Published in final edited form as:
Pediatr Blood Cancer. 2012 July 15; 59(1): 16–20. doi:10.1002/pbc.23416.

Prevention of Bacterial Infection in Pediatric Oncology: What Do We Know, What Can We Learn?

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Abstract

Bacterial sepsis continues to be a leading cause of morbidity and toxic death in children receiving intensive therapy for cancer. Empiric therapy for suspected infections and treatment of documented infections are well-established standards of care. The routine use of prophylactic strategies is much less common in pediatric oncology. This paper will review the current literature on the use and risks of antimicrobial prophylaxis as well as non-pharmacological methods for infection prevention and will address areas in need of further research.

Keywords

infection; bacteria; prevention; cancer; children

INTRODUCTION

Children receiving intensive myelosuppressive chemotherapy are at risk for febrile neutropenia, invasive infections, and infection-related mortality. Cancer patients at highest risk for serious infections include those with acute myeloid leukemia (AML), relapsed acute lymphoblastic leukemia (ALL), and those undergoing myeloablative hematopoietic cell transplantation (HCT). Bacteria are the causative agent in a substantial proportion of infections in oncology patients and remain a major contributor to treatment related morbidity and mortality. In addition, bacterial infections are associated with worse quality of life and can be associated with substantial costs [1].

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Almost all clinical trials of pediatric AML (excluding acute promyelocytic leukemia) have demonstrated a substantial burden of infectious complications [2]. For example, of the 901 patients enrolled on the AML-BFM 93 and AML-BFM 98 trials, 63 (6.9%) died of infection [3]. The majority of proven infections were bacterial and included Gram positive isolates (including viridans group *Streptococcus*), Gram negative isolates (with *Pseudomonas aeruginosa* and *Klebsiella* spp. predominating) and polymicrobial infections. In a study of 492 children with AML enrolled on the Children's Cancer Group (CCG) protocol 2961, 39–50% and 18–28% of patients developed Gram positive and Gram negative infections, respectively, during the three phases of therapy [4]. Of the 58 patients with infection related deaths, about 40% were associated with bacterial infections, including 15.5% with viridans group *Streptococcus*.

Toxic mortality for children undergoing chemotherapy for relapsed ALL is consistently greater than for those undergoing treatment for de novo disease [5,6]. A recent Children's Oncology Group (COG) study evaluated a 3-block platform of intensive chemotherapy for children with first marrow relapse. The rate of microbiologically documented infection was 79.4% per block of therapy [7]. There were five toxic deaths in 124 patients (4%), all of which were associated with bacterial sepsis [7]. Studies evaluating variations of “4-drug Induction” have rates of suspected or proven infection of 50–100% [8–10].

Infection also remains a significant contributor to mortality in HCT patients, with different groups of pathogens predominating at different phases of immune reconstitution [11]. The period of highest risk for bacterial bloodstream infection is the pre-engraftment period, that is, from the time of stem cell infusion until neutrophil recovery [12]. The incidence of bacteremia during the neutropenic period post-HCT ranges from 21 to 34% and 21 to 58% for patients undergoing autologous and allogeneic transplant, respectively, although some studies report no difference between the two groups [13–17]. In HCT patients bloodstream infections prior to engraftment are a significant independent predictor of mortality [18,19].

POTENTIAL BENEFITS OF ANTIBACTERIAL PROPHYLAXIS IN PEDIATRIC ONCOLOGY AND HCT PATIENTS

Studies of the use of prophylactic antibiotics in neutropenic adult oncology patients conducted over the last 30 years have consistently shown efficacy in reducing the incidence of fever and microbiologically documented bacterial infections, but individually the studies have failed to show an effect on overall survival [20]. Two contemporary large prospective, double-blind, randomized, placebo-controlled studies of 2,325 adult oncology patients receiving myelosuppressive chemotherapy again demonstrated that levofloxacin prophylaxis decreased the incidence of fever, probable infection and hospitalization but did not show an impact on mortality [21,22].

As opposed to individual studies, a 2005 meta-analysis of 95 randomized, controlled trials of prophylaxis for afebrile neutropenic oncology patients showed a significantly decreased risk of death in patients receiving prophylaxis [23]. The benefit was most substantial in studies utilizing fluoroquinolone prophylaxis with significant reductions in all-cause mortality, infection-related mortality, fever, and clinically and microbiologically documented

infections for those receiving prophylaxis. In patients at highest risk for serious infections, those with acute leukemia or those undergoing HCT, quinolone prophylaxis decreased the risk of death by 33% (95% confidence interval 2–54%) [24]. In this subset of high risk patients it is estimated that 55 individuals need to receive prophylaxis to prevent one death.

Data supporting the use of antibacterial prophylaxis in HCT patients are more limited, however, in one of the two large contemporary trials of levofloxacin prophylaxis 45% of those enrolled were patients undergoing autologous HCT. As was found for the chemotherapy patients, the rates of fever and bacteremia were significantly reduced in those patients receiving levofloxacin but prophylaxis did not impact mortality [21]. Similar results have been reported using ciprofloxacin and vancomycin as a prophylactic regimen for autologous HCT patients [25]. There are no contemporary large randomized trials of the use of antibiotic prophylaxis versus no prophylaxis in allogeneic HCT patients. Most existing studies in HCT patients have included small patient numbers and have compared two prophylactic regimes, as opposed to prophylaxis versus no prophylaxis, and have given rise to variable results [26–30].

The investigation of the use of prophylactic antibiotics in children has been limited to date. Early studies of daily trimethoprimsulfamethoxazole, erythromycin, and amoxicillin-clavulanate failed to show significant benefit and were hampered by poor patient accrual and difficulties with patient compliance [31–33]. A recent pilot study of ciprofloxacin prophylaxis for pediatric patients receiving delayed intensification therapy for ALL showed a significant reduction in hospitalization, intensive care admission and bacteremia compared to historical controls [34]. Streptococcal species are a common pathogens causing bacteremia in children being treated for AML. The data to support the routine use of prophylaxis directed specifically at this pathogen remains scant. A small single institution retrospective study of pediatric patients with AML treated prophylactically with cefipime or a combination of vancomycin and oral ciprofloxacin or a cephalosporin compared to historical controls described a significant decrease in the rates of sepsis from viridians group *Streptococcus* infections. There was also a decrease in morbidity from all bacterial infections and overall length of hospital stay [35]. The use of oral penicillin to prevent Streptococcal bacteremia has also been used in the minority of patients on the BFM AML studies, but published evidence of efficacy of this strategy in this patient group is not available.

POTENTIAL RISKS OF ANTIBACTERIAL PROPHYLAXIS IN PEDIATRIC ONCOLOGY AND HCT PATIENTS

The primary concern with the use of antimicrobial prophylaxis in any patient population is the possibility for the development of resistant pathogens, thereby placing the patient at risk for a future infection with a resistant organism. Transition from non-colonization to colonization with a resistant organism in a single patient is possible through a number of avenues: antibiotic selection of previously undetectable but present resistant bacteria; patient-to-patient transmission of pathogens; or via the de novo development of resistance in previously susceptible bacteria [36]. Each of these mechanisms may be directly or indirectly enhanced in the setting of antibiotic exposure.

There are a number of studies in adult patients with acute leukemia and those undergoing HCT that illustrate that invasive infection is often linked to previously noted colonization by the same organism [37–39]. Schimpff et al. [37] showed that of 43 bacteremia episodes in patients with acute leukemia, 39 of them were preceded by surveillance cultures from various locations yielding the same organism. Tancrede and Andremont [38] had similar results showing stool colonization preceded bacteremia with the same Enterobacteraciae in 31/38 cases and 13/16 patients with *P. aeruginosa* bacteremia. Wingard et al. performed a prospective observational study surveying for resistant organisms in the stool of 86 bone marrow transplant recipients. They found that 25% of patients colonized with a resistant organism went on to have an infection from the same organism while only 6% of patients developed an infection from a resistant organism that was not previously identified by surveillance stool cultures [39]. Therefore, these data suggest that if there is an increase in the frequency of colonization with resistant organisms, then there will be a dependent increase in the frequency of invasive infections from the same organisms.

The results from adult studies on the impact of fluoroquinolone prophylaxis on the resistance profiles of bacterial pathogens from sterile site cultures in oncology and HCT patients have yielded conflicting results. As might be expected, some oncology centers that use levofloxacin prophylaxis have measurable increases in the detection of clinically relevant fluoroquinolone resistant pathogens, however others have suggested that fluoroquinolone prophylaxis continued to provide benefits despite these measurable increased rates of antimicrobial resistance [40–46]. In the two contemporary, large, prospective adult trials of levofloxacin prophylaxis [21,22], surveillance for development of resistant colonizing organisms was not performed. Neither study noted an overall increase in the rate of resistant organisms causing microbiologically documented infection; however, these studies were not powered to answer this specific question.

Additional infection related risks of antibacterial prophylaxis include the potential impact on rates of *Clostridium difficile* associated diarrhea (CDAD) and rates of invasive fungal infection (IFI). In adult observational studies, prophylactic use of fluoroquinolones in patients with neutropenia was associated with an increase in CDAD. The incidence of CDAD was significantly greater in the setting of moxifloxacin as compared to levofloxacin [47]. Neither pediatric nor adult randomized trials have carefully measured the risk of CDAD for patients receiving antibiotic prophylaxis during neutropenia. Although not as high as adult rates, the incidence of CDAD has increased among hospitalized pediatric patients in the past decade [48].

Likewise there is theoretical concern that an increase in IFIs exists in the setting of prophylactic antibiotics however limited data that is available does not support this concern. A meta-analysis of 95 randomized controlled trials evaluating antibiotic prophylaxis in neutropenic patients did not identify an increase in the rate of IFIs [24]. In addition, a retrospective study of pediatric AML patients given antibiotic prophylaxis did not result in increased fungal infection rates when compared to those patients not on prophylaxis [49].

In addition to possible impact on microbial flora, antibiotics used for prophylaxis have potential specific drug related toxicities. Currently quinolone antibiotics are the most

commonly used and best studied antibiotic agents for prophylaxis in oncology patients. Analysis of the Phase 1, 2, and 3 trials and post-marketing surveillance for the currently available fluoroquinolones show that as a group, the safety profile is similar to other antimicrobial classes [50]. There is a very rare but consistent association between the use of quinolone antibiotics and a risk of tendonitis and tendon rupture with an estimated frequency of 0.5–0.6 cases per 100,000 treatments, primarily involving the Achilles tendon [50,51]. The most significant risk factors for this complication are age >60 years as well as co-administration of corticosteroid drugs.

In contrast to the issue of tendinopathy, the use of fluoroquinolones in pediatrics has been limited by concerns for the potential risk of arthropathy [52]. In juvenile animals, exposure to fluoroquinolones has been associated with a risk of arthropathy expressed clinically as lameness and with characteristic histologic findings including blisters and erosions of articular cartilage. There is, however, a significant body of evidence supporting the effectiveness and safety of quinolone antibiotics, including levofloxacin, in the pediatric population [53–57]. Ciprofloxacin is licensed by the FDA for specific clinical situations in individuals <18 years of age [58]. A recent report on the safety profile of levofloxacin in children, which included more than 2,500 subjects, found that the incidence of musculoskeletal disorders (primarily arthralgia) was significantly higher in levofloxacin-treated patients (3.4% vs. 1.8%, $P = 0.025$ at 1 year post-exposure). However, this estimate was based on reporting from non-blinded parents and thus may have been biased [59]. In addition, the quality of the musculoskeletal disorder in the levofloxacin-treated and comparator groups did not appear to be different.

CURRENT USE OF ANTIBACTERIAL PROPHYLAXIS IN PEDIATRIC ONCOLOGY AND HCT PATIENTS

Whereas quinolone prophylaxis has been widely adopted in adult oncology practice [60] its use is not routine in pediatric care, including care for those patients at highest risk. In a 2009 survey study only 13% of COG centers and 33% of BFM centers reported routinely prescribing prophylactic antibiotics to patients being treated for AML [49]. Survey data suggests that the majority of adult HCT physicians prescribe prophylactic antibiotics for patients undergoing both autologous and allogeneic transplant whereas pediatric HCT physicians use this strategy in 50% of their patients [61].

Guidelines for the Use of Antibacterial Prophylaxis

The National Comprehensive Cancer Network Guidelines from 2008 suggest consideration of fluoroquinolone prophylaxis in patients at intermediate- or high-risk of infection and the recent Infectious Disease Society of America guidelines on the use of antimicrobial agents in neutropenic patients suggests that “fluoroquinolone prophylaxis should be considered for high risk patients with expected durations of prolonged and profound neutropenia” [62,63]. These guidelines were based primarily on studies conducted in adults subjects and do not address the care of pediatric patients specifically. Guidelines for antibiotic prophylaxis for adult HCT patients are extrapolated from those in non-transplant oncology patients, with the recommendation that those with anticipated neutropenia of more than 7 days received

prophylaxis until neutrophil recovery [64]. The paucity of data in pediatric HCT patients again precludes pediatric specific recommendations.

NON-PHARMACOLOGIC AND LOCAL ANTIMICROBIAL INTERVENTIONS TO REDUCE BLOODSTREAM INFECTIONS

Evidence-based strategies to reduce bloodstream infections are well documented in the literature and include use of maximal sterile barrier precautions with line placement, hand hygiene before contact with the line, chlorhexidine gluconate (CHG) with alcohol for line site antisepsis, and prompt removal of lines when they are no longer necessary [65]. Daily bathing or generalized skin cleansing with CHG for patients with central venous catheters is a recent addition to the Centers for Disease Control and Prevention guidelines as a Category II recommendation [66]. In addition, the use of prophylactic antimicrobial catheter lock solutions also appears as a Category II recommendation in the most recent CDC guideline [66].

CHG is an antiseptic bactericidal to Gram-positive and Gram-negative bacteria including multi-drug resistant organisms. The mechanism of action involves bacterial membrane disruption; its onset is relatively rapid and the effect is persistent. A 2% CHG-impregnated cloth product (Sage Products, Inc., Cary, IL) was licensed by the FDA in 2005 for pre-operative skin preparation. This same product has been studied as a skin cleansing product in the adult critical care setting where it has been shown to decrease risk of central line associated infections by at least 50% and new acquisition of multi-drug resistant organisms by 30–50% [67–70]. Currently, there are no peer-reviewed published studies of the effect of CHG bathing on the prophylaxis of bloodstream infections in children or patients with cancer.

A prophylactic antimicrobial catheter lock involves filling the lumen of the central venous catheter with an antimicrobial solution and leaving it to dwell for a period of time. Evidence has accumulated to support the use of these locks in certain patient populations in order to prevent bloodstream infections [66]. There are a number of different antibiotic solutions that have been studied and several studies have been performed in pediatric oncology patients. The largest trial in pediatric oncology patients involved 126 patients in a randomized double-blind study comparing vancomycin/ciprofloxacin/heparin to vancomycin/heparin to heparin alone [71]. The rate of infection was significantly lower in the two antimicrobial lock arms versus the heparin only arm (0.37/1,000 catheter days for vancomycin/heparin, 0.55/1,000 catheter days for vancomycin/ciprofloxacin/heparin, and 1.72/1,000 catheter days for heparin alone, $P < 0.01$ for both comparisons). A meta-analysis of seven randomized controlled trials, five involving children with cancer, comparing vancomycin/heparin lock or flush to heparin alone, demonstrated the superiority of the vancomycin (risk ratio = 0.49, 95% confidence interval 0.26–0.95, $P = 0.03$) [72].

Use of antibiotic lock solutions raises concerns about the development of resistance, which has recently been documented in the setting of gentamicin locks [73]. Use of ethanol lock solutions would eliminate this concern. A randomized, double-blind study in adults receiving chemotherapy demonstrated the benefit of ethanol locks versus heparin (odds ratio

= 0.18, 95% confidence interval 0.05–0.65, $P = 0.008$) [74]. Studies of prophylactic ethanol locks in pediatric oncology patients are lacking.

FUTURE DIRECTIONS

Data regarding both pharmacologic and non-pharmacologic methods for infection prevention in pediatric oncology patients at highest risks for serious infection is currently limited. Clinicians can gain some guidance from adult studies and from those in non-oncology patients however the need for specific pediatric oncology data is clear. Addressing these issues are several ongoing and planned studies.

A current COG open-label, randomized, controlled trial (ACCL0934) is designed to evaluate whether prophylactic therapy with levofloxacin will decrease the incidence of bacteremia in pediatric patients being treated with intensive chemotherapy for leukemia and for those undergoing HCT. The potential impact of antibiotic prophylaxis on resistance of colonizing bacteria as well as on bacterial pathogens causing documented infections will be rigorously evaluated. Careful assessment for musculoskeletal toxicity is also included.

There is a multicenter study of critically ill pediatric patients (Impact of Daily Bathing with CHG Impregnated Cloths on Nosocomial Infections in the Pediatric Intensive Care Unit) that has completed enrollment and statistical analyses are underway. Research on the effect of CHG bathing in children with cancer is needed due to the heightened concern for skin integrity and because mucositis and graft versus host disease may provide an alternate pathway for bloodstream infection pathogenesis than the route assumed for the typical patient with a central venous catheter. A COG study is planned.

Bacterial infections continue to be a leading cause of morbidity and toxic death in children receiving intensive therapy for cancer. Investigation of pharmacologic and non-pharmacologic approaches to infection prevention are needed, with careful measurement of risks and benefits. In the future these strategies may contribute to minimizing the burden of these common and often serious infections.

Acknowledgments

Portions of this review were presented at the American Society of Pediatric Hematology Oncology (ASPHO) Annual Meeting in Baltimore, MD on April 15th, 2011. S.A. M.N., D.M.Z., B.T.F., and C.C.D. have nothing to disclose. L.S. is supported by a New Investigator Award from the Canadian Institutes of Health Research. Research is supported by the Chair's Grant U10 CA98543-08 of the Children's Oncology Group from the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCI or the NIH.

Grant sponsor: Canadian Institutes of Health Research; Grant sponsor: National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; Grant number: U10 CA98543-08.

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