SIOP PODC Supportive Care Education
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www.cure4kids.org

Red blood cell transfusions
Risks, benefits, and surprises

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Red blood cell transfusion

- Role of red blood cells (RBCs)
- Physiology of anemia
- Management of anemia
  - RBC loss – bleeding, hemolysis
  - Decreased RBC production
- Risks of transfusion
- Recommendations

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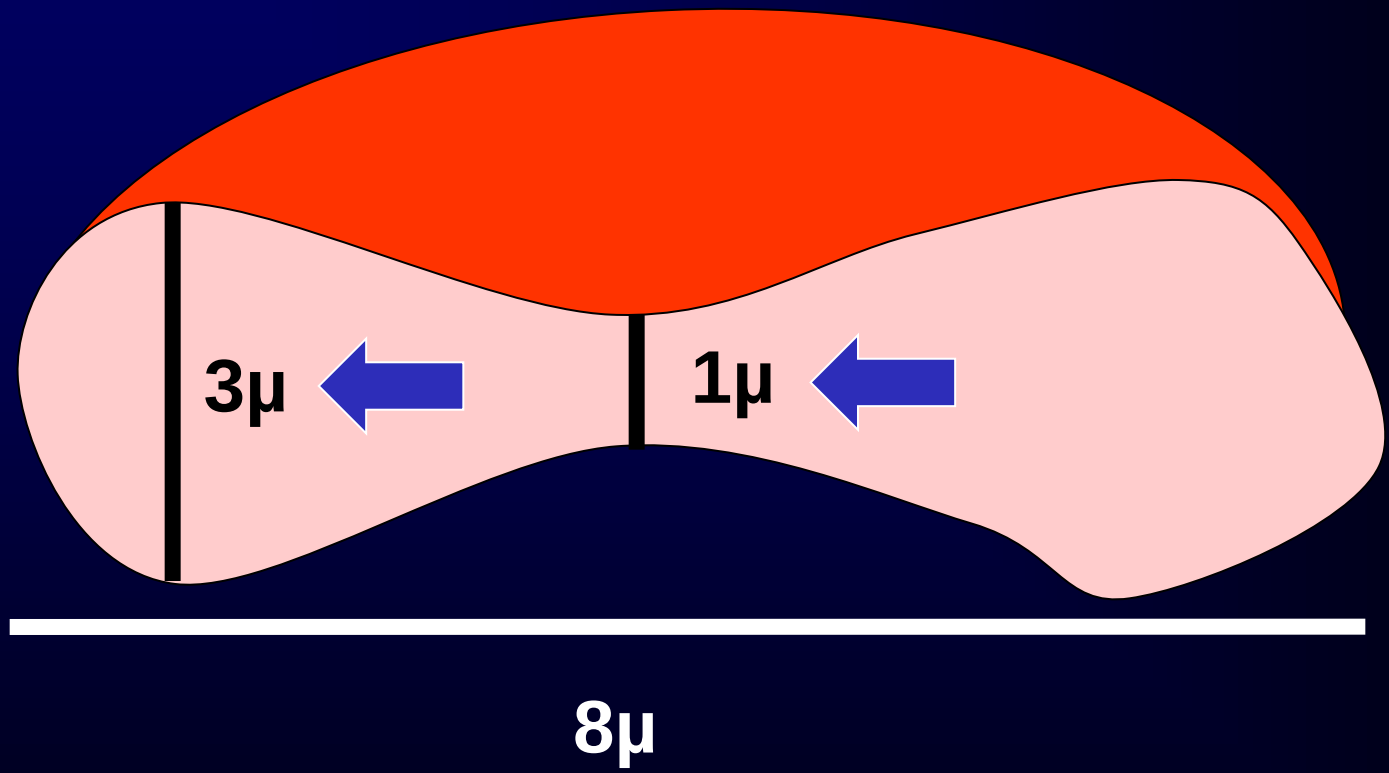
Biconcave Red Blood Cell



What is the diameter of a typical capillary in humans?

- 1 micron
- 3 microns
- 8 microns
- 12 microns
- 15 microns

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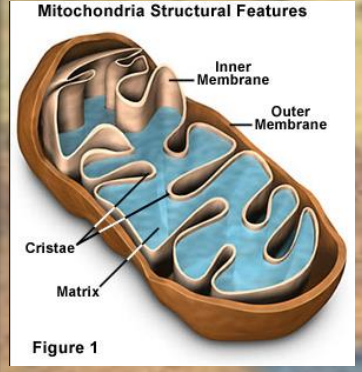
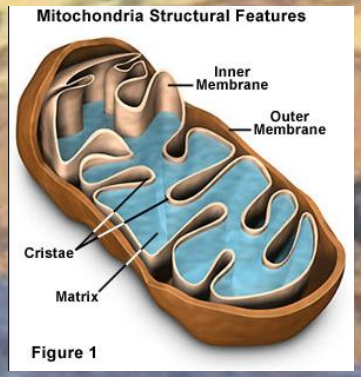
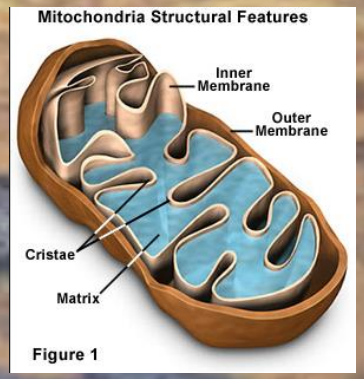
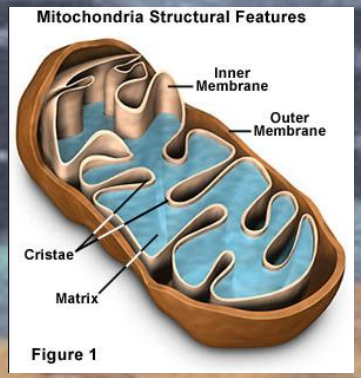
What do you not see here?

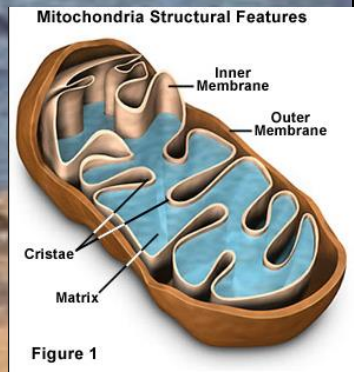






O_2 O_2 O_2 O_2 O_2 O_2



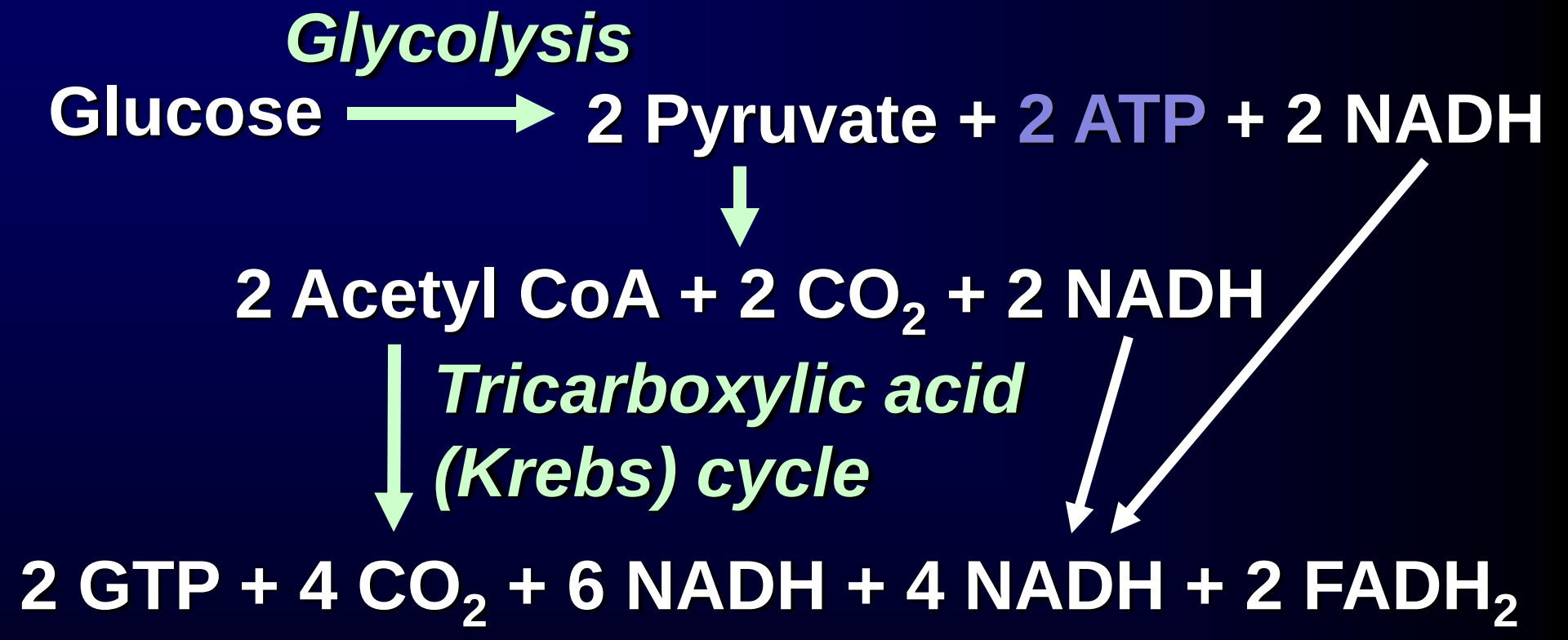


Importance of Oxygen

- Production of ATP
  - Tricarboxylic acid cycle
  - Electron transport chain
- Production of NADH/NADPH
- Comparison: energy produced by anaerobic metabolism

Glucose Metabolism

Glycolysis, TCA cycle



Glucose Metabolism
Electron Transport System

O_2 + NADH —*Electron transport system*→ 3 ATP + NAD^+

O_2 + $FADH_2$ —*Electron transport system*→ 2 ATP + FAD

Glucose → 2 ATP + 2 GTP + 10 NADH + 2 $FADH_2$

Glucose + O_2 → 38 ATP equivalents

Mitochondria Structural Features

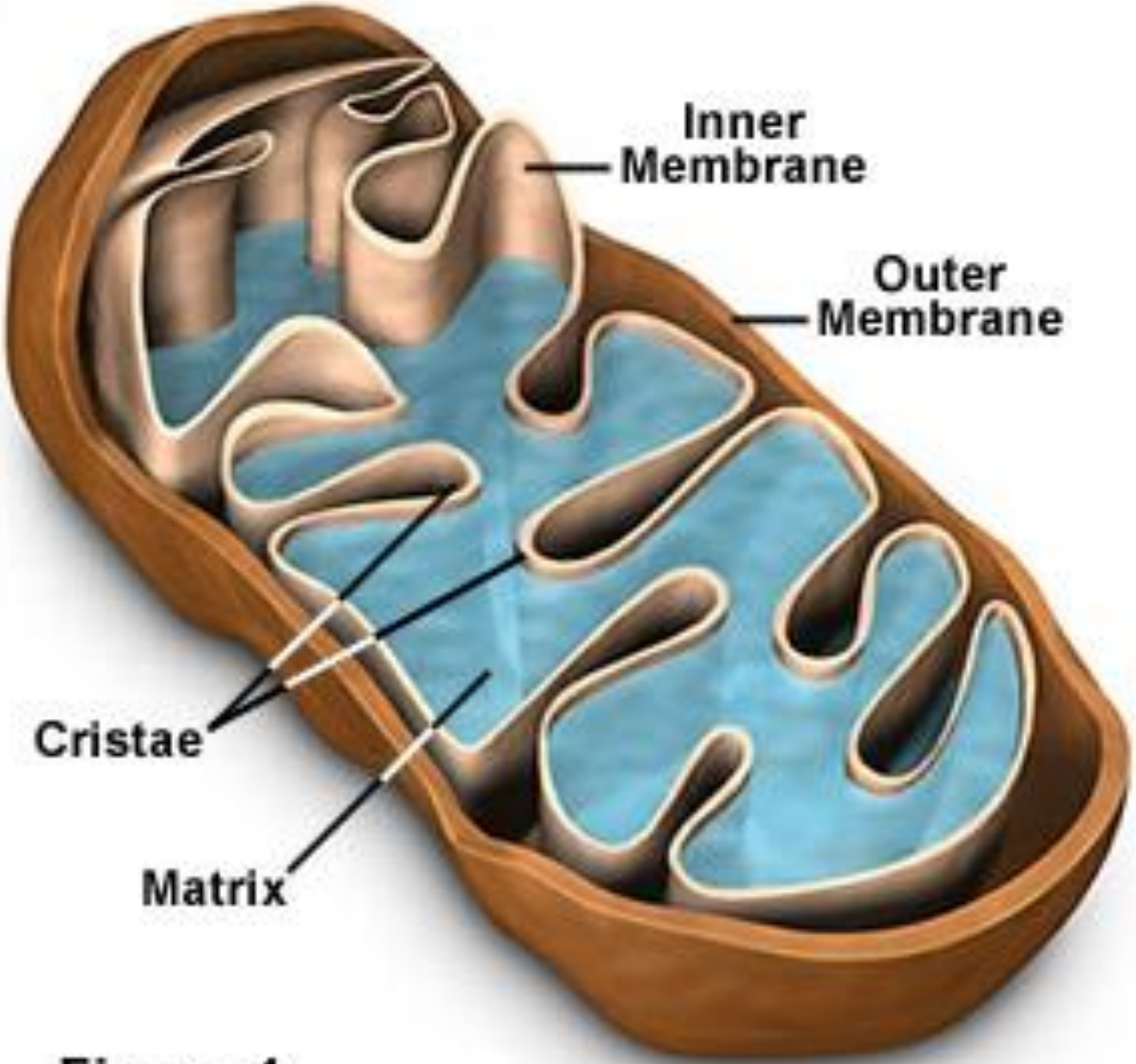
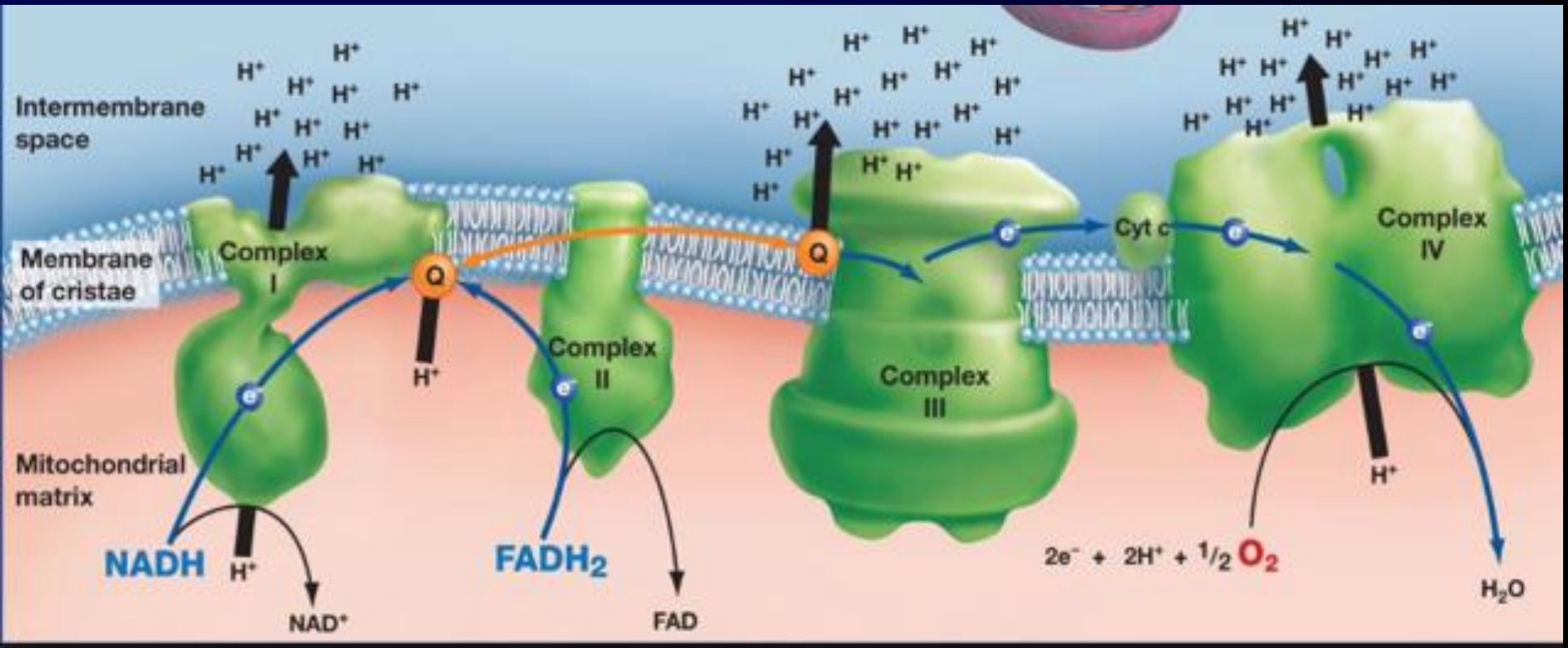
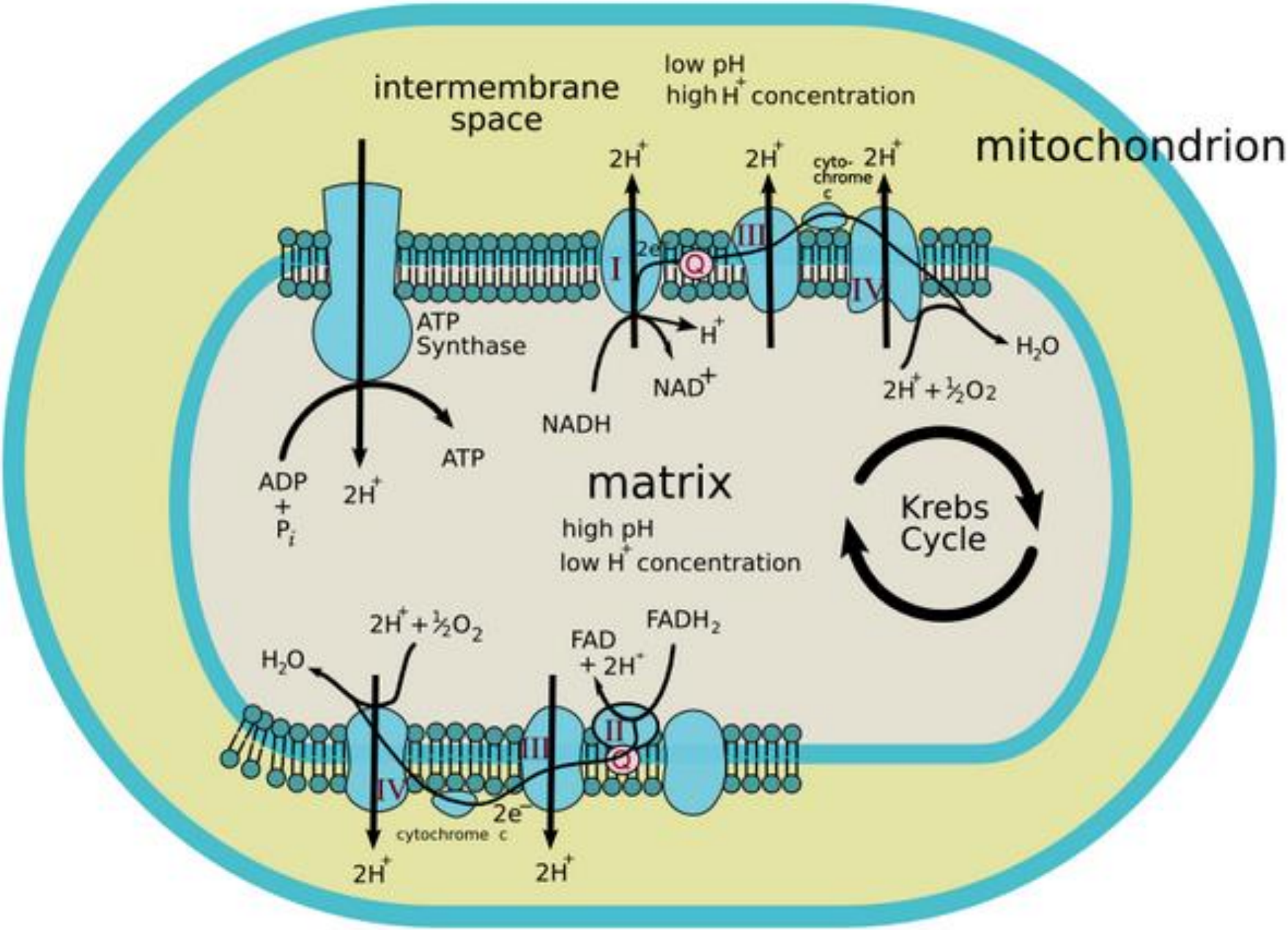


Figure 1

The beautiful mitochondria

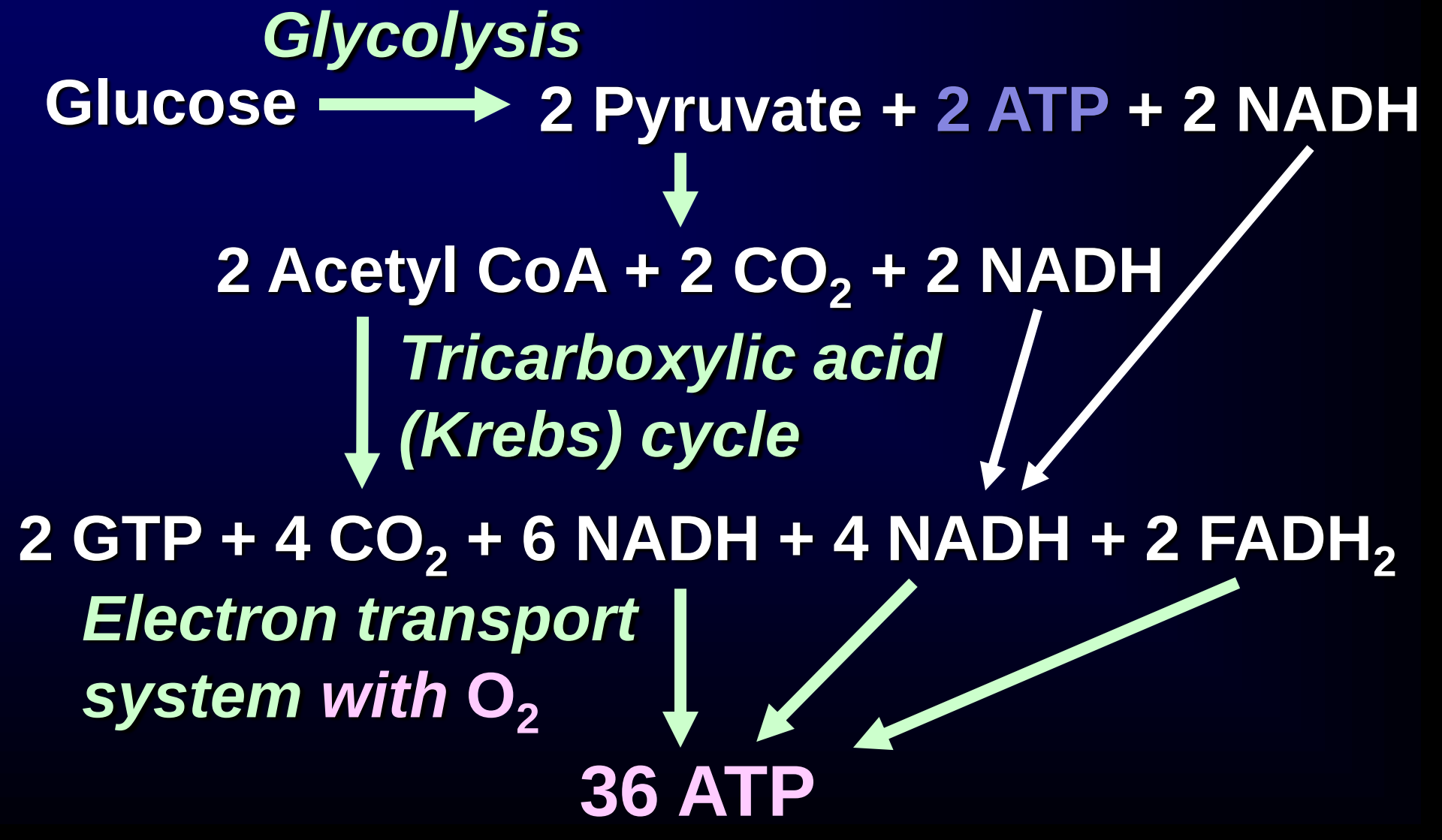


Mitochondrial Electron Transport Chain



Glucose Metabolism

Glycolysis, TCA cycle



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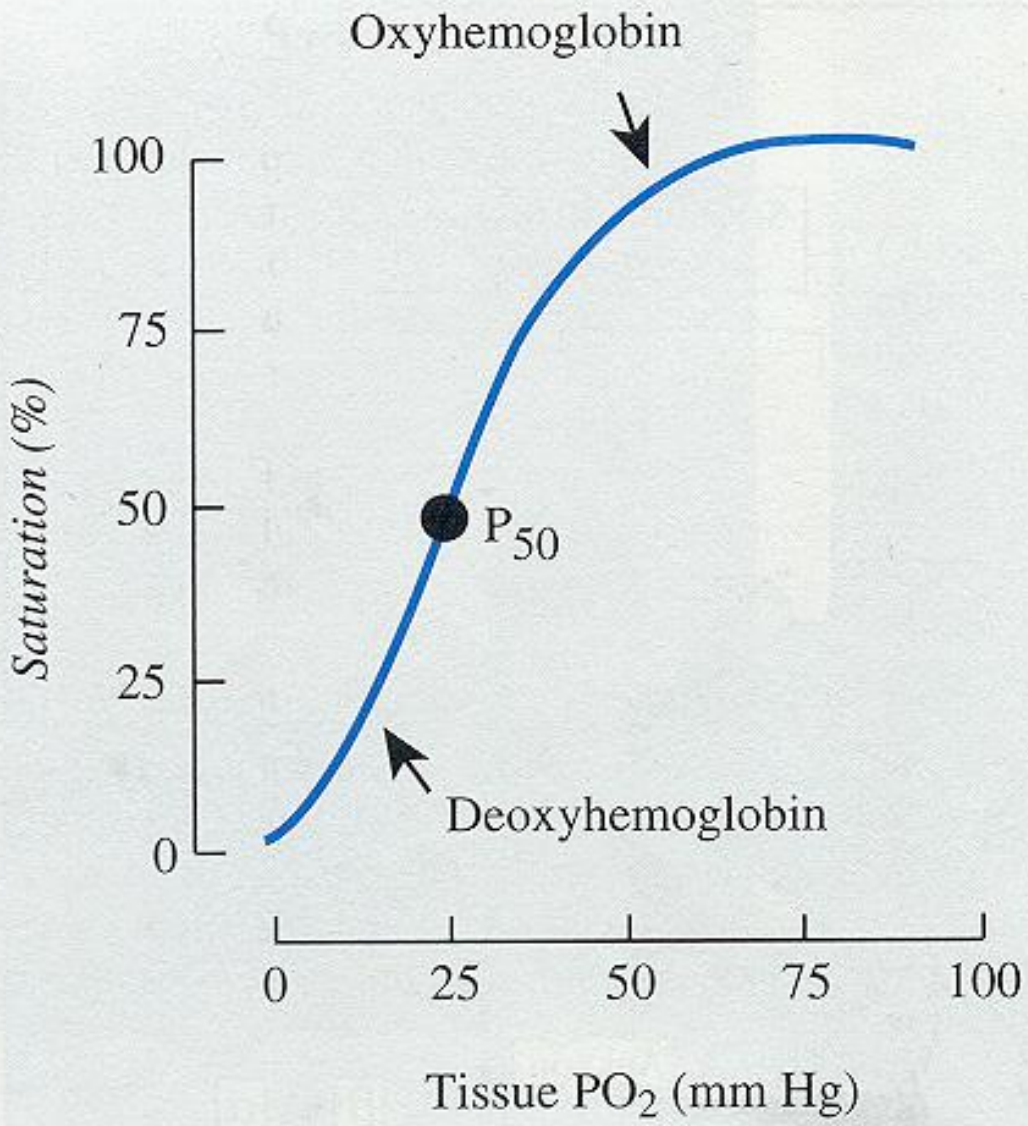
Importance of Oxygen

Aerobic versus anaerobic metabolism

- Aerobic metabolism
  - 1 glucose molecule yields 38 ATP
  - NADH, FADH are converted to ATP
  - Complex enzyme system
  - Requires O_2
- Anaerobic metabolism
  - 1 glucose molecule yields 2 ATP
  - NADH must be re-oxidized to NAD
  - “Simple” enzyme system
  - No O_2 needed

Hemoglobin-oxygen dissociation curve



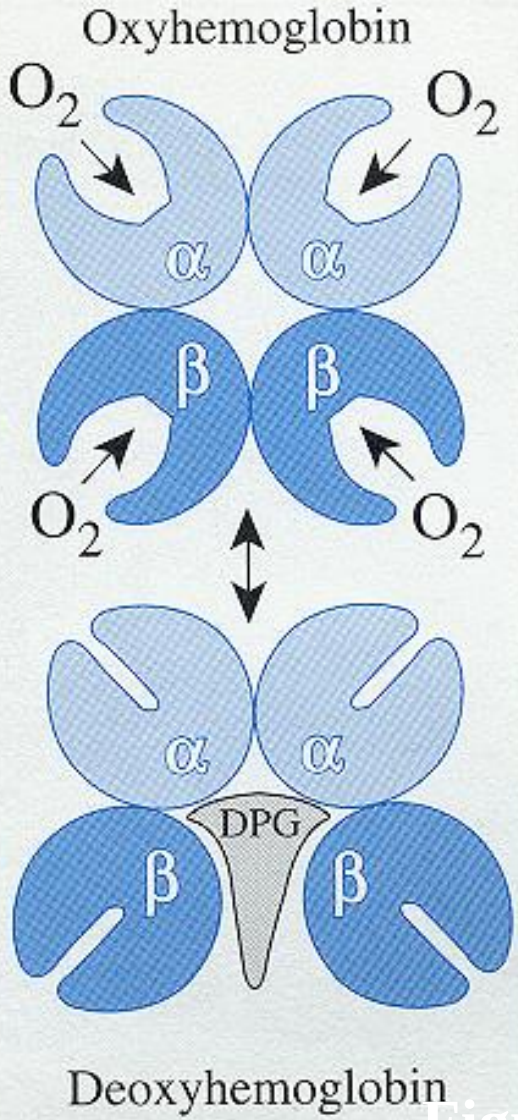


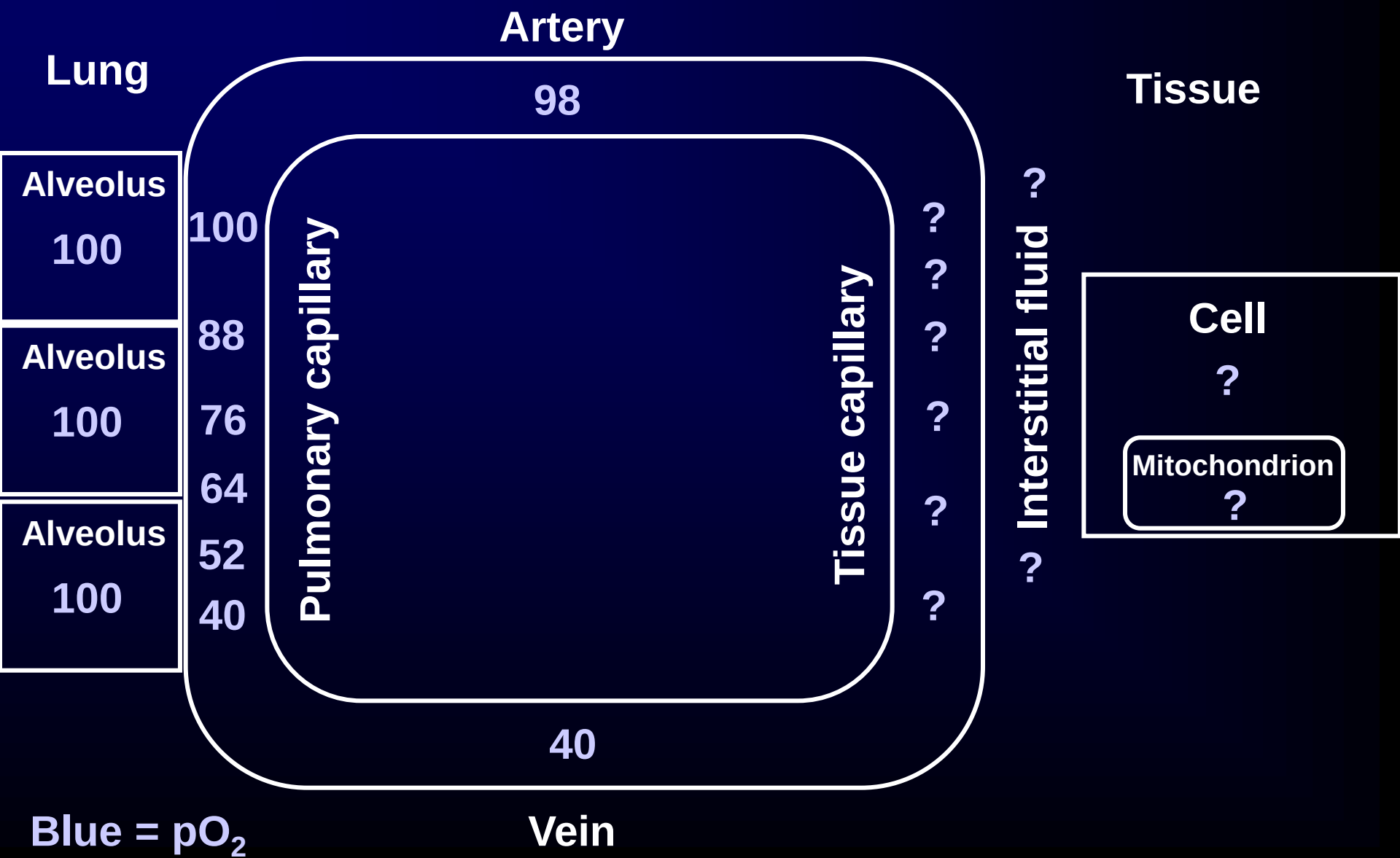
Figure 1-3

Oxygen Transport

- Airways, alveoli
- Pulmonary arteries
- Pulmonary capillaries
- Pulmonary veins
- Left atrium, left ventricle
- Systemic arteries
- Systemic capillaries
- Interstitial fluid
- Cells
- Mitochondria

Oxygen Transport

From Lungs to Tissues



Oxygen Transport

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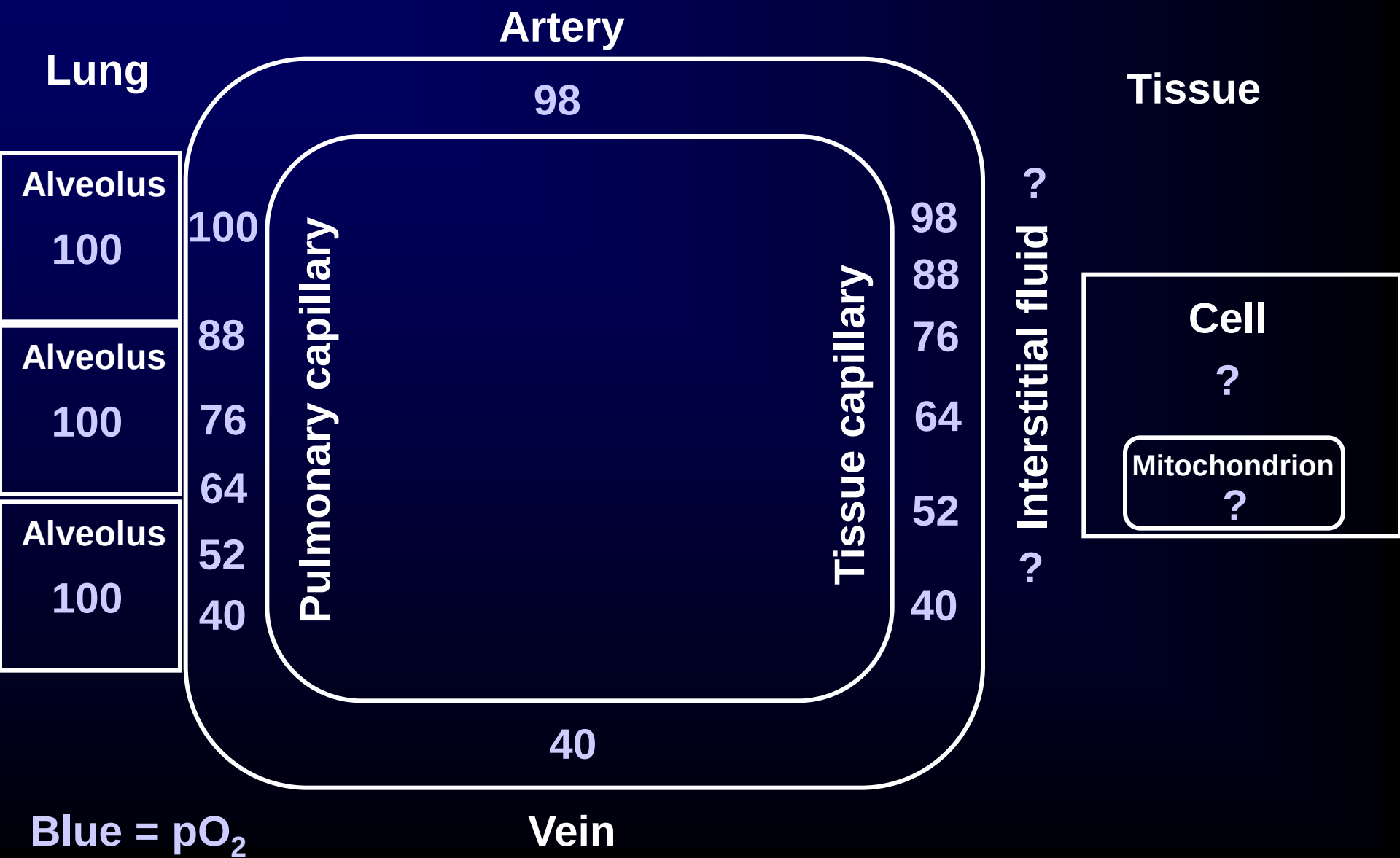
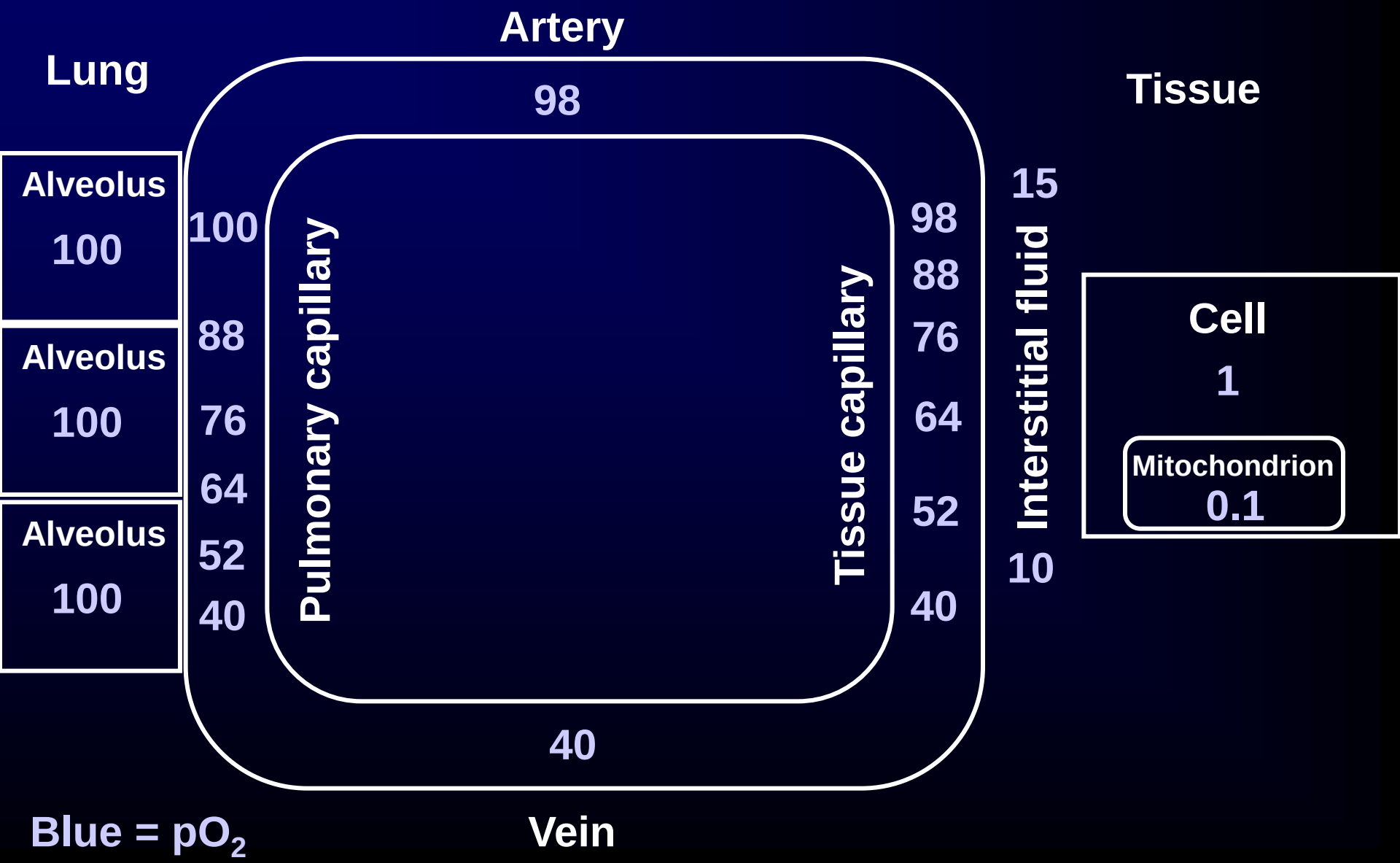


Oxygen Transport

From Lungs to Tissues



Oxygen Transport

Site	pO_2
• Pulmonary arteries	40
• Pulmonary capillaries	40 → 100
• Pulmonary veins	100
• Left atrium, left ventricle	98
• Systemic arteries	98
• Systemic capillaries	98 → 40
• Interstitial fluid	10
• Cells	1
• Mitochondria	0.1

Oxygen Content and Po_2

O_2 content = PO_2 x 0.0031 [cc O_2/mmHg] +
(O_2 sat x Hb [g/dL] x 1.34 [ccO_2/g Hb])

Site	Po_2	O_2 sat	O_2 content
Artery	100	100%	19.1 cc O_2/dL
Vein	40	70%	13.2 cc O_2/dL

O_2 delivery = CO x (Cao_2 - Cvo_2) = 30dL/m^2/min
x 5.8 cc O_2/dL = 174 cc O_2/min/m^2

Blood volume = 70 cc/kg body weight

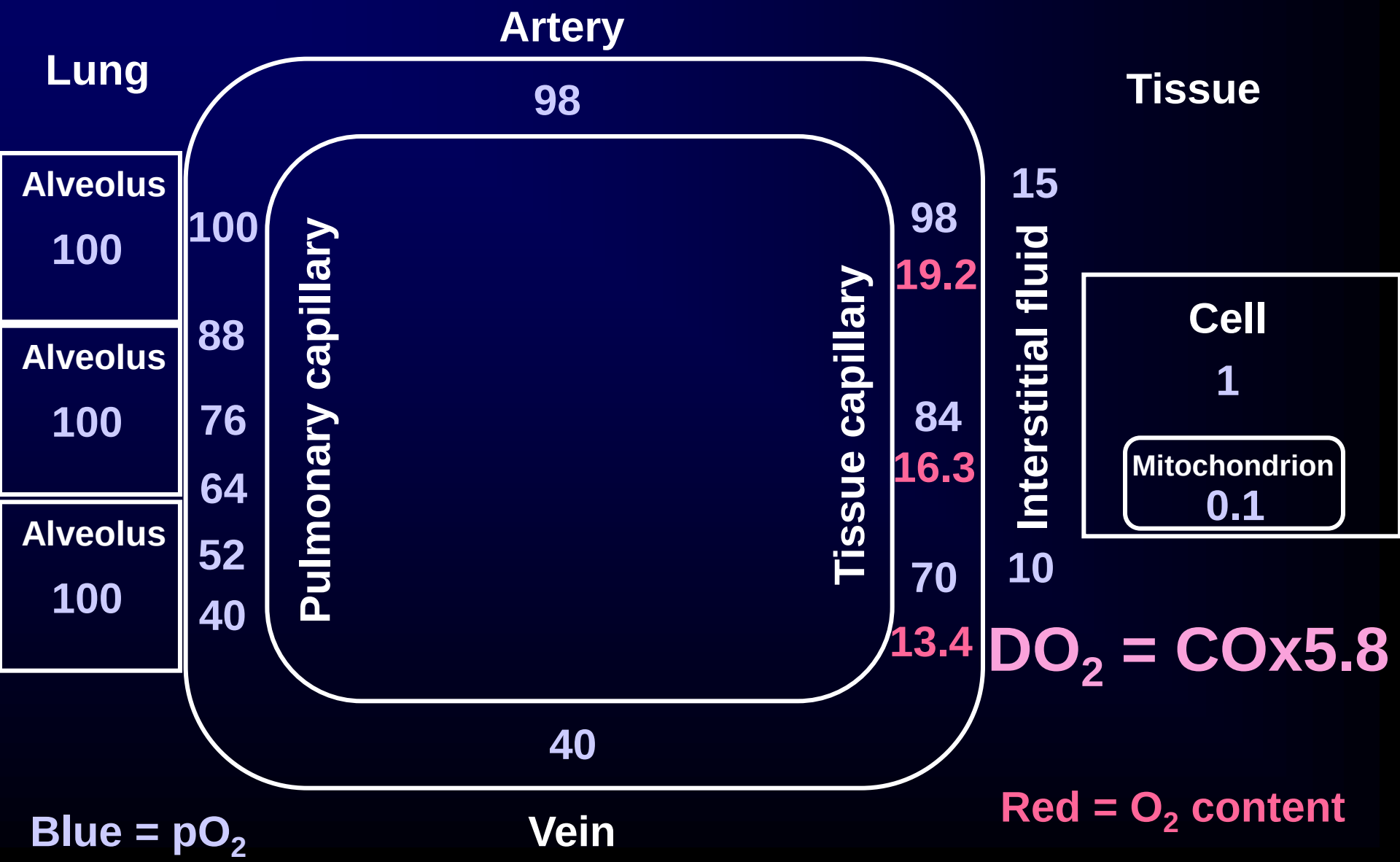
Cardiac output (CO) = 44 dL/min/m^2

Po_2 and O_2 saturation
(Assume Hb = 14 mg/dl)

Po_2	O_2 sat	O_2 content	O_2 Hb	Dissolved O_2
100	100%	19.1	18.8	0.3
80	93%	17.7	17.5	0.2
60	88%	16.9	16.7	0.2
40	70%	13.3	13.2	0.1
26	50%	9.4	9.3	0.1

Oxygen Transport

Normal Hemoglobin



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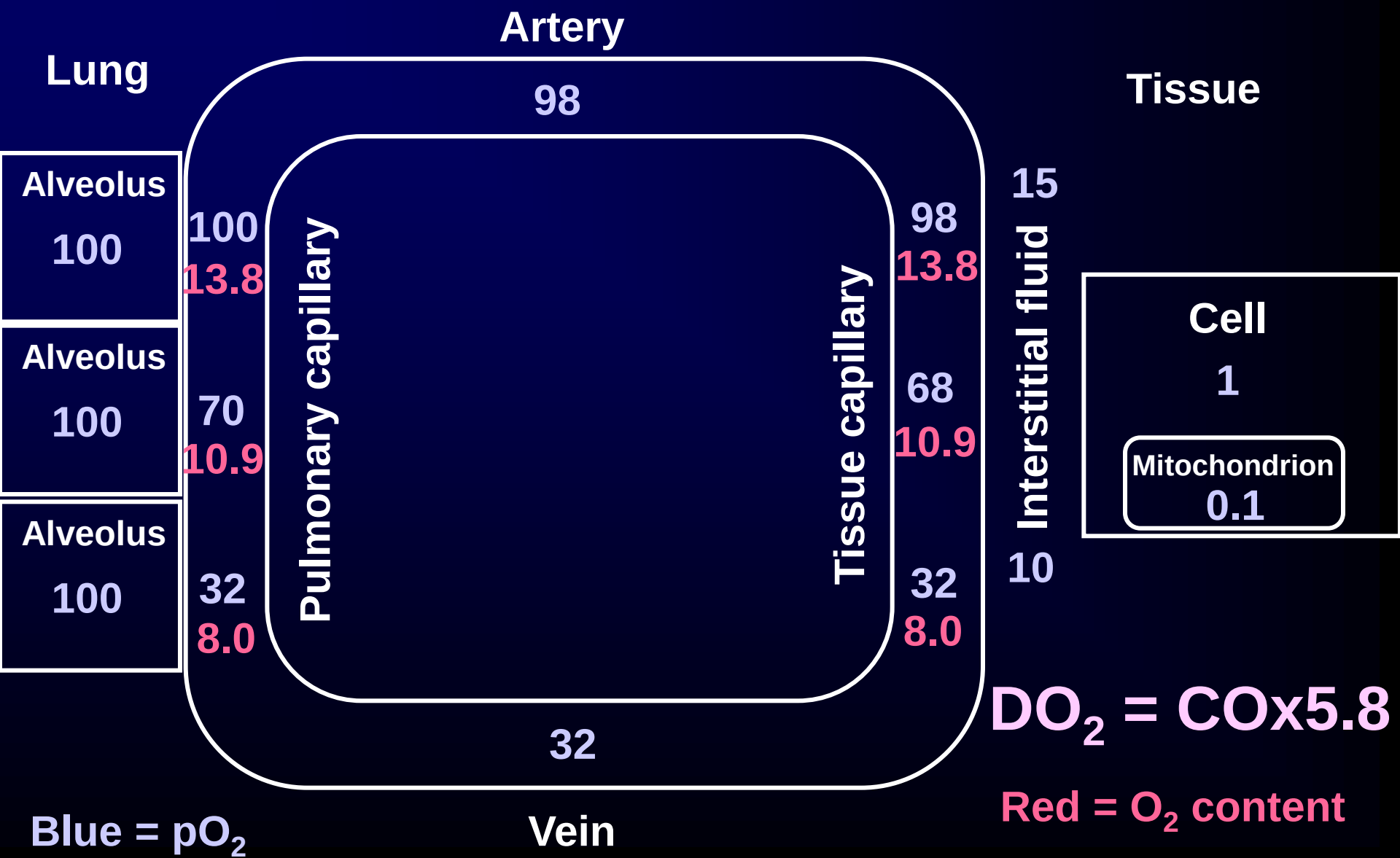
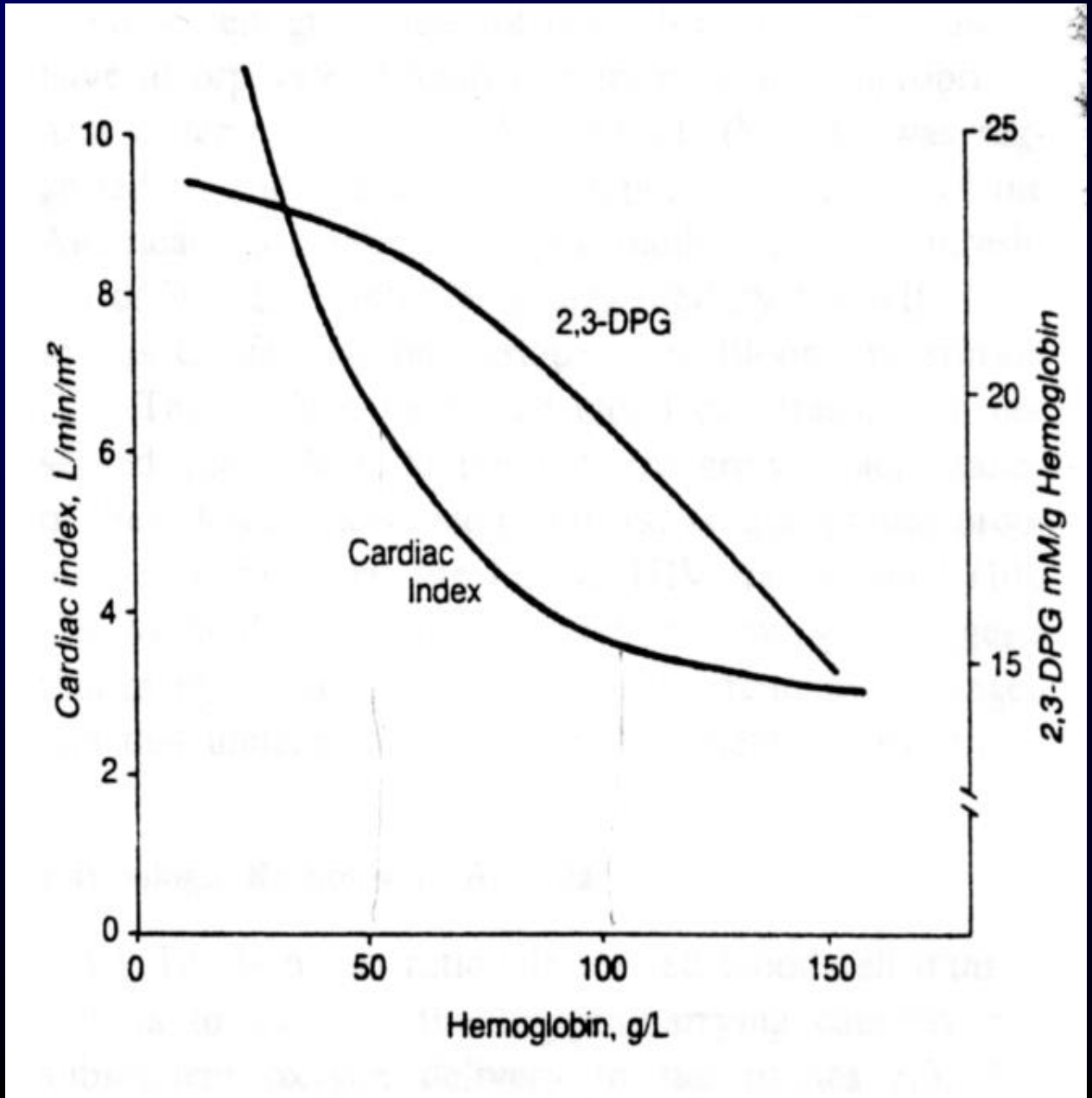
Oxygen Transport

Anemia (Hb = 10)



Hemoglobin, 2,3-DPG, and Cardiac Index



Anemia that develops slowly in otherwise healthy adults

Hemoglobin (g/dL)	Symptoms
8 to 11	Generally none - pallor, slight tachycardia
7.5	Exertional dyspnea
6.0	Some weakness
3.0	Dyspnea at rest
≤ 2.5	Cardiac failure

Response to Acute Hemodilution

	Before	After	% Change
Hematocrit (%)	33	15	-55
Arterial O_2 (cc/dL)	14	6.4	-55
O_2 delivery (cc/kg/min)	19	11	-41
Heart Rate (beat/min)	110	141	+28
Cardiac Output (L/min)	2.5	3.3	+32
O_2 Extraction (%)	38	60	+57

From Levine, et.al. Transfusion 30:11, 1990

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Management of Anemia

- Determine the urgency of the situation
- Treat the underlying cause (bleeding, hemolysis, bone marrow failure)
- Transfuse RBCs when there is insufficient oxygen being delivered to tissues
- Transfuse the smallest amount possible (that is, the smallest number of donors)
- Minimize risks of transfusion

The AABB recommendations for the *Choosing Wisely* campaign of the American Board of Internal Medicine

Jeannie L. Callum, Jonathan H. Waters, Beth H. Shaz, Steven R. Sloan, and Michael F. Murphy

Choosing Wisely is an initiative of the American Board of Internal Medicine Foundation designed to help physicians and patients engage in conversations to reduce overuse of tests and procedures and support physician efforts to help patients make smart and effective care choices. Blood transfusion is the commonest procedure performed in the hospitalized patient.[1] Unnecessary use of blood transfusion in the hospitalized patient is common worldwide. Overuse of blood transfusion has also been listed as a *Choosing Wisely* statement by the American Society of Hematology, the Society of Hospital Medicine, and the Critical Care Societies Collaborative. To support this AABB *Choosing Wisely* initiative, the AABB developed a set of 10 recommendations with input from AABB committees and

1. Don't transfuse more units of blood than absolutely necessary

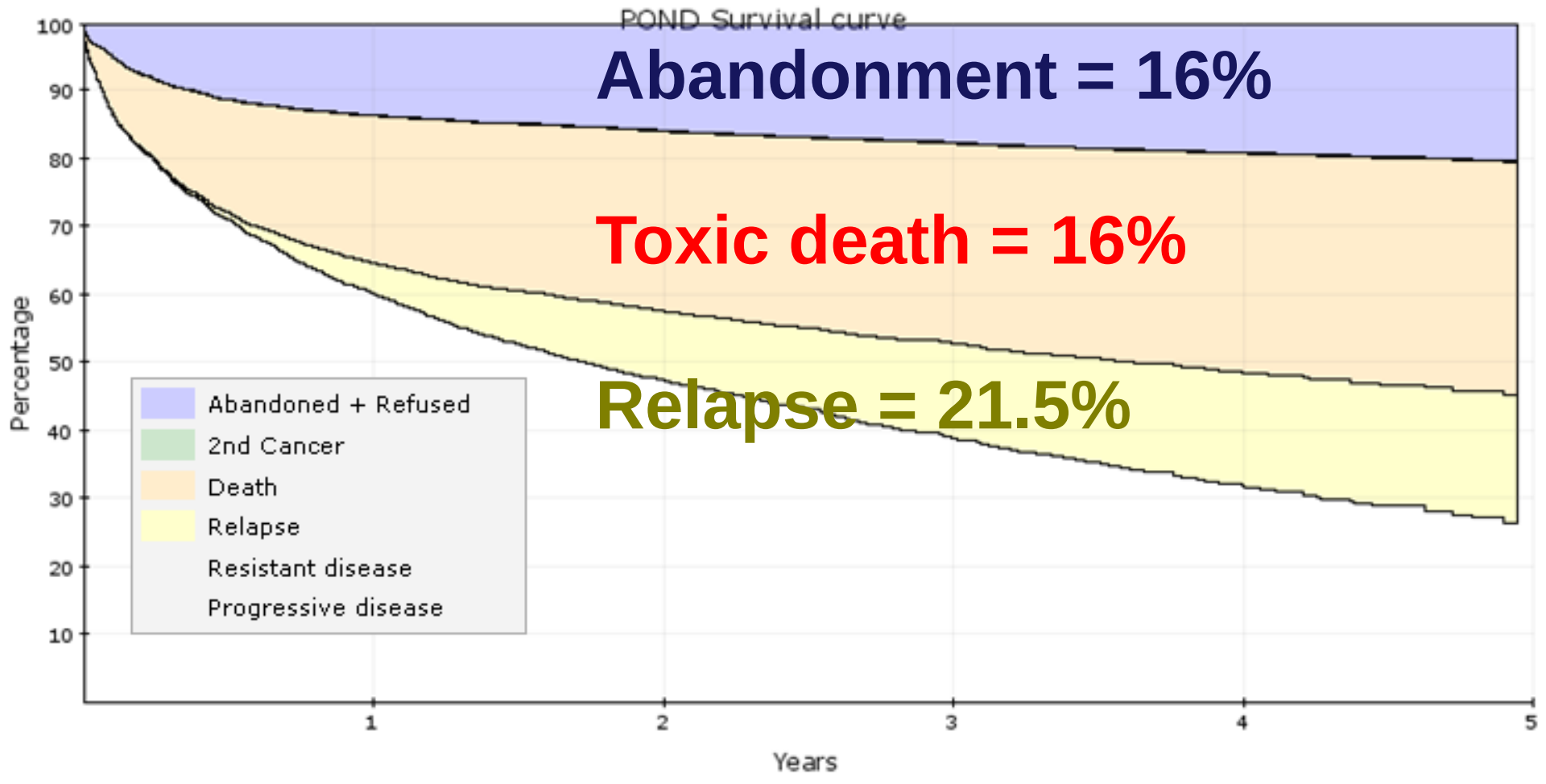
A restrictive threshold (7.0-8.0g/dL) should be used for the vast majority of hospitalized, stable patients without evidence of inadequate tissue oxygenation (evidence supports a threshold of 8.0g/dL in patients with existing cardiovascular disease). Transfusion decisions should be influenced by symptoms and hemoglobin (Hb) concentration. Single-unit red blood cell (RBC) transfusions should be the standard for nonbleeding hospitalized patients. Additional units should only be prescribed after reassessment of the patient and their Hb value.

A total of 13.8 million units of whole blood and RBCs were transfused in the United States in 2011 equating to 44 units per 1000 population,[2] which is considerably higher

Define Types of Hemorrhage

- Major
  - Fatal (CTCAE grade 5, WHO grade 4)
  - Life-threatening (CTCAE grade 4)
  - Requiring transfusion or other urgent intervention (CTCAE grade 3, WHO grade 3)
- Minor – clinically significant but not urgent (CTCAE grade 2, WHO grade 2)
- Trivial – petechiae, transient nose-bleed, microscopic hematuria, scleral hemorrhage

Causes of treatment failure for children with cancer in selected middle-income countries



WHO bleeding scale

WHO bleeding scale

The World Health Organization, or WHO, made a standardized grading scale to measure the severity of bleeding.

Grade 0	no bleeding
Grade 1	petechial bleeding;
Grade 2	mild blood loss (clinically significant);
Grade 3	gross blood loss, requires transfusion (severe);
Grade 4	debilitating blood loss, retinal or cerebral associated with fatality

References

- Webert KE, Cook RJ, Sigouin CS, et al. The risk of bleeding in thrombocytopenic patients with acute myeloid leukemia. haematologica 2006;91:1530-1537

http://www.worldlingo.com/ma/enwiki/en/WHO_bleeding_scale

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.02

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

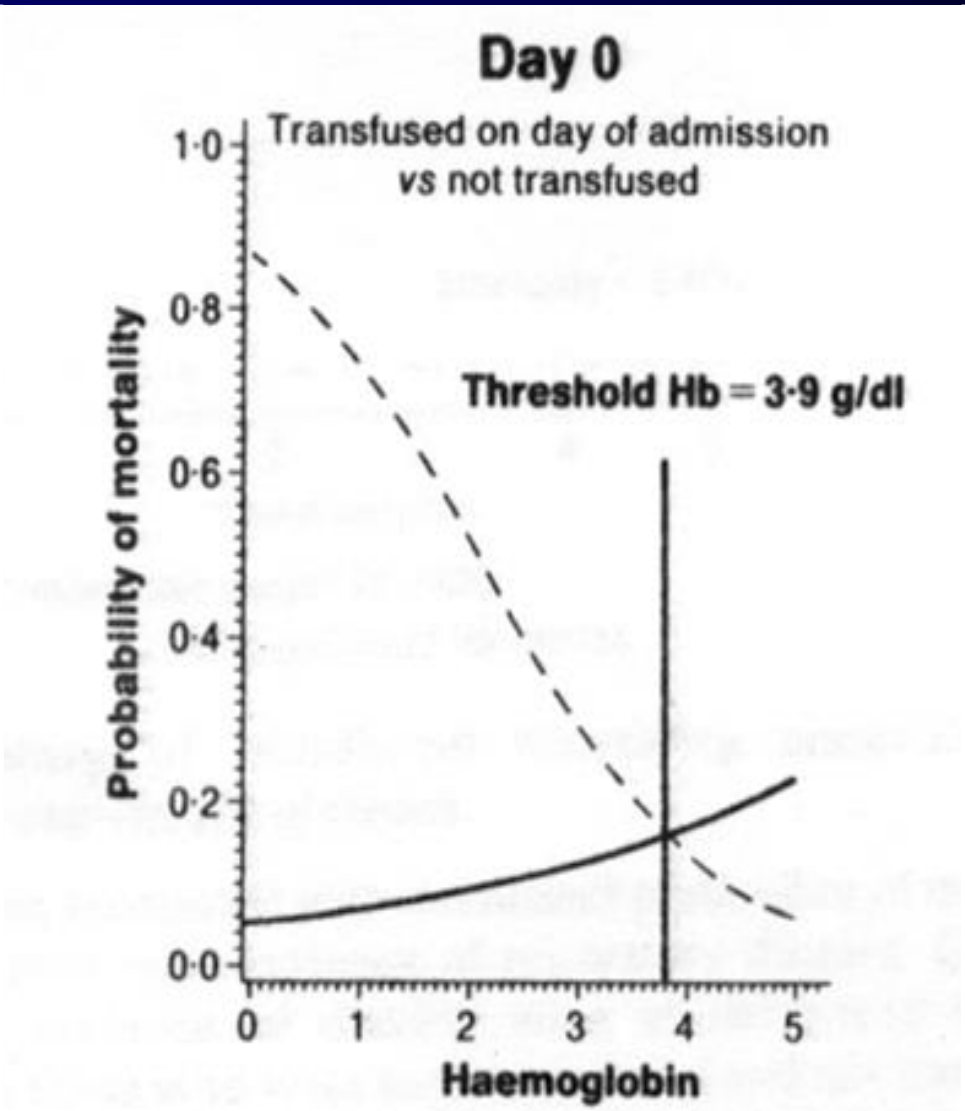
Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site.					
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the colon.					

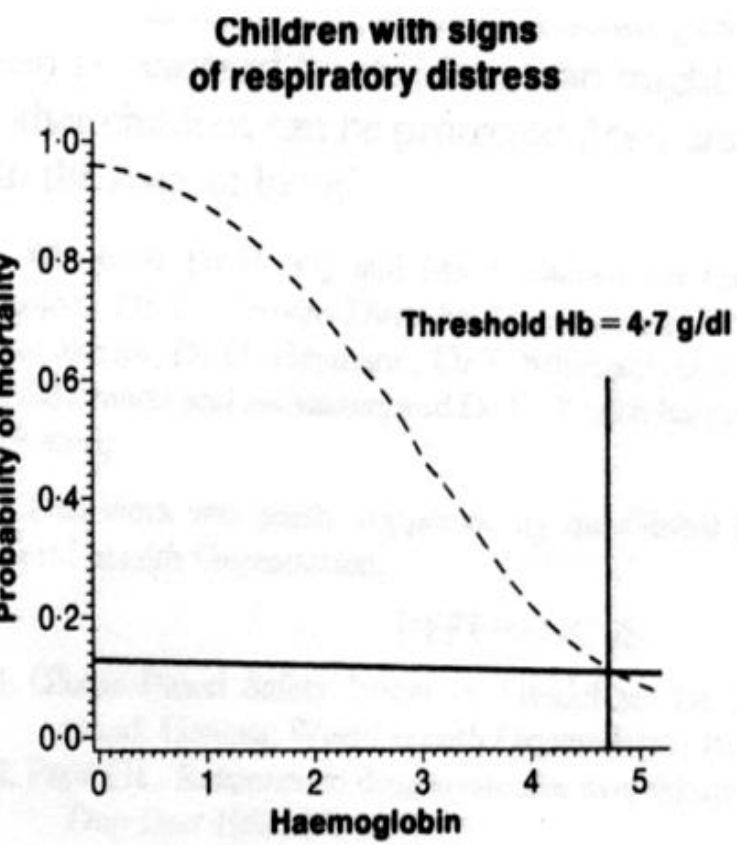
Blood Transfusion and Survival

Malaria as an example

- Lackritz, et al. The Lancet, 340: 524-8, 1992.
- Siaya District Hospital (Rural Western Kenya)
- October 1989 to October 1990
- 2433 admissions for severe malaria
- 29% Hb<5.0
- 20% received transfusions

Malaria – Hb>3.9 best to NOT transfuse

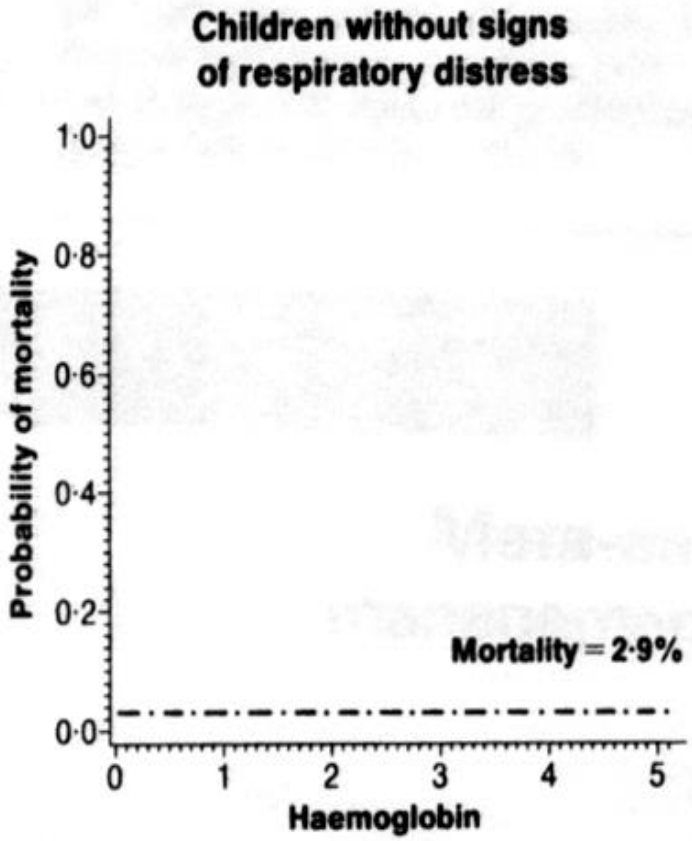




Multivariate model (n = 220):

	OR	95% CI
Transfusion	0·0063	0·0004, 0·0900
Hb (g/dl)	0·33	0·19, 0·57
Transfusion Hb	2·92	1·34, 6·39
Parasite density	0·87	0·78, 0·96
Age (months)	0·93	0·87, 1·00

Odds ratio of transfused *vs* not transfused
(using a dichotomous Hb variable
and adjusting for the above variables)
For Hb < 4·7 g/dl: n = 0·19; 95% CI = 0·09, 0·41



Multivariate model (n = 69):
No significant variables

Fig 3—Probability of childhood mortality according to presence of respiratory distress.

Transfusion was associated with decreased probability of mortality only among children with evidence of respiratory distress. Children without clinical evidence of distress were at decreased risk for mortality, among those who were both transfused and not transfused (dashed line), irrespective of admission Hb. Solid line, children transfused; dotted line, children not transfused.

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RCS
ADVANCING SURGICAL STANDARDS

REVIEW

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An evidence-based approach to red blood cell transfusions in asymptomatically anaemic patients

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ABSTRACT

INTRODUCTION Surgeons and physicians encounter blood transfusions on a daily basis but a robust evidence-based strategy on indications and timing of transfusion in asymptomatic anaemic patients is yet to be determined. For judicious use of blood products, the risks inherent to packed red blood cells, the patient's co-morbidities and haemoglobin (Hb)/haematocrit levels should be considered. This review critiques and summarises the latest available evidence on the indications for transfusions in healthy and cardiac disease patients as well as the timing of transfusions relative to surgery.

METHODS An electronic literature search of the MEDLINE®, Google Scholar™ and Trip databases was conducted for articles published in English between January 2006 and January 2015. Studies discussing timing and indications of transfusion in medical and surgical patients were retrieved. Bibliographies of studies were checked for other pertinent articles that were missed by the initial search.

FINDINGS Six level 1 studies (randomised controlled trials or systematic reviews) and six professional society guidelines were included in this review. In healthy patients without cardiac disease, a restrictive transfusion trigger of Hb 70–80g/l is safe and appropriate whereas in cardiac patients, the trigger is Hb 80–100g/l. The literature on timing of transfusions relative to surgery is limited. For the studies available, preoperative transfusions were associated with a decreased incidence of subsequent transfusions and timing of transfusions did not affect the rates of colorectal cancer recurrence.

Table 1 Summary recent transfusion articles (2006–2014)

Paper	Study design	Results / transfusion trigger
American College of Physicians clinical practice guideline, 2013[2]	Systematic literature review	Hb 70–80g/l: Transfuse in hospitalised patients with CAD
Myocardial Ischemia and Transfusion trial, 2013[3]	Multicentre RCT (n=110) Patients: ACS or unstable angina Liberal arm (Hb <100g/l) vs restrictive arm (Hb <80g/l) or any symptoms regardless of Hb level	Hb <100g/l: Transfusion at higher Hb levels associated with lower rates of composite endpoint of death, MI or unscheduled revascularisation within 30 days of randomisation (10.9% vs 25.9%, p=0.054 without age adjustment, p=0.076 with age adjustment)
Carson (Cochrane review), 2012[4]	Systematic review of 19 RCTs (n=6,264) with meta-analysis Included studies comparing a liberal vs restrictive transfusion strategy	Hb <70–80g/l: Transfusion probably not essential in patients without CAD or notable bleeding. At time of Cochrane review, no other trials done on patients with CAD so triggers in this subset of patients unknown. Restrictive strategies: > Risk of receiving future transfusions decreased by 39% (95% CI: 0.52–0.72) > No increased risk of adverse events (mortality, cardiac events, MI, stroke, pneumonia, VTE) > Decreased hospital mortality (RR: 0.77, 95% CI: 0.62–0.95) > No change to 30-day hospital mortality (RR: 0.85, 95% CI: 0.70–1.03) However, high heterogeneity between trials (p<0.00001, I^2≥93%)
American Association of Blood Banks, 2012[5]	Systematic review of 19 RCTs (using evidence from Cochrane review in 2012)	Hb 70–80g/l: Transfuse in hospitalised stable patients without CAD. High quality evidence, strong recommendation. Hb <80g/l: Transfuse in hospitalised haemodynamically stable patients with pre-existing cardiac disease or symptomatic patients. Moderate quality evidence, weak recommendation. No level specified for ACS patients (paucity of data)
CRIT pilot trial, 2011[6]	Multicentre RCT (n=45) Patients: acute MI with Hct ≤30% Liberal arm (Hct <30%) vs restrictive arm (Hct <24%)	Hct <24%: Lower incidence of composite endpoint of in-hospital death, recurrent MI, or new or worsening congestive heart failure compared with liberal strategy (38% vs 13%, p=0.046)
Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair trial, 2011 and 2015[7,8]	Multicentre RCT (n=2,016) Patients: cardiovascular disease following hip surgery, age ≥50 years Restrictive arm (Hb <80g/l) vs liberal arm (Hb <100g/l)	Hb <80g/l: Not significantly different to transfusing for Hb 100g/l in terms of death at 30 days (4.3% vs 5.2%, ARR: -0.9 percentage points, 99% CI: -1.5–3.4 percentage points), death at 60 days (6.6% vs 7.6%, ARR: -1.0 percentage points, 99% CI: -1.9–4.0 percentage points), in-hospital morbidity (4.3% vs 5.2%, ARR: -0.9 percentage points, 99% CI: -3.3–1.6 percentage points) or independent mobilisation at 60 days (35.2% vs 34.7%, p=0.90) Long-term mortality at 3 years did not differ significantly between restrictive arm (409 deaths) and liberal arm (432 deaths); HR: 1.09, 95% CI: 0.95–1.25

Society of Thoracic Surgeons, 2011[9]	Combination of literature review, grading of recommendations based on American Heart Association / American College of Cardiology system	Hb <70g/l: Transfusion reasonable Hb 70–100g/l: In CPB patients with critical non-cardiac end organ ischaemia, transfusion not unreasonable. Needs more evidence. Hb >100g/l: Do not transfuse unless critical non-cardiac end organ ischaemia
Transfusion Requirements after Cardiac Surgery trial, 2010[10]	Single centre RCT (n=50) Patients: elective cardiac surgery Liberal arm (Hct ≤30%) vs restrictive arm (Hb ≤24%)	Hct ≤24%: No difference in composite endpoint of 30-day all-cause mortality and severe morbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or haemofiltration) during hospitalisation. Occurrence of endpoint was 10% for liberal arm and 11% for restrictive arm (p=0.85).
Guidelines and Audit Implementation Network, 2009[11]	Combination of literature review and expert panel discussion	Hb <70g/l: For stable patients <65 years with no cardiovascular or cerebrovascular problems Hb <80g/l: For stable patients >65 years with no cardiovascular or cerebrovascular problems Hb <90g/l: For patients with cardiovascular or cerebrovascular history (previous MI, angina, hypertension, heart failure, peripheral vascular disease) Hb <100g/l: For symptomatic patients with anaemia (dyspnoea, angina, palpitations, tachycardia, orthostatic hypotension, syncope) or when active bleeding suspected
European Society of Cardiology, 2007[12]	Combination of literature review, expert opinion, panel discussion and open forums	Hb <80g/l or Hct <25%: Transfuse in CAD patients
American Society of Anesthesiologists, 2006[13]	Combination of literature review, expert opinion, panel discussion and open forums	Hb <60g/l: Transfuse Hb 60–100g/l: Depends on organ ischaemia, potential or actual ongoing bleeding, patient intravascular status and risk factors for inadequate oxygenation Hb >100g/l: Do not transfuse

ACS = acute coronary syndrome; ARR = absolute risk reduction; CAD = coronary artery disease; CI = confidence interval; CPB = cardiopulmonary bypass; Hb =haemoglobin; Hct = haematocrit; HR = hazard ratio; MI = myocardial infarction; RCT = randomised controlled trial; RR = relative risk; VTE = venous thromboembolism

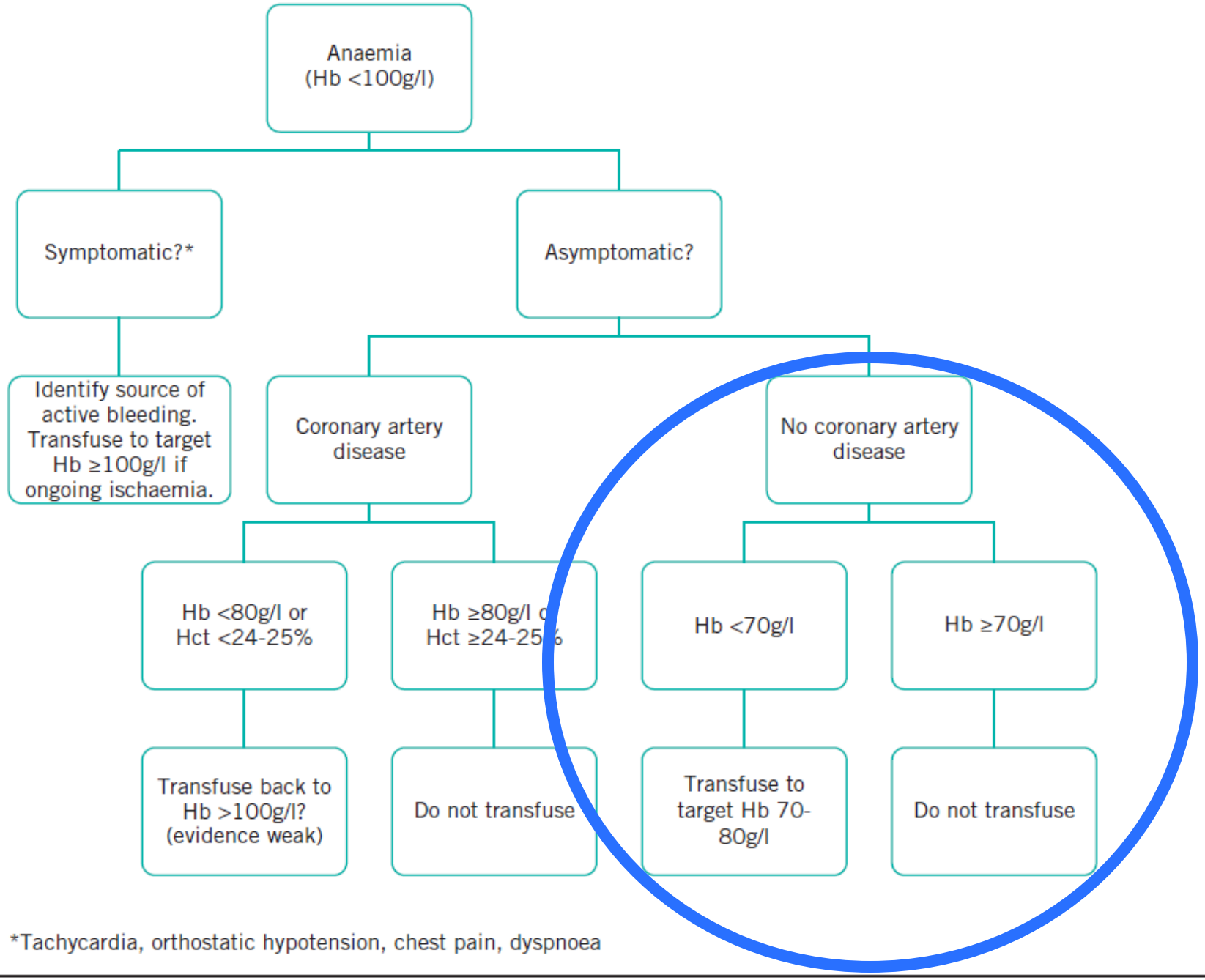
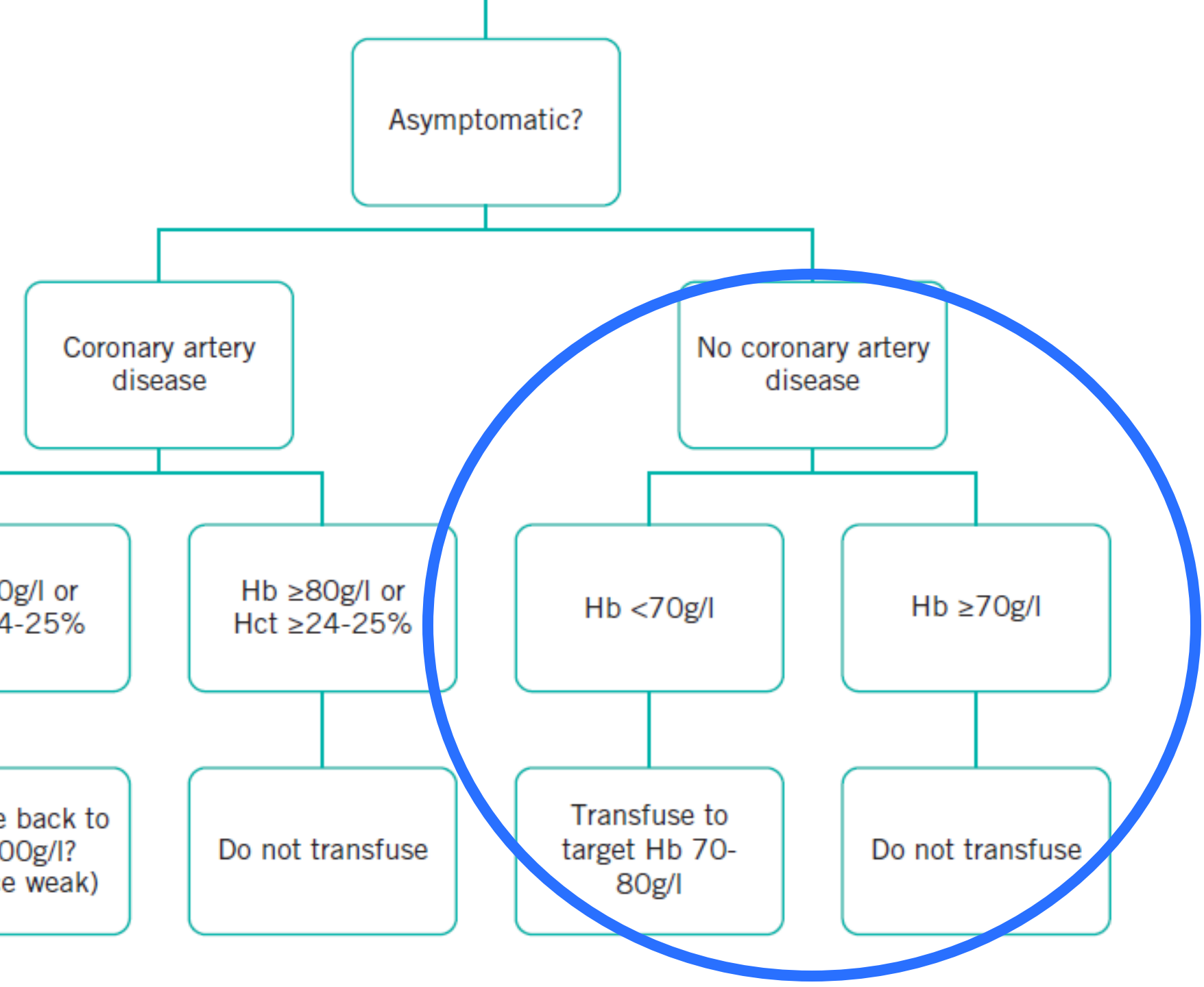


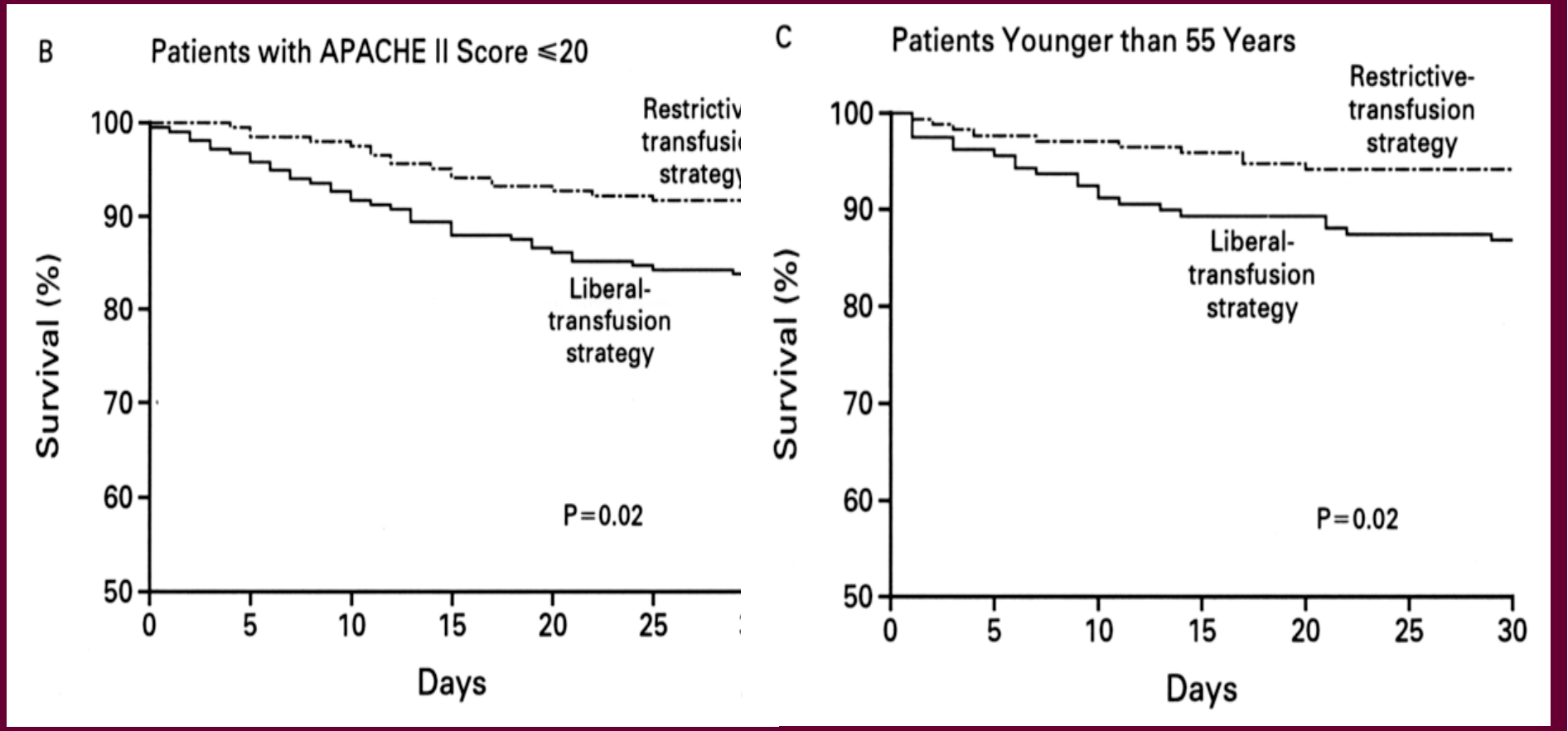
Figure 1 Decision algorithm flowchart for transfusion


Asymptomatic?
Coronary artery disease
No coronary artery disease
0g/l or
4-25%
Hb ≥80g/l or
Hct ≥24-25%
Hb <70g/l
Hb ≥70g/l
e back to
00g/l?
e weak)
Do not transfuse
Transfuse to target Hb 70-80g/l
Do not transfuse

Transfusion Requirements for Patients Receiving Critical Care (TRICC Study)

- Hebert, P., et.al. NEJM 340: 409-17, 1999 (Canadian Critical Care Trials Group).
- 838 ICU patients with Hb < 9.0 within 48 hours after ICU admission.
- Randomized to transfusion to maintain:
  - Hemoglobin 7 to 9 g/dL (Restrictive) vs
  - Hemoglobin 10 to 12 g/dL (Liberal)

TRICC Study - Subgroup Survival



EXPERT REVIEWS

Supportive medical care for children with acute lymphoblastic leukemia in low- and middle-income countries

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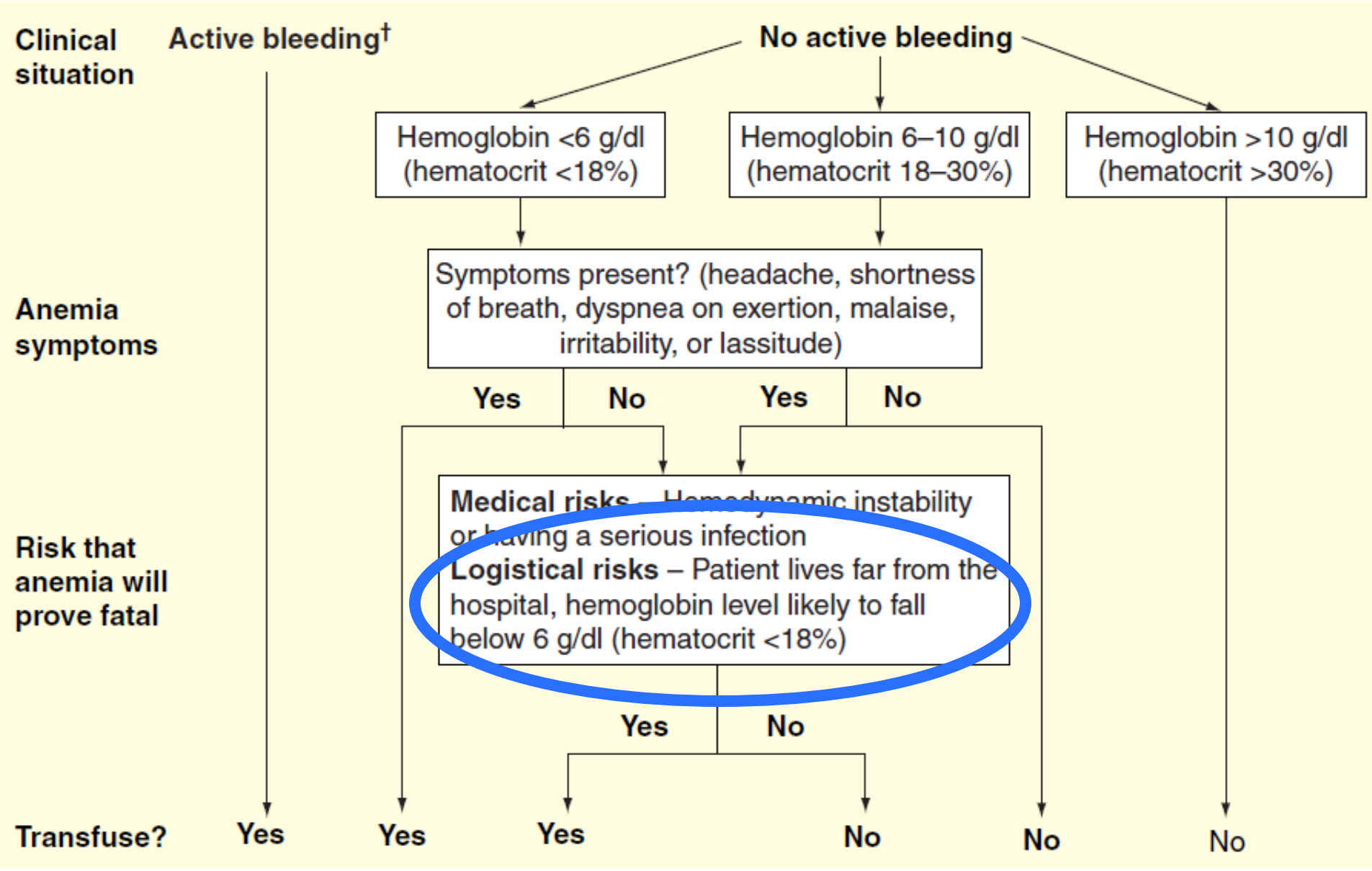
In the last two decades, remarkable progress in the treatment of children with acute lymphoblastic leukemia has been achieved in many low- and middle-income countries (LMIC), but survival rates remain significantly lower than those in high-income countries. Inadequate supportive care and consequent excess mortality from toxicity are important causes of treatment failure for children with acute lymphoblastic leukemia in LMIC. This article summarizes practical supportive care recommendations for healthcare providers practicing in LMIC, starting with core approaches in oncology nursing care, management of tumor lysis syndrome and mediastinal masses, nutritional support, use of blood products for anemia and thrombocytopenia, and palliative care. Prevention and treatment of infectious diseases are described in a parallel paper.

KEYWORDS: acute lymphoblastic leukemia • chemotherapy • low-income country • middle-income country • oncology nursing • pediatrics • supportive care

The past four decades have seen significant associated with inadequate supportive care,

Red blood cell transfusion algorithm for LMIC



Red blood cell transfusion

- Role of red blood cells (RBCs)
- Physiology of anemia
- Management of anemia
  - RBC loss – bleeding, hemolysis
  - Decreased RBC production
- Risks of transfusion
- Recommendations

Conclusions

- Anemia is not important
- Lack of oxygen delivery to tissues is extremely important (38 ATP) and should guide transfusion decisions
- Benefits of increased Hb to carry oxygen to the mitochondria must be balanced against risk of transfusion
- It is RARE to need Hb > 7 g/dL
- The patient's social situation should be considered when providing prophylactic RBC transfusions