Prevention of Infection

14

Brian T. Fisher, Christopher C. Dvorak,
and Sarah Alexander

Contents

14.1 **Introduction** 224

14.2 **Prevention of Bacterial Infection** 224
14.2.1 Risk Stratification 224
14.2.2 Antimicrobial Approaches 225
14.2.3 Risks of Prophylaxis 226
14.2.4 Guidelines and Current Usage of Antibacterial Prophylaxis 227
14.2.5 Central Venous Catheter-Related Interventions 227
14.2.6 Future Directions 228

14.3 **Prevention of Fungal Infections** 228
14.3.1 Risk Stratification 229
14.3.2 Approaches to Antifungal Prophylaxis 230
14.3.3 Guideline Recommendations for Antifungal Prophylaxis 232
14.3.4 Limitations of Current Options for Antifungal Prophylaxis 232
14.3.5 Risks of Prophylaxis 233
14.3.6 Biomarkers 233
14.3.7 Future Directions 234

14.4 **Prevention of *Pneumocystis jiroveci* Pneumonia (PCP)** 234
14.4.1 Risk Stratification 234
14.4.2 Approaches to PCP Prophylaxis 235
14.4.3 Summary of the Recommendations from Guidelines for PCP Prophylaxis 236
14.4.4 Future Directions 236

14.5 **Prevention of Viral Infections** 236
14.5.1 Postexposure Chemoprophylaxis 237
14.5.2 Suppressive Therapy 237
14.5.3 Future Directions 238

14.6 **Infection Control Practices** 239
14.6.1 Hand Hygiene 239
14.6.2 Mandatory Vaccination 239
14.6.3 Hospital Isolation Practices 239
14.6.4 Visitor Screening Policies 240
14.6.5 Work Restriction 240
14.6.6 Cytomegalovirus (CMV) Status of Transfused Blood Products 240

14.7 Summary 241

References 241

B.T. Fisher, DO, MSCE, MPH (✉)
Pediatrics, Division of Infectious Diseases,
Children's Hospital of Philadelphia,
34th Street and Civic Center Boulevard,
CHOP North Room 1515,
Philadelphia, PA 19104, USA
e-mail: fisherbria@email.chop.edu

C.C. Dvorak, MD
Pediatric Stem Cell Transplantation,
Benioff Children's Hospital,
University of California-San Francisco,
San Francisco, CA, USA

S. Alexander, MD
Pediatric Hematology/Oncology,
Hospital for Sick Children,
Toronto, ON, Canada

Abstract

Significant advances in chemotherapy protocols for the treatment of many childhood cancers have resulted in improved survival rates; however, opportunistic infections continue to plague this vulnerable population, especially with concomitant increased therapeutic intensity. Empiric antibiotic and antifungal therapy in patients with suspected infection have helped limit the effect of such infections although infection persists as a leading cause of treatment-related mortality.

J. Feusner et al. (eds.), *Supportive Care in Pediatric Oncology: A Practical Evidence-Based Approach*, Pediatric Oncology,
DOI 10.1007/978-3-662-44317-0_14, © Springer Berlin Heidelberg 2015

Preventative interventions represent an opportunity to reduce the incidence of infection and thus reduce mortality. The pediatric evidence for specific preventative measures to reduce bacterial, fungal and viral infections is reviewed. Areas for future research to improve knowledge regarding infection prevention in children with malignancy are also identified.

14.1 Introduction

The use of increasingly complex treatment regimens including intensive chemotherapy, radiation therapy and surgical interventions place patients at risk for infection due to altered anatomical barriers, impairment of various arms of innate and adaptive immunity, and worsening in their nutritional status (Lehrnbecher et al. 1997). Together, these negative sequelae of cancer therapy translate into a significant risk for infection. Early reports of acute leukemia cohorts suggested that 70 % of mortality was attributable to infection (Hersh et al. 1965; Hughes 1971). Soon after these reports, adult and pediatric studies suggested the benefit of empiric antibiotic and antifungal therapy in the setting of febrile neutropenia (FN) (Schimpff et al. 1971; Pizzo et al. 1979, 1982). While empiric antimicrobial therapy has become standard of care in FN (see Chap. 1), contemporary epidemiology studies still identify infection as the major contributing cause of treatment-related mortality in children receiving myelosuppressive chemotherapy (Creutzig et al. 2004; Sung et al. 2007; Freifeld et al. 2011).

In recent years, strategies for the management of infection in pediatric cancer patients have been broadened from a reactionary approach to a more proactive one utilizing preventative measures. Preventing the development of infection may prove more successful than attempting to clear a pathogen in an immunocompromised patient. This chapter will focus on current and potential future preventative therapeutic options for bacterial and fungal infections and discuss both pediatric and adult data. In addition, options for suppression of latent viral infection and postexposure chemoprophylaxis with antiviral therapy will be explored. Discussion of prevention of infection through vaccination is discussed in detail in Chap. 16. Consideration of the prevention or suppression of other important infections such as tuberculosis or parasitic illnesses is important in communities where such infections are more prominent; however, such a discussion is outside the scope of this chapter. At the conclusion of each section, tables of graded recommendations (Tables 14.1, 14.5 and 14.7) are included for ease of reference. Finally, the chapter concludes with a discussion on hospital-based infection control practices which can reduce hospital-acquired communicable diseases in these vulnerable patients.

14.2 Prevention of Bacterial Infection

Bacterial infection is the leading cause of treatment-related morbidity and mortality in pediatric oncology patients. Evaluation and treatment of suspected or proven bacterial infection is a core component of care in children receiving myelosuppressive chemotherapy and is discussed extensively in Chap. 1. Strategies to prevent such infection, including both pharmacologic and non-pharmacologic approaches, are not as well established; data to support prophylactic measures, as well as gaps in our current knowledge, are the focus of this section.

14.2.1 Risk Stratification

As discussed in Chap. 1, the child with cancer may have multiple risk factors for serious bacterial infection including a central venous catheter, interruption of normal mucosal surfaces secondary to mucositis, surgical wounds and altered anatomy from tumor masses. Certain cancer predisposition syndromes may contribute to increased risk of infection. For example, children with Down syndrome and acute lymphoblastic leukemia (ALL) have a higher rate of infectious

complications than those with ALL alone (Rabin et al. 2012). The factor most strongly associated with risk of serious bacterial infection is chemotherapy-related neutropenia; patients receiving the most intensive myelosuppressive regimens are at the highest risk. For example, 39–50 % of children treated on Children's Cancer Group protocol 2961 for acute myelogenous leukemia (AML) had Gram-positive infections and 18–28 % had Gram-negative sterile site infections during the three phases of therapy (Sung et al. 2007). Treatment-related mortality from bacterial infection in children with AML is consistently 3–4 % across cooperative group studies over the last several decades (Woods et al. 1996; Riley et al. 1999; Creutzig et al. 2004; Sung et al. 2007, 2009). Similarly, children with relapsed ALL receiving intensive chemotherapy have high rates of infectious morbidity and mortality related to bacterial infection (Abshire et al. 2000; Lawson et al. 2000; Thomson et al. 2004; Raetz et al. 2008; Locatelli et al. 2009).

14.2.2 Antimicrobial Approaches

14.2.2.1 Adult Data

Antibacterial prophylaxis for afebrile patients receiving myelosuppressive chemotherapy is widely adopted in adult oncology practice based on data from trials preformed over the last 30 years with more than 100 published studies evaluating various antibiotic regimens. Two large contemporary studies in adult solid tumor, lymphoma and leukemia patients compared levofloxacin to placebo using a double-blind, randomized, controlled design (Bucaneve et al. 2005, Cullen et al. 2005). Although neither study was able to show a significantly decreased rate of death in the levofloxacin arm, both studies showed that prophylaxis significantly decreased episodes of fever, clinically documented infection and hospitalization. In solid tumor and lymphoma patients, Cullen et al. (2005) reported a 34.2 % rate of infection with levofloxacin compared to 41.5 % in the placebo arm (RR 0.82, 95 % CI 0.73–0.94, $p=0.004$) while Bucaneve et al. (2005) reported 22 % infection rate in the levofloxacin arm versus 39 % with placebo (absolute risk difference –0.17, 95 % CI –0.24 to –0.10) in patients with leukemia, lymphoma and solid tumors.

Meta-analysis of randomized controlled trials has shown that prophylaxis has an impact on incidence of infection and, more important, is associated with a decreased risk of death (Gafter-Gvili et al. 2012). All-cause mortality was reduced in patients receiving prophylaxis (RR 0.66, 95 % CI 0.55–0.79), with the number of patients needed to treat to prevent death from any cause being 34 (95 % CI 26–56). The most substantial effect was found in studies that used fluoroquinolones (FQs) as prophylaxis with the greatest benefit in those at the highest risk.

14.2.2.2 Pediatric Data

Data regarding the utility of bacterial prophylaxis in neutropenic children are very limited. Early studies using trimethoprim-sulfamethoxazole, erythromycin, and amoxicillin-clavulanate were hampered by difficulties with patient accrual and compliance with oral therapies (Pizzo et al. 1983; van Eys et al. 1987; Castagnola et al. 2003). Studies which have documented benefit are limited by small patient numbers at single institutions. For instance, a single arm pilot trial of ciprofloxacin prophylaxis in children receiving a reinduction block of therapy for ALL showed a decreased incidence of hospitalization, bacteremia and intensive care unit admissions compared to historical controls (Yousef et al. 2004). Specifically, hospitalization was 90 % in the controls versus 58 % in the study group ($p<0.001$), the overall rate of proven bacteremia was 22 % in the controls versus 9 % in the ciprofloxacin group ($p=0.028$), and there were no Gram-negative bacteremias in this group as compared to 7.7 % in the controls ($p<0.001$) (Yousef et al. 2004).

Similarly, a retrospective study in pediatric AML patients of prophylactic cefepime, or prophylactic vancomycin with ciprofloxacin or a cephalosporin, showed decreased rates of septicemia and hospital days compared to historical controls while patients who received only an oral cephalosporin as prophylaxis had no significant decrement in bacterial sepsis or hospital days compared with controls (Kurt et al. 2008).

A recent survey by the Children's Oncology Group (COG) of institutional standards for supportive care during AML trial AAML0531 found that antibacterial prophylaxis significantly reduced Gram-positive sterile site infection (incidence rate ratio [IRR] 0.71, 95 % CI 0.57–0.90, $p=0.004$) with a trend toward reducing all bacterial infection (IRR 0.85, 95 % CI 0.72–1.01, $p=0.058$) (Sung et al. 2013).

14.2.3 Risks of Prophylaxis

The main concern when considering prophylactic antibiotics is the potential development of bacterial resistance. Any exposure to antibiotics increases the risk of colonization and possible subsequent infection with resistant pathogens. Resistance can be acquired by selection of previously undetectable but present bacteria or de novo in a previously susceptible organism. Resistant pathogens can be transmitted from patient to patient. Studies performed in the 1980s in patients with leukemia and in those undergoing hematopoietic stem cell transplant (HSCT) documented that surveillance stool cultures could often detect pathogens preceding the development of bacteremia (Schimpff et al. 1972; Tancrede and Andremont 1985; Wingard et al. 1986). Patients identified as having a resistant organism in their stool were much more likely to have a subsequent infection with a resistant pathogen. Systematic studies evaluating the impact of FQ prophylaxis on the bacterial resistance profiles from sterile site cultures in oncology patients are limited. As anticipated with any broad antibacterial use, centers with extensive use of FQs have documented increased rates of clinically relevant FQ-resistant pathogens (Razonable et al. 2002; Kern et al. 2005; Prabhu et al. 2005). The two large contemporary double-blind studies of levofloxacin prophylaxis, which combined included 2,325 patients, did not note increased rates of resistant organisms from sterile site cultures; however, the studies were not powered to detect this outcome (Bucaneve et al. 2005; Cullen et al. 2005). Specifically, Bucaneve et al. (2005) noted 3 % of patients in the levofloxacin group had FQ-resistant Gram-negative bacilli as compared to 1 % in the placebo group (absolute risk difference 2 %, 95 % CI –0.4 % to 3 %, $p=0.10$) while Cullen et al. (2005) did not routinely test for FQ sensitivity.

The use of antibacterial prophylaxis also has potential risk for other infectious complications. Exposure to FQs in adult oncology patients has been associated with increased incidence of *Clostridium difficile*-associated diarrhea (CDAD) (von Baum et al. 2006). Rates of CDAD in hospitalized pediatric patients remain significantly lower than their adult counterparts although has increased in the last decade (Kim et al. 2008a). Additionally, there is theoretical concern that antibacterial prophylaxis may increase the rate of invasive fungal infection (IFI) though the data available do not support this concern (Gafter-Gvili et al. 2012).

FQs are the class of antibiotic most intensively investigated for antibacterial prophylaxis in adult oncology patients; in meta-analysis, FQs are the agents associated with the greatest benefit (Gafter-Gvili et al. 2012). As a class their safety profile is similar to other antibiotics with unique toxicities including rare but consistent association with tendonitis and tendon rupture (with those >60 years of age and receiving concomitant steroids at greatest risk), as well as possible association with retinal detachment (Owens and Ambrose 2005; Etminan et al. 2012). Concern regarding potential FQ toxicity in children arose from early preclinical data that associated FQ exposure to articular cartilage damage in young animals although there is now significant literature describing the safety in children (Hampel et al. 1997; Jick 1997; Redmond 1997; Bradley et al. 2007; Schaad 2007, Noel et al. 2008). Toxicity analysis in more than 2,500 pediatric patients reported that levofloxacin exposure was associated with an increased rate (3.4 % vs. 1.8 %, $p=0.025$) of musculoskeletal complaints (primarily arthralgia) at 12 months postexposure though the quality of symptoms was not different in the exposed and unexposed groups (Noel et al. 2007). Some concern remains that the results were biased by the open-label study design. Currently only ciprofloxacin is approved in the

United States for limited indications in those <18 years of age by the Food and Drug Administration (FDA).

14.2.4 Guidelines and Current Usage of Antibacterial Prophylaxis

The Infectious Diseases Society of America (IDSA) guidelines recommend the use of FQ prophylaxis in high-risk adult patients, with high-risk being defined as anticipated prolonged and profound neutropenia (i.e., absolute neutrophil count [ANC] $\leq 0.1 \times 10^9$/L for >7 days) (Freifeld et al. 2011). Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommend FQ prophylaxis in patients whose infection risk is considered to be intermediate- or high-risk (i.e., neutropenia >7 days) (NCCN 2008). The paucity of data in children have precluded the generation of pediatric-specific recommendations and these guidelines do not address the use of prophylaxis in pediatric patients. Thus, survey data for pediatric AML patients show that only approximately 13 % receive routine antibacterial prophylaxis in North American settings (Lehrnbecher et al. 2009; Sung et al. 2013).

14.2.5 Central Venous Catheter-Related Interventions

Central venous catheters (CVCs) are a common site of infection in pediatric oncology patients and prophylactic methods including CVC care plans, lock therapy as well as chlorhexidine cleansing are reviewed briefly here. See Chap. 17 for a more detail review of CVC care.

14.2.5.1 Protocols for Line Placement and Care

Revised guidelines for the prevention of infection with intravascular catheters have been recently published (O'Grady et al. 2011). The strategies recommended include systems for training those involved in the placement and care of catheters, the use of maximal sterile barrier precautions at the time of line placement and using a >0.5 % chlorhexidine skin solution with alcohol for local antisepsis. The guidelines emphasize the quality assurance and safety aspects of standardized "bundles" of central line care and systems for evaluation of compliance with institutional standards.

14.2.5.2 Antibiotic and Ethanol Locks

Antibiotic and ethanol lock therapy involves using an antimicrobial agent to fill the lumen of the central venous catheter in an attempt to prevent line-related bacterial infections. A number of studies have shown efficacy for various antimicrobial agents used as lock therapy, including studies in children with cancer (Henrickson et al. 2000). A meta-analysis of randomized controlled studies comparing vancomycin/heparin lock versus heparin alone, which included five studies in children with cancer, showed a benefit to the use of antibiotic lock in prevention of infection (Safdar and Maki 2006). As with any antibacterial prophylactic strategy, use of the agent raises concerns for emergence of resistance which has been documented in a study of gentamicin central catheter locks (Landry et al. 2010).

Ethanol locks have a potential advantage by not creating antimicrobial resistance. Studies of ethanol locks have varied in the ethanol concentrations and luminal dwell times as well as other concurrent catheter care strategies (Majetschak et al. 1999). Several studies have been performed in children receiving home parenteral nutrition; meta-analysis of four retrospective studies in this patient group suggested that ethanol lock therapy decreased the rate of central line-related infections by 81 % (Oliveira et al. 2012). Rarely, occlusion of the central line and catheter-related clots have been described with the use of ethanol locks. Data in children with cancer are lacking (Wolf et al. 2013).

14.2.5.3 Chlorhexidine Cleansing

Chlorhexidine gluconate (CHG) is a bactericidal antiseptic agent that causes membrane disruption. A cloth product with 2 % CHG (Sage Products, Inc., Cary, IL) was approved by the FDA in 2005

Table 14.1 Graded recommendations for interventions to prevent bacterial infections in children with cancer

Recommendation	Grade			Comments	Reference
	Data from studies of non-oncology patients[a]	Data from studies of adult oncology patients[a]	Data from studies of pediatric oncology patients[a]		
Antibacterial prophylaxis with a fluoroquinolone should be considered for pediatric patients with expected durations of prolonged and profound neutropenia	Not applicable	1A	0	Recommended for high-risk adult oncology patients; insufficient data in children to formulate a recommendation	Gafter-Gvili et al. (2012)
Antibiotic or ethanol locks should be considered for prevention of central line-related bacteremia	1B	1B	0	Specifics of antibiotic and ethanol lock therapies have varied across studies; insufficient data in children with cancer to formulate a recommendation	Majetschak et al. (1999); Henrickson et al. (2000); Safdar and Maki (2006); Oliveira et al. (2012); Wolf et al. (2013)
Chlorhexidine bathing should be considered for the prevention of central line-related bacteremia	1B	0	0	Insufficient data in oncology patients to formulate a recommendation	Bleasdale et al. (2007); Popovich et al. (2009)

[a]Level of evidence per Guyatt et al. (2006); see Preface

for preoperative skin cleansing. Studies of this product in adult intensive care patients have shown a significant decrease in central line infections and acquisition of multidrug-resistant pathogens (Bleasdale et al. 2007; Climo et al. 2009; Popovich et al. 2009). No data are available utilizing this strategy in children with cancer.

14.2.6 Future Directions

Data to evaluate the efficacy and potential toxicity of various strategies for the prevention of serious bacterial infection in pediatric oncology are urgently needed. Use of prophylactic antimicrobial agents needs to be evaluated for efficacy as well as safety in terms of potential short- and longer-term impact on the evolution of bacterial resistance. Studies of levofloxacin prophylaxis (ACCL0934) and CHG cleansing (ACCL1034) in children receiving intensive therapy for cancer are underway. Such research will be critical in understanding the potential merit of various preventative strategies with the ultimate goal of decreasing the burden of bacterial infection and resultant morbidity and mortality in children with cancer. Current recommendations and evidence-based grading for prevention of bacterial infection are summarized in Table 14.1.

14.3 Prevention of Fungal Infections

Children undergoing treatment for cancer are also at increased risk of developing an IFI secondary to breakdown in natural barriers (e.g., indwelling catheter, mucositis), defects in cell-mediated immunity (i.e., lymphopenia from corticosteroids and other anti-T-cell cytotoxic agents), and deficient numbers of phagocytes (due to myelosuppressive chemotherapy) (Lehrnbecher et al. 1997). Having a single defect in the host defense system is often insufficient for development of an opportunistic IFI, but, with multiple defects, IFI

begins to emerge as a significant problem. The data on IFI development and potential prevention in immunocompromised hosts derive primarily from adult studies. However, children differ from adults in the types of IFI they develop and in their metabolism of antifungal agents. For example, invasive infections caused by *Candida parapsilosis* are more common, and *Candida glabrata* rarer, in children as compared to adults, and invasive aspergillosis (IA) can be more difficult to diagnose in children due to different radiologic findings (Malani et al. 2001, Burgos et al. 2008). Thus, extrapolating clinical decisions from adult trials may be problematic. Once IFI develops, even with the advent of newer antifungal agents, treatment success rates are suboptimal, especially for mold infections. For example, Burgos et al. (2008) found that 53 % of children diagnosed with IA died; therefore, prevention of IFI in pediatric oncology patients is likely most important in improving morbidity and mortality.

14.3.1 Risk Stratification

Based on retrospective reports, as well as toxicity data collected during therapeutic trials, several groups of pediatric patients are at high risk of developing an IFI: patients undergoing HSCT (especially from an alternative allogeneic donor), patients receiving chemotherapy for AML or relapsed ALL and patients with severe aplastic anemia (SAA) (Zaoutis et al. 2006; Burgos et al. 2008). In children being treated for AML, several studies have demonstrated a high incidence (i.e., up to 29 %) of IFI, both in newly diagnosed and relapsed patients (Table 14.2) (Groll et al. 1999; Rosen et al. 2005; Sung et al. 2007, 2009). The high rate of mold infection and secondary morbidity and mortality suggest this group of patients may benefit from antimold prophylaxis. Conversely, studies of ALL patients (Table 14.2) suggest that only those with relapsed disease have a high enough incidence of IFI to justify routine prophylaxis (Groll et al. 1999; Leahey et al. 2000; Rosen et al. 2005; Afzal et al. 2009). From a biologic standpoint, patients with relapsed ALL will have generally received years of lympholytic chemotherapy during which time they could have theoretically become colonized with fungal spores which are more likely to become invasive when treated with more aggressive myelosuppressive chemotherapy for their relapsed disease. The risk of IFI in newly diagnosed ALL and solid tumor patients is not high enough to justify routine use of prophylactic antifungals (Rosen et al. 2005; Afzal et al. 2009). A pediatric meta-analysis came to

Table 14.2 Incidence of invasive fungal infection (IFI) in pediatric oncology patients

Study design	# of patients	Disease/procedure	Prophylaxis agent	IFI incidence	Reference
Prospective (CCG 2961)	492	New AML	None[a]	14–23 % per phase	Sung et al. (2007)
Prospective (CCG 2891)	335	New AML	Nonabsorbable[a]	10–27 % per phase	Sung et al. (2009)
Prospective	18	New AML	Fluconazole or nonabsorbable antifungal agent	29 %	Groll et al. (1999)
	7	Relapsed AML		28 %	
	97	New ALL		2 %	
	35	Relapsed ALL		9 %	
Retrospective	261	ALL	None	10 %	Rosen et al. (2005)
	117	AML		9 %	
Retrospective	425	New ALL	None	1 %	Afzal et al. (2009)
Prospective (CHP-540)	21	Relapsed ALL	Fluconazole	19 %	Leahey et al. (2000)

CHP-540 Children's Hospital of Philadelphia Trial 540, *CCG* Children's Cancer Group, *AML* acute myelogenous leukemia, *ALL* acute lymphoblastic leukemia
Adapted from Dvorak et al. (2012)
[a]Some patients may have received systemic antifungals

similar conclusions, recommending antifungal prophylaxis in patients with AML/MDS (myelodysplastic syndrome) but not in those with other malignancies even if with anticipated neutropenia >7 days (Science et al. 2014).

14.3.2 Approaches to Antifungal Prophylaxis

Whether antifungal prophylaxis is beneficial in high-risk pediatric cohorts remains controversial due to a lack of sufficient data. Robenshtok et al. (2007) performed a meta-analysis of 64 antifungal prophylaxis trials and demonstrated in patients with acute leukemia that the risk of IFI development was lower with antifungal prophylaxis, yet did not result in a statistical improvement in all-cause mortality. Only 5 of the 64 analyzed trials included pediatric patients making it difficult to generalize to the pediatric oncology cohort. Additionally, data were not collected on potential altered morbidity with IFI prophylaxis such as decreased hospital days or need for intensive care.

Several published randomized prospective trials comparing antifungal agents have included pediatric patients, although rarely younger than 12 years of age, and pediatric patients have generally not been separately analyzed (Table 14.3) (Goodman et al. 1992; Slavin et al. 1995; van Burik et al. 2004; Cornely et al. 2007; Wingard et al. 2010). Therefore, conclusions about the optimal prophylactic agent in pediatric oncology patients are based almost exclusively upon extrapolation from adult data. Currently, the most commonly recommended agent for antifungal prophylaxis in high-risk children is fluconazole although this recommendation is based on two older placebo-controlled trials performed in patients >12 years older of age undergoing autologous or allogeneic HSCT (Goodman et al. 1992; Slavin et al. 1995).

Although it reduced the risk of IFI relative to placebo, fluconazole lacks activity against *Aspergillus* spp., which is the second most common cause of IFI in these patients. Given this lack of anti-mold activity, several trials have compared it to mold-active agents in hopes of further decreasing rates of IFI. The first of these trials compared fluconazole to low-dose conventional deoxycholate amphotericin B deoxycholate (D-AMB); however, D-AMB did not show improvement over fluconazole and resulted in a higher adverse event rate (Wolff et al. 2000). With the advent of liposomal amphotericin B (L-AMB), there was renewed interest in prophylaxis with an amphotericin B product, and several trials, including one in children, have evaluated L-AMB (often given only three times per week) for antifungal prophylaxis in HSCT and acute leukemia patients (Kelsey et al. 1999; Mattiuzzi et al. 2003; Penack et al. 2006; Roman et al. 2008). Again, like D-AMB, L-AMB has not been shown superior to fluconazole and typically demonstrates increased side effects.

Extended-spectrum azoles such as itraconazole, voriconazole and posaconazole do possess anti-*Aspergillus* activity (Ashley et al. 2006). Several trials of itraconazole versus fluconazole have been performed and although a meta-analysis showed significantly less IFI, increased side effects, greater drug interactions and poor tolerability have led to itraconazole being abandoned in pediatric patients (Marr et al. 2004; Vardakas et al. 2005). The results of a multicenter, double-blind trial showed that voriconazole was not superior to fluconazole in the prevention of IFI, though the safety profile was similar (Wingard et al. 2010). Given the broader spectrum of activity with voriconazole, this result was surprising, but may have been due to an incomplete understanding of the complex pharmacokinetics of voriconazole and subsequent underdosing. Posaconazole is a triazole with broad coverage of most fungi, including zygomycetes (Ashley et al. 2006). In a randomized, blinded, multicenter trial of AML/MDS patients ≥13 years of age with neutropenia, posaconazole prophylaxis was superior to fluconazole or itraconazole in the prevention of IFI (absolute risk reduction –6 %; 95 % CI, –9.7 % to –2.5 %, $p<0.001$), but was also associated with an increased risk of serious adverse events (6 % vs. 2 %, $p=0.01$) (Cornely et al. 2007).

Table 14.3 Selected antifungal prophylaxis trials

Prophylaxis	Design	# of patients (# pediatric)	Disease/procedure	Control outcome[a]	Intervention outcome[a]	Reference
Fluconazole	DB, PC, MC	356 (?)[b]	Auto- and allo-HSCT	16 % at 50 days (placebo)	3 % at 50 days	Goodman et al. (1992)
Fluconazole	DB, PC, SC	300 (?)[b]	Auto- and allo-HSCT	18 % at 75 days (placebo)	7 % at 75 days	Slavin et al. (1995)
Amphotericin B	OL, MC	355 (0)	Auto- and allo-HCT	9 % (fluconazole)	14 %	Wolff et al. (2000)
L-AMB	OL Pilot	57 (57)	Allo-HSCT	NA	0 % at 100 days[a]	Roman et al. (2008)
Itraconazole	OL, SC	304 (5)[b]	Allo-HSCT	15 % (fluconazole)	7 %	Marr et al. (2004)
Voriconazole	DB, MC	600 (51)	Allo-HSCT	11 % (fluconazole) at 6 months	7 % at 6 months	Wingard et al. (2010)
Posaconazole	OL, MC	602 (?)[b]	AML/MDS	11 % (fluconazole or itraconazole) at 100 days	5 % at 100 days	Cornely et al. (2007)
Micafungin	DB, MC	882 (84)	Auto- and allo-HSCT	1.6 % (fluconazole) at 70 days	2.4 % at 70 days	van Burik et al. (2004)
Caspofungin	OL, SC	200 (0)	AML/MDS	6 % (itraconazole)	6 %	Mattiuzzi et al. (2006)
Caspofungin	Retrospective	123 (0)	Auto- and allo-HSCT	NA	7.3 % at 100 days	Chou et al. (2007)

DB double-blind, *PC* placebo-controlled, *MC* multicenter, *Auto* autologous, *Allo* allogeneic, *OL* open-label, *SC* single-center, *L-AMB* liposomal amphotericin B, *NA* not applicable, *AML* acute myelogenous leukemia, *MDS* myelodysplastic syndrome

With permission from Dvorak et al. (2012)

[a]Incidence of probable or proven fungal infection

[b]Only patients >12 years of age were eligible

The echinocandins (i.e., caspofungin, micafungin, anidulafungin) are a novel class of antifungals that target (1,3)-β-D-glucan synthase and thus interrupt biosynthesis of the glucan polymers that make up fungal cell walls. Because mammalian cells do not possess cell walls, echinocandin administration to patients has resulted in minimal toxicity. Echinocandins possess fungicidal activity against *Candida* spp. (including *Candida krusei* and *Candida glabrata*, which possess significant degrees of fluconazole resistance) and *Pneumocystis jiroveci*, as well as fungistatic activity against *Aspergillus* spp. (Ashley et al. 2006). However, they have limited efficacy against *Candida parapsilosis*. The echinocandins may be superior to fluconazole or amphotericin B for treatment of invasive candidiasis which, when combined with their anti-*Aspergillus* activity and excellent safety profile, makes them an attractive option for antifungal prophylaxis (Mora-Duarte et al. 2002; Reboli et al. 2007). In a prophylactic trial, micafungin demonstrated reduced need for empiric antifungal therapy and an improved safety profile compared to fluconazole (van Burik et al. 2004). However, the number of pediatric subjects enrolled was small ($n=84$), and a reduction in the incidence of proven or probable IFI was not demonstrated. The lack of impact on IFI may have been because the incidence of breakthrough IFI in both groups was very low, likely due to the inclusion of low-risk patients (46 % autologous HSCT recipients) and very few patients undergoing umbilical cord blood transplant (UCBT; $n=30$). Caspofungin has been shown to be at least equivalent to itraconazole in the setting of antifungal prophylaxis for adults with AML/MDS with few adverse events (Mattiuzzi et al. 2006; Chou et al. 2007). Similarly, a randomized, blinded, multicenter study of pediatric patients with persistent febrile neutropenia found comparable tolerability, safety and efficacy between caspofungin and L-AMB (Maertens et al. 2010).

14.3.3 Guideline Recommendations for Antifungal Prophylaxis

Most antifungal prophylaxis guidelines are focused on adults with hematologic malignancies or those undergoing HSCT. The IDSA guidelines recommend patients undergoing allogeneic HSCT or intensive remission induction or salvage-induction chemotherapy for acute leukemia to receive anti-*Candida* agents, with all four azoles, micafungin, and caspofungin as acceptable choices (Freifeld et al. 2011). In patients ≥13 years of age undergoing intensive chemotherapy for AML or MDS, *Aspergillus*-directed prophylaxis with posaconazole should be considered (Freifeld et al. 2011). Conversely, anti-*Aspergillus* agents have not been shown to be beneficial in HSCT recipients unless there is a prior history of IA, anticipated neutropenia (i.e., ANC $<0.5\times10^9$/L) for >2 weeks or a prolonged period of neutropenia pre-HSCT (Freifeld et al. 2011). The European Conference on Infections in Leukemia (ECIL) guidelines are also focused on adult patients undergoing induction chemotherapy or allogeneic HSCT (Maertens et al. 2011). For patients with leukemia, the ECIL guidelines consider posaconazole as having the strongest supportive evidence, with aerosolized L-AMB combined with fluconazole, fluconazole alone, itraconazole and low-dose amphotericin B all having lesser support (Maertens et al. 2011). North American pediatric guidelines strongly recommend fluconazole at a dose of 6–12 mg/kg/day (maximum 400 mg/day) for children with AML/MDS and suggest that posaconazole 200 mg three times daily is an alternative in children ≥13 years of age in settings with a high local incidence of mold infection (Science et al. 2014). In contrast, pediatric ECIL guidelines suggest either posaconazole in children ≥13 years or itraconazole in those >2 years as a recommendation with moderate evidence in patients with high-risk ALL, AML or relapsed leukemia (Groll et al. 2014).

14.3.4 Limitations of Current Options for Antifungal Prophylaxis

The current options for antifungal prophylaxis all have certain limitations: fluconazole is generally well tolerated, but has a limited spectrum of activity that does not include invasive molds; itraconazole is poorly tolerated due to gastrointestinal side effects; voriconazole, though an attractive option in children >12 years of age (age of most

trial data), has questionable standard dosing regimens and multiple drug interactions; posaconazole lacks pharmacokinetic data in children <13 years of age, lacks an intravenous formulation, has unreliable absorption in the setting of limited oral intake, and shares many of the same enzymatic pathways and therefore drug interactions as voriconazole; and finally, echinocandins are expensive and lack an available oral formulation.

For voriconazole in particular, relatively well-established dosing regimens exist for children and adults although recent studies have questioned these standard dosing regimens and have instead proposed dosing based on serum drug levels although the optimal serum voriconazole level is still uncertain (Smith et al. 2006; Trifilio et al. 2007). Part of this variability may be due to allelic polymorphisms of the gene encoding CYP2C19, which can result in an increase or decrease in voriconazole metabolism (Pascual et al. 2008). In children the situation is further complicated by linear kinetics; the optimal dose may be 7 mg/kg twice daily for children from 2 to 12 years of age, while in children <2 years of age it may be as high as 8.5 mg/kg twice daily (Karlsson et al. 2009; Neely et al. 2010; Shima et al. 2010). Even more recent data has led to a proposed maintenance dose of 8 mg/kg twice daily for all children <12 years of age and for those 12–14 years of age weighing <50 kg (Friberg et al. 2012). Currently there is no universally accepted approach to dosing or monitoring of serum levels. Voriconazole also has significant drug interactions with commonly used agents in pediatric oncology patients: voriconazole is a substrate of CYP2CP (major), 2C19 (major), and 3A4 (minor) and an inhibitor of 2C9 (moderate), 2C19 (weak), and 3A4 (moderate) (Cronin and Chandrasekar 2010). Proton pump inhibitors increase voriconazole levels, while voriconazole increases serum levels and toxicity of corticosteroids, vincristine, imatinib, bortezomib, irinotecan and many other medications (Cronin and Chandrasekar 2010).

14.3.5 Risks of Prophylaxis

In addition to direct toxicities (such as renal or hepatic) and medication interactions (especially with azoles), utilization of an antifungal agent can induce selective pressure and lead to the development of resistant organisms. Resistance of various *Candida* spp. to fluconazole is a well-known phenomenon and recently echinocandin resistance has also been noted (Pfaller et al. 2012). There is also concern that more widespread usage of prophylactic voriconazole has led to more cases of Mucorales infection (Trifilio et al. 2007). Theoretically this may be due to competitive inhibition such that Mucorales will not invade if *Aspergillus* spp. are present, but with voriconazole inhibition of *Aspergillus*, the less common Mucorales will find an opportunity to invade. In vitro data also suggest that voriconazole directly increases the virulence of zygomycetes (Lamaris et al. 2009).

14.3.6 Biomarkers

The European Organisation for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) has established guidelines to standardize the definitions of proven, probable and possible IFI (De Pauw et al. 2008). However, in practice, the diagnosis of IFI is often difficult because of the lack of specific symptoms and the invasiveness of standard diagnostic tests. Significant attention has been focused on developing noninvasive assays such as galactomannan (GMN) and (1,3)-β-D-glucan (BDG) to diagnose IFI and as discussed in Chap. 1. GMN is a polysaccharide cell wall component that is released by *Aspergillus* during growth and BDG is a cell wall polymer found in all fungi except *Cryptococcus* spp. and zygomycetes. Although commercially available kits for detection of both GMN and BDG are approved by the FDA for adults, the role of GMN in diagnosing IFI in the pediatric population remains undefined and data on BDG testing in pediatric patients are extremely limited (Steinbach et al. 2007). Until further research on these and other noninvasive tests is performed, the potential for early diagnosis of IFI in pediatric oncology patients remains elusive.

Table 14.4 Genetic risk factors for development of invasive fungal infection (IFI) following allogeneic hematopoietic stem cell transplant (HSCT)

Infection	Gene	Source	# of HSCTs	Hypothetical mechanism	Reference
IA	TLR1 and TLR6	Host	127	Decreased recognition by phagocytes	Kesh et al. (2005)
IA	IL-10 promoter	Host	105	Less production of IL-10	Seo et al. (2005)
IA	Plasminogen	Host	236	Increased tissue damage and invasion	Zaas et al. (2008)
IA	TLR4	Donor	366	Decreased recognition by phagocytes	Bochud et al. (2008)
IA	Chemokine ligand 10	Donor	139	Less response to IFN-γ, so less Th1 cells	Mezger et al. (2008)
IA	Dectin-1	Both	205	Less production of IFN-γ and IL-10	Cunha et al. (2010)
IFI	MBL	Donor	106	Decreased complement fixation	Granell et al. (2006)
IFI	MASP2	Host	106	Decreased complement fixation	Granell et al. (2006)

IA invasive aspergillosis, *TLR* toll-like receptor, *IL* interleukin, *IFN* interferon, *Th1* T-helper 1, *MBL* mannan-binding lectin, *MASP2 MBL*-associated serine protease
With permission from Dvorak et al. (2012)

14.3.7 Future Directions

The profound lack of data for this patient population have led to a clinical situation where there is no clear agent of choice for patients at high risk of developing an IFI. Because of this, in April 2011 the COG initiated a randomized open-label trial of caspofungin compared to fluconazole to prevent IFI in children undergoing chemotherapy for AML. As noted previously, a number of therapy-induced alterations in host defense have been identified as risk factors for IFI. However, there is also considerable emerging evidence that a genetic component exists in the susceptibility and outcome of IFI for immunocompromised populations. In allogeneic HSCT recipients, several polymorphisms in both host and donor genes appear to significantly predispose patients to IFI (Table 14.4) (Kesh et al. 2005; Seo et al. 2005; Granell et al. 2006; Bochud et al. 2008; Mezger et al. 2008; Zaas et al. 2008; Cunha et al. 2010). Future investigation will likely uncover additional polymorphisms that place immunocompromised hosts at increased risk of IFI. As more details on genetic risk factors emerge and are validated, personalized risk stratification will be improved beyond the current system that only utilizes traditional IFI risk factors. Furthermore, although all such studies to date have been performed in allogeneic HSCT patients, biologically it is reasonable to assume that these polymorphisms will also play a role in the development of IFI during treatment of AML, relapsed ALL, SAA and, potentially, even lower-risk diseases. Current recommendations and evidence grading for prevention of IFI are summarized in Table 14.5.

14.4 Prevention of *Pneumocystis jiroveci* Pneumonia (PCP)

Previously referred to as *Pneumocystis carinii*, the distinct yeastlike fungal species that infects humans is now known as *Pneumocystis jiroveci*, with the classic abbreviation PCP used to refer to pneumocystis pneumonia.

14.4.1 Risk Stratification

Because PCP prophylaxis has been broadly applied in pediatric oncology patients for over 25 years, it is difficult to firmly ascertain the risk factors for PCP infection in the setting of modern chemotherapeutic regimens. Older data suggest that the intensity of chemotherapy, concomitant use of corticosteroids with other chemotherapeutic agents, and possibly craniospinal irradiation were risk factors for PCP infection (Chusid and Heyrman 1978; Harris et al. 1980). Newer data show that children <2 years of

Table 14.5 Graded recommendations for interventions to prevent fungal infections in pediatric oncology patients

	Grade			
	Data from studies of adult or adolescent patients[a]	Data from studies of or including pediatric patients[a]	Comments	References
Antifungal prophylaxis should generally not be utilized for patients with newly diagnosed ALL	0	0		None
Antifungal prophylaxis with fluconazole should be considered for patients undergoing reinduction for relapsed ALL	0	0[b]		None
Antifungal prophylaxis with a minimum of fluconazole can be considered for patients undergoing chemotherapy for AML although pediatric evidence is mixed	1A	1B[b]	Antifungal prophylaxis with an echinocandin or posaconazole can also be considered; there is no accepted dose of posaconazole for children <13 years of age	Mattiuzzi et al. (2006); Cornely et al. (2007); Robenshtok et al. (2007); Lehrnbecher et al. (2009); Sung et al. (2013); Science et al. (2014)
Antifungal prophylaxis should generally not be utilized for patients with solid tumors	0	2B		Science et al. (2014)

ALL acute lymphoblastic leukemia, *AML* acute myelogenous leukemia
[a]Level of evidence per Guyatt et al. (2006); see Preface
[b]Area in urgent need of further investigation

age and, especially, infant HSCT recipients are at highest risk for PCP infection (Kim et al. 2008b).

14.4.2 Approaches to PCP Prophylaxis

PCP reactivation or infection is generally thought preventable in patients with cancer with administration of classical prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX). However, in the setting of alternative prophylaxis agents or TMP-SMX noncompliance, episodes of PCP do still occur beginning about 2 months following initiation of chemotherapy and continuing through recovery of T-cell functional immunity. TMP acts by interfering with dihydrofolate reductase, inhibiting synthesis of tetrahydrofolic acid and thus nucleic acid synthesis. TMP-SMX administration in conjunction with antifolates for ALL treatment can lead to marrow suppression and may require lowering of chemotherapy doses (Levinsen et al. 2012). The necessary amount of TMP-SMX required to prevent PCP has not been well studied, and a variety of dosing regimens exist, with 2 or 3 days per week administration being the most common (Agrawal et al. 2011). Generally, TMP-SMX is continued for at least 3 months following chemotherapy, though this recommendation is not evidence-based as studies have shown a variable rate of T-cell recovery after chemotherapeutic regimens, potentially dependent on patient age and chemotherapeutic intensity (Mackall et al. 1995; Azuma et al. 1998; Mazur et al. 2006).

In addition to possible bone marrow suppression, many patients have allergies or other reactions to TMP-SMX that induce clinicians to prematurely discontinue its use. However, the optimal second-line prophylactic agent is not well defined and all options appear to be potentially less effective than TMP-SMX. Agents that have been used include oral dapsone, intravenous or inhaled pentamidine and oral atovaquone. Dapsone is inexpensive but has a high incidence

of adverse events, especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency (Sangiolo et al. 2005). Intravenous pentamidine every 4 weeks has also been used, though inadequate protection has been noted in children <2 years of age and in those undergoing HSCT, who may require more frequent dosing (Kim et al. 2008b). Aerosolized pentamidine is generally well tolerated other than occasional bronchospasm, but its effectiveness has been questioned and it requires a compliant patient, generally 6 years of age and older (Vasconcelles et al. 2000). Atovaquone is also well tolerated, but absorption can be limited in patients not eating diets containing fatty foods. In vitro, the echinocandin class of antifungal agents appears to have some activity against the cyst form of *P. jiroveci*. To date, no study has evaluated an echinocandin as a solitary prophylactic agent; however, a few case reports have described their potential utility in combination with TMP-SMX for the treatment of PCP (Annaloro et al. 2006; Beltz et al. 2006).

14.4.3 Summary of the Recommendations from Guidelines for PCP Prophylaxis

Perhaps because PCP prophylaxis is near-universal and of little controversy, the IDSA does not have guidelines for PCP prophylaxis in patients receiving chemotherapy. The joint guidelines of the American Society for Blood and Marrow Transplantion (ASBMT), IDSA and others list TMP-SMX as first choice, with dapsone, atovaquone and both forms of pentamidine as acceptable alternatives in pediatric HSCT patients (Tomblyn et al. 2009).

14.4.4 Future Directions

Although questions remain regarding the dosing schedule and toxicities of TMP-SMX as well as the optimal second-line agents, the relative rarity of PCP infection today (except in the setting of medication noncompliance) makes the performance of future prospective trials a daunting endeavor, as the power required to show differences in outcome would require enormous numbers of patients. In this unique infection, large retrospective analyses may be the only way to obtain useful information on how to standardize approaches to optimal PCP prophylaxis.

14.5 Prevention of Viral Infections

Although significant questions are yet to be answered, the foundation for preventing bacterial and fungal infections has been established. This foundation includes a logical approach of stratifying patients by risk of infection and then instituting prophylactic therapy for high-risk patients. For many reasons, this preventative model cannot be easily adapted to viral pathogens. First, children with cancer are at risk of infection from a wide variety of viruses with various modes of transmission including from close contacts and the surrounding environment or from reactivation within the patient. Second, establishing risk strata that can be generically applied to all viral infections is extremely challenging; host factors, such as prolonged lymphopenia in a well-appearing child with ALL that increases the risk for certain viral infections, are not traditionally considered risk factors and the course of infection can be extremely variable from benign in one immunosuppressed patient to fatal in another. Third, there are limited effective antiviral therapeutic options that can be employed in a prophylactic manner; the few antiviral options that do exist often have activity against specific viruses, thus limiting their impact as broad-spectrum prophylactic options.

Therefore, in order to effectively prevent viral infections, a more comprehensive approach that targets the patient, close contacts of the patient and the patient's environment is necessary. Despite these challenges some important strategies have been developed including preexposure prophylaxis (i.e., vaccination), postexposure passive prophylaxis (i.e., immunoglobulin), chemoprophylaxis, suppressive therapy (i.e., prevention of viral reactivation), hospital infection control practices and anticipatory guidance to be applied in the home or school setting. Here, suppressive therapy, chemoprophylaxis and hospital infection

Table 14.6 Postexposure chemoprophylaxis regimens for influenza in immunocompromised children

Prophylaxis regimen	Comment
First-line therapy options: Oseltamivir: 3–11 months: 3 mg/kg/dose once daily 1–12 years: ≤15 kg: 30 mg once daily >15 kg to ≤ 23 kg: 45 mg once daily >23 kg to ≤ 40 kg: 60 mg once daily >40 kg: 75 mg once daily > 12 years: 75 mg once daily Zanamivir: ≥ 5 years: two inhalations (10 mg) once daily	Therapy to be started within 48 h of exposure and continued for 10 days; seasonal and regional resistance patterns may dictate variation in therapeutic choices; exposed patients who have not received their yearly influenza vaccine should also be administered with the inactivated influenza vaccine

control are discussed while active and passive prophylaxis is discussed in Chap. 16.

14.5.1 Postexposure Chemoprophylaxis

Every viral infection has an incubation period which establishes a window of time during which preventative efforts, if available, may be enacted to avert progression to symptomatic infection. Currently, chemoprophylaxis is routinely employed for influenza exposure. Randomized trials have established the efficacy of antiviral prophylaxis in immunocompetent healthy household contacts of a person with influenza (Hayden et al. 2000; Welliver et al. 2001). Although similar data do not exist for immunocompromised individuals exposed to influenza, it is reasonable to extrapolate the aforementioned studies to support postexposure antiviral prophylaxis in such cases. Based on these data the Advisory Committee on Immunization Practices (ACIP) currently recommends administration of an antiviral regimen after face-to-face exposure with an influenza-infected person. The antiviral therapy should be initiated within 48 h of exposure for optimal benefit and continued for 10 days (Fiore et al. 2011). Neuraminidase inhibitors (i.e., oseltamivir, zanamivir) are typically first-line antiviral prophylactic agents; however, seasonal and regional resistance patterns may vary yearly, necessitating awareness of annual resistance characteristics (Table 14.6).

14.5.2 Suppressive Therapy

Daily suppressive antiviral therapy is an option for preventing some herpesviruses from reactivating during periods of immunosuppression. Given the available antiviral agents, predominant interest regards suppressive therapy for cytomegalovirus (CMV), herpes simplex virus (HSV) and varicella-zoster virus (VZV). Prophylaxis against each of these herpesviruses is primarily discussed in relationship to allogeneic HSCT recipients where the potential for viral reactivation secondary to patient or donor seropositivity is significant.

CMV reactivation disease has been reported in children receiving chemotherapy for malignancy; however, there are no comprehensive data to support a recommendation for universal prophylaxis or preemptive therapy in this patient population (Licciardello et al. 2011). Data from HSCT populations report the efficacy of ganciclovir in preventing CMV reactivation although comparison of prophylaxis to preemptive therapy (i.e., started if a patient becomes positive for CMV on surveillance testing) showed no difference in the rate of progression to CMV disease or death (Goodrich et al. 1993; Winston et al. 1993; Boeckh et al. 1996). Additionally, concern remains in regard to the significant myelosuppression caused by ganciclovir.

Although the mortality risk of HSV reactivation is not as significant as CMV, the high rate of HSV reactivation in adult HSCT recipients and oncology patients prompted early investigations into the benefits of suppressive therapy. Multiple controlled trials in adult seropositive allogeneic HSCT and malignancy patients have revealed the benefits of

acyclovir prophylaxis leading to a consensus among various published guidelines of endorsing acyclovir suppressive therapy in these adult populations (Saral et al. 1981, 1983; Anderson et al. 1984; Sullivan et al. 2001; Styczynski et al. 2009; Tomblyn et al. 2009). Unfortunately, there are limited pediatric-specific data to guide decisions on HSV prophylaxis in children. For children receiving chemotherapy for malignancy, it has not been recommended to routinely administer acyclovir prophylaxis but instead to monitor for evidence of breakthrough infection (Licciardello et al. 2011). There are no recommendations to guide therapeutic decisions for pediatric cancer patients suffering from recurrent HSV reactivation. In this scenario it is reasonable to consider acyclovir or valacyclovir suppressive therapy for the period of time that the patient is immunosuppressed. The clinician must balance the benefit of reducing morbidity from HSV reactivation with the side effects of daily suppressive therapy.

Beyond vaccination and passive immunoprophylaxis (see Chap. 16), suppressive therapy with acyclovir has also been explored and found effective to prevent VZV infections, mainly in adult and pediatric HSCT recipients (Boeckh et al. 2006). No data are available in regard to high-risk pediatric oncology populations.

14.5.3 Future Directions

The available diagnostic modalities to identify viruses far surpass knowledge on preventing acquisition and suppressing reactivation of these viral pathogens in pediatric oncology patients. There remain a paucity of antiviral options for a number of viral pathogens. Even when a reasonable antiviral option exists, there often are limited pediatric-specific data to guide recommendations for prophylactic or preemptive approaches. Efforts to discover improved preventative or suppressive interventions, either through antiviral medications or passive immune therapies, are necessary. As these novel therapeutic interventions become clinically utilized, it is important that pediatric-specific trials be designed so that continued extrapolation from predominantly adult data is no longer required. Recommendations and their evidence basis for suppression of viral infection are summarized in Table 14.7.

Table 14.7 Graded recommendations for chemoprophylaxis for the prevention or suppression of viral infections in pediatric oncology patients

Recommendation	Grade		Comments	Reference
	Data from studies of adult oncology patients[a]	Data from studies of pediatric oncology patients[a]		
Postexposure influenza antiviral prophylaxis should be administered after face-to-face contact with an influenza-infected person	0	0	Recommendation by ACIP based on RCTs in immunocompetent exposed household contacts	Hayden et al. (2000); Welliver et al. (2001)
No data to support either a prophylactic or preemptive approach for CMV reactivation in high-risk pediatric oncology patients	1B	Pediatric patients included in the adult trials	Published guidelines support either a prophylactic or preemptive approach	
Suppressive therapy for patients with a history of HSV can be considered in children with leukemia	1B	Few pediatric patients included in the adult trials	No definitive evidence that daily suppressive therapy is superior in children compared to initiating therapy at the time of breakthrough HSV infection	Saral et al. (1981); Saral et al. (1983); Anderson et al. (1984)

ACIP Advisory Committee on Immunization Practices, *RCT* randomized controlled trial, *CMV* cytomegalovirus, *HSV* herpes simplex virus

[a]Level of evidence per Guyatt et al. (2006); see Preface

14.6 Infection Control Practices

As evidenced by the preceding sections, much of the focus for infection prevention has been on interventions (i.e., antimicrobial prophylaxis, suppressive therapy) aimed at reducing the incidence of specific pathogens. Although these specific interventions are vital in reducing the impact of infection in pediatric oncology patients, such strategies can only account for a minority of pathogens that patients are exposed to in the hospital and community. Therefore, infection control practices should be considered paramount in these vulnerable patients. This section highlights various hospital-based interventions that should be employed to reduce exposures to infectious pathogens. Community- and home-based infection control practices are also important but are outside the scope of this chapter.

14.6.1 Hand Hygiene

Healthcare worker (HCW) compliance with hand hygiene is arguably the most important practice for reducing patient exposures to infectious pathogens. The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have each endorsed protocols for appropriate hand hygiene (Boyce et al. 2002; WHO 2009). Despite the known benefits of hand hygiene, HCW compliance on oncology wards has been reported to be <60 % (Siegel and Korniewicz 2007). Given recent national focus on hand hygiene compliance, this rate has likely improved; however, anything less than 100 % compliance should be considered unacceptable.

14.6.2 Mandatory Vaccination

Vaccination of family members is an important practice in creating a cocoon of protection against certain vaccine-preventable diseases for immunocompromised patients. HCWs should consider themselves "family members" to inpatients and should be motivated to help establish this cocoon of protection in the hospital setting. Unfortunately, despite the personal benefits of vaccination and potential for some vaccines such as influenza to extend protection to vulnerable patients, HCW compliance with vaccination has been traditionally poor (Feemster et al. 2011). Although mandatory HCW influenza vaccination has been debated, recent data on mandating influenza vaccine for all hospital staff employees support this as an appropriate action plan (Helms and Polgreen 2008; Isaacs and Leask 2008; Feemster et al. 2011).

In addition to influenza, it has been well documented that children with malignancy have a reduction in their humoral and cellular immunities to pertussis during chemotherapy and up to 18 months after chemotherapy completion (Cheng et al. 2010). The recent epidemic increase in cases of pertussis in the United States amplifies the potential for pertussis infection in children with malignancy (Cherry 2012). Because immunity to pertussis after childhood and adolescent vaccination wanes, booster vaccination in adults is necessary and specifically recommended in healthcare personnel (ACIP 2012; Klein et al. 2012). Similar to influenza vaccine, mandatory vaccination of HCWs against pertussis has been successfully employed at a university hospital and should be considered by all medical institutions to extend protection to the vulnerable pediatric oncology population (Weber et al. 2012).

14.6.3 Hospital Isolation Practices

Appropriate isolation of patients diagnosed with a communicable infection or with symptoms consistent with such infection is also pivotal in reducing transmission between patients. A general guideline for isolation precautions has been published by the Healthcare Infection Control Practices Advisory Committee sponsored by the CDC (Siegel et al. 2007). Although this document does not dictate specific isolation practices for each infectious organism, it does serve as a foundation for hospitals to establish their own infection control protocols. Additionally, the guideline briefly discusses isolation practices in immunocompromised patients. In many instances, the application of infection control policies can be consistent across immunocompetent and immunocompromised patient

populations. However, in certain circumstances, adapting isolation precautions to children with malignancy or HSCT recipients can be challenging. In 2000, a collaborative effort between the CDC, IDSA and ASBMT resulted in a guideline for infection control practices in HSCT recipients, with a majority of the recommendations based on expert opinion or committee consensus, not specific to pediatric patients, and not focused on patients undergoing chemotherapy for malignancy (CDC et al. 2000). Updated guidelines are warranted so gaps in knowledge can be effectively identified and further investigated. In the meantime, local oncologists are encouraged to interact with their hospital infection control teams in applying isolation guidelines that are most appropriate for their patient populations.

14.6.4 Visitor Screening Policies

In addition to isolation of hospitalized patients with infectious pathogens, visitors should be considered a potential reservoir for infectious organisms, especially in hospital units caring for high-risk patients (Siegel et al. 2007). The aforementioned HSCT-specific infection control guidelines recommend visitors with symptomatic infectious illnesses be restricted from entering the HSCT unit, and a similar approach is reasonable for the oncology ward (Sullivan et al. 2001). In order to identify visitors with such illnesses, hospitals should establish formal visitor screening protocols; however, there is limited evidence to guide the most effective mechanism for such screening. Some hospitals have used passive programs including signs to communicate symptoms of infections to visiting family members and friends, while other hospitals have employed more active surveillance programs that include screening questions administered to visitors prior to hospital entry (Siegel et al. 2007). The effectiveness of either strategy has not been well delineated in the medical literature. While an active surveillance approach would seemingly be more effective, the implementation of such a practice requires trained hospital personnel to be consistently available for screening of all visitors. Future investigations are necessary to determine an effective visitor screening policy that is feasible to implement.

14.6.5 Work Restriction

Patient visitors are not the only source of community-acquired pathogens. HCWs represent an additional important reservoir from which patients can be exposed to communicable diseases. A survey of HCWs found that 86 % of hospital personnel with a recent upper respiratory infection admitted to providing care after their symptoms had started (LaVela et al. 2007). This misguided dedication to patient care can place pediatric oncology patients at risk for significant morbidity. Guidelines exist that recommend institutions to restrict HCWs with viral upper respiratory symptoms from attending clinical duties for high-risk patients (Bolyard et al. 1998). While it is unlikely that HCWs will restrict themselves, institutions should enact policies that prevent HCWs with such symptoms from coming to work.

14.6.6 Cytomegalovirus (CMV) Status of Transfused Blood Products

Transfusion of platelets or packed red blood cells represents a source for transmission of CMV infection via latent virus in white blood cells that are in the transfusion product (Ziemann et al. 2007). The potential for transmission is of particular concern in CMV-seronegative children presenting for allogeneic HSCT as reactivation of CMV during the posttransplant period can be devastating (Bueno et al. 2002). No data in regard to CMV infection in high-risk pediatric oncology patients are available in the literature. In HSCT patients, transfusion of leukocyte-reduced blood products has been shown to be as safe as transfusion from a CMV-seronegative donor and should be considered standard of care (Bowden et al. 1995; Thiele et al. 2011). See Chap. 2 for a more detailed discussion of this topic.

14.7 Summary

Infection remains a significant contributor to both morbidity and mortality in children with cancer. Because of the difficulty in treating some infections in the setting of a compromised immune system, the importance of safe and effective preventative strategies is paramount. Knowledge from studies performed in adult oncology patients can be informative. However, issues unique to children such as the types of cancer, therapeutic regimens employed, immune system ontogeny, as well as age-related drug metabolism and toxicities underlie the need for pediatric-specific data. A number of studies are underway which will fill some of the current gaps in knowledge. It is anticipated that research into the prevention of infection in children with cancer will ultimately have a significant impact on reducing the burden of disease and improving disease suppression.

References

Abshire TC, Pollock BH, Billett AL et al (2000) Weekly polyethylene glycol conjugated L-asparaginase compared with biweekly dosing produces superior induction remission rates in childhood relapsed acute lymphoblastic leukemia: a Pediatric Oncology Group Study. Blood 96:1709–1715

Advisory Committee on Immunization Practices (2012) Recommended adult immunization schedule: United States. Ann Intern Med 156:211–217

Afzal S, Ethier MC, Dupuis LL et al (2009) Risk factors for infection-related outcomes during induction therapy for childhood acute lymphoblastic leukemia. Pediatr Infect Dis J 28:1064–1068

Agrawal A, Chang P, Feusner J (2011) Twice weekly Pneumocystis jiroveci pneumonia prophylaxis with trimethoprim-sulfamethoxazole in pediatric patients with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 33:e1–e4

Anderson H, Scarffe JH, Sutton RN et al (1984) Oral acyclovir prophylaxis against herpes simplex virus in non-Hodgkin lymphoma and acute lymphoblastic leukaemia patients receiving remission induction chemotherapy. A randomised double blind, placebo controlled trial. Br J Cancer 50:45–49

Annaloro C, Della Volpe A, Usardi P et al (2006) Caspofungin treatment of Pneumocystis pneumonia during conditioning for bone marrow transplantation. Eur J Clin Microbiol Infect Dis 25:52–54

Ashley ES, Lewis R, Lewis JS et al (2006) Pharmacology of systemic antifungal agents. Clin Infect Dis 43:28–39

Azuma E, Nagai M, Qi J et al (1998) CD4+ T-lymphocytopenia in long-term survivors following intensive chemotherapy in childhood cancers. Med Pediatr Oncol 30:40–45

Beltz K, Kramm C, Laws H et al (2006) Combined trimethoprim and caspofungin treatment for severe Pneumocystis jiroveci pneumonia in a five year old boy with acute lymphoblastic leukemia. Klin Padiatr 218:177–179

Bleasdale SC, Trick WE, Gonzalez IM et al (2007) Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. Arch Intern Med 167:2073–2079

Bochud P-Y, Chien JW, Marr KA et al (2008) Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med 359:1766–1777

Boeckh M, Gooley TA, Myerson D et al (1996) Cytomegalovirus pp 65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. Blood 88: 4063–4071

Boeckh M, Kim HW, Flowers ME et al (2006) Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation—a randomized double-blind placebo-controlled study. Blood 107:1800–1805

Bolyard EA, Tablan OC, Williams WW et al (1998) Guideline for infection control in healthcare personnel, 1998. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 19:407–463

Bowden RA, Slichter SJ, Sayers M et al (1995) A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. Blood 86:3598–3603

Boyce JM, Pittet D (2002) Guideline for hand hygiene in health-care settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Soceity for Healthcare Epidemiology of America/ Association for Professionals in Infection Control/ Infectious Disease Society of America. MMWR Recomm Rep 51:1–45

Bradley JS, Arguedas A, Blumer JL et al (2007) Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia. Pediatr Infect Dis J 26:868–878

Bucaneve G, Micozzi A, Menichetti F et al (2005) Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 353: 977–987

Bueno J, Ramil C, Green M (2002) Current management strategies for the prevention and treatment of cytomegalovirus infection in pediatric transplant recipients. Paediatr Drugs 4:279–290

Burgos A, Zaoutis TE, Dvorak CC et al (2008) Pediatric invasive aspergillosis: a multicenter retrospective analysis of contemporary cases. Pediatrics 121: e1286–e1294

Castagnola E, Boni L, Giacchino M et al (2003) A multicenter, randomized, double blind placebo-controlled trial of amoxicillin/clavulanate for the prophylaxis of fever and infection in neutropenic children with cancer. Pediatr Infect Dis J 22:359–365

Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation (2000) Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 49(1–125):CE1–CE7

Cheng FW, Leung TF, Chan PK et al (2010) Recovery of humoral and cellular immunities to vaccine-preventable infectious diseases in pediatric oncology patients. Pediatr Hematol Oncol 27:195–204

Cherry JD (2012) Epidemic pertussis in 2012–the resurgence of a vaccine-preventable disease. N Engl J Med 367:785–787

Chou L, Lewis R, Ippoliti C et al (2007) Caspofungin as primary antifungal prophylaxis in stem cell transplant recipients. Pharmacotherapy 27:1644–1650

Chusid MJ, Heyrman KA (1978) An outbreak of Pneumocystis carinii pneumonia at a pediatric hospital. Pediatrics 62:1031–1035

Climo MW, Sepkowitz KA, Zuccotti G et al (2009) The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. Crit Care Med 37:1858–1865

Cornely OA, Maertens J, Winston DJ et al (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356:348–359

Creutzig U, Zimmermann M, Reinhardt D et al (2004) Early deaths and treatment-related mortality in children undergoing therapy for acute myeloid leukemia: analysis of the multicenter clinical trials AML-BFM 93 and AML-BFM 98. J Clin Oncol 22:4384–4393

Cronin S, Chandrasekar P (2010) Safety of triazole antifungal drugs in patients with cancer. J Antimicrob Chemother 65:410–416

Cullen M, Steven N, Billingham L et al (2005) Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 353:988–998

Cunha C, Di Ianni M, Bozza S et al (2010) Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. Blood 116:5394–5402

De Pauw B, Walsh T, Donnelly J et al (2008) Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 46:1813–1821

Dvorak CC, Fisher BT, Sung L et al (2012) Antifungal prophylaxis in pediatric hematology/oncology: new choices and new data. Pediatr Blood Cancer 59:21–26

Etminan M, Forooghian F, Brophy JM et al (2012) Oral fluoroquinolones and the risk of retinal detachment. JAMA 307:1414–1419

Feemster KA, Prasad P, Smith MJ et al (2011) Employee designation and health care worker support of an influenza vaccine mandate at a large pediatric tertiary care hospital. Vaccine 29:1762–1769

Fiore AE, Fry A, Shay D et al (2011) Antiviral agents for the treatment and chemoprophylaxis of influenza – recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 60:1–24

Freifeld A, Bow E, Sepkowitz K et al (2011) Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 52:427–431

Friberg L, Ravva P, Karlsson M et al (2012) Integrated population pharmacokinetics of voriconazole in children, adolescents, and adults. Antimicrob Agents Chemother 56:3032–3042

Gafter-Gvili A, Fraser A, Paul M et al (2012) Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev 1, CD004386

Goodman J, Winston D, Greenfield R et al (1992) A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 326:845–851

Goodrich JM, Bowden RA, Fisher L et al (1993) Ganciclovir prophylaxis to prevent cytomegalovirus disease after allogeneic marrow transplant. Ann Intern Med 118:173–178

Granell M, Urbano-Ispizua A, Suarez B et al (2006) Mannan-binding lectin pathway deficiencies and invasive fungal infections following allogeneic stem cell transplantation. Exp Hematol 34:1435–1441

Groll A, Kurz M, Schneider W et al (1999) Five-year-survey of invasive aspergillosis in a paediatric cancer centre. Epidemiology, management and long-term survival. Mycoses 42:431–442

Groll AH, Castagnola E, Cesaro S et al (2014) Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. Lancet Oncol 15:e327–e340

Guyatt G, Gutterman D, Baumann MH et al (2006) Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. Chest 129:174–181

Hampel B, Hullmann R, Schmidt H (1997) Ciprofloxacin in pediatrics: worldwide clinical experience based on

compassionate use–safety report. Pediatr Infect Dis J 16:127–129; discussion 60–62
Harris R, McCallister J, Allen S et al (1980) Prevention of pneumocystis pneumonia. Use of continuous sulfamethoxazole-trimethroprim therapy. Am J Dis Child 134:35–38
Hayden FG, Gubareva LV, Monto AS et al (2000) Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. N Engl J Med 343:1282–1289
Helms CM, Polgreen PM (2008) Should influenza immunisation be mandatory for healthcare workers? Yes. BMJ 337:a2142
Henrickson KJ, Hoover SM, Kuhn SM et al (2000) Prevention of central venous catheter–related infections and thrombotic events in immunocompromised children by the use of vancomycin/ciprofloxacin/heparin flush solution: a randomized, multicenter, double-blind trial. J Clin Oncol 18:1269–1278
Hersh EM, Bodey GP, Nies BA et al (1965) Causes of death in acute leukemia: a ten-year study of 414 patients from 1954–1963. JAMA 193:105–109
Hughes WT (1971) Fatal infections in childhood leukemia. Am J Dis Child 122:283–287
Isaacs D, Leask J (2008) Should influenza immunisation be mandatory for healthcare workers? No. BMJ 337:a2140
Jick S (1997) Ciprofloxacin safety in a pediatric population. Pediatr Infect Dis J 16:130–133; discussion 3–4, 60–62
Karlsson M, Lutsar I, Milligan P (2009) Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. Antimicrob Agents Chemother 53:935–944
Kelsey S, Goldman J, McCann S et al (1999) Liposomal amphotericin (AmBisome) in the prophylaxis of fungal infections in neutropenic patients: a randomised, double-blind, placebo-controlled study. Bone Marrow Transplant 23:163–168
Kern WV, Klose K, Jellen-Ritter AS et al (2005) Fluoroquinolone resistance of Escherichia coli at a cancer center: epidemiologic evolution and effects of discontinuing prophylactic fluoroquinolone use in neutropenic patients with leukemia. Eur J Clin Microbiol Infect Dis 24:111–118
Kesh S, Mensah N, Peterlongo P et al (2005) TLR1 and TLR6 polymorphisms are associated with susceptibility to invasive aspergillosis after allogeneic stem cell transplantation. Ann N Y Acad Sci 1062:95–103
Kim J, Smathers SA, Prasad P et al (2008a) Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001–2006. Pediatrics 122:1266–1270
Kim S, Dabb A, Glenn D et al (2008b) Intravenous pentamidine is effective as second line Pneumocystis pneumonia prophylaxis in pediatric oncology patients. Pediatr Blood Cancer 50:779–783
Klein NP, Bartlett J, Rowhani-Rahbar A et al (2012) Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 367: 1012–1019
Kurt B, Flynn P, Shenep JL et al (2008) Prophylactic antibiotics reduce morbidity due to septicemia during intensive treatment for pediatric acute myeloid leukemia. Cancer 113:376–382
Lamaris GA, Ben-Ami R, Lewis RE et al (2009) Increased virulence of zygomycetes organisms following exposure to voriconazole: a study involving fly and murine models of zygomycosis. J Infect Dis 199:1399–1406
Landry DL, Gobielle SL, Haessler SD et al (2010) Emergence of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock catheter prophylaxis. Clin J Am Soc Nephrol 5:1799–1804
LaVela S, Goldstein B, Smith B et al (2007) Working with symptoms of a respiratory infection: staff who care for high-risk individuals. Am J Infect Control 35:448–454
Lawson SE, Harrison G, Richards S et al (2000) The UK experience in treating relapsed childhood acute lymphoblastic leukaemia: a report on the medical research council UKALLR1 study. Br J Haematol 108:531–543
Leahey AM, Bunin NJ, Belasco JB et al (2000) Novel multiagent chemotherapy for bone marrow relapse of pediatric acute lymphoblastic leukemia. Med Pediatr Oncol 34:313–318
Lehrnbecher T, Foster C, Vázquez N et al (1997) Therapy-induced alterations in host defense in children receiving therapy for cancer. J Pediatr Hematol Oncol 19:399–417
Lehrnbecher T, Ethier MC, Zaoutis T et al (2009) International variations in infection supportive care practices for paediatric patients with acute myeloid leukaemia. Br J Haematol 147:125–128
Levinsen M, Shabaneh D, Bohnstedt C et al (2012) Pneumocystis jiroveci pneumonia prophylaxis during maintenance therapy influences methotrexate/6-mercaptopurine dosing but not event-free survival for childhood acute lymphoblastic leukemia. Eur J Haematol 88:78–86
Licciardello M, Pegoraro A, Cesaro S (2011) Prophylaxis and therapy of viral infections in pediatric patients treated for malignancy. Pediatr Rep 3:e5
Locatelli F, Testi AM, Bernardo ME et al (2009) Clofarabine, cyclophosphamide and etoposide as single-course re-induction therapy for children with refractory/multiple relapsed acute lymphoblastic leukaemia. Br J Haematol 147:371–378
Mackall CL, Fleisher TA, Brown MR et al (1995) Age, thymopoiesis, and CD4+ Tlymphocyte regeneration after intensive chemotherapy. N Engl J Med 332:143–149
Maertens J, Madero L, Reilly A et al (2010) A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. Pediatr Infect Dis J 29:415–420
Maertens J, Marchetti O, Herbrecht R et al (2011) European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3–2009 update. Bone Marrow Transplant 46:709–718

Majetschak M, Flohe S, Obertacke U et al (1999) Relation of a TNF gene polymorphism to severe sepsis in trauma patients. Ann Surg 230:207–214

Malani P, Bradley S, Little R et al (2001) Trends in species causing fungaemia in a tertiary care medical centre over 12 years. Mycoses 44:446–449

Marr KA, Crippa F, Leisenring W et al (2004) Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood 103:1527–1533

Mattiuzzi G, Estey E, Raad I et al (2003) Liposomal amphotericin B versus the combination of fluconazole and itraconazole as prophylaxis for invasive fungal infections during induction chemotherapy for patients with acute myelogenous leukemia and myelodysplastic syndrome. Cancer 97:450–456

Mattiuzzi G, Alvarado G, Giles F et al (2006) Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies. Antimicrob Agents Chemother 50:143–147

Mazur B, Szczepański T, Karpe J et al (2006) Decreased numbers of CD4+ T lymphocytes in peripheral blood after treatment of childhood acute lymphoblastic leukemia. Leuk Res 30:33–36

Mezger M, Steffens M, Beyer M et al (2008) Polymorphisms in the chemokine (C-X-C motif) ligand 10 are associated with invasive aspergillosis after allogeneic stem-cell transplantation and influence CXCL10 expression in monocyte-derived dendritic cells. Blood 111:534–536

Mora-Duarte J, Betts R, Rotstein C et al (2002) Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 347:2020–2029

National Comprehensive Cancer Network (2008) Practice guidelines in oncology. Prevention and treatment of cancer related infections. www.nccn.org

Neely M, Rushing T, Kovacs A et al (2010) Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis 50:27–36

Noel GJ, Bradley JS, Kauffman RE et al (2007) Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders. Pediatr Infect Dis J 26:879–891

Noel GJ, Blumer JL, Pichichero ME et al (2008) A randomized comparative study of levofloxacin versus amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media. Pediatr Infect Dis J 27:483–489

O'Grady NP, Alexander M, Burns LA et al (2011) Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 52:e162–e193

Oliveira C, Nasr A, Brindle M et al (2012) Ethanol locks to prevent catheter-related bloodstream infections in parenteral nutrition: a meta-analysis. Pediatrics 129:318–329

Owens RC Jr, Ambrose PG (2005) Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 41:S144–S157

Pascual A, Calandra T, Bolay S et al (2008) Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 46:201–211

Penack O, Schwartz S, Martus P et al (2006) Low-dose liposomal amphotericin B in the prevention of invasive fungal infections in patients with prolonged neutropenia: results from a randomized, single-center trial. Ann Oncol 17:1306–1312

Pfaller M, Castanheira M, Lockhart S et al (2012) Frequency of decreased susceptibility and resistance to echinocandins among fluconazole-resistant bloodstream isolates of Candida glabrata. J Clin Microbiol 50:1199–1203

Pizzo PA, Robichaud KJ, Gill FA et al (1979) Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. Am J Med 67:194–200

Pizzo PA, Robichaud KJ, Gill FA et al (1982) Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 72:101–111

Pizzo PA, Robichaud KJ, Edwards BK et al (1983) Oral antibiotic prophylaxis in patients with cancer: a double-blind randomized placebo-controlled trial. J Pediatr 102:125–133

Popovich KJ, Hota B, Hayes R et al (2009) Effectiveness of routine patient cleansing with chlorhexidine gluconate for infection prevention in the medical intensive care unit. Infect Control Hosp Epidemiol 30:959–963

Prabhu RM, Piper KE, Litzow MR et al (2005) Emergence of quinolone resistance among viridans group streptococci isolated from the oropharynx of neutropenic peripheral blood stem cell transplant patients receiving quinolone antimicrobial prophylaxis. Eur J Clin Microbiol Infect Dis 24:832–838

Rabin KR, Smith J, Kozinetz CA (2012) Myelosuppression and infectious complications in children with Down syndrome and acute lymphoblastic leukemia. Pediatr Blood Cancer 58:633–635

Raetz EA, Borowitz MJ, Devidas M et al (2008) Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study[corrected]. J Clin Oncol 26:3971–3978

Razonable RR, Litzow MR, Khaliq Y et al (2002) Bacteremia due to viridans group Streptococci with diminished susceptibility to Levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. Clin Infect Dis 34:1469–1474

Reboli A, Rotstein C, Pappas P et al (2007) Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 356:2472–2482

Redmond AO (1997) Risk-benefit experience of ciprofloxacin use in pediatric patients in the United Kingdom. Pediatr Infect Dis J 16:147–149; discussion 60–62

Riley LC, Hann IM, Wheatley K et al (1999) Treatment-related deaths during induction and first remission of acute myeloid leukaemia in children treated on the Tenth Medical Research Council acute myeloid leukaemia trial (MRC AML10). The MCR Childhood Leukaemia Working Party. Br J Haematol 106:436–444

Robenshtok E, Gafter-Gvili A, Goldberg E et al (2007) Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation:

systematic review and meta-analysis. J Clin Oncol 25:5471–5489
Roman E, Osunkwo I, Militano O et al (2008) Liposomal amphotericin B prophylaxis of invasive mold infections in children post allogeneic stem cell transplantation. Pediatr Blood Cancer 50:325–330
Rosen G, Nielsen K, Glenn S et al (2005) Invasive fungal infections in pediatric oncology patients: 11-year experience at a single institution. J Pediatr Hematol Oncol 27:135–140
Safdar N, Maki DG (2006) Use of vancomycin-containing lock or flush solutions for prevention of bloodstream infection associated with central venous access devices: a meta-analysis of prospective, randomized trials. Clin Infect Dis 43:474–484
Sangiolo D, Storer B, Nash R et al (2005) Toxicity and efficacy of daily dapsone as Pneumocystis jiroveci prophylaxis after hematopoietic stem cell transplantation: a case–control study. Biol Blood Marrow Transplant 11:521–529
Saral R, Burns WH, Laskin OL et al (1981) Acyclovir prophylaxis of herpes-simplex-virus infections. N Engl J Med 305:63–67
Saral R, Ambinder RF, Burns WH et al (1983) Acyclovir prophylaxis against herpes simplex virus infection in patients with leukemia. A randomized, double-blind, placebo-controlled study. Ann Intern Med 99:773–776
Schaad UB (2007) Will fluoroquinolones ever be recommended for common infections in children? Pediatr Infect Dis J 26:865–867
Schimpff S, Satterlee W, Young VM et al (1971) Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med 284:1061–1065
Schimpff SC, Young VM, Greene WH et al (1972) Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. Ann Intern Med 77:707–714
Science M, Robinson PD, MacDonald T et al (2014) Guideline for primary antifungal prophylaxis for pediatric patients with cancer or hematopoietic stem cell transplant recipients. Pediatr Blood Cancer 61:393–400
Seo K, Kim D, Sohn S et al (2005) Protective role of interleukin-10 promoter gene polymorphism in the pathogenesis of invasive pulmonary aspergillosis after allogeneic stem cell transplantation. Bone Marrow Transplant 36:1089–1095
Shima H, Miharu M, Osumi T et al (2010) Differences in voriconazole trough plasma concentrations per oral dosages between children younger and older than 3 years of age. Pediatr Blood Cancer 54:1050–1052
Siegel JD, Rhinehart E, Jackson M et al (2007) 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control 35:S65–S164
Siegel JH, Korniewicz DM (2007) Keeping patients safe: an interventional hand hygiene study at an oncology center. Clin J Oncol Nurs 11:643–646
Slavin M, Osborne B, Adams R et al (1995) Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation–a prospective, randomized, double-blind study. J Infect Dis 171:1545–1552
Smith J, Safdar N, Knasinski V et al (2006) Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother 50:1570–1572
Steinbach W, Addison R, McLaughlin L et al (2007) Prospective Aspergillus galactomannan antigen testing in pediatric hematopoietic stem cell transplant recipients. Pediatr Infect Dis J 26:558–564
Styczynski J, Reusser P, Einsele H et al (2009) Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the Second European Conference on Infections in Leukemia. Bone Marrow Transplant 43:757–770
Sullivan KM, Dykewicz CA, Longworth DL et al (2001) Preventing opportunistic infections after hematopoietic stem cell transplantation: the Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation Practice Guidelines and beyond. Hematology Am Soc Hematol Educ Program 392–421
Sung L, Lange BJ, Gerbing RB et al (2007) Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. Blood 110:3532–3539
Sung L, Gamis A, Alonzo TA et al (2009) Infections and association with different intensity of chemotherapy in children with acute myeloid leukemia. Cancer 115: 1100–1108
Sung L, Aplenc R, Alonzo TA et al (2013) Effectiveness of supportive care measures to reduce infections in pediatric AML: a report from the Children's Oncology Group. Blood 121:3573–3577
Tancrede CH, Andremont AO (1985) Bacterial translocation and gram-negative bacteremia in patients with hematological malignancies. J Infect Dis 152:99–103
Thiele T, Kruger W, Zimmermann K et al (2011) Transmission of cytomegalovirus (CMV) infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation (CME). Transfusion 51: 2620–2626
Thomson B, Park JR, Felgenhauer J et al (2004) Toxicity and efficacy of intensive chemotherapy for children with acute lymphoblastic leukemia (ALL) after first bone marrow or extramedullary relapse. Pediatr Blood Cancer 43:571–579
Tomblyn M, Chiller T, Einsele H et al (2009a) Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Preface. Bone Marrow Transplant 44:453–455
Tomblyn M, Chiller T, Einsele H et al (2009b) Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 15:1143–1238
Trifilio S, Singhal S, Williams S et al (2007) Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole. Bone Marrow Transplant 40:451–456

van Burik J, Ratanatharathorn V, Stepan D et al (2004) Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 39:1407–1416

van Eys J, Berry DM, Crist W et al (1987) Effect of trimethoprim/sulfamethoxazole prophylaxis on outcome of childhood lymphocytic leukemia. A Pediatric Oncology Group Study. Cancer 59:19–23

Vardakas K, Michalopoulos A, Falagas M (2005) Fluconazole versus itraconazole for antifungal prophylaxis in neutropenic patients with haematological malignancies: a meta-analysis of randomised-controlled trials. Br J Haematol 131:22–28

Vasconcelles M, Bernardo M, King C et al (2000) Aerosolized pentamidine as pneumocystis prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. Biol Blood Marrow Transplant 6:35–43

von Baum H, Sigge A, Bommer M et al (2006) Moxifloxacin prophylaxis in neutropenic patients. J Antimicrob Chemother 58:891–894

Weber DJ, Consoli SA, Sickbert-Bennett E et al (2012) Assessment of a mandatory tetanus, diphtheria, and pertussis vaccination requirement on vaccine uptake over time. Infect Control Hosp Epidemiol 33:81–83

Welliver R, Monto AS, Carewicz O et al (2001) Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA 285:748–754

Wingard JR, Dick J, Charache P et al (1986) Antibiotic-resistant bacteria in surveillance stool cultures of patients with prolonged neutropenia. Antimicrob Agents Chemother 30:435–439

Wingard JR, Carter SL, Walsh TJ et al (2010) Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allogeneic hematopoietic cell transplantation. Blood 116:5111–5118

Winston D, Ho W, Bartoni K et al (1993) Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipients. Results of a placebo-controlled, double-blind trial. Ann Intern Med 118:179–184

Wolf J, Shenep JL, Clifford V et al (2013) Ethanol lock therapy in pediatric hematology and oncology. Pediatr Blood Cancer 60:18–25

Wolff S, Fay J, Stevens D et al (2000) Fluconazole vs low-dose amphotericin B for the prevention of fungal infections in patients undergoing bone marrow transplantation: a study of the North American Marrow Transplant Group. Bone Marrow Transplant 25:853–859

Woods WG, Kobrinsky N, Buckley JD et al (1996) Timed-sequential induction therapy improves postremission outcome in acute myeloid leukemia: a report from the Children's Cancer Group. Blood 87:4979–4989

World Health Organization (2009) WHO guidelines on hand hygiene in health care. World Health Organization, Geneva

Yousef AA, Fryer CJ, Chedid FD et al (2004) A pilot study of prophylactic ciprofloxacin during delayed intensification in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 43:637–643

Zaas A, Liao G, Chien J et al (2008) Plasminogen alleles influence susceptibility to invasive aspergillosis. PLoS Genet 4:e1000101

Zaoutis TE, Heydon K, Chu JH et al (2006) Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. Pediatrics 117:e711–e716

Ziemann M, Krueger S, Maier AB et al (2007) High prevalence of cytomegalovirus DNA in plasma samples of blood donors in connection with seroconversion. Transfusion 47:1972–1983