Introduction

For patients who are immunocompromised because of cancer or cancer treatment, an infection can be devastating. Consequently, prevention of infection can significantly decrease morbidity and mortality in this population. This monograph reviews interventions to prevent infection in patients with cancer. This update of the 2009 Oncology Nursing Society (ONS) Putting Evidence Into Practice (PEP) resource for prevention of infection also incorporates relevant evidence in patients undergoing hematopoietic cell transplantation (HCT) and evidence in pediatric patients. Material covered here does not include evidence for treatment of febrile neutropenia (FN); rather, prevention of infection as reviewed here includes prevention of FN.

The PEP topic team of nurse clinicians and nurse scientists categorized individual interventions according to the decision rules shown in Figure 1. The literature search strategy and inclusion and exclusion criteria are shown in the appendix.

Problem

FN is one of the most concerning complications of cancer therapy. Morbidity and mortality from FN are significant concerns for providers in oncology care (de Naurois et al., 2010). Fever during cancer treatment–induced neutropenia may be the only indication of underlying infection because usual signs can be absent with reduced neutrophil counts (Freifeld et al., 2011). FN complications such as infection and sepsis are life-threatening adverse effects of cancer treatment. Neutropenia during chemotherapy also may require dose reductions or delays that can impact the effectiveness of therapy (Aapro et al., 2011).

HCT patients are much more susceptible to opportunistic infections because of the profound neutropenia induced by high-dose marrow-ablative chemotherapy in the preparative regimen. Allogeneic HCT recipients, who also require post-transplantation immunosuppression to prevent graft-versus-host disease (GVHD), are at the highest risk for infection. HCT recipients are particularly susceptible to bacteria such as Staphylococcus and viruses including cytomegalovirus (CMV), herpes zoster virus, Epstein-Barr virus (EBV), and human herpesvirus-6, as well as common respiratory viruses such as respiratory syncytial virus, influenza A
### Recommended for Practice

*Interventions for which effectiveness has been demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews and for which expectation of harms is small compared with the benefits*

- Supportive evidence from at least two well-conducted randomized controlled trials that were performed at more than one institutional site and that included a sample size of at least 100 participants
- Evidence from a meta-analysis or systematic review of research studies that incorporated quality ratings in the analysis and included a total of 100 patients or more in its estimate of effect size and confidence intervals
- Recommendations from a panel of experts that derive from an explicit literature search strategy and include thorough analysis, quality rating, and synthesis of the evidence

### Likely to Be Effective

*Interventions for which the evidence is less well-established than for those listed under Recommended for Practice*

- Supportive evidence from a single well-conducted randomized controlled trial that included fewer than 100 patients or was conducted at one or more institutions
- Evidence from a meta-analysis or systematic review that incorporated quality ratings in the analysis and included fewer than 100 patients or had no estimates of effect size and confidence intervals
- Evidence from a synthetic review of randomized trials that incorporated quality ratings in the analysis
- Guidelines developed largely by consensus/expert opinion rather than primarily based on the evidence and published by a panel of experts that are not supported by synthesis and quality rating of the evidence

### Benefits Balanced With Harms

*Interventions for which clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities*

- Supportive evidence from one or more randomized trials, meta-analyses, or systematic reviews but where the intervention may be associated, in certain patient populations, with adverse effects that produce or potentially produce mortality, significant morbidity, functional disability, hospitalization, or excess length of stay

### Effectiveness Not Established

*Interventions for which there are currently insufficient data or data of inadequate quality*

- Supportive evidence from a well-conducted case control study
- Supportive evidence from a poorly controlled or uncontrolled study
- Evidence from randomized clinical trials with one or more major or three or more minor methodologic flaws that could invalidate the results
- Evidence from nonexperimental studies with high potential for bias (such as case series with comparison to historical controls); evidence from case series or case reports
- Conflicting evidence but where the preponderance of the evidence is in support of the recommendation or meta-analysis showing a trend that did not reach statistical significance

(Continued on next page)
PREVENTION OF INFECTION

Figure 1. PEP Decision Rules for Summative Evaluation of Evidence (Continued)

Effectiveness Unlikely

*Interventions for which lack of effectiveness is less well-established than for those listed under Not Recommended for Practice*

- Evidence from a single well-conducted randomized trial with at least 100 participants or conducted at more than one site and which showed no benefit for the intervention
- Evidence from a well-conducted case control study, a poorly controlled or uncontrolled study, a randomized trial with major methodologic flaws, or an observational study (e.g., case series with historical controls) that showed no benefit and a prominent and unacceptable pattern of adverse events and serious toxicities (CTCAE grade 3–4)

Not Recommended for Practice

*Interventions for which ineffectiveness or harmfulness has been demonstrated by clear evidence, or the cost or burden necessary for the intervention exceeds anticipated benefit*

- Evidence from two or more well-conducted randomized trials with at least 100 participants or conducted at more than one site and which showed no benefit for the intervention and excessive costs or burden expected
- Evidence from a single well-conducted trial that showed a prominent and unacceptable pattern of adverse events and serious toxicities (CTCAE grade 3–4)
- Evidence from a meta-analysis or systematic review of research studies that incorporated quality ratings in the analysis, included a total of 100 patients or more in its estimate of effect size and confidence intervals with demonstrated lack of benefit or prominent and unacceptable toxicities
- Intervention discouraged from use by a panel of experts in the related subject, after conducting a systematic examination, quality rating, and synthesis of the available evidence

Expert Opinion

Low-risk interventions that are (1) consistent with sound clinical practice, (2) suggested by an expert in a peer-reviewed publication, and (3) for which limited evidence exists. An expert is an individual who has published articles in peer-reviewed journals in the domain of interest.

CTCAE—National Cancer Institute Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events


and B, and parainfluenza (Rolston, 2011). These patients are also highly susceptible to fungal infections, including Aspergillus and Candida (Perumbeti & Sacher, 2011).

In addition to morbidity and mortality associated with FN and infection in patients with cancer, infectious complications can have significant financial and quality-of-life consequences for patients and family members. From the healthcare system perspective, prevention of FN and infection can reduce the need for hospitalizations and antibiotic usage (Aapro et al., 2011). Prevention of infectious complications among patients with cancer is a high-priority nursing-sensitive area to affect patient outcomes.
Incidence

FN occurs in up to 50% of patients with solid tumors and 80% or more of patients with hematologic malignancies who receive at least one cycle of chemotherapy. Documented infection is identified in approximately 20%–30% of patients with cancer with FN. The most common sites of infection include the respiratory tract, urinary tract, bloodstream, gastrointestinal tract, and skin or skin structures. In the case of bloodstream infections where an organism is identified, common isolates include coagulase-negative *Staphylococci*, *Enterobacter* species, *Escherichia coli*, *Klebsiella*, *Pseudomonas aeruginosa*, and *Stenotrophomonas* species (Freifeld et al., 2011). Incidence of drug-resistant infection has increased because of extended-spectrum beta lactamase (ESBL) gram-negative and gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) (Freifeld et al., 2011). Infections at sites other than the bloodstream are more often caused by gram-negative bacilli and are frequently polymicrobial (Rolston, 2011).

Fungal infections are most frequently caused by *Candida* or *Aspergillus* and are most often seen in patients with hematologic malignancies or HCT recipients who have prolonged severe neutropenia. Molds such as *Aspergillus* are most likely to cause life-threatening infections (Freifeld et al., 2011).

Viral infections are also more common in patients with hematologic malignancies and those undergoing HCT because of either opportunistic infection from exposure or reactivation of previous infection. The mortality rate from influenza virus among patients with cancer has been reported to be as high as 9%, yet fewer than 50% of patients are vaccinated (Pollyea, Brown, & Horning, 2010). Allogeneic HCT recipients have a 20%–50% chance of developing a varicella zoster virus (VZV) infection, mainly because of endogenous reactivation. The risk of herpes simplex virus (HSV) infection is about 80%. Reactivation of EBV after allogeneic transplant may result in post-transplant lymphoproliferative disorder (PTLD), which has a poor prognosis. The incidence of PTLD is generally low (0.5%–2%) but can be as high as 20% in patients with multiple risk factors such as T-cell depletion and mismatched transplants (Sandherr et al., 2006).

Infections occur in more than 60% of HCT recipients, and the incidence of febrile complications following HCT is 60%–100% (Weissinger et al., 2012). Recipients of a myeloablative HCT typically experience a profound neutropenic period lasting days to weeks depending on the source of their graft. In patients receiving peripheral blood hematopoietic stem cells, the neutropenic period averages two weeks; in those with marrow grafts, it can last three weeks; and in those with umbilical cord blood grafts, it is closer to four weeks. During this period, patients are extremely susceptible to a variety of infections. The risk of infection among patients receiving a non-myeloablative transplantation regimen is lower because the severity and duration of neutropenia is lower, but they remain at risk for opportunistic infections because of post-transplantation immunosuppression (Tomblyn et al., 2009). In addition, conditioning regimens that employ high-dose chemotherapy or radiation damage the skin and mucosal cells. This impairs skin and mucosal integrity, which can facilitate entry of potentially pathogenic microorganisms (Tomblyn et al., 2009).
Survivorship and Late Effects

Patients undergoing HCT, as well as those with certain hematologic malignancies, especially those receiving long-term immunosuppressive drugs, have lifelong considerations related to immunosuppression. Immune recovery is slower for allogeneic HCT recipients, in patients with GVHD, and in those receiving systemic immunosuppressive treatment. Although the risk of infectious complications is highest in the first two years after transplantation, this risk may continue long term for some allogeneic transplant recipients (Majhail et al., 2012; Tomblyn et al., 2009). Late complications caused by CMV and VZV contribute to morbidity and mortality, and community-acquired respiratory viruses also pose an important risk for immunocompromised HCT survivors (Tierney & Robinson, 2013). Many survivors may no longer be under the care of transplant centers, and other healthcare providers may not be familiar with potential infectious risks in this group of patients (Rizzo et al., 2006). In this regard, it is important for survivor education to include signs and symptoms of infection, appropriate use of prescribed prophylactic medications and immunizations, and behaviors to reduce exposure to opportunistic infections.

Antibodies to vaccine-preventable diseases, such as tetanus, polio, measles, mumps, and rubella, decline in 1–10 years after HCT. A limited number of cases of such diseases have been reported among HCT recipients, but these still pose risks to the population (Ljungman et al., 2009). Several groups have identified vaccines that are recommended for patients, considered optional, and not recommended (Ljungman et al., 2009).

Assessment

Preventing infection in patients with cancer may involve assessment and intervention related to (a) risk for infection (National Comprehensive Cancer Network [NCCN], 2012a, 2012b; Tomblyn et al., 2009), (b) risk for neutropenia (Aapro et al., 2011; NCCN, 2012a, 2012b; Waller et al., 2010), (c) risk for FN (Aapro et al., 2011; Freifeld et al., 2011; NCCN, 2012a, 2012b), and (d) risk for FN complications (Aapro et al., 2011; NCCN, 2012a, 2012b). Factors cited in all of these risk assessments can help to identify patients with cancer at risk for infection and the potential cascade of associated adverse outcomes.