RARE-Best practices Conference

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2016 RARE Best Practices guideline on Sickle Cell Disease: a pilot adolopment of guidelines for rare diseases

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Disclosure Statement

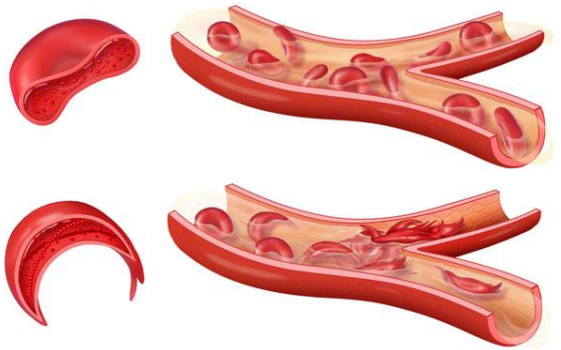
- Member of the GRADE working group.

Background and Objective

Sickle cell disease (SCD) is a life threatening genetic hemoglobin disorder.

It can cause adverse events such as:

1. severe pain
2. end-organ damage
3. pulmonary complications
4. premature death



The objective of this project was to:

- Pilot test the use of the GRADE methodology and the adolopment approach to develop clinical practice guidelines for SCD for the European healthcare setting

Methods

- We used the adolopement methodology in the 2016 RARE Best Practices guideline on SCD.
  - ❖ The adolopement methodology is based on the *"Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise"* and builds on the advantages of:

- We presented the summarized evidence using GRADE Evidence to Decision (EtD) frameworks.

Prioritization of Questions

The NIH guidelines addressed five different areas in SCD prevention and management:

1. Health maintenance for people with SCD
2. Managing acute complications of SCD
3. Managing chronic complications of SCD
4. Hydroxyurea therapy in the management of SCD
5. Blood transfusion in the management of SCD

The guideline executive committee chose to address the last two categories in order to be pragmatic and to produce a coherent set of recommendations (i.e., within the same type of management) due to:

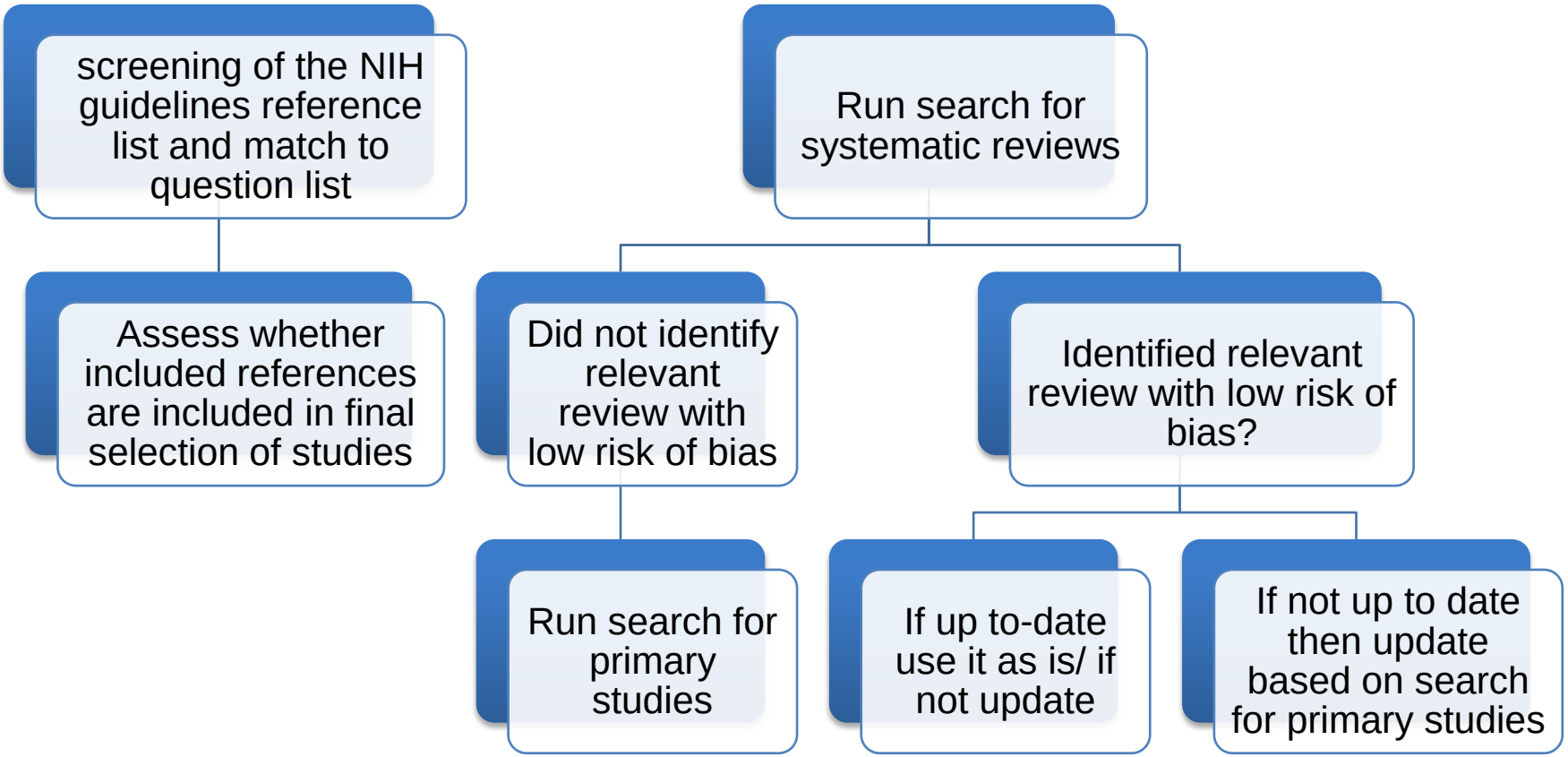
1. Time constraints
2. Resource constraints

Search for evidence on health effects

We conducted our literature search in three sequential steps:

Screening of the NIH guidelines reference list	Matched studies to the questions and complemented what we found with the below searches	
Search for systematic reviews	• Monthly auto alert set • No time limit set	1. OVID Medline 2. Epistemonikos 3. Cochrane Database of Systematic Reviews.
Search for primary studies	• monthly auto alert set **Time limit:** 1. 2010- 2016 for Blood Transfusion 2. 2011- 2016 for hydroxyurea therapy	1. OVID Medline 2. Epistemonikos 3. Cochrane CENTRAL.

Search for evidence on health effects



Search for contextual evidence

We conducted the following to identify relevant information regarding patients' values and preferences and resource use:

1. Search OVID Medline
2. Search Epistemonikos
3. Search Cochrane CENTRAL
4. Surveyed the panelists requesting additional studies for baseline risk and economic data.

Evidence presentation

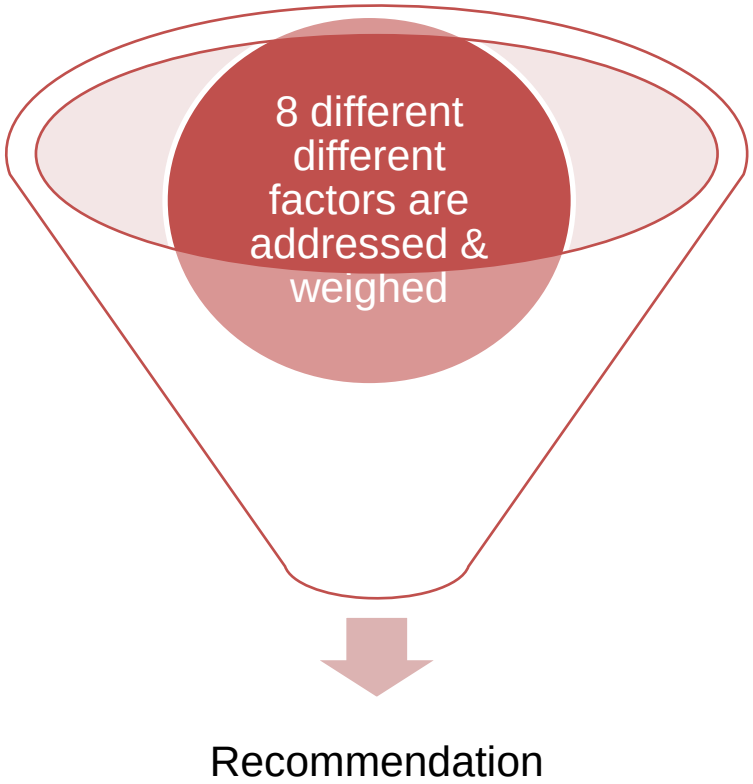
We used the GRADEpro software to address each question in the guideline by:

1. Summarizing the evidence (through a meta-analysis or narratively)
2. Rating the quality of the evidence
3. Developing GRADE evidence tables (Evidence Profiles and Summary of Findings tables) for selected patient-important outcomes.
4. Rating the strength of the recommendation.

Formulating the recommendations

The factors that play a role in determining the strength and direction of recommendation are:

1. Priority of the problem
2. Benefits and harms of the option
3. Certainty in the evidence
4. Values and preferences
5. Resource use
6. Feasibility
7. Acceptability
8. Equity



Results

- We decided on a set of 13 questions that were relevant to both blood transfusion and hydroxyurea therapy in the management of SCD.
- The evidence was discussed during a panel meeting that was held in Freiburg, Germany where a team of 15 panelists voted on the different factors and formulated the final recommendations for 9 of the 13 questions.
- The other 4 questions were voted on online through the Guideline Development Tool (GDT).

Results of the general search

Our literature search identified for health effects:

- 7 relevant systematic reviews
- 59 eligible primary studies

Our search for other contextual factors yielded:

- 11 eligible studies related to patients' values and preferences
- 18 eligible studies related to resource use

Search for blood transfusion therapy in SCD

	Search for Systematic Reviews	Search for Primary Studies	Search for Resource Use Studies	Search for Patients' Values and Preference Studies
Total number retrieved	357	1005	53	156
Selected after duplicate removal and title abstract and full text screening	5	33	12	7

Search for hydroxyurea therapy in SCD

	Search for Systematic Reviews	Search for Primary Studies	Search for Resource Use Studies	Search for Patients' Values and Preference Studies
Total number retrieved	71	315	23	72
Selected after duplicate removal and title abstract and full text screening	2	26	6	4

Blood transfusion- recommendations

1. In patients with SCD undergoing surgery under general anesthesia, should we use pre-operative transfusion vs. no pre-operative transfusion?	2 SRs (retrieved 2 trials); no other primary studies	Conditional recommendation for; very low quality evidence).
2. In patients with SCD undergoing surgery under general anesthesia, should we use aggressive pre-operative transfusion vs. conservative pre-operative transfusion?	2 SRs (retrieved 1 trial); no other primary studies	Conditional recommendation against; very low quality evidence).
3. In patients with SCD, should we use deferasirox vs. deferoxamine?	2 SRs (retrieved 2 trials); no other primary studies	Conditional recommendation for; very low quality evidence

Blood transfusion- recommendations

4. In individuals with SCD who are to be transfused, should we match for C, E and K antigens vs. not match?	1 SR by NIH (>60 eligible studies) + 16 obs studies	Conditional recommendation for; very low quality evidence
5. In chronically transfused children with SCA, should we transfuse to maintain the HbS level at or below 30% vs. above 30%?	9 eligible obs. studies	a. Strong recommendation for; very low quality evidence (high risk of stroke) b. Conditional recommendation for; very low quality evidence (not at high risk of stroke)
6. In patients who receive chronic transfusion therapy, should we use serial assessment of liver iron overload (using MRI R2* or T2* techniques or SQUID) vs. repeated assessment of iron status through lab parameters such as ferritin?	2 SRs (one by NIH: 19 obs studies; 2nd SR used as indirect evidence for 1 outcome) + 7 obs studies	Conditional recommendation for; very low certainty in the evidence.

Hydroxyurea therapy- recommendations

7. In children with SCA regardless of clinical severity, should we use HU vs. no HU?	1 SR+ 2 RCTs + 9 obs studies	Conditional recommendation for; low quality evidence.
8. In adults with SCA regardless of clinical severity, should we use HU vs. no HU?	1 SR + 11 obs studies	Conditional recommendation against; very low quality evidence).
9. In people with SCD with pain or acute chest syndrome, should we use HU vs. no HU?	4 obs studies+ 1 RCT	Conditional recommendation for; very low quality evidence

Hydroxyurea therapy- recommendations

10. In children and adolescent adults with SCD with severe or symptomatic chronic anemia, should we use HU vs. no HU?	1 SR(8 obs studies)	Conditional recommendation for; very low quality evidence).
11. In females with SCD who become pregnant, should we use HU vs. no HU?	4 obs studies	Conditional recommendation against; very low quality evidence).
12. In females with SCD who are breastfeeding, should we use HU vs. no HU?	1 obs (case report) study	Conditional recommendation for; very low quality evidence
13. In people with SCD at high risk of stroke after an initial period of transfusion, should we use HU vs. blood transfusion?	2 trials	Conditional recommendation for; very low quality evidence

Strong recommendation; low/ very low quality of evidence

Paradigmatic situation	Confidence in effect estimates for health outcomes (quality of evidence)		Balance of benefits and harms	Values and preferences
	Benefits	Harms		
Life-threatening situation	Low or very low confidence	Immaterial (very low to high)	Intervention may reduce mortality in a life-threatening situation. Adverse events not prohibitive	A very high value is placed on an uncertain but potentially life-preserving benefit
Uncertain benefit, certain harm	Low or very low	High or moderate	Possible but uncertain benefit. Substantial established harm	A much higher value is placed on the adverse events in which we are confident than in the benefit, which is uncertain
Potential equivalence, one option clearly less risky or costly	Low or very low	High or moderate	Magnitude of benefit apparently similar—though uncertain—for alternatives. We are confident less harm or cost for one of the competing alternatives	A high value is placed on the reduction in harm
High confidence in similar benefits, one option potentially more risky or costly	High or moderate	Low or very low	Established that magnitude of benefit similar for alternative management strategies. Best (though uncertain) estimate is that one alternative has appreciably greater harm.	A high value is placed on avoiding the potential increase in harm
Potential catastrophic harm	Immaterial (very low to high)	Low or very low	Potential important harm of the intervention, magnitude of benefit is variable	A high value is placed on avoiding potential increase in harm

GRADE for rare diseases

Developing methodology for the creation of clinical practice guidelines for rare diseases: A report from RARE-Bestpractices

Menaka Pai, Alfonso Iorio, Joerg Meerpohl, Domenica Taruscio, Paola Laricchiuta, Pierpaolo Mincarone, Cristina Morciano, Carlo Giacomo Leo, Saverio Sabina, Elie Akl, Shaun Treweek, Benjamin Djulbegovic, Holger Schunemann & Consortium for the RARE-Bestpractices

Challenges and potential solutions

Challenges:

1. Paucity of published data
2. High risk of bias studies
3. Indirectness
4. Inconsistency
5. Imprecision lowering the quality of evidence further
6. Challenge in integrating qualitative research into guidelines
7. Panel COI

Challenges and potential solutions

1. In terms of searching for evidence, we were broad in our search terms as we did not want to be too specific due to paucity of data

2. Using indirect evidence if no direct evidence found or if it supplements the scarce data available.

3. COI management:
   - Invited a diverse group of panelists that represented different organisations worldwide
   - Solicited conflicts from panelists prior to the start of the guideline project and sent out a documet describing how the conflicts will be managed.
   - Documented and presented the panel with their conflicts and for each question readdressed if any conflicts were missing
   - Those that were conflicted were asked to participate in the discussion without influencing the panel but were asked to refrain from voting.

Acknowledgements

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Any Questions?

Thank you