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Protocol for updating a Systematic Review of Randomized Controlled Trials on the prophylactic use of Intravenous Immunoglobulin for patients undergoing Hematopoietic Stem Cell Transplantation

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Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Infectious diseases, Oncology, Immunology (including allergy)
Keywords:	Immunoglobulin, Prophylaxis, Hematopoietic stem cell transplantation, clinical outcomes

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Abstract

Introduction: Hematopoietic Stem Cell Transplantation (HSCT) is commonly employed in the management of hematological malignancies. This intervention results in an increased risk of infectious and immune related complications. Prophylactic immunoglobulin therapy has been used to prevent post-HSCT complications including infections with varying efficacy. We sought to update the current evidence supporting the use of immunoglobulins in the modern HSCT era.

Methods/Analysis: Using a structured search strategy, we will perform a systematic review of the literature from MEDLINE, EMBASE and all EBM Reviews databases. We will include randomized clinical trials investigating clinical outcomes of prophylactic polyvalent immunoglobulin or CMV specific immunoglobulin or plasma in patients undergoing HSCT. Clinical outcomes will include overall survival, transplant-related mortality, CMV infection, CMV disease, graft versus host disease, interstitial pneumonitis/fibrosis, and hepatic veno-occlusive disease. Studies that only reported the results of biochemical tests will be excluded. Data will be extracted by two investigators independently. Study quality assessment will be evaluated using a validated five point system as proposed by Jadad. Trial quality will be further assessed by identifying whether there was adequate allocation concealment. Where appropriate, a meta-analysis will be performed where relative risk will be used as the primary summary measure with 95% confidence intervals. Pooled measures will be calculated for randomized clinical trials using a random effects model. The Cochrane Q/Chi squared test and I^2 statistic will also be calculated to evaluate heterogeneity. We will also use a visual inspection of a funnel plot to assess potential publication bias.

Discussion: This systematic review aims to provide current evidence to justify the use of immunoglobulin prophylaxis in HSCT recipients. We will discuss whether current HSCT guidelines are supported by the current evidence, and whether further trials are needed given the changing landscape of patients undergoing HSCT and immunoglobulin manufacturing process.

Systematic review registration: PROSPERO CRD42015016684

Keywords: Immunoglobulin, prophylaxis, hematopoietic stem cell transplantation, clinical outcomes

Strengths and Limitations

- Rigorous study selection, data extraction, quality assessment and data synthesis
- Predefined priori sensitivity analyses
- There may be limited number of recent trials representing HSCT population in the modern era

Introduction

Hematopoietic Stem Cell Transplantation (HSCT) is commonly employed in the management of a variety of malignancies[1, 2]. High dose chemotherapy and/or radiotherapy are given to maximize the tumoricidal effects, followed by the timely infusion of stem cells to reconstitute the bone marrow and immune system. Pancytopenia and immunodeficiency from therapy may cause potentially fatal bacterial, viral or fungal infections such as cytomegalovirus (CMV) and immune complications such as graft versus host disease[3-5] following transplantation.

Intravenous immunoglobulin is a complex biologic product with multiple potential mechanisms of action[6]. Intravenous immunoglobulin (IVIG) is used in many HSCT centres to prevent infectious complication post HSCT[7, 8]. For instance, at our centre we have previously reported 31 and 13 doses of IVIG use during the first month post-HSCT in 77 autologous and 39 allogeneic transplant recipients[9]. CMV specific immunoglobulin and plasma preparations are also available, and have been reported to be superior to polyvalent intravenous immunoglobulin in the management of CMV infections[10, 11]. However, a recent systematic review of immunoglobulin prophylaxis did not demonstrate a mortality benefit but rather an increased risk of veno-occlusive side effect[12]. Consequently, current societal guidelines do not recommend the routine use of immunoglobulin prophylaxis in recipients of HSCT[13, 14]. However, the clinical trials included in the previous systematic review were mostly published before the year 2000[12]. Further, there are other limitations in this review that deserve mention. Firstly, the review included non-randomized studies[15]; secondly, some studies only looked at biochemical surrogates, and lastly, results from higher quality studies were not separately analyzed. Moreover, the landscape of patients receiving HSCT has evolved in the past decade. Patients

undergoing HSCT are older and are more likely to be immunocompromised[16]. Further, HSCT technology including conditioning and chemo-suppressive measures has also evolved[2, 17-19]. Finally, the technology of immunoglobulin production has evolved which resulted in intact IgG preparations with normal half-life and effector functions, and with higher pathogen safety[20]. Taken together, the prior available evidence may not be adequate to inform current HSCT practice.

We sought to conduct a comprehensive systematic review of available evidence from prospective randomized controlled clinical trials assessing the use of immunoglobulins in hematopoietic stem cell transplantation and reporting clinically important endpoints.

Aims, objectives

This systematic review aims to update, summarize and quantify the clinical effects of prophylactic immunoglobulins in the context of HSCT. We will also review and discuss current guidelines with respect to infectious complication prevention in HSCT.

Methods/Design

Search strategy

The systematic search strategy will include MEDLINE (1966 to February 2015), EMBASE (1980 to February 2015) and all EBM Reviews (December 2014). A Dickersin filter[21] will be used to aid identification of randomized controlled trials (RCTs). A Google Scholar search will be performed in order to identify any grey literature. Studies relevant to animals but not humans will be excluded. Publications regardless of language or whether they were published as

conference proceedings, abstracts or journals will be included in our review. Local hematopoietic stem cell transplant physicians will also be approached to identify additional relevant studies/trials. References to selected articles will be examined by 2 reviewers (JT and JC) to identify relevant citations.

Draft of search strategy

Database: Embase Classic+Embase <1947 to 2015 February >, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

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4 stem cell transplant$.tw.
5 Peripheral Blood Stem Cell Transplantation/ or pbsct.tw.
6 (peripheral blood cell transplant$ or peripheral blood stem cell transplant$ or peripheral stem cell transplant$).tw.
7 Bone Marrow Transplantation/ or (bone marrow transplant$ or bmt).tw.
8 blood transplant$.tw.
9 ((autologous or allogeneic or allogenic) adj2 (transplant$ or graft$)).tw.
10 or/1-9
11 exp Immunoglobulins/ and (exp Immunization, Passive/ or exp Administration, Intravenous/ or exp Injections, Subcutaneous/ or exp Infusions, Subcutaneous/)
12 Immunoglobulin$.tw.
13 Immune Globulin$.tw.
14 (ivig or (Intravenous adj5 IG) or (iv adj5 ig) or (iv adj5 igg)).tw.
15 or/11-14
16 10 and 15
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 random$.tw.
20 placebo.ab.
21 clinical trials as topic.sh.
22 trial.ti.
23 or/17-22
24 animals/ not humans/
25 23 not 24
26 16 and 25
27 guideline.pt.
28 practice guideline.pt.
29 guidelines as topic/ or practice guidelines as topic/
30 guideline$.tw.
31 27 or 28 or 29 or 30
32 16 and 31

33 26 or 32
34 33 use prmz
35 exp hematopoietic stem cell transplantation/
36 h?ematopoietic stem cell transplant$.tw.
37 (hsct or h?ematopoietic sct).tw.
38 stem cell transplant$.tw.
39 peripheral blood stem cell transplantation/
40 pbsct.tw.
41 (peripheral blood cell transplant$ or peripheral blood stem cell transplant$ or peripheral stem cell transplant$).tw.
42 bone marrow transplantation/
43 (bone marrow transplant$ or bmt).tw.
44 blood transplant$.tw.
45 ((autologous or allogeneic or allogenic) adj2 (transplant$ or graft$)).tw.
46 or/35-45
47 exp immunoglobulin/iv, sc [Intravenous Drug Administration, Subcutaneous Drug Administration]
48 exp immunoglobulin/ and (intravenous drug administration/ or subcutaneous drug administration/ or passive immunization/)
49 immunoglobulin$.tw.
50 Immune Globulin$.tw.
51 (ivig or (Intravenous adj5 IG) or (iv adj5 ig) or (iv adj5 igg)).tw.
52 or/47-51
53 46 and 52
54 random$.tw. or placebo$.mp. or double-blind$.tw.
55 practice guideline/
56 guideline$.tw.
57 54 or 55 or 56
58 53 and 57
59 58 use emczd
60 34 or 59
61 remove duplicates from 60
62 61 use prmz Medline Search
63 61 use emczd Embase Search

Inclusion and exclusion criteria

Inclusion criteria will be prospective randomized controlled clinical trials, patients undergoing hematopoietic stem cell transplantation, patients receiving polyvalent intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG), CMV specific immunoglobulin or plasma (CMVIG) prophylaxis, use of a comparator arm, studies reporting clinical outcomes of Overall survival (Primary Outcome), Transplant related mortality, CMV

infections, CMV diseases, non-CMV Infections, graft versus host disease, interstitial pneumonitis and veno-occlusive disease. Studies that only reported the results of biochemical tests will be excluded from our review.

Outcome measures

Primary outcome: overall survival is defined as survival with varying following follow-up times as defined by the individual studies (at least 100 days).

Secondary outcomes: 1) Transplant related mortality is defined as death within 100-120 days of hematopoietic stem cell transplantation. 2) CMV Infection is defined as recovery of the virus from the throat, urine or blood, seroconversion of a patient or significant increase in CMV viral copies in the absence of any clinical signs or symptoms of disease. 3) CMV Disease is defined as symptomatic infection, recovery of virus from a visceral site or histologic evidence of infection. 4) Hepatic veno-occlusive disease is broadly defined as weight gain or fluid accumulation, elevated bilirubin and abdominal pain. 5) Graft versus host disease and interstitial pneumonitis/fibrosis is defined by the individual studies.

Data extraction

Two reviewers (JT & JC) will independently review the abstracts and apply our trial eligibility criteria. Any discrepancies will be documented, discussed and adjudicated by a third party (BC). The 2 reviewers (JT & JC) will assess trial quality and extract the data using a standardized data abstraction form and data entry onto Microsoft Excel to assist with data management. Similarly, discrepancies will be documented, discussed and adjudicated by a third party (BC).

Quality assessment

The methodological quality of randomized studies will be evaluated by two reviewers (JT & JC) using a validated 5 point system as proposed by Jadad[22]. A quality score of 3 or greater will be considered high quality[22]. Trial quality will be further assessed by identifying whether there was adequate allocation concealment[23]. The quality of evidence across studies will be assessed for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Data analysis/synthesis

Relative risk will be used as the primary summary measure with 95% confidence intervals. Pooled measures will be calculated for randomized clinical trials using a random effects model. A relative risk of less than 1 would suggest a beneficial effect of intravenous immunoglobulin, while a relative risk of greater than 1 would suggest a harmful effect. Individual trial estimates and pooled estimates will be performed using the Review Manager software (Cochrane Collaboration's Information Management System)[24]. The Cochrane Q/Chi squared test and I^2 statistic will also be calculated to evaluate heterogeneity. We will use a visual inspection of a funnel plot to assess potential publication bias[25, 26].

We will perform several a priori sensitivity analyses to understand the data and to identify any subpopulations that may benefit from the use of intravenous immunoglobulin. These analyses include: type of hematopoietic stem cell transplantation (autologous or allogeneic), type of intravenous immunoglobulin used (IVIG or CMVIG), dose of IVIG used (≤2g/kg, >2g/kg,

≤5g/kg and >5g/kg), IgG levels (IgG < 4g/L and ≥ 4 g/L), methological quality of RCTs (Jadad scores ≥3 or <3), as well as year of publication of the study (before or after 2000).

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. The narrative synthesis will explore the relationship and findings both within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination

Discussion

A systematic review of immunoglobulin prophylaxis in HSCT published in 2009 analysed thirty studies[12]. Some were not randomised controlled-trials or only measured biochemical test results. Most studies were published before the year 2000 when patients were less complex. The current guidelines[14] recommended against use of prophylactic IVIG in HSCT although IVIG prophylaxis may be considered in patients with severe hypogammaglobulinemia (IgG < 4 g/L). The latter statement was not supported by strong evidence.

Our systematic review will update the current evidence on the use of immunoglobulin prophylaxis and may stimulate a re-evaluation of our current practice and practice guidelines. It is likely that the available data is outdated and more current randomized trials are required to inform practice.

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Authors' contributions

JT is the guarantor. All authors conceived and designed the review. JC drafted the protocol. JT critically reviewed and revised the protocol. JC and JT will perform the data extraction, data interpretation, and manuscript preparation. JT, DWC and GK will be consulted with the interpretation of results and preparation of the manuscript. All authors read and approved the final manuscript.

Stage of review

The review is at preliminary search stage.

Funding source

This work was supported by Department of Medicine Developmental Research Grant, University of Ottawa. Funder has no role in developing the protocol.

Competing interests

The listed authors do have not any relevant competing interests.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	p.1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	p.1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	p.3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	p.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	p.14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	p.14
Sponsor	5b	Provide name for the review funder and/or sponsor	p.14
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	p.14
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	p.4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	p.5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	p.5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	p.5-6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	p.6

Study records:			p.8
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	p.7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	p.8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	p.8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	p.8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	p.9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	p.9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	p.9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	p.9-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	p.10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	p.9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	p.9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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from higher quality studies were not separately analyzed, potentially introducing bias. Moreover, the landscape of patients receiving HSCT has evolved in the past decade. Patients undergoing HSCT are older and are more likely to be immunocompromised[16]. Further, HSCT technology including conditioning and chemo-suppressive measures has also evolved[2, 17-19]. Finally, the technology of immunoglobulin production has evolved which resulted in intact IgG preparations with normal half-life and effector functions, and with higher pathogen safety[20]. Taken together, the prior available evidence may not be adequate to inform current HSCT practice.

We seek to conduct a comprehensive systematic review of available evidence from prospective randomized controlled clinical trials assessing the use of immunoglobulins in hematopoietic stem cell transplantation that report clinically important endpoints.

Aims and Objectives

Our overarching objective is to update, summarize and quantify the clinical effects of prophylactic immunoglobulins in the context of HSCT. Specifically, we seek to evaluate the utility of peri-HSCT use of IVIG on mortality, post-HSCT complications, infections and relapse post-HSCT.

Methods/Design

Search strategy

The systematic search strategy will include MEDLINE (1966 to February 2015), EMBASE (1980 to February 2015) and all EBM Reviews (December 2014). A Dickersin filter[21] will be

used to aid identification of randomized controlled trials (RCTs). A Google Scholar search will be performed in order to identify any grey literature. Studies relevant to animals but not humans will be excluded. Publications regardless of language or whether they were published as conference proceedings, abstracts or journals will be included in our review. Local hematopoietic stem cell transplant physicians will also be approached to identify additional relevant studies/trials. References to selected articles will be examined by 2 reviewers (JT and JC) to identify relevant citations.

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9 ((autologous or allogeneic or allogenic) adj2 (transplant$ or graft$)).tw.
10 or/1-9
11 exp Immunoglobulins/ and (exp Immunization, Passive/ or exp Administration, Intravenous/ or exp Injections, Subcutaneous/ or exp Infusions, Subcutaneous/)
12 Immunoglobulin$.tw.
13 Immune Globulin$.tw.
14 (ivig or (Intravenous adj5 IG) or (iv adj5 ig) or (iv adj5 igg)).tw.
15 or/11-14
16 10 and 15
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 random$.tw.
20 placebo.ab.
21 clinical trials as topic.sh.
22 trial.ti.
23 or/17-22
24 animals/ not humans/
25 23 not 24
26 16 and 25

27 guideline.pt.
28 practice guideline.pt.
29 guidelines as topic/ or practice guidelines as topic/
30 guideline$.tw.
31 27 or 28 or 29 or 30
32 16 and 31
33 26 or 32
34 33 use prmz
35 exp hematopoietic stem cell transplantation/
36 h?ematopoietic stem cell transplant$.tw.
37 (hsct or h?ematopoietic sct).tw.
38 stem cell transplant$.tw.
39 peripheral blood stem cell transplantation/
40 pbsct.tw.
41 (peripheral blood cell transplant$ or peripheral blood stem cell transplant$ or peripheral stem cell transplant$).tw.
42 bone marrow transplantation/
43 (bone marrow transplant$ or bmt).tw.
44 blood transplant$.tw.
45 ((autologous or allogeneic or allogenic) adj2 (transplant$ or graft$)).tw.
46 or/35-45
47 exp immunoglobulin/iv, sc [Intravenous Drug Administration, Subcutaneous Drug Administration]
48 exp immunoglobulin/ and (intravenous drug administration/ or subcutaneous drug administration/ or passive immunization/)
49 immunoglobulin$.tw.
50 Immune Globulin$.tw.
51 (ivig or (Intravenous adj5 IG) or (iv adj5 ig) or (iv adj5 igg)).tw.
52 or/47-51
53 46 and 52
54 random$.tw. or placebo$.mp. or double-blind$.tw.
55 practice guideline/
56 guideline$.tw.
57 54 or 55 or 56
58 53 and 57
59 58 use emczd
60 34 or 59
61 remove duplicates from 60
62 61 use prmz Medline Search
63 61 use emczd Embase Search

Inclusion and exclusion criteria

Inclusion criteria will be prospective randomized controlled clinical trials, patients undergoing hematopoietic stem cell transplantation, patients receiving polyvalent intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG), CMV specific

immunoglobulin or plasma (CMVIG) prophylaxis, use of a comparator arm, studies reporting clinical outcomes of Overall survival (Primary Outcome), Transplant related mortality, CMV infections, CMV diseases, non-CMV Infections including bacterial, fungal, other viral infections, graft versus host disease, interstitial pneumonitis veno-occlusive disease and relapse of the underlying hematologic condition. Studies that only reported the results of biochemical tests will be excluded from our review given the potential that it may not correlate with patient centered hard outcomes.

Outcome measures

*Primary outcome***:** overall survival is defined as survival with varying following follow-up times as defined by the individual studies (at least 100 days).

Secondary outcomes: 1) Transplant related mortality. 2) CMV Infection. 3) CMV Disease. 4) Non-CMV infection which will be further stratified to bacterial, fungal and other viral infection. 5) Hepatic veno-occlusive disease is broadly defined as weight gain or fluid accumulation, elevated bilirubin and abdominal pain. 6) Graft versus host disease and interstitial pneumonitis/fibrosis is defined by the individual studies. 7) Disease relapse.

Definition

Transplant related mortality = death within 100-120 days of hematopietic stem cell transplantation

CMV infection = recovery of the virus from the throat, urine or blood, seroconversion of a patient or significant increase in CMV viral copies in the absence of any clinical signs or symptoms of disease

CMV disease = symptomatic infection, recovery of virus from a visceral site or histologic evidence of infection

Bacterial infection = reported infection due to microbiologically confirmed bacteria

Viral infection = reported infection due to microbiologically confirmed virus other than CMV

Fungal infection = reported infection due to microbiologically confirmed fungus

Data extraction

Two reviewers (JT & JC) will independently review the abstracts and apply our trial eligibility criteria. Any discrepancies will be documented, discussed and adjudicated by a third party (BC). The 2 reviewers (JT & JC) will assess trial quality and extract the data using a standardized data abstraction form and data entry onto Microsoft Excel to assist with data management. Similarly, discrepancies will be documented, discussed and adjudicated by a third party (BC).

Quality assessment

The methodological quality of randomized studies will be evaluated by two reviewers (JT & JC) using a validated 5 point system as proposed by Jadad[22]. A quality score of 3 or greater will be considered high quality[22]. Trial quality will be further assessed by identifying whether there was adequate allocation concealment[23]. The quality of evidence across studies will be assessed for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Risk of bias assessment

The following domains of potential bias will assessed by two reviewers (JT & JC) and any discrepancies will be discussed and adjudicated by DC and GK: 1) Selection bias (random sequence generation and allocation concealment), 2) Performance bias (Blinding of participants and personnel), 3) Detection bias (Blinding of outcome assessment), Attrition bias (Incomplete outcome data) and Reporting bias (Selective reporting)

Data analysis/synthesis

Relative risk will be used as the primary summary measure with 95% confidence intervals. Pooled measures will be calculated for randomized clinical trials using a random effects model. A relative risk of less than 1 would suggest a beneficial effect of intravenous immunoglobulin, while a relative risk of greater than 1 would suggest a harmful effect. Individual trial estimates and pooled estimates will be performed using the Review Manager software (Cochrane Collaboration's Information Management System)[24]. The Cochrane Q/Chi squared test and I^2 statistic will also be calculated to evaluate heterogeneity. We will use a visual inspection of a funnel plot to assess potential publication bias[25, 26].

We will perform several a priori sensitivity analyses to understand the data and to identify any subpopulations that may benefit from the use of intravenous immunoglobulin. These analyses include: type of hematopoietic stem cell transplantation (autologous or allogeneic), conditioning regimen, indication for transplant, type of intravenous immunoglobulin used (IVIG or CMVIG), dose of IVIG used (≤2g/kg, >2g/kg, ≤5g/kg and >5g/kg), IgG levels (IgG < 4g/L and ≥ 4 g/L),

methological quality of RCTs (Jadad scores ≥3 or <3), as well as year of publication of the study (before or after 2000).

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. The narrative synthesis will explore the relationship and findings both within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination

Discussion

A systematic review of immunoglobulin prophylaxis in HSCT published in 2009 analysed thirty studies[12]. Some were not randomised controlled-trials or only measured biochemical test results. Most studies (25/30) were published before the year 2000 when patients were less complex. The current guidelines[14] recommended against use of prophylactic IVIG in HSCT although IVIG prophylaxis may be considered in patients with severe hypogammaglobulinemia (IgG < 4 g/L). The latter statement was not supported by strong evidence.

Our systematic review will update the current evidence on the use of immunoglobulin prophylaxis and may stimulate a re-evaluation of our current practice and practice guidelines. It is likely that the available data is outdated and more current randomized trials are required to inform practice.

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Authors' contributions

JT is the guarantor. All authors conceived and designed the review. JC drafted the protocol. JT critically reviewed and revised the protocol. JC and JT will perform the data extraction, data interpretation, and manuscript preparation. JT, DWC and GK will be consulted with the interpretation of results and preparation of the manuscript. All authors read and approved the final manuscript.

Stage of review

The review is at preliminary search stage.

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Competing interests

The listed authors do have not any relevant competing interests.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	p.1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	p.1
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	p.3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	p.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	p.15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	p.15
Sponsor	5b	Provide name for the review funder and/or sponsor	p.15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	p.15
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	p.4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	p.5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	p.5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	p.5-6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	p.6

Study records:			p.7-9
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	p.7-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	p.9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	p.8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	p.8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	p.10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	p.10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	p.10-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	p.10-11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	p.10-11
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	p.9-10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	p.9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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