blood advances

The ASH-ASPHO Choosing Wisely Campaign: 5 hematologic tests and treatments to question

Sarah H. O'Brien,[1,*] Sherif M. Badawy,[2,3,*] Seth J. Rotz,[4] Mona D. Shah,[5] Julie Makarski,[6] Rachel S. Bercovitz,[2,3] Mary-Jane S. Hogan,[7] Lori Luchtman-Jones,[8,9] Julie A. Panepinto,[10] Ginna M. Priola,[11] Char M. Witmer,[12] Julie A. Wolfson,[13] Marianne Yee,[14,15] and Lisa K. Hicks[16]

[1]Division of Pediatric Hematology/Oncology, Nationwide Children's Hospital/The Ohio State University, Columbus, OH; [2]Division of Hematology, Oncology and Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; [3]Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL; [4]Department of Pediatric Hematology, Oncology, and Blood and Marrow Transplantation, Cleveland Clinic Children's Hospital, Cleveland, OH; [5]Division of Hematology and Oncology, Department of Pediatrics, Baylor College of Medicine, Houston, TX; [6]Independent consultant methodologist, Hamilton, ON, Canada; [7]Department of Pediatrics, Section of Hematology and Oncology, Yale School of Medicine, New Haven, CT; [8]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; [9]Division of Hematology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [10]Division of Pediatric Hematology/Oncology, Children's Wisconsin/Medical College of Wisconsin, Milwaukee, WI; [11]Division of Pediatric Hematology/Oncology, Mission Children's Hospital, Asheville, NC; [12]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA; [13]Division of Pediatric Hematology-Oncology, Institute for Cancer Outcomes and Survivorship, University of Alabama, Birmingham, AL; [14]Division of Hematology/Oncology, Department of Pediatrics, Emory University, Atlanta, GA; [15]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA; and [16]Division of Hematology/Oncology, St. Michael's Hospital, Toronto, ON, Canada

Choosing Wisely is a medical stewardship and quality-improvement initiative led by the American Board of Internal Medicine Foundation in collaboration with leading medical societies in the United States. The American Society of Hematology (ASH) has been an active participant in the Choosing Wisely project. In 2019, ASH and the American Society of Pediatric Hematology/Oncology (ASPHO) formed a joint task force to solicit, evaluate, and select items for a pediatric-focused Choosing Wisely list. By using an iterative process and an evidence-based method, the ASH-ASPHO Task Force identified 5 hematologic tests and treatments that health care providers and patients should question because they are not supported by evidence, and/or they involve risks of medical and financial costs with low likelihood of benefit. The ASH-ASPHO Choosing Wisely recommendations are as follows: (1) avoid routine preoperative hemostatic testing in an otherwise healthy child with no previous personal or family history of bleeding, (2) avoid platelet transfusion in asymptomatic children with a platelet count $>10 \times 10^3/\mu L$ unless an invasive procedure is planned, (3) avoid thrombophilia testing in children with venous access-associated thrombosis and no positive family history, (4) avoid packed red blood cells transfusion for asymptomatic children with iron deficiency anemia and no active bleeding, and (5) avoid routine administration of granulocyte colony-stimulating factor for prophylaxis of children with asymptomatic autoimmune neutropenia and no history of recurrent or severe infections. We recommend that health care providers carefully consider the anticipated risks and benefits of these identified tests and treatments before performing them.

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*S.H.O. and S.M.B. contributed equally to this work as joint first authors.

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Introduction

Choosing Wisely is a medical stewardship and quality-improvement initiative led by the American Board of Internal Medicine (ABIM) Foundation in collaboration with national medical specialty societies as well as organizations that represent other members of the clinical care team. Participating societies were asked to identify 5 tests or procedures commonly used in their field whose necessity should be questioned and discussed, with the ultimate goal of helping patients receive care that is supported by evidence and is nonduplicative, free from harm, and truly necessary.[1] Since the program's launch in 2012, the ABIM has partnered with more than 80 organizations, and more than 550 recommendations have been published.

The American Society of Hematology (ASH) has been an active participant in the Choosing Wisely initiative, with campaigns completed in 2013 and 2014 that resulted in 10 hematologic tests and treatments that health care providers should question.[2,3] Furthermore, in 2016, the ASH Choosing Wisely Task Force developed a methodology to identify and prioritize 10 Choosing Wisely recommendations from other medical societies that would be of high relevance and importance to patients with blood disorders and their health care providers.[4] In 2019, ASH and the American Society of Pediatric Hematology/Oncology (ASPHO) formed a joint panel to solicit, evaluate, and select items for a pediatric hematology–focused Choosing Wisely list. This article reports the methods and results of the ASH-ASPHO Choosing Wisely campaign.

Methods

In 2019, the ASH-ASPHO Choosing Wisely Task Force (CWTF) was formed and was asked to identify 5 hematologic tests, procedures, or treatments that health care providers and patients should question. Each society selected 5 members and 1 co-chair with expertise in pediatric malignant, nonmalignant, and/or laboratory hematology, for a total of 12 CWTF members. The lead author of past ASH Choosing Wisely recommendations (L.K.H.) provided methodologic guidance to the Task Force.

The ASH-ASPHO Choosing Wisely item selection process was anchored by 6 core principles (Table 1). Four of these principles (numbers 2-5) are recommended by the ABIM Foundation. As with previous ASH Choosing Wisely recommendations, the committee added 2 guiding principles to consider: the degree of impact on clinical practice for recommendations and consideration of harm to patients. Overall, tests, procedures, or treatments that involved greater risk of harm to patients and limited evidence of utility were prioritized over interventions with limited evidence of utility and lower risk of harm.

Suggestions for Choosing Wisely items were solicited from the CWTF, all ASPHO members, and members of relevant ASH committees, including the ASH Committee on Quality (COQ), ASH Committee on Practice (COP), ASH Subcommittee on Stewardship and Systems-Based Hematology (SSSBH), ASH Practice Partnership (APP), ASH Guideline Panel on the Treatment of Pediatric Venous Thromboembolism (VTE), the ASH Practice Update mailing list, and the ASH NewsLink mailing list. CWTF members also directly solicited items from colleagues at their institution or elsewhere with different domains of expertise. In total, 108 items (81 unique items) were submitted for consideration from 64 individuals.

Table 1. Guiding principles for the ASH Choosing Wisely campaign

1. Harm avoidance	Recommendations should aim to reduce potential harm to patients.
2. Evidence	Recommendations should be evidence-based.
3. Cost	Recommendations should aim to decrease the cost of health care.
4. Frequency	Recommendations should target tests, procedures, or treatments that are common.
5. Purview of the hematologist	Recommendations should target tests, procedures, or treatments within the purview of the hematologist.
6. Impact	Recommendations that are likely to have a greater impact (lead to greater positive changes) should be prioritized over those of lesser impact.

By using nominal group technique,[5] the ASH-ASPHO CWTF reduced the list of suggested Choosing Wisely items to a short list of 18 items. Nominal group technique entails small group discussion with 4 stages: silent idea generation, round robin, clarification, and ranking.[5] In April 2019, a ranking survey for these 18 potential items was sent to the ASPHO and ASH groups detailed above and was completed by 135 individuals (35% ASPHO members, 10% ASH members, 54% members of both societies, 1% members of neither society). The Task Force members then independently scored these items on the basis of priority in relation to the guiding principles in Table 1; these scores were used to select a short list of 8 items.

In August 2019, a methodologist performed a systematic search of the literature to identify clinical practice guidelines for each of the 8 items on the final shortlist. Both evidence-based and consensus-based guidelines were considered. A search of MEDLINE (1946-September 2019) and the following guideline databases (August-September 2019) was undertaken to identify relevant clinical practice guidelines for each item (see supplemental Data for key words searched for each item): Canadian Medical Association Infobase (CMA Infobase); National Institute for Health and Care Excellence (NICE); Scottish Intercollegiate Guidelines Network (SIGN); British Society for Haematology (BSH) [previously British Committee for Standards in Haematology, BCSH]; American Society of Clinical Oncology (ASCO); and the Standards and Guidelines Evidence (SAGE) database of the Canadian Partnership Against Cancer (CPAC). The search was limited to guidelines in the English language and those related to pediatric (children age 0-18 years) topics. We did not put any date restrictions on the searches because we anticipated a low number of articles specific to the pediatric population.

An evidence summary was prepared for each item. Members of the ASH-ASPHO CWTF reviewed the evidence summaries for the 8 items on the final short list. By using nominal group technique[6] informed by the evidence summaries and guided by the principles in Table 1, the Task Force selected 5 final items for the ASH-ASPHO Choosing Wisely Campaign. Final items were approved by the ASPHO Committee on Practice and the Executive Committees of both ASH and ASPHO.

Results

In October 2019, 5 ASH-ASPHO Choosing Wisely items were submitted to the ABIM Foundation. Minor language changes were

Table 2. ASH-ASPHO 2019 Choosing Wisely campaign

Recommendation	Key references
1. Don't perform routine preoperative hemostatic testing (PT, aPTT) in an otherwise healthy child with no previous personal or family history of bleeding.	7,8,10,12
2. Don't transfuse platelets in an asymptomatic (ie, nonbleeding) pediatric patient with hypoproliferative thrombocytopenia (eg, aplastic anemia, leukemia), with a platelet count $>10 \times 10^3/\mu L$ who is at least 1 year old unless signs and/or symptoms for bleeding develop or the patient is to undergo an invasive procedure.	14-17
3. Don't order thrombophilia testing on children with venous access (ie, peripheral or central)–associated thrombosis in the absence of a positive family history.	23-27,30
4. Don't transfuse packed red blood cells (pRBCs) for iron deficiency anemia in asymptomatic pediatric patients when there is no evidence of hemodynamic instability or active bleeding.	37,42,43,46,47
5. Don't routinely administer granulocyte colony-stimulating factor (G-CSF) for empiric treatment of pediatric patients with asymptomatic autoimmune neutropenia in the absence of recurrent or severe bacterial and/or fungal infections.	48,49,51,52,54

recommended by the ABIM Foundation and were endorsed by the ASH-ASPHO CWTF. Table 2 summarizes the 5 final recommendations of the ASH-ASPHO Choosing Wisely campaign and lists the key references supporting each of these recommendations.

Discussion

Recommendation 1: Avoid routine preoperative hemostatic testing in an otherwise healthy child with no previous personal or family history of bleeding.

Rather than performing hemostatic testing on all preoperative pediatric patients, it is necessary to perform a thorough personal, family, and medication history relating to abnormal bleeding signs and/or symptoms. Previous studies have shown that untargeted screening does not effectively identify those at risk of surgical bleeding.[7-11] Severe inherited bleeding disorders are rare, and most patients and family members with severe inherited bleeding disorders have experienced the signs and/or symptoms of excessive bleeding at early ages, are aware of their family history of a bleeding disorder, and report their conditions to their health care providers.[11]

Typical hemostatic tests ordered in preoperative screening include prothrombin time (PT) and activated partial thromboplastin time (aPTT). Mild prolongations of the PT and aPTT are common in children and are often caused by clinically asymptomatic conditions such as inherited factor XII deficiency or a transient lupus anticoagulant antibody, which do not result in excessive bleeding or increase the risk of perioperative bleeding. Other causes of abnormal PT and aPTT that have no impact on actual patient coagulation ability include phlebotomy difficulties, issues with specimen transport or processing, and normal population variance. In addition, type 1 von Willebrand disease, the most common inherited mild bleeding disorder, can manifest with normal PT and aPTT values, thus missing the diagnosis of von Willebrand disease and potentially creating a false sense of security.[9,11] Cost analyses have revealed that hemostatic screening is not cost-effective in children undergoing tonsillectomy and adenoidectomy[12]; however, the evidence related to other surgical procedures is limited. Finally, delays resulting from abnormal hemostatic testing cause harm by inducing stress and anxiety in patients and families and lead to inefficiencies in use of resources (ie, late or same-day cancellations of surgical procedures) with increased costs resulting from superfluous subspecialty consultation and testing.[9,13]

Recommendation 2: Avoid platelet transfusion in asymptomatic children at least 1 year of age with hypoproliferative thrombocytopenia and a platelet count $>10 \times 10^3/\mu L$ unless an invasive procedure is planned.

The second ASH-ASPHO recommendation advises against transfusing platelets into children with hypoproliferative thrombocytopenia conditions such as bone marrow failure or malignancy who experience a platelet count above $10 \times 10^3/\mu L$ unless signs and/or symptoms of bleeding develop or the patient is to undergo an invasive procedure. In children with hypoproliferative thrombocytopenia, attainment of higher platelet transfusion thresholds (above $10 \times 10^3/\mu L$) has not been associated with a decreased risk of bleeding.[14] Platelet transfusions, although usually well tolerated, can have significant adverse effects after multiple transfusions, thus exposing children to an increased risk for acute transfusion reactions, viral and bacterial infections, and platelet alloimmunization.

Platelets are an expensive, resource-intensive, biologic product, and the stewardship of this life-supporting, limited blood supply is critical to patient safety. The recommendation for a prudent use of platelet transfusions is consistent with the recently published clinical guidelines established by multiple professional medical organizations, including the National Institute for Health and Care Excellence, BSH, and ASCO.[15-17] It is important to note that the ASH-ASPHO recommendation is not intended to include children younger than 1 year of age,[18,19] does not account for additional comorbidities and medications that may alter bleeding risk (ie, in the setting of therapeutic anticoagulation), and is not relevant to patients with immune-mediated thrombocytopenia (eg, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia).[20]

Recommendation 3: Avoid thrombophilia testing in children with venous access–associated thrombosis and no positive family history.

The third ASH-ASPHO recommendation advises against inherited thrombophilia (IT) testing in children with peripherally inserted or tunneled central venous catheter (CVC)–associated thrombosis in the absence of a family history of thrombosis. Although VTE is rare in children,[21] it is more common in hospitalized children with chronic conditions,[22] particularly those with venous catheters, which represent the single most common risk factor associated with provoked pediatric thrombosis.[23] A meta-analysis in children with CVCs reported a low prevalence of IT disorders and a weak association with CVC-related VTE events, suggesting that routine testing for IT disorders in children with CVCs has very limited value.[24] Furthermore, results from IT disorder testing does not influence the initial anticoagulation management of children with their first episode of provoked VTE from any acquired cause, as suggested in the ASH

2018 guidelines for pediatric VTE.[25] Clinical practice guidelines in other countries, such as the United Kingdom, Scotland, and Canada, recommend against routine testing for IT disorders in patients with provoked VTE, including children.[23,26-29] This recommendation is consistent with ASH Choosing Wisely recommendations for adults.[3]

IT testing has substantial financial cost. In addition, a positive result has the potential for harm resulting from misinterpretation of clotting risk assessment, which leads to undue psychological distress and may have an impact on childbearing plans as well as possible discrimination regarding life insurance for affected patients.[25-27] Furthermore, since the results of IT testing have not been shown to predict recurrence of provoked VTE[24,30] or inform the intensity and duration of anticoagulant therapy in children with CVC-related VTE,[25] IT testing should not be performed routinely in the absence of a family history of thrombophilia. Nevertheless, the Task Force does acknowledge that additional research is needed to reach a consensus definition for what qualifies as a positive family history of thrombosis and to better understand the impact of thrombophilia on other causes of provoked clots in studies of pediatric VTE.[31]

Recommendation 4: Avoid packed red blood cell transfusion for asymptomatic children with IDA and no active bleeding.

The fourth ASH-ASPHO recommendation advises against the transfusion of packed red blood cells (pRBCs) in asymptomatic children with iron deficiency anemia (IDA) with no evidence of hemodynamic instability or active bleeding. IDA is the most common cause of anemia across all age groups, and it affects 2 billion individuals worldwide, including 2 million in the United States.[32] IDA usually develops over time (ie, chronic process), and most patients are asymptomatic, even those with very low hemoglobin.[32] The 2 key steps in managing IDA in children are (1) initiating iron replacement therapy by oral or intravenous routes, which usually leads to a rapid increase in hemoglobin levels[33-35] and (2) treating the underlying etiologies (eg, restricting excessive cow's milk intake for toddlers or starting hormonal contraceptive therapy for adolescents with heavy menstrual bleeding).[36] Ferrous sulfate is a frequently prescribed oral iron formulation divided into 2 or 3 daily doses,[32,36] or as a low-dose once-per-day regimen.[37] Often ferrous sulfate is poorly tolerated because of adverse gastrointestinal effects.[32,35,36] Furthermore, there has been growing evidence to support the utility and the benefits of using alternate-day oral iron supplementation among adults with IDA, especially women.[38-41] Several studies, including recent randomized controlled trials, reported evidence to suggest comparable hemoglobin response with higher fractional iron absorption and better tolerability using an alternate-day regimen compared with a twice-per-day regimen[38-41]; there are no similar data in the current literature on pediatric IDA, and future studies are needed to address this research question. Recent studies have also reported data supporting the safety and efficacy of intravenous iron replacement in children and teens[42-44] who have demonstrated a poor response to oral iron formulations.

Transfusion with pRBCs does not ensure complete treatment of IDA because the form of iron obtained from transfused pRBCs is not immediately bioavailable for erythropoiesis and does not replenish iron stores. In addition, unnecessary pRBC transfusions expose patients to risks of transfusion reactions, blood-borne infections, RBC alloimmunization, and volume overload.[45] The judicious use of pRBC transfusions has been associated with cost savings for health care systems.[46,47] Although patients with severe IDA need close cardiovascular monitoring, the decision to transfuse pRBCs is typically guided by assessment of hemodynamic stability and ongoing blood loss rather than hemoglobin or iron levels.[36] Effective treatment of severe IDA consists of replenishing iron stores using oral or intravenous iron supplementation while addressing the underlying causes. The recommendation that pRBC transfusion should be avoided in asymptomatic, hemodynamically stable children with IDA and no active bleeding is supported by recently published practice guidelines in Canada.[46,47]

Recommendation 5: Avoid routine administration of G-CSF for prophylaxis in children with asymptomatic autoimmune neutropenia and no history of recurrent or severe infections.

The fifth ASH-ASPHO recommendation advises against the routine administration of granulocyte colony-stimulating factor (G-CSF) as empiric treatment for children with asymptomatic autoimmune neutropenia (AIN) and no history of recurrent or severe bacterial and/or fungal infections. AIN is rare, affecting 1 in 100 000 children in the United States annually, with a median age at diagnosis of 8 to 11 months (range, 3-38 months). Typically, AIN is characterized by severe neutropenia with median absolute neutrophil counts of 200 $\times$ $10^3/\mu L$ (range, 0 to 500 $\times$ $10^3/\mu L$), which often increase to normal during times of physical stress, such as with viral or bacterial infections.[48,49] Children with AIN experience minor upper respiratory infections at only a slightly higher frequency than the general population, and occasionally have gingivitis. Rare serious or invasive bacterial infections have been reported in young infants.[48,49] Anti-neutrophil antibodies are sometimes detectable, but the results of this testing have low sensitivity and specificity in diagnosing AIN.[50] Moreover, in a large Italian cohort study of AIN in children, the presence or absence of anti-neutrophil antibodies was not associated with risk or frequency of infections, age at recovery, or overall prognosis.[51] Almost all children with AIN normalize their absolute neutrophil counts within a median of 20 months (range, 6-54 months), with no risk of recurrence.[48,49,51]

There are limited data regarding the use of subcutaneous G-CSF in children with AIN. Two recent studies report administering G-CSF in 7.5% to 16% of children with AIN, mainly as on-demand regimens in the event of recurrent infections or before planned invasive procedures.[51,52] However, neither study demonstrated clear benefits in reducing infection rates, including pathogenic bloodstream infections.[51,52] Therefore, in children with asymptomatic AIN, there is insufficient evidence to support the routine use of G-CSF as a prophylaxis strategy for improving health outcomes.[48,49,53,54] The unnecessary routine use of G-CSF could lead to intolerable adverse effects, such as bone pain from excess neutrophil pool expansion in the marrow, injection site pain or infection, and avoidable health care costs.[48,49,52] The use of G-CSF in this population should be guided by assessment of infection risks using the minimal effective dose to avoid unnecessary adverse effects.[48]

Conclusions

In summary, the ASH-ASPHO Choosing Wisely campaign has identified 5 tests and treatments that expose children and adolescents

to potential harm and/or increased cost with limited or no benefit when used in an inappropriate medical setting. All recommendations are based on the current evidence, which will be revisited annually by the SSSBH in consultation with ASPHO. As additional evidence becomes available, some recommendations may need to be amended. We encourage all health care providers to consider the ASH-ASPHO Choosing Wisely guidelines when treating pediatric patients, educating trainees, and considering future quality improvement and research efforts.[3]

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Authorship

Contribution: All authors participated in different activities of the ASH-ASPHO Choosing Wisely Task Force; S.H.O., S.M.B., and S.J.R. drafted the paper; M.D.S., J.M., R.S.B., L.L-J., J.A.P., G.M.P., C.M.W., J.A.W., M.Y., M.-J.S.H., and L.K.H. critically revised the paper; and all authors approved the final submitted version of the paper.

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ORCID profiles: S.H.O., 0000-0001-8855-9746; S.M.B., 0000-0002-4739-265X; S.J.R., 0000-0003-2896-1113; J.A.W., 0000-0002-3711-2239; M.Y., 0000-0001-6082-8385.

Correspondence: Sarah H. O'Brien, The Research Institute at Nationwide Children's Hospital, 700 Children's Dr, Columbus, OH 43205; e-mail: sarah.obrien@nationwidechildrens.org.

References

1. Choosing Wisely®, an initiative of the ABIM Foundation. Promoting conversations between patients and clinicians. 2012. https://www.choosingwisely.org/. Accessed 4 February 2021.
2. Hicks LK, Bering H, Carson KR, et al. Five hematologic tests and treatments to question. *Blood.* 2014;124(24):3524-3528.
3. Hicks LK, Bering H, Carson KR, et al. The ASH Choosing Wisely® campaign: five hematologic tests and treatments to question. *Blood.* 2013;122(24):3879-3883.
4. Hicks LK, Rajasekhar A, Bering H, et al. Identifying existing Choosing Wisely recommendations of high relevance and importance to hematology. *Am J Hematol.* 2016;91(8):787-792.
5. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ.* 1995;311(7001):376-380.
6. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm.* 2016;38(3):655-662.
7. Alzahrani A, Othman N, Bin-Ali T, et al. Routine preoperative coagulation tests in children undergoing elective surgery or invasive procedures: Are they still necessary? *Clin Med Insights Blood Disord.* 2019;12:1179545X18821158.
8. Asaf T, Reuveni H, Yermiahu T, et al. The need for routine pre-operative coagulation screening tests (prothrombin time PT/partial thromboplastin time PTT) for healthy children undergoing elective tonsillectomy and/or adenoidectomy. *Int J Pediatr Otorhinolaryngol.* 2001;61(3):217-222.
9. Bidlingmaier C, Olivieri M, Hütker S, Dietl S, Kurnik K. Perioperative management of hemostasis in children and adolescents. *Blood Cells Mol Dis.* 2017;67:91-95.
10. Chee YL, Crawford JC, Watson HG, Greaves M; British Committee for Standards in Haematology. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. *Br J Haematol.* 2008;140(5):496-504.
11. van Veen JJ, Spahn DR, Makris M. Routine preoperative coagulation tests: an outdated practice? *Br J Anaesth.* 2011;106(1):1-3.
12. Cooper JD, Smith KJ, Ritchey AK. A cost-effectiveness analysis of coagulation testing prior to tonsillectomy and adenoidectomy in children. *Pediatr Blood Cancer.* 2010;55(6):1153-1159.
13. Bidlingmaier C, Treutwein J, Olivieri M, Kurnik K. Repeated coagulation testing in children. Does it improve the diagnostic value? *Hamostaseologie.* 2011;31(suppl 1):S51-S56.
14. Estcourt LJ, Stanworth SJ, Murphy MF. Platelet transfusions for patients with haematological malignancies: who needs them? *Br J Haematol.* 2011;154(4):425-440.
15. National Institute for Health and Care Excellence (NICE). Blood transfusion NICE guideline [NG24]. Published date: 18 November 2015. https://www.nice.org.uk/guidance/ng24. Accessed 4 February 2021.

16. New HV, Berryman J, Bolton-Maggs PH, et al; British Committee for Standards in Haematology. Guidelines on transfusion for fetuses, neonates and older children. *Br J Haematol.* 2016;175(5):784-828.

17. Schiffer CA, Bohlke K, Delaney M, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2018;36(3):283-299.

18. Curley A, Stanworth SJ, Willoughby K, et al; PlaNeT2 MATISSE Collaborators. Randomized trial of platelet-transfusion thresholds in neonates. *N Engl J Med.* 2019;380(3):242-251.

19. Fustolo-Gunnink SF, Fijnvandraat K, van Klaveren D, et al; PlaNeT2 and MATISSE collaborators. Preterm neonates benefit from low prophylactic platelet transfusion threshold despite varying risk of bleeding or death. *Blood.* 2019;134(26):2354-2360.

20. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood.* 2011;117(16):4190-4207.

21. van Ommen CH, Heijboer H, Büller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. *J Pediatr.* 2001;139(5):676-681.

22. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics.* 2009;124(4):1001-1008.

23. Thrombosis Canada. Central venous catheter-related deep vein thrombosis. 2020. https://thrombosiscanada.ca/clinicalguides/?search=Central%20Venous%20Catheter-Related%20Deep%20Vein%20Thrombosis#. Accessed 4 February 2021.

24. Neshat-Vahid S, Pierce R, Hersey D, Raffini LJ, Faustino EV. Association of thrombophilia and catheter-associated thrombosis in children: a systematic review and meta-analysis. *J Thromb Haemost.* 2016;14(9):1749-1758.

25. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv.* 2018;2(22):3292-3316.

26. National Institute for Health and Care Excellence (NICE). Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NICE guideline [NG158]. Published date: 26 March 2020. https://www.nice.org.uk/guidance/ng158. Accessed 4 February 2021.

27. Scottish Intercollegiate Guidelines Network (SIGN) - Healthcare Improvement Scotland. Prevention and management of venous thromboembolism. SIGN 122, October 2014. https://www.sign.ac.uk/our-guidelines/prevention-and-management-of-venous-thromboembolism/. Accessed 4 February 2021.

28. Baglin T, Gray E, Greaves M, et al; British Committee for Standards in Haematology. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol.* 2010;149(2):209-220.

29. Chalmers E, Ganesen V, Liesner R, et al; British Committee for Standards in Haematology. Guideline on the investigation, management and prevention of venous thrombosis in children. *Br J Haematol.* 2011;154(2):196-207.

30. Avila ML, Amiri N, Stanojevic S, et al. Can thrombophilia predict recurrent catheter-related deep vein thrombosis in children? *Blood.* 2018; 131(24):2712-2719.

31. Hau A, Wegener E, Ignjatovic V, Revel-Vilk S, Monagle P. Family history of venous thromboembolism in the paediatric population: The need for a standardized definition. *Thromb Res.* 2019;173:91-95.

32. Camaschella C. Iron-deficiency anemia. *N Engl J Med.* 2015;372(19):1832-1843.

33. Powers JM, Buchanan GR. Diagnosis and management of iron deficiency anemia. *Hematol Oncol Clin North Am.* 2014;28(4):729-745.

34. Powers JM, McCavit TL, Buchanan GR. Management of iron deficiency anemia: a survey of pediatric hematology/oncology specialists. *Pediatr Blood Cancer.* 2015;62(5):842-846.

35. Powers JM, Nagel M, Raphael JL, Mahoney DH, Buchanan GR, Thompson DI. Barriers to and facilitators of iron therapy in children with iron deficiency anemia. *J Pediatr.* 2020;219:202-208.

36. Ning S, Zeller MP. Management of iron deficiency. *Hematology Am Soc Hematol Educ Program.* 2019;2019:315-322.

37. Powers JM, Buchanan GR, Adix L, Zhang S, Gao A, McCavit TL. Effect of low-dose ferrous sulfate vs iron polysaccharide complex on hemoglobin concentration in young children with nutritional iron-deficiency anemia: A randomized clinical trial. *JAMA.* 2017;317(22):2297-2304.

38. Kaundal R, Bhatia P, Jain A, et al. Randomized controlled trial of twice-daily versus alternate-day oral iron therapy in the treatment of iron-deficiency anemia. *Ann Hematol.* 2020;99(1):57-63.

39. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood.* 2015;126(17):1981-1989.

40. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *Lancet Haematol.* 2017; 4(11):e524-e533.

41. Stoffel NU, Zeder C, Brittenham GM, Moretti D, Zimmermann MB. Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. *Haematologica.* 2020;105(5):1232-1239.

42. Boucher AA, Pfeiffer A, Bedel A, Young J, McGann PT. Utilization trends and safety of intravenous iron replacement in pediatric specialty care: A large retrospective cohort study. *Pediatr Blood Cancer.* 2018;65(6):e26995.

43. Crary SE, Hall K, Buchanan GR. Intravenous iron sucrose for children with iron deficiency failing to respond to oral iron therapy. *Pediatr Blood Cancer.* 2011;56(4):615-619.

44. Powers JM, Shamoun M, McCavit TL, Adix L, Buchanan GR. Intravenous ferric carboxymaltose in children with iron deficiency anemia who respond poorly to oral iron. *J Pediatr.* 2017;180:212-216.

45. Sahu S, Hemlata, Verma A. Adverse events related to blood transfusion. *Indian J Anaesth.* 2014;58(5):543-551.

46. Toward Optimized Practice (TOP). Iron deficiency anemia (IDA): Clinical Practice Guideline, March 2018. https://top.albertadoctors.org/CPGs/Lists/CPGDocumentList/IDA-CPG.pdf. Accessed 4 February 2021.

47. British Columbia, BC Guidelines. Iron Deficiency – Diagnosis and Management- Province of British Columbia. https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/iron-deficiency?keyword=Iron&keyword=Deficiency&keyword=%E2%80%93&keyword=Diagnosis&keyword=and&keyword=Management. Accessed 4 February 2021.

48. Dale DC. How I manage children with neutropenia. *Br J Haematol.* 2017;178(3):351-363.

49. Walkovich K, Boxer LA. How to approach neutropenia in childhood. *Pediatr Rev.* 2013;34(4):173-184.

50. Boxer LA, Bolyard AA, Marrero TM, et al. Is there a role for anti-neutrophil antibody testing in predicting spontaneous resolution of neutropenia in young children [abstract]. *Blood.* 2015;126(23). Abstract 2211.

51. Farruggia P, Fioredda F, Puccio G, et al. Idiopathic neutropenia of infancy: Data from the Italian Neutropenia Registry. *Am J Hematol.* 2019;94(2):216-222.

52. Kirk SE, Grimes AB, Shelke S, Despotovic JM, Powers JM. The cost of a "benign" condition: Healthcare utilization and infectious outcomes in young children with primary autoimmune neutropenia. *Pediatr Blood Cancer.* 2020;67(4):e28146.

53. Dale DC, Boxer LA. Guidelines for pediatric management of severe chronic neutropenia. *Am J Hematol.* 2012;87(2):133.

54. Fioredda F, Calvillo M, Bonanomi S, et al; Neutropenia Committee of the Marrow Failure Syndrome Group of the AIEOP (Associazione Italiana Emato-Oncologia Pediatrica). Congenital and acquired neutropenias consensus guidelines on therapy and follow-up in childhood from the Neutropenia Committee of the Marrow Failure Syndrome Group of the AIEOP (Associazione Italiana Emato-Oncologia Pediatrica). *Am J Hematol.* 2012;87(2):238-243.