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Conflicts of Interest and Clinical Recommendations: Comparison of Two Concurrent Clinical Practice Guidelines for Primary Immune Thrombocytopenia Developed by Different Methods

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Abstract

The growing influence of practice guidelines has increased concern for potential sources of bias. Two recent guidelines for primary immune thrombocytopenia (ITP) provided a unique opportunity for a systematic comparison of different methods of practice guideline development. One guideline (International Consensus Report [ICR]) was supported by pharmaceutical companies that produce products for ITP. The ICR panel members were selected for expertise in ITP; 16 (73%) reported associations with pharmaceutical companies. The other guideline was sponsored by the American Society of Hematology (ASH); panel members were selected for lack of conflicts and for expertise in guideline development as well as for ITP. Discrepancies were conspicuous when the guidelines addressed treatment. In contrast to the ASH guideline, the ICR gave stronger recommendations for agents manufactured by companies from which the ICR or its panel members received support. These data provide direct evidence that differences in financial support and methods of evidence evaluation can influence recommendations.

Keywords

evidence evaluation, practice guidelines, conflicts of interest, immune thrombocytopenia

Since the emergence of evidence-based medicine in the 1980s,[1] clinical practice guidelines have become increasingly important tools for promoting excellence in patient care and providing a metric for measuring quality and performance. Guidelines can set the standard of care and may become incorporated into quality improvement initiatives and reimbursement policies. The growing influence of guidelines has drawn increasing scrutiny to the methods by which they are developed.[2-5] Guidelines should be evidence based, explicitly reflecting and disclosing the strengths and limitations of the supporting scientific evidence. Increasingly sophisticated systems for grading the strength of recommendations have evolved over 2 decades.[6-8] Guidelines also should be informed by expert opinion. Expert opinion is important to establish the validity of recommendations but it is also a potential source of financial conflict and intellectual bias.[5,9] Recent attention has focused on the sources of bias in recommendations, such as the composition of panels, conflicts of interest, and the influence of industry.[10,11] In 2011, the Institute of Medicine published a report outlining explicit methods for developing clinical practice guidelines that minimize the risk of bias.[12] Multiple medical groups are now adopting more systematic guideline development methods.[5,13,14] However, documentation that methods to minimize bias actually influence guideline recommendations remains indirect.[10]

Since the publication of previous clinical practice guidelines for primary immune thrombocytopenia (ITP),[15,16] an acquired immune-mediated disorder of children and adults that is characterized by isolated thrombocytopenia,[17] new treatments have become available including Rho(D)-immune globulin (referred to as anti-D) and thrombopoietin (TPO)-receptor agonists

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(romiplostim, eltrombopag). The previous guidelines had recommended splenectomy for adult patients who had failed initial treatment with corticosteroids because of the high rate of sustained remissions.[15,16] TPO-receptor agonists enhance platelet production and are effective treatment for ITP but require indefinite administration.[18] The release of these new agents created a need for updated treatment recommendations, and 2 panels recently issued new guidelines.[19,20]

The release of these guidelines in close proximity provided a unique opportunity for a systematic comparison of different methods of guideline development. Both guidelines addressed the diagnosis and treatment of the same disorder, ITP. Both were published in *Blood*, the peer-reviewed journal of the American Society of Hematology (ASH). They were published in close succession (2010, 2011); therefore, both guideline panels were reacting to a similar body of scientific knowledge. Both panels were composed primarily of hematologists. However, the 2 projects differed in terms of financial support, project management, the backgrounds of panel members, literature search methods, and the methods of grading the strength of evidence and recommendations. To investigate the possible relationship between the methodology of guideline development and clinical recommendations, this study compared the methods and outcomes of these 2 guidelines.

Methods

One guideline was titled an "International Consensus Report" (identified here as the ICR).[19] Although the word "guideline" was not included in the title, its stated goal was to assess the literature and provide clinical recommendations; it contained all the elements of a clinical practice guideline and met the definition of a clinical practice guideline provided by the National Guideline Clearinghouse of the Agency for Healthcare Research and Quality.[21] The other guideline, sponsored by ASH (identified here as the ASH guideline),[20] also met this definition.[21] The present analysis was based only on the information presented in these 2 publications and their electronic supplements, with 1 exception: the Web site for ApotheCom ScopeMedical, Ltd,[22] a company that participated in the preparation of the ICR report, also was reviewed.

The 2 guidelines were evaluated for (*a*) financial support, project management, and panel membership; (*b*) literature search methods and analysis; (*c*) grading the strength of the evidence and recommendations; (*d*) manuscript preparation and external review; (*e*) articulation of recommendations and documentation of scientific support; and (*f*) clinical recommendations, consistent with the Institute of Medicine's standards for developing trustworthy guidelines.[12] The review focused on tests and treatments that at least 1 panel firmly recommended. The weakest class of recommendations (grade C recommendations in the ICR and grade 2 recommendations in the ASH guideline, described as "suggestions") was not reviewed unless the other panel issued a stronger recommendation for a similar clinical presentation. All recommendations that were reviewed are available from the authors on request; recommendations with the most conspicuous discrepancies (grade A vs grade 2, grade C vs grade 1) are presented in the text. For the majority of the text of Results, statements from the guidelines are quoted verbatim. To describe the guidelines' recommendations, statements are quoted verbatim. To describe the structure of the guidelines and the methods of guideline development, statements are quoted verbatim as much as possible. For simplicity, quotation marks are omitted. The primary data source articles used by the panels are not cited.

Results

Financial Support, Project Management, and Panel Membership

The ICR reported no sponsorship by a professional medical society or a government agency. The project was supported by unrestricted grants from 3 pharmaceutical companies that produce and/or market products for ITP that were assessed in this guideline: Amgen, Ltd (romiplostim), Baxter, Ltd (intravenous immune globulin [IVIg], anti-D), and GlaxoSmithKline, Ltd (eltrombopag; Table 1). These are the only 4 products that the Food and Drug Administration approves for the treatment of ITP. Romiplostim and eltrombopag were approved in 2008 for adults with a diagnosis of ITP who have failed 1 previous treatment, with or without previous splenectomy. The project was managed by ApotheCom ScopeMedical, Ltd, described by its Web site[22] as a provider of medical education and marketing services to the pharmaceutical industry, including the in-house preparation of publications. Panel members were selected for their recognized clinical and research expertise in ITP and their international representation; 2 were laypersons who represented patient support associations in the United States and the United Kingdom. The lead writing committee (9 panel members) had 2 face-to-face meetings. Sixteen (73%) of the 22 panel members reported associations with pharmaceutical companies that produce and/or market products discussed in this guideline. Payment of the panel members for their time or reimbursement for travel costs was not described.

The ASH guideline was sponsored by ASH, a medical specialty society established in 1958. Panel members were selected for their expertise in guideline development

Table 1. Financial Support, Project Management, and Panel Membership.

Project and Panel Characteristics	ICR	ASH Guideline
Sponsoring organization	None	ASH
Financial support	Amgen Ltd, Baxter Ltd, GlaxoSmithKline Ltd	ASH
Project management	ApotheCom ScopeMedical, Ltd	ASH
Itemized expenses		
Face-to-face meetings	2	0
Teleconferences	Not reported	ASH
Author payment	Not reported	None
Panel members		
Number	22	6
Selection criteria	Hematologists with recognized clinical and research expertise in ITP (20); patient advocacy representatives (2)	Hematologists with expertise in systematic reviews and guideline development, expertise in management of ITP, and absence of conflicts of interest
Publications on ITP by panel members, 2005-2009[a]	273 (1-67 publications per panel member)	8 (0-4 publications per panel member)
Countries represented	8	3
Panel members' financial associations with companies that manufacture products related to ITP		
Speakers bureau/lecturer	6	0
Consultant	8	0
Advisory board	7	0
Research support	7	0
Stock ownership	2	0
Travel expenses	1	0
Total number of panel members with financial associations	16	0

Abbreviations: ASH, American Society of Hematology; ICR, International Consensus Report; ITP, immune thrombocytopenia.
[a]Publications were determined by a PubMed search on September 1, 2010, for each author using the MeSH term "purpura, thrombocytopenic, idiopathic."

and management of ITP, and for absence of conflicts of interest (Table 1). They received administrative support from ASH staff for coordination of teleconferences; no face-to-face meetings were described. Literature review, evidence table generation, and report writing were performed by the panel members with no additional support. None of the ASH panel members declared any form of financial support from pharmaceutical companies that manufacture products discussed in the guideline during the preceding 24 months. Panel members received no compensation for their participation.

Literature Search Methods and Data Analysis

Articles reviewed for the ICR were identified by a search of English language literature using the US National Library of Medicine PubMed database, 2001 to 2008 (Table 2). A subsequent search was performed using the corresponding Medline Medical Subject Heading terms and cross-referenced with the original search to consolidate the primary results. The search was limited to articles published after 2000 to focus on new data. Abstracts of ASH, European Haematology Association, and International Society of Thrombosis and Haemostasis meetings, 2003 to 2007, were reviewed. The ICR did not identify who performed the literature search or the criteria for article selection. Among 275 citations in 6 evidence tables, 62 (23%) were abstracts (not full-length research publications). A total of 248 (90%) articles and abstracts contained patient data; 59 (24%) reported fewer than 10 patients, 32 of which described 1 patient. Data were analyzed by 4 panel members; levels of evidence were reviewed by the lead writing committee. All panel members had the opportunity to dispute the levels of evidence assigned to the articles at each review stage. Forty-two (20%) of the 213 articles (excluding abstracts) cited by the ICR panel also were cited by the ASH guideline.

All ASH guideline panel members participated in the literature search, article selection, and data analysis (Table 2). The search included articles published since 1996, when the initial ASH ITP guideline[15] was published, through 2009. Articles were selected for each topic in a hierarchical manner. If systematic reviews or meta-analyses were identified, only subsequently published studies were identified. If no

Table 2. Literature Search Methods, Manuscript Preparation, and External Review.

Task	ICR	ASH Guideline
Literature search	PubMed database, 2001-2008. Search terms described. Abstracts of ASH, European Hematology Association, International Society of Thrombosis and Haemostasis, 2003-2007	Embase and Medline databases, 1996-2009. Search terms not described. No abstract search.
Article, abstract selection	Article selection criteria not specified; abstracts reviewed for relevance	Hierarchy of article selection: (*a*) systematic reviews and meta-analyses, (*b*) relevant randomized clinical trials, (*c*) cohort or case–control studies, (*d*) case series of >50 adults or >25 children
Data analysis	4 panel members	All panel members
Manuscript preparation	9 panel members, ApotheCom ScopeMedical, Ltd	All panel members
Manuscript review	All panel members	All panel members
External review	None	1. External panel including members of ASH Committee on Practice, ASH Subcommittee on Quality of Care, and additional content experts 2. External panel of 12 content experts
Organizational approval	None	ASH Committee on Practice, ASH Subcommittee on Quality of Care, ASH Executive Committee

Abbreviations: ASH, American Society of Hematology; ICR, International Consensus Report.

systematic reviews or meta-analyses were identified, randomized controlled trials were identified. If no randomized controlled trials were identified, cohort or case–control studies were identified. Case series were selected only if the previous types of publications were not identified. Case series were reviewed if they reported more than 50 adults or 25 children; abstracts were not reviewed. The 32 evidence tables cited 106 articles that were published before 2009 (the time period of the ICR review); 42 (44%) also were cited by the ICR.

Grading the Strength of the Evidence and Recommendations

The ICR adapted the methodology of the National Guideline Clearinghouse to grade the strength of the evidence (Table 3). All randomized controlled trials were assigned equal weight. The strength of the recommendations was directly linked to the evidence grades.

The ASH guideline used the GRADE system,[7] which divides recommendations into 2 categories: strong and weak (Table 3). Weak recommendations were described as "suggestions." Each category could be supported by any of the 3 levels of evidence.

Manuscript Preparation and External Review

The ICR writing committee prepared the manuscript. All panel members reviewed the manuscript. No external review was described. ApotheCom ScopeMedical[22] provided writing and editorial assistance throughout the project (Table 2).

All ASH panel members wrote the manuscript (Table 2). It was reviewed by 2 external panels. One included members of the ASH Committee on Practice and its Subcommittee on Quality as well as other content experts. The other panel included 12 content experts, 2 of whom had served on the ICR panel. The external panels ensured that all pertinent articles were identified and accurately assessed, that all clinically relevant areas were addressed, and that recommendations were concise and organized. External panel members' conflicts of interest were not assessed. Before submission for publication, the manuscript was approved by the ASH Executive Committee.

Articulation of Recommendations and Documentation of Scientific Support

Recommendations of the ICR were summarized in a supplement table; some recommendations also were described in the text. For some recommendations, there were inconsistencies between these 2 locations within the document. Inconsistencies also occurred between the supplement recommendations or text recommendations and the evidence tables. The ICR used 1 format for all 6 evidence tables, providing the citation, evidence designation, study design description, number of patients reported, and a summary of results. Appraisal of study methodology was not provided in the evidence tables.

Table 3. Grading the Strength of Evidence and Recommendations.

Evidence	Recommendation
ICR[a]	
Ia: meta-analysis of RCTs[b]	**A** (strong)
Ib: ≥1 RCT	
IIa: ≥1 well-designed controlled study without randomization	**B** (intermediate)
IIb: ≥1 other type of well-designed quasi-experimental study	
III: well-designed nonexperimental descriptive studies	
IV: expert opinion, clinical experience	**C** (weak)
ASH guideline[c]	
A: RCTs or exceptionally strong observational studies	**1** (strong): high degree of confidence that the desirable outcome of an intervention exceeds the undesirable effects (or vice versa)
B: RCTs with important limitations or strong observational studies	
C: RCTs with serious flaws, weaker observational studies, or indirect evidence	**2** (weak): lower degree of confidence. Described as "suggestions"

Abbreviations: ASH, American Society of Hematology; ICR, International Consensus Report; RCT, randomized controlled trial.
[a]Adapted from National Guidelines Clearinghouse (www.guideline.gov).
[b]All RCTs were assigned equal weight.
[c]GRADE System.[7]

Recommendations of the ASH guideline were summarized in Table 1 of the text, using the same language that is used in the text for each recommendation and suggestion. Recommendations were introduced by clinical questions, and each clinical question was supported by an evidence table. The ASH guideline customized its 32 evidence tables for different topics, presenting the rationale for the evidence grade and providing an appraisal of the study methodology. For example, evidence tables for randomized trials included columns describing randomization, concealed treatment allocation, blinding, intention-to-treat analysis, patients lost to follow-up, outcome assessment, and duration of follow-up.

Clinical Recommendations

Although the 2 guidelines gave similar recommendations for the diagnosis of ITP in children and adults, for initial management of children with minimal bleeding symptoms, and for initial management of adults, other treatment recommendations differed. Discrepancies between the 2 guidelines were most conspicuous when the guidelines addressed treatment with agents manufactured by companies from which the ICR project or its panel members received support. The ICR gave stronger recommendations for the TPO-receptor agonists, romiplostim and eltrombopag, and anti-D and weaker recommendations for splenectomy and corticosteroids (Table 4).

TPO-Receptor Agonists. The ICR's only A recommendations for treatment of adults were given to the use of romiplostim and eltrombopag; they were the only treatments that had been evaluated by randomized controlled trials. For adults who have failed initial treatment, the panel recommended TPO-receptor agonists before splenectomy, citing 8 articles and 14 abstracts in 2 evidence tables. Two randomized controlled trials, one involving romiplostim and the other eltrombopag, which compared these treatments to placebo, were assigned level Ib evidence. Three articles reporting phase I or phase I-II clinical trials, which primarily evaluated dose range, safety, and pharmacokinetics, and 8 abstracts also were assigned level Ib evidence. The panel also gave A recommendations for TPO-receptor agonists for adults who had failed treatment with splenectomy.

The ASH guideline recommended TPO-receptor agonists only for adults who have severe thrombocytopenia after splenectomy or in whom splenectomy is contraindicated (grade 1B; Table 4), citing 4 randomized controlled trials (2 involving romiplostim, 2 eltrombopag; 2 were cited by the ICR and 2 were published after the ICR review). For patients who have not undergone a splenectomy, the panel only suggested TPO-receptor agonists (grade 2C), citing the recurrence of thrombocytopenia when TPO-receptor agonists are discontinued and the uncertainty of long-term adverse effects.

Splenectomy. The ICR panel gave a weak recommendation for splenectomy for adults who have failed initial treatment (grade C, level IV evidence). However, the language of the recommendation did not clarify whether the recommendation applied to performing splenectomy or to waiting at least 6 months from diagnosis before performing splenectomy. Among the 15 studies cited in the

Table 4. Comparison of ICR and ASH Guideline Recommendations for Treatment of Adults and Children.

ICR		ASH Guideline	
Text	Grade	Text	Grade
Second-line treatment for adults			
TPO-receptor agonists (romiplostim and eltrombopag) have provided excellent responses in both splenectomized and nonsplenectomized patients	A	TPO-receptor agonists may be considered for patients who have failed 1 line of therapy such as corticosteroids or IVIg and who have not had splenectomy	2C
Splenectomy remains the treatment option with by far the highest likelihood of producing cure. In general, it is recommended to wait at least 6 months from diagnosis before performing splenectomy because of the chance for spontaneous remission	C	Splenectomy for patients who have failed corticosteroid therapy	1B
Initial management of children with more severe bleeding symptoms			
Anti-D immunoglobulin has similar efficacy to IVIg when given as a single dose of 75 µg/kg and is rarely associated with severe hemolysis	A	A single dose of anti-D can be used as first-line treatment in Rh-positive, nonsplenectomized children requiring treatment	2B
		Anti-D therapy is not advised in children with a hemoglobin concentration that is decreased because of bleeding, or with evidence of autoimmune hemolysis	1C
Management during pregnancy			
Oral corticosteroids or IVIg are considered first-line treatment	C	Pregnant patients requiring treatment receive either corticosteroids or IVIg	1C
Anti-D in Rh (D)-positive nonsplenectomized women appears to be well tolerated and effective based on results from a pilot study	B		

Abbreviations: Anti-D, Rho(D) immune globulin; ASH, American Society of Hematology; ICR, International Consensus Report; IVIg, intravenous immune globulin; TPO, thrombopoietin.

evidence table for splenectomy, 12 were assigned level IIb and 3 were assigned level III evidence, which would support a grade B recommendation. Although the recommendation may have applied to the timing of splenectomy, none of the cited articles addressed this topic.

The ASH guideline recommended splenectomy for adults who fail initial therapy (grade 1B), citing the recommendation of the previous ASH guideline,[15] but no articles related to splenectomy were included in the evidence table.

Anti-D in Children. The ICR recommended 3 treatments (anti-D, IVIg, prednisone) for children with overt bleeding (grade A). The recommendation for anti-D was supported by 5 articles and 3 abstracts; 2 articles were randomized controlled trials.

The ASH guideline recommended IVIg or corticosteroids (grade 1B) but only suggested anti-D (grade 2B). For anti-D, 3 randomized controlled trials were cited (1 cited by the ICR), which were interpreted as reporting contradictory results regarding the benefit of anti-D over IVIg but greater risk for hemolysis. The ASH guideline recommended against the use of anti-D for children with a low hemoglobin concentration because of bleeding, or with autoimmune hemolysis (grade 1C); the ICR did not address these issues.

Anti-D During Pregnancy. The ICR recommended anti-D treatment in nonsplenectomized pregnant women (grade B), stating that it appears to be well tolerated and effective based on a pilot study of 8 patients that was assigned level IIb evidence. The ICR gave a weak recommendation (grade C) for treatment with corticosteroids or IVIg, citing 2 articles with level III evidence.

The ASH guideline made no recommendation or suggestion for the use of anti-D during pregnancy, citing the same pilot study as the ICR. It recommended either corticosteroids or IVIg for pregnant patients requiring treatment (grade 1C); no articles were cited in the evidence table.

Discussion

This study compared 2 concurrent clinical practice guidelines for the diagnosis and treatment of ITP that were

developed by different methods.[19,20] Although recommendations for diagnosis were similar in both guidelines, some treatment recommendations of the ICR panel, a project with financial ties to pharmaceutical companies that manufacture or market agents for ITP treatment,[19] were different from recommendations of the ASH guideline panel that had no pharmaceutical ties.[20]

The different treatment recommendations may have resulted in part from different criteria for grading evidence. The ICR accepted randomized controlled trials for level I evidence and grade A recommendations regardless of the study question addressed by the randomized controlled trial or the methodology and design of the trial. This standard limited grade A recommendations for second-line treatment of adults to the recently FDA-approved TPO-receptor agonists (romiplostim and eltrombopag), because these were the only agents that have been evaluated in randomized controlled trials. There have been no randomized controlled trials of splenectomy, the previous standard of care for these patients.[15,16] The low prevalence of ITP[23] makes randomized controlled trials difficult and expensive and, therefore, often dependent on support from the pharmaceutical industry. For example, a recent Amgen-sponsored trial of romiplostim treatment for ITP required 85 sites in 14 countries to enroll 234 patients in 22 months.[24] The ASH guideline assessed evidence from randomized controlled trials based on the relevance of the study question and the quality of the design and execution, a fundamental tenet of the evidence-based movement since the early work of Cochrane.[6-8,12,25,26]

In addition to differences in treatment recommendations, there also were differences in articulation of the recommendations and documentation of scientific support for the recommendations. These differences may have been related to differences in panel composition and project management. ICR panel members were selected for recognized expertise in ITP rather than for expertise in guideline development. The ICR project was managed by ApotheCom ScopeMedical, a company that provides marketing services and prepares publications for the pharmaceutical industry.[22] The respective roles of the panel members and ApotheCom ScopeMedical in the production of the guideline were not explicitly described. The ICR guideline underwent no external review, a process that could have identified and corrected the problems of clarity and consistency in the recommendations. In contrast, the ASH guideline was supported by ASH, a medical specialty society, and panel members were selected for lack of conflicts, expertise in guideline development, as well as for clinical expertise in the management of ITP. Panel members personally performed the article selection, grading the strength of evidence and recommendations, and manuscript preparation. The ASH guideline underwent review by 2 external panels composed of methodology and content experts before submission for publication.

This study adds to an existing literature about the influence of guideline sponsorship, panel composition, and methodology on clinical practice recommendations. These 3 parameters all appeared to be important in the determination of the clinical recommendations, and all 3 parameters appeared to be interrelated. Previous research has raised concerns about the biases introduced when guideline projects or panel members receive support from industry.[9-11,27] Panels with greater specialization tend to produce stronger advocacy for treatments[28] while panels that are more multidisciplinary invite more heterogeneous perspectives on the evidence and ultimately produce more conservative recommendations.[10,26,29-32] Although both the ICR and ASH guideline panels were composed primarily of specialists in hematology, the selection of ASH guideline panel members for expertise in guideline development and for absence of conflicts of interest may have contributed to a pattern of more conservative recommendations with respect to using new pharmaceutical products.

The strength of this study is the unique opportunity to compare 2 clinical practice guidelines for the same disorder published in the same journal 1 year apart, but developed by different methods. Differences in financial support, project management, panel membership, and methods of evidence evaluation that led to different clinical recommendations were documented. The evidence presented here lends support for the growing concern that commercial influence on guideline development should be limited and for the more rigorous disclosure requirements recently advocated by the Institute of Medicine.[12]

Authors' Note

None of the authors had any role in the planning, development, or external reviews of the clinical practice guidelines that are the subject of this report.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr George was chair of the guideline panel that produced the previous American Society of Hematology (ASH) clinical practice guideline for primary immune thrombocytopenia (ITP) published in 1996; he has served in leadership positions for ASH including president in 2005; he currently receives honoraria as a consultant for Amgen, Inc, and also receives research funding from Amgen, Inc, for clinical studies of romiplostim. Dr Vesely serves on the faculty for the ASH Clinical Research Training Institute; she served as a biostatistician on the Data Safety Monitoring Board of the APOLLO Study for Sanofi Pharmaceuticals, 2002 to 2004. Dr Woolf was a methodology consultant for ASH from 1994 to 2000 and was a member of the 1996 ASH clinical practice guideline panel. He recently coauthored a background paper on guideline development that was commissioned by the Institute of Medicine and is cited in

this article. He has never received financial support from the pharmaceutical industry.

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