blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Distinguishing ASH Clinical Practice Guidelines from Other Forms of ASH Clinical Advice

Tracking no: ADV-2023-011102-CR1

Adam Cuker (University of Pennsylvania, United States) Robert Kunkle (American Society of Hematology, United States) Rachel Bercovitz (Northwestern University Feinberg School of Medicine, United States) Michael Byrne (Tennessee Oncology, United States) Benjamin Djulbegovic (Medical University of South Carolina, United States) Sandra Haberichter (Versiti Blood Center of Wisconsin, United States) Jennifer Holter-Chakrabarty (University of Oklahoma, Health Sciences Center, United States) Richard Lottenberg (University of Florida, United States) Menaka Pai (McMaster University, Canada) Suely Rezende (Universidade Federal de Minas Gerais, Brazil) Matthew Seftel (University of British Columbia, Canada) Roy Silverstein (Medical College of Wisconsin, United States) Deirdra Terrell (University of Oklahoma Health Sciences Center, United States) Matthew Cheung (Sunnybrook Health Sciences Centre, University of Toronto, Canada)

Abstract:
The American Society of Hematology (ASH) develops a variety of resources that provide guidance to clinicians on the diagnosis and management of blood diseases. These resources include clinical practice guidelines (CPGs) and other forms of clinical advice. While both ASH CPGs and other forms of clinical advice provide recommendations, they differ with respect to the methods underpinning their development, the principal type of recommendations they offer, their transparency and concordance with published evidence, and the time and resources required for their development. It is crucial that end users be aware of the differences between CPGs and other forms of clinical advice and that producers and publishers of these resources use clear and unambiguous terminology to facilitate their distinction. The objective of this article is to highlight similarities and differences between ASH CPGs and other forms of ASH clinical advice and to discuss the implications of these differences for end users.

Conflict of interest: COI declared - see note

COI notes: AC has served as a consultant for MingSight, New York Blood Center, Sanofi, and Synergy and has received authorship royalties from UpToDate. RK is an employee of ASH. DT has served as a consultant for Sanofi. All other authors have no conflicts of interest to declare. All authors except RK are members of the ASH Guideline Oversight Subcommittee.

Preprint server: No;

Author contributions and disclosures: AC and MCC wrote the manuscript. All other authors critically reviewed and revised the manuscript.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Not applicable. The manuscript does not include original data.

Clinical trial registration information (if any):

Distinguishing ASH Clinical Practice Guidelines from Other Forms of ASH Clinical Advice

Running head: ASH Guidelines vs. Other Clinical Advice

Adam Cuker[1]
Robert Kunkle[2]
Rachel S. Bercovitz[3]
Michael Byrne[4]
Benjamin Djulbegovic[5]
Sandra L. Haberichter[6,7]
Jennifer Holter-Chakrabarty[8]
Richard Lottenberg[9]
Menaka Pai[10]
Suely M. Rezende[11]
Matthew D. Seftel[12]
Roy L. Silverstein[13]
Deirdra R. Terrell[14]
Matthew C. Cheung[15]

[1]Department of Medicine and Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[2]American Society of Hematology, Washington, DC
[3]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL
[4]Tennessee Oncology, Nashville, TN
[5]Division of Hematology/Oncology, Department of Medicine, Medical University of South Carolina, Charleston, SC
[6]Versiti Diagnostic Labs and Blood Research Institute
[7]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI
[8]Department of Medicine, BMT and Cellular Therapy, Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK
[9]Department of Medicine, University of Florida, Gainesville, FL
[10]Department of Medicine, McMaster University, Hamilton, Canada
[11]Department of Internal Medicine, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[12]Canadian Blood Services, University of British Columbia, Vancouver, Canada
[13]Department of Medicine, Medical College of Wisconsin and Versiti Blood Research Institute, Milwaukee, WI
[14]Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK
[15]Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

Corresponding author:
Adam Cuker, MD, MS
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104
Telephone: (215) 615-8015
Fax: (215) 615-6599

Email: adam.cuker@pennmedicine.upenn.edu

Article type: Advanced viewpoint
Abstract word count: 150 (max 150)
Body of manuscript word count: 1,440 (max 2000)
Tables/Figures: 2 tables
References: 18 (max 100)

Abstract

The American Society of Hematology (ASH) develops a variety of resources that provide guidance to clinicians on the diagnosis and management of blood diseases. These resources include clinical practice guidelines (CPGs) and other forms of clinical advice. While both ASH CPGs and other forms of clinical advice provide recommendations, they differ with respect to the methods underpinning their development, the principal type of recommendations they offer, their transparency and concordance with published evidence, and the time and resources required for their development. It is crucial that end users be aware of the differences between CPGs and other forms of clinical advice and that producers and publishers of these resources use clear and unambiguous terminology to facilitate their distinction. The objective of this article is to highlight similarities and differences between ASH CPGs and other forms of ASH clinical advice and to discuss the implications of these differences for end users.

Introduction

The American Society of Hematology (ASH) produces a wide range of resources that provide guidance to clinicians on the diagnosis and management of blood diseases. These resources include clinical practice guidelines (CPGs) and CPG-derived products (e.g., pocket guides, patient versions of guidelines, teaching slide sets) as well as other forms of clinical advice [e.g., *How I Treat* articles, webinars, frequently asked questions (FAQs), ASH annual meeting education sessions, the ASH Self-Assessment Program, and the Hematology Review Series].

It may not be clear to all users how these resources differ, particularly with respect to the methods underpinning their development and the recommendations they provide. The purpose of this article is to highlight similarities and differences between ASH CPGs and other forms of ASH clinical advice and to discuss the implications of these differences for end users.

Methodology

Methods for development of ASH CPGs adhere to international standards[1-3] and have been detailed elsewhere.[4,5] Key elements include panel formation with diverse stakeholder representation including patients, explicit and transparent conflict of interest (COI) management, identification and prioritization of PICO (Patient, Intervention, Comparison, Outcome) questions, systematic reviews of the evidence, development of recommendations using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework,[6,7] public review and commentary, organizational review, and peer review. These attributes distinguish ASH CPGs as methodologically rigorous, transparent, and trustworthy, as defined by standards established by organizations including the National Academy of Medicine (formerly the Institute of Medicine).[2]

Other forms of ASH clinical advice may not incorporate some or all of these elements. For example, *How I Treat* articles, webinars, FAQs, ASH annual meeting education sessions, the ASH Self-Assessment Program, and the Hematology Review Series are usually based on personal opinion and informal rather than systematic reviews of the evidence; usually include one or only a small number of authors who are not necessarily representative of diverse stakeholder interests; usually do not develop recommendations through GRADE or another structured framework; and usually do not seek public feedback prior to publication or presentation. While many other forms of ASH clinical advice include disclosure of COI, they may not formalize a mitigation strategy when COIs exist; for example, they may not limit participation or require recusal based on COI as ASH CPGs do.

Recommendations

The usable end products of both ASH CPGs and other forms of ASH clinical advice are recommendations. Recommendations are actionable statements intended to guide decision-making about alternative healthcare options in a specific patient population. Several different types of recommendations are recognized.[8] ASH CPGs and other forms of ASH clinical advice differ with respect to the types of recommendations they include.

The backbone of ASH CPGs are formal recommendations. Formal recommendations are actionable statements based on systematic reviews of the evidence that name an explicit intervention and comparison and a specific population. Such recommendations include a *direction* and *strength*; the former advises an action while the latter is related to the balance of desirable and undesirable consequences and the quality of evidence that informs the recommendation.[8] In addition to formal recommendations, ASH CPGs may include remarks, good practice statements, research-only recommendations, and implementation considerations (defined in Lofti et al[8]).

In contrast to ASH CPGs, other forms of ASH clinical advice do not include formal recommendations. Instead, they consist mainly of informal recommendations. Like formal recommendations, informal recommendations are actionable and explicitly list a target population and intervention. They may or may not include a comparison, direction, or strength. Unlike formal recommendations, informal recommendations are not based on a systematic review of the evidence and they do not include rating of the quality of the evidence.[8] Examples of formal and informal recommendations are shown in Table 1.

Advantages and disadvantages of ASH CPGs and other forms of ASH clinical advice

Use of rigorous and explicit methods serve to minimize bias and enhance the transparency of ASH CPGs. These methods result in recommendations that have a clear and predictable relationship to the best available supporting evidence. In contrast, informal recommendations are at risk of bias from selective use of evidence or from COI. For example, Yao et al. analyzed 81 CPGs from the American College of Cardiology/American Heart Association and the American Society of Clinical Oncology. Of the 908 recommendations based on low quality evidence in these CPGs, 416 were formal recommendations based on systematic reviews of the evidence and 492 were informal recommendations based on consensus. Recommendations were classified as discordant if they were strong recommendations with low quality evidence and inappropriately discordant if they did not satisfy GRADE criteria for issuing a strong recommendation based on low quality evidence. Compared with formal evidence-based recommendations, informal consensus-based recommendations were more likely to be discordant (OR 1.9, 95% confidence interval 1.4 to 2.7) and inappropriately discordant (OR 2.5, 95% confidence interval 1.7 to 3.5).[9]

A major disadvantage of ASH CPGs is that they tend to be more time-consuming to develop than other forms of ASH clinical advice. This vulnerability was particularly relevant early in the COVID-19 medical

emergency, a time when there was an urgent need for clinical guidance. Despite adoption of a rapid approach to guideline development, the first ASH CPG on COVID-19 and anticoagulation was not completed until December 2020 and was not published until February 2021,[10] some 9 to 11 months after COVID-19 was declared a pandemic by the World Health Organization. At the same time, ASH was able to stand up less rigorous forms of clinical advice such as online FAQs[11] within a matter of weeks. Although development of CPGs may never be as rapid as some other forms of clinical advice, efforts are needed to further streamline CPG development without compromising methodologic rigor, transparency, or trustworthiness, particularly during medical emergencies.

CPGs are also more expensive than other forms of clinical advice, often substantially so. Guideline development costs include administrative staff support, travel and meetings, and systematic evidence reviews. Although most organizations including ASH do not publicize their guideline development costs, systematic evidence reviews alone often cost in excess of 100,000 USD.[12] Technological advances including virtual meeting platforms and systematic reviews supported by machine learning and artificial intelligence offer the potential to reduce labor and costs associated with CPG development.

A third disadvantage of CPGs is that they tend to be lengthy and complex.[13] In addition, they often consist of isolated recommendations that are not linked together via pathways or decision trees. Other forms of clinical advice may be more concise and better equipped to articulate a comprehensive diagnostic or management strategy to meet the needs of clinicians.[14] ASH produces CPG-derived products (e.g., pocket guides, patient versions of guidelines, teaching slide sets) to facilitate implementation of its guidelines and is exploring incorporation of decision trees in future CPG efforts.[15]

Terminology

In light of the substantial differences between CPGs and other forms of clinical advice, it is crucial that developers and publishers use clear language and labels to disambiguate these different types of guidance. For example, all ASH CPGs include "American Society of Hematology guidelines" in the title and are grouped within the *Blood Advances* website under a CPG article type.

The label "guidelines" should not be used to describe other forms of clinical advice. Terms that hint at or could easily be confused with CPGs such as "guidance" or "consensus" should also ideally be avoided. Some organizations distinguish "evidence-based" guidelines from "expert-based" or "consensus-based" guidelines. ASH has avoided this nomenclature because it is misguided and misleading. All CPGs should be based on a systematic review of the evidence, even if the evidence is low quality, and all guidelines require expert opinion and consensus building to appraise and interpret such evidence.[16]

Currently, *Blood Advances* requires that CPG submissions be consistent with criteria laid out by the Institute of Medicine.[2] *Blood* does not list specifications or formal criteria for CPG submissions. Neither journal imposes restrictions on the use of terms such as "guidance" and "consensus". We recommend that ASH consider standardizing nomenclature across its publication portfolio with the goal of clearly distinguishing CPGs from other forms of clinical advice.

Conclusion

ASH CPGs and other forms of ASH clinical advice both provide recommendations for the diagnosis and management of blood diseases, but differ with respect to methodology, the primary type of recommendations they provide, their transparency and concordance with the best available evidence, and the time and resources they require (Table 2). It is important for clinicians and other users to distinguish CPGs from other forms of clinical advice and to be aware of the differences between these

tools when they are applied in clinical practice. Developers and publishers of these products, including ASH, have a responsibility to use clear and unambiguous labels to facilitate this distinction for end users.

Author contributions

AC and MCC wrote the manuscript. All other authors critically reviewed and revised the manuscript.

Conflict of interest disclosures

AC has served as a consultant for MingSight, New York Blood Center, Sanofi, and Synergy and has received authorship royalties from UpToDate. RK is an employee of ASH. DT has served as a consultant for Sanofi. All other authors have no conflicts of interest to declare. All authors except RK are members of the ASH Guideline Oversight Subcommittee.

References

1. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med.* 2012;156(7):525-531.
2. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical Practice Guidelines We Can Trust.* Washington (DC): National Academies Press (US); 2011.
3. Schunemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *CMAJ.* 2014;186(3):E123-142.
4. Wiercioch W, Nieuwlaat R, Akl EA, et al. Methodology for the American Society of Hematology VTE guidelines: current best practice, innovations, and experiences. *Blood Adv.* 2020;4(10):2351-2365.
5. Panepinto JA, Pai M. The value of clinical practice guidelines in hematology. *Blood Adv.* 2018;2(22):3196-3197.
6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.
7. GRADE Working Group. GRADE Handbook. Schunemann H, Brozek J, Guyatt G, Oxman A, eds.2013.
8. Lotfi T, Hajizadeh A, Moja L, et al. A taxonomy and framework for identifying and developing actionable statements in guidelines suggests avoiding informal recommendations. *J Clin Epidemiol.* 2022;141:161-171.
9. Yao L, Ahmed MM, Guyatt GH, et al. Discordant and inappropriate discordant recommendations in consensus and evidence based guidelines: empirical analysis. *BMJ.* 2021;375:e066045.
10. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv.* 2021;5(3):872-888.
11. COVID-19 Resources - Hematology.org. https://www.hematology.org/covid-19. Accessed 15 August 2023.
12. Michelson M, Reuter K. The significant cost of systematic revies and meta-analyses: A call for greater involvement of machine learning to assess the promise of clinical trials. *Contemp Clin Trials Commun*. 2019;16:100443.
13. Kann BH, Johnson SB, Aerts HJWL, Mak RH, Nguyen PL. Changes in Length and Complexity of Clinical Practice Guidelines in Oncology, 1996-2019. *JAMA Netw Open*. 2020;3(3):e200841
14. Djulbegovic B, Hozo I, Lizarraga D, et al. Evaluation of a fast-and-frugal clinical decision algorithm ('pathways') on clinical outcomes in hospitalised patients with COVID-19 treated with anticoagulants. *J Eval Clin Pract*. 2023;29(1):3-12.
15. Djulbegovic B, Hozo I, Cuker A, Guyatt G. Improving current methods of clinical practice guidelines: from guidelines to pathways to fast-and-frugal decision trees and generalized decision curve analysis to develop individualized patient care. *J Eval Clin Pract*. 2023;in press.
16. Djulbegovic B, Guyatt G. Evidence vs Consensus in Clinical Practice Guidelines. *JAMA*. 2019;322(8):725-726.
17. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020;4(19):4693-4738.
18. Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. *J Thromb Thrombolysis*. 2016;41(1):32-67.

Tables

Table 1. Examples of formal and informal recommendations. Formal recommendations are actionable statements based on systematic reviews of the evidence that list a specific patient population, intervention, and comparison and include a direction and strength as well as a rating of the quality of the evidence. In the example formal recommendation in the table, the patient population is patients with uncomplicated deep vein thrombosis, the intervention is home treatment, the comparison is hospital treatment, the direction of the recommendation is in favor of home treatment, the strength of the recommendation is conditional or weak, and the quality of the evidence is low. Informal recommendations are also actionable statements that list a specific patient population and intervention, but they may not include a comparison, direction, or strength and they do not include rating of the quality of evidence nor are they based on a systematic review of the evidence. In the example informal recommendation, the patient population is patients with deep vein thrombosis and the intervention is home or outpatient treatment. The comparison is not stated but is implied to be inpatient treatment. The direction of the recommendation is in favor of outpatient treatment, but the strength of the recommendation and quality of the evidence are not given.

Type of recommendation	Example
Formal recommendation	For patients with uncomplicated deep vein thrombosis (DVT), the American Society of Hematology (ASH) guideline panel *suggests* offering home treatment over hospital treatment (conditional recommendation based on low certainty in the evidence of effects).[17]
Informal recommendation	We suggest that most patients with DVT can be managed as outpatients.[18]

Table 2. Comparison of ASH CPGs and other forms of ASH clinical advice.

	Diverse stakeholder representation including patients	COI management	Identification and prioritization of PICO questions	Systematic reviews of the evidence	Development of recommendations using GRADE or another structured framework	Public review and commentary	Peer review	Main type of recommendation	Transparency and concordance with best available evidence	Time to develop	Cost to develop
ASH CPGs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Formal	High	Months to years	High
Other forms of ASH clinical advice[a]	Usually not	Varies	Usually not	Usually not	Usually not	Usually not	Varies	Informal	Lower	Weeks to months	Low to moderate

[a]Includes but not limited to *How I Treat* articles, webinars, FAQs, ASH annual meeting education sessions, the ASH Self-Assessment Program, and the Hematology Review Series