Reviewed by ASH officers on 8/2/2023

Plan to Develop New ASH Clinical Practice Guidelines on Aplastic Anemia

Background and Rationale

Aplastic anemia (AA) is a rare condition that occurs when a person's bone marrow (i.e., hematopoietic stem cells in the marrow) fails to produce blood cells (i.e., pancytopenia). This results in life-threatening complications, primarily infectious diseases and bleeding. Clonal evolution to myelodysplastic syndrome and sometimes leukemia can occur over time in a minority of patients.

The incidence of AA has been estimated to range from 1.5 to 7 per million per year, with a higher incidence in Asia (Abello et al. 2019). Incidence could be substantially higher because of underdiagnosis and under-reporting, especially in underserved populations. AA can be a hereditary or acquired condition. Assessment and diagnostic testing aim to rule out diverse other causes of pancytopenia to provide treatment quickly. The risk of death without treatment is estimated to be high, with an approximately 80-90% mortality over time in reports from when effective therapies were not available (Camitta et al. 1979; Williams et al. 1973).

First-line treatments include allogeneic bone marrow transplantation and immunosuppressive therapy (e.g., antithymocyte globulin [ATG] and cyclosporine). These treatment options are supported by evidence from prospective randomized, controlled trials and from some large prospective and retrospective cohort studies. For example, 68% (CI 56%–80%) of patients with severe AA responded to treatment with horse ATG plus cyclosporine (CsA) in a randomized, controlled trial by Scheinberg and colleagues (2011). With bone marrow transplant, 10-year survival has been estimated to be 73% (all ages) and 79% (children) (Locasciulli et al. 2007). Emerging evidence includes trials of thrombopoietin-receptor agonists such as eltrombopag, data from longer follow-up studies of patients enrolled in pivotal trials, and analyses of registry data [REFS]. This emerging evidence describes new management options and prognostic factors, including cytogenetic factors.

In most clinical settings globally, transplant is infrequently used because of lack of histocompatible donors, challenging logistics and required support, lack of clinical expertise, and cost. Non-transplant treatment modalities are, therefore, most widely applied worldwide. Management approaches vary internationally and regionally. In some developing countries and low-resource settings, standard immunosuppressive regimens are unavailable. Even in higher-resourced settings, AA may be underrecognized, delaying effective treatment.

Existing guidance about the management of AA includes guidelines from the British Society of Haematology (BSH; Killick et al. 2015; Samarasinghe et al. 2017), "How I Treat" articles (e.g., Bacigalupo 2017; Scheinberg & Young 2012), and other review articles (e.g., DeZern & Churpek 2021; Olson & Dunbar 2022). According to BSH staff, revised guidelines on AA were approved in 2022 and are currently in submission for journal publication (as of February 2023). These existing resources have not been developed using formal methods including systematic reviews of evidence. Other limitations include narrow perspective (e.g., for the British or U.S. healthcare systems), narrow scope, limited utility for

typical practicing hematologists, and limited organizational support for dissemination and implementation.

The American Society of Hematology (ASH) will therefore develop new clinical practice guidelines for an international audience using the best methods, including systematic evidence review. A staged approach to development will be used. As described in this plan, initial guidelines by a single guideline panel will focus on questions related to *key decisions* during a typical patient's disease journey. This includes the initial assessment and diagnosis of AA, first-line treatment with transplant vs. immunosuppressive therapy, supportive care, and medical management of patients who receive immunosuppressive therapy short and long-term. Recommendations will address patients most affected by AA, including children to the elderly.

These initial guidelines will also prioritize questions for which *strong recommendations* may be expected. Such recommendations typically reflect clear trade-offs between benefits and harms and are typically based on reliable supporting evidence (Andrews et al. 2013). By focusing on key decisions and strong recommendations, ASH aims to provide initial guidelines that meet the needs of typical hematologists and patients internationally, including in settings where state-of-the-art diagnostic testing and first-line treatments are unavailable.

Registry Coordination

ASH will coordinate the development of these initial guidelines with the continued development of the Latin American Registry of Aplastic Anemia (LARAA). LARAA is a collaborative effort by ASH and 10 national hematology societies in Latin America (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Paraguay, Peru, Uruguay, and Venezuela). The registry currently includes retrospective data for 204 patients with AA in these countries (Abello et al. 2019).

Coordination will aim to support the analysis of the existing retrospective data and develop the registry for prospective data collection using data elements commonly defined within the ASH guidelines and the registry.

LARAA experts have drafted a data collection form for the registry that defines many data elements (Appendix A). During planning meetings and early in the guideline development process, experts from the guideline panel will review this collection form against patient populations (e.g., concerning disease definition, disease severity, and partial or complete response to treatment), interventions (e.g., main therapeutic regimens including usual dosages), and outcomes to be defined within the guidelines. Through discussion, the experts will standardize all of these elements within the guidelines and the registry. To facilitate consensus across both groups, at least 1 expert with a leadershiop role for LARAA will be included on the guideline panel. The data elements will be further refined during systematic evidence review and during panel deliberations and agreement about recommendations.

Coordination of data elements is expected to benefit both efforts: For the registry, coordination will ensure that data elements reflect international expert agreement about the best available evidence. For the guidelines, coordination will ensure that the registry may prospectively collect data that directly inform future development and revision of recommendations.

Coordination with other registries will also be explored, such as with the Monash University's Aplastic Anaemia and other bone marrow failure syndromes Registry (AAR) (https://aaregistry.org.au/).

ASH will explore with the Latin America hematology societies that own LARAA how to fund registry changes and enhancements.

During systematic evidence review for guideline development, existing (retrospective) data in LARAA (and other registries) will be evaluated for relevance to guideline questions. If the data provide best available evidence for any guideline question, ASH will request permission to analyze and use the data, in collaboration with LARAA experts on the guideline panel. In this way, guideline development may support retrospective data analyses that are planned but not yet completed.

Guideline Questions

The initial guidelines will address approximately 15 clinical questions. As described above, these questions will focus on *key decisions* during a typical patient's disease journey.The following table presents *example* questions. Final questions will be determined by the guideline panel:

#	Patient population	Intervention	Comparison	
Assessment and diagnosis				
1.	Patients with suspected AA	Evaluation for toxic drug or chemical exposure and discontinuation if found	None	
2.	Patients with suspected AA *Subpopulations* - Newly suspected - Annually - PNH-screen positive	Screening for paroxysmal nocturnal hemoglobinuria (PNH)	None	
3.	Patients with suspected AA	Family history, Fanconi anemia testing, telomere length testing, and other evaluations for inherited/genetic disorders characterized by bone marrow failure	None	
4.	Patients with suspected AA	Molecular testing	None	
5.	Patients with a high clinical probability of having AA based on initial evaluations	Bone marrow biopsy, cytogenetics, immunophenotyping, bone marrow aspirate, immunohistochemistry	None	
Initial treatment and supportive care				
6.	- Subgroups of patients with newly diagnosed AA, when transplant is available:Non-severe AA - Patients without matched sibling donor - Patients ≤40 - Patients 40-50 years old	Bone marrow transplant	Immunosuppressive therapy, e.g., horse ATG (ATG-ATGAM) combined with ciclosporin (CSA)	

#	Patient population	Intervention	Comparison	
	- Patients >40-50 - Patients with AA refractory to immunosuppressive therapy			
7.	Patients with AA	Blood transfusions for quality of life	None	
8.	Patients with AA who receive blood transfusions	Phenotype matched blood	Non-matched blood	
9.	Stable patients with AA receiving active treatment	Prophylactic platelet transfusion	None	
10.	Patients with AA *Subpopulations* - Patients undergoing bone marrow transplant - Patients receiving ATG-based immunosuppression	Irradiated blood products	Non-irradiated	
11.	Patients with AA *Subpopulation:* Patients who are neutropenic	Interventions to prevent infection (e.g., hospital isolation, prophylactic antibiotics, prophylactic antifungals)	None	
12	Patients with AA	Interventions to prevent and manage toxicities of ATG administration, e.g., serum sickness	None	
13	Patients with AA	Horse ATG formulation	Rabbit ATG formulation	
14	Patients with AA	Horse ATG plus cyslosporine	Horse ATG plus cyclosporine plus eltrombopag	
15	Patients with AA	Horse ATG plus cyclosporine plus a 3rd agent	Horse ATG plus cyclosporine	
16	Patients with non-severe AA (moderate)	Cyclosporine Androgen Corticosteriods Growth Factors Transfusions	Horse ATG plus cyclosporine Eltrombopag	
Medical management				
17.	Elderly patients	ATG-ATGAM with CSA	CSA alone	
18.	Pregnant patients	Supportive care	*Multiple comparisons* - ATG-ATGAM with CSA - CSA alone	

#	Patient population	Intervention	Comparison	
19.	Patients unwilling to accept or unable to tolerate immunosuppressive therapy	Supportive care	None	
20.	Patients with partial response to an initial course of immunosuppressive therapy	Observe (follow-up) in patients with a PR	*Multiple comparisons* - Supportive care / no treatment - Cyclophosphamide - Eltrombopag - Stem cell transplantation - Alternative Tpo-agonists	
21	Patients with no response to an initial course of immunosuppression	Stem cell transplantation	*Multiple comparisons* - Supportive care / no treatment - Cyclophosphamide - Eltrombopag - Repeat immunosuppression - Alternative Tpo-agonists	
22	Patients who relapsed after initial immunosuppression	Repeat immunosuppression	*Multiple comparisons* - Supportive care / no treatment - Cyclophosphamide - Eltrombopag - Stem cell transplantation	
23	Patients with cytogenetic abnormalities in follow-up	Stem cell transplantation	Non-stem cell transplantation modalities	

The guideline panel will brainstorm other possible questions, then prioritize approximately 15 questions using methods described below. From the above example questions, experts agree that it will be practical to prioritize questions likely to lead to *strong recommendations*. For many of questions, the supporting evidence for doing or not doing the intervention is at least moderate quality. For other questions, the supporting evidence may be low quality, but clear tradeoffs of benefits and harms may satisfy criteria for issuing a strong recommendation (Andrews et al. 2013).

Questions with multiple subpopulations or multiple comparisons may count as multiple questions, depending on coherence of supporting evidence review.

For practical reasons, many important clinical questions are expected to be excluded from this initial effort. These may include questions that are clinically unusual or infrequent and questions for which published evidence is unavailable or of low quality. ASH aims to produce comprehensive guidelines on this topic over multiple years. Therefore, questions not prioritized for these initial guidelines will be saved and considered for future ASH guidelines, as described below under Guideline Extension and Revision.

Good Practice Statements

For some questions, there may be an inarguable, overwhelming net benefit for the intervention, supported by high-certainty evidence that would be difficult to review systematically, e.g., because of

indirectness. In this situation, the guideline panel may agree to issue a "good practice statement," i.e., an actionable statement for which no systematic review of evidence is conducted, for practical reasons (Izcovich et al. 2020, Guyatt et al. 2016). For example, indirect evidence from many patient populations shows that a complete medical and family history is essential to rule out many potential non-AA diagnoses. Questions addressed by a good practice statement will not count toward the approximately 15 total questions to be addressed by the guidelines.

Outcomes

For each question, the guideline panel will prioritize up to 7 patient-centered outcomes that are determined to be crucial for decision-making. Outcomes will include both benefits and harms. The panel will define all outcomes in a format previously piloted for ASH guidelines on venous thromboembolism (i.e., "health outcome descriptors") (Wiercioch et al. 2021). Outcomes may include both objective outcomes such as platelet counts and subjective outcomes such as quality of life. As described above under Registry Coordination, experts on the panel will collaborate with experts designing LARAA to agree how to record all prioritized outcomes within the registry for optimal future analysis.

Background Questions

Within the guideline report, graded recommendations that address the approximately 15 prioritized questions will be presented in the context of discussion about disease prevalence and course, differential diagnosis, and how to implement recommended interventions including in low-resource settings. This discussion will not be informed by systematic evidence review.

Example background questions to be addressed within the guidelines by contextual discussion include the following:

Assessment and diagnosis

- What are the principal diagnoses to differentiate from AA (e.g., myeloproliferative neoplasms [MPNs], PNH)?
- Are there preferred or standard methods for the preparation, processing and reporting of bone marrow aspirates and specimens in patients with AA?
- Are any cytogenic abnormalities known to be associated with prognosis or treatment response?
- When should a germline defect be suspected?
- Can extensive scale sequencing detect molecular abnormalities relevant for the diagnosis or treatment of AA?
- Can very young patients (<2 years old) have idiopathic acquired AA?
- What are the risk factors for AA in pregnancy?

Initial treatment and supportive care

- When should human leukocyte antigen (HLA) testing for transplant be done?
- Can transplant from a matched unrelated donor be considered first-line therapy?
- What if first-line immunosuppressive therapies are unavailable in the patient's clinical setting?
- What is the disease course in patients with non-severe AA?
- Which specific antimicrobial prophylaxis should be used?

Medical management

- What protocols have been used for ATG infusion management? In children? In elderly patients? Maximum age for elderly patients?
- Is management different for patients diagnosed pre-pregnancy vs. during?
- How define no disease response (how long to wait)?
- What clinical factors are associated with response to immunotherapy?
- How often should marrow cytogenetics be checked after immunosuppression?
- What is known about combining eltrombopag with ciclosporine, ATG, or both?
- Has romiplostim been evaluated for AA?

Panel Composition

ASH will form a single guideline panel of about 25 individuals. The panel will mainly include adult and pediatric hematologists who are expert in AA. Other areas of expertise and perspectives to be included will be as follows:

- At least 2 hematopathologists, with knowledge of molecular genetics
- 1 infectious disease specialist
- At least 3 transplant specialists
- 1-3 transfusion medicine specialists
- 1-3 patient representatives, i.e., individuals with lived experience of AA, such as a past patient or a caregiver. Ideally, patient representatives will not *also* be physicians.
- At least 1 early career hematologist who can represent the perspective of physician learners
- At least 3 panelists who can represent the perspective of hematologists practicing in a typical community setting (i.e., not a major research academic setting). These individuals will not be experts in AA. They may include individuals from low- or middle-income countries.
- At least 1 individual who can liaise with LARAA experts
- 1 or more medical paraprofessionals, such as a physician assistant

The panel will be diverse with respect to institution, geography, demographics, and intellectual points of view on the guideline questions. Consistent with the goal of developing recommendations for international audiences, panelists will be considered from North and South America, Europe, Africa, and Asia pacific regions.

Individuals with methodological expertise may be included on the panel, or this expertise may be provided by the methodology team that supports the panel under a paid agreement with ASH.

A member of the ASH Guideline Oversight Subcommittee will serve on the guideline panel as an ex officio member. This individual's role will be to ensure that the guideline development process is conducted in accordance with this project plan and ASH policies and procedures, including ensuring that questions are within scope, reviewing participant disclosures and ensuring adherence to ASH COI policies, and critically reviewing the guideline report for publication.

One guideline panelist may be asked to serve in a "writer" role. Responsibilities of this role will include drafting background clinical content, recording panel decisions and discussion points, drafting the guideline report, integrating edits by authors into the guideline report, and addressing comments

receiving during public review. At the beginning of the project, panel leadership will discuss and agree with the writer how to appropriately recognize his or her contributions on publication.

At the beginning of the project, panelists with clinical expertise will be designated as primary liaisons and have main responsibility for writing, editing, or reviewing the dissemination and implementation tools described below, e.g., guideline snapshot, teaching slide set, pocket guide, and digital mobile version. At least one panelist will be designated for each tool.

Perspective

These guidelines are intended for clinicians and patients internationally, including those in developing countries and low-resource clinical settings. In consideration of the currently available evidence, the guideline panel will be instructed to provide graded recommendations for high-resource settings, taking an individual patient perspective (i.e., rather than the perspective of a health system or of policymakers). However, discussion with each recommendation will describe implementation considerations in low-resource settings, facilitating adaptation of the recommendations for low-resource settings and for different perspectives such as by health systems in different countries or regions.

Organizational Collaborators

ASH will explore collaboration and coordination with other organizations to support the dissemination and implementation of these guidelines.

For example, other organizations may be invited to review the guidelines during the public comment step, endorse the guidelines on publication, and disseminate or promote the published guidelines through announcements, summaries, commentaries, or educational programs.

Organizations to be considered include Latin American hematology societies that are collaborating on LARAA, BSH, the European Society of Hematology, and EBMT (formely the European Society for Blood and Marrow Transplantation).

Methods

The ASH guideline development process includes the following steps:

1. ASH forms a guideline panel.
2. The panel prioritizes guideline questions.
3. A methodology team in collaboration with experts on the guideline panel systematically reviews available evidence.
4. The guideline panel reviews and finalizes evidence summaries and forms recommendations.
5. ASH makes the recommendations available for public comment.
6. The guideline panel and the methodology team write a report of the guidelines for publication and dissemination.
7. ASH committees and officers review and approve publication of the guidelines under the imprimatur of ASH.
8. Authors submit the guidelines report to *Blood Advances* for review and publication.

The above steps depend on substantial collaboration by the guideline panel, methodology team, and ASH. The panel's main responsibilities are to prioritize questions (step 1), form recommendations (step 4), and author a guideline report (steps 6 and 8). Under a paid agreement with ASH, a methodology team helps the panel to structure questions (step 2), conducts systematic reviews of available evidence (step 3), and helps the panel to use appropriate methods to form recommendations (step 4). ASH staff provide coordination of the above steps, e.g., by scheduling meetings, organizing project information, managing public comment (step 5) and organizational approval (7), and managing contractual and volunteer obligations. The specific roles and responsibilities of all participants in the process is described in Appendix B, Roles and Responsibilities.

Question Prioritization

The guideline panel will brainstorm other potential questions in addition to those described above under Guideline Questions. To enrich for *strong recommendations*, experts on the guideline panel will be asked to rate each potential question as follows:

1. Based on your clinical experience or knowledge of the literature, how certain are you that the benefits of this intervention vs. the comparison outweigh the harms (or vice versa)? For example, you might be more certain if the potential beneficial effects of the intervention are relatively large and the harmful effects small. Please answer using a 1-4 scale where 1 represents "very uncertain" and 4 represents "very certain."

2. Based on your knowledge of patient values across settings, how certain are you that typical patients would agree that the benefits of this intervention vs. the comparison outweigh the harms (or vice versa)? For example, you might be more certain if there is little variation in how patients value the potential benefits and harms. Please answer using a 1-4 scale where 1 represents "very uncertain" and 4 represents "very certain."

3. Based on your knowledge of the literature, how would you characterize the best available evidence for the health effects of this intervention vs. the comparison? Please answer using a 1-4 scale where 1 represents "very low quality" and 4 represents "high quality." High quality evidence is defined as a body of evidence that is without serious limitations from risk of bias, is direct (applicable) to the question, is consistent across studies, and is precise with respect to clinically meaningful thresholds of effects. For example, evidence from multiple randomized, controlled trials with consistent results and without serious limitations could be considered high quality, while evidence from nonrandomized studies or from randomized studies with serious limitations could be considered low quality evidence.

4. Based on your clinical experience, when deciding between this intervention and the comparison, what is the role of factors other than the health effects, i.e., feasibility, acceptability, cost, and equity considerations? Please answer using a 1-4 scale where 1 represents "very important" and 4 represents "very unimportant."

Questions with higher aggregate scores from expert polling will be prioritized for systematic evidence review and graded recommendations. If necessary, scoping reviews of available evidence may also be done to inform prioritization.

As noted above, questions that lead to good practice statements will not count toward total questions.

As noted above, questions not prioritized for these initial guidelines will be recorded and considered for future ASH guidelines on this topic.

Evidence Review and Recommendations

The GRADE approach will be used to assess certainty of evidence (Guyatt et al. 2008). The GRADE Evidence-to-Decision framework (Alonso-Coello et al. 2016) will be used to make judgments about the available evidence and form guideline recommendations using standardized language that has well-defined interpretations for clinicians, patients, and policymakers (Izcovich et al. 2020).

Systematic reviews will be conducted according to standards defined by the Cochrane Collaboration or equivalent. Specific methods used will depend upon the nature and quality of the best available evidence. As noted above under Registry Coordination, systematic review may include analysis of LARAA retrospective data, depending on relevance to guideline questions.

For each guideline question, the best available evidence will be used to make estimates about the health effects of alternative interventions. These estimates, in combination with other judgments, will support recommendations by the guideline panels.

Consistent with the aim of focusing on strong recommendations supported by at least moderate quality evidence, systematic reviews may be limited to randomized trials or large studies. Inclusion criteria will be determined by the methodology team and the guideline panel.

Meetings

Three in-person meetings will occur as follows:

Date	**Location**	**Meeting Purpose**
Thursday, April 27, 2023 (day before Highlights of ASH Latin America)	Sao Paulo, Brazil	Planning, coordination of guidelines and LARAA
TBD	Washington, DC	Guideline panel orientation and question prioritization
TBD	Washington, DC or Latin America before Highlights of ASH	Recommendations

Panel meetings will also be held virtually via Zoom. Frequency of virtual meetings will depend on project needs. For some project phases, meetings may occur every other week; for other phases, monthly.

Online Tools

Online tools including the GRADEPro Guideline Development Tool will be used to summarize evidence, obtain panel voting, and document panel judgments and decisions.

Management of Conflicts of Interest

Conflicts of interest of all participants will be managed in accordance with general ASH policies, as described on the ASH website (https://www.hematology.org/about/governance/conflict-of-interest),

and with specific ASH policies and procedures determined by the ASH Guideline Oversight Subcommittee. The most recent version of these policies is attached as Appendix C.

Publication Strategy

Publication strategy for the guidelines and any other intellectual property will be determined by ASH, including the ASH Guideline Oversight Subcommittee. As described in Appendix D, the current strategy is to submit and publish all work relating to this project including the guideline reports and systematic reviews within ASH's online-only open access scientific journal, *Blood Advances*. At the beginning of the project, a presubmission inquiry to the editors of *Blood Advances* will describe all planned work. The inquiry and discussions with the editors will be led by the lead authors and by the GOS ex officio member(s) of the panels.

One guideline report is expected. In addition, an expert commentary "Putting evidence and guidelines in the context" is planned.

Systematic reviews may be developed for submission to *Blood Advances* as separate, simultaneous publications. If the reviews are not prepared as separate publications, details about the reviews will be included with the guideline reports as supplements.

Authorship, sponsorship, and acknowledgements of such publications will be in accordance with academic standards and customs and requirements of the journal of publication. ASH authorship criteria for the guidelines are presented as Appendix E.

Timeline

Appendix F provides a step-by-step plan for the development of the guidelines, with expected start and end dates for each step.

Dissemination and Implementation

To support understanding and implementation of the guidelines, the panel will be asked to write recommendations and remarks that are clear and actionable. The focus of these initial guidelines on strong recommendations is expected to inform research, educational, and quality improvement efforts that are practical to measure, including within LARAA.

During and after recommendations are drafted, ASH staff will work with the chair and panelists to develop a dissemination and implementation plan for the guidelines. The plan will identify expected implementation barriers for specific recommendations, e.g., insufficient clinician awareness or education or lacking information systems support. The plan will then define resources to be developed, such as an informational handout with messaging tailored for clinician, patient, policymaker, and other stakeholders ("snapshot"); a video interview with the chair highlighting key aspects of the guideline; educational teaching slides; a recorded educational webinar; and a digital summary version of the guidelines for the ASH guidelines app. New activities to support the implementation of the guidelines will also be considered, including the development of both clinician and patient-facing decision-making materials.

Dissemination and implementation opportunities are described in Appendix G.

Guideline Extension and Revision

These guidelines will be followed by extension efforts, i.e., to address additional questions not initially prioritized. A new guideline panel will be formed, and different methods may be used depending on the planned scope. Organizational collaborations may also change. Individuals who serve on the initial effort will be invited to continue on the new panel. However, some substitutions and additions are likely.

After publication, ASH will maintain initial and subsequent guidelines through regular revision. The need for revision will be determined through a process that includes annual monitoring for new evidence, expert review, and committee decision-making.

References

Abello V, Vidal-Senmache G, Milovic V, Calado RT, Aránguiz N, López JL, López S, Tokumura C, Beligoy L, Sossa CL, Pardo CA, Rojas C, LaTorre-Matuk A, Mendoza C, Fantl D, Navarro JR, Gabus R. Latin American Collaborative Research on Aplastic Anemia (LARAA): creating a regional registry. Blood Adv. 2019 Dec 6;3(Suppl 1):51-54. doi: 10.1182/bloodadvances.2019GS121478. PMID: 31809540; PMCID: PMC7034122.

Alonso-Coello P, Schünemann H J, Moberg J, Brignardello-Petersen R, Akl E A, Davoli M et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction BMJ 2016; 353 :i2016 doi:10.1136/bmj.i2016.

Andrews JC, Schünemann HJ, Oxman AD Pottie K, Meerpohl JJ, Alonso Coello P, Rind D, Montori VM, Brito JP, Norris S, Elbarbary M, Post P, Nasser M, Shukla V, Jaeschke R, Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. J Clin Epidemiol 2013; 66(7):726-735. DOI: https://doi.org/10.1016/j.jclinepi.2013.02.003.

Bacigalupo A. How I treat acquired aplastic anemia. Blood 2017; 129 (11): 1428–1436. doi: https://doi.org/10.1182/blood-2016-08-693481.

Camitta BM, Thomas ED, Nathan DG, Gale RP, Kopecky KJ, Rappeport JM, Santos G, Gordon-Smith EC, Storb R. A prospective study of androgens and bone marrow transplantation for treatment of severe aplastic anemia. Blood. 1979 Mar;53(3):504-14. PMID: 32941.

DeZern AE, Churpek JE; Approach to the diagnosis of aplastic anemia. Blood Adv 2021; 5 (12): 2660–2671. doi: https://doi.org/10.1182/bloodadvances.2021004345.

Guyatt GH, Alonso-Coello P, Schünemann HJ, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol. 2016; 80:3-7. doi: 10.1016/j.jclinepi.2016.07.006

Izcovich A, Cuker A, Kunkle R, Neumann I, Panepinto J, Pai M, Seftel M, Cheung MC, Lottenberg R, Byrne M, Plovnick R, Terrell D, Holter-Chakrabarty JL, Djulbegovic B, Hicks LK, Wiercioch W, Nieuwlaat R, Schünemann HJ; A user guide to the American Society of Hematology clinical practice guidelines. Blood Adv 2020; 4 (9): 2095–2110.

Killick SB, Brown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, Hillmen P, Ireland R, Kulasekararaj A, Mufti G, Snowden JA, Samarasinghe S, Wood A, Marsh JCW on behalf of the British Society for Standards in

Haematology. Guidelines for the diagnosis and management of adult aplastic anaemia. *British Journal of Haematology.* First published: 16 November 2015 https://doi.org/10.1111/bjh.13853.

Locasciulli A, Oneto R, Bacigalupo A, Socié G, Korthof E, Bekassy A, Schrezenmeier H, Passweg J, Führer M; Severe Aplastic Anemia Working Party of the European Blood and Marrow Transplant Group. Outcome of patients with acquired aplastic anemia given first line bone marrow transplantation or immunosuppressive treatment in the last decade: a report from the European Group for Blood and Marrow Transplantation (EBMT). Haematologica. 2007 Jan;92(1):11-8. doi: 10.3324/haematol.10075. PMID: 17229630.

Mustafa RA, Garcia CAC, Bhatt M, Riva JJ, Vesely S, Wiercioch W, Nieuwlaat R, Patel P, Hanson S, Newall F, Wiernikowski J, Monagle P, Schünemann HJ. GRADE notes: How to use GRADE when there is "no" evidence? A case study of the expert evidence approach. J Clin Epidemiol. 2021 Sep;137:231-235. doi: 10.1016/j.jclinepi.2021.02.026. Epub 2021 Mar 3. PMID: 33675954.

Olson TS, Dunbar CE. Treatment of aplastic anemia in adults. UpToDate. Last updated December 7, 2022. Accessed January 30, 2023. https://www.uptodate.com/contents/treatment-of-aplastic-anemia-in-adults.

Samarasinghe S, Veys P, Vora A, Wynn R. Paediatric amendment to adult BSH Guidelines for aplastic anaemia. *British Journal of Haematology.* First published: 28 December 2017 https://doi.org/10.1111/bjh.15066.

Scheinberg P, Young NS; How I treat acquired aplastic anemia. Blood 2012; 120 (6): 1185–1196. doi: https://doi.org/10.1182/blood-2011-12-274019.

Scheinberg P, Nunez O, Weinstein B, Scheinberg P, Biancotto A, Wu CO, Young NS. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. N Engl J Med. 2011 Aug 4;365(5):430-8. doi: 10.1056/NEJMoa1103975. Erratum in: N Engl J Med. 2018 Jun 13;:null. PMID: 21812672; PMCID: PMC3721503.

Wiercioch W, Nieuwlaat R, Dahm P, Iorio A, Mustafa RA, Neumann I, Rochwerg B, Manja V, Alonso-Coello P, Ortel TL, Santesso N, Vesely SK, Akl EA, Schünemann HJ; ASH VTE Panels Working Group. Development and application of health outcome descriptors facilitated decision-making in the production of practice guidelines. J Clin Epidemiol. 2021 Oct;138:115-127. doi: 10.1016/j.jclinepi.2021.04.016. Epub 2021 May 13. PMID: 33992716.

Williams et al. Seminars in Hematology 10: 195, 1973.