virus infection; temporal lobe involvement is strongly suggestive of HSV; and grouped vesicles in a dermatomal pattern may suggest VZV although the absence of a rash does not rule out VZV from consideration. VZV can also be associated with isolated facial palsy, other cranial neuropathies, vasculopathy, and myelitis; imaging may show enhancement of affected nerve roots.[46] There are no specific therapies for most CNS viral infections with the exceptions being high-dose acyclovir for HSV and VZV and ganciclovir or foscarnet for CMV and HHV6.

Focal Brain Lesions—Focal mass lesions include polymicrobial bacterial abscess, nocardiosis, toxoplasmosis, and invasive fungal infections.[46] In one study of autologous and allogeneic HSCT recipients at a tertiary cancer center, the incidence of CNS infections was 4.2% (15/361) with cerebral toxoplasmosis and fungal infections being the leading causes.[52] Toxoplasmosis, which has also been described in patients with Hodgkin's lymphoma and other HM, represents reactivation of latent disease and can be fatal if untreated. The most commonly used regimen is the combination of pyrimethamine with sulfadiazine and folinic acid.

Fungal brain abscesses can present with a focal neurologic abnormality, headache, and/or seizure due to the local destruction or compression of adjacent brain tissue with or without angioinvasion.[53] Clinically relevant pathogens include yeasts (e.g., *Candida*, *Cryptococcus*), molds (e.g., *Aspergillus*, *Rhizopus*, *Mucor*, *Pseudallescheria*, *Fusarium*), and dimorphic fungi (e.g., *Histoplasma*, *Coccidioides*). Definitive diagnosis requires tissue biopsy for histopathologic examination and culture. Amphotericin B and its lipid formulations as well as the azoles (e.g., fluconazole, voriconazole, posaconazole) are the two primary antifungal classes employed to treat CNS fungal infections, but their attendant toxicities can make therapy challenging, particularly when treatment lasts months.[46,53]

URINARY TRACT INFECTIONS (UTIs)

Infections associated with Urinary Diversion

Radical cystectomy (RC) with urinary diversion (e.g., continent cutaneous diversion, ileal conduit, orthotopic neobladder) is an important urological procedure, but UTIs can occur when there is incomplete voluntary voiding or when bacteria is introduced into the reservoir via suboptimal catheterization practices.[54] Approximately 20% of these infections are associated with sepsis. Diabetes, perioperative blood transfusion, continent diversion, and urine leak correlate with UTI risk following RC.[55] *E. coli*, *Enterococcus* sp., *Klebsiella* sp., and *S. aureus* are the most frequently recovered bacteria.[54,55]

Infections associated with ureteral stents or percutaneous nephrostomy tubes (PNT)

Obstructive uropathy is frequent in patients with advanced solid tumors, primarily prostate, retroperitoneal, or pelvic tumors, and is managed by placing ureteral stents or PNT.[11] However, complicated UTIs are common. At one tertiary cancer center, the rate of PNT-associated pyelonephritis was 19% (38/200) with risk factors being prior UTI and neutropenia.[56]

Pathogenesis—The pathogenesis of implant-associated UTIs starts with bacterial adhesion onto the indwelling implant surfaces and subsequent biofilm formation.[57] Many uropathogens are capable of making biofilms and include *E. coli*, *E. faecalis*, *P. aeruginosa*, *P. mirabilis*, *S. aureus*, and *Candida* sp. The likelihood of bacterial colonization is higher as the duration of implant retention increases. Because indwelling stents can be associated with vesicoureteral reflux of urine, this facilitates retrograde ascension of bacteria into the kidney, leading to pyelonephritis. The entry of bacteria from the renal parenchyma into the renal circulatory system can lead to bacteremia, sepsis, septic shock, and/or renal failure.

Clinical Presentation and Management—Pyelonephritis is defined by the presence of $\geq 10^5$ colony forming units/mL of a uropathogen in the urine accompanied by symptoms (e.g., fever, chills, nausea, vomiting, costovertebral angle tenderness, flank pain).[57] Cancer patients who also have diabetes may be at risk for emphysematous pyelonephritis and papillary necrosis. CT of the abdomen and pelvis is generally reserved for patients who are severely ill, have persistent symptoms despite ≥48 hours of appropriate antimicrobial therapy, or have suspected urinary tract obstruction. The approach to empiric antibiotic therapy for hospitalized patients depends in part on the risk for infection with MDR bacteria. For septic patients requiring ICU care, a conservative approach is to combine a carbapenem for coverage of extended-spectrum beta-lactamase (ESBL)-producing organisms and *P. aeruginosa*, as well as IV vancomycin for MRSA coverage, until urine and blood culture results are available.[58]

SKIN AND SOFT TISSUE INFECTIONS (SSTI)

SSTI range from mild (e.g., impetigo) to life-threatening (e.g., necrotizing fasciitis). For immunocompromised patients, the broad differential diagnosis includes drug eruptions, tumor infiltration of the skin and soft tissue, reaction to chemo- or radiation therapy, GVHD, Sweet's syndrome, erythema multiforme, and leukocytoclastic vasculitis.[59] Dermatologic evaluation, including biopsy of skin lesion, is usually warranted. The principal portal of entry is a breach in skin integrity with *S. aureus* and streptococci largely responsible for SSTI in general. Careful history should be obtained to consider unusual organisms potentially associated with specific exposures (e.g., shellfish ingestion and *Vibrio vulnificus*). In patients with impaired cellular immunity, HSV or VZV reactivation with possible secondary bacterial infection can occur. SSTI may also be a manifestation of disseminated infection such as that seen with ecthyma gangrenosum in neutropenic patients.[59] This condition results from perivascular invasion of small vessels with secondary ischemic necrosis and is classically associated with *P. aeruginosa*, *S. aureus*, *Aeromonas* sp., atypical mycobacteria, *Candida* sp., and *Fusarium*. Severe infections like necrotizing

fasciitis and clostridial myonecrosis require urgent surgical debridement in addition to antibiotic therapy.

ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship (AS) refers to a systematic effort to educate and persuade healthcare providers to follow evidence-based prescribing in order to reduce antibiotic overuse or misuse with the goals of stemming further antimicrobial resistance, improving patient outcomes, and reducing unnecessary healthcare costs.[60] AS is particularly pertinent to the ICU, and specific interventions, such as development of clinical guidelines, prospective audit and feedback, antibiotic time-outs, incorporation of rapid diagnostics, and computerized decision support, have been studied for feasibility in the critical care setting.[61] Timely and appropriate empiric antibiotic therapy has been demonstrated in a variety of infections to reduce mortality, but antibiotic de-escalation, even in critically ill cancer patients, is also important once microbiologic results are available to decrease unnecessary broad-spectrum exposure.[62]

Summary

The gamut of infectious complications in critically ill cancer patients is broad and can affect single or multiple organ systems. Neutropenia remains an important risk factor for infection although the degree and severity depend on the type of malignancy and subsequent cancer treatment. The astute clinician should maintain a high index of suspicion to properly diagnose and manage infections, recognizing also that non-infectious mimics add complexity to the care of these patients.

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Synopsis

Critically ill cancer patients are vulnerable to infections as a result of the underlying malignancy, tumor-directed therapy, immunosuppression, breaches in mucosa or skin, malnutrition, and other factors. Of these, neutropenia remains the most important risk factor for infection although the degree and severity depend on the type of malignancy and subsequent cancer treatment. Infectious complications occurring in critically ill cancer patients are broad and can affect the bloodstream, lungs, gastrointestinal tract, central nervous system, urinary tract, and the skin. Pneumonias are the leading cause of infection in cancer patients admitted to the intensive care unit. Consideration of opportunistic pathogens in the differential diagnosis is important in patients with impaired cellular and/or humoral immunity or compromised splenic function.

Key Points

- Infection remains a significant cause of morbidity and mortality in critically ill cancer patients.
- Neutropenia is an important risk factor for infection in cancer patients.
- Respiratory infections are the leading cause of infection in cancer patients admitted to the intensive care unit.

Table 1.

Respiratory pathogens causing pulmonary infiltrates in critically ill cancer patients

Organism	Epidemiologic Clues	Immune Defect Predisposing to Infection
Gram-positive bacteria		
Nocardia sp.	Prolonged corticosteroids	Cell-mediated
Rhodococcus equi	Zoonotic exposure (horse farms, race tracks)	Cell-mediated
Staphylococcus aureus, including methicillin-resistant strains	Agent of CAP and HAP/VAP	
Streptococcus pneumoniae	Most common bacterial agent of CAP	Humoral
Streptococcus pyogenes	Agent of CAP	
Enterococcus sp., including vancomycin-resistant strains	Agent of HAP/VAP	
Gram-negative bacteria		
Acinetobacter baumannii complex *	Agent of HAP/VAP	
Citrobacter sp.	Agent of HAP/VAP	
Enterobacter sp.	Agent of HAP/VAP	
*Escherichia coli**	Agent of CAP and HAP/VAP	
Haemophilus influenzae	Agent of CAP	Humoral
Klebsiella sp. *	Agent of CAP and HAP/VAP	
Moraxella catarrhalis	Agent of CAP	
Proteus sp.	Agent of HAP/VAP	
*Pseudomonas aeruginosa**	Agent of HAP/VAP; structural lung disease (bronchiectasis)	Neutropenia
Serratia marcescens	Agent of HAP/VAP	
*Stenotrophomonas maltophilia**	Agent of HAP/VAP	
Atypical bacteria		
Chlamydia pneumoniae	Agent of CAP	
Chlamydia psittaci	Zoonotic exposure (birds)	
Coxiella burnetii	Zoonotic exposure (abattoir workers, farm animals)	
Legionella sp.	Agent of CAP and HAP (contaminated hospital water supply)	Cell-mediated
Mycoplasma pneumoniae	Agent of CAP	
Anaerobes	Alcoholism; aspiration; endobronchial obstruction; poor dental hygiene	
Mycobacteria		
Atypical mycobacteria	Receipt of tumor necrosis factor inhibitors (infliximab)	Cell-mediated; intrinsic/acquired defects of the Th1 cell and macrophage pathway
Mycobacterium tuberculosis	Alcoholism; hematologic malignancy or head and neck cancer; HIV infection; malnutrition; receipt of Bruton tyrosine kinase inhibitor (ibrutinib), corticosteroids, or tumor necrosis factor inhibitors	
Fungi		

Organism	Epidemiologic Clues	Immune Defect Predisposing to Infection
Aspergillus sp.	GVHD; prolonged neutropenia; receipt of Bruton tyrosine kinase inhibitor or corticosteroids	Neutropenia; cell-mediated
Blastomyces dermatitidis	Endemic mycosis (exposure to moist soils and in wooded areas along waterways and swamps in North America)	Cell-mediated
Coccidioides immitis	Endemic mycosis (southwestern US)	Cell-mediated
Cryptococcus sp.	Exposure to pigeon or chicken droppings	Cell-mediated
Dematiaceous molds	Exposure to soil and decaying vegetation	
Fusarium sp.	GVHD; prolonged neutropenia; receipt of Bruton tyrosine kinase inhibitor	Neutropenia; cell-mediated
Histoplasma capsulatum	Endemic mycosis (Ohio and Mississippi River valleys or Central America); exposure to bird or bat droppings; receipt of Bruton tyrosine kinase inhibitor	Cell-mediated
Mucor sp. (and other agents of mucormycosis)	Diabetes; GVHD; iron overload; receipt of Bruton tyrosine kinase inhibitor or corticosteroids	Neutropenia; cell-mediated
Pneumocystis jiroveci	HSCT recipient; receipt of anti-CD52 monoclonal antibody (alemtuzumab), anti-CD20 antibody (rituximab), Bruton tyrosine kinase inhibitor, corticosteroids, oral alkylating agents (temozolomide), purine analogs (fludarabine), or tumor necrosis factor inhibitors	Cell-mediated
Parasites		
Strongyloides stercoralis	Exposure to soil contaminated with human feces (coal miners); previous residence in tropical or subtropical regions (immigrants, military personnel, travelers); residence in southeastern US	Cell-mediated
Respiratory viruses	Frequent agents of CAP; seasonal variation	
Adenovirus		
Bocavirus		
Coronavirus		
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Cause of pandemic in 2020	
Human metapneumovirus		
Influenza A and B		
Parainfluenza	Association with post-infectious complications (e.g., air-flow obstruction or bronchiolitis obliterans) in HSCT recipients	
Respiratory syncytial virus		Humoral, cell-mediated
Rhinovirus		
Other viruses		
Cytomegalovirus	GVHD; HSCT recipient; receipt of corticosteroids	Cell-mediated

* Includes MDR strains

Abbreviations: CAP, community-acquired pneumonia; GVHD, graft-versus-host disease; HAP, hospital-acquired pneumonia; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; MDR, multidrug-resistant; US, United States; VAP, ventilator-associated pneumonia