

Cancer-Related Infections

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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Abstract

Cancer-related infections are complex and remain a leading cause of cancer-related morbidity and mortality. Susceptibility to cancer-related infections is due to the nature of the malignancy and cancer treatments. Epidemiologic trends for cancer-related infectious pathogens have changed dramatically over the past 2 decades, with alarming rates of antimicrobial resistance. In addition, patients living with cancer face unique infectious threats from novel chemotherapeutic and immunomodulating biologic agents, creating new challenges for practitioners. Knowledge gaps, inadequate prophylactic strategies, inappropriate antibiotic therapy, and improper infection control practices are prevalent. Current clinical practice remains out of sync with the rapid pace of research advancements. It is critical for oncology advanced practitioners to recognize the unique risk factors and potential emergent nature for patients who may develop cancer-related infections. Evidence-based clinical practice guidelines are essential tools to translate best practices in real time in order to achieve the best patient outcomes.

J Adv Pract Oncol 2011;2:356-371

Globally, cancer is a leading cause of death, and it has the greatest impact in terms of premature death and disability worldwide (American Cancer Society [ACS], 2010). The ACS estimates 571,950 Americans are expected to die from cancer this year, and over 1.5 million new cases will be diagnosed in 2011 (ACS, 2011). Cancer-related infections continue to cause significant morbidity and mortality, interfering with successful cancer treatment (Centers for Disease Control [CDC], 2010; Kamboj & Sepkowitz, 2009; Segal et al., 2008). Seminal research

has established the correlation of dose intensity, reduction, or delay impacting negatively on response rates, treatment outcome, and survival benefit (Bonadonna et al., 2005; Lyman, 2009). Furthermore, patients now face unique infectious threats from novel chemotherapeutic and immunomodulating biologic agents, creating new challenges for practitioners (Koo, Marty, & Baden, 2011; Neuburger & Maschmeyer, 2006).

It is critical for advanced practitioners (APs) in the care of oncology patients to be clinically vigilant in their identification of those patients at risk for infections, to provide both timely

and appropriate prophylaxis and treatment. The purpose of this article is to explore the current state of knowledge regarding the etiology of and risk factors for cancer-related infections, and to provide a brief summary of current national clinical practice guidelines.

Background

Although innovations in cancer diagnosis and treatments have contributed to increased longevity and survivorship, cancer-related infections can occur and in turn cause multiple complications across the continuum of cancer care. The scope of cancer-related infections is complex, given the heterogeneity of cancer patients and their susceptibility to infection due to the nature of malignancy and treatment (Segal et al., 2008). The epidemiology of infectious pathogens is rapidly evolving and has changed dramatically over the past 2 decades, with antimicrobial resistance emerging as a serious problem (Maschmeyer & Haas, 2008; Rice et al., 2008). Moreover, the high prevalence of cancer-related infections in the cancer population has significant epidemiologic impact for the broader population as well (Hamburg, Levi, Elliot, & Williams, 2008).

Compounding this problem, current research has identified knowledge gaps demonstrating inadequate prophylactic strategies and inadequate antibiotic therapy along with improper infection control practices (Dellit et al., 2007; Friese, 2007; Kaye et al., 2008). Analysis of cancer-related infection, rates, types, risk factors, and the evidence base for management in general and specifically in hematologic cancers, remains weak due to the limitations of randomized controlled trials (Paul, Gafter-Gvili, Goldberg, & Yahav, 2011; Tacconelli & Cataldo, 2009). While the randomized controlled trial remains the gold standard underpinning evidence-based practice, designing empirical studies and randomizing extremely ill cancer patients may not be appropriate for their care; this

can pose ethical challenges to researchers in gathering the evidence base needed to improve practice (Sandherr et al., 2006; Smith et al., 2006).

The majority of studies in the literature are cohort, cross-sectional, or case control studies (Tacconelli & Cataldo, 2009). It is suggested that systematic reviews and meta-analyses have the potential to organize evidence accumulated in randomized controlled trials, provide a stronger evidence base for the management of cancer-related infections, identify knowledge gaps in existing evidence, address broader clinical questions, and guide further research (Paul et al., 2011; Tacconelli & Cataldo, 2009). However, caution is necessary to recognize the heterogeneity of clinical studies for an appropriate and meaningful meta-analysis.

Literature Search Methods

A literature search revealed limited data specific to the terms “etiology and risk for cancer-related infections.” However, there was a wealth of literature for etiology and risk for specific types of infections in cancer patients, neutropenic states, granulocyte colony-stimulating factor (G-CSF) support, hospitalizations secondary to sepsis, morbidity/mortality due to infection, delays in treatment and dose reduction secondary to infection, antimicrobial treatments, and prophylaxis in the cancer patient population; therefore, the literature search was broadened to obtain information through these sources. Computerized databases MEDLINE, PubMed, Cochrane ScienceDirect, and EBSCO were searched between 1990 and 2011. Search terms used were keywords that included cancer, infection, risk, etiology, infectious complications, immunocompromised, immunobiologics, viral, bacterial, fungal, antibiotic prophylaxis, prevention, neoplasm, malignancy, “cancer-related infection,” “infection in cancer patients,” treatment delay, dose-reduction, hospitalizations, infection-related morbidity, infection-related mortality. Online databases, including the National Comprehensive Cancer Network, Centers for Disease Control, National Cancer Institute, Cancer.gov, Oncology Nursing Society, American Society of Clinical Oncology, and the Infectious Diseases Society of America, were searched using the same keywords. Ancestry and descending search methods were also employed to access pertinent information.



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SEE PAGE 371

The search yielded 6,897 articles from these databases, and 78 articles were selected for review based on the following criteria: Articles for review were limited to those between from 2005 and 2011; however, seminal articles cited in the literature beyond these search dates were also included. To gather up-to-date information for review regarding the etiology of and risk factors for infections in cancer patients, articles for review were also limited to those addressing the adult cancer patient population, those published in English, topics specifically related to cancer patients, cancer-immunocompromised states, cancer treatment-related complications secondary to infection, emerging antimicrobial resistance, morbidity, mortality, sepsis, hospitalizations, treatment interruptions and dose reduction secondary to infection, infection prophylaxis, and preventive strategies.

Discussion

ETIOLOGY OF CANCER-RELATED INFECTIONS

Cancer and cancer treatment impair both a host's defenses and protection from infectious pathogens; diminished host defenses impede the ability to fight infection (Lehrnbecher et al., 2008; NCCN, 2011). Patients with cancer are susceptible to infections before, during, and after cancer therapy, with the coexistence of multiple immune defects (Freifeld & Segal, 2007; Morrison, 2007). Some treatments cause long-lasting cellular immunosuppression with increased susceptibility to opportunistic organisms such as *Listeria*, *Pneumocystis jiroveci* pneumonia, viruses, fungi, and mycobacteria (Maschmeyer & Haas, 2008; Morrison, 2007; Safdar & Armstrong, 2003). Pathogens with a low potential for virulence in the noncancer patient may lead to invasive and often life-threatening conditions in cancer patients (Safdar, 2003a).

Prompt diagnosis of infection can be difficult because early signs and symptoms may be absent, subtle, atypical, or nonspecific in neutropenic or immunosuppressed patients (Pongas, Hamilos, Rolston, & Kontoyiannis, 2010). Complicating this, early laboratory and radiographic findings are frequently unremarkable (Safdar, 2003b). Fever may be the only early nonspecific sign, with approximately 48% to 60% of febrile neutropenic

(FN) patients demonstrating an occult infection (NCCN, 2011). A recent survey of 430 patients undergoing chemotherapy revealed 61% had more than one infection, with 52% requiring emergency room treatment, 42% requiring hospitalization, and 43% experiencing a treatment interruption due to infection (Ruddon, 2009).

HOST FACTORS PREDISPOSING TO CANCER-RELATED INFECTIONS

The risk of opportunistic infections has been found to be directly related to the duration and severity of neutropenia (Bow, 2005). Febrile neutropenia is a medical emergency with risk of opportunistic infection and mortality directly related to the duration and severity of neutropenia and the time elapsed before the first dose of antibiotics are administered (Bow, 2005; Shaaban & Perez, 2009). It has also been estimated that in patients with FN, approximately 50% of episodes have no clinical focus or causative pathogen that can be found. However, in 15% to 20% of cases, a primary bacteremia, fungemia, lung infiltrate, or other microbial infection can be identified (Joos & Tamm, 2005; Neuburger & Maschmeyer, 2006). The highest mortality rates observed in FN are in patients with documented infection and those with gram-negative bacteremia (Caggiano, Weiss, & Linde-Zwirble, 2005; Klastersky, Awada, Paesmans, & Aoun, 2011; Kuderer, Dale, Crawford, Cosler, & Lyman, 2006); see Table 1.

Certain malignancies are inherently associated with immune defects and susceptibility to specific pathogens. For instance, patients with chronic lymphocytic leukemia (CLL) are frequently hypogammaglobulinemic, causing susceptibility to encapsulated bacteria (NCCN, 2011; Yee & O'Brien, 2006). Multiple myeloma patients are often functionally hypogammaglobulinemic with restricted production of effective antibodies. Solid tumors predispose to infection because of anatomic factors (NCCN, 2011). Endobronchial tumors can cause obstructive pneumonias. Abdominal tumors predispose to infection of the hepatobiliary, genitourinary, gynecologic, and GI tracts with obstruction, direct invasion, necrosis, and local abscess formation (Segal, 2008).

Patients with hematologic malignancies and myelodysplastic syndrome may have marrow replacement with malignant cells or a dysfunc-

Table 1. Common Infectious Pathogens in Neutropenic Patients

Initial infections are primarily bacteria; subsequent infections are primarily antibiotic-resistant bacteria, yeast, other fungi, and viruses

Major gram-positive pathogens

Coagulase-negative staphylococci
Staphylococcus aureus, including methicillin-resistant strains
Enterococcus species, including vancomycin-resistant strains
Viridans group streptococci
Streptococcus pneumoniae
Streptococcus pyogenes

Major gram-negative pathogens

Escherichia coli
Klebsiella species
Enterobacter species
Pseudomonas aeruginosa
Citrobacter species
Acinetobacter species
Stenotrophomonas maltophilia

Initial viral pathogens

Herpes simplex virus
 Respiratory syncytial virus
 Parainfluenza
 Influenza A & B

Infection from *Candida* species occurs later in the course of neutropenia, often as a consequence of GI mucositis

Aspergillus species and other filamentous fungi are causes of morbidity and mortality with severe and prolonged neutropenia

Note. Adapted, with permission, from "NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) Prevention and Treatment of Cancer-Related Infections. V 1.2011." © 2011 National Comprehensive Cancer Network, Inc. All rights reserved; Freifeld et al. (2011).

tional marrow that contributes to immune dysfunction (NCCN, 2011). Specifically in patients with acute leukemia, studies have shown that approximately 90% of their intensive chemotherapy cycles are complicated by fever and infections (Gil, Styczynski, & Komarnicki, 2007; Neuburger & Maschmeyer, 2006). Patients receiving high-dose corticosteroids are also at risk due to suppression of cellular immunity; in addition, fever and local signs of infection are blunted (Segal et al., 2008).

Splenectomized or functionally asplenic cancer patients (induced by splenic radiation or a late complication of graft-vs.-host disease [GVHD]) are at a lifetime risk for infections from encapsulated bacteria and at high risk for overwhelming sepsis (NCCN, 2011; Sumaraju, Smith, & Smith, 2001). There are multiple other risk factors for infection in cancer patients: comorbid diseases, age, performance status, renal/hepatic insufficiency, immunodeficiency associated with primary malignancies/treatments, tumor inva-

sion, disruption of skin/mucosal barriers, vascular access devices, radiation treatment, remission status, and nutrition (NCCN, 2011; Segal et al., 2008); see Tables 2 and 3.

Patients undergoing hematopoietic stem cell transplant (HSCT) have unique infectious complications with the type of pathogens and timing of infectious threats dependent on the type of HSCT, GVHD, conditioning regimen, and neutrophil engraftment, to name a few (Tomblyn et al., 2009; Wingard, Hsu, & Hiemenz, 2011). Most autologous HSCT recipients' infections occur during neutropenia and within the first few months after transplantation, before reconstitution of cellular immunity (NCCN, 2011; Tomblyn et al., 2009), whereas susceptibility of pathogens for allogeneic HSCT follows a timeline corresponding to the predominant immune defects for initial neutropenia, myeloid engraftment, and the severity of GVHD, affecting both cell-mediated and humoral immunity (NCCN, 2011; Tomblyn et al., 2009); see Tables 4 and 5.

Table 2. Host Factors Predisposing Patients to Infectious Complications

Immunodeficiencies associated with primary malignancy

- Neutropenia
- Disruption of mucosal barriers
- Splenectomy and functional asplenia
- Corticosteroids and other lymphotoxic agents
- Hematopoietic stem cell transplantation
- Comorbid conditions
- Remission status
- Prior exposure to chemotherapy and intensity of immunosuppressive therapy
- Implantable venous access devices and catheters
- Malnutrition, hypoalbuminemia

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Table 3. Net State of Immunosuppression

- Underlying disease/tumor burden
- Cytotoxic chemotherapy: depth and duration of neutropenia
- T- and B-cell suppressants, steroids, purine analogs, alemtuzumab, etc.
- Barriers breached: VAD, mucositis, surgery
- Radiation therapy
- Stem cell transplant/GVHD
- Hypogammaglobulinemia
- COPD
- Renal/hepatic insufficiency
- Performance status
- Age > 65 yr
- Nutritional status (low albumin)

Note. COPD = chronic obstructive pulmonary disease; GVHD = graft-vs.-host disease; VAD = ventricular assist device. Adapted, with permission, from Freifeld & Segal (2007).

Lymphotoxic and Immunomodulating Agents

The use of immunomodulating monoclonal antibodies in cancer treatment has been shown to be effective in the treatment of hematologic malignancies and thought to be less immuno-

suppressive than conventional cytotoxic chemotherapy. However, the mechanisms of action for monoclonal antibodies are related to interaction with the immune system through either antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity (Adams & Weiner, 2005); see Figures 1 and 2. While they have a significant effect on treating malignancies, immunomodulating therapies contribute to the rate of cancer-related infections by altering immune function (Koo et al., 2011; Rafailidis, Kakisi, Vardakas, & Falagas, 2007; Siddique et al., 2007).

In the treatment of hematologic malignancies, purine analogs induce a profound depletion of CD4+ T cells lasting months to several years (Segal et al., 2008). Of particular importance is alemtuzumab (Campath), an anti-CD52 monoclonal antibody used most extensively in those with CLL who have failed purine analogs, (i.e., fludarabine). Studies have shown alemtuzumab induces a severe, long-lasting lymphocytopenia with loss of circulating T cells, resulting in defective cell-mediated immunity (Koo et al., 2011; Martin, Marty, Fiumara, Trean, & Baden, 2006). Grade 3/4 neutropenia is reported in 70% of all patients who have received alemtuzumab; in addition, a wide spectrum of opportunistic infections have been reported, causing substantial morbidity and mortality (Koo et al., 2011; NCCN, 2011).

Rituximab (Rituxan) leads to prolonged B-lymphocyte depletion. Theoretically, rituximab has minimal effects on cell-mediated immunity; how-

Table 4. Effect of Transplant Characteristics on Infectious Risk

Transplant parameter	Effect on host barriers and immunity	Infectious consequences
Type of transplant	Allogeneic: Slower B- and T-cell immune reconstitution	Greater risk for infections of all types, especially invasive fungal and herpesvirus infections; longer interval of risk
Type of allogeneic donor	Unrelated or mismatched donor: Slower B- and T-cell immune reconstitution	Greater risk for infections of all types, but especially invasive fungal and herpesvirus infections; longer interval of risk
Type of stem cell graft	Peripheral blood: Faster neutrophil engraftment, more chronic GVHD Cord blood: Slower neutrophil engraftment, less GVHD, slower B- and T-cell immune reconstitution	Different risks for infections associated with neutropenia and GVHD
Stem cell graft manipulation	T-cell depletion: Greater risk for graft rejection, slower B- and T-cell immune reconstitution	Greater risk for neutropenic infections, lower risk for infections associated with chronic GVHD, greater and longer risk for herpesvirus and invasive fungal infections
Conditioning regimen	Intensive regimens: More mucosal injury, shorter time to neutropenia and longer duration of neutropenia	Greater risk for neutropenic infections, especially typhlitis
Immunosuppressive regimen (allogeneic)	ATG: More profound deficiency of T-cell immunity Methotrexate: More mucosal injury, longer time to neutrophil recovery	Greater risk for invasive fungal and herpesvirus infections
Central venous catheter	Breach in skin barrier	Greater risk for bacterial and (less frequently) fungal infections

Note. ATG = antithymocyte globulin; GVHD = graft-vs.-host disease. Adapted, with permission, from Wingard et al. (2011).

ever, depletion of B lymphocytes in patients with severe deficits in cellular immunity increases the risk of opportunistic infections (Koo et al., 2011). Two recent meta-analyses of rituximab maintenance therapy in lymphoma patients reported a higher relative risk of grade 3/4 infections (Koo et al., 2011). Rituximab has had a black box warning for progressive multifocal leucoencephalopathy (PML), which is caused by the polyomavirus JC, since 2007. From the initial US Food and Drug Administration (FDA) approval in 1997 to 2008, there were 76 cases of PML associated with rituximab use; however, most of these cases were in patients with lymphoproliferative disorders and in association with other immunosuppressive therapies (Koo et al., 2011). It remains controversial as to whether the development of PML is caused by primary infection, reactivation of latent infection, or

virulent mutation of an active asymptomatic infection, yet most patients are immunosuppressed at diagnosis (Carson et al., 2009).

Reactivation of latent hepatitis B virus (HBV) after receiving the monoclonal antibody rituximab can occur in HBV carriers with lymphoid malignancies; at high risk are those who have received an anthracycline-based regimen (NCCN, 2011). There are reports of seroconversion with loss of protective HBV surface antibody and reactivation of HBV infection, especially in those with chronic HBV who had detectable surface antigen before treatment (Koo et al., 2011).

Epidemiology of Cancer-Related Infections

The epidemiology of pathogen prevalence and antimicrobial susceptibilities is unique to the

Table 5. Types of Infections Encountered at Various Times After HSCT

Type of infectious pathogen	Early preengraftment (first 2-4 weeks)	Early postengraftment (2nd and 3rd month)	Late postengraftment (after 2nd or 3rd month)	Time Independent
Bacteria	Gram-negative bacteria (related to mucosal injury and neutropenia) Gram-positive bacteria (related to venous catheters) <i>Clostridium difficile</i> (related to neutropenia, antibiotics, antacid medications)	Gram-positive bacteria (related to venous catheters) Gram-negative bacteria (related to enteric involvement of GVHD, venous catheters)	Encapsulated bacteria (related to poor opsonization with chronic GVHD) Nocardia (related to chronic GVHD)	
Fungi	Candida (related to mucosal injury and neutropenia)	<i>Aspergillus</i> , other molds, and <i>Pneumocystis jirovecii</i> (related to GVHD)	<i>Aspergillus</i> , other molds and <i>Pneumocystis jirovecii</i> (related to GVHD)	
Herpesvirus	HSV	CMV (related to GVHD and impaired cellular immunity) EBV (in patients who have T-cell-depleted grafts, receive ATG, or whose donor is mismatched)	CMV and VZV (related to GVHD and impaired cellular immunity and viral latency before transplant) EBV (in patients who have T-cell-depleted grafts, receive ATG, or whose donor is mismatched)	
Other viruses	BK virus (related to GVHD and cyclophosphamide in conditioning regimen)			Respiratory viruses (temporally tracks with community outbreaks) Adenoviruses

Note. ATG = antithymocyte globulin; CMV = cytomegalovirus; EBV = Epstein-Barr virus; GVHD = graft-vs.-host disease; HSCT = hematopoietic stem cell transplantation; HSV = herpes simplex virus; VZV = varicella-zoster virus. Adapted, with permission, from Wingard et al. (2011).

epidemiology of locations, patient population, clinical settings, and the course of time related to spread and resistance (Paul et al., 2011). Early in the course of fever and neutropenia, pathogens primarily responsible for infections are bacteria, whereas antibiotic-resistant bacteria, yeast, fungi, and viruses are frequent causes of subsequent infections (NCCN, 2011).

BACTERIAL INFECTIONS

With reference to the spectrum of cancer-related pathogens encountered in patients—bacterial, viral, and fungal—bacterial infections are the most prevalent infectious pathogens occurring in those patients who receive standard chemotherapy. Current data indicate that the trends in the epidemiology of bacterial infections have changed dramatically over the past 2 decades. Previously, gram-negative bacteria dominated. Gram-positive cocci are now the most frequently isolated pathogens in many cancer centers; it is estimated that gram-positive organisms account for 60% to 70% of microbiologically documented

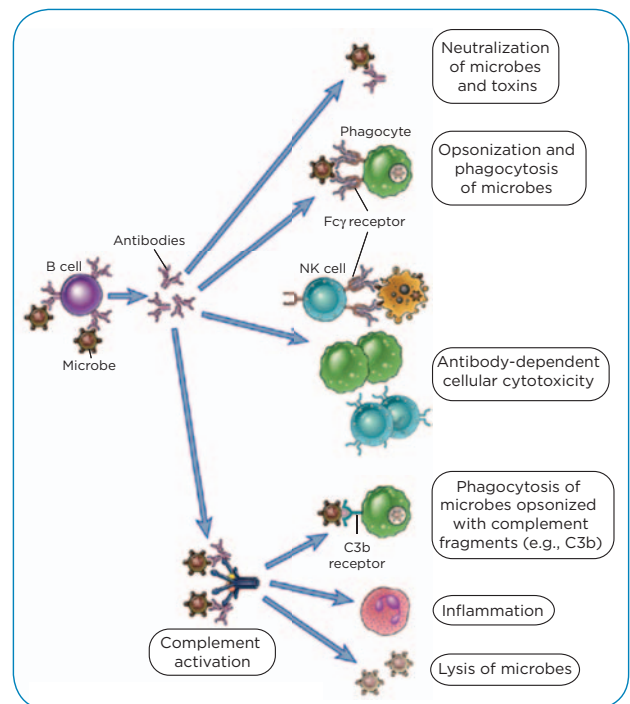


Figure 1. Effector functions of antibodies. Reprinted, with permission, from Abbas, Lichtman, & Pillai (2011).

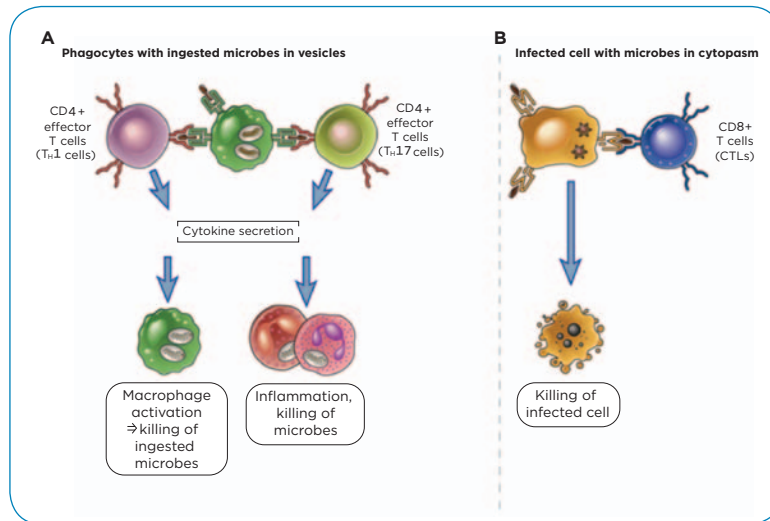


Figure 2. Types of T-cell-mediated immune reactions. Reprinted, with permission, from Abbas, Lichtman, & Pillai (2011).

infections (Gafer-Gvili et al., 2005b; Maschmeyer & Haas, 2008). It is presumed that this is due to widespread use of prophylactic fluoroquinolones and indwelling catheters and the increased use of proton pump inhibitors (Thirumala, Ramaswamy, & Chawla, 2010).

VIRAL INFECTIONS

While there are multiple factors contributing to viral infections in cancer patients, including the underlying malignancy and treatments, diminishing immunocompetence is the primary cause. Risk for viral infections is greatly exacerbated by HSCT, GVHD, and immunosuppressive therapy such as prolonged steroids, monoclonal antibodies, purine analogs, and proteasome inhibitors (De Paolo, Whitworth, Anderson, & Miller, 2008; NCCN, 2011; Segal et al., 2008). Epidemiologic data for viral infections indicate most of the general population has been exposed to several viruses during the course of life (Angarone & Ison, 2008; Spence, Hay, & Johnston, 2006). Reactivation of these viruses commonly occurs in immunocompromised cancer patients, particularly those undergoing treatment (Angarone & Ison, 2008; Spence et al., 2006).

In the immunocompromised patient, influenza has high morbidity, causing both pulmonary and extrapulmonary complications. For transplant recipients, influenza increases the risk for both graft dysfunction and rejection (Kamboj & Sepkowitz, 2009). Respiratory syncytial virus (RSV)

can cause severe disease in the lower respiratory tract for HSCT recipients and those with hematologic malignancies (see Figure 3). Patients infected with RSV may asymptotically shed for months after resolution of symptoms and contribute to the spread of infection (Kamboj & Sepkowitz, 2009). Community respiratory viruses can cause significant morbidity and mortality in those with lymphopenia. HSCT patients are especially at increased risk for bacterial superinfections, persistent viral shedding, and resistance to antiviral therapy (Kamboj & Sepkowitz, 2009); see Tables 4 and 5.

FUNGAL INFECTIONS

Fungal infections are a significant problem in neutropenic patients, especially for high-risk patients such as those with hematologic malignancies after treatment with high-dose therapy, immunomodulatory agents, and stem cell transplant (Joos & Tamm, 2005; Neuburger & Maschmeyer, 2006). Studies have demonstrated an overall increase of fungal health-care-associated infections in the past 2 decades. This has also been seen among those with high-risk hematologic malignancies (Alangaden, 2011; Neuburger & Maschmeyer, 2006). While *Candida albicans* remains the most common fungal pathogen in cancer patients, non-*albicans* species are becoming more prevalent, possibly related to the widespread use of fluconazole for antifungal prophylaxis in neutropenic patients (Hachem, Hanna, Kontoyiannis,

Jiang, & Raad, 2008; Neuburger & Maschmeyer, 2006). Invasive aspergillosis and other invasive mold infections have increased significantly in high-risk populations, surpassing invasive candidiasis as the major cause of mortality (Neuburger & Maschmeyer, 2006; Person, Kontoyiannis, & Alexander, 2011).

CATHETER-RELATED INFECTIONS

While they are a necessary intervention in cancer therapy, intravascular catheters are associated with frequent infectious complications. This often occurs with organisms resistant to many antimicrobials, making them difficult to treat. Intravascular catheter infections are the most commonly occurring health-care-associated infection (Kamboj & Sepkowitz, 2009; Yeung, Escalante, & Gagel, 2009). Major causes of infection depend on the type and location of the catheter or implantable device (Mermel et al., 2009; Neuburger & Maschmeyer, 2006; Yeung et al., 2009). Risk of bloodstream infection is dependent upon several factors, such as type of intravascular catheter placed, experience of clinicians placing the catheter, the catheter's insertion site, frequency of access, duration of placement, individual patient characteristics, and use of infection control strategies (Mermel et al., 2009). Catheter-related candidemia can be associated with serious complications of septic thrombosis and endocarditis (Yeung et al., 2009).

SEPSIS

Sepsis, a life-threatening condition, is the presence of infectious organisms or their toxins in the bloodstream, which can lead to septic shock and death (Penack et al., 2007). Sepsis is the most frequent cause of hospitalization for the general population, occurring in 750,000 people each year, and it is increasing (Thirumala et al., 2010). The 2009 US Mortality Data for the general population ranks septicemia in the top 15 leading causes of death, with 36,587 documented deaths from sepsis (CDC, 2011). Researchers have found the most common comorbid medical condition in septic patients is cancer, with a 30% higher risk for death secondary to sepsis (Danai, Moss, Manino, & Martin, 2006; Thirumala et al., 2010).

High mortality is partly related to resistant microorganisms; any delay in time to therapy decreases survival rates (Lepak & Andes, 2011).

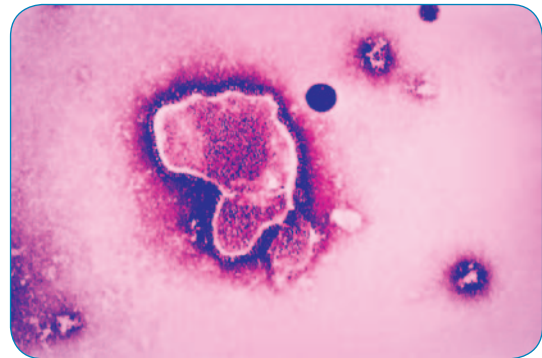
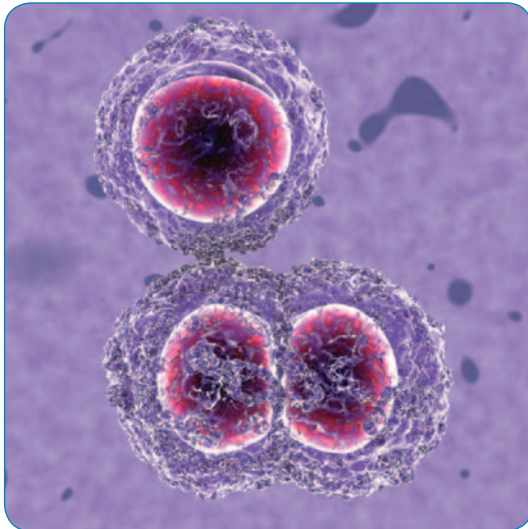


Figure 3. Respiratory syncytial virus (RSV) particles. This pneumovirus, a type of paramyxovirus, is a major cause of human respiratory tract infections in patients of all ages. Each virion consists of RNA (ribonucleic acid) genetic material enclosed in a protein coat, or capsid, within a phospholipid envelope. The envelope is covered in protein spikes, which enable the virus to attach to and enter a host cell. In the general adult population, RSV affects the upper respiratory tract; however, RSV can progress rapidly to lower respiratory tract infection in the hematopoietic stem cell transplant population.

Different predisposing etiologic factors are associated in patients with solid tumors, such as infections secondary to obstructive pneumonia, damage to anatomic barriers of skin and mucous membranes, invasive procedures, radiation, catheters, shunts, and stents (Anatoliotaki et al., 2004; Dhainaut, Claessens, James, & Nelson, 2005; NCCN, 2011). Patients with hematologic malignancies have a 10-fold increased risk of bacteremia compared with other cancers (Pedersen et al., 2007).

In summary, cancer remains a strong predictor of mortality in sepsis compared to the general population. The rate of sepsis in cancer patients has been estimated between 31% in non-neutropenic and 36% in neutropenic patients (Wisplinghoff, Seifert, Wenzel, & Edmond, 2003). Independent predictors for mortality include gram-negative and gram-positive bacteremia, invasive aspergillosis, invasive candidiasis, and pneumonia (Dhainaut et al., 2005; Kuderer et al., 2006; Segal et al., 2008). Furthermore, FN patients were found to have the highest mortality (18%–34%) for gram-negative bacteremia (Feld, 2008; Klastersky et al., 2007). A study of sepsis



Michael Taylor/Shutterstock.com

Figure 4. Methicillin-resistant *S. aureus* (MRSA).

in patients with solid tumors revealed that a startling 51% of these infections were health-care associated (Anatoliotaki et al., 2004).

Antimicrobial Resistance

Another growing concern affecting rates of infectious complications in cancer patients is antimicrobial resistance, which bears equal risk for noncancer patients (Daum, 2007). Antimicrobial resistance is complex, with contributing factors of antibiotic misuse, overuse, and the ability of microbes to share resistant genes (Dellit et al., 2007; Rice et al., 2008). There is mounting evidence that vancomycin is losing its efficacy for *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA; Sakoulas & Moellering, 2008); see Figure 4. A major cause of nosocomial infections are vancomycin-resistant enterococci (Ghanem, Hachem, Jiang, Chemaly, & Raad, 2007). The emergence of ciprofloxacin-resistant *Escherichia coli* has become an escalating problem in cancer patients (Kern et al., 2005). Several current studies have supported quinolone prophylaxis with evidence that it reduces infection-related morbidity in cancer patients (Gafter-Gvili et al., 2005a; Leibovici, Paul, Cullen, et al., 2006). However, with routine use, there is concern that alarming rates of quinolone resistance among gram-negative species may emerge (Maschmeyer & Haas, 2008).

In addition to the risk of rapidly increasing resistance rates with quinolone prophylaxis, is

the dramatic rise in the number of patients developing *Clostridium difficile*-associated enterocolitis (Maschmeyer & Haas, 2008). *Clostridium difficile*, an unintended consequence of antimicrobial use, has become more prevalent with increasing severity over the past few years. This prevalence has been linked to a previously uncommon but more virulent strain of *Clostridium difficile* (Kamboj & Sepkowitz, 2009).

Antimicrobial stewardship is vital to correct overuse and misuse of antimicrobial agents. Inappropriate antimicrobial use contributes to the emergence of multidrug-resistant organisms in addition to adverse drug reactions that cause detrimental effects for the individual patient and puts cost burden on the health-care system (Tamma & Cosgrove, 2011). Prompt recognition of those patients requiring complex medical management for infection necessitates a formal infectious disease consultation to insure proper treatment to resolution (Pongas et al., 2010).

Navigating clinical practice strategies in treating cancer-related infections remains difficult, considering increasing antimicrobial resistance, unique cancer and treatment risk factors, atypical symptoms, and acuity for timely diagnosis and management.

Clinical Practice Guidelines for the Management of Cancer-Related Infection

It is critical for clinicians to understand evidence-based infection control practices, appropriate prophylaxis, preemptive therapy, and treatment strategies for implementation in real time. Clinical practice guidelines create a scientifically researched foundation to achieve consistency, efficiency, effectiveness, quality, and safety in providing care (Timmermans & Mauck, 2005). However, they are intended as a knowledge tool to assist in clinical decision-making, not to take the place of it. Guidelines also serve as knowledge translation tools that can enhance awareness of the current scientific advances underpinning evidence-based practice.

Respected national cancer care and infectious disease organizations have published evidence-based clinical practice guidelines specific to cancer-related infection and neutropenia. A brief summary of the most widely used resources follows, yet the list is not inclusive; there are

multiple guidelines specific to individual infectious conditions, location, and patient population. Separate institutional-based guidelines have also been developed based in part on published guidelines and information unique to the needs of a specific institution.

The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of the country’s 21 leading cancer centers, is an authoritative source for evidence-based, high-quality cancer care (NCCN, 2011). The NCCN has created evidence-based clinical guidelines to promote effective clinical practice. Formerly, the NCCN established guidelines to reduce cancer-related infections only for neutropenic patients. While these remain key risk factors for infections, other cancer non-neutropenic immunocompromised states pose equal risk. However, until recently, no standards of care had been established with this broader scope (NCCN, 2011). The NCCN expanded their guidelines beyond neutropenia to prevent and treat cancer-related infections. Major

categories of immunologic deficits predisposing both non-neutropenic and neutropenic cancer patients to increased infectious risk have been identified and stratified into low-, moderate-, and high-risk groups (NCCN, 2011); see Table 6. All recommendations are based on the level of evidence category 2A unless otherwise indicated.

The Multinational Association for Supportive Care in Cancer Risk-Index Score (MASCC), a well-validated risk schema, is a scoring method that the NCCN recommends should be utilized to further define a patient’s risk by evaluating burden of illness at the time of initial evaluation (Klastersky et al., 2000); see Table 7. These comprehensive guidelines have a broad base of clinical consensus and are in the process of a discussion update (NCCN, 2011).

The Infectious Diseases Society of America (IDSA), a national authority for evidence-based practice regarding infectious diseases, has been a long-standing resource for clinical guidelines related to neutropenia and neutropenic fever.

Table 6. National Comprehensive Cancer Network: Risk Categories for Overall Infection Risk in Cancer Patients

Overall infection risk in cancer patients	Disease/therapy examples	Fever and neutropenia risk category	Antimicrobial prophylaxis recommendations
Low	Standard chemotherapy Anticipated neutropenia < 7 days	Low	Bacterial—none Fungal—none Viral—none unless prior HSV episode
Moderate	Autologous HSCT Lymphoma Multiple Myeloma CLL Purine analog therapy (i.e., fludarabine, 2-CDA) Anticipated neutropenia 7–10 days	Usually high but some experts suggest modifications depending on patient status	Bacterial—consider fluoroquinolone prophylaxis Fungal—consider fluconazole during neutropenia and for anticipated mucositis Viral—during neutropenia and at least 30 days after HSCT
High	Allogeneic HSCT Acute leukemia • Induction • Consolidation Alemtuzumab therapy GVHD treated with high-dose steroids Anticipated neutropenia > 10 days	Usually high, but significant variability exists related to duration of neutropenia, immunosuppressive agents, and status of underlying malignancy	Bacterial—consider fluoroquinolone prophylaxis Fungal—see INF-3 ^a Viral—during neutropenia and at least 30 days after HSCT

Note. CLL = chronic lymphocytic leukemia; GVHD = graft-vs.-host disease; HSCT = hematopoietic stem cell transplant; HSV = herpes simplex virus. Adapted, with permission, from “NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) Prevention and Treatment of Cancer-Related Infections. V 1.2011.” © 2011 National Comprehensive Cancer Network, Inc. All rights reserved.

^aItraconazole recommendation as prophylaxis changed from a category 1 to a category 2B level of evidence and consensus.

Table 7. The Multinational Association for Supportive Care in Cancer Risk-Index Score^a

Characteristic	Weight
Burden of febrile neutropenia without symptoms or with mild symptoms	5
Burden of febrile neutropenia with moderate symptoms	3
No hypotension (systolic blood pressure > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy without previous fungal infection	4
No dehydration requiring intravenous fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age < 60 years	2

Note. Adapted, with permission, from Klastersky et al. (2000).

^aThe MASCC score is a sum of weighted risk factors evaluated by “burden of illness.” A cumulative MASCC score < 21 is used to define patients at high risk for serious complications during febrile neutropenia; low-risk patients are identified by a cumulative score of ≥ 21 .

These guidelines are based on quality of evidence and strength of recommendations. The IDSA updated their Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients With Cancer in 2010. These guidelines also clinically define low- and high-risk neutropenic patients (Freifeld et al., 2011); see Table 8. The IDSA also utilizes the MASCC risk index score to identify subgroups of febrile neutropenic patients with low or high risk for complications and death (Klastersky et al., 2000).

In a recent analysis, Klastersky et al. confirm that a major advance in the successful management of febrile neutropenia has been through risk stratification, which remains a standard to guide management of solid tumors and lymphomas but may be less predictive in patients with hematologic malignancies (Klastersky et al., 2011).

The IDSA website is a comprehensive clinical resource for multiple infection-related conditions, with guidelines for antimicrobial use, antimicrobial stewardship, infections by organ system, infections by organism, and other unique clinical conditions/patient populations such as opportunistic infections in the stem cell transplant patient and catheter-related infections. These guidelines can be accessed online and downloaded to mobile devices (IDSA, 2011).

The American Society for Blood and Marrow Transplantation (ASBMT) is an international

professional association supporting transplantation research and the development of clinical practice standards in the medical care for autologous and allogeneic transplant recipients (ASBMT, 2011). Guidelines specific to the prevention of infectious complications in HSCT recipients have been published in a report cosponsored by the ASBMT, with a distinguished panel of national and internationally recognized expert organizations (Tomblyn et al., 2009). These guidelines, updated in 2009, provide comprehensive information regarding the background of HSCT; immune system recovery; management and prevention of infections throughout the phases of preengraftment, postengraftment, and late-phase posttransplantation; and vaccination recommendations (Tomblyn et al., 2009).

The Oncology Nursing Society (ONS), a premier professional body promoting oncology nursing education, evidence-based nursing practice, and research, is dedicated to quality nursing care for the oncology patient. To this end, the ONS promotes translation of research into clinical practice through its “Interventions for Patient Outcomes Project Team,” an educational resource for oncology nurses and advanced practice nurses, and the creation of its “Putting Evidence Into Practice” (PEP) website (ONS, 2011a). The PEP website provides a rich resource to enhance oncology nurses and advanced prac-

titioners' knowledge, utilization, and contributions toward current evidence-based clinical research for interventions specific to oncology patient outcomes.

A classification schema helps evaluate the current collective body of evidence for interventions to assist in clinical decisions on implementation. Three major components (quality of the data, magnitude of the outcome, and concurrence among the evidence) are considered in classifying the collective evidence about an intervention and put into one of six "Weight of Evidence" categories: recommended for practice, likely to be effective, benefits balanced with harms, effectiveness not established, effectiveness unlikely, and not recommended for practice (ONS, 2011a). The ONS website provides a clinical practice resource specific for neutropenia and a site for "Prevention of Infection," providing a compilation of definitions, tables of evidence for clinical practice guidelines, publications, and quick view resources (ONS, 2011b).

Other vital website databases that can provide clinical resources for the advanced practitioner are the Centers for Disease Control, American Society of Clinical Oncology, American Society of Hematology, National Cancer Institute, American Cancer Society, the Leukemia & Lymphoma Society, and the Agency for Healthcare Research and Quality National Guideline Clearinghouse. Antibiotic guides for use on mobile devices are also available.

Conclusion

Advanced practitioners in oncology are uniquely positioned to provide supportive care of patients in order to promote optimal health before, during, and after cancer therapy. Knowledge of the etiology, epidemiology, risk factors, and appropriate clinical management of cancer-related infection is vitally important to achieve successful cancer treatment and improve over-

Table 8. Infectious Diseases Society of America: Risk Factors for Serious Complications During Episode of Febrile Neutropenia

High risk

Profound neutropenia (absolute neutrophil count < 100 cells/ μ L > 7 days

Presence of any comorbid medical conditions but not limited to:

- Hemodynamic instability
- Oral/gastrointestinal mucositis causing dysphagia or diarrhea
- New neurologic or mental status changes, intravascular catheter infection, especially tunneled catheter infection
- New pulmonary infiltrate/hypoxemia or chronic lung disease

Evidence of hepatic insufficiency (defined as aminotransferase levels > 5 x normal values)

Evidence of renal insufficiency (defined as a creatinine clearance of < 30 mL/min)

Low risk

Neutropenia < 7 days

No comorbid medical conditions

Hemodynamically stable

Normal hepatic and renal function

Note. Adapted, with permission, from Freifeld et al. (2011).

all survival. The escalating costs of cancer care, novel treatments predisposing cancer patients to unique infectious threats, along with the rapidly evolving spectrum of antimicrobial pathogens and resistance, are critical clinical dilemmas urging the improvement of cancer care in real time. Evidence-based clinical practice guidelines are essential tools for standard of care practices in achieving the best clinical outcomes for patients living with cancer.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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