Effectiveness of prophylactic intravenous immunoglobulins in preventing infection in pediatric oncology patients: a systematic review protocol

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Review question/objective: The objective of this review is to identify the effectiveness of prophylactic intravenous immunoglobulins (IVIGs) for the prevention of infection in pediatric oncology patients, and to identify which types of patients would benefit from the intervention, such as patients with specific diagnoses or those with previous infections. A further objective of this review is to identify the effectiveness of prophylactic IVIGs on the prevention of diffuse interstitial pneumonitis and mortality in pediatric oncology patients.

The review questions are:
- Does the administration of prophylactic IVIGs prevent infection compared with no IVIG administration in pediatric oncology patients?
- Would only specific pediatric oncology patients benefit from prophylactic IVIG administration, and if so, which type of pediatric oncology patients?
- Does administration of prophylactic IVIGs decrease episodes of diffuse interstitial pneumonitis in pediatric oncology patients?
- Does administration of prophylactic IVIGs decrease mortality in pediatric oncology patients?

Keywords carcinoma; leukemia; oncology; pediatric; prophylactic intravenous immunoglobulins

Background

Over 200,000 children are diagnosed with cancer annually around the world.1 Although technological, pharmaceutical and medical advances have increased survival from pediatric cancers in most industrialized nations, morbidity and mortality secondary to infections in this immunocompromised population remain high. In 2009, the Agency of Healthcare Research and Quality reported 7300 hospitalizations secondary to infection in 73,300 children in the United States admitted with a secondary diagnosis of cancer. The primary diagnoses for these hospitalizations included fever or unknown origin, septicemia, pneumonia, viral infection or influenza.2 For many of these children infection ends in death. One large study conducted in the United States reviewed pediatric intensive care admissions and deaths of pediatric cancer patients. Of the 16,085 admissions to the pediatric ICU of children with malignancies, 10,365 were related to infections, which resulted in 730 deaths or 4.6% of those admissions.3 Another study compared mortality of adolescents and young adults (AYA) with younger children. Of the 42 deaths in the AYA population, 36 (85.7%) of non-transplant deaths in the AYA population stemmed from infection.4 Bone marrow transplantation patients receive intense chemotherapy and radiation treatments destroying their immune systems. These patients are at very high risk for multiple types of infections. Pneumonia occurs in up to 50% of bone marrow transplant recipients and is one of the main causes of mortality. These pneumonia manifests as focal or diffuse interstitial pneumonitis.5 Despite treatment with modern medications, many children with cancer continue to die from infections for which further investigation into the prevention of infection versus treatment is required.

Children receiving immunosuppressive therapies and their caregivers are instructed to be vigilant about notifying their healthcare providers regarding fever. Febrile neutropenia is typically one oral...
Febrile neutropenia can be caused by multiple factors, including bacteria, viruses, fungi, inflammatory reactions to the cancer, drug reactions or hosts of other cause, including fever of unknown origin. Febrile neutropenia can escalate quickly into a fulminant, life-threatening sepsis if left untreated. Children with febrile neutropenia usually require costly in-hospital treatments with intravenous antibiotic administration. In Canada, a standard hospitalization for treatment of febrile neutropenia in the pediatric oncology patient costs C$14,493. In Australia, hospitalization to treat gram-negative bacteremia averages a 14-day in-patient stay with 1.6 of those days requiring complex medical care in the ICU. Of those patients, 5.2% require invasive ventilation. Prevention of infections would greatly decrease in-patient hospital costs and increase patient quality of life. One solution may be prevention of infections through prophylactic administration of intravenous immunoglobulins (IVIGs).

Intravenous immunoglobulins are therapeutic preparations of concentrated normal human immunoglobulin, primarily immunoglobulin G (IgG), that are obtained and pooled from healthy blood donors containing a wide spectrum of antibacterial and antiviral properties. Administration of IVIG transfers passive immunity to a patient. The IgG protects against bacterial diseases by neutralizing toxins, facilitating opsonization of microbial organisms by altering them so they may be engulfed by host phagocytes and stimulating the host’s complement system to attack organisms resulting in bacteriolysis. Immunoglobulin G protects against viral disease by blocking the entry of viruses into healthy cells, promoting antibody-directed cell-mediated cytotoxicity by natural killer cells and neutralizing viruses directly or with the help of the complement system.

Intravenous immunoglobulins may also be considered a replacement for antibiotics and antivirals that are no longer proving to be efficacious. Recently, bacterial pathogens have become increasingly resistant to important antimicrobials in the neutropenic population and are once again endangering the lives of these patients. Antibiotics that once killed common Enterococcus and Staphylococcus organisms are no longer effective. New, seemingly benign viral infections are resulting in increased morbidity and mortality. Therefore, finding new preventive antibacterial and antiviral measures becomes exceedingly important. One study demonstrated that the use of prophylactic antibiotics in pediatric patients with cancer was associated with increased antimicrobial resistance rates and recommended preventive measures be instituted to decrease the rate of emergence of multiresistant pathogens. The study of IVIG therapy in the adult and pediatric cancer population is scant. A search of international research resulted in conflicting reports. Some authors note that considerable data exist to support passive immune therapeutic measures in both primary and secondary causes of immunosuppression. Other literature proposes the use of IVIG in specific cancer populations, such as those with chronic lymphocytic leukemia and multiple myeloma. One report recommends IVIG use for those patients with recurrent bacterial infections rather than prophylactic administration. Other authors propose that IVIG therapy cannot be recommended to the same populations described above.

Two quantitative systematic reviews using IVIG were identified in the literature. The first review was a meta-analysis of randomized controlled trials of adult patients with chronic lymphocytic leukemia or multiple myeloma and those undergoing bone marrow or stem cell transplantation, which recommended use of prophylactic IVIG in those populations. The second systematic review of prophylaxis and treatment of viral infections in pediatric patients with malignancies focused on specific viruses and recommended prophylaxis or treatment with hyperimmunoglobulin administrations, such as varicella zoster immune globulin for varicella exposure or palivizumab, as a treatment option for respiratory syncytial virus. The identified systematic reviews focused on adults or specialized immunoglobulin therapy rather than children alone with non-specific IVIG containing broad antibacterial and antiviral coverage specifically administered prophylactically to prevent rather than treat infection. The high rate of morbidity and mortality in the pediatric oncology population secondary to infection along with ever-increasing antimicrobial resistance and minimal antiviral therapies available requires a systematic review to evaluate the effectiveness of prophylactic IVIG in the pediatric oncology population. This systematic review aims to determine if and under which circumstances, such
as specific diagnoses or previous infection, the administration of prophylactic IVIG would decrease morbidity and/or mortality in immunocompromised children undergoing chemotherapy.

Inclusion criteria

Types of participants

The review will consider studies that include pediatric and adolescent patients, undergoing chemotherapy, diagnosed and treated for any blood or solid malignancy resulting in an immunocompromised state as noted by neutropenia of less than 500 cells/μl. Patients with or without previously documented infection will be included as these patients are at risk for recurrent infections from various sources and prevention of any new infection is desired. Patients being treated by pediatric oncologists or grouped as pediatric patients will be included. The age range will be set from birth through 22 years of age. This wide age range was decided upon as a review of literature in this area demonstrated study patients categorized as pediatric through age 22 years.

Types of intervention(s)/phenomena of interest

The review will consider studies that evaluate prophylactic administration of IVIGs for prophylactic prevention of infection in pediatric oncology patients. The control that will be compared with those receiving IVIGs will be those patients who were not administered IVIGs for prevention of fever. All brands, doses and administration frequencies, as long as administered for preventive and not treatment purposes, of IVIGs will be included. Studies which have no control group will be excluded.

Outcomes

The review will consider studies that include the following outcome measures: incidence of infections, incidence of diffuse interstitial pneumonitis and mortality secondary to infection. Outcomes will be measured by comparing the number of patients who received prophylactic IVIGs and acquired infection with those patients who did not receive prophylactic IVIG and acquired infection. Secondary outcomes will be measured by comparing the number of patients who received prophylactic IVIGs and acquired diffuse interstitial pneumonia with those patients who did not receive prophylactic IVIG and acquired diffuse interstitial pneumonia as well as comparing the number of patients who received prophylactic IVIG and died from infection with those who did not receive prophylactic IVIG and died from infection.

Types of studies

The review will consider both experimental and epidemiological study designs, including randomized controlled trials, non-randomized controlled trials, quasi-experimental, controlled before and after studies, prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies for inclusion.

Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of PubMed and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract and the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review. No limitations of publication dates will be applied to this search.

The databases to be searched include: PubMed, CINAHL, Scopus, Ovid Healthstar, Cochrane Central Register of Controlled Trials, Embase

The search for unpublished studies will include: WORLDCAT for dissertations and theses, Google Scholar

Initial keywords to be used will be: pediatric, child, adolescent, leukemia, carcinoma, neoplasms, cancer, tumor, tumour, hematologic neoplasms, malignancy, immunoglobulin, globulin, infection, febrile neutropenia, childhood cancer

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.
Data extraction

Data will be extracted from studies included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Quantitative data will, wherever possible be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard $\chi^2$ and also explored using subgroup analyses based on the different study designs included in this review. A subgroup analysis will be used, if possible, to identify which types of patients would benefit from the intervention. Where statistical pooling is not possible, the findings will be presented in narrative form, including tables and figures to aid in data presentation, wherever appropriate.

References

Appendix I: Appraisal instruments

**MAStARI appraisal instrument**

### JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

**Reviewer**  
**Date**

**Author**  
**Year**  
**Record Number**

1. Was the assignment to treatment groups truly random?  
2. Were participants blinded to treatment allocation?  
3. Was allocation to treatment groups concealed from the allocator?  
4. Were the outcomes of people who withdrew described and included in the analysis?  
5. Were those assessing outcomes blind to the treatment allocation?  
6. Were the control and treatment groups comparable at entry?  
7. Were groups treated identically other than for the named interventions?  
8. Were outcomes measured in the same way for all groups?  
9. Were outcomes measured in a reliable way?  
10. Was appropriate statistical analysis used?  

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**Overall appraisal:**  
**Include**  
**Exclude**  
**Seek further info.**

**Comments (Including reason for exclusion)**

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### JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

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<td>1. Is sample representative of patients in the population as a whole?</td>
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Overall appraisal: Include □ Exclude □ Seek further info. □

Comments (Including reason for exclusion)
Appendix II: Data extraction instrument

**MAStARI data extraction instrument**

**JBI Data Extraction Form for Experimental / Observational Studies**

Reviewer  Date

Author  Year

Journal  Record Number

**Study Method**

RCT  Quasi-RCT  Longitudinal

Retrospective  Observational  Other

**Participants**

Setting

Population

**Sample size**

Group A  Group B

**Interventions**

Intervention A

Intervention B

**Authors Conclusions:**

**Reviewers Conclusions:**
Study results

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