Evidence Development and Standards Branch at Health Quality Ontario

Special Report

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Bone Marrow Examination in Diagnosis of Immune Thrombocytopenia

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Context

Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder. There are two categories of ITP: primary and secondary. In primary ITP, no other causes are identified, and in secondary ITP, clinical manifestation occurs as a result of another underlying condition. These underlying conditions can have immune or nonimmune origins. Clinical symptoms of ITP include a low platelet count, bleeding, and changes in skin appearance. For its diagnosis, a patient's medical history, physical exam, and blood analysis are typically assessed to determine the presence of ITP.

Research Question

Is there a requirement for bone marrow examination in the diagnosis of ITP? Specifically, we were interested in whether evidence existed beyond what was included in the published 2011 American Society of Hematology guidelines.

Conclusion

The evidence supports Choosing Wisely Canada's recommendation, "Do not perform a bone marrow aspirate and biopsy in patients less than 60 years of age with ITP in the absence of concerning features."

In children and adolescents, bone marrow examination is not required in diagnosing ITP that presents with typical features. In adults, low-quality evidence from 3 observational studies shows bone marrow examination is not required in diagnosing ITP.

Methodology

Research questions are developed by Choosing Wisely Canada, in consultation with experts, end users, and/or applicants in the topic area. Evidence Development and Standards then produces one of two types of rapid reviews, or a special report to answer the research question. A rapid review of Systematic Reviews is conducted when a systematic literature search identifies relevant systematic reviews, health technology assessments, or meta-analyses that meet the inclusion criteria specified in the methods section. A rapid review of primary studies is conducted when none of the aforementioned study designs are available. On occasion, a special report may be provided that does not strictly follow the rapid review methodology set out by HQO. These reports are completed in a 2- to 8-week time frame. For more detail on rapid review methodology, please visit the Health Quality Ontario website at: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews

Context

Choosing Wisely Canada is a national campaign that aims to help physicians and patients engage in informative conversations about tests, treatments, and procedures, and help physicians and patients make smart and effective choices to ensure high-quality care. It will support physicians as they work with patients to ensure they not only get the care they need, but avoid tests, treatments, and procedures that have no value and could cause them harm.

As part of this campaign, Health Quality Ontario (HQO) has developed rigorous, evidence-based reviews of tests, treatments, and/or procedures that may be overused. Choosing Wisely Canada has made recommendations based on the evidence provided by HQO. These recommendations are available on the Choosing Wisely Canada website.

Objective of Review

This analysis aimed to examine whether bone marrow examination is required in the diagnosis of immune thrombocytopenia (ITP).

Clinical Need and Target Population

Immune thrombocytopenia is an autoimmune bleeding disorder. There are two categories of ITP: primary and secondary. In primary ITP, no other causes are identified, and in secondary ITP, clinical manifestation results from another underlying condition. These underlying conditions can have immune or nonimmune origins. Clinical symptoms of ITP include a low platelet count, bleeding, and changes in skin appearance. (1) Diagnosis typically uses results from a patient's medical history, physical exam, and blood analysis to determine the presence of ITP. (2)

Technology

Bone marrow examinations are performed to determine the health of the bone marrow and whether it is producing blood cells in the required amounts. The 2 types of bone marrow tests involve sampling bone marrow fluid in aspiration and its cells in biopsy. The harms of bone marrow examination are minimal but can include bleeding or infections. (3)

Existing Guidelines

In 2011 the American Society of Hematology (ASH) used an evidence-based approach to examine management of ITP. The ASH reviewed and formulated recommendations from published literature to 2009 on diagnosis of ITP in children and adults. (4)

Question, Methods, and Findings

Research Question

Is bone marrow examination required for diagnosis of ITP? Specifically, we were interested in whether evidence existed beyond what was included in the published 2011 ASH guidelines.

Methods

Literature Search Strategy

See Appendix 1 for a detailed description of the search strategy, including terms and results.

A literature search was performed on August 8, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process, and all EBM Databases for studies published from January 1, 2009, to August 8, 2014. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language articles published between January 1, 2009, and August 8, 2014
- studies that were observational or randomized controlled trials
- studies that included patients with suspected ITP
- studies that examined the diagnostic effect of a bone marrow examination

Exclusion Criteria

- case reports or case series
- animal or in vitro studies
- studies that included patients with diseases other than suspected ITP
- studies that examined the diagnostic effect of other technologies or blood parameters

Outcomes of Interest

- proportion of patients diagnosed with ITP
- proportion of secondary causes of ITP
- harms outcomes (e.g., bleeding, infection)

Findings

The database search yielded 69 citations published between January 1, 2009, and August 8, 2014 (duplicates removed). Articles were excluded on the basis of information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

No relevant studies were identified from the current systematic literature search.

2011 ASH Guidelines

Given the lack of current published evidence, the 2011 ASH guidelines were reviewed in detail. (4) The 2011 ASH guidelines used an evidence-based approach to examine management of ITP. A systematic literature search was conducted for the years 1996 to December 2009 and the evidence reviewed before formulating the recommendations. The guideline authors evaluated the strength of the recommendations using Grading of Recommendations Assessment, Development, and Evaluation (GRADE). For our purposes, the quality of these guidelines was evaluated using the Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool. (5) Overall, the 2011 ASH guidelines received an AMSTAR score of 7 (Appendix 2).

The 2011 ASH guidelines reviewed the use of bone marrow examination in the diagnosis of ITP separately for children and adults. Recommendations were as follows:

- In children, the 2011 ASH guidelines recommend that "bone marrow examination is not necessary in children and adolescents with the typical features of ITP" (Grade 1B).
- In adults, the 2011 ASH guidelines suggest "further investigations if there are abnormalities (other than thrombocytopenia and perhaps findings of iron deficiency) in the blood count or peripheral blood smear" (Grade 2C).
- In adults, the 2011 ASH guidelines suggest that "a bone marrow examination is not necessary irrespective of age in patients presenting with typical ITP" (Grade 2C).

Evidence Base

Notably, all of the above recommendations are based on observational studies (children: 1 study; adults: 3 studies). The study conducted in children was larger than the studies conducted in adults. Results showed no other important diagnosis (such as leukemia) in 332 children studied with typical features of suspected ITP. Researchers calculated the risk of missing another important diagnosis, such as leukemia, as less than 1%, perhaps warranting the stronger recommendation given by ASH. Samples in the 3 studies of adults ranged from 66 to 86 patients. The ages also ranged from under 65 to 89 years of age. All 3 studies conducted in adult populations concluded that a bone marrow examination was unnecessary if the medical exam is thorough (e.g., clinical history, physical examination), and if blood work shows no abnormalities beyond thrombocytopenia. (4)

Conclusions

We conclude that the evidence from ASH and this special report supports Choosing Wisely Canada's recommendation, "Do not perform a bone marrow aspirate and biopsy in patients less than 60 years of age with ITP in the absence of concerning features."

Specifically, our conclusions are the following:

- In children and adolescents, bone marrow examination is not required in diagnosing ITP that presents with typical features.
- In adults, low-quality evidence from 3 observational studies shows a bone marrow examination is not required to diagnose ITP.

Acknowledgements

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Appendices

Appendix 1: Research Methods

Literature Search Strategy

Search date: August 08, 2014
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, Embase and All EBM Databases

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2014>, EBM Reviews - ACP Journal Club <1991 to July 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <July 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <3rd Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <3rd Quarter 2014>, Ovid MEDLINE(R) <1946 to July Week 5 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 07, 2014>

Search Strategy:
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1 Purpura, Thrombocytopenic, Idiopathic/ (4711)
2 (((immune or autoimmun* or idiopathic or purpura* or primary or secondary or acute or chronic) adj2 thrombocytopeni*) or ITP or werlhof* disease*).ti,ab. (16566)
3 or/1-2 (17228)
4 Bone Marrow Examination/ (6036)
5 (marrow adj2 (exam* or biops* or aspirat* or test*)).ti,ab. (12667)
6 or/4-5 (17535)
7 3 and 6 (358)
8 limit 7 to (english language and yr="2009 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained] (75)
9 remove duplicates from 8 (69)

Appendix 1: Evidence Quality Assessment

Evaluation of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodological quality of systematic reviews. (5)

Table A1: Detailed AMSTAR Scores of Systematic Reviews

Author, Year	AMSTAR Score[a]	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Neunert et al (2011)	7	1	0	1	1	0	1	1	1	N/A	0	1

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; N/A, not applicable.

[a]Maximum possible score is 11. Each column represents a subscore: yes (1 point) or no (0 points). Details of AMSTAR score are described in Shea et al, 2007. (5)

References

(1) Thota S, Kistangari G, Daw H, Spiro T. Immune thrombocytopenia in adults: an update. Cleve Clin J Med. 2012;79(9):641-50.

(2) Lo E, Deane S. Diagnosis and classification of immune-mediated thrombocytopenia. Autoimmun Rev. 2014;13(4-5):577-83.

(3) National Heart Lung and Blood Institute. What are bone marrow tests? Bethesda, MD: NHLBI Health Information Center; 2011 [cited 2014 August 8]. Available from: http://www.nhlbi.nih.gov/health/health-topics/topics/bmt/.

(4) Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190-207.

(5) Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.

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Conflict of Interest Statement

All authors in the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Disclaimer

This report is the work of the Evidence Development and Standards branch at Health Quality Ontario and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. This report may not reflect all the available scientific research and is not intended as an exhaustive analysis. The analysis may not have captured every relevant publication and relevant scientific findings may have been reported since completion of the review. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its reports. This report is current as of the date of the literature search specified in the Research Methods section. This report may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

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Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

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To create its CWC reports, the Evidence Development and Standards branch and its research partners review the available scientific literature, making every effort to consider all relevant national and international research and solicit any necessary supplemental information.

In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

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