Preventing Infections in Children with Cancer

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Practice Gap

1. Although guidelines exist for infectious prophylaxis in those who have received allogeneic hematopoietic stem cell transplants, there is a lack of guidance for preventing infections in nontransplant pediatric oncology patients.

Objectives

After completing this article, the reader should be able to:

1. Provide recommendations for bacterial prophylaxis for children experiencing severe and prolonged neutropenia.
2. Screen and recommend prophylaxis against *Mycobacterium tuberculosis* for children receiving immunosuppressive regimens.
3. Provide recommendations for secondary prophylaxis against *Clostridium difficile* infection, a common infection causing morbidity in the pediatric oncology population.
4. Recommend appropriate antifungal prophylaxis for pediatric patients who have high-risk cancers.
5. Review primary and second-line options for *Pneumocystis jiroveci (carinii)* pneumonia prophylaxis in children who fail trimethoprim/sulfamethoxazole therapy.
6. Prevent reactivation of viral infections in children receiving cancer treatment.
7. Screen for latent parasitic infections in newly diagnosed pediatric oncology patients.
8. Review vaccination regimens for patients receiving oncology treatment as suggested by the Infectious Diseases Society of America.

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INTRODUCTION

Clear guidelines exist for the prevention of infections in patients undergoing hematopoietic stem cell transplantation (HSCT), (1)(2) but there is no guidance

regarding prophylactic antimicrobial therapy for pediatric cancer patients receiving systemic chemotherapy. Infection, whether due to bacterial, fungal, viral, or parasitic pathogens, is a leading cause of morbidity and mortality in this patient population. (3)(4)(5) For example, more than 60% of children being treated for acute myeloid leukemia (AML) experienced at least 1 microbiologically documented infection during therapy, and the cumulative infectious mortality rate was 11%. (5) Therefore, infection prevention is of the utmost importance. Due to the lack of standard guidelines for infection prevention in most children being treated for cancer, current strategies often vary among institutions. In this article, we focus on our infection prophylaxis approach at an urban academic medical center for bacterial, fungal, viral, and parasitic infections as well as vaccination strategies for pediatric oncology patients undergoing treatment with systemic chemotherapy.

ANTIBACTERIAL PROPHYLAXIS

General Principles

Bacterial infections remain a common and potentially life-threatening complication of childhood cancer therapy. Several factors predispose the children to infectious complications. Certain malignancies are inherently associated with immune deficits. Patients with hematologic malignancies may have leukopenia due to infiltration of the marrow with malignant cells. Chemotherapy administration often results in neutropenia, which is defined as an absolute neutrophil count (ANC) (mature granulocytes + neutrophil band cells) of less than 500/μL (0.5 $\times$ 10^9/L). When children have neutropenia, they are at increased risk of infection, with the probability of infection directly related to the severity and duration of neutropenia. (6) Chemotherapy can also impair innate and acquired immune responses and disrupt physical immune defenses, such as the gut mucosal barrier, producing an additive negative effect on the protective immune response. Children younger than age 2 years are especially vulnerable to infections because the detrimental effect of cytoreductive therapy is superimposed on a developing, age-dependent immature immune system.

The standard of care for the febrile neutropenic patient is clearly described in guidelines written by national organizations such as the Infectious Diseases Society of America (IDSA), Centers for Disease Control and Prevention (CDC), and the National Comprehensive Cancer Network (NCCN). (2)(7) In more than 50% of cases of febrile neutropenia, no microbiologic source is identified. The most commonly identified clinical syndromes are bloodstream infections (often related to a break in the mucosal border or to a central venous catheter), respiratory infections, and skin and mucosal infection. Gram-positive organisms presently account for 66% of bacteremias. Low-virulence, coagulase-negative *Staphylococcus* species and viridans group streptococci are commonly recovered. Other commonly isolated Gram-positive organisms include α-hemolytic streptococci, enterococci, and *Streptococcus pneumoniae*. Gram-negative organisms such as *Escherichia coli*, *Pseudomonas* species, and *Klebsiella* species are identified in approximately 33% of patients with bacteremia, fever, and neutropenia.

Although fever and neutropenia are common in children undergoing cancer treatment, prophylactic antibiotic therapy for nonfebrile neutropenic patients is not routinely recommended in national guidelines. In contrast, guidelines from the IDSA and the NCCN recommend use in adult patients who have high-risk cancers. (2)(8) In most centers treating adults with malignancies, a fluoroquinolone is the agent of choice for prophylaxis because of its broad coverage of both Gram-negative (including *Pseudomonas*) and Gram-positive bacteria. A recent meta-analysis of 95 randomized, controlled trials of prophylaxis for adult afebrile neutropenic oncology patients showed a significantly decreased risk of death in those receiving prophylaxis, with the most benefit (33% decreased risk) from fluoroquinolones. (9)

Antibacterial Prophylaxis in Children with Severe and Prolonged Neutropenia

Theoretically, prophylactic levofloxacin could prevent morbidity and possibly mortality in children with severe (ANC $<100/\mu$L [0.1 $\times$ 10^9/L]) and prolonged (>7 days) neutropenia associated with chemotherapy. Currently, fluoroquinolones are recommended as prophylaxis only for children undergoing allogeneic HSCT. (1)(2) For other high-risk cancers, such as AML, where the risk of serious infection is associated with mortality in the range of 6.9% to 11%, clear recommendations do not exist. (5)(10) Recurrent acute lymphoblastic leukemia (ALL) also carries a significant risk of severe infection. One Children's Oncology Group (COG) study in children with relapsed ALL reported rates of febrile neutropenia and clinically or microbiologically documented infections at 59.7%, 39.6%, and 79.4%, respectively, per block of therapy. (11) Subsequently, small studies have found substantially reduced rates of infections in children with AML and ALL who received antibiotic prophylaxis. (12)(13)(14)(15) Fluroquinolones levofloxacin and ciprofloxacin have similar gram-negative coverage, but levofloxacin may have broader gram-positive coverage, especially against viridans streptococci, a common cause of invasive disease in children with neutropenic mucositis. (7) An ongoing, randomized COG trial (NCT01371656) investigating the use of prophylactic therapy with levofloxacin in patients being

treated with intensive chemotherapy for acute leukemia and those undergoing HSCT will determine the effect of bacterial prophylaxis on incidence of bacteremia as well as evaluate resistance patterns, antibiotic use, adverse effects, and *C difficile* infection rates in these at-risk populations.

Some centers recommend levofloxacin prophylaxis for afebrile patients with severe and prolonged neutropenia to prevent systemic bacterial infection and to decrease the overall incidence of hospitalization due to fever. Such patients include those with recurrent ALL, or AML and autologous HSCT recipients (Table 1). Among the potential benefits of using levofloxacin for severe and prolonged neutropenia are prevention of a significant infection, which has inherent risks of morbidity and mortality, and avoidance of chemotherapy delays, which could contribute to increased risk of disease recurrence. Moreover, cost analysis studies have shown that antibiotic prophylaxis in severe and prolonged neutropenia in both adults and children is substantially less expensive than treating bloodstream infections. (15)(16) A small retrospective study on children with AML found that patients receiving prophylaxis with ciprofloxacin had significantly less infections caused by gram-negative bacteria but an increase in viridans streptococci than the patients who had not received prophylaxis. (17)

A theoretical risk of using levofloxacin is the selection of resistant bacteria. To date, no studies in children or adults have shown an increased rate of infection with resistant organisms, (17) but some studies suggest an increased rate of colonization with resistant organisms. (18) For this reason, it is prudent for each institution to implement a systemic strategy for monitoring the development of fluoroquinolone resistance among Gram-negative bacilli. In addition, patients should be monitored for adverse effects related to levofloxacin, including nausea, diarrhea, headache, and dizziness. Tendonitis and tendon rupture are estimated to have an incidence range of 0.14% to 0.4% and are more commonly associated with age older than 60 years and coadministered corticosteroid use. (19) A trial in 2500 children, 50% of whom received levofloxacin, reported slightly higher rates of arthralgia (2.1%) in the levofloxacin-treated group when compared to the control group (0.9%). (20)

Prophylaxis Against *Mycobacterium tuberculosis*

All children should undergo a screening test for latent *M tuberculosis* infection before initiation of immunosuppressive therapy. As per American Academy of Pediatrics (AAP) recommendations, any child with a tuberculosis risk factor who will receive an immunomodulating biologic agent should have both an interferon-γ release assay (IGRA) and purified protein derivative (PPD) skin test performed before therapy initiation (Table 1). (21) A positive PPD skin test (defined by risk factors and millimeters of induration) or IGRA should be followed up with a chest radiograph to determine if there is active tuberculosis (TB). All asymptomatic children with a positive PPD or IGRA result and negative chest radiograph (thereby meeting the definition of latent TB) should receive isoniazid prophylaxis for 9 months, which should be initiated before chemotherapy. (22)(23) Children with active TB should begin treatment with at least 3 anti-TB medications before beginning chemotherapy. Because these medications may interact with chemotherapeutic agents and cause hepatotoxicity, clinicians should consult with a pediatric infectious diseases or pulmonology specialist.

Prophylaxis Against *Clostridium difficile* in Children with Prior *C difficile* Infection

An estimated 25% of all pediatric cases of *C difficile* infection occur in children who have underlying malignancies, and 5% of children with cancer develop *C difficile* infection during their multiple hospitalizations. (24)(25)(26)(27) One study found that approximately 33% of pediatric oncology patients tested upon hospital admission were colonized with *C difficile*, as indicated by a positive polymerase chain reaction test in the absence of gastrointestinal symptoms, and more than 50% remained colonized upon retesting 20 weeks later. (28) Moreover, the recurrence rate of *C difficile* infection is about 30%. (29) Given the high prevalence of *C difficile* colonization and infection in the pediatric oncology population as well as the strong chance of recurrence, our institutional guidelines suggest "secondary prophylaxis" with oral vancomycin for children with a history of *C difficile* infection who are receiving systemic antibiotics (Table 1). Oral vancomycin could be continued for the duration of receipt of systemic antibiotics and up until 3 to 7 days after discontinuation of the systemic antibiotics. Although evidence supporting this practice is scant and randomized, controlled trials are lacking, recent literature supports this approach. (30)(31)

ANTIFUNGAL PROPHYLAXIS

General Principles

Fungal infections are increasing in incidence among pediatric patients with cancer due to aggressive chemotherapeutic and immunosuppressive regimens, the use of broad-spectrum antibiotics and corticosteroids, and prolonged neutropenia. (32)(33) Previous studies have reported a 5% to 7% incidence of fungal infections in children with hematologic and oncologic malignancies, with a mortality rate of up to 60%, depending on the fungus. (32)(33)(34)(35)(36)(37)

Overall, *Candida* species cause the majority of fungal infections, but non-albicans *Candida* and *Aspergillus* fungal infections are increasing in prevalence. (35) Because *Candida*

TABLE 1. Infection Prophylaxis Recommendations for Pediatric Patients Being Treated for Cancer

Standard chemotherapy for solid tumors (anticipated neutropenia <7 days)	**Bacterial**: None. **Fungal**: None. **Viral**: HSV seropositive or previous HSV infection: acyclovir* 250 mg/m^2 per dose IV every 8-12 h or valacyclovir* 15-20 mg/kg per dose (maximum 500 mg/dose) PO every12 h. Continue for duration of neutropenia. ***Pneumocystis***: None.
Acute lymphoblastic leukemia (ALL)	*High risk (current or expected prolonged severe neutropenia [<100/μL {0.1 × 10^9/L} for >7 days]):* **Bacterial**: Levofloxacin* • >6 mo to ≤4 y: 10 mg/kg per dose IV/PO every 12 h (maximum daily dose 500 mg). • ≥5 y: 10 mg/kg per dose IV/PO every 24 h (maximum daily dose 750 mg). • Continue until ANC >200 /μL (0.2 × 10^9/L) and rising following nadir. • Levofloxacin should be discontinued if patient requires broad-spectrum antimicrobials for fever/neutropenia. **Fungal**: • Fluconazole 6 mg/kg (maximum 400 mg) IV/PO every 24 h. *All ALL patients:* **Viral**: • HSV seropositive or previous HSV infection: acyclovir* 250 mg/m^2 per dose IV every 8-12 h or valacyclovir* 15-20 mg/kg per dose (maximum 500 mg/dose) PO every 12 h. • VZV: Postexposure prophylaxis with VZIG or acyclovir 500 mg/m^2 per dose IV every 8 h*. Ensure family is immunized. • Influenza: Children and household members older than 6 mo should receive trivalent inactivated influenza vaccine. If close contact to individual is known to have influenza, provide postexposure chemoprophylaxis with oseltamivir* for no more than 10 days. • RSV: Infants (November-March): palivizumab 15 mg/kg per dose IM once monthly • Hepatitis B infection: Age-dependent treatment regimen. Contact pediatric infectious diseases or gastroenterology specialist. ***Pneumocystis***: • Trimethoprim-sulfamethoxazole*# at a dose of trimethoprim 5 mg/kg per day divided BID 2-3 consecutive days per week.§ • Initiate after completion of induction and continue until 3-6 months after therapy completion. **Parasitic**: • If patient has lived or travelled to an endemic region (tropics, Southeast Asia), obtain serology to rule out *Strongyloides* **PRIOR** to initiating chemotherapy. • Measure *Toxoplasma gondii* IgG to determine latent infection. Treat with trimethoprim-sulfamethoxazole if positive (should be administered already to prevent PCP). **Mycobacterial**: • If patient has risk factor for *Mycobacterium tuberculosis* exposure, before initiating chemotherapy, place PPD in children <5 y and perform IGRA in children ≥5 y. If positive, obtain pediatric infectious disease or pulmonology consultation. ***Clostridium difficile*** • Patients with prior *C difficile* infection should be offered oral vancomycin 10 mg/kg (maximum 125 mg) every 12 h when placed on antibiotics. IgG levels may be monitored throughout treatment. If IgG values are less than normal for age, IVIg at 400 mg/kg may be administered.
Acute Myeloid Leukemia	**Bacterial**: Levofloxacin* • >6 mo to ≤4 y: 10 mg/kg per dose IV/PO every 12 h (maximum daily dose 500 mg). • ≥5 y: 10 mg/kg per dose IV/PO every 24 h (maximum daily dose 750 mg). • Continue until ANC >200 /μL (0.2 × 10^9/L) and rising following nadir or day 60 if ANC >200/μL (0.2 × 10^9/L) is not reached. • Levofloxacin should be discontinued if patient requires broad-spectrum antimicrobials for fever/neutropenia. **Fungal**: • Fluconazole 6 mg/kg (maximum 400 mg) IV/PO every 24 h. **Viral**: • HSV seropositive or prior HSV infection: acyclovir* 250 mg/m^2 per dose IV every 8-12 h or valacyclovir* 15-20 mg/kg per dose (maximum 500 mg/dose) PO every 12 h. • VZV: Postexposure prophylaxis with VZIG or acyclovir*. Ensure family is immunized. • Influenza: Children and household members older than 6 mo should receive trivalent inactivated influenza vaccine. If close contact to individual is known to have influenza, provide postexposure chemoprophylaxis with oseltamivir* for no more than 10 days. • RSV: Infants (November-March): palivizumab 15 mg/kg per dose IM once monthly. • Hepatitis B infection: Age-dependent treatment regimen. Contact pediatric infectious diseases or gastroenterology specialist. ***Pneumocystis***: • Trimethoprim-sulfamethoxazole*# at a dose of trimethoprim 5 mg/kg per day divided BID 3 consecutive days per week.§ • Initiate with induction and continue until 3-6 mo after therapy completion.

TABLE 1. (Continued)

	Parasitic: • If patient has lived or travelled to an endemic region (tropics, Southeast Asia), obtain serology to rule out *Strongyloides* **PRIOR** to initiating chemotherapy. • Measure *T gondii* IgG to determine latent infection. Treatment with trimethoprim-sulfamethoxazole if positive (should be given already to prevent PCP). **Mycobacterial**: • If patient has risk factor for *M tuberculosis* exposure, prior to initiating chemotherapy, place PPD in children <5 y and perform IGRA in children ≥5 y. If positive, obtain pediatric infectious diseases or pulmonology consultation. ***Clostridium difficile*** • Patients with prior *C difficile* infection should be offered oral vancomycin 10 mg/kg (maximum 125 mg) every 12 h when receiving antibiotics. In children with Down syndrome (trisomy 21): IgG levels should be monitored throughout treatment. If IgG values are less than normal for age, IVIg at 400 mg/kg per dose may be administered.
Autologous hematopoietic stem cell transplant	*High risk (current or expected prolonged severe neutropenia [<100/μL {0.1 × 10^9/L}] for >7 d):* **Bacterial**: Levofloxacin* • >6 mo to ≤4 y: 10 mg/kg per dose IV/PO every 12 h (maximum daily dose 500 mg). • ≥5 y: 10 mg/kg per dose IV/PO every 24 h (maximum daily dose 750 mg). • Continue until ANC >200/μL (0.2 × 10^9/L) and rising following nadir or day 60 if ANC >200/μL (0.2 × 10^9/L) is not reached. • Levofloxacin should be discontinued if patient requires broad-spectrum antimicrobials for fever/neutropenia. **Fungal**: • Fluconazole 6 mg/kg (maximum 400 mg) IV/PO every 24 h (initiate Day +1 and continue until engraftment). **Viral**: • HSV seropositive or prior HSV infection: acyclovir* 250 mg/m^2 per dose IV every 8 h or valacyclovir* 15-20 mg/kg per dose PO every 12 h (initiate Day+1 and continue until day of discharge). • VZV: Post exposure prophylaxis with VZIG or acyclovir*. Ensure family is immunized. • Influenza: Children and household members older than 6 mo should receive trivalent inactivated influenza vaccine. If close contact to individual is known to have influenza, provide postexposure chemoprophylaxis with oseltamivir* for no more than 10 days. • RSV: Infants (November-March): palivizumab 15 mg/kg per dose IM once monthly. • Hepatitis B infection: Age-dependent treatment regimen. Contact pediatric infectious diseases or gastroenterology specialist. ***Pneumocystis***: • Trimethoprim-sulfamethoxazole*# at a dose of trimethoprim 5 mg/kg per day divided BID 2 consecutive days per week.§ • Continue until 3-6 months after therapy completion. **Parasitic**: • If patient has lived or travelled to an endemic region (tropics, Southeast Asia), send serology to rule out *Strongyloides* **PRIOR** to initiating chemotherapy. • Measure *T gondii* IgG to determine latent infection. Treatment with trimethoprim-sulfamethoxazole if positive (should be given already to prevent PCP). **Mycobacterial**: • If patient has risk factor for *M tuberculosis* exposure, prior to initiating chemotherapy, place PPD in children <5 y and perform IGRA in children >5 y. If positive, obtain pediatric infectious diseases or pulmonology consultation. ***Clostridium difficile*** • Patients with prior *C difficile* infection should be offered oral vancomycin 10 mg/kg (maximum 125 mg) every 12 h when placed on antibiotics.

*ANC=absolute neutrophil count, HSV=herpes simplex virus, Ig=immunoglobulin, IGRA=interferon γ release assay, IM=intramuscular, IV=intravenous, IVIg=intravenous immunoglobulin, PCP=*Pneumocystis carinii *pneumonia, PO=oral, PPD=purified protein derivative, RSV=respiratory syncytial virus, VZIG=varicella zoster immune globulin, VZV=varicella zoster virus.*

*Requires adjustment for renal impairment: Use Schwartz formula for children between ages 1-18 years and the Cockcroft and Gault equation for patients >18 years. For children <1 year, seek recommendation from clinical pediatric pharmacist or pediatric infectious diseases

Schwartz formula using k of 0.413 is $\mathrm{CrCl} = \frac{(0.413^{*}\mathrm{Ht})}{\mathrm{Cr}_{\mathrm{serum}}}$

Height (Ht) is measured in cm. Serum creatinine ($\mathrm{Cr}_{\mathrm{serum}}$) is measured in mg/dL. Measured creatinine should be in steady state. This formula tends to overestimate the actual creatinine clearance and should be used with caution. Estimates of glomerular filtration >75 mL/min per 1.73 m^2 should not be reported as an exact number (National Kidney Disease Education Program recommendation).

#Use with caution in patients with impaired hepatic function

With impaired liver function, calculate Child-Pugh Score by using following:

§Alternatives if patient is experiencing excessive myelosuppression with trimethoprim-sulfamethoxazole, decrease frequency (3 d/wk to 2 d/wk) and then lower dose

If patient is allergic to trimethoprim-sulfamethoxazole:

- Pentamidine 4 mg/kg per dose IV once every 3 weeks (preferred alternative)
- Atovaquone 1-3 months or >24 months: 30 mg/kg per dose once daily; 4-24 months: 45 mg/kg per dose daily (maximum dose 1500 mg)
- Aerosolized pentamidine 8 mg/kg (maximum 300 mg/dose) every 4wk (last line)
- Dapsone, check glucose-6-phosphate dehydrogenase before administration

species are normal colonizers of mucosal and skin surfaces, mucositis places patients at higher risk for *Candida* infections. At-risk populations include patients undergoing allogeneic or autologous HSCT, those with AML or relapsed ALL, and patients who have an anticipated duration of neutropenia of more than 7 days. (38) We currently recommend antifungal prophylaxis for each of these at-risk groups at our institution.

Fluconazole, a triazole medication that interferes with the fungal cytochrome P450 activity, provides coverage against many *Candida* species, although innate resistance exists against *C glabrata* and *C krusei*. Fluconazole also lacks coverage for *Aspergillus*. Two meta-analyses suggested that antifungal prophylaxis should be used in patients with severe, prolonged neutropenia based on findings of fewer invasive fungal infections and less fungal-related mortality in those who had received fluconazole. (3)(39) The first meta-analysis included 38 trials and found that fungal prophylaxis reduced the use of parenteral antifungal therapy (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.48-0.68), superficial fungal infections (OR 0.29, 95% CI 0.20-0.43), invasive fungal infection (OR 0.44; 95% CI 0.35-0.55), and infection-related mortality (OR 0.58, 95% CI 0.41-0.82). (3) The second meta-analysis included 64 trials and found that fungal prophylaxis decreased all-cause mortality compared with placebo, no treatment, or nonsystemic antifungals (relative risk [RR] 0.84, 95% CI 0.74-0.95). (39) When antifungal prophylaxis was administrated with antibacterial prophylaxis, the RR was larger (RR 0.80, 95% CI 0.67-0.96) than in trials without antibacterial prophylaxis (RR 0.90, 95% CI 0.76-1.07). (39) Fluconazole prophylaxis specifically reduced early (30 days posttreatment) mortality significantly in 13 trials (RR 0.78, 95% CI 0.64-0.95) and with borderline significance in 15 trials (RR 0.88, 95% CI 0.75-1.02). (39)

Currently, broader antifungal agents have failed to show benefit over fluconazole. Recent published guidelines continue to recommend fluconazole prophylaxis in patients with severe and prolonged neutropenia. (38)(40) The ongoing COG trial (NCT01307579) investigating the efficacy of caspofungin acetate, an echinocandin, compared with fluconazole in preventing invasive fungal infections in children with AML undergoing chemotherapy should provide valuable insight into potentially broadening antifungal coverage in this population. Voriconazole, another triazole medication, should be considered for patients who are at risk for *Aspergillus* infections, such as those with possible environmental exposures (eg, dust from recent construction or exposure to faulty ventilation systems) or patients receiving vinca alkaloids to avoid neurotoxicity due to cytochrome P450 inhibition.

Outside of these indications, fungal prophylaxis is not routinely recommended, although individual practitioners often prescribe fluconazole for patients receiving high-dose corticosteroid therapy.

If empiric treatment for an invasive fungal infection is required in a patient who is receiving prophylactic fluconazole, we recommend initially increasing the fluconazole to treatment dosing levels. If the patient does not experience clinical improvement, fungal coverage should be broadened to an echinocandin, voriconazole, or amphotericin B.

Pneumocystis (jiroveci [carinii]) Pneumonia (PCP) Prophylaxis

PCP is an opportunistic fungal infection that affected approximately 40% of children with cancer before antibiotic prophylaxis. (41) PCP infection in non-human immunodeficiency virus (HIV)-infected patients is characterized by fever, dry cough, hypoxia, and shortness of breath, which can progress to fulminant respiratory failure. Colonization with *P jiroveci* is widely observed in the general population, and most children acquire serologic response in early childhood. (8)

PCP prophylaxis is necessary for all children being treated for hematologic malignancies, such as lymphoma or leukemia (Table 2). Patients receiving the immunosuppressive regimens listed in Table 3 require prophylaxis. The primary regimen for PCP prophylaxis is trimethoprim (TMP)-sulfamethoxazole (SMX) administered 2 to 3 consecutive days per week, which has been recommended in several guidelines by major organizations. (2)(42)(43) A meta-analysis of 13 randomized controlled trials involving 1,412 immune compromised non-HIV infected patients showed TMP-SMX significantly reduced PCP-related mortality (OR 0.17, 95% CI 0.03-0.94). (44) TMP-SMX prophylaxis was associated with a 91% reduction in the occurrence of PCP (RR 0.09, 95% CI 0.02-0.32) in a subgroup analysis; included within this review were 520 children with ALL. Myelosuppression is a common adverse event caused by TMP-SMX prophylaxis, and no difference in efficacy has been found in reducing weekly doses to either 2 consecutive days per week (45)(46)(47) or a single day per week. (48)(49)

For patients who cannot tolerate TMP-SMX, alternative regimens used for PCP prophylaxis in non-HIV-infected patients include intravenous or aerosolized pentamidine, atovaquone, and dapsone with or without pyrimethamine. Pentamidine has both antifungal and antiparasitic activity. Although the exact mechanism of action is not yet defined, it is believed to inhibit microbial enzymes as well as the oxidative phosphorylation of protozoan DNA, RNA, protein, and phospholipids. When delivered intravenously, the blood pressure, glucose, electrolytes, and liver and renal function of the patient should be monitored. Aerosolized pentamidine

TABLE 2. **Children Being Treated for Cancer who Should Receive *Pneumocystis jiroveci* Prophylaxis (1)(8)**

• Receiving a glucocorticoid dose equivalent to ≥20 mg of prednisone daily for 1 month or longer who also have another cause of immunocompromise (eg, certain hematologic malignancies or a second immunosuppressive drug)
• Receiving alemtuzumab (ie, for the treatment of acute leukemia) for a minimum of 2 months after completion of therapy or until the CD4 count is >200 cells/μL, whichever occurs later
• Receiving concomitant temozolomide and radiotherapy (for neuro-oncologic disease processes) until recovery of lymphopenia
• Allogeneic HSCT recipients after engraftment and for 3 months after completion of immunosuppressive therapy
• Select autologous HSCT recipients, including those who have an underlying hematologic malignancy, such as lymphoma, myeloma, or leukemia, especially when intensive treatment or conditioning regimens have included a purine analog (eg, fludarabine, cladribine) or high-dose glucocorticoids
• Children receiving a purine analog, such as fludarabine, in combination with cyclophosphamide

HSCT=hematopoietic stem cell transplantation.

provides efficacy similar to that achieved with intravenous administration with less systemic adverse effects (although this method requires specific medication handling). When administering aerosolized pentamidine, the patient should be premedicated with a bronchodilator (albuterol) to avoid pentamidine-induced bronchospasm. Despite minimal hematologic and severe toxicities, atovaquone is rarely used as prophylaxis because most children do not tolerate the unpleasant taste. Dapsone (with or without pyrimethamine) is also a reasonable alternative, but this agent is significantly more expensive than the other regimens, and there are theoretical concerns of methemoglobinemia in individuals with glucose-6-phosphate dehydrogenase deficiency along with other hematologic toxicities. Of note, a recent case-control study in HCT recipients failed to identify any hematologic toxicity with dapsone among patients allergic to TMP-SMX. (47) In nonallogeneic HSCT recipients, PCP prophylaxis should continue until 3 to 6 months after completion of chemotherapy.

ANTIVIRAL PROPHYLAXIS

Viral infections during childhood are common, and primary management includes prevention of exposure by hand hygiene, vaccination, and isolation of infected patients and exclusion of infected health-care workers. Most viral infections in pediatric oncology patients are mild respiratory infections. Those who have neutropenia may display more severe symptoms with viral infections, specifically when the inciting virus is respiratory syncytial virus (RSV), herpes simplex virus (HSV), varicella zoster virus (VZV), influenza virus, and parainfluenza virus type 3. (50)

The most common nonrespiratory viral infections during neutropenia are due to HSV reactivation, with chemotherapy-induced immunosuppression or underlying malignancy increasing the likelihood of HSV reactivation. (51)(52) Severe mucositis can impair the mucosal barrier, leading to increased risk of bacterial infection, and can cause severe pain, reduction in nutritional intake, and cachexia. These potential complications may warrant prophylactic therapy to prevent HSV reactivation. Randomized, controlled studies show that prophylactic oral acyclovir significantly reduces the incidence of clinical HSV infection. (2)(52)(53) However, such prophylaxis has not been shown to reduce mucositis-associated bacteremia or mortality. (52)(54)

To prevent HSV reactivation, prophylaxis with acyclovir or valacyclovir should be provided for all seropositive children who are likely to experience prolonged neutropenia. These include children who undergo autologous HSCT, those with AML, and those receiving induction chemotherapy for high-risk leukemia or reinduction therapy for relapsed leukemia (Table 1). Prophylaxis should begin on day 1 for children undergoing autologous HSCT and continue to engraftment or until day 30, whichever is sooner. All others begin prophylaxis the day after completion of systemic chemotherapy and continue until resolution of neutropenia. Patients who are receiving antivirals for secondary HSV prophylaxis generally continue the agent until 3 months after completion of chemotherapy.

VZV reactivation is associated with significant morbidity in immunosuppressed children, including dermatomal rash, pain, and fever; however, the reactivation is rarely life-threatening. Secondary prophylaxis for VZV is recommended for all patients with hematologic malignancies who have had an exposure using varicella zoster immune globulin or acyclovir during neutropenia and at least 30 days after HSCT. (2)(21)

TABLE 3. Recommendations for Patients Receiving Medications for a Specific Diagnosis or for Maintenance

THERAPY	RECOMMENDED AGENT	DURATION OF PROPHYLAXIS
Alemtuzumab therapy Rationale for antimicrobial prophylaxis: This is an anti-CD52 monoclonal antibody and is used for B-cell lymphocytic leukemia. It causes lymphopenia, CMV viremia, and candidemia or known complications.	**Bacterial**: None. **Fungal**: If neutropenic or not responding well to therapy for underlying malignancy, fluconazole* 6 mg/kg per dose PO once daily (maximum dose 400 mg). **Viral**: • HSV seropositive or prior HSV infection: acyclovir* 250 mg/m^2 per dose IV every 8 h or valacyclovir* 15-20 mg/kg per dose PO every 12 h. • CMV antibody-positive: oral valganciclovir* for a minimum of 2 months after alemtuzumab; once weekly CMV surveillance until 2 months after alemtuzumab therapy. (2) • Hepatitis B infection: Age-dependent treatment regimen. Contact pediatric infectious diseases or gastroenterology. ***Pneumocystis***: Trimethoprim-sulfamethoxazole*# at a dose of trimethoprim 5 mg/kg per day divided BID 3 sequential days per week.§	Continue antifungal, antiviral, and PCP prophylaxis for minimum 2 months after treatment and until CD4 ≥200 cells/μL (for all except hepatitis B)
Temozolomide + radiation therapy Rationale for antimicrobial prophylaxis: Temozolomide is an alkylating agent used for myelomas and lymphomas that can cause lymphopenia and T-cell dysfunction.	***Pneumocystis***: Trimethoprim-sulfamethoxazole*# at a dose of trimethoprim 5 mg/kg per day divided BID 2-3 consecutive days per week.§	Until recovery from lymphocytopenia
Bortezomib therapy Rationale for antimicrobial prophylaxis: Bortezomib inhibits proteasomes and an adverse effect is HSV reactivation.	**Viral**: HSV-seropositive or prior HSV infection: acyclovir* 250 mg/m^2 per dose IV every 8-12 h or valacyclovir* 15-20 mg/kg per dose (maximum 500 mg/dose) PO every 12 h.	During course of therapy
Rituximab therapy Rationale for antimicrobial prophylaxis: Rituximab is used to treat CD20+ non-Hodgkin lymphomas and CD20+ CLL. Associated new and reactivated viral infections, PCP, and Mtb reactivation.	***Pneumocystis***: Trimethoprim-sulfamethoxazole*# at a dose of trimethoprim 5 mg/kg per day divided BID 2-3 consecutive days per week.§ **Viral**: • Determine hepatitis B status. Hepatitis B infection: Age-dependent treatment regimen. Contact pediatric infectious diseases or gastroenterology. • In susceptible patients (defined as heavily pretreated), consider once weekly EBV and CMV surveillance. **Mycobacterial**: If patient has risk factor for Mtb exposure, before initiating chemotherapy, place PPD in children <5 y and perform IGRA in children ≥5 y. If positive, obtain pediatric infectious diseases consultation.	6 months posttherapy

*CLL=chronic lymphocytic leukemia, CMV=cytomegalovirus, EBV=Epstein-Barr virus, HSCT=hematopoietic stem cell transplantation, HSV=herpes simplex virus, IGRA=interferon γ release assay, IV=intravenous, Mtb=*Mycobacterium tuberculosis*, PCP=*Pneumocystis carinii *pneumonia, PO=oral, PPD=purified protein derivative*

*Requires adjustment for renal impairment: Use Schwartz formula for children between ages 1-18 years and the Cockcroft and Gault equation for patients >18 years. For children <1 year, seek recommendation from clinical pediatric pharmacist or pediatric infectious diseases

Schwartz formula using k of 0.413 is $\mathrm{CrCl} = \frac{(0.413^{*}\mathrm{Ht})}{\mathrm{Cr}_{\mathrm{serum}}}$

TABLE 3. (Continued)

Height (Ht) is measured in cm. Serum creatinine (Cr_{serum}) is measured in mg/dL. Measured creatinine should be in steady state. This formula tends to overestimate the actual creatinine clearance and should be used with caution. Estimates of glomerular filtration >75 mL/min per 1.73 m^2 should not be reported as an exact number (National Kidney Disease Education Program recommendation).

[#]Use with caution in patients with impaired hepatic function

FACTOR	1 POINT	2 POINTS	3 POINTS
Total bilirubin	<2.0 mg/dL (34.2 μmol/L)	2.0-3.0 mg/dL (34.2-51.3 μmol/L)	>3.0 mg/dL (51.3 μmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8-3.5 g/dL (280-350 g/L)	<2.8 g/dL (280 g/L)
International Normalized Ratio	<1.7	1.7-2.2	>2.2
Ascites	No ascites	Controlled ascites	Poorly controlled ascites
Encephalopathy	No encephalopathy	Controlled encephalopathy	Poorly controlled encephalopathy

PUGH SCORE	% OF DOSE
Mild (5-6)	100%
Moderate (7-9)	Loading dose 100%, maintenance dose 70%
Severe (>9)	Hold

[§]Alternatives if patient is experiencing excessive myelosuppression with trimethoprim-sulfamethoxazole, decrease frequency (3 d/wk to 2 d/wk) and then lower dose

Children with leukemia are more susceptible to influenza infection than their healthy peers because they experience prolonged symptoms and viral shedding, increased hospitalization, and prolonged bone marrow suppression. (55) Consistent with recent guidelines and CDC recommendations, yearly influenza vaccination with inactive vaccine is recommended for all patients age 6 months or older who are undergoing treatments for malignancy. Chemoprophylaxis with oseltamivir is recommended for all patients with known influenza exposure. (7)

RSV is a major cause of infection and the primary cause of acute bronchiolitis in children. (56)(57) Immunocompromised patients may experience RSV-induced upper and lower respiratory tract infections, pneumonia, or even acute respiratory distress syndrome, resulting in a greater than 20% admission rate to the intensive care unit. (4) Due to the risks associated with RSV in immunocompromised infants, monthly prophylaxis with palivizumab during RSV season is suggested for children younger than age 24 months undergoing myelosuppressive chemotherapy, consistent with recommendations from the COG and AAP. (58)

Hepatitis B surface antigen and core antibody should be assessed before HSCT and receipt of B-cell depleting therapies, such as rituximab and ofatumumab, due to risk of reactivation. (59) Patients who test positive for chronic hepatitis B infection should be closely monitored for the duration of therapy and several months after completion because reactivation has been reported after therapy discontinuation.

ANTIPARASITIC PROPHYLAXIS

Parasitic infections are usually not considered a risk for morbidity in children treated for cancer in the United States, but any child undergoing chemotherapy should have his or her lifetime travel history documented. *Strongyloides stercoralis* and *S fuelleborni* are intestinal nematodes that cause the disease strongyloidiasis. Immunocompromised persons are at risk for developing the life-threatening clinical manifestation of this infection called "hyperinfection syndrome" or disseminated strongyloidiasis. *Strongyloides* is endemic in tropical and subtropical regions. Unlike other nematodes, *Strongyloides* can complete its lifecycle without exiting the human host. Hence, infection may persist for many years. When the human host's immune system becomes compromised either by disease or immunosuppressive agents, multiple infective larvae can develop in what is known as

accelerated autoinfection. These larvae disseminate throughout the body and invade other organs, resulting in the hyperinfection syndrome. This clinical syndrome, which may present with severe diarrhea, abdominal pain, fever, respiratory disease, rash, and hypotension with meningitis and bacteremia by enteric flora organisms, has a high mortality rate. (60) Infection has been well documented in the literature in previously asymptomatic patients after undergoing HSCT, chemotherapy, or corticosteroid treatment for malignancy and in those who were immunocompromised due to their condition even before treatment. (61)(62)(63) Based on these risks, some centers assess *Strongyloides* serology before initiation of chemotherapy if a patient has lived or traveled to a region where the parasite is endemic. Peripheral eosinophilia is not a reliable screening measure (and, in fact, the hyperinfection syndrome is associated with an absence of eosinophilia). The treatment of choice is ivermectin. (64)

Clinical disease by the apicomplexan parasite *Toxoplasma gondii* can be the result of *de novo* infection of the child, transmission during pregnancy (congenital toxoplasmosis), transmission via a graft, or reactivation of latent infection in the context of immunodeficiency. Children should be tested for *T gondii*-specific immunoglobulin G before commencing immunosuppressive therapy (as defined in Table 2) to determine whether they are chronically infected with *T gondii* and at risk for reactivation of latent infection. (21) Cases of toxoplasmosis are uncommon, but if a child is seropositive, prophylaxis is recommended because of the benefit of preventing a potentially life-threatening infection with a relatively well-tolerated regimen. (65)(66)(67)(68)

Historically, treatment with pyrimethamine has been shown to be efficacious in patients who are immunocompromised as a result of chemotherapy. (69)(70) Because TMP-SMX protects against *Toxoplasma* reactivation disease in persons with AIDS, it is likely that children receiving TMP-SMX are effectively protected from *Toxoplasma* as well. (71)(72) To date, only relatively small studies have been performed, but the results appear to support this strategy. (73)(74)(75)(76) Patients and their families also should be advised to avoid the consumption of raw meat and to exercise extreme caution when handling pet feces (cats in particular).

VACCINATIONS

Chemotherapy and its associated immunosuppression often disrupt routine vaccination schedules in pediatric oncology patients, placing these children at further risk for infection. The *2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host* has addressed this issue and made recommendations on the administration of vaccinations for children who are immunocompromised as a result of chemotherapy. (77)

Vaccines ideally should be administered before planned immunosuppression, although this is rarely possible, given the urgency to begin chemotherapy. Inactivated vaccines, including pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine (if >2 years), should be administered >2 weeks before immunosuppression, whereas live vaccines should be given >4 weeks before immunosuppression. Another method of protecting the immunocompromised patient is to provide "cocoon care," in which every household member is updated on inactivated and live vaccines (excluding oral polio vaccine), including influenza. The immunocompromised child should avoid contact with a household member if skin lesions erupt following vaccination with varicella or zoster vaccine.

Routine inactivated vaccines should be administered to children receiving maintenance chemotherapy according to the CDC schedule (although these do not count as valid vaccinations). The inactivated influenza vaccine should be administered annually to all patients equal to or greater than age 6 months undergoing chemotherapy, except patients receiving anti-B-cell antibodies or intensive chemotherapy (induction or consolidation chemotherapy) because it is unlikely the child will make an immunoprotective response to the vaccine. Live vaccines, including live attenuated influenza, the routine measles-mumps-rubella, and varicella-zoster vaccines, should not be administered to immunocompromised persons.

Standard vaccination according to the CDC schedule should be resumed 3 months after completion of chemotherapy or 6 months after receiving chemotherapy that includes anti-B-cell antibodies.

Because the data on whether children retain serologic immunity to routine childhood vaccines following systemic chemotherapy are limited and conflicting, there are no guidelines for revaccination or monitoring serologic immunity of children who have already completed the routine childhood vaccination schedule before chemotherapy. The 2013 IDSA guideline mentions that routine revaccination with a single dose of each vaccine antigen or serologic testing could be considered, although there is no statement on whether this should be done. At our institution, we recommend revaccination with 1 dose of all prior vaccinations that the child had received following completion of chemotherapy. Because measurement of titers is often not a reliable or sensitive test for immunoprotection, we choose to forgo serology testing to avoid confusion and provide a one-time revaccination as the most effective method of ensuring immunity.

Summary

- On the basis of some research evidence (evidence quality B), providing antimicrobial prophylaxis will likely decrease morbidity and mortality in children being treated for cancer. (1)(3)(4)(5)
- On the basis of research evidence (evidence quality C), antibiotic prophylaxis for severe and prolonged neutropenia leads to a reduction in morbidity and mortality in this population. (11)(12)(13)(14)(15)(17)
- On the basis of some research evidence as well as consensus (evidence quality C), children who are undergoing autologous hematopoietic stem cell transplant or chemotherapy for acute myeloid leukemia may avoid *Candida* infections if fluconazole is used for prophylaxis. ((3)(5)(39)
- On the basis of strong research evidence (evidence quality A), screening via history taking and testing for *Mycobacterium tuberculosis*, viral, and parasitic infections is essential for avoiding what could be preventable illness. (21)(52)(61)
- On the basis of some research evidence as well as consensus, aggressive early vaccination (77) (evidence quality C) and revaccination after chemotherapy will further protect these children (evidence quality D).

CME quiz and References for this article are at http://pedsinreview.aappublications.org/content/37/6/247.

PIR Quiz

There are two ways to access the journal CME quizzes:
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1. A 14-year-old child has prolonged neutropenia secondary to chemotherapy for high-risk acute lymphoblastic leukemia. On physical examination, the boy is drooling and has areas of erythema and ulceration on his oral mucosa. Of the following, the most appropriate fungal prophylaxis for this patient is:
    A. Amphotericin.
    B. Caspofungin.
    C. Fluconazole.
    D. Nystatin.
    E. Voriconazole.
2. A 5-year-old African-American boy presents to your office with a generalized urticarial rash and scleral icterus. He was recently diagnosed with acute lymphoblastic leukemia and is receiving trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci [carinii]* pneumonia prophylaxis. Given this reaction to trimethoprim-sulfamethoxazole, of the following, the preferred alternative medication is:
    A. Dapsone.
    B. Pentamidine.
    C. Pyrimethamine.
    D. Rifampin.
    E. Vancomycin.
3. A 3-year-old child has been diagnosed with acute myeloid leukemia. Of the following, the most appropriate recommendation for infection prevention in this child is to administer:
    A. Monthly palivizumab during respiratory syncytial virus season.
    B. Prophylactic oseltamivir during influenza season.
    C. Rotavirus vaccine.
    D. Varicella booster vaccine.
    E. Yearly inactivated influenza vaccine.
4. A 5-year-old boy, who recently emigrated from Laos to seek treatment for leukemia, presents to the emergency department with fever, severe diarrhea, and abdominal pain. He has an oral temperature of 39.2°C (102.5°F), abdominal tenderness, and a generalized rash. Of the following, the parasite that is most likely to cause "hyperinfection syndrome" in this patient is:
    A. *Cryptosporidium.*
    B. *Giardia.*
    C. *Strongyloides.*
    D. *Toxocara.*
    E. *Toxoplasma.*
5. The parent of a 4-year-old girl recently diagnosed with acute lymphoblastic leukemia calls you regarding vaccinations. The child is currently undergoing induction chemotherapy and the parent is very concerned about protecting her from serious infections. According to the child's medical record, she received all of her routine vaccinations through 3 years of age and is due for her 4-year-old vaccinations. Of the following, the most appropriate management is to:
    A. Administer a single dose of each vaccine antigen at this time.
    B. Administer only inactivated vaccines at this time.
    C. Measure titers for all standard vaccines at this time.
    D. Repeat all standard vaccinations during maintenance chemotherapy.
    E. Resume vaccination schedule 3 months after completion of chemotherapy.

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Preventing Infections in Children with Cancer

Jennifer Lighter-Fisher, Kaitlin Stanley, Michael Phillips, Vinh Pham and Liana M. Klejmont

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Diagnosis

The diagnosis of AFRS is based on clinical findings. In 1994, Bent and Kuhn proposed a set of criteria based on characteristic clinical, radiographic, pathologic, and immunologic features. The 5 major criteria are: 1) nasal polyposis, 2) eosinophilic mucus containing fungal hyphae without evidence of fungal invasion into sinus tissue, 3) characteristic CT scan findings, 4) presence of fungi on direct microscopy or culture of a surgically obtained mucus specimen, and 5) skin or serologic testing demonstrating a type 1 hypersensitivity reaction to fungi. Minor criteria include: 1) history of asthma, 2) peripheral eosinophilia, and 3) predominance of unilateral disease.

CT scan is the preferred radiologic imaging test. On noncontrast scans, the hallmark finding is opacification of affected sinuses with material of heterogenous densities. Serpiginous areas of increased attenuation surrounded by areas of low attenuation represent calcium in the allergic mucin. Total serum IgE concentrations are typically raised to between 1,200 and 9,600 μg/L (1.2 and 9.6 mg/L). Due to rare reports of AFRS and concurrent allergic bronchopulmonary aspergillosis, the clinical evaluation must rule out pulmonary involvement. Isolated fungal balls without the presence of allergic mucin in paranasal sinuses represent another form of noninvasive fungal rhinosinusitis and should be considered in the differential diagnosis. Previous sinus surgery, oral-sinus fistulas, previous chemotherapy, and atopy have been discussed as risk factors. In contrast to AFRS, surgical resection alone appears curative for fungal balls. Finally, forms of invasive fungal sinusitis typically encountered in immunosuppressed patients can usually be ruled out by carefully reviewing the patient's clinical history and by histology demonstrating the absence of mucosal invasion with fungal hyphae.

Treatment

Effective management of AFRS involves a combination of medical and surgical treatment and requires a team approach between the otolaryngologist and the allergist, with other specialists consulted as needed. Functional endoscopic sinus surgery is performed to remove the fungal allergenic load, restore drainage of the sinuses, and obtain a mucus specimen for microscopy and culture. Surgery is followed by first systemic and then topical intranasal corticosteroids to effectively reduce the inflammatory reaction in the affected tissues and prevent recurrence. Careful clinical follow-up evaluation of patients is required because multiple recurrences over months and years are common. Recurrences are often managed with corticosteroid rescue regimens and/or repeat surgical debridement. In this context, monitoring total serum IgE concentrations can help assess disease activity. Other treatment options, including systemic/topical antifungal therapy, immunotherapy, and leukotriene modulators, have been used in refractory cases. However, very little evidence supports such treatment modalities, and no clear treatment guidelines exist.

Lessons for the Clinician

- Clinicians should consider allergic fungal rhinosinusitis (AFRS) in children and especially adolescents who have difficult-to-treat chronic rhinosinusitis with polyps.
- The mainstay of treatment of this inflammatory process is surgical removal of allergic mucin followed by oral corticosteroids.
- For patients with AFRS and sensitization to *Aspergillus* species antigens, clinicians must exclude a diagnosis of concomitant allergic bronchopulmonary aspergillosis.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/37/10/439.

Corrections

A sharp-eyed reader pointed out a typographical error in the June 2016 article "Preventing Infections in Children with Cancer" (Lighter-Fisher J, Stanley K, Phillips M, Pham V, Klejmont, LM. *Pediatr Rev.* 2016;37(6):247–258, doi: 10.1542/pir.2015-0059). On page 252, column one, the odds ratio (OR) of "0.11" given for the reduction of invasive fungal infection with use of antifungal prophylaxis is incorrect. The OR should read "0.44." The online version of the article has been corrected. The journal regrets the error.

A Canadian reader noted an error in one of the SI calculations in the September 2016 review "Evaluation and Initial Management of Hypopituitarism" (Pierce M, Madison L. *Pediatr Rev.* 2016;37(9):370, DOI: 10.1542/pir.2015-0081). On page 373, column 1, line 1, the passing value of 18 μg/dL should be 496.6 nmol/L. The online version of the article has been corrected. The journal regrets the error.

The April 2016 review "Physical Abuse of Children" (Glick JC, Lorand MA, Bilka KR. *Pediatr Rev.* 2016;37(4):146, DOI: 10.1542/pir.2015-0012) contained a typographical error on page 147, column 2, in the Epidemiology section, where the fourth sentence should read: "Neglect is the most common form of child maltreatment, constituting 75% of indicated reports; 17% are attributable to physical abuse." The online version of the article has been corrected. The journal regrets the error.

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