Immunization Practice in Pediatric Oncology

16

Anurag K. Agrawal

Contents

Abstract

The need for vaccination before, during and after chemotherapeutic regimens remains an area of controversy due to the lack of evidence-based guidelines. Although multiple consensus statements and guidelines are available in regard to the timing and necessity of (re)vaccination, these recommendations are variable, leading to significant differences in clinical practice. In this chapter we review the literature in regard to immune status prior to chemotherapy initiation, during chemotherapy and data on immune recovery after completion of therapy for pediatric patients with malignancy. This serves as background for the available evidence on immunization practice prior to, during and after chemotherapy completion. Population-based risk assessment is also a key component of (re)vaccination guidelines; therefore, we review the evidence for active immunization in settings of high disease prevalence. Finally, we review passive and active immunization practice after exposure to disease and vaccination of household contacts.

A.K. Agrawal, MD
Department of Hematology/Oncology,
Children's Hospital and Research Center Oakland,
747 52nd Street, Oakland, CA 94609, USA
e-mail: aagrawal@mail.cho.org

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_16, © Springer Berlin Heidelberg 2015

16.1 Introduction

The need for vaccination before, during and after chemotherapeutic regimens remains an area of controversy due to the lack of evidence-based guidelines. Although multiple consensus statements and guidelines are available in regard to the timing and necessity of (re)vaccination these recommendations are variable, leading to significant differences in clinical practice (Centers for Disease Control and Prevention 1993; Sung et al. 2001; Royal College of Paediatrics and Child Health 2002; Allen 2007; Esposito et al. 2010a; Ruggiero et al. 2011). Crawford et al. (2010) showed that 39 % of childhood cancer survivors in Australia had no booster vaccinations; they theorize that lack of evidence leads to variability in practice. This was in contrast to a survey in the United Kingdom where stated compliance with reimmunization was 94.3 % (Bate et al. 2010a). No report of practice in the United States can be found in the medical literature.

Although Fioredda et al. argued in 2005 that antibody deficiency to vaccine-preventable diseases was not significantly different in children after chemotherapy as compared to healthy controls, multiple other studies have shown the development of antibody deficiency after commencement of chemotherapy with no resolution over time following the completion of therapy (van der Does-van den Berg et al. 1981; Smith et al. 1995; Feldman et al. 1998; von der Hardt et al. 2000; Nilsson et al. 2002; Reinhardt et al. 2003; Ek et al. 2004; Zignol et al. 2004; Brodtman et al. 2005; Ek et al. 2006; Cheng et al. 2009; Lehrnbecher et al. 2009; Zengin and Sarper 2009; Alavi et al. 2010; Cheng et al. 2010; Paulides et al. 2011; Kwon et al. 2012; Patel et al. 2012; Van Tilburg et al. 2012). A review of such studies was most recently conducted by Esposito et al. (2010a) and van Tilburg et al. (2006). Only two additional studies could be found corroborating the data by Fioredda et al. (Ercan et al. 2005; El-Din et al. 2012).

In this chapter we review the literature in regard to immune status prior to chemotherapy initiation, during chemotherapy, and data on immune recovery after completion of therapy for pediatric patients with malignancy. This serves as background for the available evidence on immunization practice prior to, during and after chemotherapy completion (Table 16.1). Population-based risk assessment is also a key component of (re)vaccination guidelines; therefore, we review the evidence for active immunization in settings of high disease prevalence. Finally, we review passive and active immunization practice after exposure to disease and vaccination of household contacts.

16.2 Immune Status Prior to Chemotherapy Initiation

Immune status is normal in most cases prior to the commencement of chemotherapeutic regimens except, potentially, in hematologic malignancies that affect lymphocyte and granulocyte number and function and lymphomas which affect peripheral T- and B-lymphocytes.

Nilsson et al. (2002) quantified bone marrow plasma cells in a small number of pediatric acute lymphoblastic leukemia (ALL) patients at diagnosis and found the percentage was significantly decreased compared to healthy controls. In most studies, antibody levels to vaccine-preventable diseases are similar to a healthy population at diagnosis although van Tilburg et al. (2012) showed that children with ALL had tetanus antibody levels statistically lower than a healthy group (Feldman et al. 1998; Reinhardt et al. 2003; Ercan et al. 2005; Zengin and Sarper 2009; Alavi et al. 2010). Data on immune deficiency at diagnosis in lymphoma patients are lacking in the pediatric literature. Studies in adult lymphoma patients have shown lower baseline immunoglobulin levels and decreased lymphocyte stimulation to phytohemagglutinin and concanavalin A compared to controls (Fuks et al. 1976; Biggar et al. 2009).

16.3 Immune Status During Chemotherapy

The decline in immune status with chemotherapy initiation is due to medication effect rather than the underlying malignancy. Moritz et al. (2001) studied T-cell regenerative capacity after ALL induction chemotherapy and found that patients

Table 16.1 Immunization recommendations with chemotherapeutic regimens[a]

	Prior to chemotherapy[b]	During chemotherapy[c]	After chemotherapy completion[c, d]
Diphtheria-tetanus-acellular pertussis		Continuation of primary series during lower-intensity phases of therapy (i.e., ALL in maintenance)	Continuation of primary series; booster 3–6 months after therapy completion in those that finished primary series
Haemophilus influenzae type b		Continuation of primary series during lower-intensity phases of therapy (i.e., ALL in maintenance)	Continuation of primary series; booster 3–6 months after therapy completion in those that finished primary series and <5 years of age
Inactivated poliovirus		Continuation of primary series during lower-intensity phases of therapy (i.e., ALL in maintenance)	Continuation of primary series; booster 3–6 months after therapy completion in those that finished primary series
Pneumococcus		Continuation of primary series during lower-intensity phases of therapy (i.e., ALL in maintenance)	Continuation of primary series; booster 3–6 months after therapy completion in those that finished primary series and <5 years of age
Hepatitis B	Consider starting immunization series in high-risk settings in seronegative[a]	Continuation of primary series during lower-intensity phases of therapy (i.e., ALL in maintenance)	Continuation of primary series; booster 3–6 months after therapy completion in those that finished primary series
Measles-mumps-rubella			Continuation of primary series; booster 3–6 months after therapy completion in those that finished primary series[e]
Varicella		Consider vaccination during lower-intensity phases of therapy (i.e., ALL in maintenance) in high-risk settings[a]	Continuation of primary series; booster 3–6 months after therapy completion in those that finished primary series
Meningococcus			Booster dose for those previously vaccinated; otherwise per routine schedule
Inactivated influenza	Consider if high seasonal incidence	Annually for children ≥6 months of age	Annually for children ≥6 months of age

ALL acute lymphoblastic leukemia
[a]See text for details
[b]Level of evidence 2C per Guyatt et al. (2006); see Preface
[c]Level of evidence 1C per Guyatt et al. (2006); see Preface
[d]Can consider postvaccination titers in less immunogenic vaccines, specifically hepatitis B and varicella
[e]Washout period required after blood products and immunoglobulin therapy; see text for details

were able to regenerate T-cell subsets at this time point. They concluded that the long-lasting T-cell dysfunction seen after the completion of therapy is due to chemotherapy rather than the underlying disease process itself. At least in number, B-lymphocytes are more affected than T-lymphocytes and NK cells during therapy. Studies of children with ALL have found

decreased total lymphocyte counts, lymphocyte subsets and immunoglobulin levels as compared to controls with statistically decreased levels in those treated with more intensive protocols compared to standard risk and reduced-intensity groups and with improvement in levels, especially IgG, occurring in the maintenance phase of therapy (Caver et al. 1998; Kostaridou et al. 2004; Luczynski et al. 2004; El-Chennawi et al. 2008; Eyrich et al. 2009; Van Tilburg et al. 2012).

Seroprotection to vaccine-preventable diseases declines significantly during chemotherapy, both for patients with hematologic malignancies and in those with solid tumors (Feldman et al. 1998; Reinhardt et al. 2003; Ek et al. 2004; Zignol et al. 2004; Ek et al. 2006; Zengin and Sarper 2009; Alavi et al. 2010; Kwon et al. 2012; van Tilburg et al. 2012). Comparing ALL regimens with different levels of intensity, van Tilburg et al. (2012) found that antibody levels to diphtheria, tetanus and *Bordetella pertussis* declined sharply during induction and high-dose methotrexate treatment in both groups with this decline continuing at a slower rate through therapy. Decrease in total IgG did not correlate with the level of antibody to vaccine-preventable diseases. By the end of chemotherapy, 90 % of the 41 children had lower levels of antibody compared to population-based norms. Only decline in diphtheria antibody showed a significant difference between the standard and reduced-intensity ALL regimens. On univariate analysis, Zignol et al. (2004) showed that loss of antibody protection correlated with younger patient age, while Paulides et al. (2011) showed the same on multivariate analysis.

16.4 Immune Recovery After Chemotherapy Completion

The pace of immune recovery after the completion of chemotherapy remains poorly quantified and is multifactorial, being related to the underlying malignancy, treatment intensity and age of the patient. Kovacs et al. (2008) analyzed 88 children 1 year after the completion of chemotherapy for malignancies and found that 19 % of leukemia patients and 9 % of solid tumor patients had decrement in at least one immunoglobulin level ($p < 0.001$ in the leukemia patients). At least one marker of cellular immunity was decreased in 42 % of leukemia patients and 29 % of solid tumor patients. Mustafa et al. (1998) similarly found that 1 year after therapy completion, 35 of the 43 studied patients maintained some immunologic abnormality. Patients had rapid normalization of B-lymphocyte numbers while CD4+ T-lymphocytes lagged and lymphocyte stimulation remained low in a subset of patients 9–12 months after therapy completion. IgG levels normalized rapidly while IgA and IgM were slower to recover. The number of abnormalities at 1 year correlated statistically with patient age; the younger the patient the more abnormalities at this time point. Type of malignancy and duration of therapy were not relevant factors in their study. Other studies have similarly shown the rapid pace of recovery for IgG, with IgA being restored more slowly and IgM remaining low for years after therapy completion (de Vaan et al. 1982; Abrahamsson et al. 1995). Azuma et al. (1998) and Mazur et al. (2006) also found that a subset of patients retained low CD4+ counts. This contrasts with others who have shown that immunoglobulin levels and mitogenic response recover by 6 months after therapy completion (Alanko et al. 1992; Abrahamsson et al. 1995; Kantar et al. 2003; Ek et al. 2005; Kosmidis et al. 2008). Mackall et al. (1995) found that younger patients had greater recovery of CD4+ T-lymphocytes at 6 months compared to older patients who persisted with severe depletion. They theorized that thymic production is important in T-lymphocyte regeneration in the younger patients. Although Mustafa et al. (1998) did not show a statistical difference in immune recovery based on underlying malignancy, other studies have shown variable recovery between hematologic malignancies and solid tumors (Alanko et al. 1994, 1995).

In a complex statistical study using principal components analysis, Ek et al. (2011) found

that increased treatment intensity led to poorer response to vaccination, even 6 months after therapy completion. Previously their group had shown that patients who received more intensive ALL therapy were significantly less likely to respond to tetanus toxoid after therapy completion (Ek et al. 2006). These results contrast to other studies such as Mustafa et al. (1998) and Ercan et al. (2005). Immune recovery after therapy completion is defined based on antibody seroresponse to vaccine-preventable disease although anamnestic response may occur even with low or absent antibody levels complicating measures of immunity and immune recovery (Banatvala and Van Damme 2003). Yetgin et al. (2007) studied 82 children with ALL who were vaccinated against HBV during maintenance therapy and 87 that were unvaccinated. Although the seroconversion rate was only 35.4 %, the HBV infection rate was significantly decreased as compared to the unvaccinated group (4.8 % vs. 28.7 %). This remained significant when comparing the vaccinated nonresponders with the unvaccinated (7.5 % vs. 28.7 %). On other hand, Ek et al. (2006) studied 31 pediatric patients with ALL and found that antibody avidity to tetanus toxoid and *Haemophilus influenzae* type b (Hib) correlated with antibody levels.

Among the multiple studies that have (re)vaccinated children after chemotherapeutic regimens, the timing of seroresponse is quite variable making generalizations about pace of immune recovery impossible. Some studies have shown a rapid response in all patients while others have shown persistence of immune dysfunction years after therapy completion. Smith et al. (1995), Nilsson et al. (2002) and Brodtman et al. (2005) all studied children with a history of ALL and found that even years after therapy completion some children failed to mount an appropriate postvaccination antibody response. In contrast, other studies have shown a uniform and rapid immune response after therapy completion. Ercan et al. (2005) immunized 21 patients 3–6 months after completion of ALL therapy and found no statistical difference compared with 14 healthy controls for tetanus, diphtheria, pertussis, measles and mumps antibody response. Lehrnbecher et al. (2009) randomly assigned 24 patients who received non-high-risk treatment for ALL to receive booster vaccination for tetanus, diphtheria, polio and Hib 3, 6 or 9 months after the completion of therapy. Response at these different time points was not significantly different. Cheng et al. (2009) administered three doses of DTP booster vaccination 6, 8 and 10 months post-chemotherapy completion in patients with hematologic malignancies and solid tumors with a 100 % seroresponse rate which was maintained for at least 1 year (the end of the study period).

Most likely, antibody response is imperfect, and a subset of patients will not attain seroprotection even if immunized multiple times well after immune competence should be restored, especially to less immunogenic vaccines such as hepatitis B, measles and rubella. Reinhardt et al. (2003) studied 139 children with malignancies who showed a decline in antibody seropositivity to vaccine-preventable diseases through therapy. Patients were revaccinated 3–5 months after the completion of therapy to measles, mumps, rubella, diphtheria and tetanus. The majority of vaccinees recovered similar levels of seroprotection as was present prior to therapy; on the other hand, 6 of 83 children (7.2 %) did not respond to revaccination. Zignol et al. (2004) studied 192 pediatric oncology patients after the completion of chemotherapy. They found that a subset lost antibody protection to vaccine-preventable diseases. On reimmunization, 12 months after the completion of therapy, 93 % of those revaccinated had an appropriate seroresponse (three did not respond to hepatitis B, one did not respond to measles).

16.5 Defining the Risk from Vaccine-Preventable Diseases

In the setting of impaired immune competence both during therapy and for some time period after the completion of therapy, determining when and whom to (re)vaccinate should be based

on population-based assessment to define when the potential benefit of (re)vaccination outweighs the cost, potential lack of seroresponse and risk of immunization (with live virus vaccines).

Many of the studies regarding disease prevalence in children with malignancy from the United States are before routine vaccination campaigns to Hib, *Streptococcus pneumoniae* and varicella. The data from such studies can now be generalized to resource-limited settings in which routine immunization practice to these diseases is not yet in place but more children are being treated for malignancy. Varicella is the best example of change in practice over time due to routine vaccination in the United States and the subsequent protection of the immunocompromised from herd immunity. Over time, the potential risks of live attenuated varicella vaccination during chemotherapy and delay in treatment have begun to outweigh the risk of varicella exposure and disease during chemotherapy. Yet, practice must be based on risk assessment in each particular community.

Risk versus benefit of varicella vaccination during maintenance chemotherapy must be considered with increasing rates of immunization, especially in North America. Caniza et al. (2012) found a 0.057 % mortality from VZV infection, with 70 % of those children dying during the first year of treatment and 1 dying after varicella vaccination. Based on the available data and the need to hold chemotherapy for VZV immunization, they conclude that the benefit of vaccination during maintenance does not outweigh the risks. Although the incidence of varicella in immunocompromised children in the United States has dropped precipitously since the studies by Gershon and Steinberg (1989), outbreaks are still reported. Adler et al. (2008) discuss the dissemination of disease between pediatric oncology patients after an index case in a hospital group housing facility. Interestingly, more than half the children had previously received varicella vaccination. Poulsen et al. (1993) studied Danish children from 1986 to 1991 and found that among 67 children with ALL, 25 were susceptible to VZV and the cumulative risk of varicella exposure was 90 % at 32 months with 5 patients developing varicella during this time period.

Encapsulated bacteremia from Hib and pneumococcus are also exposures that have changed significantly over time. Surveillance reporting for the years 1994–1995 in the United States shows near elimination of invasive Hib disease with routine vaccination; invasive disease among children aged 4 years or younger declined by 98 % since the introduction of Hib conjugate vaccines (Bisgard et al. 1998). Pneumococcal disease has also declined sharply after introduction of the 7-valent conjugate vaccine. Surveillance data from eight children's hospitals in the United States showed a 66 % decline in invasive disease in children ≤24 months of age in 2002 compared with the mean number of annual infections from 1994 to 2000 (Kaplan et al. 2004). How this affects immunocompromised children, especially with the emergence of non-vaccine serotypes and now routine immunization with the 13-valent conjugate vaccine, is unknown.

Over a 6-year study period in a setting without routine pneumococcal vaccination, Meisel et al. (2007) studied the relative risk of invasive pneumococcal disease in pediatric ALL patients as compared to the general population. Eleven of 3,200 patients had invasive pneumococcal disease, 2 at diagnosis, 4 in induction therapy and 5 during maintenance therapy. One patient died of pneumococcal sepsis. The relative risk of invasive pneumococcal disease was 11.4 times the general population, with the highest risk being in those patients 5–9 years of age. Siber (1980) looked at the incidence of infection with *S. pneumoniae* and *H. influenzae* from 1968 to 1977 and found that the majority of episodes of infection occurred during therapy although a small fraction also occurred after therapy completion. Feldman et al. (1990) found eight cases of Hib among 5,288 pediatric cancer patients, a significantly greater incidence than the general population. The majority of Hib infection was in children <4 years, but it was also seen in those >14 years of age. Nevin et al. (2013) recently reported a case of invasive *H. influenzae* in a 7-year-old who was fully immunized prior to ALL therapy but received no additional vaccine doses after chemotherapy completion.

Consensus guidelines from the American Academy of Pediatrics (2012a) still recommend

considering vaccination in patients with Hodgkin lymphoma against encapsulated organisms prior to the initiation of chemotherapy, a risk based on studies when splenectomy was a routine part of Hodgkin staging. Donaldson et al. (1978) studied 181 pediatric patients with Hodgkin lymphoma and found that although the risk of any bacterial infection was not different in the splenectomized versus non-splenectomized group, all incidents of encapsulated bacteremia with vaccine-preventable disease (specifically *S. pneumoniae* and *H. influenzae*) occurred in the splenectomized group. Similarly, Chilcote et al. (1976) found that 60 % of infections in splenectomized children treated for Hodgkin lymphoma were due to encapsulated bacteria (pneumococcus in 50 %, hemophilus and meningococcus in 5 % each). The risk of encapsulated bacteremia and necessity of vaccination in Hodgkin lymphoma in the setting where routine splenectomy is no longer practiced are unclear but appear unnecessary. Additionally, it is impractical to delay chemotherapy initiation for vaccine delivery and response in such a context.

In areas of high prevalence, risk of HBV transmission is significant during chemotherapeutic regimens. Sevinir et al. (2003) studied 198 Turkish children with cancer and found 6.0 % became positive for HBsAg during therapy after failing HBV prophylaxis. One patient died of fulminant hepatitis B infection and most subsequently developed chronic disease. Yetgin et al. (2007) reported a similar transmission rate of 7.5 % in Turkish children that failed HBV prophylaxis and a 28.7 % rate in the unvaccinated cohort. Meral et al. (2000) described a 39 % infection rate in Turkish pediatric oncology patients that failed HBV prophylaxis. In an Indian study of pediatric ALL patients, Somjee et al. (1999) reported an HBV infection rate of 43 % even after an intensified HBV vaccination schedule. Finally, in Iraq, Al-Jadiry et al. (2013) recorded a 27.3 % seroconversion rate in children, with decreasing risk in those receiving multiple HBV vaccinations.

Increased risk from influenza is well documented in immunocompromised children. In a study of US associated deaths from influenza in 2003–2004, 5 of the 149 children (3.3 %) with reportable health status who died were immunocompromised (4 from long-term corticosteroids, 1 from long-term rituximab) (Bhat et al. 2005). Moulik et al. (2013) recently reported on a measles outbreak in an Indian pediatric oncology unit in which 2 of 15 infected children died; those who were previously immunized to measles had milder disease. The risk of disseminated tuberculosis (miliary TB or TB meningitis) in high-prevalence settings and the potential benefit of BCG vaccination after chemotherapeutic regimens are unknown.

16.6 Immunization Practice Prior to Chemotherapy Initiation

Using a population-based risk stratification for vaccine-preventable disease, a more rational approach to vaccination can be employed. The potential benefit of vaccination in high-risk populations prior to the start of chemotherapy is unclear. In a Dutch study of ALL patients, van Tilburg et al. (2012) reported a cohort of patients who recently received booster immunization to tetanus, diphtheria and *B. pertussis*. This recent immunization, however, did not impact the decline in antibody levels with treatment which was not statistically different from those children without recent booster immunization. Thus, it is uncertain what protection, if any, would be afforded by pre-chemotherapy immunizations.

In his review of varicella vaccination practice in immunocompromised children, Levin (2008) discusses the potential to provide varicella vaccination prior to the delivery of chemotherapy in seronegative children in higher-risk populations. Considering that 70 % of the mortality from VZV occurred in the first year of treatment in the report by Caniza et al. (2012) (a window where varicella vaccination is contraindicated), this is a recommendation that deserves further study. Cristófani et al. (1991) administered live attenuated varicella vaccine to pediatric oncology patients on the first day of chemotherapy. Twenty-two children without clinical history of varicella (retrospectively, 13 that were seronegative and 9 that were seropositive) were immunized. No serious adverse events were noted although three patients developed a

small number of vesiculopapular lesions. Three of the 13 seronegative children (23 %) failed to seroconvert. As seen by Heath et al. (1987), antibody protection was lost with time; 42 % lost seropositivity by 3 years. Eight of the immunized children (all seroconverters) were exposed to varicella and none developed disease. Of the seven control subjects that were exposed to VZV, four developed symptomatic disease. In their recommendation for pre-chemotherapy immunization for Hodgkin lymphoma patients, the AAP (2012a) mentions that efficacy is increased if vaccination is given 10–14 days prior to the start of chemotherapy; this delay is not always feasible with the urgency of commencing therapy, especially in leukemia patients. Additional randomized controlled trials are required to determine the safety and efficacy of this recommendation in at-risk populations which will be difficult from a feasibility standpoint.

Sinisalo et al. (2007) vaccinated adult patients with chronic lymphocytic leukemia (CLL) and controls to determine response to the 7-valent pneumococcal conjugate vaccine (PCV7) as pneumococcal disease is an important cause of morbidity in this patient population. Response to PCV7 was significantly decreased in the CLL group as compared to controls, although almost all patients that became seropositive were immunized prior to the onset of chemotherapy and subsequent development of hypogammaglobulinemia. In a separate report, Sinisalo et al. (2002) showed a moderate seroresponse rate in adult patients to immunization with Hib. They conclude, as with their study on PCV7, that immunization with Hib should occur prior to the onset of chemotherapy to have the highest seroresponsivity rate.

Many of the studies on HBV vaccination begin with immunization at the time of chemotherapy initiation with variable efficacy (Goyal et al. 1998; Somjee et al. 1999; Meral et al. 2000). Meral et al. (2000) had the highest seroconversion rate (78 %) when giving vaccination at diagnosis and then at months 1, 2 and 12 of therapy in addition to monthly passive immunization during the intensive parts of leukemia therapy. Using the same regimen without the passive immunization, Goyal et al. (1998) showed only a 10.5 % seroconversion rate in 162 pediatric ALL patients. To follow up their previous study, the same group (Somjee et al. 1999) gave a more intensified regimen with five doses at monthly intervals followed by a booster at 1 year but only showed 19 % seroconversion.

16.7 Recommendations for Vaccination During Chemotherapy

Five of the six cited guidelines on immunization practice come to similar conclusions in regard to immunization with inactivated or killed vaccines during chemotherapy (Centers for Disease Control and Prevention 1993; Sung et al. 2001; Royal College of Paediatrics and Child Health 2002; Allen 2007; Esposito et al. 2010a). All agree that it is reasonable to continue with the primary immunization series during the less intensive parts of therapy (i.e., ALL maintenance) in addition to providing yearly inactivated influenza vaccination (Table 16.1). Among the group, only Esposito et al. (2010a) give consideration to providing varicella vaccination in settings of high exposure risk and lack of universal vaccination. Here we review the evidence for each particular vaccination.

16.7.1 Diphtheria, Tetanus, and Acellular Pertussis

Two studies were found in regard to response to diphtheria-tetanus-pertussis (DTP) during chemotherapy. Ercan et al. (2005) immunized 17 patients with ALL during maintenance chemotherapy and found no statistical difference compared with 14 healthy controls for tetanus and diphtheria antibody response, although pertussis titers were significantly lower. No adverse reactions were seen. Kung et al. (1984) administered DTP vaccination to 27 children during maintenance chemotherapy for various malignancies and found response to at least 1 of the 2 antigens in 26 of the children (only tetanus and diphtheria were measured for response). Based on their findings, they recommended continuing with the primary vaccination series for inactivated or killed vaccines during maintenance therapy.

16.7.2 Pneumococcal Conjugate Vaccine

In areas without routine pneumococcal vaccination, invasive pneumococcal disease remains a potential risk during and after chemotherapy (Meisel et al. 2007). Allen and Weiner (1981) reviewed 40 episodes of sepsis in 28 children with leukemia and lymphoma and found that 35 % of these episodes were secondary to *S. pneumoniae*, the most commonly isolated organism. Interestingly, *S. pneumoniae* was the only organism that caused infection during remission therapy; five of the 40 episodes (12.5 %) were during this time and due to *S. pneumoniae*. Lehrnbecher et al. (2009) studied 53 children treated for ALL and found persistent lack of protection to pneumococcal antigens which was significantly lower than age-matched, unvaccinated, healthy controls up to 9 months after the completion of therapy (the study period).

Protection during chemotherapy from vaccine strains in those with previous immunization is unknown. Patel et al. (2012) studied 42 children with a history of leukemia ≥6 months off of chemotherapy to assess for serotype-specific antibodies to *S. pneumoniae*. None of the subjects were noted to have protective antibody concentrations to pneumococcal conjugate vaccine serotypes. Cheng et al. (2012) administered two doses of PCV7 to 44 pediatric oncology patients, including 20 ALL patients in maintenance. Eighty-six to 100 % of patients obtained seropositivity depending on the pneumococcal serotype. No subgroup analysis was reported to determine if differences in seropositivity occurred with different underlying malignancies or based on timing of vaccination. Beyond patients that have received splenectomy as part of their therapy, there is no indication for immunization with the 23-valent pneumococcal polysaccharide vaccine.

16.7.3 Hemophilus Influenzae Type b

In settings with routine vaccination to Hib, invasive disease has plummeted (Bisgard et al. 1998). Risk still remains though in areas without routine immunization (Siber 1980; Feldman et al. 1990). Multiple studies have described the effect of Hib conjugate immunization during chemotherapy (Feldman et al. 1990; Kaplan et al. 1992; Shenep et al. 1994; Cheng et al. 2012). Feldman et al. (1990) vaccinated 50 children with Hib; the overall response rate was 50 %. Shenep et al. (1994) studied 50 children with solid tumors who had not previously been vaccinated for Hib. Seroresponse was noted in 42 % after first vaccination and another 45 % responded to a second dose. Kaplan et al. (1992) studied 18 children with malignancy and found a 50 % seroresponse rate to Hib after 1 immunization. One-third of children responded to a second dose. Weisman et al. (1987) studied 27 children with malignancy, 6 of whom had completed therapy to measure response to Hib vaccination. Eighty-five percent of patients had an appropriate response. Solid tumor patients had a 100 % response; there was no difference in response for those off therapy. Of note, all of these studies were done at a time of significantly decreased chemotherapeutic intensity making it unclear as to their generalizability with modern therapeutic protocols.

16.7.4 Inactivated Poliovirus

The risk of polio is negligible due to the near worldwide eradication of the virus. Only one relevant study by Ogra et al. (1971) could be found, comparing antibody response in patients with leukemia, solid tumors and healthy controls. Response in healthy controls and solid tumor patients was similar while those with leukemia had a blunted response. Again, due to the age of this study, the generalizability to modern therapeutic protocols is unknown. Of note, oral poliovirus (OPV) is contraindicated.

16.7.5 Influenza

16.7.5.1 Inactivated Influenza Vaccine

Although in a Cochrane review Goossen et al. (2009) conclude that there is a paucity of well designed randomized controlled trials to define

whether influenza vaccination in children with malignancy during therapy is beneficial considering their blunted response to vaccination, no significant adverse effects were seen in the studies reviewed, and the general consensus is that the benefit of vaccination outweighs cost and any other potential risks, even if seroresponse is blunted (Centers for Disease Control and Prevention 1993; Sung et al. 2001; Royal College of Paediatrics and Child Health 2002; Allen 2007; Esposito et al. 2009, 2010a; Ruggiero et al. 2011; Kersun et al. 2013a).

Multiple small studies have analyzed response to influenza vaccination, mainly during maintenance of ALL therapy and reviewed by Esposito et al. (2009) and Kersun et al. (2013a) (Allison et al. 1977; Sumaya et al. 1977; Ganz et al. 1978; Gross et al. 1978; Smithson et al. 1978; Lange et al. 1979; Schafer et al. 1979; Steinherz et al. 1980; Brydak et al. 1996, 1998; Chisholm et al. 2001; Porter et al. 2004; Matsuzaki et al. 2005; Bektas et al. 2007; Shahgholi et al. 2010; Wong-Chew et al. 2012; Kersun et al. 2013a). In general, the vaccine was well tolerated with no serious adverse side effects. When comparing response for patients receiving chemotherapy versus patients off therapy and healthy controls, rate of seroconversion was lower in patients still receiving therapy. Additionally, response in patients with solid tumors was more similar to patients off therapy and healthy controls. Kersun et al. (2013b) showed that ALL patients vaccinated during induction had an improved response compared to patients receiving the vaccine post-induction or in maintenance. Timing of immunization during an ALL maintenance cycle has not been studied to determine if the rate of response is improved when the vaccine is given separated from a 5-day steroid pulse. Additionally, patients are recommended to receive a two-shot series their first year of immunization and subsequently one annual shot. It is unclear if there would be additional benefit by continuing with a yearly two-shot series or increased dose while immunocompromised.

16.7.5.2 2009 H1N1 Pandemic Vaccine

Seven studies have reported on efficacy of the 2009 H1N1 pandemic influenza vaccine (Bate et al. 2010b; Cheng et al. 2011; Yen et al. 2011; Hakim et al. 2012; Shahin et al. 2012; Leahy et al. 2013; Mavinkurve-Groothuis et al. 2013). In general, response rates were increased after two doses of vaccine in those patients with solid tumors and in those not receiving treatment. For a mixed pediatric oncology cohort, seroresponse ranged from 25.6–100 % (Bate et al. 2010b; Cheng et al. 2011; Yen et al. 2011; Hakim et al. 2012; Leahy et al. 2013; Mavinkurve-Groothuis et al. 2013). Absolute lymphocyte counts greater than the upper limit of normal for age (or ≥1.0–1.5 x 10^9/L depending on the study) were a significant factor in antibody response in three studies (Yen et al. 2011; Hakim et al. 2012; Mavinkurve-Groothuis et al. 2013). Leahy et al. (2013) showed significantly improved seropositivity in children who received the higher 0.5 mL dose on univariate but not multivariate analysis. No severe adverse reactions were noted in any of the studies. As with the annual trivalent influenza vaccine, clear data as to the most efficacious timing of immunization during ALL therapy, appropriate dose and the need for one versus two doses of vaccine are lacking although repeated, higher doses appear most effective.

16.7.5.3 Live Attenuated Influenza Vaccine

Two studies have been completed to measure seroresponse and safety of the live attenuated influenza vaccine (LAIV) in immunocompromised patients (Carr et al. 2011; Halasa et al. 2011). Halasa et al. (2011) conducted a small pilot study on the safety and immunogenicity of LAIV in mild to moderately immunocompromised children with cancer. Children with severe immunodeficiency as defined by an absolute neutrophil count (ANC) <0.5 x 10^9/L, concurrent high-dose steroid usage (≥2 mg/kg/day) or CD4+ T-lymphocyte percentage <15 % were excluded. The ten patients with hematologic malignancies and solid tumors who were immunized did not have any serious

adverse events or an excessive period of viral shedding. Immunogenicity ranged from 33–44 % depending on the assay utilized. Carr et al. (2011) compared seroresponse in 52 children who were mild to moderately immunocompromised and randomly assigned to LAIV or inactivated vaccine. Seroprotection was found to be greater to influenza A strains with the inactivated vaccine. No difference was seen in seroprotection to influenza B. No serious adverse events were noted; specifically, viral shedding was not increased with the live attenuated vaccine. With limited safety data and no evidence of increased immunogenicity with LAIV, this form of the influenza vaccine remains relatively contraindicated in pediatric oncology patients.

16.7.6 Hepatitis B Virus Vaccine

In areas of high prevalence, especially East Asia and lower-income countries, the risk of HBV transmission during chemotherapeutic regimens is significant and therefore vaccination in these settings should be strongly considered (Somjee et al. 1999; Meral et al. 2000; Sevinir et al. 2003; Yetgin et al. 2007). Multiple studies using different vaccination schedules, a combination of passive and active immunization, and significant difference in transmission risk are present in the literature (Berberoğlu et al. 1995; Hovi et al. 1995; Kavakli et al. 1996; Goyal et al. 1998; Somjee et al. 1999; Meral et al. 2000; Yetgin et al. 2001; Somjee et al. 2002; Köksal et al. 2007; Yetgin et al. 2007; Baytan et al. 2008). The lowest rate of HBV transmission appears to be in those patients that receive a combination of passive and active immunization although the cost-effectiveness of this approach is questionable (Kavakli et al. 1996; Meral et al. 2000; Somjee et al. 2002). For seronegative patients with ALL in maintenance, seroconversion rates ranged from 35.1–62.5 % after a 2–5 shot HBV series (Yetgin et al. 2001, 2007; Baytan et al. 2008). Although HBV transmission still occurs in those that are immunized during therapy, Yetgin et al. (2007) showed that infection was significantly decreased compared to unvaccinated patients, even if seroconversion did not occur. Additional studies among pediatric oncology patients with variable timing of immunization and vaccination schedules showed a seroconversion rate of 50–78 % (Berberoğlu et al. 1995; Hovi et al. 1995; Köksal et al. 2007). Hovi et al. (1995) studied 165 pediatric oncology patients; of the 51 on therapy, 67 % responded to a three-dose immunization schedule as compared to a 97 % seroresponse in the 114 off therapy. HBV immunization is important in settings outside of the United States and Western Europe where risk of transmission during therapy is high, although firm recommendations on the optimal timing and schedule of vaccination cannot be made based on the studies to date.

16.7.7 Meningococcal Conjugate Vaccine

The risk of meningococcus in immunocompromised pediatric oncology patients is unknown. Yu et al. (2007) studied vaccine response to protein-conjugated meningococcal C vaccine in 25 children with ALL and found improved response in those vaccinated 3 months after the completion of chemotherapy as compared to those in maintenance therapy (4 of 15 responders in maintenance versus 9 of 10 responders after chemotherapy completion).

16.7.8 Varicella Zoster Virus

Due to the herd immunity provided by routine varicella vaccination, especially in North America, guidelines for immunization during ALL maintenance have changed, and immunization is no longer recommended in these settings (Centers for Disease Control and Prevention 2007; American Academy of Pediatrics 2012c; Caniza et al. 2012). However, varicella immunization should still be a consideration in higher-risk populations,

especially lower-income countries and, potentially, those higher income countries without universal varicella vaccination campaigns (Levin 2008; Esposito et al. 2010a).

Sartori (2004) provides an excellent review of varicella vaccination in immunocompromised patients. Early studies of the efficacy and safety of live attenuated varicella vaccine in children with acute leukemia were done in Japan with further safety data in the United States (Gershon et al. 1984; Takahashi et al. 1985; Gershon et al. 1986; Gershon and Steinberg 1989).

In their initial study, Gershon et al. (1984) showed the safety of live attenuated varicella vaccination when given to children with ALL that were in continuous clinical remission for 1 year, had a lymphocyte count $\geq 0.7 \times 10^9$/L, an IgG level $\geq$100 mg/dL, responded to at least one mitogen, and had all chemotherapy suspended for 1 week before and after vaccination. Seroresponse was 80 % after one dose of VZV. Rash was the only side effect which also increased seroconversion as well as the chance of transmission. Vaccination was quite protective, decreasing rate of infection after exposure to 18 % from an expected 90 % and also presenting as mild disease in those with clinical illness after exposure. A follow-up study by the same group with a larger cohort showed 88 % seroconversion after one dose of vaccination and 98 % seroconversion after two doses with no notable serious adverse events (Gershon and Steinberg 1989). Multiple other small studies have shown similar results with no serious adverse events (Heath and Malpas 1985; Ninane et al. 1985; Heath et al. 1987; Ecevit et al. 1996; Cakir et al. 2012).

A recent case report by Schrauder et al. (2007) on a child with ALL who developed fulminant varicella infection 32 days after varicella vaccination deserves mention. Vaccination was given with an interruption in chemotherapy, 1 week prior and 1 week after, but was given 5 months after complete remission had been achieved and prior to intensive reinduction chemotherapy, not in accordance with the stringent guidelines set forth by Takahashi et al. (1985) and Gershon et al. (1984, 1986; Gershon and Steinberg 1989). Based on their case, the authors recommend waiting at least 9 months after all therapy completion (including maintenance chemotherapy) prior to administering varicella vaccination. Their recommendation is not supported by the existing literature but does emphasize the care and attention that is necessary when administering this live attenuated vaccine to children that remain immunocompromised (Centers for Disease Control and Prevention 2007).

16.8 Recommendations for Vaccination After Chemotherapy Completion

Immune reconstitution is variable after the completion of chemotherapy leading to inconsistent guidelines for (re)vaccination. Among the published guidelines, four authors recommend commencing (re)vaccination 3 months after therapy completion (Centers for Disease Control and Prevention 1993; Sung et al. 2001; Allen 2007; Esposito et al. 2010a). For three of the four authors, this recommendation is inclusive of live viral vaccines (Centers for Disease Control and Prevention 2007). Esposito et al. (2010a) recommend waiting 6 months for live vaccines. The UK guidelines (Royal College of Paediatrics and Child Health 2002) recommend waiting 6 months for all vaccinations while Ruggiero et al. (2011) recommend waiting 6 months for inactivated/killed vaccines and measles but 12 months for VZV. Fioredda et al. (2005) also recommend waiting 6 months after therapy completion. Guidelines are unclear in regard to children that interrupted their primary immunization series (Esposito et al. 2010a; Ruggiero et al. 2011). Based on their review, van Tilburg et al. (2012) conclude that although revaccination is important, further study is still required to determine what the appropriate immunizations are, depending on the local herd immunity and risk for vaccine-preventable disease after chemotherapy. They do feel based on their review that 3 months after the completion of therapy is a good time point to begin the evaluatory process. Whether the evaluatory process should include pre- and/or post-immunization titers is also unclear; additionally there is a significant associated cost with such a strategy and seroprotection may not always

equate with seropositivity by antibody level. The main factors that must be considered are minimizing the period of risk to the patient while balancing the risk for lack of seroconversion with premature immunization. Risk of vaccine-related infection from live viral vaccination seems less of a concern after therapy completion since patients can safely be immunized with varicella during ALL maintenance. For influenza, Esposito et al. (2010b) show that the biggest risk to pediatric patients with malignancy is during treatment and 6 months after the completion of therapy (including risk of infection and hospitalization). Beyond this point, risk becomes similar to the general pediatric population.

Based on the UK guidelines as outlined in the Royal College of Paediatrics and Child Health (RCPCH) best practice statement from 2002, Patel et al. (2007) enrolled 59 children with a history of leukemia ≥6 months after chemotherapy completion for revaccination. They found the large majority who were deficient achieved optimal antibody concentrations that persisted when rechecked 12 months after immunization. Based on their results they recommend following the RCPCH timing for booster vaccination. Of their studied vaccinations, inactivated poliovirus vaccine was the least immunogenic (HBV was not part of the study) but seroconversion rates were similar to published response in healthy individuals. Treatment intensity was not significantly associated with seroresponse. Similar rates of seroconversion are plausible with earlier vaccination as well; thus, 3 months post the completion of therapy is recommended by several authors based on their data (Lehrnbecher et al. 2009; Zengin and Sarper 2009). Large, randomized controlled trial data are lacking to make firm recommendations.

16.9 Active/Passive Immunization After Disease Exposure

16.9.1 Varicella

Live virus vaccination is contraindicated after varicella disease exposure (2 days prior to rash or before all lesions crusted over in contact) in immunocompromised individuals, although passive immunization and antivirals may be of utility. Multiple studies of variable quality have shown the potential benefit of varicella zoster immune globulin (VariZIG; VZIG) in immunocompromised children, nicely summarized by Fisher et al. (2011) (Brunell et al. 1972; Gershon et al. 1974; Judelsohn et al. 1974; Feldman et al. 1975; Evans et al. 1980; Orenstein et al. 1981; Hanngren et al. 1983; Zaia et al. 1983; Feldman and Lott 1987). VZIG often will not prevent disease in immunocompromised patients but has been shown to decrease disease severity (in most patients). Efficacy of VZIG has been shown to decline if given >72 h after exposure; therefore, previous US recommendations were to administer it within 96 h of exposure (Feldman and Lott 1988; American Academy of Pediatrics 2006). With the potential to attenuate disease even beyond this 72–96 h window, newer US guidelines as well as UK guidelines recommend VZIG up to 10 days after exposure (Royal College of Paediatrics and Child Health 2002; American Academy of Pediatrics 2012c). Due to the lack of quality studies, VariZIG remains an investigational agent in the United States and requires institutional review board approval and completion of an investigational new drug form. If VZIG is not available, intravenous immunoglobulin (IVIG) may be given.

Oral acyclovir antiviral prophylaxis has been claimed to show benefit in multiple studies, summarized by Fisher et al. (2011) (Ishida et al. 1996; Goldstein et al. 2000; Martin-Hernandez 2000; Shinjoh and Takahashi 2009). As with VZIG, these studies are case reports or nonrandomized uncontrolled studies. Studies in healthy children have specifically shown a decrease in disease when acyclovir is given as a 7-day course starting 1 week after exposure; efficacy was decreased when prophylaxis was started 3 or 11 days after exposure (Asano et al. 1993; Suga et al. 1993; Huang et al. 1995; Fisher et al. 2011). Current US guidelines recommend a 7-day course starting 7–10 days after exposure, while UK guidelines recommend a 14-day course starting 7 days after exposure (Royal College of Paediatrics and Child Health 2002; American Academy of Pediatrics 2012c). See Table 16.2 for VZIG, IVIG and acyclovir dosing recommendations. Fisher et al. (2011)

Table 16.2 Passive immunization after varicella or measles disease exposure[a]

Exposure to varicella 2 days prior to rash or before crusting of all lesions in contact:
If within 4–10 days of exposure:
VZIG 125 units/10 kg for the first 10–40 kg; >40 kg, 625 units IM (max 2.5 mL per injection site)
Or
IVIG 400 mg/kg IV
Or
If within 7–10 days of exposure and neither VZIG nor IVIG administered:
Acyclovir 80 mg/kg/day PO div QID (max dose 800 mg QID), for 7–14 days
Exposure to measles 5 days prior to or 4 days after onset of rash in contact:
If within 6–14 days of exposure:
Immunoglobulin 0.5 mL/kg IM (max dose 15 mL; max 3 mL per injection site in children)
Or
IVIG 400 mg/kg IV

VZIG varicella zoster immunoglobulin, *IVIG* intravenous immunoglobulin
Adapted from Royal College of Paediatrics and Child Health (2002), American Academy of Pediatrics (2012b, c)
[a]See text for details; level of evidence 1C per Guyatt et al. (2006); see Preface

comment in their review that a formal comparison between VZIG and acyclovir is lacking.

16.9.2 Measles

Measles immunization is contraindicated after measles exposure in immunocompromised patients. Passive immunization with immunoglobulin (Ig) should be utilized especially with virologic confirmation of exposure and exposure occurring 5 days prior to and up to 4 days after the onset of rash in the infectious contact. Ig may be given either intramuscularly or intravenously, especially if thrombocytopenic. Ideally passive prophylaxis should be given within 72 h of exposure; US guidelines recommend Ig up to 6 days after exposure, UK guidelines up to 14 days after contact (Royal College of Paediatrics and Child Health 2002; American Academy of Pediatrics 2012b). See Table 16.2 for dosing. Of note, a washout period after any immunoglobulin product (and blood products) is required prior to administration of measles vaccination. In the previously immunocompromised patient, MMR should be given a minimum of 6 months after Ig (American Academy of Pediatrics 2012b). In settings without Ig availability, early initiation of ribavirin for the treatment or postexposure prophylaxis of measles can be considered (Moulik et al. 2013).

16.10 Treatment of Hypogammaglobulinemia During Chemotherapy

The impact of low immunoglobulin levels on the risk of infectious sequelae during chemotherapy has not been well characterized. Although van Tilburg et al. (2012) showed that IgG levels were significantly lower in ALL patients receiving more intensive therapy and these patients also suffered more infectious complications, this fact could not be directly correlated to IgG levels. Kovacs et al. (2008) analyzed 88 children 1 year after the completion of chemotherapeutic regimens for malignancies. Leukemia patients suffered a statistically increased number of febrile episodes as compared to solid tumor patients, although this did not correlate with immunoglobulin levels. Similarly, solid tumor patients with low immunoglobulin levels suffered more febrile episodes than those with normal Ig levels, but not to the point of statistical significance. Multiple consensus statements on the use of IVIG do not include routine use in acquired hypogammaglobulinemia due to chemotherapy (Hemming 2001; Orange et al. 2006; Robinson et al. 2007). In a Canadian consensus statement, Robinson et al. (2007) note that IVIG is often a part of oncologic study protocols (though not evidence-based) and may also be considered in patients with a history of severe invasive infection or recurrent sinopulmonary infection in the setting of acquired hypogammaglobulinemia.

16.11 Vaccination of Household Contacts

Minimizing the risk of exposure in immunocompromised patients to vaccine-preventable diseases by immunization of household contacts is a vital

Table 16.3 Vaccination recommendations in household contacts of immunocompromised patients[a]

Vaccines that should be routinely given[b]
Yearly inactivated influenza vaccine
Live attenuated varicella vaccine in susceptible individuals
Rotavirus vaccine per routine schedule
All inactivated/killed vaccines and measles-mumps-rubella per routine schedule
Vaccines that are contraindicated
Live attenuated influenza vaccine
Oral poliovirus vaccine
Smallpox vaccine

Adapted from Centers for Disease Control and Prevention (1993), American Academy of Pediatrics (2012a)
[a]Level of evidence 1C per Guyatt et al. (2006); see Preface
[b]Live attenuated yellow fever vaccine may be given if necessary; unclear evidence for BCG and oral typhoid in high-risk settings

aspect of supportive care (Table 16.3). As discussed, immunogenicity to vaccine-preventable disease will be blunted during the period of highest risk; thus, minimizing any potential infectious contacts is more important than vaccine guidelines in those receiving therapy. Immunization of healthcare workers is therefore also important and summarized in Chap. 14. Live virus vaccines including measles-mumps-rubella, rotavirus and varicella have all been deemed safe due to the minimal risk of disease spread. Oral poliovirus vaccine is contraindicated and live attenuated influenza vaccine is relatively contraindicated (American Academy of Pediatrics 2012a). Household contacts should receive yearly inactivated influenza vaccine and young, susceptible contacts should be immunized against varicella. Vaccinees who develop a postvaccination rash should be separated from susceptible individuals due to the theoretical risk of infection transmission (Hughes et al. 1994; LaRussa et al. 1997; Chaves et al. 2008; Galea et al. 2008). However, no transmission of vaccine strain varicella has been reported to immunocompromised patients in the United States after 55 million doses of vaccine have been given (Chaves et al. 2008; Galea et al. 2008). Outside of the United States, in countries without national varicella vaccination programs, immunization of household contacts has been problematic due to concerns of safety as well as a lack of identification by pediatric oncologists (Timitilli et al. 2008; Fisher et al. 2011).

16.12 Summary

Much is yet to be understood in regard to the pace of immune recovery after current chemotherapeutic regimens due to the lack of large, prospective studies. Likely, due to multifactorial reasons, the tempo will be variable when considering the array of ages, diagnoses and treatment regimens employed in pediatric oncology. In settings with expansive vaccine programs, immunocompromised children will be well protected from vaccine-preventable diseases due to herd immunity. In high-prevalence settings, vaccination during chemotherapy and periods of risk is more vital and further study is required as to the optimal timing and safety of such recommendations. (Re)vaccination after chemotherapy is important although the optimal timing and extent of (re)immunization is unclear. Large, randomized controlled trials are required to make firm decisions. Patients should be offered booster immunization 3–6 months after therapy completion by either the pediatric oncologist or in concert with the general pediatrician. Prevention of exposure by stringent vaccination of household contacts and treatment of exposure with passive immunization are also important aspects of supportive care in regard to vaccine-preventable disease.

References

Abrahamsson J, Marky I, Mellander L (1995) Immunoglobulin levels and lymphocyte response to mitogenic stimulation in children with malignant disease during treatment and follow-up. Acta Paediatr 84:177–182

Adler AL, Casper C, Boeckh M et al (2008) An outbreak of varicella with likely breakthrough disease in a population of pediatric cancer patients. Infect Control Hosp Epidemiol 29:866–870

Alanko S, Pelliniemi TT, Salmi TT (1992) Recovery of blood B-lymphocytes and serum immunoglobulins after chemotherapy for childhood acute lymphoblastic leukemia. Cancer 69:1481–1486

Alanko S, Pelliniemi TT, Salmi TT (1994) Recovery of blood lymphocytes and serum immunoglobulins after treatment of solid tumors in children. Pediatr Hematol Oncol 11:33–45

Alanko S, Salmi TT, Pelliniemi TT (1995) Recovery of natural killer cells after chemotherapy for childhood acute lymphoblastic leukemia and solid tumors. Med Pediatr Oncol 24:373–378

Alavi S, Rashidi A, Arzanian MT et al (2010) Humoral immunity against hepatitis B, tetanus, and diphtheria following chemotherapy for hematologic malignancies: a report and review of the literature. Pediatr Hematol Oncol 27:188–194

Al-Jadiry MF, Al-Khafagi M, Al-Darraji AF et al (2013) High incidence of hepatitis B infection after treatment for paediatric cancer at a teaching hospital in Baghdad. East Mediterr Health J 19:130–134

Allen UD (2007) Immunizations for children with cancer. Pediatr Blood Cancer 49:1102–1108

Allen JB, Weiner LB (1981) Pneumococcal sepsis in childhood leukemia and lymphoma. Pediatrics 67: 292–295

Allison JE, Glezen WP, Taber LH et al (1977) Reactogenicity and immunogenicity of bivalent influenza A and monovalent influenza B virus vaccines in high-risk children. J Infect Dis 156:S672–S676

American Academy of Pediatrics (2012a) Active and passive immunization: immunization in special clinical circumstances—immunocompromised children. In: Pickering LK (ed) Red book: 2012 report of the committee on infectious diseases, 29th edn. American Academy of Pediatrics, Elk Grove Village

American Academy of Pediatrics (2012b) Summaries of infectious diseases: measles. In: Pickering LK (ed) Red book: 2012 report of the committee on infectious diseases varicella-zoster, 29th edn. American Academy of Pediatrics, Elk Grove Village

American Academy of Pediatrics (2012c) Summaries of infectious diseases: infections. In: Pickering LK (ed) Red book: 2012 report of the committee on infectious diseases, 29th edn. American Academy of Pediatrics, Elk Grove Village, IL

American Academy of Pediatrics (2006) Summaries of infectious diseases: infections. In: Pickering LK (ed) Red book: 2006 report of the committee on infectious diseases, 27th edn. American Academy of Pediatrics, Elk Grove Village, IL

Asano Y, Yoshikawa T, Suga S et al (1993) Postexposure prophylaxis of varicella in family contact by oral acyclovir. Pediatrics 92:219–222

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

Banatvala JE, Van Damme P (2003) Hepatitis B vaccine—do we need boosters? J Viral Hepat 10:1–6

Bate J, Patel SR, Chisholm J et al (2010a) Immunisation practices of paediatric oncology and shared care oncology consultants: a United Kingdom survey. Pediatr Blood Cancer 54:941–946

Bate J, Yung CF, Hoschler K et al (2010b) Immunogenecity of pandemic (H1N1) 2009 vaccine in children with cancer in the United Kingdom. Clin Infect Dis 51:e95–e104

Baytan B, Gunes AM, Gumay U (2008) Efficacy of primary hepatitis B immunization in children with acute lymphoblastic leukemia. Indian Pediatr 45: 265–270

Bektas O, Karadeniz C, Oguz A et al (2007) Assessment of the immune response to trivalent split influenza vaccine in children with solid tumors. Pediatr Blood Cancer 49:914–917

Berberoğlu S, Büyükpamkcu M, Sarialioglu F et al (1995) Hepatitis B vaccination in children with cancer. Pediatr Hematol Oncol 12:171–178

Bhat N, Wright JG, Broder KR et al (2005) Influenza-associated deaths among children in the United States, 2003–2004. N Engl J Med 353:2559–2567

Biggar RJ, Christiansen M, Rostgaard K et al (2009) Immunoglobulin subclass levels in patients with non-Hodgkin lymphoma. Int J Cancer 124:2616–2620

Bisgard KM, Kao A, Leake J et al (1998) Haemophilus influenzae invasive disease in the United States, 1994–1995: near disappearance of a vaccine-preventable childhood disease. Emerg Infect Dis 4:229–237

Brodtman DH, Rosenthal DW, Redner A et al (2005) Immunodeficiency in children with acute lymphoblastic leukemia after completion of modern aggressive chemotherapeutic regimens. J Pediatr 146: 654–661

Brunell PA, Gershon AA, Hughes WT et al (1972) Prevention of varicella in high risk children: a collaborative study. Pediatrics 50:718–722

Brydak LB, Rokicka-Milewska R, Jackowska T (1996) Kinetics of humoral response in children with acute lymphoblastic leukemia immunized with influenza vaccine in 1993 in Poland. Pediatr Hematol Oncol 13:231–238

Brydak L, Rokicka-Milewska R, Machala M et al (1998) Immunogenicity of subunit trivalent influenza vaccine in children with acute lymphoblastic leukemia. Pediatr Infect Dis J 17:125–129

Cakir FB, Timur C, Yoruk A et al (2012) Seroconversion status after single dose and double doses of varicella vaccination in children with leukemia. Pediatr Hematol Oncol 29:191–194

Caniza MA, Hunger SP, Schrauder A et al (2012) The controversy of varicella vaccination in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 58:12–16

Carr S, Allison KJ, Van De Velde L et al (2011) Safety and immunogenicity of live attenuated and inactivated influenza vaccines in children with cancer. J Infect Dis 204:1475–1482

Caver TE, Slobod KS, Flynn PM et al (1998) Profound abnormality of the B/T lymphocyte ratio during chemotherapy for pediatric acute lymphoblastic leukemia. Leukemia 12:619–622

Centers for Disease Control and Prevention (1993) Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. MMWR Recomm Rep 42:1–24

Centers for Disease Control and Prevention (2007) Prevention of varicella: recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR Recomm Rep 56:25

Chaves SS, Haber P, Walton K et al (2008) Safety of varicella vaccination after licensure in the United States: experience from reports to the vaccine adverse event reporting system, 1995–2005. J Infect Dis 197:S170–S177

Cheng FW, Leung TF, Chan PK et al (2009) Humoral immune response after post-chemotherapy booster diphtheria-tetanus-pertussis vaccine in pediatric oncology patients. Pediatr Blood Cancer 52:248–253

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

Cheng FW, Chan PK, Leung WK et al (2011) Pandemic (H1N1) 2009 vaccine in paediatric oncology patients: one dose or two doses? [letter]. Br J Haematol 154:408–409

Cheng FW, Ip M, Chu YY et al (2012) Humoral response to conjugate pneumococcal vaccine in paediatric patients. Arch Dis Child 97:358–360

Chilcote RR, Baehner RL, Hammond D (1976) Septicemia and meningitis in children splenectomized for Hodgkin's disease. N Engl J Med 295:798–800

Chisholm JC, Devine T, Charlett A et al (2001) Response to influenza immunization during treatment for cancer. Arch Dis Child 84:496–500

Crawford NW, Heath JA, Ashley D et al (2010) Survivors of childhood cancer: an Australian audit of vaccination status after treatment. Pediatr Blood Cancer 54:128–133

Cristófani LM, Weinberg A, Peixoto V et al (1991) Administration of live attenuated varicella vaccine in children with cancer before starting chemotherapy. Vaccine 9:873–876

De Vaan GA, van Munster PJ, Bakkeren JA (1982) Recovery of immune function after cessation of maintenance therapy in acute lymphoblastic leukemia (ALL) of childhood. Eur J Pediatr 139:113–117

Donaldson SS, Glatstein E, Vosti KL (1978) Bacterial infections in pediatric Hodgkin's disease. Cancer 41:1949–1958

Ecevit Z, Büyükpamukçu M, Kanra G et al (1996) Oka strain live varicella vaccine in children with cancer. Pediatr Infect Dis J 15:169–170

Ek T, Mellander L, Hahn-Zoric M et al (2004) Intensive treatment for childhood acute lymphoblastic leukemia reduces immune responses to diphtheria, tetanus, and Haemophilus influenzae type b. J Pediatr Hematol Oncol 26:727–734

Ek T, Mellander L, Andersson B et al (2005) Immune reconstitution after childhood acute lymphoblastic leukemia is most severely affected in the high risk group. Pediatr Blood Cancer 44:461–468

Ek T, Mellander L, Hahn-Zoric M et al (2006) Avidity of tetanus and Hib antibodies after childhood acute lymphoblastic leukaemia—implications for vaccination strategies. Acta Paediatr 95:701–706

Ek T, Josefson M, Abrahamsson J (2011) Multivariate analysis of the relation between immune dysfunction and treatment intensity in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 56:1078–1087

El-Chennawi FA, Al-Tonbary YA, Mossad YM et al (2008) Immune reconstitution during maintenance therapy in children with acute lymphoblastic leukemia, relation to co-existing infection. Hematology 13:203–209

El-Din HM, Loutfy SA, Abdel-Rahman H et al (2012) Measles, mumps, varicella zoster, diphtheria and hepatitis B surface antibody status in pediatric acute leukemic patients. J Blood Disord Transfus S1: S1–S8

Ercan TE, Soycan LY, Apak H et al (2005) Antibody titers and immune response to diphtheria-tetanus-pertussis and measles-mumps-rubella vaccination in children treated for acute lymphoblastic leukemia. J Pediatr Hematol Oncol 27:273–277

Esposito S, Cecinati V, Russo FG et al (2009) Influenza vaccination in children with cancer receiving chemotherapy. Hum Vaccin 5:430–432

Esposito S, Cecinati V, Brescia L et al (2010a) Vaccinations in children with cancer. Vaccine 28:3278–3284

Esposito S, Cecinati V, Scicchitano B et al (2010b) Impact of influenza-like illness and effectiveness of influenza vaccination in oncohematological children who have completed cancer therapy. Vaccine 28:1558–1565

Evans EB, Pollock TM, Cradock-Watson JE et al (1980) Human anti-chickenpox immunoglobulin in the prevention of chickenpox. Lancet 1:354–356

Eyrich M, Wiegering V, Lim A et al (2009) Immune function in children under chemotherapy for standard risk acute lymphoblastic leukaemia—a prospective study of 20 paediatric patients. Br J Haematol 147: 360–370

Feldman S, Hughes WT, Daniel C (1975) Varicella in children with cancer: 77 cases. Pediatrics 80:388–397

Feldman S, Lott L (1987) Varicella in children with cancer: impact of antiviral therapy and prophylaxis. Pediatrics 80:465–472

Feldman S, Lott L (1988) Passive immunization against varicella in children receiving chemotherapy. Pediatrics 82:954–955

Feldman S, Gigliotti F, Shenep JL et al (1990) Risk of haemophilus influenzae type b disease in children with cancer and response of immunocompromised leukemic children to a conjugate vaccine. J Infect Dis 161:926–931

Feldman S, Andrew M, Norris M et al (1998) Decline in rates of seropositivity for measles, mumps, and rubella antibodies among previously immunized children treated for acute leukemia. Clin Infect Dis 27:388–390

Fioredda F, Plebani A, Hanau G et al (2005) Re-immunisation schedule in leukaemic children after intensive chemotherapy: a possible strategy. Eur J Haematol 74:20–23

Fisher JP, Bate J, Hambleton S (2011) Preventing varicella in children with malignancies: what is the evidence? Curr Opin Infect Dis 24:203–211

Fuks Z, Strober S, Bobrove AM (1976) Long term effects of radiation on T and B lymphocytes in peripheral blood of patients with Hodgkin's disease. J Clin Invest 58:803–814

Galea SA, Sweet A, Beninger P et al (2008) The safety profile of varicella vaccine: a 10-year review. J Infect Dis 197:S165–S169

Ganz PA, Shanley JD, Cherry JD (1978) Responses of patients with neoplastic diseases to influenza virus vaccine. Cancer 42:2244–2247

Gershon AA, Steinberg SP (1989) Persistence of immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. N Engl J Med 320:8892–8897

Gershon AA, Steinberg SP, Brunell PA (1974) Zoster immune globulin. A further assessment. N Engl J Med 290:243–245

Gershon AA, Steinberg SP, Gelb L et al (1984) Live attenuated varicella vaccine: efficacy for children with leukemia in remission. JAMA 252:355–362

Gershon AA, Steinberg SP, Gelb L (1986) Live attenuated varicella vaccine use in immunocompromised children and adults. Pediatrics 78:757–762

Goldstein SL, Somers MJ, Lande MB et al (2000) Acyclovir prophylaxis of varicella in children with renal disease receiving steroids. Pediatr Nephrol 14:305–308

Goossen GM, Kremer LC, van de Wetering MD (2009) Influenza vaccination in children being treated with chemotherapy for cancer. Cochrane Database Syst Rev (2):CD006484

Goyal S, Pai SK, Kelkar R et al (1998) Hepatitis B vaccination in acute lymphoblastic leukemia. Leuk Res 22:193–195

Gross PA, Lee H, Wolff J et al (1978) Influenza immunization in immunosuppressed children. J Pediatr 92:30–35

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

Hakim H, Allison KJ, Van De Velde L et al (2012) Immunogenicity and safety of inactivated monovalent 2009 H1N1 influenza A vaccine in immunocompromised children and young adults. Vaccine 30:879–885

Halasa N, Englund JA, Nachman S et al (2011) Safety of live attenuated influenza vaccine in mild to moderately immunocompromised children with cancer. Vaccine 29:4110–4115

Hanngren K, Falksveden L, Grandien M et al (1983) Zoster immunoglobulin in varicella prophylaxis. A study among high-risk patients. Scand J Infect Dis 15:327–334

Heath RB, Malpas JS (1985) Experience with the live Oka-strain varicella vaccine in children with solid tumours. Postgrad Med J 61:107–111

Heath RB, Malpas JS, Kangro HO et al (1987) Efficacy of varicella vaccine in patients with solid tumours. Arch Dis Child 62:569–572

Hemming VG (2001) Use of intravenous immunoglobulins for prophylaxis or treatment of infectious diseases. Clin Diagn Lab Immunol 8:859–863

Hovi L, Valle M, Siimes M et al (1995) Impaired response to hepatitis B vaccine in children receiving anticancer chemotherapy. Pediatr Infect Dis J 14:931–934

Huang YC, Lin TY, Chiu CH (1995) Acyclovir prophylaxis of varicella after household exposure. Pediatr Infect Dis J 14:152–154

Hughes P, LaRussa PS, Pearce JM et al (1994) Transmission of varicella-zoster virus from a vaccinee with underlying leukemia, demonstrated by polymerase chain reaction. J Pediatr 124:932–935

Ishida Y, Tauchi H, Higaki A et al (1996) Postexposure prophylaxis of varicella in children with leukemia by oral acyclovir. Pediatrics 97:150–151

Judelsohn RG, Meyers JD, Ellis RJ et al (1974) Efficacy of zoster immune globulin. Pediatrics 53:476–480

Kantar M, Çetingül N, Kansoy S et al (2003) Immune deficiencies following cancer treatment in children. J Trop Pediatr 49:286–290

Kaplan SL, Duckett T, Mahoney DH et al (1992) Immunogenicity of Haemophilus influenzae type b polysaccharide-tetanus protein conjugate vaccine in children with sickle hemoglobinopathy or malignancies, and after systemic Haemophilus influenzae type b infection. J Pediatr 120:367–370

Kaplan SL, Mason EO, Wald ER et al (2004) Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. Pediatrics 113:443–449

Kavakli K, Cetingul N, Oztop S (1996) Combined administration of hepatitis B vaccine and hepatitis B immune globulin in children with cancer. Pediatr Hematol Oncol 13:295–298

Kersun LS, Reilly A, Coffin SE, Sullivan KE (2013a) Protecting pediatric oncology patients from influenza. Oncologist 18:204–211

Kersun LS, Reilly A, Coffin SE et al (2013b) A prospective study of chemotherapy immunologic effects and predictors of humoral influenza vaccine responses in a pediatric oncology cohort. Influenza Other Respir Viruses 7:1158–1167

Köksal Y, Varan A, Aydin GB (2007) Comparison of accelerated and rapid schedules for monovalent hepatitis B and combined hepatitis A/B vaccines in children with cancer. Pediatr Hematol Oncol 24:587–594

Kosmidis S, Baka M, Bouhoutsou D et al (2008) Longitudinal assessment of immunological status and rate of recovery following treatment in children with ALL. Pediatr Blood Cancer 50:528–532

Kostaridou S, Polychronopoulou S, Psarra K et al (2004) Decrease of CD4+ and B-lymphocyte populations is not associated with severe infectious complications in children with acute lymphoblastic leukemia during maintenance. Int J Hematol 80:354–360

Kovacs GT, Barany O, Schlick B et al (2008) Late immune recovery in children treated for malignant diseases. Pathol Oncol Res 14:391–397

Kung FH, Orgel HA, Wallace WW et al (1984) Antibody production following immunization with diphtheria and tetanus toxoids in children receiving chemotherapy during remission of malignant disease. Pediatrics 74:86–89

Kwon HJ, Lee JW, Chung NG et al (2012) Assessment of serologic immunity to diphtheria-tetanus-pertussis after treatment of Korean pediatric hematology and oncology patients. J Korean Med Sci 27:78–83

Lange B, Shapiro SA, Waldman MT et al (1979) Antibody responses to influenza immunization of children with acute lymphoblastic leukemia. J Infect Dis 140:402–406

LaRussa PS, Steinburg S, Meurice F et al (1997) Transmission of vaccine strain varicella-zoster from a healthy adult with vaccine-associated rash to susceptible household contacts. J Infect Dis 176:1072–1075

Leahy TR, Smith OP, Bacon CL et al (2013) Does vaccine dose predict response to the monovalent pandemic H1N1 influenza A vaccine in children with acute lymphoblastic leukemia? A single-centre study. Pediatr Blood Cancer 60:1656–1661

Lehrnbecher T, Schubert R, Behl M et al (2009) Impaired pneumococcal immunity in children after treatment for acute lymphoblastic leukaemia. Br J Haematol 147:700–705

Levin MJ (2008) Varicella vaccination of immunocompromised children. J Infect Dis 197:S200–S206

Luczynski W, Stasiak-Barmuta A, Krawczuk-Rybak M (2004) Immunologic monitoring of maintenance therapy for acute lymphoblastic leukaemia in children—preliminary report. Pediatr Blood Cancer 42:416–420

Mackall CL, Fleisher TA, Brown MR et al (1995) Age, thymopoiesis, and CD4+ T-lymphocyte regeneration after intensive chemotherapy. N Engl J Med 332:143–149

Martin-Hernandez E (2000) Acyclovir prophylaxis of varicella in children with nephritic syndrome. Pediatr Nephrol 15:326–327

Matsuzaki A, Suminoe A, Koga Y et al (2005) Immune response after influenza vaccination in children with cancer. Pediatr Blood Cancer 45:831–837

Mavinkurve-Groothuis AM, van der Flier M, Stelma F et al (2013) Absolute lymphocyte count predicts response to new influenza virus H1N1 vaccination in pediatric cancer patients. Clin Vaccine Immunol 20:118–121

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

Meisel R, Toschke AM, Heiligensetzer C et al (2007) Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukaemia. Br J Haematol 137:457–460

Meral A, Sevinir B, Günay Ü (2000) Efficacy of immunization against hepatitis B virus infection in children with cancer. Med Pediatr Oncol 35:47–51

Moritz B, Eder J, Meister B et al (2001) Intact T-cell regenerative capacity in childhood acute lymphoblastic leukemia after remission induction therapy. Med Pediatr Oncol 36:283–289

Moulik NR, Kumar A, Jain A, Jain P (2013) Measles outbreak in a pediatric oncology unit and the role of ribavirin in prevention of complications and containment of the outbreak. Pediatr Blood Cancer 60:e122–e124

Mustafa MM, Buchanan GR, Winick NJ et al (1998) Immune recovery in children with malignancy after cessation of chemotherapy. J Pediatr Hematol Oncol 20:451–457

Nevin J, Washko JK, Arnold J (2013) Haemophilus influenzae type b in an immunocompetent, fully vaccinated ALL survivor. Pediatrics 131:e1639–e1642

Nilsson A, De Milito A, Engström P et al (2002) Current chemotherapy protocols for childhood acute leukemia induce loss of humoral immunity to viral vaccination antigens. Pediatrics 109:e91

Ninane J, Latinne D, Heremans-Bracke MT et al (1985) Live varicella vaccine in severely immunodepressed children. Postgrad Med J 61:97–102

Ogra PL, Sinks LF, Karzon DT (1971) Poliovirus antibody response in patients with acute leukemia. J Pediatr 79:444–449

Orange JS, Hossny EM, Weller CR et al (2006) Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma, and Immunology. J Allergy Clin Immunol 117:S525–S553

Orenstein W, Heymann D, Ellis R et al (1981) Prophylaxis of varicella in high risk children: response effect of zoster immune globulin. J Pediatr 98:368–373

Patel SR, Ortin M, Cohen BJ et al (2007) Revaccination of children after completion of standard chemotherapy for acute leukemia. Clin Infect Dis 44:635–642

Patel SR, Bate J, Borrow R et al (2012) Serotype-specific pneumococcal antibody concentrations in children treated for acute leukaemia. Arch Dis Child 97: 46–48

Paulides M, Stöhr W, Laws H et al (2011) Antibody levels against tetanus and diphtheria after polychemothearpy for childhood sarcoma: a report from the Late Effects Surveillance System. Vaccine 29:1565–1568

Porter CC, Edwards KM, Zhu Y et al (2004) Immune responses to influenza immunization in children receiving maintenance chemotherapy for acute lymphoblastic leukemia. Pediatr Blood Cancer 42:36–40

Poulsen A, Schmiegelow K, Yssing M (1993) Varicella zoster infections in children with acute lymphoblastic leukemia. Leuk Lymphoma 9:177–192

Reinhardt D, Houliara K, Pekrun A et al (2003) Impact of conventional chemotherapy on levels of antibodies against vaccine-preventable diseases in children treated for cancer. Scand J Infect Dis 35:851–857

Robinson P, Anderson D, Brouwers M et al (2007) Evidence-based guidelines on the use of intravenous immune globulin for hematologic and neurologic conditions. Transfus Med Rev 21:S3–S8

Royal College of Paediatrics and Child Health (RCPCH) (2002) Immunisation of the immunocompromised child—best practice statement. London, RCPCH

Ruggiero A, Battista A, Coccia P et al (2011) How to manage vaccinations in children with cancer. Pediatr Blood Cancer 57:1104–1108

Sartori AM (2004) A review of the varicella vaccine in immunocompromised individuals. Int J Infect Dis 8:259–270

Schafer AI, Churchill H, Ames P et al (1979) The influence of chemotherapy on response of patients with hematologic malignancies to influenza vaccine. Cancer 43:25–30

Schrauder A, Henke-Gendo C, Seidemann K et al (2007) Varicella vaccination in a child with acute lymphoblastic leukaemia. Lancet 369:1232

Sevinir B, Meral A, Günay Ü et al (2003) Increased risk of chronic hepatitis in children with cancer. Med Pediatr Oncol 40:104–110

Shahgholi E, Ehsani MA, Salamati P et al (2010) Immunogenicity of trivalent influenza vaccine in children with acute lymphoblastic leukemia during maintenance therapy. Pediatr Blood Cancer 54: 716–720

Shahin K, Lina B, Billaud G et al (2012) Successful H1N1 influenza vaccination of children receiving chemotherapy for solid tumors. J Pediatr Hematol Oncol 34:e228–e231

Shenep JL, Peldman S, Gigliotti F (1994) Response of immunocompromised children with solid tumors to a conjugate vaccine for Haemophilus influenzae type b. J Pediatr 125:581–584

Shinjoh M, Takahashi T (2009) Varicella zoster exposure on paediatric wards between 2000 and 2007: safe and effective postexposure prophylaxis with oral acyclovir. J Hosp Infect 72:163–168

Siber GR (1980) Bacteremias due to Haemophilus influenzae and Streptococcus pneumoniae: their occurrence and course in children with cancer. Am J Dis Child 134:668–672

Sinisalo M, Aittoniemi J, Käyhty H et al (2002) Haemophilus influenzae type b antibody concentrations and vaccination responses in patients with chronic lymphocytic leukaemia: predicting factors for response. Leuk Lymphoma 43:1967–1969

Sinisalo M, Vipo J, Itälä M et al (2007) Antibody response to 7-valent conjugated pneumococcal vaccine in patients with chronic lymphocytic leukaemia. Vaccine 26:82–87

Smith S, Schiffman G, Karayalcin G et al (1995) Immunodeficiency in long-term survivors of acute lymphoblastic leukemia treated with Berlin-Frankfurt-Münster therapy. J Pediatr 127:68–75

Smithson WA, Siem RA, Ritts RE et al (1978) Response to influenza virus vaccine in children receiving chemotherapy for malignancy. J Pediatr 93:632–634

Somjee S, Pai S, Kelkar R et al (1999) Hepatitis B vaccination in children with acute lymphoblastic leukemia: results of an intensified immunization schedule. Leuk Res 23:365–367

Somjee S, Pai S, Parikh P et al (2002) Passive active prophylaxis against hepatitis B in children with acute lymphoblastic leukemia. Leuk Res 26:989–992

Steinherz PG, Brown AE, Gross PA et al (1980) Influenza immunization of children with neoplastic diseases. Cancer 45:750–756

Suga S, Yoshikawa T, Ozaki T et al (1993) Effect of oral acyclovir against primary and secondary viraemia in incubation period of varicella. Arch Dis Child 69: 639–642

Sumaya CV, Williams TE, Brunell PA (1977) Bivalent influenza vaccine in children with cancer. J Infect Dis 156:S656–S660

Sung L, Heurter H, Zokic KM et al (2001) Practical vaccination guidelines for children with cancer. Paediatr Child Health 6:379–383

Takahashi M, Kamiya H, Baba K et al (1985) Clinical experience with Oka live varicella vaccine in Japan. Postgrad Med J 61:61–67

Timitilli A, Bertoluzzo L, Micalizzi C et al (2008) Antivaricella-zoster vaccination in contacts of children receiving antineoplastic chemotherapy: a prospective pilot study. Infez Med 16:144–147

Van der Does-van den Berg A, Hermans J, Nagel J et al (1981) Immunity to diphtheria, pertussis, tetanus, and poliomyelitis in children with acute lymphocytic leukemia after cessation of chemotherapy. Pediatrics 67:222–229

Van Tilburg CM, Sanders EA, Rovers MM et al (2006) Loss of antibodies and response to (re-)vaccination in children after treatment for acute lymphocytic leukemia: a systematic review. Leukemia 20: 1717–1722

Van Tilburg CM, Bierings MB, Berbers GA et al (2012) Impact of treatment reduction for childhood acute lymphoblastic leukemia on serum immunoglobulins and antibodies against vaccine-preventable disease. Pediatr Blood Cancer 58:701–707

Von der Hardt K, Jüngert J, Beck JD et al (2000) Humoral immunity against diphtheria, tetanus and poliomyelitis after antineoplastic therapy in children and adolescents—a retrospective analysis. Vaccine 18: 2999–3004

Weisman SJ, Cates KL, Allegretta GJ et al (1987) Antibody response to immunization with Haemophilus influenzae type b polysaccharide vaccine in children with cancer. J Pediatr 111:727–729

Wong-Chew RM, Frías MN, García-León ML et al (2012) Humoral and cellular immune responses to influenza vaccination in children with cancer receiving chemotherapy. Oncol Lett 4:329–333

Yen TY, Jou ST, Yang YL et al (2011) Immune response to 2009 pandemic H1N1 influenza virus A monovalent vaccine in children with cancer. Pediatr Blood Cancer 57:1154–1158

Yetgin S, Tunç B, Koç A et al (2001) Two booster dose hepatitis B virus vaccination in patients with leukemia. Leuk Res 25:647–649

Yetgin S, Tavil B, Aytac S et al (2007) Unexpected protection from infection by two booster hepatitis B virus

vaccination in children with acute lymphoblastic leukemia. Leuk Res 31:493–496

Yu JW, Borkowski A, Danzig L et al (2007) Immune response to conjugated meningococcal C vaccine in pediatric oncology patients. Pediatr Blood Cancer 49:918–923

Zaia J, Levin M, Preblud S et al (1983) Evaluation of varicella-zoster immune globulin: protection of immunosuppressed children after household exposure to varicella. J Infect Dis 147:737–743

Zengin E, Sarper N (2009) Humoral immunity to diphtheria, tetanus, measles, and hemophilus influenzae type b in children with acute lymphoblastic leukemia and response to re-vaccination. Pediatr Blood Cancer 53: 967–972

Zignol M, Peracchi M, Tredello G et al (2004) Assessment of humoral immunity to poliomyelitis, tetanus, hepatitis B, measles, rubella, and mumps in children after chemotherapy. Cancer 101:635–641