Evidence summary

to support

PICO question 2:

Diagnosis preoperative anaemia

April 2018 (version 1.0)

Centre for Evidence-Based Practice (CEBaP)

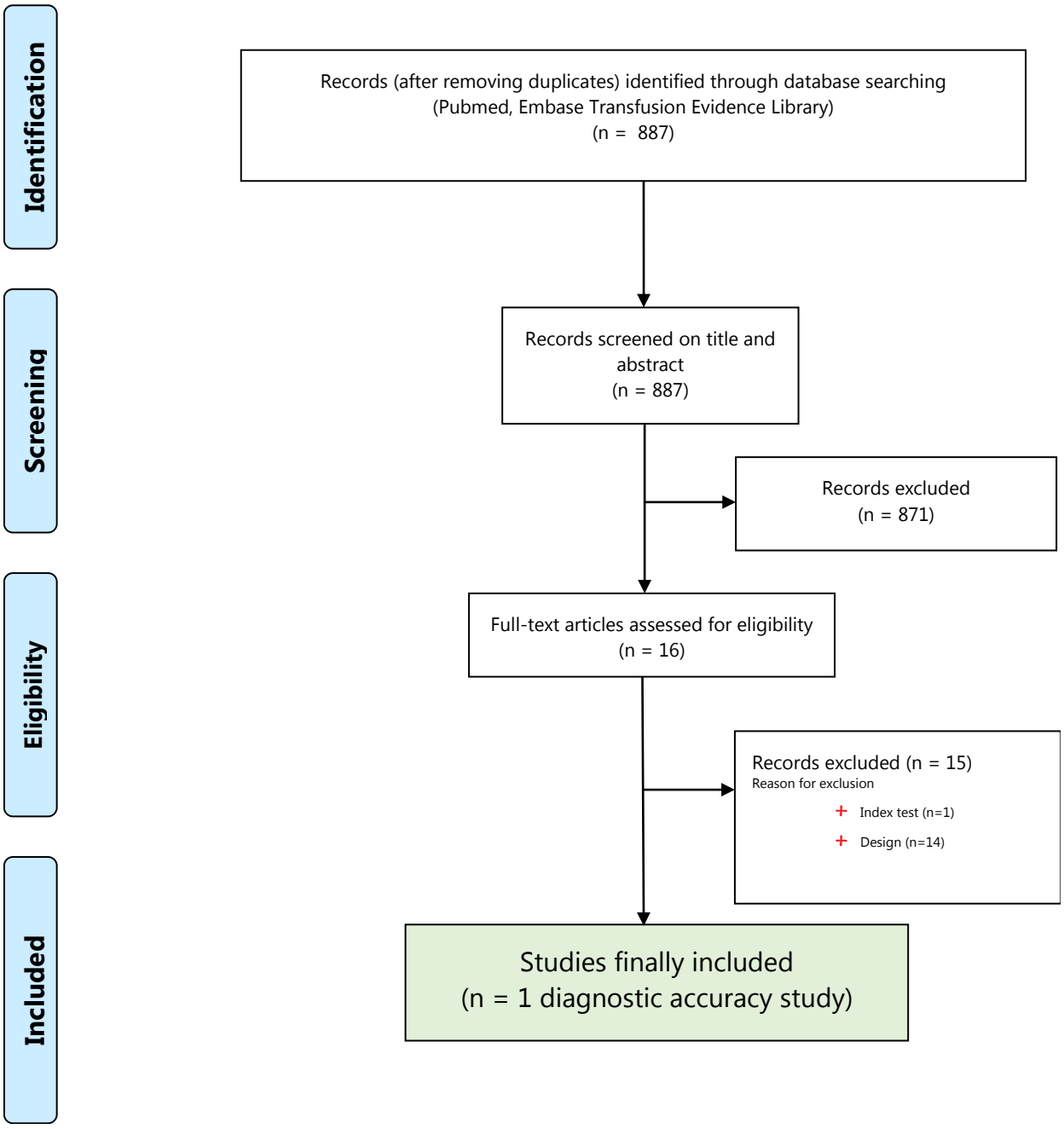
Belgian Red Cross

Belgian
Red Cross

Evidence-based
by CEBaP

Content

Flow chart


Identification
Screening
Eligibility
Included
Records (after removing duplicates) identified through database searching
(Pubmed, Embase Transfusion Evidence Library)
(n = 887)
Records screened on title and abstract
(n = 887)
Records excluded
(n = 871)
Full-text articles assessed for eligibility
(n = 16)
Records excluded (n = 15)
Reason for exclusion
Index test (n=1)
Design (n=14)
Studies finally included
(n = 1 diagnostic accuracy study)

Overview of included studies[1]

1. Klement MR, Peres-Da-Silva A, Nickel BT, et al. What Should Define Preoperative Anemia in Primary THA? Clin Orthop Relat Res 2017;475:2683-91.

Overview evidence table GRADE software

Question: Should Hb <11 g/dL (males) vs. Hb >13 g/dL (males) be used to diagnose transfusion in preoperative elective surgery patients?

Hb <11 g/dL (males)		Hb >13 g/dL (males)	
Sensitivity	0.33 (95% CI: -- to --)	Sensitivity	0.67 (95% CI: -- to --)
Specificity	0.99 (95% CI: -- to --)	Specificity	0.87 (95% CI: -- to --)

Prevalences	10%		

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100 patients tested		Test accuracy CoE
								pre-test probability of 10%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Hb <11 g/dL (males)	Hb >13 g/dL (males)	
True positives (patients with transfusion)	1 studies patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	3 (0 to 0)	7 (0 to 0)	⨁⨁◯◯ LOW
								4 fewer TP in Hb <11 g/dL (males)		
False negatives (patients incorrectly classified as not having transfusion)								7 (10 to 10)	3 (10 to 10)	
								4 more FN in Hb <11 g/dL (males)		
True negatives (patients without transfusion)	1 studies patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	89 (0 to 0)	78 (0 to 0)	⨁⨁◯◯ LOW
								11 more TN in Hb <11 g/dL (males)		
False positives (patients incorrectly classified as having transfusion)								1 (90 to 90)	12 (90 to 90)	
								11 fewer FP in Hb <11 g/dL (males)		

Explanations

a. Lack of generalizibility to other populations

b. Limited sample size

Question: Should Hb 11-13 g/dL (males) vs. Hb >13 g/dL (males) be used to diagnose transfusion in preoperative elective surgery?

Hb 11-13 g/dL (males)		Hb >13 g/dL (males)	
Sensitivity	0.50 (95% CI: -- to --)	Sensitivity	0.67 (95% CI: -- to --)
Specificity	0.96 (95% CI: -- to --)	Specificity	0.87 (95% CI: -- to --)

Prevalences	10%		

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100 patients tested		Test accuracy CoE
								pre-test probability of 10%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Hb 11-13 g/dL (males)	Hb >13 g/dL (males)	
True positives (patients with transfusion)	studies patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	5 (0 to 0)	7 (0 to 0)	⨁⨁◯◯ LOW
								2 fewer TP in Hb 11-13 g/dL (males)		
False negatives (patients incorrectly classified as not having transfusion)								5 (10 to 10)	3 (10 to 10)	
								2 more FN in Hb 11-13 g/dL (males)		
True negatives (patients without transfusion)	studies patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	86 (0 to 0)	78 (0 to 0)	⨁⨁◯◯ LOW
								8 more TN in Hb 11-13 g/dL (males)		
False positives (patients incorrectly classified as having transfusion)								4 (90 to 90)	12 (90 to 90)	
								8 fewer FP in Hb 11-13 g/dL (males)		

Explanations

a. Lack of generalizibility to other populations

b. Limited sample size

Question: Should Hb <10 g/dL (females) vs. Hb >12 g/dL (females) be used to diagnose transfusion in preoperative elective surgery patients?

Hb <10 g/dL (females)		Hb >12 g/dL (females)	
Sensitivity	0.08 (95% CI: -- to --)	Sensitivity	0.60 (95% CI: -- to --)
Specificity	0.99 (95% CI: -- to --)	Specificity	0.86 (95% CI: -- to --)

Prevalences	10%		

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100 patients tested		Test accuracy CoE
								pre-test probability of 10%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Hb <10 g/dL (females)	Hb >12 g/dL (females)	
True positives (patients with transfusion)	studies patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	1 (0 to 0)	6 (0 to 0)	⨁⨁◯◯ LOW
								5 fewer TP in Hb <10 g/dL (females)		
False negatives (patients incorrectly classified as not having transfusion)								9 (10 to 10)	4 (10 to 10)	
								5 more FN in Hb <10 g/dL (females)		
True negatives (patients without transfusion)	studies patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	89 (0 to 0)	77 (0 to 0)	⨁⨁◯◯ LOW
								12 more TN in Hb <10 g/dL (females)		
False positives (patients incorrectly classified as having transfusion)								1 (90 to 90)	13 (90 to 90)	
								12 fewer FP in Hb <10 g/dL (females)		

Explanations

a. Lack of generalizibility to other populations

b. Limited sample size

Question: Should Hb 10-12 g/dL (females) vs. Hb >12 g/dL (females) be used to diagnose transfusion in preoperative elective surgery patients?

Hb 10-12 g/dL (females)		Hb >12 g/dL (females)	
Sensitivity	0.29 (95% CI: -- to --)	Sensitivity	0.60 (95% CI: -- to --)
Specificity	0.97 (95% CI: -- to --)	Specificity	0.86 (95% CI: -- to --)

Prevalences	10%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100 patients tested pre-test probability of 10%		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Hb 10-12 g/dL (females)	Hb >12 g/dL (females)	
True positives (patients with transfusion)	studies patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	3 (0 to 0)	6 (0 to 0)	⨁⨁◯◯ LOW
								3 fewer TP in Hb 10-12 g/dL (females)		
False negatives (patients incorrectly classified as not having transfusion)								7 (10 to 10)	4 (10 to 10)	
								3 more FN in Hb 10-12 g/dL (females)		
True negatives (patients without transfusion)	studies patients	cross-sectional (cohort type accuracy study)	not serious	serious [a]	not serious	serious [b]	none	87 (0 to 0)	77 (0 to 0)	⨁⨁◯◯ LOW
								10 more TN in Hb 10-12 g/dL (females)		
False positives (patients incorrectly classified as having transfusion)								3 (90 to 90)	13 (90 to 90)	
								10 fewer FP in Hb 10-12 g/dL (females)		

Explanations
a. Lack of generalizibility to other populations
b. Limited sample size

WHO definition: which underlying evidence did they use?

In order to get an answer to the question which evidence WHO used to formulate its widely-known and commonly-used Hb levels to define anemia, a search was conducted and took me back to the 1950s-1960s! **(see figure 1).**

The starting point was the **WHO publication 'Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity'**, published in 2011.
(http://www.who.int/vmnis/indicators/haemoglobin/en/)
In this publication, table 1 shows the WHO definition that is used to diagnose anaemia: Hb <130g/L (males) and Hb <120 g/L (females). In the legend of this table, WHO refers to the references 5 and 6, that serve as the (evidence-based?) sources to support this definition.

Having a closer look to **reference 5**[1] (International Conference document from WHO/United Nations, 1992), no relevant study/evidence to support the WHO definition was found.

A more detailed view to **reference 6**[2] (WHO/CDC document from 2004) resulted in the following information:

- The WHO definition (Hb levels) to diagnose anaemia is based on arbitrarily selected cut-offs from 1958 (+ revised in 1968)

WHO provided 5 references/studies/reports (4 from the 1960s[3-6] and 1 from 1985[7]) to support their proposed criteria.

Finally, after reading, analyzing and critically appraise these 5 references **(see figure 2)**, I concluded that these studies are 1) of poor quality (observational/cross-sectional studies) and will therefore never meet our selection criteria, 2) outdated (extrapolation to 2018 is questionable?) and 3) not supporting the adult male (Hb<130g/L) and female (Hb<120g/L) cut-off (in a preoperative setting): pregnancy was the focused setting in 3/5 papers, 1 paper (Natvig 1966) only investigated prevalence of anaemia (cross-sectionally) in a group of 312 healthy 12-21 aged Norwegians and 1 paper (DeMaeyer 1985) only reviewed the prevalence of anaemia worldwide between 1960-1984 and concluded that children and women appear to have been studied more frequently than any other age or sex category.

Conclusion: the WHO definition (Hb <130g/L (males) or Hb <120g/L (females)) to diagnose anaemia are not "evidence-based" but based on expert opinion and arbitrarily selected cut-offs 60 years ago.

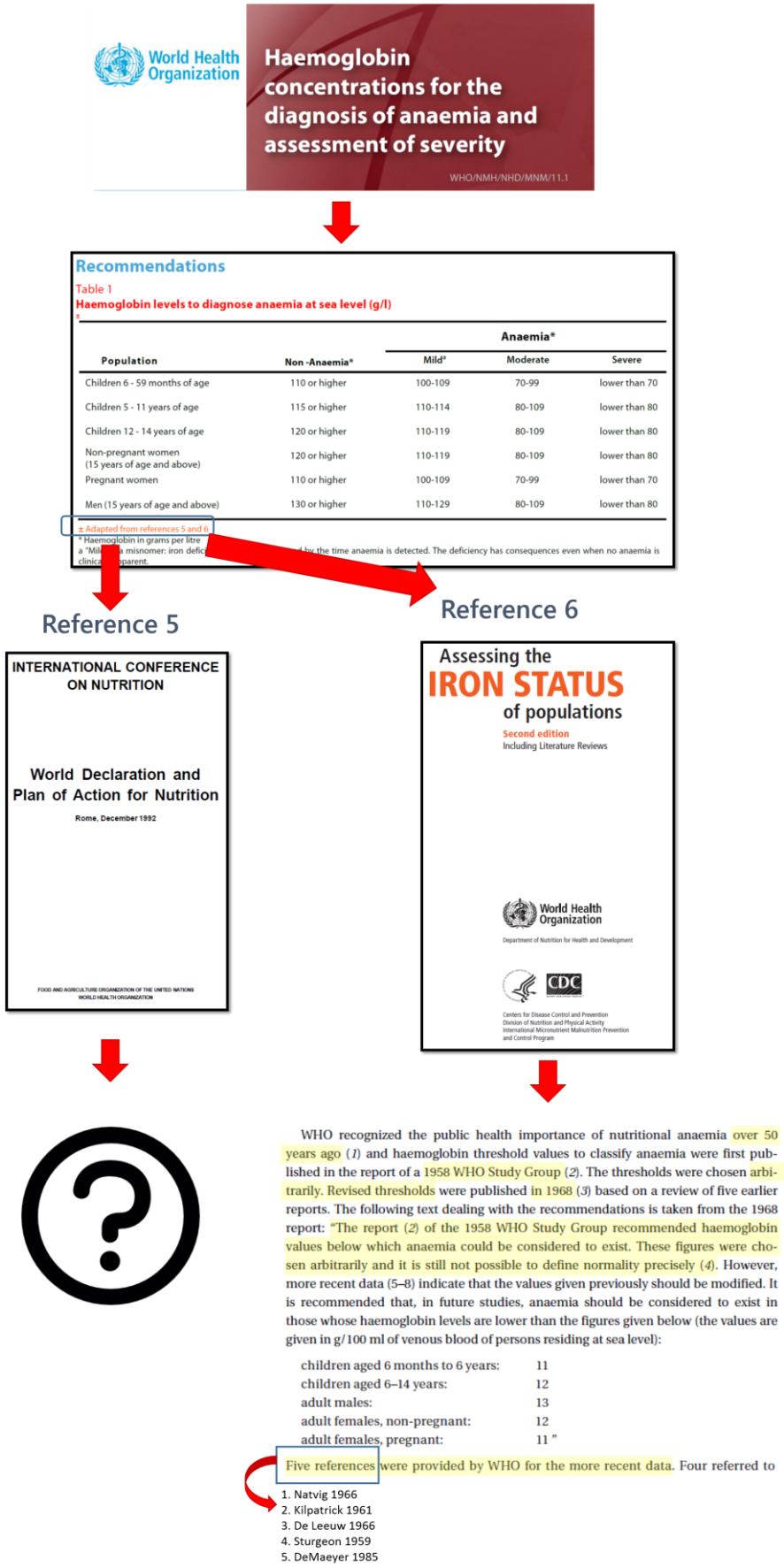
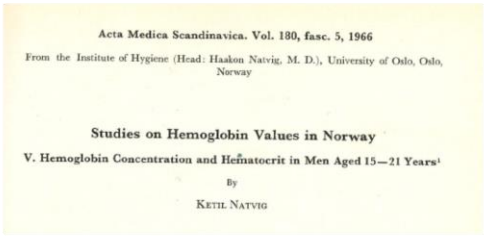


Figure 1. Underlying sources of evidence for the WHO definition (Hb levels) to diagnose anaemia.

Natvig 1966



Acta Medica Scandinavica. Vol. 180, fasc. 5, 1966

From the Institute of Hygiene (Head: Haakon Natvig, M. D.), University of Oslo, Oslo, Norway

Studies on Hemoglobin Values in Norway

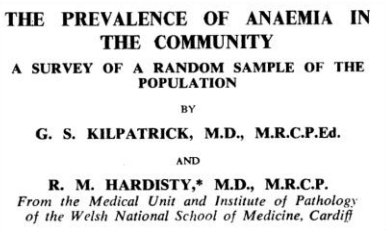
V. Hemoglobin Concentration and Hematocrit in Men Aged 15—21 Years[1]

By

KETIL NATVIG

"a series of observations in 312 healthy Norwegian men, aged 15-21 years. Capillary blood samples were used. A haemoglobin concentration <130 g/L was observed in 3,5% of the sample."

Kilpatrick 1961



THE PREVALENCE OF ANAEMIA IN THE COMMUNITY

A SURVEY OF A RANDOM SAMPLE OF THE POPULATION

BY

G. S. KILPATRICK, M.D., M.R.C.P.Ed.

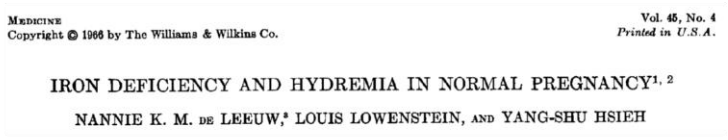
AND

R. M. HARDISTY,* M.D., M.R.C.P.

From the Medical Unit and Institute of Pathology of the Welsh National School of Medicine, Cardiff

"an evaluation of venous blood samples from 149 pregnant women and did not provide any specific recommendations."

De Leeuw 1966



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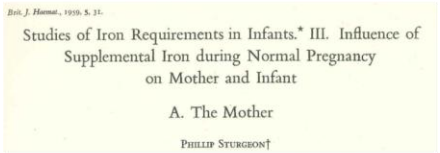
IRON DEFICIENCY AND HYDREMIA IN NORMAL PREGNANCY[1, 2]

NANNIE K. M. DE LEEUW,* LOUIS LOWENSTEIN, AND YANG-SHU HSIEH

"series of experimental observations of venous blood samples from 82 pregnant women. There were four groups of volunteers: one group served as a control, one received 1000 mg iron intra-muscularly and the remaining two were given a dose of 39 mg oral iron either once or twice a day. The authors suggested that a threshold of 104 g/l should be used to classify anaemia in the last trimester of pregnancy."

Sturgeon 1959



Brit. J. Haemat., 1959, 5, 31.

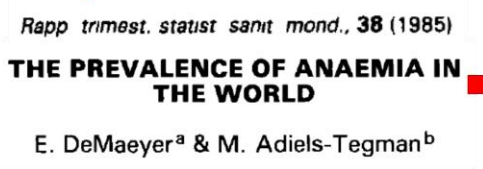
Studies of Iron Requirements in Infants.* III. Influence of Supplemental Iron during Normal Pregnancy on Mother and Infant

A. The Mother

PHILIP STURGEON†

"report of 600 men aged 35-64 years and 200 women aged 55-64 years in Wales. Venous blood samples were used. The study contained individuals who responded to iron therapy. No specific recommendations for thresholds for anaemia were given."

DeMaeyer 1985



Rapp trimest. statist sanit mond., **38** (1985)

THE PREVALENCE OF ANAEMIA IN THE WORLD

E. DeMaeyer[a] & M. Adiels-Tegman[b]

"landmark paper which is still often quoted as the basis for estimates of the global prevalence of both all anaemia and iron deficiency anaemia. DeMaeyer and Adiels-Tegman recognized the importance of distinguishing between iron deficiency and other causes of anaemia, and proposed deriving the prevalence of iron deficiency anaemia by subtracting the prevalence of anaemia in men (assuming that the prevalence of nutritional iron deficiency in this group would be negligible in most countries) from the prevalence in other groups, thereby deriving the prevalence of iron deficiency anaemia in these groups. By this means they calculated that generally a little less than 50% of the anaemia could be attributed to iron deficiency. They had no way of estimating the prevalence of iron deficiency without anaemia."

Figure 2. Five references used by WHO to recommend Hb levels for the diagnosis of anaemia.

WHO references

1. Food and Agriculture Organization of the United Nations, World Health Organization. International Conference on Nutrition. World Declaration and Plan of Action for Nutrition.; 1992.

2. World Health Organization, Centers for Disease Control and Prevention. Assessing the iron status of populations. Second edition. Including Literature Reviews.; 2004.

3. De Leeuw NK, Lowenstein L, Hsieh YS. Iron deficiency and hydremia in normal pregnancy. Medicine (Baltimore) 1966;45:291-315.

4. Kilpatrick GS, Hardisty RM. The prevalence of anaemia in the community. A survey of a random sample of the population. Br Med J 1961;1:778-82.

5. Natvig K. Studies on hemoglobin values in Norway. V. Hemoglobin concentration and hematocrit in men aged 15-21 years. Acta Med Scand 1966;180:613-20.

6. Sturgeon P. Studies of iron requirements in infants. III. Influence of supplemental iron during normal pregnancy on mother and infant. A The mother. Br J Haematol 1959;5:31-44.

7. DeMaeyer E, Adiels-Tegman M. The prevalence of anaemia in the world. World Health Stat Q 1985;38:302-16.

Detailed evidence summary

Topic	Preoperative anaemia
Subtopic	Diagnosis of preoperative anaemia
Intervention	Hemoglobin levels to diagnose preoperative anaemia
Question (PICO)	In preoperative elective surgery (P), should the Hb levels according to the WHO definition or other Hb levels (I) be used to diagnose anaemia (O)?
Search Strategy	Databases **MEDLINE** (via PubMed interface) for diagnostic studies using the following search strategy: 1. "Elective Surgical Procedures"[Mesh] OR surg*[TIAB] OR preoperative[TIAB] OR pre-operative[TIAB] 2. "Anemia/diagnosis"[Mesh] OR "Anemia/diagnostic imaging"[Mesh] OR anemia[TIAB] OR anaemia[TIAB] 3. "Sensitivity and Specificity"[Mesh] OR "sensitivity"[TIAB] OR "specificity"[TIAB] OR "pre-test probability"[TIAB] OR "pretest probability"[TIAB] OR "post-test probability"[TIAB] OR "posttest probability"[TIAB] OR "predictive value"[TIAB] OR "predictive values"[TIAB] OR "likelihood ratio"[TIAB] OR "likelihood ratios"[TIAB] 4. 1-3 AND **Embase** (via Embase.com interface) using the following search strategy: 1. 'Elective surgery'/exp OR surg*:ab,ti OR 'preoperative':ab,ti OR ''pre-operative':ab,ti 2. Anemia/exp OR Anemia:ab,ti OR Anaemia:ab,ti 3. 'diagnostic accuracy'/exp OR 'sensitivity and specificity'/exp OR sensitivity:ab,ti OR specificity:ab,ti OR (('pre-test' OR pretest) NEAR/5 probability):ab,ti OR 'post-test probability':ab,ti OR 'posttest probability':ab,ti OR 'predictive value':ab,ti OR 'predictive values':ab,ti OR 'likelihood ratio':ab,ti OR 'likelihood ratios':ab,ti 5. 1-3 AND **Transfusion Evidence Library** ('Pre-operative' OR preoperative) AND (Anemia OR Anaemia) AND (sensitivity OR specificity OR pre-test probability OR pretest probability OR post-test probability OR posttest probability OR predictive value OR predictive values OR likelihood ratio OR likelihood ratios)
Search date	30th of January 2018
In/Exclusion criteria	**Population:** *Include:* Pre-operative elective surgery patients **Index test:** *Include:* Hb levels according to WHO definition anaemia (i.e. Hb <120 g/dL (adult females) and Hb <130 g/dL (adult males) or other Hb levels **Comparator test:** *Include:* other Hb levels **Outcome:** *Include:* diagnosis of preoperative anaemia (true positives, false positives, true negatives, false negatives, sensitivity, specificity), level of agreement between two methods (i.e. level of agreement). Study design: *Include:* A systematic review: inclusion of diagnostic studies of the systematic review if the search strategy and selection criteria are clearly described and if at least the Cochrane Library, MEDLINE and Embase were searched. If no systematic review of diagnostic studies is present, individual diagnostic studies (randomized controlled trial or diagnostic accuracy study) will be included.

Characteristics of included studies

Author, year, Country	Study design	Population	Comparison	Remarks
Klement, 2017, USA	Observational: Cohort study	558 patients undergoing primary unilateral total hip arthroplasty at an academic tertiary care center: 60 patients required a blood transfusion during or after THA versus 498 patients that didn't	Index test: Hemoglobin levels Comparator (test): transfusion versus no transfusion A postoperative Hb <7 g/dL is an automatic transfusion for trigger at	All patients underwent the same preoperative evaluation and surgical clearance through the department of anaesthesia. All patients received weight-based intravenous TXA unless contraindicated.

		require a blood transfusion.	our institution. Transfusions also were given postoperatively if the patient showed new clinical symptoms consistent with symptomatic anemia even if the postoperative Hb was 7 g/dL or greater.	

Synthesis of findings

Outcome	Comparison	Effect Size	#studies, # participants	Reference
Transfusion versus no transfusion	Hb <11 g/dL (males)	4/12 vs 2/265 Sensitivity: 33% Specificity: 99% Positive predictive value: 67%	1, 12 vs 265 §	Klement, 2017
	Hb 11-13 g/dL (males)	4/12 vs 32/265 Sensitivity: 50% Specificity: 96% Positive predictive value: 35%		
	Hb >13 g/dL (males)	4/12 vs 231/265 Sensitivity: 67% Specificity: 87% Positive predictive value: 48%		
	Hb 13.5 g/dL (males)	Sensitivity: 92% Specificity: 76%		
	Hb <10 g/dL (females)	4/48 vs 2/233 Sensitivity: 8% Specificity: 99% Positive predictive value: 67%	1, 48 vs 233 §	
	Hb 10-12 g/dL (females)	25/48 vs 30/233 Sensitivity: 29% Specificity: 97% Positive predictive value: 64%		
	Hb >12 g/dL (females)	19/48 vs 201/233 Sensitivity: 60% Specificity: 86% Positive predictive value: 19%		
	Hb 12.5 g/dL (females)	Sensitivity: 88% Specificity: 87%		

§ Imprecision (limited sample size)

Quality of evidence

Author, Year	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?	Other limitations
Klement, 2017	Yes Retrospective chart survey	No	No	No	*No*

Certainty of the body of evidence

	Initial grading High [A]	Downgrading due to
Limitations of study design	0	See table 'Quality of evidence'
Imprecision	-1	Limited sample size
Inconsistency	0	
Indirectness	-1	Lack of generalizibility

Publication bias	0	[Conflict of interest]
		Upgrading due to
Large magnitude of effect	0	
Dose-response gradient	0	
Plausible confounding	0	
QUALITY (GRADE)	**Final grading Low [C]**	

Conclusion	
Reference(s)	**Articles** Klement MR, Peres-Da-Silva A, Nickel BT, Green CL, Wellman SS, Attarian DE, Bolognesi MP, Seyler TM. *What should define preoperative anemia in primary THA?* Clin Orthop Relat Res 2017, 475:2683-2691.
Evidence used for	Guideline
Project	ICC-PBM 2018
Reviewer(s)	Hans Van Remoortel