IMMUNE THROMBOCYTOPENIA GUIDELINES: A NOVEL METHODOLOGY

EMERGENCY MANAGEMENT OF CRITICAL BLEEDS IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA: DEVELOPING A NOVEL METHODOLOGY FOR RARE DISEASES GUIDELINES

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TITLE: Emergency management of critical bleeds in patients with immune thrombocytopenia: developing a novel methodology for rare diseases guidelines

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Lay Abstract

Guidelines for rare diseases can be hard to develop because of a lack of information. Doctors and researchers make decisions on rare disease management based on their experiences, which can be limited. Low blood platelets and emergency bleeding can be caused by a rare disease called immune thrombocytopenia (ITP). When emergency bleeds occur, patients need care from the Emergency Department immediately. The problem is that there is no standard way for doctors to treat these ITP bleeding emergencies.

My PhD thesis project will fill an important gap for ITP emergency treatment. First, we will assess how ITP patients are diagnosed. Second, we will define an ITP bleeding emergency. Third, we will collect existing information about ITP bleeds. Fourth, we will overcome the challenge of not having enough information by collecting new data from patient records. The method we use to develop ITP guidelines can be used for other rare diseases.

Abstract

Developing clinical practice guidelines (CPGs) for rare diseases is methodologically challenging. As each disease has so few patients, published literature includes low-quality studies or studies that do not directly address the questions of interest. As a result, CPG panelists have limited evidence on which to base their recommendations. Historically, when no evidence was available, CPGs have relied on physician opinion. This does not align with the mandate of CPGs which transparently identifies, appraises, and relies on evidence.

The challenges of developing CPGs for rare diseases are exemplified by immune thrombocytopenia (ITP), a rare autoimmune disease that affects approximately 1 in 8,000 people. It predominantly affects females and young adults, and is characterized by low blood platelets that increase the risk of bleeding. Bleeding emergencies in ITP patients are critical, life-threatening events that can cause life-long morbidity and associated health care costs. Treatment of ITP bleeding emergencies requires a rapid, coordinated approach that involves emergency department staff, hematologists, pharmacy, and the laboratory. However, there is no evidence-based CPG for the management of ITP bleeding emergencies.

The objectives of my PhD thesis are (1) exploring the heterogeneity of ITP diagnosis using antiplatelet autoantibodies; (2) developing a standardized definition of ITP bleeding emergencies; (3) outlining the synthesis of existing evidence on the treatment of ITP bleeding emergencies through a systematic review; and (4) developing a novel methodology to address the lack of evidence in rare disease CPGs and applying it to develop a CPG for the management of ITP bleeding emergencies.

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The day that I joined McMaster University and the Department of Health Research Methods, Evidence, and Impact as a Master student, I did not foresee the amazing journey I was embarking on or the impact of my academic achievements. I was continuously challenged to think critically and apply my ideas to real world problems. Seeing the opportunity to make a difference in clinical research and patient care inspired me to begin my PhD studies. Creating knowledge and applying it practically was a difficult task, however, the opportunities to share my research in a dynamic and complex field with the world fuelled my motivation. Completing a PhD has been an incredible privilege for which I will always be grateful.

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destination in my PhD journey, I know that we will continue to collaborate for many years to come.

1 Contents

Lists of Figures and Tables

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List of Abbreviations

ACD-A	Acid Citrate Dextrose Solution A
AML	Acute Myeloid Leukemia
ASH	American Society of Hematology
AUC	Area Under the Curve
CAPS	Catastrophic Antiphospholipid Syndrome
CBMTR	Center For Blood and Marrow Transplant Registry
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Intervals
CPG	Clinical Practice Guideline
ED	Emergency Department
GP	Glycoprotein
GRADE	Grading Of Recommendations, Assessment, Development, And Evaluation
ICH	Intracranial Hemorrhage
IgG	Immunoglobulin G
IQR	Interquartile Range
ITP	Immune Thrombocytopenia
ISTH	International Society for Thrombosis And Haemostasis
IVIG	Intravenous Immune Globulin
MEDLINE	Medical Literature Analysis and Retrieval System Online
NHF	National Hemophilia Foundation
NPV	Negative Predictive Values
OD	Optical Density
OR	Odds Ratio
PPV	Positive Predictive Values
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

PROSPERO	International Prospective Register of Systematic Reviews
PRP	Platelet-Rich Plasma
RBC	Red Blood Cell
RCT	Randomized Controlled Trials
SCD	Sickle Cell Disease
SD	Standard Deviation
SSC	Scientific Standardization Committee
TPO	Thrombopoietin
TPO-RA	Thrombopoietin Receptor Agonists

Declaration of Academic Achievement

I declare that the PhD thesis contained herein is my own work. This document has been prepared in the format of a "sandwich thesis" whereby it contains four individual studies prepared for publication in scholarly, peer-reviewed journals. At the time of writing, the first two studies have been published, Chapter 2 in British Journal of Haematology, and Chapter 3 in Journal of Thrombosis and Haemostasis. The third article has been submitted to the journal of Systematic Reviews. The fourth article is prepared for submission. The citations for all four articles can be found below.

With the guidance received by my primary supervisor, Dr. Donald Arnold, and my two committee members, Dr. Gordon Guyatt and Dr. Michael Walsh, I contributed to all three projects as follows: designing and conceptualizing the studies, collecting and analysing data, drafting the manuscripts, giving final approval of the manuscript versions and submitting them to the journals, addressing the peer-reviewed feedback received on the manuscript submissions, and proofing manuscripts accepted for publication. To varying extents, my co-authors on the manuscripts, assisted with the following tasks: collecting and analysing data, critically revising the manuscripts, and giving final approval of the manuscript versions to be submitted to the journals. The studies comprising this thesis were conducted between September 2018 and May 2022.

Thesis Study Citations:

1. Gabe, C., Sirotich, E., Li, N., Ivetic, N., Nazy, I., Smith, J., Kelton, J.G. and Arnold, D.M. (2021), Performance characteristics of platelet autoantibody testing for the diagnosis of immune thrombocytopenia using strict clinical criteria. Br. J. Haematol., 194: 439-443. https://doi-org.libaccess.lib.mcmaster.ca/10.1111/bjh.17566

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3. Sirotich, E, Nazaryan, H, Guyatt, G, et al. Treatment of critical bleeding events in patients with immune thrombocytopenia: a protocol for a systematic review and meta-analysis. Submitted March 14, 2022 to Systematic Reviews.
4. Private Communication from Emily Sirotich: Dept. of Health Research Methods, Evidence, and Impact, McMaster University.

1 Chapter 1: Introduction

1.1 Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is a rare, heterogenous acquired autoimmune platelet disorder characterized by thrombocytopenia, or a low blood platelet count of <100 x 10^9/L.[1] ITP affects approximately 1 in 8,000 adults and 1 in 10,000 children.[2-4] It predominantly affects females, with peak incidences in childhood, early adulthood (20-29 years) and late adulthood (>80 years).[4-7] Children often experience an acute onset of the disorder and most will spontaneously recover.[8,9]

Platelets are recruited from the circulating blood when a blood vessel is damaged and the normal endothelial-cell barrier is disrupted.[10] There is adhesion and aggregation of platelets to form an occlusive plug and stem the hemorrhage.[10] Normally, total platelet mass is regulated by a balance between production and clearance of platelets.[11] In ITP, platelet mass is reduced due to autoantibody-mediated destruction and impaired platelet production.[12-14] Platelet autoantibodies that target platelets or megakaryocytes are considered the primary cause of thrombocytopenia in patients with ITP.[12,15]

1.2 Diagnosis of ITP

There is currently no gold standard diagnostic testing for ITP.[16,17] In 2009, the international ITP working group established a standard definition for the diagnosis of primary ITP: platelet count of less than 100 × 10^9/L in the absence of an underlying cause.[1] Being a diagnosis of exclusion, this criterion lacks specificity and can lead to misdiagnosis and inappropriate treatments.[16]

One in seven patients suspected of having primary ITP were misdiagnosed at some point during their disease course.[16] Misdiagnosis of ITP patients is common due to the heterogenous clinical manifestations and treatment responses across patients.[16,18] This variability suggests that ITP can have different underlying causal pathways.[19,20] One objective of this PhD thesis is to improve the diagnostic criteria for ITP by assessing the performance characteristics of autoantibodies in ITP patients with a confirmed clinical diagnosis. Improved diagnostic testing could lead to better classification of patients and ultimately more individualized and appropriate treatment strategies.

1.3 Emergency Bleeding in ITP Patients

As the function of platelets is to help clotting, severe thrombocytopenia, specifically a platelet count $<20 \times 10^9$/L, predisposes patients to spontaneous bleeding.[21,22] Pediatric patients tend to experience a more acute onset of ITP, with severe bleeding occurring in an estimated 3% of children with ITP.[8,22,23] At any point, the weighted proportion for severe, non-intracranial hemorrhage (ICH) bleeding is estimated to be 9.6% for adults (95% CI, 4.1-17.1%) and 20.2% for children (95% CI, 10.0-32.9%).[24]

ICH is the most severe complication in ITP and occurs in approximately 1.4% of adults (95% CI, 0.9-2.1%) and 0.4% of children (95% CI, 0.2-0.7%).[24] The consequences of severe bleeding can be fatal.[25] The case fatality rate of ICH in children is approximately 25%.[25] Pooled estimates of the 5-year risk of death from bleeding in ITP are as high as 47.8% for patients >60 years.[22]

Acute bleeding events in adults and children with ITP, especially ICH, are highly time-sensitive medical emergencies that can cause life-long morbidity.[21] Early hematoma growth, the principal cause of neurological deterioration after ICH, occurs in up to 40% of patients within

three hours of ICH onset and increases 30-day mortality.[26] Hospitalization for bleeding in patients with ITP tends to be longer, with higher costs, and is associated with a risk of death that is 22% (95% CI: 19%-24%) higher than the overall hospitalized population adjusted for age and sex.[27,28] Approximately four visits per year per emergency department are ITP-related emergencies.[29]

Despite the observed risks of bleeding events in adults and children with ITP and the need for time-sensitive treatment, the definition of 'bleeding emergency' has not been well established. The second objective of this PhD thesis is to develop a standardized definition of bleeding emergencies in ITP patients. A standardized definition of bleeding emergencies in ITP patients will allow patients to be identified consistently for research and clinical purposes.

1.4 Emergency Management Protocols are Lacking

Current international ITP guidelines sponsored by the American Society of Hematology (ASH)[30] provide treatment recommendations for patients with severe thrombocytopenia in the outpatient setting, including high-dose corticosteroids, intravenous immune globulin (IVIG) and/or rhesus immune globulin. Despite the need for a coordinated approach to treating ITP bleeding in emergency situations, the current ASH guideline does not address the treatment of bleeding beyond minor bleeds or skin manifestations in patients with ITP.[30,31]

The effectiveness of available treatment strategies for emergency bleeding remains unknown. Studies have addressed potential treatments for bleeding including platelet transfusions, antifibrinolytic medications, recombinant factor VIIa, urgent splenectomy, vinka alkaloids, thrombopoietin receptor agonists, or combinations thereof.[30,32-40] Therefore, a clinical guideline for 'bleeding emergencies' in ITP is needed to identify patients who require acute management and the appropriate interventions. The third objective of this PhD thesis is to outline

a systematic review protocol to assess the effectiveness of treatments in ITP patients experiencing 'bleeding emergencies' that will inform the development of the guideline.

1.5 Challenges of Guideline Development in Rare Diseases

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach to guideline development provides a transparent and structured approach to draw conclusions and make clinical recommendations based on evidence.[41,42] However, developing a guideline for patients with rare diseases poses unique methodological challenges.[43-47] Due to the rarity of the disease, limited evidence is available to inform guideline panel recommendations. Published literature can include low-quality studies, studies that do not directly address the questions of interest, or no studies at all.[47,48]

Various strategies have been used to supplement the limited evidence for existing rare disease guidelines, including expert experience where clinicians recall their clinical encounters.[44,47,48] The evidence that is accessed to inform recommendations needs to be optimized. A novel methodology for guideline development that addresses the lack of available evidence would potentially allow for stronger recommendations as well as allow recommendations to be made where they were previously prevented due to a lack of evidence. The fourth objective of this PhD thesis is to develop this methodology to address limited evidence that can be applied to rare disease guidelines.

1.6 Objectives of the PhD Thesis

My PhD thesis will inform aspects of the identification and treatment of 'bleeding emergencies' in ITP patients for the development of a clinical guideline. Firstly, I will evaluate the performance characteristics of antiplatelet autoantibodies in the diagnosis of ITP and heterogeneity of ITP patients. Secondly, I will develop a standardized definition of ITP 'bleeding

emergencies' to identify the intended patient population of the clinical guideline. Thirdly, I will outline the synthesis of existing evidence through a systematic review of the literature to evaluate the effectiveness of interventions for treating emergency bleeding. To fill an important gap for developing guidelines when evidence is lacking, I will develop a new methodology for creating clinical guidelines that can be applied to all rare diseases, which I will implement to develop the ITP Emergency Bleeding Guideline. The contents of the thesis chapters may overlap in the introductions of each article.

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2 Chapter 2: Performance characteristics of platelet autoantibody testing for the diagnosis of immune thrombocytopenia using strict clinical criteria

2.1 Author's Preface

Establishing the diagnosis of ITP is challenging, especially with the diagnostic criteria of a platelet count < 100 x 10^9 /L and the exclusion of other causes. Clinical manifestations and treatment responses are variable across ITP patients, suggesting that ITP is a heterogeneous syndrome, possibly representing a group of disorders. A description of the clinical diversity across patients could lead to better classification of patients and ultimately more individualized treatment strategies. Improving the diagnosis of ITP using strict clinical criteria and exploring the performance characteristics of platelet autoantibodies will help identify the role of platelet autoantibodies as a form of diagnostic criteria. As co-first author, I contributed to the design of the study and writing of the manuscript. The collaborating first author was responsible for the platelet antibody testing laboratory work, co-designed the study and co-wrote the manuscript.

Authors: Emily Sirotich*, Caroline Gabe*, Na Li, Nikola Ivetic, Ishac Nazy, James Smith, John G. Kelton, Donald M. Arnold. *co-first authors.

2.2 Summary

Misclassification of immune thrombocytopenia (ITP) is common, which might undermine the value of platelet autoantibody testing. We determined the sensitivity and specificity of platelet autoantibody testing using the direct antigen capture assay for anti-glycoprotein (GP) IIb/IIIa or anti-GPIbIX in patients with 'definite ITP', defined as those with a documented treatment response. Sensitivity of platelet autoantiboody testing increased from 48.3% [95% confidence interval (CI) 43.5–53.2] for all ITP patients to 64.7% (95% CI 54.6–73.9) for definite ITP patients. Specificity was unchanged [75.3% (95% CI 67.5–82.1)]. High optical density values (>0.8) improved the specificity of platelet autoantibody testing but lowered sensitivity. In patients with a high pretest probability, platelet autoantibodies can aid in the diagnosis of ITP and may be most prevalent in certain patient subsets.

Key points:

The application of strict clinical criteria to classify patients with immune thrombocytopenia (ITP) increased the sensitivity of platelet autoantibody testing using the direct antigen capture assay by 16.4% (from 48.3–64.7%).

With high specificity, the platelet autoantibody test may be useful to rule-in ITP; patients with the highest platelet autoantibody values had the highest likelihood of having ITP.

2.3 Introduction

Establishing the diagnosis of immune thrombocytopenia (ITP) is challenging[1] as specific biomarkers are lacking. Platelet autoantibodies that target platelets or megakaryocytes are thought to be the primary cause of thrombocytopenia in patients with ITP; but the clinical utility of platelet autoantibody testing is limited in practice.[2] In a recent systematic review, the

sensitivity and specificity of direct anti-glycoprotein (GP) IIb/IIIa or GPIbIX was 53% and 93% respectively.[3] However, the population tested was heterogeneous with respect to disease classification, duration and severity.

In this study, we evaluated the performance characteristics of platelet autoantibodies in a homogeneous population of patients with ITP, defined by a prior response to ITP-specific treatment. We explored the association between platelet autoantibodies and disease characteristics.

2.4 Patients and Methods

Adult patients were identified from the McMaster ITP Registry.[4] Data were captured up to November 30, 2019. The registry was approved by the Hamilton Integrated Research Ethics Board and all patients provided consent. Patients were designated as having ITP if they had a platelet count $<100 \times 10^9$/L with no other underlying cause, based on criteria from the American Society of Hematology.[5] We defined the subgroup of 'definite ITP' as having a documented response to high-dose intravenous immune globulin (IVIG) or high-dose corticosteroids (platelet count $>50 \times 10^9$/L and doubling of baseline within 4 weeks).[1] This group had a high clinical pretest probability of ITP. ‘Possible ITP’ patients were defined as those who did not fulfil this criterion. Patients with thrombocytopenia due to non-immune causes were used as controls. Clinical data, platelet counts and bleeding assessments[6] were captured. The study population was chosen to reflect thrombocytopenic patients who would be seen by a haematologist for evaluation and for whom the cause of the thrombocytopenia might be uncertain.

Platelet antibody testing

Autoantibodies bound to GPIIb/IIIa and GPIb/IX on platelets were measured using the modified direct antigen capture assay.[2,7] Briefly, peripheral blood was collected from patients into acid citrate dextrose solution A (ACD-A, 6:1, v/v) and platelet-rich plasma (PRP) was isolated from ACD-A whole blood. After three washes to isolate platelets from PRP, platelet counts were adjusted to 300×10^9/L, lysed and stored at −70°C. We used in-house capture monoclonal anti-GPIIb/IIIa (Raj-1) or anti-GPIb/IX (TW-1).[8] Platelet lysates (50 µl) were added to duplicate wells and the amount of bound antibody, detected with anti-human IgG, was measured by optical density (OD) at 405 nm. A positive result was OD > 0.21 based on the mean ± 2 standard deviation of 30 normal healthy individuals.[9]

Statistical analysis

Receiver operating characteristic (curves with logistic regression models were used to assess the performance of platelet autoantibodies as a diagnostic test for ITP. Sensitivity and specificity of the test with 95% confidence intervals (CIs) were calculated for the entire cohort of ITP patients and for patient subgroups compared with non-immune thrombocytopenic controls. Positive predictive values (PPV) and negative predictive values (NPV) were calculated to provide information on the utility of platelet autoantibody testing in clinical practice. The area under the curve (AUC) was calculated for each model.[10] The nadir platelet count was compared using the Wilcoxon rank-sum test. Fisher's exact test was used to test for associations between the presence or absence of platelet autoantibodies and response to splenectomy or rituximab, defined as an increase in the platelet count level to 50×10^9/L or higher and doubling of the baseline within 12 weeks of either splenectomy or rituximab, without additional treatment.

2.5 Results

We identified 766 adult patients with thrombocytopenia, including 568 (74.2%) with platelet autoantibody test results. There were 422 (74.3%) patients with ITP, of whom 102 had 'definite ITP' and 320 had 'possible ITP'; 146 (25.7%) patients had non-immune thrombocytopenia (Table I). The distribution of platelet OD values was skewed, as most patients with a positive platelet autoantibody test had low OD values **(Figure 1)**. Of all the patients in this cohort, the diagnosis changed over time for 55 (9.7%) patients, either from non-immune thrombocytopenia to ITP (n = 30) or from ITP to non-immune thrombocytopenia (n = 25). For the 102 definite ITP patients, three (2.9%) changed from non-immune thrombocytopenia to definite ITP.

For all ITP patients, the sensitivity and specificity of platelet autoantibody testing were 48.3% (95% CI 43.5–53.2) and 75.3% (67.5–82.1) respectively. PPV was 85.0% (80.8–88.4) and NPV was 33.5% (30.7–36.5). The AUC was 0.62. For definite ITP, the sensitivity and specificity were 64.7% (54.6–73.9) and 75.3% (67.5–82.1) respectively; PPV and NPV were 64.7% and 75.3% respectively and the AUC was 0.70.

There were no differences in nadir platelet count [median (interquartile range, IQR): 3 (1–8.5) × 109/l vs. 5.5 (2–12.3) × 109/l; P = 0.184], number of grade 2 bleeds [10 (15.2%) vs. 1 (2.8%); odds ratio (OR) 6.17, 95% CI 0.81–278.49, P = 0.092], response to splenectomy [6 (60%) vs. 3 (42.9%); OR 1.92, 95% CI 0.19–21.62, P = 0.637], or response to rituximab [3 (27.3%) vs. 2 (66.7%) OR 0.22, 95% CI 0.003–5.54, P = 0.505] between antibody-positive and antibody-negative definite ITP patients.

We described the characteristics of definite ITP patients in the upper third quartile of antibody results (n = 30 with OD values >0.8; n = 26 definite ITP and n = 4 non-immune

thrombocytopenia). Using this OD cut-off, the sensitivity and specificity were 25.5% (17.4–35.1) and 97.3% (93.1–99.3), AUC was 0.61, PPV was 86.7% (70.1–94.8) and NPV was 65.1% (62.4–67.7) (**Table 1**). Definite ITP patients with a maximum OD value >0.8 had a median nadir platelet count of 2×10^9/L (1–8.5) and had received a median of five prior ITP treatments.[4-7]

For the 55 patients whose diagnosis changed over time (30 with an ultimate diagnosis of ITP, and 25 with an ultimate diagnosis of non-immune thrombocytopenia), the sensitivity and specificity of platelet autoantibody testing were 26.7% (12.3–45.9) and 68% (46.5–85.1) respectively, using an OD cutoff of 0.21. PPV was 50% (30.5–69.5) and NPV was 43.6% (35.4–52.2). For the 513 patients with clear diagnosis from the start [ITP (n = 392) or non-immune thrombocytopenia (n = 121)], the sensitivity and specificity were 50% (44.9–55.1) and 76.9% (68.3–84.0).

2.6 Discussion

We postulated that the poor performance characteristics of platelet antibody testing might relate to misclassification of patients.4 After categorizing patients by their response to high-dose IVIG or corticosteroids, we found that the sensitivity of platelet antibody testing increased from 48.3% to 64.7% (specificity was unchanged at 75.3%). Although improved, the sensitivity was still low for a stand-alone diagnostic test.

The distribution of OD values for platelet autoantibody test was skewed with 150 (26.4%) patients having low levels of autoantibody only (OD 0.21–0.4). When we examined the subgroup of definite ITP patients with the highest platelet autoantibody levels (OD > 0.8), the specificity increased to 97.3%, but sensitivity decreased to 25.5%. Thus, a high platelet autoantibody level can be useful to rule in the diagnosis of ITP. In our sample, this subgroup corresponded to 26 patients (25.4% of definite ITP patients).

Al-Samkari et al.[11] found a significantly higher sensitivity (90%) in ITP patients who fulfilled the diagnostic criteria established by the American Society of Hematology 2011 guidelines at the time of initial clinical evaluation. They used elution to detect platelet autoantibodies and excluded patients who received IVIG within the previous 30 days, which may explain some of the differences noted. In addition to anti-GPIIb/IIIa and anti-GPIb/IX, other platelet autoantibodies may contribute to thrombocytopenia, including anti-GPIa/IIa[11] and anti-GPV;[12, 13] however, most patients with these autoantibodies also have anti-GPIIb/IIIa or anti-GPIbIX.[11-13] The variation in the performance of platelet autoantibody testing may also be explained by different test methods and reagents in addition to differences in the study population.[14] Indeed, another possible explanation for the low antibody levels observed for most ITP patients could be related to the test methods, which may require re-examination.

We did not find a correlation between clinical characteristics and the presence of platelet autoantibodies. A previous study[15] demonstrated an association between the absence of platelet autoantibodies and non-responsiveness to rituximab; however, we did not observe such an association, which may have been due to an overrepresentation of rituximab-resistant ITP.

Strengths of our study include (i) data collection from a registry designed specifically to study ITP, (ii) platelet autoantibody testing done in the same reference laboratory using the same testing technique and (iii) the use of non-immune thrombocytopenic controls replicated the population to which this test would be applied in practice. Other strengths include the relatively large sample size, duration of follow-up and duplicate assessment of the ITP diagnosis. A limitation was the post-hoc designation of ‘definite ITP’ based on a previous treatment response, which excludes rare ITP patients who are refractory to all treatments. Prospective classification

tools are needed. We used the highest autoantibody test result for our analyses rather than a change in autoantibody levels over time.

In conclusion, the sensitivity of platelet autoantibody testing increased from 48.3% to 64.7% when patients were classified using strict clinical criteria (high pretest probability), and specificity was unchanged (75.3%). We found that patients with the highest platelet autoantibody levels were most likely to have ITP and severe thrombocytopenia. While platelet autoantibody testing may not be an adequate screening test on its own, it may help rule-in the diagnosis of ITP. Improved diagnostic tools, such as risk prediction models and additional basic and translational research, are needed to identify reliable biomarkers for ITP.

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2.9 Author contributions

CG and ES helped design the study, wrote the manuscript. NL helped design the study, performed the statistical analysis, edited the manuscript. NI and IN conceived the study, edited the manuscript. JS helped perform the experiments, edited the manuscript. JGK conceived the study and edited the manuscript. DMA conceived the study, wrote the manuscript. All authors read and approved the final manuscript.

2.10 Conflict of interest

The authors declare no conflicts of interests.

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3 Chapter 3: Development of a standardized definition of critical bleeds in ITP patients

3.1 Author's Preface

As the function of platelets is to help clotting, low platelet counts that characterize ITP predispose patients to increased risk of bleeding. Severe thrombocytopenia, specifically a platelet count <20 $x10^9$/L predisposes patients to spontaneous bleeding. Treatment of acute bleeding in adults and children is highly time-sensitive. The potential impacts of bleeding on morbidity and mortality in ITP patients have been well-documented. However, there are variations in bleeding definitions that make it difficult to identify homogeneous patient populations for research and clinical purposes.

The ITP Emergency Management Guideline Panel assembled to begin the guideline development process. At the initial stages of developing the research questions, it became clear that the patient population of interest was not well defined. A standardized definition of bleeding emergencies in ITP patients will allow patients to be identified consistently to identify relevant evidence from the literature and create guidelines for the intended patient population that can be applied to clinical settings.

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3.2 Abstract

Background

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by low platelet counts and increased risk of bleeding. In preparation for an upcoming guideline, the ITP Emergency Management Guideline Panel, including clinical experts in hematology, emergency medicine, research methodology as well patient representatives, identified the need for a standardized definition of a *critical ITP bleed*. The goal of the definition was to distinguish critical bleeds from bleeds that may not require urgent treatment, typically in the context of severe thrombocytopenia.

Methods

The Panel met in-person and virtually to achieve consensus on the criteria for critical bleeding events among patients with ITP. Existing ITP bleeding scores and published definitions of major bleeds in patients receiving anticoagulation informed the definition of a critical ITP bleed. The Platelet Immunology Scientific Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis endorsed the definition.

Results

A critical ITP bleed was defined as: (1) a bleed in a critical anatomical site including intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome; or (2) an ongoing bleed that results in hemodynamic instability or respiratory compromise.

Conclusion

The definition of a critical ITP bleed was developed by the ITP Emergency Management

Guideline Panel and endorsed by the Platelet Immunology SSC. It incorporates both anatomic and physiologic risk, and pertains to patients with confirmed or suspected ITP who typically have severe thrombocytopenia (platelet count below 20 $x10^9$/L).

Key words: Purpura, Thrombocytopenic, Idiopathic; Hemorrhage; Emergencies; Blood Platelets

Essentials:

- Defining a Critical ITP Bleed will guide treatment recommendations for life-threatening events.
- Developed by a multi-disciplinary group based on existing literature and consensus.
- The definition of a critical ITP bleed incorporates both anatomic and physiologic risk.
- Occurs primarily in patients with severe thrombocytopenia (platelet count below 20 $x10^9$/L).

3.3 Introduction

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder characterized by a low blood platelet count in the absence of other causes.[1] Severe thrombocytopenia, specifically a platelet count <20 $x10^9/L^2$, predisposes patients to spontaneous bleeding. Pooled estimates of the 5-year risk of death from bleeding in ITP are as high as 49% for patients > 60 years.[3] In children, ITP is typically acute in onset with approximately 3% of children experiencing major bleeding at presentation.[4,5] A systematic review of 51 prospective studies reported that the weighted proportion of intracranial hemorrhage (ICH) was 1.4% [95% confidence interval (CI), 0.9–2.1] for adults and 0.4% (95% CI, 0.2–0.7) for children.[6] Although its incidence in adults and children is low, life-threatening bleeding requires urgent treatment to prevent significant morbidity and mortality.[3]

The classification of bleeding severity in patients with ITP remains unstandardized. The literature includes at least 12 different definitions of 'severe bleeding'; yet these do not distinguish critical (or life-threatening) bleeds from non-critical bleeds.[6] Identifying patients at greatest risk of adverse outcomes and who require emergency treatment requires a standardized definition for a critical ITP bleed. Such a definition is equally important to identify those patients who *do not* need urgent treatment, thus avoiding potential toxicities.[7] The ITP Emergency Management Guideline Panel is an independent group of clinical investigators in hematology, emergency medicine and research methodology, and patient representatives tasked with developing evidence-based guidelines for the treatment of bleeding emergencies in patients with ITP. The guideline initiative was funded by the Canadian Institutes for Health Research and endorsed by the American Society of Hematology. Members of the panel recognized the need for a definition of a critical ITP bleed to identify the population that would be eligible for the guideline. This article describes the process and outcome of the panel's deliberations, and presents a definition of a critical ITP bleed, endorsed by the Platelet Immunology Scientific Standardization Committee (SSC) of the International Society for Thrombosis and Haemostasis (ISTH).

3.4 Methods

The ITP Emergency Management Guideline Panel consisted of 9 hematologists (3 pediatric and 4 adult), 1 pediatrician, 2 emergency medicine physicians, 1 registered nurse, 4 methodologists, and 5 patient representatives from 3 countries. The panel was convened to develop evidence-informed guidelines for the treatment of bleeding emergencies in patients with ITP.

To define critical ITP bleeding, the panel reviewed existing bleeding tools for ITP and existing bleeding scores for patients on anticoagulation to inform the new definition. A dedicated working group searched the literature for systematic reviews of ITP bleeding assessments and bleeding scores up to January 2021, the results informed panel deliberations. The ISTH definition of major bleeding in non-surgical patients who were receiving anticoagulation provided a framework for the new definition (**Figure 2**).[8]

Members of the panel met by teleconference on 5 occasions and once in-person to discuss the criteria for a critical ITP bleed. The iterative discussions and follow up correspondences considered all feedback and suggestions from the panel. Consensus was achieved through synchronous and asynchronous group discussions, including formal presentations at meetings and informal discussions. The panel presented a preliminary version of the definition of a critical ITP bleed at the Platelet Immunology SSC meeting in July 2020 and incorporated feedback from that meeting into the definition. The SSC chair and co-chairs approved this manuscript.

3.5 Results

Terminology

The panel used the term 'critical' ITP bleed to indicate a bleed that was life or organ-threatening and thus requiring urgent intervention. Critical ITP bleeds typically occur in the context of severe thrombocytopenia, defined as a platelet count $<20 \times 10^9/L^2$, but may occur at higher platelet counts in patients with additional risk factors (e.g. trauma, concomitant anticoagulation medications, etc).

Review of existing ITP bleeding definitions and scores

Neunert *et al.* reported the prevalence and severity of bleeding in ITP (n=10,908), describing 12 different definitions of major bleeding (**Table 2**).[6] Of the 12 definitions, 6 classified bleeds by severity using rating scales with varying definitions.[9, 10, 11, 12, 13, 14] Most major bleeds included a range of severity from moderate mucocutaneus bleeding to life-threatening or fatal bleeding. Some definitions included numerous (5 or more) large (over 2cm) bruises, diffuse petechiae or 'extensive' skin bleeding manifestations.[6,15] Variations across existing definitions of bleeding are reflective of the use of a range of bleeding scores that included site-specific scores, composite scores and global bleeding scores.

Bylsma *et al.* conducted a systematic review of second-line treatments for ITP and bleeding was reported in 10 out of 12 randomized controlled trials, either as an efficacy or safety outcome.[15] The assessment of the signs and severity of bleeding varied across studies, some of which used generic tools including the World Health Organization bleeding scale and adverse events reporting.[14,15] In addition, the authors noted that the lack of consistency in the outcome definitions limited comparisons of bleeding data across both observational and randomized controlled trials.

Review of bleeding definitions for patients receiving anticoagulation

Critical bleeding in patients with ITP is conceptually similar to bleeding in patients receiving anticoagulation, since both populations have an underlying impairment in hemostasis. The ISTH definition of major bleeding in non-surgical patients receiving anticoagulation provided a framework that informed the definition of a critical ITP bleed.[8] That definition includes (1) fatal bleeding, and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or (3) bleeding causing a fall in hemoglobin

level of 20g/L (1.24mmol/L) or more, or leading to red blood cell (RBC) transfusion of two or more units of whole blood or red cells in patients receiving anticoagulation. The panel used a similar approach to define a critical ITP bleed, except for the requirement for a reduction in hemoglobin or the need for transfusion of RBCs since ITP bleeds often occur independently and often earlier than either of these events.

Consensus Definition of a Critical ITP Bleed

For the definition of a critical ITP bleed, the panel considered patient important outcomes as those which led to physical impairment and could reasonably be associated with death or reduced quality of life, as highlighted by the patient representatives on the panel, including parents of children with ITP. The anatomical site of the bleed was a defining feature of a critical ITP bleed. The panel agreed that the definition should include intracranial, intraspinal, intraocular, retroperitoneal or pericardial bleeds, or intramuscular bleeds with resultant compartment syndrome. In addition, the panel agreed that a bleed resulting in life-threatening physiological derangements should be considered critical regardless of the anatomical site. Thus, ongoing or active bleeding causing hemodynamic instability or respiratory compromise were included in the definition. **Table 3** presents the final definition of a critical ITP bleed.

Relevant patient population

The definition of a critical ITP bleed is intended for patients with confirmed or suspected ITP. Although one expects critical ITP bleeding to occur primarily in patients with severe thrombocytopenia, defined as a platelet count below 20 $x10^9/L$[18], it may also occur in patients with a platelet count above this threshold especially for patients with concomitant risk factors such as trauma or concomitant use of anticoagulation. The definition of a critical ITP bleed

applies to both pediatric and adult patients, although age-specific parameters may be required to define hemodynamic instability and respiratory compromise.

3.6 Discussion

Critical bleeding in patients with severe ITP can lead to significant morbidity and mortality and therefore requires a rapid, coordinated approach to treatment. A standardized definition for a critical ITP bleed is needed to identify patients at greatest risk for death, physical disability, or impaired quality of life. When developing its treatment guidelines, the treatment guideline panel will use this definition to describe the patient population who require emergency treatment and to define which treatments are required.

In conjunction with the Platelet Immunology SSC of ISTH, the ITP Emergency Management Guideline Panel developed a new definition of critical bleeding in patients with ITP. The definition has two components (anatomical site and physiological consequences of the bleed), and is intended for patients with presumed or confirmed ITP who typically have a platelet count below 20 $x10^9$/L. The anatomical location of a critical ITP bleed include intracranial, intraspinal, intraocular, retroperitoneal, pericardial or intramuscular with compartment syndrome. The physiological consequences of the bleed include hemodynamic instability or respiratory compromise.

The ISTH definition of major bleeding in non-surgical patients receiving anticoagulation was used as a framework to inform the definition of a critical ITP bleed since both populations have an inherent risk of bleeding.[8] Other bleeding tools have been developed for children[24] and for patients with hematological malignancy.[25,26] The Bleeding Severity Measurement Scale was developed for patients with chemotherapy-induced thrombocytopenia. It also includes central nervous system bleeding and hemodynamic instability in its definition of major bleeding.[27] The

World Health Organization bleeding scale is commonly used for patients with cancer, although the categorization of bleeding was overly broad for the purposes of the ITP patient population.[28]

This is the first initiative to define a standard definition of critical bleeding in patients with ITP. Previous studies have reported bleeding variably labeled as 'major or severe', and using composite outcomes of variable type and severity.[1,15] Understanding the heterogeneity of bleeding in ITP is a research priority. The creation of standardized definition of a critical ITP bleed will advance those investigations.

The ITP Emergency Management panel recognizes that not all critical bleeds will be captured by the proposed definition and that the application of the definition may depend on the clinical judgement of the treating physician. Moreover, the proposed definition identifies patients with critical bleeding but does not identify patients *at risk* of critical bleeding, even though both populations may warrant urgent treatments. Strengths of this research are the simplicity of the definition, which will facilitate its use in emergency situations; the direct applicability of the definition to treatment guidelines, which are currently in development; and the logical application of this definition to identify patients at risk of developing a critical ITP bleed.

In conclusion, this consensus definition of a critical ITP bleed, developed by a multi-disciplinary panel, may be used in future ITP studies to standardize reporting and facilitate evidence-based guidelines for the co-ordinated management of ITP patients.

Addendum

All authors have substantially contributed to the concept and design, results, critical writing, and final approval of the version to be published.

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4 Chapter 4: Treatment of critical bleeding events in patients with immune thrombocytopenia: a protocol for a systematic review and meta-analysis

4.1 Author's Preface

To synthesize the existing evidence from the literature, I outline the protocol for a systematic review to identify articles that report critical bleeding in ITP patients, their treatment, and their outcomes. The review was conducted with a team of literature screeners, medical and graduate students. The systematic review will allow us to understand and compare the various treatment options in ITP patients experiencing a critical bleed and their effectiveness. The systematic review is underway and the protocols can be found on PROSPERO. My role as first author was to oversee the design of the project and draft the manuscript.

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4.2 Abstract

Background: Critical bleeding events in adults and children with ITP is a medical emergency; however, evidence-based treatment protocols are lacking. Due to the severe thrombocytopenia, (typically platelet count less than 20 x 10^9/L), a critical bleed portends a high risk of death or disability. We plan to perform a systematic review and meta-analysis of treatments for critical bleeding in patients with ITP that will inform evidence-based recommendations.

Methods: Literature searches will be conducted in four electronic databases: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed. Eligible studies will be randomized controlled trials or observational studies that enrolled patients with ITP describing one or more intervention for the management of critical bleeding. Title and abstract screening, full-text screening, data extraction, and risk of bias evaluation will be conducted independently and in duplicate using Covidence and Excel. Outcomes will be pooled for meta-analysis where appropriate or summarized descriptively. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology will be used to evaluate the certainty of the evidence. Primary outcomes of interest will include frequency of critical bleeds, mortality and bleeding -related mortality, bleeding resolution, disability, and platelet count.

Discussion: Evidence-based treatments for critical bleeding in patients with ITP are needed to improve patient outcomes and standardize care in the emergency setting.

Systematic review registration: CRD42020161206.

Key words: Immune thrombocytopenia, thrombocytopenia, emergency management, critical bleeding.

4.3 Background

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder characterized by platelet counts below 100 x 10^9/L in the absence of other causes.[1, 2] The disease affects both children and adults and has a female predominance.[2, 3] Although the majority of bleeding complications related to ITP are minor with no lasting effects, major bleeding episodes, especially in patients with severe thrombocytopenia (platelet counts below 20 x10^9/L) can lead to significant morbidity and mortality.[4] Pooled estimates of the 5-year risk of death from bleeding in ITP are as high as 47.8% for patients >60 years.[5] For children, the risk of severe bleeding is approximately 3%.[6,7] Intracranial hemorrhage (ICH) is the most severe type of bleeding event in patients with ITP. The incidence of ICH is 1.1% ± 0.1% for adults and 0.7% ± 0.1% for children.[8] The case fatality rate of ICH in children is approximately 25%.[8]

Critical bleeds are defined as: (i) a bleed in a critical anatomical site including intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome; or (ii) an ongoing bleed that results in hemodynamic instability or respiratory compromise.[9] Critical bleeds require urgent multimodal treatment in the emergency department or the in-patient setting with the goal of rapidly raising platelet counts and achieving hemostasis.[10] Acute management of a critical bleed might include typically ITP treatments such as intravenous immune globulin (IVIG) and corticosteroids, plus additional treatments including platelet transfusions[10,11], antifibrinolytic medications [12], recombinant factor VIIa [13], urgent splenectomy, and thrombopoietin (TPO) receptor agonists, alone or in combination.[1, 14-18]

Evidence-based guidelines for the management of a critical bleed in patients with ITP are lacking. Broad ITP treatment guidelines from the American Society of Hematology (ASH), published in 2019, did not address the management of critical bleeding.[19] We are conducting a

systematic review and meta-analysis of treatments for adults and children, with the goal of informing the development of evidence-based guidelines.

4.4 Methods

The protocol for this systematic review was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (see additional files for checklist)[18], and registered in PROSPERO (CRD42020161206). The systematic review will be conducted and reported in accordance with PRISMA guidelines.

Search strategy

With the aid of a medical librarian, searches will be conducted in four electronic databases from inception to January 2021: Ovid MEDLINE, Embase, PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL) (see additional files for search strategies). A combination of keywords and medical subject heading (MeSH) terms will be used: Purpura, Thrombocytopenic, Idiopathic; Epidemiologic Studies, and Randomized Controlled Trial. No language restrictions will be applied and publication status. Citation lists of identified reviews and primary publications will be screened for additional studies.

Eligibility criteria

We will include randomized controlled trials (RCTs) and observational studies that enrolled patients who have suspected or confirmed ITP and critical bleeding. Studies must include a description or evaluation of one or more interventions, alone or in combination, with or without a comparator. We will use the ISTH definition of critical bleeding: (i) a bleed in a critical anatomical site including intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome; or (ii) an ongoing bleed that results in

hemodynamic instability or respiratory compromise.[9] Given the recognized difficulties in establishing the diagnosis of ITP among patients with thrombocytopenia, we anticipate a high case mix in primary ITP studies.

For this systematic review, we will include studies that enrolled at least 80% ITP patients, or studies that reported data separately for patients with ITP. Outcome assessments will be restricted to 7 days or the duration of hospitalization since the objective is to describe acute management critical bleeds. Along those lines, we focused this review on interventions that typically have a rapid or immediate effect on increasing platelet counts or restoring hemostasis, including corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin, platelet transfusion, tranexamic acid, TPO receptor agonists (romiplostim, eltrombopag, avatrombopag), recombinant factor VIIa, and urgent splenectomy. Outcomes of interest are mortality (all-cause and bleeding-related), resolution of bleeding, disability, platelet counts, platelet count responses (minimal, >30 $x10^9$/L; overall, >50 $x10^9$/L)[20], new onset of bleeding, duration of hospital stay, need for and duration of intensive care unit admission, and treatment-related adverse events.

Study selection

Reviewers will work independently and in pairs to conduct title and abstract screening and full-text reviews using pre-defined eligibility criteria and standardized forms. Disagreements will be resolved by a third reviewer.

Data extraction and risk of bias assessment

Any study data relevant to the research questions outlined above will be collected. The following study data will be abstracted: study citation and author contact details, study design, duration and setting, country, number of participants, demographics (age, sex, comorbidities),

ITP diagnoses of participants (primary, secondary, chronic, etc.), intervention details (dose, frequency, etc.), reported outcomes according to the outcomes of interest listed above (outcome definitions, time-points collected, unit of measurement, sample size, statistical significance testing) and funding sources.

Risk of bias will be assessed using the Cochrane Risk of Bias version 2.0 assessment tool for randomized trials[21], and the Newcastle-Ottawa Scale for Risk of Bias Assessment for observational studies[22]. Risk of bias will be classified as ‘‘low’’, ‘‘probably low’’, ‘probably high’’, or ‘‘high’’ for the following domains: bias due to randomization, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and other biases. We will rate the overall risk of bias as the highest risk attributed to any criterion. Reviewers will conduct abstractions and risk of bias assessments independently and in duplicate using standardized forms. Discrepancies will be resolved by consensus, with input from a third reviewer if needed. For missing data, reviewers will attempt to contact study authors when possible.

Assessment of certainty of the evidence

We will consider the overall certainty in evidence for each outcome using the GRADE framework, based on the following domains: Risk of bias, imprecision, inconsistency, indirectness, and publication bias. Overall certainty of evidence will be rated as very low, low, moderate, or high. We will consider rating down the certainty of evidence for risk of bias based on lack of blinding for subjective outcomes only. We will make judgments of imprecision using a minimally contextualized approach. We will consider any CI encompassing the null effect to be imprecise, with consideration of important and trivial effect.

Statistical analysis

We plan to conduct random-effects meta-analysis, with continuous outcomes presented as standardized mean differences, and dichotomous outcomes presented as risk ratios, all with 95% CIs. We will assume a normal distribution for continuous outcomes and will convert interquartile ranges to standard deviations (SD) as per guidance from the Cochrane Collaboration. We will assess heterogeneity between studies using the I^2 measure. We will judge inconsistency for GRADE ratings based on the magnitude and direction of heterogeneity. Publication bias will be assessed based on visual inspection forest plots.

We anticipate that there will be limited direct evidence available from published reports and significant heterogeneity between study types, interventions evaluated, and outcomes which may preclude statistical meta-analysis. In that case, we will summarize study findings descriptively and provide aggregate results per intervention and outcome where appropriate. Since we also anticipate that many studies will be high risk of bias, we will conduct subgroup analyses based on risk of bias judgements (high risk of bias versus low risk of bias) and consider that high risk of bias studies may exaggerate treatment effects.

4.5 Discussion

This systematic review aims to identify effective treatments for patients with ITP and critical bleeding. Outcome of interest reflect clinical practice and relevant clinical outcomes including platelet count levels, mortality, disability and hospital length of stay. Results of this systematic review will be used to inform evidence-based guidelines for the management of ITP patients with critical bleeding.

This review has potential limitations. We anticipate that the primary studies included in this review will have heterogeneous designs, with critical bleed outcomes being reported mainly

in case series or observational studies and having minimal reporting in randomized trials. Since the definition of critical bleeds in ITP patients was recently standardized, studies that report bleeding according to this definition will not be available. Therefore, comparing the various definitions of bleeding across studies may limit the interpretability of bleeding results. Lastly, the availability of randomized trials that evaluate interventions during a critical bleed will be limited because of the urgent nature of the event. The identification of optimal treatment and management strategies for ITP bleeding emergencies will have immediate implications for patients and providers. This information will be used by hematologists and physicians in the emergency department when faced with this rare but life-threatening event.

Protocol amendments

Any amendments to this protocol in the carrying out of this systematic review will be documented and reported in both the PROSPERO register and any subsequent publications.

Dissemination plans

The findings of this systematic review will be disseminated through publication in peer-reviewed journals and via relevant conferences. In addition, the results will also be shared with potential stakeholders, including the Platelet Disorder Support Association and the Canadian Institutes for Health Research.

4.6 Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Consent for publication was received from all authors.

Availability of data and materials: All data and materials were accessed through institutional library domains.

Competing interests: DA has no relevant conflicts of interest; receives research funding for non-relevant work: Novartis; Consultancy: Novartis, Amgen, UCB, Principia, Rigel. Other authors declare they have no competing interests.

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Authors' contributions: DA is the guarantor of this review. ES and DA defined the research question. ES developed the search strategy and determined inclusion and exclusion criteria. Methodological support and assessment of exposure methods and tests for this review was provided by MH. ES and HN created the first draft of this manuscript, and all authors reviewed and approved the final draft.

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5 Chapter 5: Development of A Novel Methodology for Generating Direct Evidence in Rare Disease Guidelines: Informed by A Systematic Search of Existing Strategies

5.1 Author's Preface

The rarity of ITP poses unique methodological challenges to the creation of clinical practice guidelines, specifically the limited available evidence in the literature to address research questions. Previous clinical practice guidelines (CPGs) for rare diseases have highlighted the difficulty of making recommendations when limited evidence is available in the literature. To solve the methodological challenges posed by limited available evidence, this PhD project utilizes the collection of original data through retrospective chart reviews to inform recommendations in the development of CPGs for rare diseases, as exemplified by the ITP Emergency Management Guideline. This section will evaluate the advantages of collecting original data compared to strategies used in other guidelines. My role as first author was to design the novel methodology and write the manuscript.

5.2 Introduction

Evidence-informed clinical practice guidelines (CPGs) merge best evidence, local contexts, and patient choice to improve quality of care, and improve patient outcomes.[1] Formulating appropriate research questions and collecting evidence to address the research questions are central to CPG development.[2] Panels, comprised of various experts, identify research questions of interest and collect evidence relating to all important outcomes, as well as the values patients place on these outcomes.[3] Panels rely on existing high quality systematic reviews or develop their own new systematic reviews to collect available evidence.

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE)Working Group system[4] suggests possible approaches to rating 'certainty of the evidence' for systematic reviews, health technology assessments, and guidelines.[5] Certainty of evidence refers to the degree of assurance that the reviewer has that the effect is above a prespecified threshold.[5] Based on five factors, systematic review authors can rate the certainty of evidence from high to very low.[3] Infrequently, an additional three factors can rate up the certainty of evidence for observational studies.[6] Evidence is used to produce GRADE evidence profile and summary of findings table that will inform the type and strength of a recommendation made by a guideline panel related to the health care question of interest.[7-11] Ideally, the guideline will collect and refer to direct evidence, where studies compare the interventions of interest in the specific population for the CPG, as well as report outcomes important to patients.[12]

A rare disease is defined as disease with a prevalence of fewer than 1 in 2,000 individuals.[13] Although one rare disease may impact a small proportion of the population, cumulatively, rare diseases impact 400 to 700 million people globally and pose a large and costly

burden on the health system.[14] Developing CPGs for rare diseases poses several challenges. Due to the small population size and thus, limited availability of patients[15], studies that address the research questions of a CPG may not exist or may be at a greater risk of bias: it may be difficult to enroll sufficient patients to power randomized controlled trials or high quality studies.[16] Other potential limitations in rare disease studies that would decrease the certainty of evidence, even when errors to bias have been avoided, include inconsistency of results, indirectness, or imprecision.[17] When direct evidence is limited, recommendations can be informed by indirect evidence, but this too is likely to be of low quality.[12,17] The lack of available evidence in the literature thus poses a methodological challenge for a CPG's research questions.

Immune thrombocytopenia (ITP) is a rare autoimmune disease with a prevalence of 9.5 per 100,000 people, or approximately 1 in 10,000 children and 1 in 8,000 adults.[18-20] ITP is characterized by an increased risk of bleeding from low platelet counts (below 100 x 10^9/L).[21] The reported rate of all major bleeds in ITP is approximately 10% in adults and up to 20% in children.[22,23] Critical bleeds in patients with ITP, while occurring less frequently, require urgent and multipronged treatments typically delivered in the emergency department (ED) setting.[24,25] CPGs for the emergency management of critical ITP bleeds are lacking, contributing to substantial variability in practice and patient outcomes.[26] We identified the need for a guideline for the management of critical bleeding in ITP patients to help clinicians manage these life-threatening events.

To address the methodological challenges posed by limited available evidence in CPG development for rare diseases, we develop a novel methodology for generating evidence where existing published evidence is lacking. In this paper, we outline the methodology of original data collection within the CPG development process and compare this approach with other strategies

for addressing limited evidence in rare disease CPG design. We outline how data collected from patient medical records can be combined with publish literature to inform recommendations, in the context of the ITP Emergency Management Guideline.

5.3 Methods

To determine the appropriate methodology for the development of a CPG for the management of critical bleeding in patients with ITP, we identify existing strategies for addressing limited evidence from rare disease CPGs. We conduct a systematic literature search using the terms “Practice Guideline” and “Rare Diseases” in Embase, MEDLINE, and the grey literature. The references of relevant articles are screened. We include articles that discussed approaches of CPG development when evidence is lacking and CPGs for rare diseases that implemented novel strategies for addressing limited evidence.

Following the evidence pyramid[27], we develop a hierarchy of strategies based on the GRADE approach that addresses limited evidence in rare disease CPGs, specifically when not only randomized controlled trials, but satisfactory cohort studies and even case series are not available. Strategies are ranked based on the five GRADE factors that may decrease the certainty of evidence and the potential impacts on the strength of the recommendation for the CPG. We outline the advantages and disadvantages for each strategy and consider their application to the ITP Emergency Management Guideline. Upon reviewing the existing strategies for addressing limited evidence, we develop a novel methodology for application to the ITP Emergency Management Guideline.

5.4 Results

Existing Strategies for Addressing Limited Evidence

The systematic search of the literature identified 1,340 publications. Of which, 15 studies are included (**Figure 2**). Grey literature searches identified an additional three relevant CPGs. In total, we included five rare disease CPGs that apply unique strategies for evidence synthesis[28-32] and 10 articles outlining considerations and strategies for developing rare disease CPGs[33-42] (**Table 4**). **Table 5** summarizes the identified strategies that were applied to inform recommendations. We discuss the existing strategies in decreasing order of quality according to the hierarchy below. The advantages and disadvantages of each strategy are outlined in **Table 6**.

Hierarchy of Strategies from Existing Rare Disease Guidelines

a) Existing Patient Registries

Patient registries are observational studies that capture patient outcomes cross-sectionally, prospectively, or retrospectively.[42,43] Two CPGs were identified that incorporated direct evidence from existing patient registries to inform recommendations. The McMaster RARE BestPractices guideline on diagnosis and management of Catastrophic Antiphospholipid Syndrome (CAPS) used patient registry data to inform panel considerations on the natural history and impact of the disease.[44] The international CAPS registry featured information from patients and published reports from 1992 to 2014. At the time of the guideline, data was available for over 500 patients but was yet to be published.[45] Raw mortality scores were generated for available therapies during the meeting, which introduced a unique approach to informing recommendations. For example, during the discussion on rituximab, the panel searched the international CAPS registry to identify patients who received rituximab and a contemporaneous cohort of patients not treated with rituximab.[31] A crude odds ratio representing patient mortality with rituximab was calculated and presented to the panel. Conclusions from the

analyses were included in evidence summaries to inform recommendations and published separately.[31,45]

The American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation collaborated with the Center for Blood and Marrow Transplant Registry, a working group of over 300 transplantation centers that contribute data on consecutive allogeneic and autologous transplantations, examined data from an established registry.[30] Due to the absence of studies that directly compared outcomes in the intended population, during the meetings, the panel examined data from the registry to determine the relative effects of donor type, source of stem cells, and transplantation conditioning intensity on outcomes in patients.[30] Conclusions from the analyses were included in evidence summaries to inform recommendations and published separately.[30,46]

The advantages of utilizing data from patient registries include the availability of already existing data that may be collected from multiple sites. Despite these advantages, there are some concerns with relying on registries for evidence. Firstly, the development of registries for rare disease is resource intensive. Registries may not exist when evidence is needed to inform CPGs. Also, registries may not be representative or enroll the population of interest for the guideline[12], i.e. ITP patients with critical bleeds. In addition, there are concerns regarding the accuracy and completion of registry information.[47-49] The CPG would need to rely on variables that were already specified, which might not address the particular research questions of the CPG. Even with these limitations, registries offer a valuable source of information when evidence is lacking. Protocols to search patient registries and identify relevant patients/outcomes should be established *a priori*.

b) Systematic Recollection of Clinical Experiences by Experts

Experts can provide their recollection of clinical experiences using structured case report forms or surveys as a form of evidence. Three guidelines utilized structured observational forms or surveys to capture the clinical experiences of experts and inform recommendations. In the Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines 2022[29], a survey was conducted to evaluate the practice of the international experts who constituted the Task Forces on hypoparathyroidism. Since very limited evidence addressing monitoring in hypoparathyroidism was identified through a systematic literature review, a survey allowed for a systematic approach to describe current practice by asking experts in the field to select the responses that best reflect their current practice.[29] Respondents reported how frequently they assessed a wide variety of variables for monitoring, with testing being considered useful if a minimum of 70% of respondents used the test in over 70% of their patients.[29] The survey collected the practices of the clinical experts, but not their patient experiences.[29]

The McMaster RARE BestPractices guideline on diagnosis and Management of CAPS panel members provided their 'expert experience' by recollecting their clinical experiences with a patient population without referring to patient charts.[31,44] Expert experiences were systematically solicited through structured observation forms to collect diagnostic information, demographic characteristics, interventions, and the effect of the intervention on outcomes of interest for the CPG.[31]

Similar forms were designed for the NHF-McMaster Guideline on Care Models for Haemophilia Management CPG.[32] Clinical observations were captured systematically from the panel and external experts in the field.[32] Uniquely, the effect of healthcare management on patient-important outcomes was reported as beneficial or harmful, with effects ranging from

large to small or no effect. Data from the recollection of clinical experiences was incorporated into the evidence summaries to inform recommendations by the panel.

In the American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults, panel members were surveyed systematically to provide their recollection of patient experiences.[29] The survey results included responses from 10 experts and their practice patterns within the patient population of interest. It reported the experts' recollection of patient mortality at certain time points, reported quality of life, burden on caregivers, and toxicity for those who continued therapy indefinitely.[29] They reported their recollection of the outcomes of patients who stopped therapy as well.[29]

In these CPGs, evidence was provided by the clinical experts through systematic recollection of clinical experiences. When panel members provide responses that depend on their ability to recall past events, there is a risk of recall bias. Recall bias can be related to several factors including length of the recall period, characteristics of the disease under investigation (acute, chronic), and patient/sample characteristics (age, event rate).[50,51] For example, clinicians may be more likely to recall patients with poorer outcomes. Recall bias can either underestimate or overestimate the true effect or association of an intervention on the outcome.[50] In addition, relying on recall introduces the risk of confirmation bias, where a decision is made according to the clinician's preconceptions, beliefs, or preferences.[52,53] This can result in contradictory evidence being ignored or overlooked.[52,53] While clinical experts often reflect on their clinical experiences to inform their opinions on best practices, systematic recollection of clinical experience creates a formal method to include evidence that has not been typically captured in CPGs.

c) Indirect Evidence

Evidence is considered indirect when studies are conducted in a different patient population or assess different interventions than those of interest, resulting in lower quality of evidence being rated down.[12] This strategy has been used in many guidelines where comparable populations have sufficient evidence, but the intended population/intervention for the CPG does not.

The CPG for hemophilia integrated care models included an a priori plan to seek indirect evidence from other common chronic conditions.[32] Studies in people with asthma or chronic obstructive pulmonary disease were considered to be sufficiently direct by the panel members, since the subject of interest was the mode of care delivery, which may be shared across diseases. In the previously mentioned sickle cell disease CPG, a systematic review was performed to assess the effects of transplantation on outcomes of interest.[30] The panel identified published systematic reviews and key RCTs that separately evaluated various types of standards of care and compared with other transplantation trials as a form of pooled results to inform its transplantation recommendations. In addition, the acute myeloid leukemia CPG incorporated indirect evidence from studies of comparable patient populations.[29]

Evidence is limited when no studies involving the populations and/or interventions of interest to the guideline are available. When evidence from alternative patient populations or interventions are used as a source of information, the overall quality of evidence is rated down due to indirectness.

Summary of Existing Strategies Utilized by Rare Disease Guidelines

CPG working groups apply various strategies to mitigate the impact of limited evidence in rare disease guidelines.[40] All the strategies applied to rare disease CPGs outlined above aimed

to improve CPG development by incorporating additional evidence to inform recommendations when existing literature was very limited. Strategies that use indirect evidence, recollection of expert experiences, or ad hoc searches of patient registry data, all have strengths and limitations (**Table 6**). However, there are inherent biases to these strategies that limit the strength of recommendations. Ideally, a method of collecting novel data to inform guidelines is completed a priori, directly from patients or their medical records, and completed systematically to capture the patient population and variables of interest of the CPG at multiple locations.

Identifying the Lack of Evidence in ITP Critical Bleeds

The ITP Emergency Management Guideline Panel is an independent group of clinical experts in hematology and emergency medicine, research methodologists, and patient partners, who are developing an evidence-based CPG for the treatment of critical bleeding in patients with ITP. The panel identified questions of interest. However, the guideline panel hypothesized a priori that the rarity of ITP and critical bleeding in this patient population would limit the availability of evidence. A systematic review conducted to inform the CPG confirmed that direct evidence addressing treatment and management of critical bleeding in ITP patients was lacking. The systematic review identified 14,134 articles that discussed ITP patients (review ongoing). Only 50 articles that reported critical bleeding in ITP patients were included, including case reports.

The panel reflected upon the three identified strategies for addressing limited evidence in rare disease CPGs: existing patient registries, systematic recollection of clinical experiences, and indirect evidence. While there is an existing ITP registry, the McMaster ITP Registry does not capture ITP patients that met the newly defined criteria for a critical bleed and does not capture ITP patients who present to the ED.[54] Secondly, indirect evidence from other patient populations,

i.e., ITP patients without critical bleeding, would weaken recommendations that could be made for the ITP Emergency Management Guideline. Lastly, the recollection of clinical experiences could still potentially introduce recall and confirmation bias. Therefore, having exhausted the possibility of using existing strategies for rare disease CPG development, we proceeded to develop a new methodology.

Developing a Novel Methodology of Original Data Collection to Generate Evidence

Members of the ITP Emergency Management Guideline Panel proposed integrating the collection of data through a multisite retrospective study as a form of direct evidence to strength recommendations that can be made and address the gap in available evidence. The panel agreed to conduct a cohort study with the CPG development process to maximize the directness of the evidence for the purposes of the CPG and minimize potential risks of bias inherent to the study. Evidence collected from the retrospective cohort study will be analyzed and combined with existing evidence from the literature to inform the ITP Emergency Management Guideline recommendations (**Figure 3**).

There are important methodological features of observational studies that would be required to minimize the risks of bias.[9] To optimize the representativeness of the sample, multiple sites will be enrolled in the study. Rigorous eligibility criteria will be developed to reflect the population of interest for the guideline, i.e., ITP patients experiencing a critical bleed. Variables of interest and potential confounders will be identified by the guideline panel and informed by previous observational studies. Data will be collected using electronic case report forms. Variability in information and possible missingness of data across sites will be incorporated into the design of the case report forms. The feasibility of collecting data from patient medical records will be assessed in the pilot work of the cohort study and inform the data

elements of the case report forms. An operations manual will be created and provided to all sites to outline the cohort study procedures for retrieving relevant information for each variable. All sites will collect data from patient medical records systematically and in duplicate to validate the data collected. Any discrepancies or errors will be resolved through adjudication by the site leads and clinical experts on the guideline panel.

5.5 Discussion

The rarity of ITP poses unique methodological challenges to the creation of CPGs, specifically the limited available evidence in the literature to address research questions.[15,36,37,39,55] Previous rare disease CPGs addressed the lack of evidence by using indirect evidence, recollection of expert experiences, or ad hoc searches of patient registry data. However, there are inherent biases to these strategies that limit the strength of recommendations.

In situations where evidence in the literature is lacking, guideline methodology can collect original data retrospectively from patient medical records to use as direct evidence to inform recommendations. This new method will include conducting a cohort study to reflect and inform the health care questions of interest for the CPG and minimize the risk of bias. This methodology was developed to generate the highest quality of evidence available to inform the development and recommendations of the ITP Emergency Management Guideline. We will conduct a multicenter cohort study of ITP patients with critical bleeding presenting to the ED. Results from the cohort study will be integrated into the evidence-to-decision framework to supplement existing literature and inform recommendations. The novel methodology of collecting direct evidence from patient medical records to inform recommendations can be applied to the development of CPGs for other rare diseases.

There are strengths to integrating the generation of direct evidence into the CPG development process for rare diseases. The novel approach of integrating data collecting in the form of a cohort study will capture data from multiple locations and populations, and be designed to address the research question directly. It also provides a network of sites that can be updated in future revisions of the guideline. Secondly, the novel approach to incorporating data captured from patient medical charts limits confirmation bias and recall bias due to the systematic process of identifying patients and capturing available data. Thirdly, the novel approach of original data collection embedded within the CPG development process eliminates the need to rely on indirect evidence that would rate down the certainty of evidence.

In rare disease CPGs, it is anticipated that existing evidence in the literature will be mainly case series or case reports, resulting in very low certainty of evidence.[15,38] One potential limitation of this novel approach is that newly generated direct evidence can still be graded as low certainty of evidence depending on the study design, inconsistency of results, or imprecision; however, it may be considered an improvement when compared to evidence already available. In the ITP Emergency Management Guideline, the multi-site retrospective cohort study will likely be rated as low-quality evidence, which is an improvement from the anticipated very low certainty based on case reports and case series. Other limitations of the novel approach to CPG development implemented by the ITP Emergency Management Guideline include the availability of funding to support data collection simultaneously to the development of a CPG, the availability of clinical experts willing to oversee data collection at their site, and the lack of randomization or prospective data collection that rates down the quality of the study.

5.6 Conclusion

Since developing CPGs for rare diseases poses methodological challenges due to the limited available evidence in the literature, we propose a novel approach to CPG development and will implement the method in the formation of the ITP Emergency Management Guideline. The novel methodology includes generating direct evidence through a cohort study embedded in the CPG development process. The cohort study will be informed by the research questions of interest for the CPG. The aim of incorporating original data collection into the rare disease CPG development process is to improve the certainty of evidence and ultimately, the strength of recommendations. By conducting a retrospective cohort study, potential biases can be minimized compared to other available strategies for addressing limited evidence. This novel methodology for rare disease CPG development can be applied to other rare diseases where evidence is lacking.

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6 Conclusions

Critical bleeding in ITP patients are life-threatening events that can cause life-long morbidity and require rapid, coordinated treatment. Current international ITP guidelines sponsored by the American Society of Hematology provide treatment recommendations for patients with severe thrombocytopenia in the outpatient setting, but does not address the treatment of bleeding beyond minor bleeds or skin manifestations. The ITP Emergency Management Guideline was initiated to fill this gap in CPGs and inform patient care.

The heterogeneity of ITP poses diagnostic challenges, with one in seven ITP patients being misdiagnosed over their disease course. The first objective of this PhD thesis was evaluated through a study of the performance characteristics of platelet autoantibodies in ITP patients following strict clinical criteria to increase the accuracy of diagnosis. The sensitivity of platelet autoantibody testing increased when patients were classified using strict clinical criteria (high pretest probability), and specificity was unchanged. We found that patients with the highest platelet autoantibody levels were most likely to have ITP and severe thrombocytopenia. While platelet autoantibody testing may not be an adequate screening test on its own, it may help rule-in the diagnosis of ITP.

Variability in the definitions of bleeding in ITP patients introduces difficulties to identifying the appropriate patient population for the ITP Emergency Management Guideline. The second objective of this PhD thesis was achieved through developing a standardized definition of bleeding emergencies in ITP patients, now known as critical bleeding. A critical ITP bleed was defined as: (1) a bleed in a critical anatomical site including intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome; or (2) an ongoing bleed that results in hemodynamic instability or respiratory

compromise. It incorporates both anatomic and physiologic risk, and pertains to patients with confirmed or suspected ITP who typically have severe thrombocytopenia (platelet count below 20 $x10^9$/L). The standardized definition of critical bleeding in ITP patients will allow patients to be identified consistently for the ITP Emergency Management Guideline, as well as future research and clinical purposes.

The effectiveness of available treatment strategies for critical bleeding remains unknown. Studies have addressed potential treatments for bleeding, however, they have not been systematically reviewed in the context of emergency management. The third objective of this PhD thesis was accomplished by developing a protocol to identify and analyze published literature that assesses the effectiveness of treatments in ITP patients with critical bleeding. Results of this systematic review will inform the ITP Emergency Management Guideline panel recommendations.

Developing CPGs for rare diseases is methodologically challenging and various strategies have been used to supplement the limited evidence for existing rare disease guidelines. The fourth objective of this PhD thesis was accomplished by developing a novel methodology for rare disease CPG that addresses the lack of available evidence by generating direct evidence through a cohort study embedded in the CPG development process. The aim of incorporating original data collection into the rare disease CPG development process is to improve the certainty of evidence and ultimately, the strength of recommendations. This novel methodology for rare disease CPG development can be applied to other rare diseases where evidence is lacking.

Future publications based on the work of this PhD thesis include: the “treatment of critical bleeding events in patients with immune thrombocytopenia: a systematic review and meta-

analysis"; protocol for the multi-center retrospective cohort study integrated into the CPG process; results of the multi-center retrospective cohort study of ITP patients presenting to the ED; the adult ITP Emergency Management Guideline; and the pediatric ITP Emergency Management Guideline.

The ITP Emergency Management Guideline panel was formed in 2019 and continues to work on the completion of CPGs for adults and children with ITP who need emergency management for critical bleeds. This undertaking has been endorsed by ASH. Upon completion of the cohort study, the CPG panel will begin the process of creating recommendations. All the components of this PhD thesis have allowed the ITP Emergency Management Guideline to prepare for the implementation of the novel methodology and publish CPGs to inform ITP emergency management.

7 Figures

7.1 Chapter 2 Figures

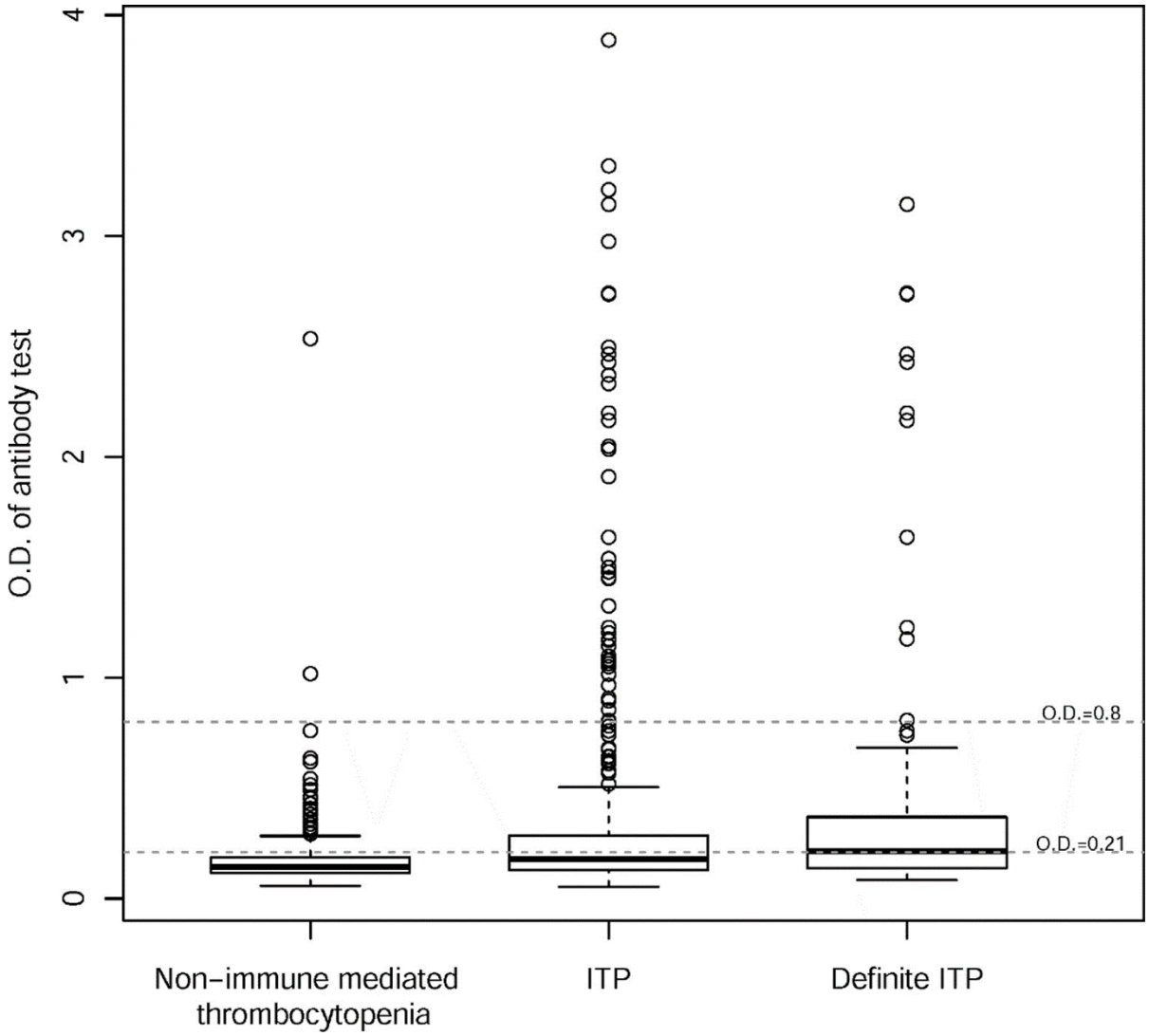

Figure 1. Box plot of optical density (OD) values for platelet autoantibody testing for non-immune-mediated thrombocytopenia patients [median 0.15; interquartile range (IQR) 0.12–0.20], all immune thrombocytopenia (ITP) patients (median 0.18; IQR 0.13–0.29) and for definite ITP patients (median 0.21; IQR 0.14–0.37).

7.2 Chapter 3 Figures

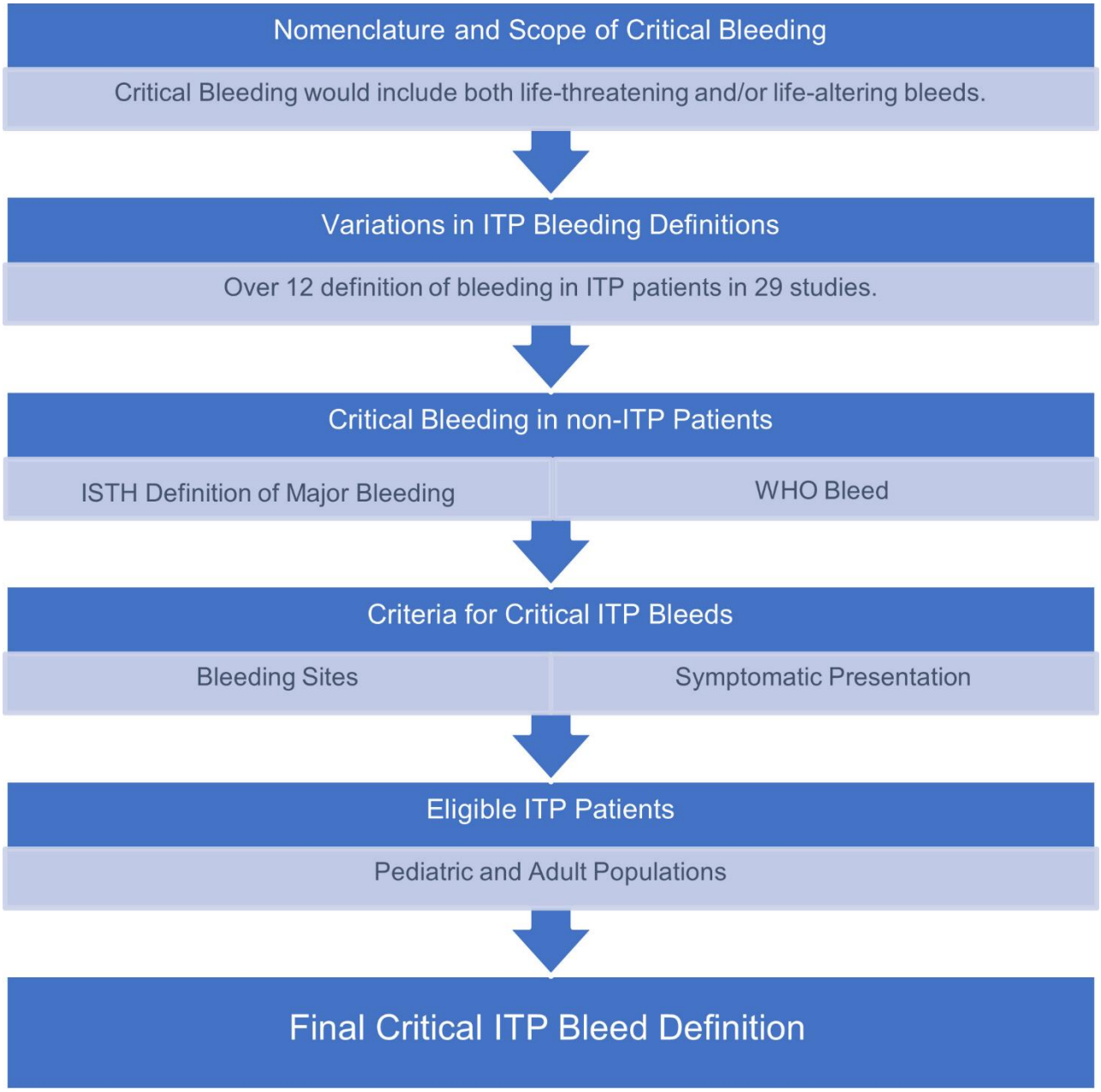

Figure 2. Method for defining critical ITP bleeds by the ITP Emergency Management Guideline Panel.

7.3 Chapter 5 Figures

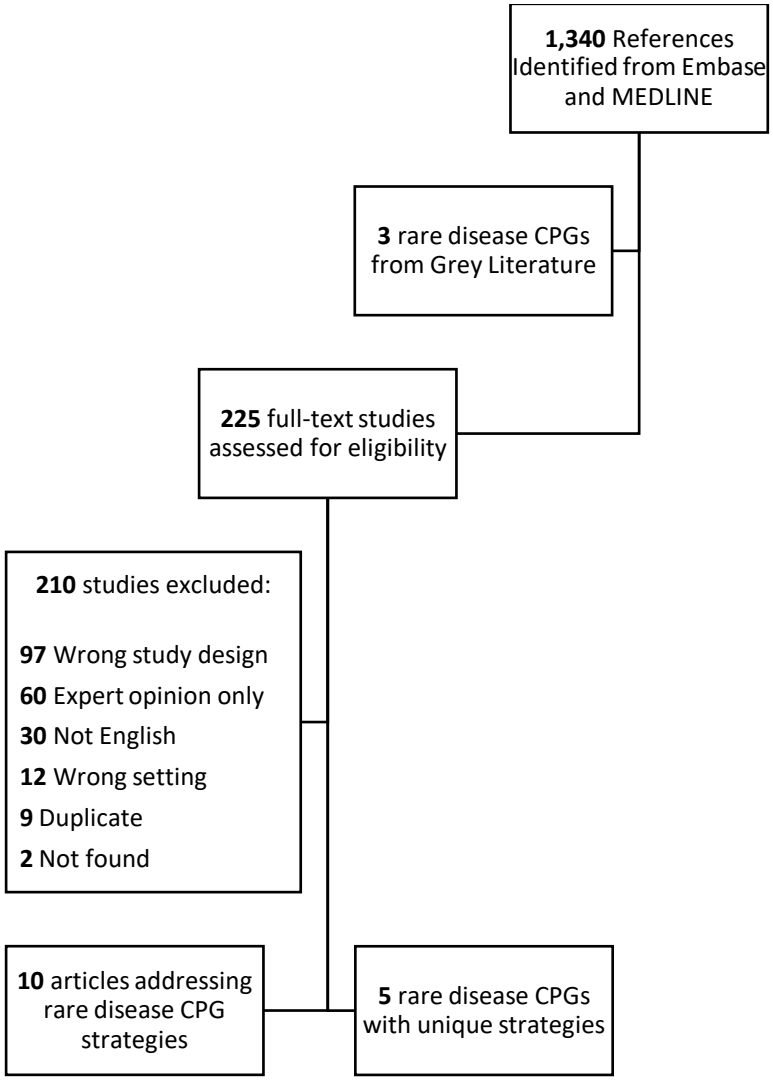

Figure 3. PRISMA diagram of article selection, inclusion, and exclusion. A total of 1,340 references were identified from systematic literature searches in Embase and MEDLINE, and additional 3 rare disease CPGs were identified from the grey literature. 225 full-text studies were assessed for eligibility and 210 were excluded. A total of 10 articles addressing strategies for rare disease CPGs and 5 rare disease CPGs using unique strategies were identified.

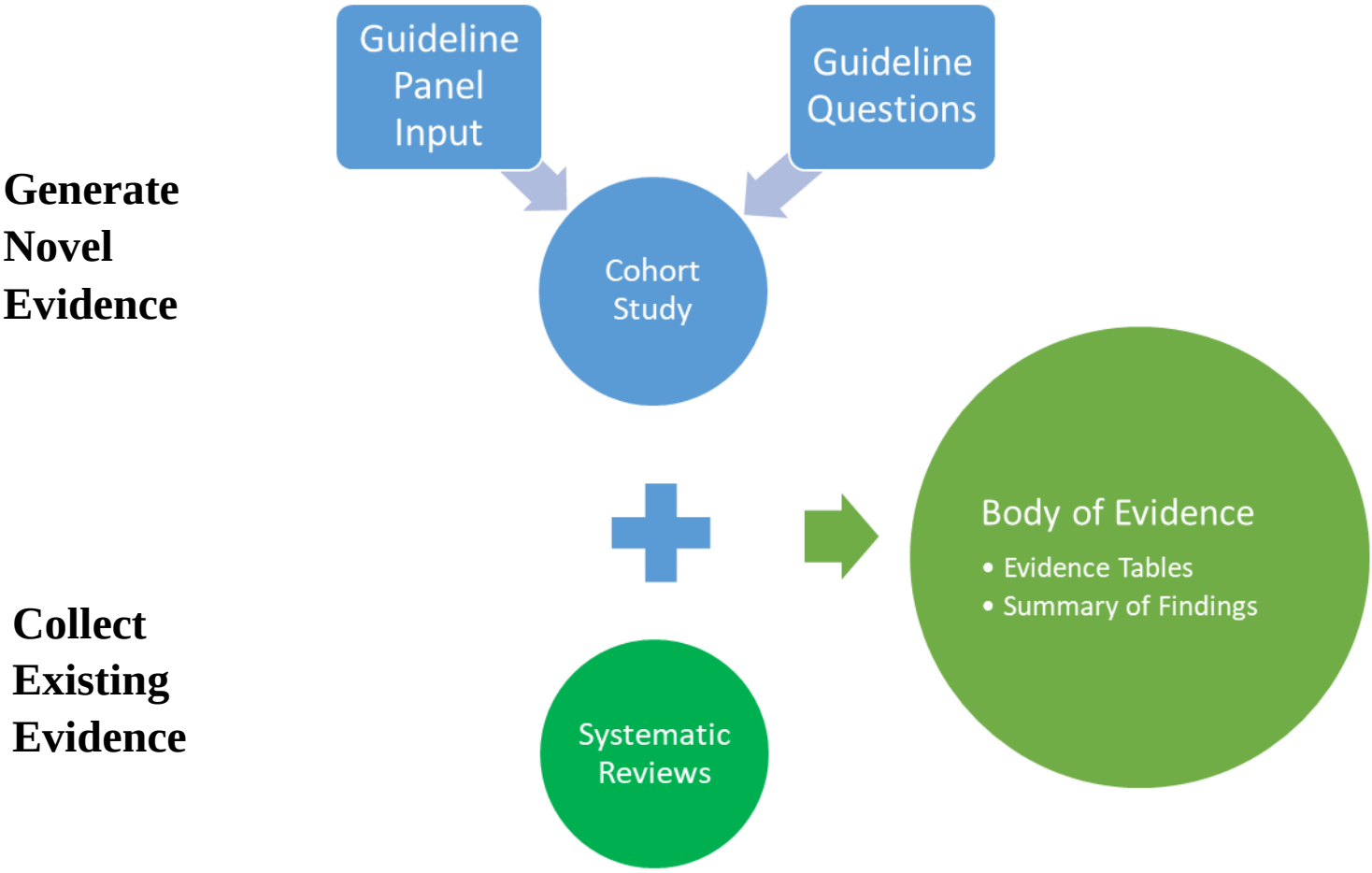

Figure 4. Novel method of integrating data collection into the clinical practice guideline development process to identify direct evidence. Patient partners, clinical experts, knowledge users, and methodologists inform the design of the cohort study to capture relevant evidence for the guideline. Cohort study data is combined with existing evidence identified through systematic reviews of the literature. Both sources of evidence are incorporated into the evidence summaries and summary of findings for the CPG to inform recommendations, with emphasis on the highest quality of evidence captured in the cohort study component of the novel methodology.

8 Tables

8.1 Chapter 2 Tables

(a)

	ITP patients	**'Definite ITP' subgroup***	**Non-immune-mediated thrombocytopenia‡**
	***n* = 422**	***n* = 102**	***n* = 146**
Baseline patient characteristics			
Age at diagnosis, mean (SD), years	48.0 (19.3)	46.3 (19.8)	52.9 (19.0)
Female, *n* (%)	256 (60.7)	62 (60.8)	69 (47.3)
Follow-up, median (IQR), years	3.43 (1.1–7.8)	5.1 (2.2–8.6)	1.0 (0.2–2.4)
Lowest platelet count ever median (IQR)	20 (5–57)	4 (2–10.8)	56 (24.3–83.8)
ITP treatments received median (IQR)	2 (1–4)	4 (2–5)	0 (0–1)
Patients with grade 2 bleeds, *n* (%)	40 (9.5)	11 (10.8)	5 (3.4)

(b)

	ITP	**Definite ITP**	**Definite ITP with high antibody levels**
	***n* = 422, % (95% CI)**	***n* = 102 (95% CI)**	***n* = 26 (95% CI)**
Performance of platelet antibody tests			
Sensitivity	48.3 (43.5–53.2)	64.7 (54.6–73.9)	25.5 (17.4–35.1)
Specificity	75.3 (67.5–82.1)	75.3 (67.5–82.1)	97.3 (93.1–99.3)
Positive predictive value	85.0 (80.8–88.4)	64.7 (57.2–71.6)	86.7 (70.1–94.8)
Negative predictive value	33.5 (30.7–	75.3 (69.8–80.2)	65.1 (62.4–67.7)

36.5)

Table 1. Demographics of patients with immune thrombocytopenia (ITP) and non-immune thrombocytopenia and performance of the platelet antibody test for all patients with ITP, patients with definite ITP*, and patients with definite ITP and high antibody levels (optical density, OD > 0.8).

CI, confidence interval; IQR, interquartile range.

* Definite ITP is defined as patients a platelet count rise >50 × 10^9/l with doubling of baseline within 4 weeks after receiving high-dose intravenous immunoglobulin or high-dose corticosteroids.

† Causes of non-immune-mediated thrombocytopenia: unknown: *n* = 3; alcohol-related thrombocytopenia: *n* = 5; drug-related bone marrow suppression: *n* = 1; familial thrombocytopenia: *n* = 34; liver disease: *n* = 15; myelodysplastic syndrome: *n* = 24; splenomegaly/hypersplenism: *n* = 49; thrombocytopenia associated with malignancy: *n* = 1; thrombotic microangiopathy (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome): *n* = 14.

8.2 Chapter 3 Tables

Bleeding Assessment Tool	**Definition**
Buchanan scale 2002[9] (Grade 3 or higher)*	Grade 3: Moderate- overt mucosal bleeding (epistaxis, gum bleeding, oropharyngeal blood blisters, menorrhagia, gastrointestinal bleeding, etc.) that does not require immediate medical attention; Grade 4: Severe- mucosal bleeding or suspected internal hemorrhage (in the brain, lung, muscle, joint, etc.) that requires immediate medical attention or intervention; Grade 5: Life-threatening or fatal- documented intracranial hemorrhage or life-threatening or fatal hemorrhage in any size. †Modified Buchanan scale: Grade 3: "wet" mucosal bleeding; Grade 4: hemorrhage requiring immediate medical attention including suspected ICH; Grade 5: ICH or fulminant life-threatening bleeding
Page score[10] (Grade 2)*	Grade 2 ('marked' bleeding) defined as >5 bruises with size >2 cm and/or diffuse petechiae; multiple blood blisters and/or gum bleeding lasting longer than 5 minutes on history; epistaxis >5 minutes per episode; gross gastrointestinal bleeding; macroscopic hematuria; vaginal bleeding more than spotting outside of regular period or very heavy period; pulmonary hemorrhage; or intracerebral hemorrhage.
Mazzucconi scale[11] (Grade 3 or higher)*	Grade 3: major mucous hemorrhage with copious loss of blood without sequelae; Grade 4: major mucous and/or parenchymal hemorrhage with copious loss of blood with sequelae and/or life-threatening or death
Buchanan scale 1984[12] (Grade 3 or higher)*	Grade 3: moderate to severe cutaneous or mucosal bleeding without measurable decline in hemoglobin; Grade 4: severe external bleeding of sufficient magnitude to cause a decline in the patients' hemoglobin by more than 1.0 g/dl; Grade 5= life-threatening; Grade 6: fatal. (Grade 5 and 6 were added to the Buchanan scale by the study).
Blanchette scale[19] (Severe)*	Severe: Extensive mucosal hemorrhage; a marked increase in the extent of bruising/ petechial lesions, or both, after administration to the hospital; fundal hemorrhage, and significant overt bleeding defined as epistaxis requiring replacement erythrocyte transfusion support, macroscopic hematuria, GI bleeding, or ICH.
Dutch protocol[20] (Grade 3 or higher)*	Grade 3: persistent mucosal bleeds and/or hemoglobin decrease of >1.6 g/dl; Grade 4: life-threatening bleeds.
Khellaf score[21] (Cumulative score >8)*	Weighted cumulative score based on the following: age, extent of cutaneous bleeding, degree of mucosal bleeding, gastrointestinal bleeding, urinary bleeding, genitourinary tract bleeding, and central nervous system bleeding.

CTCAE scale[13] (Grade 3 or higher)	Grade 3: severe; Grade 4: life-threatening; Grade 5: fatal.
WHO scale[14] (Grade 3 or higher)	Grade 3: gross blood loss; Grade 4: debilitating blood loss.
Anticoagulant bleeding tool[6] (Major bleeding)	Major: Clinically overt bleeding associated with either a decrease in hemoglobin of at least 2 g/dL or the requirement for transfusion of at least 2 units of red blood cells; or bleeding that was intracranial, intraocular, retroperitoneal, or intraarticular in a major joint.
Adverse Events[15]	Bleeding events report as adverse events.
Categorical[6, 15] (varied)	Bleeding events were rated as severe, life-threatening, or fatal.
Descriptive[6, 15] (varied)	Skin: extensive petechiae and bruises associated with large ecchymoses; Nose: repeated or continuous bleeding requiring nasal packing; Oral cavity: continuous bleeding; Genitourinary tract: major menorrhagia and/or metrorrhagia, gross haematuria; Internal: gastrointestinal, retinal, intracranial haemorrhage, bleeding into the lungs, joints, muscles and other vital organs.

Table 2. Existing definitions of severe bleeds used in patients with immune thrombocytopenia (ITP)
* Bleeding assessment tools specific to ITP patient populations.

A bleed in an anatomical site including intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome; or An ongoing bleed that results in hemodynamic instability or respiratory compromise.[a]

Table 3. Consensus definition of a critical ITP bleed. This definition is intended for patients with confirmed or suspected ITP who typically have severe thrombocytopenia (platelet count $<20 \times 10^9$/L).

[a] The definitions of hemodynamic instability and respiratory compromise are center and context specific. In adults, bleeding that results in hemodynamic instability may be defined as bleeding that causes a decrease in systolic blood pressure of 20 mmHg from baseline, or a decrease in mean arterial pressure by 10 mmHg, or blood pressure of less than 90 mmHg at admission.[16, 17] Bleeding that results in respiratory compromise may be defined as respiratory rate ≥30/min, or blood oxygen saturation ≤92%, or partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, or the need for invasive or non-invasive mechanical ventilation as a direct result of bleeding (e.g., blood in the airway) or an indirect result of bleeding (supportive care).[22] For infants and children, age and weight based pediatric-specific definitions should be considered.[23]

8.3 Chapter 5 Tables

Rare Disease CPGs with Unique Strategies for Addressing Lack of Evidence
McMaster RARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome[49]
NHF-McMaster Guideline on Care Models for Haemophilia Management[50]
American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation[51]
American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults[52]
Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines 2022[29]
Articles Outlining Strategies to Address the Lack of Evidence in Rare Disease CPGs
The Rare Knowledge Mining Methodological Framework for the Development of Practice Guidelines and Knowledge Translation Tools for Rare Diseases[46]
European reference networks and guideline development and use: Challenges and opportunities[53]
Recommendations and guidelines in the JIMD: suggested procedures and avoidance of conflicts of interest[54]
Improving care for rare diseases: A methodological guideline to develop effective clinical guidelines[45]
Developing methodology for the creation of clinical practice guidelines for rare diseases: A report from RARE-Bestpractices[44]
The Challenge of Guideline Development When Evidence Is Sparse[55]
Clinical practice guidelines in rare diseases[56]
Strategies for eliciting and synthesizing evidence for guidelines in rare diseases[57]

Providing guidance in the dark: Rare renal diseases and the challenge to improve the quality of evidence[58]
Rare Disease Registries Are Key to Evidence-Based Personalized Medicine: Highlighting the European Experience[59]

Table 4. Included Articles.

Guideline	Description	Strategies for Addressing Limited Evidence in Hierarchy
McMaster RARE BestPractices guideline on diagnosis and Management of Catastrophic Antiphospholipid Syndrome [49]	•Pilot exercise in guideline development for a rare disease to provide a proof of principle that guidelines can be developed for rare diseases and assist in clinical decision making for CAPS. •GIN-McMaster Guideline Development checklist and GRADE approach.	**Patient registry data.** o During the Panel meeting, a search for the mortality of registry patients who had received rituximab was performed and compared to the mortality of a contemporaneous cohort of patients not treated with rituximab. **Systematic recollection of clinical experiences.** o Systematically solicited through structured observation forms.
American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation (SCD)[51]	•Evidence-based guidelines of the American Society intended to support patients, clinicians, and health professionals in their decisions about hematopoietic stem cell transplantation for SCD. •Based on the GRADE approach.	**Patient registry data.** o Collaborated with the Center for Blood and Marrow Transplant Registry (CIBMTR), a working group of >300 transplantation centers that contribute data on consecutive allogeneic and autologous transplantations. **Indirect evidence**. o Indirect evidence from non-SCD populations.
American Society of Hematology 2020 guidelines for treating	•Evidence-based guidelines to support patients, clinicians, and other health care professionals in their	**Systematic recollection of clinical experiences.** o Conducted a survey

newly diagnosed acute myeloid leukemia in older adults[52]	decisions about management of AML in older adults. •Based on the GRADE approach.	among the panel members to systematically collect their experiences. ○ The survey was based on the panelists' best recollection of experiences because it was not feasible to collect information from clinical records given the timelines for the development of these guidelines. **Indirect evidence.** ○ Studies of comparable patient population.
National Hemophilia Foundation - McMaster Guideline on Care Models for Haemophilia Management[50]	•Identify evidence-based best practices in haemophilia care delivery, and discuss the range of care providers and services that are most important to optimize outcomes for persons with haemophilia across the United States. •Based on the GRADE approach.	**Systematic recollection of clinical experiences.** ○ Conducted a survey among the panel members to systematically collect their experiences. ○ The survey was based on the panelists' best recollection of experiences. **Indirect evidence.** ○ Specified in an a priori plan to seek indirect evidence from other common chronic conditions.
Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International	•Evidence-based recommendations to address the prevention, diagnosis and management of hypoparathyroidism. •Based on the GRADE	**Systematic recollection of clinical experiences.** ○ Conducted a survey among the panel members to systematically describe current practice.

Workshop	approach.	
ITP Emergency Management Guideline	• Evidence-based guidelines to support patients, clinicians, and other health care professionals in their decisions about emergency management of critical bleeds in ITP patients. • Based on the GRADE approach.	**Direct evidence from observational study.** o Collected data for the purposes of the guideline in a multi-site retrospective cohort study.

Table 5. Rare Disease CPGs Addressing Limited Evidence.

Strategy for Addressing Limited Evidence in Hierarchy	Advantages	Disadvantages
Direct evidence from observational study.	• Interventions and outcomes collected for the purpose of the guideline questions of interest. • Representativeness of sample.	• Feasibility. • Retrospective and non-randomized study.
Patient registry data.	• Direct evidence from patient registry. • Systematically collected expert experience forms.	• Limited generalizability. • Recall bias. • Confirmation bias. • Protocol for reviewing patient registry data not specified a priori.
Systematic recollection of clinical experiences.	• Systematically collected expert experience through systematic survey with structured forms.	• Limited generalizability. • Recall bias. • Confirmation bias.
Indirect evidence.	• Readily available evidence that can be obtained from comparable populations.	• Recall bias. • Confirmation bias. • Protocol for reviewing patient registry data not specified a priori. • Indirectness.

Table 6. Advantages and disadvantages of methodologies addressing limited evidence in developing clinical practice guidelines for rare diseases.

9 Supplementary Materials

9.1 Chapter 4 Supplementary Materials.

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations (Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present)

Search Strategy:

1 Purpura, Thrombocytopenic, Idiopathic/ (6219)
2 ITP.mp. (6994)
3 ((idiopath* or immun* or autoimmun*) adj3 (thrombocytopen* or thrombo-cytopen*)).mp. (13105)
4 werlhof*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (301)
5 or/1-4 (15181)
Annotation: ITP block
6 randomized controlled trial.pt. (501343)
7 controlled clinical trial.pt. (93566)
8 randomized.ab. (472423)
9 placebo.ab. (205820)
10 drug therapy.fs. (2185180)
11 randomly.ab. (328804)
12 trial.ab. (497519)
13 groups.ab. (2020445)
14 or/6-13 (4653137)
Annotation: Cochrane HSSS RCT filter
15 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. (593236)
16 Randomized Controlled Trial/ (501343)
17 exp Randomized Controlled Trials as Topic/ (134022)
18 "Randomized Controlled Trial (topic)"/ (0)
19 Controlled Clinical Trial/ (93566)
20 exp Controlled Clinical Trials as Topic/ (139239)
21 "Controlled Clinical Trial (topic)"/ (0)
22 Randomization/ (102249)
23 Random Allocation/ (102249)
24 Double-Blind Method/ (156428)
25 Double Blind Procedure/ (0)
26 Double-Blind Studies/ (156428)
27 Single-Blind Method/ (28191)
28 Single Blind Procedure/ (0)
29 Single-Blind Studies/ (28191)
30 Placebos/ (34751)

31 Placebo/ (0)
32 Control Groups/ (1658)
33 Control Group/ (1658)
34 (random* or sham or placebo*).ti,ab,hw,kf,kw. (1469526)
35 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. (233336)
36 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. (978)
37 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw. (961925)
38 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw. (43025)
39 allocated.ti,ab,hw. (64040)
40 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw. (33713)
41 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. (7917)
42 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw. (389)
43 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw. (4834)
44 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. (7507)
45 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw. (27481)
46 or/15-45 (2114506)
Annotation: CADTH CCT filter
47 Epidemiologic Studies/ (8235)
48 exp Case-Control Studies/ (1061386)
49 exp Cohort Studies/ (1964837)
50 Case control.tw. (122549)
51 (cohort adj (study or studies)).tw. (197278)
52 Cohort analy$.tw. (7749)
53 (Follow up adj (study or studies)).tw. (48569)
54 (observational adj (study or studies)).tw. (102444)
55 Longitudinal.tw. (238438)
56 Retrospective.tw. (512294)
57 Cross sectional.tw. (339614)
58 Cross-sectional studies/ (320256)
59 or/47-58 (2938516)
Annotation: SIGN Observational studies filter
60 14 or 46 or 59 (7117946)
61 animals/ not humans/ (4642996)
62 60 not 61 (6347796)
63 5 and 62 (5984)

Database: EMBASE <1974 to 2020 March 10>

Search Strategy:

1 idiopathic thrombocytopenic purpura/ (14293)
2 ITP.mp. (11010)
3 ((idiopath* or immun* or autoimmun*) adj3 (thrombocytopen* or thrombocytopen*)).mp. (21810)
4 werlhof*.mp. (113)
5 or/1-4 (24094)
6 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (27059885)
7 human/ or normal human/ or human cell/ (20702328)
8 6 and 7 (20639718)
9 6 not 8 (6420167)
10 5 not 9 (22697)
11 random:.tw. or placebo:.mp. or double-blind:.tw. (1762920)
12 ((treatment or control) adj3 group*).ab. (852999)
13 (allocat* adj5 group*).ab. (32306)
14 ((clinical or control*) adj3 trial).ti,ab,kw. (404761)
15 or/11-14 (2466991)
Annotation: modified HIRU RCT filter
16 10 and 15 (2176)
17 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. (0)
18 Randomized Controlled Trial/ (593554)
19 exp Randomized Controlled Trials as Topic/ (175299)
20 "Randomized Controlled Trial (topic)"/ (175299)
21 Controlled Clinical Trial/ (463562)
22 exp Controlled Clinical Trials as Topic/ (182424)
23 "Controlled Clinical Trial (topic)"/ (10604)
24 Randomization/ (86167)
25 Random Allocation/ (82388)
26 Double-Blind Method/ (145847)
27 Double Blind Procedure/ (170229)
28 Double-Blind Studies/ (127818)
29 Single-Blind Method/ (36195)
30 Single Blind Procedure/ (38189)
31 Single-Blind Studies/ (38189)
32 Placebos/ (290937)
33 Placebo/ (347180)
34 Control Groups/ (110448)
35 Control Group/ (110448)
36 (random* or sham or placebo*).mp. (2011398)
37 ((singl* or doubl*) adj (blind* or dumm* or mask*)).mp. (301261)
38 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).mp. (1305)
39 (control* adj3 (study or studies or trial* or group*)).mp. (8016522)

40 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (54137)
41 allocated.mp. (82712)
42 ((open label or open-label) adj5 (study or studies or trial*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (61524)
43 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).mp. (11832)
44 (pragmatic study or pragmatic studies).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (564)
45 ((pragmatic or practical) adj3 trial*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (5188)
46 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (11837)
47 (phase adj3 (III or "3") adj3 (study or studies or trial*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (121854)
48 or/17-47 (8800670)
Annotation: CADTH CCT filter
49 10 and 48 (5470)
50 clinical study/ (154759)
51 case control study/ (152869)
52 family study/ (25993)
53 longitudinal study/ (136670)
54 retrospective study/ (888509)
55 prospective study/ (585814)
56 cohort analysis/ (556646)
57 (Cohort adj (study or studies)).mp. (294384)
58 (Case control adj (study or studies)).tw. (130860)
59 (follow up adj (study or studies)).tw. (62364)
60 (observational adj (study or studies)).tw. (161004)
61 (epidemiologic$ adj (study or studies)).tw. (104626)
62 (cross sectional adj (study or studies)).tw. (209351)
63 or/50-62 (2626761)
Annotation: SIGN observational studies filter
64 10 and 63 (2868)
65 16 or 49 or 64 (7146)
66 10 and (15 or 48 or 63) (7146)

Database: Cochrane Library
Search Strategy:

Search Name: ITP
Date Run: 11/03/2020 21:11:27

ID	Search Hits
#1	MeSH descriptor: [Purpura, Thrombocytopenic, Idiopathic] explode all trees 269
#2	(ITP):ti,ab,kw (Word variations have been searched) 654
#3	(idiopath* or immun* or autoimmun*) near/3 (thrombocytopen* or thrombo-cytopen*) 954
#4	(werlhof*):ti,ab,kw (Word variations have been searched) 0
#5	#1 or #2 or #3 or #4 in Trials 995

Database: PubMed
Search Strategy:

Search ((((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))) AND (((((((idiopath* or immune or autoimmune*) AND (thrombocytopen* or thrombo- cytopen*))))) OR ITP) OR werlhof*)
Sort by: PublicationDate 1916