Clinical Strategies for Managing Hemorrhage and Anemia Without Blood Transfusion in Critically Ill Patients*

GENERAL ICU MANAGEMENT PRINCIPLES

1. Exercising clinical judgment, **be prepared to modify routine practice** (e.g., extra vigilance, expeditious control of bleeding).
2. **Formulate an individualized clinical management plan** to facilitate rapid decision-making and avoid treatment delays. Prospective planning includes prediction, prevention, prompt recognition, and treatment of blood loss and anemia by the use of multiple appropriate therapeutic interventions.
3. **Discuss anticipated or potential procedures** and their risks and benefits with the patient/substitute decision-maker.
4. **Adopt an interdisciplinary and collaborative team approach** among involved clinical specialties (medicine, surgery, radiology, hematology, nursing, pharmacy) with active management by the lead clinician.
5. **Maintain ongoing communication** regarding patient management among members of the critical care team and consultants, especially during transitions of staff. Where there are multiple conditions treated by multiple physicians, interspecialty collaboration and coordination is particularly important.
6. **Consult with specialist** physicians who have experience in the management of patients without allogeneic blood transfusion. Recognition of risk factors for bleeding or anemia may help clinicians to predict/anticipate the need for preventive or control measures.
7. **Maintain continuous, close surveillance for signs and symptoms of blood loss** or deterioration. If a suspicion of bleeding arises from either clinical or laboratory findings, promptly initiate diagnosis and appropriate management.
8. **Prompt action to arrest blood loss and judicious volume management is lifesaving.** The clinical urgency of low-level persistent bleeding may not be recognized until compensatory mechanisms fail and blood pressure falls. In the face of severe hemorrhage, early recourse to definitive measures to control bleeding is of paramount importance. In general, avoid a watch-and-wait approach to the bleeding patient.
9. **Transfer** a stabilized patient, if necessary, to a major center **before the patient's condition deteriorates.**

GENERAL THERAPEUTIC PRINCIPLES IN ICU

1. Prevent and rapidly arrest any bleeding with decisive and immediate action (e.g., surgery, hemostatic pharmacological agents). Avoid delays.
2. Minimize iatrogenic blood loss (e.g., restrict phlebotomy for laboratory tests, cautious thromboembolic prophylaxis).
3. Optimize cardiac and respiratory support as soon as possible (e.g., early supplemental oxygen, individualized fluid therapy for adequate tissue perfusion, vasoactive agents).
4. Minimize oxygen consumption (analgesia, sedation).
5. Early aggressive treatment of anemia (e.g., erythropoiesis-stimulating agents, iron, nutrition).
6. Maintain normovolemia in the anemic patient. In the presence of uncontrolled hemorrhage, consider permissive moderate hypotension and controlled fluid resuscitation until bleeding is promptly arrested.

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1. PREVENTION AND ARREST OF BLEEDING

A. Close Surveillance for Blood Loss[1,2]

1. Clinical diagnosis of bleeding

a. Pain, wound swelling, or firmness at surgical site (e.g., hematoma)

b. Saturation of surgical dressings; oozing; tube drainage

c. Hematemesis, bloody nasogastric aspirate, melena/hematochezia

d. Hemodynamic instability; spontaneous drop in blood pressure

e. Clinical examination (e.g., pallor, ecchymosis, dyspnea, tachycardia, tachypnea, diaphoresis, decreased level of consciousness, oliguria)

f. Perfusion markers/metabolic variables (See **3.A.**)

g. Declining serial hemoglobin or platelet count

h. Fluid/volume status (ongoing bleeding should be suspected when a patient shows evidence of hypovolemia despite reasonable hydration)

Notes:

1. Avoid delay in identification or localization of bleeding by close monitoring and frequent serial clinical examinations by the same examiner.[3]
2. The observation protocol should include regular serial monitoring of vital signs, urine output, hematocrit, and blood gases.
3. The clinical urgency of low-level persistent blood loss (e.g., bleeding from small vessels, capillaries) from potentially multiple sites may not be recognized until compensatory mechanisms fail and blood pressure falls.

B. Rapid Diagnosis and Control of Hemorrhage[4-7]

1. Maintain a high level of clinical suspicion

a. Maintain acute clinical awareness of potential bleeding

(1) Any drop in hemoglobin/hematocrit, platelet count, or blood pressure, and any increase in heart rate requires urgent clarification

b. Adopt a lower threshold for intervention (i.e., consider surgical exploration/reexploration on less clear-cut indications)

2. Systematic screening/diagnosis of bleeding

a. Review medical history, including drug history, and perform physical examination as well as concomitant systematic and expeditious diagnostic imaging and laboratory tests

b. Use available, appropriately selected screening/diagnostic methods, e.g., ultrasonography (FAST), diagnostic peritoneal lavage (DPL), computed tomography (CT) scan, or angiography, that will yield results rapidly and facilitate timely intervention[8,9]

c. Determine if bleeding is localized or due to a systemic coagulation defect

(1) The most common causes of bleeding after surgery or trauma are technical (e.g., incomplete surgical hemostasis due to an unligated vessel or an uncontrolled/unrecognized arterial injury). Do not assume that excessive bleeding is the result of a coagulopathy

(2) Causes of systemic coagulation defects include thrombocytopenia, platelet dysfunction, excessive fibrinolysis, dilution of clotting components, excessive anticoagulation, inadequate heparin neutralization, disseminated intravascular coagulation, congenital deficiencies (e.g., protein C, protein S, Factor V Leiden)[10,11]

3. Prompt intervention to stop bleeding

a. Control blood loss as quickly as possible by any means necessary. Temporizing measures should not delay definitive interventions to stop bleeding[12]

b. Consider less invasive approaches to control bleeding[13,14] (e.g., angiographic, pharmacological, endoscopic)

c. Early surgical exploration is mandatory, even if the patient is anemic, if there is evidence of ongoing bleeding or potential bleeding that can be controlled operatively or if imaging procedures are unsuccessful or may delay definite diagnosis and result in prolonged blood loss[15-19]

d. Employ techniques to control hemorrhage that can be rapidly applied.[20,21] Use a combination of bleeding control strategies[22,23] (e.g., pelvic sheet, damage control surgery, packing, external fixation, angiography and embolization, skeletal traction)

4. "Damage control" strategy for massive blood loss[24]

a. Damage control as a therapeutic procedure should be anticipated and implemented as early as possible. Surgical intervention should be simple, quick, and well performed.[25] Damage control laparotomy includes limited surgery (e.g., staples, clamps, rapid sewing) for control of hemorrhage and/or contamination, packing, temporary abdominal closure, resuscitation in ICU, and later reoperation for definitive repair[26-28]

b. Consider angiographic embolization as an adjunct

5. Control other sources of blood loss

a. Screen for concomitant sources of occult blood loss and injuries that could present later

b. Consider control of low-grade blood loss such as gynecological hemorrhage (e.g., menstrual bleeding, menorrhagia), hemorrhoids, GI lesions

6. Early management of sepsis and septic shock[29]

a. Judicious fluid resuscitation[30]

b. Early initiation of appropriate antimicrobial therapy[31]

c. Adequate source control[32]

d. Glucocorticoid replacement in patients with adrenal insufficiency[33,34]

e. Intensive insulin therapy/tight glycemic control[35,36]

Notes:

1. Blood transfusion has not been shown to improve oxygen consumption in septic patients.[37-40]
2. Drotrecogin alfa (recombinant activated protein C) is associated with a significant bleeding risk.

7. Prompt management of disseminated intravascular coagulation (DIC)

a. Early identification and urgent reversal of the underlying disease or process triggering the coagulopathy[41,42] (e.g., antibiotic therapy, abscess drainage in bacteremia)

b. Consider use of recombinant activated factor VIIa (rFVIIa)[43-46] or cryoprecipitate

C. Expeditious Angiographic Embolization[47-50]

1. Prompt arrest of bleeding

a. If bleeding is suspected but the source is not obvious, employ early angiography and embolization[51,52]

2. Preemptive embolization therapy

a. Consider early radiographic evaluation and prophylactic angioembolization for injuries that may not currently be bleeding but with potential for deterioration or delayed hemorrhage[53,54]

D. Permissive Moderate Hypotension During Bleeding[55,56]

1. In uncontrolled bleeding, normalization of blood pressure can be detrimental

a. There is evidence that elevation of blood pressure to preinjury levels (e.g., by fluid resuscitation, pressor medications) before definitive control of bleeding may result in progressive and repeated rebleeding[57,58] from uncontrolled hemorrhage sites by inhibiting spontaneous hemostasis or disrupting initial protective soft thrombus[59,60]

b. Permissive hypotension causing low-normal cerebral perfusion pressure in the absence of head injury has not been shown to be harmful[61,62]

2. Controlled/limited fluid resuscitation

a. In patients with acute life-threatening hemorrhage, consider tolerance of mild to moderate hypotension, i.e., blood pressure at the lowest possible level that maintains tissue perfusion (e.g., MAP of 50-70 mm Hg in a normotensive patient without severe head injury)[63-65]

Notes:

1. MAP (mean arterial blood pressure) is a better reflection of organ perfusion than the systolic pressure.
2. Patients with severe chronic hypertension may be relatively hypotensive even when the MAP exceeds 70 mm Hg.
3. To minimize the risk of provoking bleeding, adequate vital organ perfusion (cerebral, coronary, renal) can be maintained for short periods with moderate underresuscitation.

E. Blood Pressure Management

1. Slow, gradual return to normal blood pressure after control of bleeding

a. Moderate postoperative hypotension (systolic blood pressure of 80-90 mm Hg in a normotensive patient) is sufficient to maintain vital organ perfusion and avoids a hypertensive overshoot with the risk of precipitating further hemorrhage[66]

2. Avoid hypertension

a. Consider pharmacological control of blood pressure to avoid hypertension and possible rebleeding[67,68]

3. Management of hypotension

a. To maintain blood pressure in a hemorrhaging patient, stop the bleeding

F. Pharmacological Enhancement of Hemostasis[69]

1. Systemic agents to augment hemostasis and clotting factor activity

a. **Tranexamic acid**[70-72] (e.g., Cyklokapron®)

b. **Epsilon-aminocaproic acid**[73-75] (e.g., Amicar®)

c. **Aprotinin**[76,77] (e.g., Trasylol®)

Note: In surgical patients, aprotinin or desmopressin may reduce bleeding due to acquired platelet dysfunction.[78,79]

d. **Desmopressin**[80,81] (e.g., DDAVP®)

Notes:

1. Desmopressin may decrease bleeding in patients *with otherwise normal hemostatic function* by improving platelet adhesion to sites of vascular injury[82,83] and increasing plasma levels of coagulation factor VIII and vWF.[84]
2. Desmopressin infusion causes a transient dose-dependent increase in plasminogen activator activity. Consider coincident use of an antifibrinolytic agent such as tranexamic acid for clinically significant fibrinolysis.[85,86]

e. **Conjugated estrogens**[87-89] (e.g., Premarin®)

f. **Vitamin K**[90,91] (phytonadione)

Notes:

1. Consider prophylactic administration of vitamin K.[92,93]
2. Vitamin K deficiency may occur due to malabsorption, administration of broad-spectrum antibiotics, anticoagulants, and other drugs (e.g., salicylates, quinidine, quinine).

g. **Recombinant activated factor VII (rFVIIa)** (e.g., NovoSeven®, NiaStase®)

(1) Early use of rFVIIa can be lifesaving in patients without preexisting coagulopathy who are bleeding at sites with limited possibilities for mechanical hemostasis[94-96]

(2) Recombinant FVIIa has been reported to reduce blood loss in nonhemophilia patients in various clinical situations including trauma,[97-99] postoperative bleeding,[100-102] obstetric hemorrhage,[103] liver disease,[104,105] renal failure,[106,107] thrombocytopenia,[108-110] congenital or acquired platelet function disorders,[111-113] and acquired bleeding tendencies[114] (See ***1.I.2.*** for rFVIIa and drug-induced coagulopathies.)

(3) Doses ranging from 60 µg/kg to 212 µg/kg have been used successfully in nonhemophilia patients in published case reports. Higher doses have been safely used in hemophilia patients.[115] Both the dose and the administration interval may require adjustment[116,117]

(4) Although certain characteristics of rFVIIa appear likely to increase the risk of thrombosis, analysis of existing clinical data suggests a highly favorable safety and efficacy profile[118]

h. **Clotting factor (concentrate) replacement therapy**[119] (Factors VIIa, VIII, IX are available as recombinant products[120])

i. **Prothrombin complex concentrate (PCC)**[121] (e.g., Autoplex®)

j. **Cryoprecipitate**[122]

2. Topical hemostatic agents

a. **Tissue adhesive/fibrin glue/sealant**[123-125] (e.g., Beriplast®, Hemaseel®, Tisseel®)

b. **Collagen**[126,127] (e.g., Avitene®, CoStasis®, Instat®)

c. **Gelatin-based hemostats, gelatin-thrombin matrix**[128-130] (e.g., FloSeal®, Gelfoam®, Surgifoam®)

d. **Oxidized cellulose**[131] (e.g., Oxycel®, Surgicel®)

e. **Thrombin, thrombin-soaked packing**[132] (e.g., Thrombogen®, Thrombostat®)

Note: Pharmacological hemostatic agents should be considered when bleeding is generalized or the bleeding site is not accessible.

G. Autotransfusion/Blood Cell Salvage

1. Intraoperative[133-135]

2. Postoperative[136-138]

H. Rapid Warming/Maintenance of Normothermia

1. Use active and passive warming strategies[139,140]

a. Heat loss in patients occurs by various routes (convection, radiation, and evaporation). Endeavor to control/minimize potential mechanisms of thermal loss. Also consider elevation of the ambient temperature

2. Warm intravenous fluids[141]

Notes:

1. Hypothermia may increase blood loss due to impairment of platelet and coagulation protein function.[142,143]
2. Restoration of normothermia may also reduce risk of infection.[144]

I. Hemostasis/Anticoagulation Management

1. Individualized protamine/heparin management after CPB

2. Management of coagulation disorders

a. When unrecognized or undertreated at an early phase, disorders of coagulation or erythropoiesis can lead to irreversible conditions

b. Consider point-of-care coagulation monitoring[145]

3. For urgent reversal of anticoagulation

a. Vitamin K (phytonadione)[146,147]

b. Prothrombin complex concentrate[148-150]

c. Recombinant coagulation factor VIIa[151-154] or IX[155,156]

d. Consider desmopressin (See ***1.F.1.d.***)

J. Prophylaxis of Upper Gastrointestinal Hemorrhage[157,158]

1. Pharmacological Agents

a. **Histamine H_2-receptor antagonists**[159-161] (e.g., ranitidine)

Note: H_2-blockers have been associated with thrombocytopenia in some patients.

b. **Cytoprotective agents**[162] (e.g., sucralfate)

Note: Sucralfate appears to be less effective than H_2-blockers but is associated with fewer side effects, such as nosocomial pneumonia. Sucralfate may reduce the bioavailability of other drugs if administered simultaneously.

c. **Proton pump inhibitors**[163,164] (e.g., omeprazole, lansoprazole, pantoprazole)

Note: Preliminary studies show that proton pump inhibitors are most effective and have few adverse effects.

2. **Enteral nutrition**[165,166]

K. Prophylaxis and Management of Infection

1. **Judicious antibiotic prophylaxis**[167,168]
   a. Diagnostic precision and optimal antibiotic therapy
      (1) Appropriate single or combination antibiotic regimen[169,170]
2. **Prevention and early management of infection**
   a. Catheter-related bloodstream infections[171,172]
      (1) Aseptic technique, timely discontinuation[173]
      (2) Antibiotic-impregnated catheters[174,175]
   b. Surgical-site or wound infections[176,177]
      (1) Avoid secondary contamination (e.g., colon, rectum)
3. **Hand hygiene**[178,179]

L. Blood Conservation in Burn Care

1. **Rigorous hemostasis and surgical technique**[180,181]
2. **Judicious wound management**
   a. Early wound excision[182-184]
   b. Staged/limited debridement[185]
   c. Consider alternatives to autografting[186,187]
3. **Arterial tourniquets during extremity debridement**[188,189]
4. **Pharmacological hemostatic agents (See *1.F.*)**
   a. Topical vasoconstrictors[190-193] (e.g., epinephrine)
   b. Vasopressin/terlipressin (IV)[194-196] (e.g., Pitressin®)
   c. Recombinant activated factor VII (rFVIIa)[197]
   d. Topical hemostatic agents[198-201] (e.g., fibrin sealant, thrombin)
   e. Calcium alginate[202]
5. **Acute normovolemic hemodilution**[203]
6. **Blood salvage**[204,205]
7. **Controlled intraoperative hypotension**[206]
8. **Strict control of hypertension in early postoperative period**
   a. Judicious fluid resuscitation[207]
9. **Prevention of hypothermia (See *1.H.*)**
10. **Early erythropoietic stimulant therapy**[208-211] **(See *5.A.*)**
    a. Nutritional supplementation to support erythropoiesis[212-214]

Note: Employ a multimodality blood conservation strategy for the management of burn wounds.[215-218]

2. MINIMIZATION OF IATROGENIC BLOOD LOSS

A. Restricted Diagnostic Phlebotomy[219,220]

1. **Perform only essential tests**[221]
   a. Eliminate routine, multiple daily phlebotomies. Order only tests or procedures that are likely to alter management[222]
2. **Coordinate and consolidate blood tests**[223,224]
   a. Minimize frequency of diagnostic sampling[225]
   b. Multiple tests per sample[226]
      (1) Consider performing tests using stored blood specimens
3. **Minimize volume of diagnostic blood sampling**
   a. Pediatric (small-volume) phlebotomy tubes for adults[227,228]
   b. Blood microsampling/microchemistry techniques[229-232]
   c. Minimally invasive monitoring (e.g., pulse oximetry, transcutaneous oximetry, sublingual capnometry, end-tidal CO_2 monitoring)[233,234]
   d. Restrict use of indwelling lines; remove as early as possible[235,236]
   e. In-line blood reservoirs; eliminate purge discard volume[237,238]

B. Reduce Nondiagnostic Blood Loss

1. **Invasive Medical Procedures**
   a. Minimize procedure-associated bleeding during insertion of arterial or central venous catheters, hemofiltration, dialysis, cardiac catheterization[239,240]
   b. Judicious performance of invasive procedures in patients receiving anticoagulants or platelet aggregation inhibitors

C. Cautious Thromboembolic Prophylaxis

1. **Consider alternatives to anticoagulants/antiplatelet agents**
   a. Since bleeding has more serious implications than morbidity associated with thrombotic complications, anticoagulants should be used with extreme caution, especially in situations of increased hemorrhagic risk.[241-243] Patients with recent trauma or surgery should first achieve hemostasis (e.g., after 36-72 hours)

b. The risk of bleeding is closely related to the intensity of anticoagulation therapy, adequacy of clinical monitoring of dosage, route of administration, concurrent pharmacotherapy, the patient's age and underlying clinical status

c. For patients at high risk for venous thromboembolism and bleeding, consider mechanical prophylaxis (e.g., intermittent pneumatic compression devices, graduated compression stockings, inferior vena cava [IVC] filters) alone or in combination with low-dose pharmacological anticoagulation[244-248]

d. For patients at low or moderate risk for bleeding and thromboembolism, consider mechanical prophylaxis alone or in combination with reduced-intensity anticoagulation therapy (e.g., low-dose unfractionated heparin, low-molecular-weight heparin, or alternatives with short half-lives). Maintain close clinical monitoring of dosage to keep the INR at the lower limit of the therapeutic range[249]

e. Consider mechanical fragmentation for management of large pulmonary embolisms[250]

Note: After withholding anticoagulants, avoid performing surgery as soon as the INR or PTT has normalized, as these tests can normalize when coagulation factors reach 30 to 40% of normal concentrations.[251]

D. Anticipation of Adverse Effects of Medications

1. Anemia, thrombocytopenia, coagulopathy[252]

a. Consider the clinical setting (medication history, underlying disorder, duration of ICU stay, and time of onset)[253-255]

b. NSAIDs (e.g., ketorolac), platelet aggregation inhibitors, anticoagulants, antibiotics, beta blockers, calcium channel blockers, and furosemide may be associated with thrombocytopenia, platelet dysfunction, or hypoprothrombinemia

c. Antibiotics (e.g., beta-lactams, rifampin), sulfonamides, antineoplastic agents, and quinidine may be associated with iatrogenic anemia and thrombocytopenia[256]

2. Management of multiple medications/ drug interactions

a. Some drugs (e.g., NSAIDs, salicylates, cephalosporin/penicillin antibiotics, lipid-lowering medications, corticosteroids, herbal preparations) may potentiate the effects of anticoagulation medications[257-259]

b. NSAIDs and other medications may affect platelet, kidney, or bone marrow function or blunt the erythropoietic response

c. Consider dose reduction, drug discontinuation, or drug substitution (e.g., substitution of H2-blocker with sucralfate or a proton pump inhibitor). In polypharmacy, consider medications with fewer potential drug interactions

3. Minimize drug delivery errors[260,261]

a. Careful consideration of dosage and timing of administration of new or unfamiliar medications

3. OPTIMIZATION OF OXYGEN DELIVERY

A. Assess Perfusion and Tissue Oxygenation

1. Evaluate indexes of global perfusion

a. Markers of hypoperfusion include oliguria, diminished sensorium, lactic acidosis, base excess/deficit, and tachycardia. Also assess parameters of oxygen transport: oxygen delivery (DO_2), oxygen consumption (VO_2), mixed venous oxygen saturation (SvO_2), tissue CO_2 tension (PCO_2)

2. Evaluate indexes of regional perfusion

a. Adequacy of regional perfusion can be assessed by evaluating markers of organ function. These include evidence of myocardial ischemia (ST-segment abnormalities), renal dysfunction (decreased urine output and an increased blood urea nitrogen to creatinine ratio), gastric mucosal hypoxia, and central nervous system dysfunction (altered mental state)

Notes:

1. Observe trends in a combination of indexes of tissue perfusion/hypoxia[262], particularly in response to interventions.

2. Perfusion markers such as SvO_2, blood lactate, base excess/deficit, and/or PCO_2 (e.g., gastric or sublingual tonometry) may identify patients who are in compensated shock, i.e., underperfused but still with relatively normal vital signs.

B. Augment Cardiac Output

1. Optimize circulating volume[263-265]

a. Optimization of cardiac output and volume status requires understanding of the active pathophysiological processes and knowledge of the patient's cardiac performance. The MAP, heart rate, breathing pattern, urine output, and fluid balance should be assessed

b. Fluid resuscitation must be individualized based on physiological parameters that include continual reassessment of tissue perfusion and oxygenation as well as hemodynamic function using a combination of indexes rather than predetermined endpoints such as blood pressure or heart rate

c. If correctly volume-resuscitated, the anemic patient will have an increased cardiac output in response to fluids.[266] The absence of such an increase may be a sign of adequate intravascular volume expansion

d. If in doubt about the volume status or cardiac output of an anemic patient, perform assessment appropriate to the clinical situation, e.g., judicious fluid challenge, lithium dilution technique (e.g., LiDCO™),[267] esophageal Doppler echocardiography,[268] transpulmonary thermodilution technique (e.g., PiCCO™),[269] or pulmonary artery catheter, to optimize fluid management[270-272]

(1) Variations in either systolic arterial pressure or pulse pressure with the ventilatory cycle may indicate volume depletion in a mechanically ventilated patient[273,274]

(2) If response to intervention, as indicated by noninvasive monitoring methods, is appropriate, then less invasive monitoring can be continued. If the response is not appropriate, then invasive monitoring may be warranted

e. Avoid circulatory overload, especially in profoundly anemic patients.[275-277] Fluid administration by rigid adherence to a protocol without ongoing clinical judgment should be avoided

f. Even during relative hypotension, microcirculatory blood flow and oxygenation are not always dependent on blood pressure.[278-280] Vasoactive drugs should be used to improve hypoperfusion. Artificially raising arterial pressure to an arbitrary goal with vasoactive drugs may shut down microcirculatory beds rather than improve perfusion

g. In the septic patient with a low systemic vascular resistance (SVR), consider adding a pressor agent to improve vascular tone and tissue oxygen delivery[281]

2. Nonblood volume expanders[282]

a. Crystalloids

(1) Normal saline

(2) Balanced electrolyte solutions (Ringer's lactate/ Hartmann's)[282-284]

(3) Hypertonic saline[285-287]

b. Colloids[288]

(1) Starch solutions[289] (in saline or balanced electrolyte solutions)

i. High-molecular-weight starches[290,291] (hydroxyethyl starch, e.g., Hespan®, Hextend®)

ii. Medium-molecular-weight starches[292,293] (pentastarch, e.g., Pentaspan®, HAES-Sterile®)

iii. Low-molecular-weight starches[294,295] (quadrastarch, e.g., Voluven®)

(2) Gelatin[296-298] (e.g., Haemaccel®, Gelofusine®)

(3) Dextran[299]

c. Oxygen therapeutics[300-302] (when available for clinical use)

3. Judicious fluid replacement

a. Volume management strategy[303-305]

(1) In a hypovolemic patient, the volume replacement strategy (timing, rate of administration, and amount) may be more important than the choice of fluid.[306] The risk of mild-to-moderate hypovolemia must be balanced with the risk of inciting further bleeding by excessive blood pressure elevation and hemodilution

(2) Judicious volume management at low hemoglobin levels may optimize microvascular flow and oxygenation as well as increase tolerance of anemia[307,308]

b. Coagulation issues

(1) In moderate amounts, crystalloids are not associated with significant side effects, particularly on hemostasis. There is laboratory evidence that infusion of crystalloids may induce a state of hypercoagulability.[309-311] Large volumes of crystalloids are more likely to cause edema formation, impair pulmonary function, and lead to dilutional coagulopathy

(2) High-molecular-weight hydroxyethyl starches (HES) (e.g., 450 kDa) with high degrees of substitution (DS: 0.7), other highly substituted HES preparations, and dextrans may in a dose-dependent manner increase the risk of bleeding in patients who have either congenital or acquired coagulation abnormalities[312-315]

(3) Pentastarch and low-molecular-weight starches with low substitution ratios are associated with fewer effects on coagulation than first-generation HES[316-319]

(4) While all colloids and crystalloids dilute platelets and coagulation factors, dextrans are associated with an increased bleeding tendency by inhibiting platelet aggregation, reducing activation of Factor VIII, and promoting fibrinolysis[320]

(5) Desmopressin may partially offset the antithrombotic effect and increased bleeding risk associated with hydroxyethyl starches and dextrans[321,322]

c. Microcirculation issues

(1) Medium- and low-molecular-weight starches may be more effective in optimizing macro- and microcirculation than crystalloids and other colloids.[323-326] In critically ill patients at risk of capillary leak syndrome, medium-molecular-weight starches may be more effective than other colloids in avoiding whole-body fluid overload and edema[327,328]

d. **Other issues**

(1) Administration of large amounts of saline-based fluids has been associated with coagulation abnormalities/bleeding, decreased urine output, and hyperchloremic metabolic acidosis, which may be clinically relevant in some patients[329,330]

(2) Infusion of large quantities of lactated Ringer's has been associated with hyponatremia and metabolic alkalosis[331]

(3) Dextrans and gelatin solutions have been associated with life-threatening hypersensitivity reactions

(4) Dextrans[332] and high-molecular-weight hydroxyethyl starches[333] may be associated with adverse effects on renal function in patients with kidney disease[334]

(5) Albumin fluid resuscitation or supplementation in hypoalbuminemic critically ill patients has not been shown to be of benefit[335-337]

C. Early Enhancement of Oxygenation[338,339]

1. Supplemental oxygen (increase FiO_2)[340-344]

2. Early optimization of cardiac output[345]

a. Optimize cardiac preload, afterload, and contractility (fluid optimization, inotropic therapy, vasodilator or vasopressor agents)

(1) The effects of vasoactive drugs vary among patients. Monitor response and titrate therapy

b. In the severely anemic patient, when oxygen transport cannot be sufficiently enhanced by patient positioning, oxygen therapy, and augmentation of cardiac output, increased doses of sedation, analgesia, or other measures such as therapeutic cooling may be required to reduce oxygen demand

Notes:

1. The sooner tissue hypoxia is detected and corrected, the greater the chance that outcome will be improved.[346]
2. In the severely anemic patient, the amount of oxygen dissolved in plasma, normally a small fraction of the oxygen carried, may contribute substantially to the oxygen content and thus support life temporarily. Because hypoxemia poses greater immediate risks than oxygen toxicity or hypercapnia, such a patient may warrant the risk attendant to supranormal fractions of inspired oxygen.[347,348]
3. Use of mechanical ventilation or HBO therapy to achieve a very high arterial oxygen tension (PaO_2) is potentially lifesaving in the patient with severe anemia.
4. Ensure appropriate airway humidification and warming.

3. Mechanical ventilation

a. For patients with insufficient response to other measures to improve oxygenation (i.e., correction of circulating volume, vasoactive agents, inotropes), employ sedation and ventilatory support (e.g., CPAP, IPPV, PEEP)

b. Consider use of a combination of supplemental/adjunctive techniques to improve oxygenation in severely ill patients (e.g., prone positioning/rotation,[349,350] inhaled nitric oxide/prostacyclin,[351,352] permissive hypercapnia,[353] surfactant replacement,[354] high-frequency oscillatory ventilation[355,356])

(1) Nitric oxide[357] may cause transient inhibition of platelet adhesion. Closely monitor hemostasis, especially patients at risk for hemorrhage

(2) Hypercapnia may induce hyperventilation, vasoconstriction, and bleeding

c. Consider semirecumbent positioning of patient to reduce the risk of ventilator-associated pneumonia (VAP)

4. Hyperbaric oxygen (HBO) therapy[358-362]

a. Indications for HBO therapy in severe anemia:

(1) Adequate oxygenation cannot be achieved by simultaneous use of multiple techniques, i.e., 100% oxygen, increasing cardiac output, adjusting mechanical ventilation strategies, and reducing oxygen consumption (deep sedation and paralysis)

(2) Determination of tissue hypoxia by assessment of trends in markers of perfusion (see **3.A.**) as well as clinical evaluation

b. Employ intermittent "air breaks" as required by HBO protocol[363-365]

c. Consider adjunctive antioxidant therapy[366,367] (e.g., tocopherol)

(1) Monitor closely to determine appropriate HBO dosage and onset of adverse effects (e.g., pulmonary or CNS function)

4. MINIMIZATION OF OXYGEN CONSUMPTION

A. Appropriate Analgesia[368-370]

B. Sedation and Muscle Relaxants[371-375]

1. Administer lowest effective dose for the shortest duration of analgesia and sedation

a. Close monitoring and titration of medications

b. If a profound level of sedation is warranted, ensure adequate oxygen delivery to avoid tissue hypoxia[376]

c. Judicious use of agents associated with respiratory depression

2. Consider neuromuscular blockade[377-379]

a. Decrease oxygen consumption by reduction of metabolic rate and prevention of shivering, agitation, anxiety[380,381]

C. Mechanical Ventilation

D. Thermal Management

1. Actively warm hypothermic patients. Cool febrile patients[382]

a. Consider trial of NSAIDs when not contraindicated

2. Consider therapeutic hypothermia (32°C-33°C)

a. Use of therapeutic cooling has been reported in ICU patients with severe anemia[343,379,383] (to reduce tissue oxygen requirements and lower metabolic rate) and for cerebral protection in subgroups of patients.[384-386] The clinician should use clinical judgment, taking into consideration the risk of bleeding

5. OPTIMIZATION OF ERYTHROPOIESIS

A. Early Erythropoiesis-Stimulant Therapy[387-390]

1. Dosage

a. Outside the setting of chronic renal failure, reported recombinant erythropoietin (rHuEPO) doses range from 150 to more than 1000 U/kg/wk, with various dosing intervals, to accelerate recovery from acute anemia[391,392]

b. A randomized, controlled trial involving 160 medical and surgical ICU patients demonstrated that rHuEPO at a dose of 300 U/kg daily for 5 days and then on alternate days for a minimum of 2 weeks significantly reduced the rate of blood transfusion[393]

c. Some patients require higher rHuEPO doses to achieve an adequate response. In the critically ill, there is evidence suggesting that a rHuEPO dosing interval of 24-72 hours (e.g., 150-300 U/kg) may be more effective than single weekly doses (e.g., 600 U/kg). If the cause of poor response to rHuEPO cannot be identified or corrected, consider using a higher dose[394-399]

d. For severe anemia, concomitant IV iron may potentiate the response to erythropoietic agents.[400-402] Aggressive anemia therapy should not be delayed until the hemoglobin level falls to critical levels[403]

e. Erythropoietin has been used in infants and children with no significant adverse reactions.[404,405] rHuEPO administration of up to 2,000 U/kg/day in divided doses has been safe and well tolerated in children[406]

f. Rate of response to multiple-dose erythropoietic agents is dose dependent and variable among individuals

g. Concomitant anabolic androgen therapy may potentiate the response to erythropoietic agents by increasing sensitivity of erythroid progenitor cells[407-410]

2. Route of administration

a. For severe acute anemia, consider initial IV administration of erythropoietin followed by subcutaneous dosing. The IV route achieves higher plasma erythropoietin concentrations, while the subcutaneous route provides more sustained levels[411-415]

b. In critical illness, poor subcutaneous absorption (e.g., due to edema or alterations in blood flow) may impair response to erythropoietin therapy.[416,417] Consider IV administration of half-doses of erythropoietin every 12 hours[418]

3. Anemia of critical illness

a. Critical illness is associated with deficient erythropoietin production and a blunted response to endogenous erythropoietin[419-422]

b. Irrespective of the endogenous serum EPO level, the erythropoietic system in critically ill patients remains responsive to high-dose erythropoiesis-stimulant therapy[423,424]

4. Other considerations

a. Early initiation of erythropoietic stimulant therapy will address the lag time to adequate response by the bone marrow

b. Erythropoietin may produce an increase 2,3-DPG content of red blood cells (RBCs) to improve oxygen delivery[425]

c. Recombinant erythropoietin may produce a moderate, transient dose-dependent rise in platelet reactivity and in the platelet count, within the normal range, during treatment. This regresses during the course of continued therapy[426-428]

d. Aside from iron deficiency, factors associated with a poor response to erythropoietic stimulant therapy include infection, inflammatory or malignant processes, occult blood loss, and hematologic disease[429,430]

e. In patients with chronic kidney disease or hypertension, erythropoietic agents have been associated with increased hypertension. Monitor for hypertension and consider initiation or increase in antihypertensive therapy

f. Data is emerging that systemic administration of recombinant erythropoietin may have a neuroprotective effect in head trauma and stroke patients[431] as well as cardio- and renoprotective effects[432,433] independent of the hemoglobin level

g. Pure red-cell aplasia is a rare complication restricted mainly to chronic renal failure patients receiving long-term subcutaneous erythropoietin therapy (i.e., renal dialysis patients)[434]

B. Iron Replacement and Hematinic Support

1. Iron replacement

a. Functional or absolute iron deficiency is a common cause of limited response to erythropoietin

b. Virtually all patients will require supplementary iron therapy to maximize response to multiple-dose erythropoiesis stimulant therapy.[435,436] Parenteral iron should be considered if oral iron fails to support accelerated erythropoiesis[437-440]

Notes:

1. There is evidence to suggest that iron may be safely administered to critically ill patients receiving erythropoietic agents to support erythropoiesis.[441-443] Patients at high risk of bacterial infection should already be receiving adequate and appropriate antimicrobial agents.
2. In critical illness, iron metabolism is abnormal (e.g., low iron levels, normal or elevated serum ferritin levels); monitoring of reticulocyte status may provide a better indication of deficiency of iron or erythropoietic stimulation.
3. Consider iron sucrose/saccharate, iron sorbitol, or gluconate complex (or other parenteral iron products) instead of iron dextran to reduce the risk of anaphylactic reaction.[444,445] Consider using a premedication strategy if using iron dextran.[446]
4. Systemic inflammation (e.g., postoperative) impairs oral iron absorption and release of storage iron.[447] However, intravenous iron may be rapidly utilized.[448]
5. If using iron dextran, administer a test dose. If the patient is simultaneously receiving vasoactive support (epinephrine), the test result may be invalid or misleading.
6. After the test dose, administer iron dextran by dilution in normal saline (e.g., 500 ml) and slow IV infusion (e.g., over 1-8 hours) to reduce the risk of adverse reaction.[449-451]

2. Consider folic acid, vitamin B_{12} administration[452,453]

C. Nutrition

1. Early enteral feeding, as tolerated[454,455]

a. Consider elevating head of bed, where possible up to 45 degrees, to reduce risk of gastroesophageal regurgitation and pulmonary aspiration[456]

2. Parenteral nutrition for patients who cannot be fed enterally[457]

3. Protein supplementation to support erythropoiesis[458]

6. TOLERANCE OF ANEMIA

A. Compensatory Mechanisms in Normovolemic Anemia[459]

1. Increased cardiac output (stroke volume and heart rate)

2. Redistribution of blood flow

a. Alterations in distribution of blood flow to augment the coronary and cerebral (vital organ) perfusion

3. Increased tissue oxygen extraction

4. Decreased oxygen affinity of hemoglobin

a. Oxygen delivery to tissues is increased due to a rightward shift of the oxygen-hemoglobin dissociation curve as a result of an increase in 2,3-DPG levels. Time is required for this adaptation

B. Acceptance of Normovolemic Anemia

1. Moderate normovolemic anemia is well tolerated

a. In hemodynamically stable critically ill patients with coexisting disease, moderate euvolemic anemia is well tolerated[460-463]

(1) Hemodilution may have beneficial effects, such as less organ failure attributable to improved oxygen delivery at the microcirculatory level and fewer thrombotic complications as a consequence of less platelet aggregation

Notes:

1. A randomized, controlled trial involving 838 euvolemic critically ill patients demonstrated that a restrictive RBC transfusion strategy (hemoglobin level between 70 and 90 g/L) was associated with significantly lower mortality rates and was at least as safe and probably superior to a liberal transfusion strategy (hemoglobin level between 100 and 120 g/L) in critically ill patients, including most patients with cardiovascular disease.[464]
2. In a prospective, randomized, double-blind pilot study investigating the effects of transfusion of "fresh" or "stored" RBCs in ventilated euvolemic critically ill anemic (hemoglobin concentration=90 g/L) patients, at 5 hours posttransfusion neither type was associated with an improvement in tissue oxygenation.[465]

2. Cardiac output increase/reduced blood viscosity[466]

a. Under conditions of normovolemic anemia, decreased blood viscosity results in decreased systemic vascular resistance and increased venous return and cardiac output. Decreased blood viscosity may also lower the risk of thrombosis[467]

b. Transfusion of stored RBCs may reduce cardiac output and tissue perfusion by increasing blood viscosity[468,469]

3. Management of patients with cardiovascular disease[470]

a. For patients with unstable coronary syndromes, consider use of angiotensin converting enzyme (ACE) inhibitors,[471] beta blockers,[472] and other agents.[473-475] Heparin, antiplatelet agents, or aspirin therapy should be used with caution in patients at risk for bleeding

4. 10/30 transfusion threshold has no scientific basis[476-480]

a. Studies in healthy, resting adults have shown good oxygen delivery and tolerance of normovolemic anemia to a hemoglobin level of 45 g/L[481,482]

b. Hemodilution to a hematocrit of 15% is well tolerated in anesthetized adult patients[483-485]

c. The efficacy of RBC transfusion has not been demonstrated in a controlled, prospective study.[486] The data preclude any scientific conclusion in support of any fixed transfusion trigger or threshold[487-489]

C. Effects of Storage on Red Blood Cells[490]

1. Decreased deformability

a. Decreased deformability of red blood cells may cause microcirculatory occlusion and tissue ischemia in some organs[491-494]

2. Impaired oxygen unloading capacity

a. Decreased oxygen unloading capacity of hemoglobin (increased oxygen affinity) due to decreased levels of 2,3-DPG. This may be reversible within 24-48 hours[495,496]

3. Other adverse clinical outcomes

a. Allogeneic blood transfusion is associated with an increased risk of infection[497-500] and increased length of stay[501] and is independently associated with higher mortality[502-506]

b. Allogeneic transfusion is also associated with prolonged mechanical ventilation,[507,508] impaired wound healing,[509] inflammation,[510] and transfusion-related acute lung injury (TRALI)[511,512] in ICU patients

FACTORS AFFECTING OXYGENATION

Factor	Modulated by	Therapy
Cardiac output	• Intravascular/circulating blood volume • Cardiac function • Negative inotropic agents	• Volume and fluid management • Vasoactive drugs • Inotropic support
Arterial oxygenation	• Pulmonary function • Fraction of inspired oxygen (FiO_2)	• Supplementary oxygen • Patient positioning • Mechanical ventilation
Oxygen affinity	• Temperature • CO_2 level (PCO_2) • pH • 2,3-DPG	• Oxygen release to tissues enhanced with increased temperature, CO_2, acidosis, and 2,3-DPG concentration (rightward shift in the oxyhemoglobin dissociation curve)
Regional blood flow	• Vessel patency • Microcirculation • Blood viscosity	• Volume and fluid management • Vasoactive drugs
Oxygen consumption	• Sympathetic activation (pain, agitation, anxiety, shivering) • Metabolic rate (increased by fever, infection, systemic inflammatory response, burns, trauma, surgery, etc.) • Mechanical ventilation	• Analgesia, sedation, or paralysis • Thermal management

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Database Abbreviations:
PMID: Medline®/PubMed® Unique Identifier (Index Medicus)
EMBASE: Embase® Accession Number (Excerpta Medica)
ISI: Institute for Scientific Information IDS Number

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