Clinical Strategies for Avoiding and Controlling Hemorrhage and Anemia Without Blood Transfusion in Surgical Patients*

GENERAL NONBLOOD MANAGEMENT PRINCIPLES

1. **Formulate a detailed and individualized clinical management plan** to minimize blood loss and treat anemia. Comprehensive prospective planning should make optimal use of a combination of modalities to prevent or respond to hemorrhage or anemia. A blood conservation program cannot depend on a single modality.
2. Obtain informed **consent for anticipated or potential procedures.** Discuss the risks and benefits (both short- and long-term) of proposed interventions with the patient/family.
3. Considering the risk of transfusion and available blood management options, refer patient to another institution if better resources are available elsewhere.
4. Employ **a multidisciplinary team approach.** Collaborate with other disciplines to develop the most appropriate blood management strategy. Communicate management plan to all team members, assigning clear roles and responsibilities. Maintain ongoing communication regarding patient management, especially where there are multiple conditions treated by multiple physicians.
5. Maintain **surveillance for blood loss or physiological deterioration.** Early recognition and involvement of appropriate senior staff and prompt action to prevent/control abnormal bleeding are essential. The threshold for intervention should be lower than for patients who will accept allogeneic blood transfusion.
6. Prompt action to **secure hemostasis in the actively bleeding patient** who refuses blood transfusion is lifesaving. Use diagnostic tests that will provide rapid results, minimize delays, and thus reduce blood loss. In general, avoid a "watch and wait" approach to the bleeding patient.
7. Exercising **clinical judgment,** be prepared to modify routine practice when conditions change.
8. Consult promptly with senior specialists with experience in managing patients without allogeneic transfusion at an early stage if complications arise.
9. Transfer a stabilized patient, if necessary, to a major center before the patient's condition deteriorates.

GENERAL THERAPEUTIC PRINCIPLES

1. Adopt a **proactive approach including anticipation,** preparation, and management steps to prevent uncontrolled blood loss, utilizing a combination of interventions.
2. Perform a thorough preoperative workup. **Methodical history taking, physical examination, and judicious diagnostic tests** should be part of an integrated assessment approach to facilitate perioperative planning. Identify abnormalities of coagulation and previous treatments that may increase the risk of blood loss.
3. Identify appropriate **management strategies** to optimize the patient's condition before surgery. Interventions applied prospectively to create a favorable physiological environment are more likely to result in a favorable outcome than those applied retroactively as treatment.
4. Restrict diagnostic phlebotomy. **Perform essential tests** only and use less blood for analysis.
5. Combine surgical and anesthetic **blood conservation techniques:** meticulous surgical hemostasis and minimization of blood loss, and rigorous intraoperative blood management using appropriate autologous blood procurement strategies.
6. **Optimize oxygen delivery and consider measures to minimize oxygen consumption.**
7. In trauma or postoperative patients with active bleeding, **perform immediate concomitant investigation and diagnosis and early intervention** aimed at rapidly controlling hemorrhage. Consider moderate fluid underresuscitation in the presence of uncontrolled hemorrhage.

CONTENTS PAGE

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1. CLINICAL EVALUATION/PREOPERATIVE PLANNING

A. Medical History and Physical Examination[1]

1. History of anemia
2. History of abnormal bleeding (personal and family history)[2]
   a. Congenital/acquired bleeding disorders[3,4] (known from birth; spontaneous or easy bruising; prolonged bleeding with epistaxis or minor trauma; obstetric or gynecologic history, e.g., menometrorrhagia, pregnancy)
3. Coexisting disease/injury (renal, hepatic, cardiac, or pulmonary)
4. Medical/surgical history
   a. Types of procedures and amount of blood loss (e.g., circumcision; tonsillectomy; dental extraction, especially molar)
   b. Previous treatments or factors that may increase the risk of blood loss (e.g., repeat surgery at proposed operative site, known or suspected significant adhesions, radiation therapy)
5. Identify current medications that may adversely affect hemostasis[5-7]
   a. ASA, NSAIDs, anticoagulants, platelet aggregation inhibitors (e.g., abciximab, ticlopidine), antibiotics (e.g., beta-lactams such as penicillin, ticarcillin)
   b. Prescription and nonprescription drugs containing ASA or NSAIDs[8,9]
   c. Dietary or herbal supplements that may affect coagulation[10-14]
6. Physical exam (e.g., hepatomegaly, splenomegaly, petechiae, purpura, ecchymoses, hemarthrosis, evidence of collagen-vascular defects, telangiectases, evidence of other disease associated with hemostatic dysfunction)

B. Selective Laboratory Assessment

1. Diagnosis of anemia[15-17]
   a. Complete blood count (CBC)
   b. Serum ferritin
   c. Serum vitamin B_{12}[18]
   d. Serum folate
   e. Peripheral blood smear examination
2. Judicious additional tests (if indicated by medical history, abnormal clinical data, current medications, and degree of hemostatic challenge)[19]
   a. Coagulation tests
      (1) PT, PTT, template bleeding time
      (2) Platelet function, adhesion, aggregation tests
      (3) Fibrinogen concentration
      (4) Fibrin degradation products (FDP)/D-Dimer
      (5) Specific coagulation factor assays
      (6) Assay for ristocetin cofactor activity
   b. Liver function tests
   c. Renal function tests

Notes:

1. A detailed workup may be advisable if a procedure is associated with significant blood loss.
2. If the preoperative laboratory investigation is abnormal, consider postponement of surgery until correctable abnormalities are treated.
3. In the presence of a history of abnormal or excessive bleeding or suspected platelet dysfunction, consider consulting a hematologist.

C. Management of Medications and Coagulation Status[20]

1. Avoid drug-induced coagulopathies
   a. Analgesics. Consider discontinuing drugs associated with increased bleeding complications (from 3 to 14 days preoperatively) and temporary substitution with alternate therapy (e.g., NSAIDs with short half-lives):
      (1) Aspirin/ASA and aspirin-containing compounds (discontinue at least 7 days before surgery)
      (2) NSAIDs with long half-lives (e.g., tenoxicam, phenylbutazone) (discontinue 3 to 14 days or longer before surgery)

      Note: Half-lives of NSAIDs may be increased in the elderly.
   b. Antibiotics (e.g., beta-lactams such as high-dose penicillin, ticarcillin)
2. Management of Anticoagulants
   a. Consider discontinuation or substitution (e.g., heparin instead of warfarin) of anticoagulants or antiplatelet agents before surgery. Consider medical indication for the anticoagulant, emergency nature of surgery, type of surgical procedure planned, and type of anesthetic planned
   b. Postpone nonurgent surgery for patients on anticoagulant/antiplatelet medications (some may irreversibly inhibit platelet function for up to 14 days)
   c. For urgent surgery, normalize coagulation with appropriate agents[21-24] (e.g., vitamin K, recombinant or concentrated clotting factors VIIa and IX)
   d. Consider appropriate clotting factor replacement therapy (See ***4.F.***)
3. Review other current medications
   a. Identify and discontinue dietary or herbal supplements that may affect coagulation or platelet function (See ***1.A.***5.)
   b. Review adverse reactions and drug interactions (e.g., platelet dysfunction, thrombocytopenia, bleeding, suppression of erythropoiesis, anemia)
4. Treatment for congenital/acquired hemorrhagic disorders[25]
   (See ***4.F.*** Pharmacological Enhancement of Hemostasis)

D. Management of Anemia

1. Identify and address possible causes of anemia[26]
   a. Control significant gynecological hemorrhage with preoperative hormone manipulation
2. Address iron deficiency[27] (oral/parenteral)
   a. Intravenous iron may replenish iron stores more quickly and efficiently than oral or intramuscular iron therapy.[28,29] Consider administration by saline infusion[30]
   b. Intravenous iron should be considered for patients with low iron stores, intolerance to oral iron, inadequate absorption, or noncompliance or for patients with chronic or severe blood loss.[31,32] Administer a test dose[33]
   c. Bioavailability of oral iron may be improved with concomitant administration of ascorbic acid[34]

Note: The parenteral administration of a drug or an agent (e.g., iron dextran) bears the potential for an allergic or anaphylactic reaction and should be administered with appropriate precautions. Prompt recognition of signs and symptoms of adverse drug reactions and timely management are required.

3. Recombinant erythropoietin (r-HuEPO) therapy[35,36]
   a. Response to r-HuEPO is dose dependent and varies among patients.[37] Increase dosage or change route of administration to improve response[38]

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b. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by r-HuEPO[39-41]

c. r-HuEPO has been reported used in infants and children with no significant adverse reactions[42-44]

d. Identify and treat factors associated with a diminished response to r-HuEPO:

(1) Iron deficiency. Consider a trial of IV iron

(2) Hematinic deficiencies. Consider supplementary folate and vitamin B_{12}[45] (especially in the elderly and patients who have had gastric surgery[46])

(3) Hyperparathyroidism

(4) Presence of an infectious, inflammatory, or malignant process

4. Consider androgen therapy if there is a poor response to r-HuEPO despite increase to high dose or if r-HuEPO is unavailable[47]

Note: Use androgenic therapy with caution in patients with cardiac, renal, or hepatic disease.

5. Nutritional support

E. Optimize Preoperative Red Blood Cell Production

1. Administer supplementary iron to support postoperative erythropoiesis, even in patients with normal iron stores[48,49]
2. Use r-HuEPO to increase the hematocrit in marginally anemic patients undergoing procedures associated with substantial blood loss to facilitate intraoperative autologous blood procurement and/or minimize postoperative anemia[50-56]
3. Consider using r-HuEPO to raise preoperative hemoglobin concentrations in patients with ischemic heart disease to reduce risks related to myocardial ischemia[57,58]

F. Additional Preoperative Planning[59-63]

1. Estimate the postoperative hematocrit by calculating the patient's blood volume and the expected blood loss (considering the patient's condition, diagnosis, type of surgery, as well as the skill of the surgeon and anesthesiologist)
2. If hemodilution is being considered, the blood volume to be removed (V) or the optimal initial hematocrit (Hct_i) can be determined using the formula: $V = EBV \times (Hct_i - Hct_f) / Hct_{av}$ (where EBV is the estimated blood volume, Hct_f is the minimum hematocrit, and Hct_{av} is the average hematocrit $[(Hct_i + Hct_f)/2]$)
3. If the anticipated blood loss will have a serious adverse effect on the patient's hematocrit:
   a. Consider a modified surgical approach. Technical factors and operative approach are important determinants of blood loss[64]
   b. Identify appropriate combinations of preoperative strategies to optimize perioperative hemoglobin level, coagulation status, and the patient's condition[65]
   c. Select appropriate combinations of intra- and postoperative blood conservation and autologous blood management methods
4. Therapy for coexisting disease (e.g., treatment of cardiopulmonary disease[66,67])
5. Optimize weight and/or physiological condition. Consider postponement of elective surgery to optimize condition of patient

2. MINIMIZATION OF PERIOPERATIVE BLOOD LOSS

A. Restrict Diagnostic Phlebotomy[68-70]

1. Limit phlebotomy to necessary diagnostic testing
2. Decrease volume drawn for laboratory tests (use pediatric-size tubes for adults)
3. Perform multiple tests per sample
4. Microsampling/microanalysis techniques
5. Consider noninvasive blood gas monitoring and instrumentation

B. Minimize Nondiagnostic Iatrogenic Blood Loss[71,72]

C. Prevent Gastrointestinal Bleeding

1. Consider prophylaxis of stress ulcers in at-risk patients[73,74]
   a. Enteral nutrition
   b. Sucralfate
   c. H_2-receptor antagonists
   d. Proton pump inhibitors

3. MAINTENANCE OF OXYGEN DELIVERY

A. Optimize Cardiac Output/Volume Status

1. Maintain circulating volume
   a. Crystalloids
      (1) Ringer's lactate
      (2) Normal saline
      (3) Hypertonic saline[75-81]
   b. Colloids
      (1) Pentastarch (and low-molecular-weight starches)
      (2) Hydroxyethyl starch[82,83] (may adversely affect coagulation—see Note 4)
      (3) Dextran[84] (affects coagulation—see Note 4)
      (4) Gelatin[85,86]

Notes:

1. Volume replacement should be prompt and judicious in terms of choice of solution and the volume, rate, and timing of its administration.[87-89]
2. In the bleeding patient, aggressive restoration of blood pressure to the normal range before control of hemorrhage may increase blood loss.[90] Consider moderate underresuscitation and permissive hypotension and concomitant measures to stop the bleeding.[91-93]
3. Avoid fluid overload.[94] Avoid unnecessary dilution of red cell mass and coagulation factors. Consider use of pulmonary artery catheter or CVP line to monitor volume replacement. Alternatively, consider noninvasive monitoring.[95]
4. Avoid negative interference with hemostasis and coagulation, i.e., dextrans and high-molecular-weight hetastarches.[96-101] Consider use of low-molecular-weight hetastarches or pentastarch.[102-104]
5. Desmopressin may partially reverse the antithrombotic effects of hydroxyethyl starches[105,106] and dextrans.[107,108] (See also ***4.F.***)
6. Hemoglobin level determinations can be misleading and are affected by sampling techniques and in vivo and in vitro variables.[109]
   (1) Hematocrits may be artificially decreased due to transient alterations of intravascular volume due to administration of colloids and crystalloids, impaired renal function, etc.

c. Oxygen-carrying red cell substitutes (when available for clinical use)

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(1) Perfluorochemicals
(2) Hemoglobin-based oxygen carriers
2. Inotropic agents
3. Vasoactive agents

B. Optimize Ventilation and Oxygenation

1. Increase the fraction of inspired oxygen (FiO_2)[110,111]
   a. Consider high FiO_2 and concomitant interventions to treat anemia[112,113]
      (1) Hypoxemia poses greater risks than oxygen toxicity
      (2) Consider concomitant antioxidant therapy
   b. Consider controlling factors responsible for hemoglobin affinity for oxygen (pH, PCO_2, temperature)
2. Individualize ventilator management to minimize ventilator-induced lung injury[114] (e.g., ventilation mode, prone position,[115] inhaled nitric oxide[116])
   Note: Use of nitric oxide to improve oxygenation may have a clinically significant effect on bleeding due to transient inhibition of platelet aggregation.
3. Hyperbaric oxygen therapy[117-122]

C. Minimize Oxygen Demand

1. Controlled hypothermia (See ***4.G.2.***)
2. Sedation
3. Muscle relaxation
4. Mechanical ventilation
5. Adequate and appropriate analgesia

4. INTRAOPERATIVE BLOOD CONSERVATION AND AUTOLOGOUS BLOOD MANAGEMENT

A. Multimodality Approach

1. The greater the expected blood loss, the greater the indication for the use of multiple blood conservation modalities tailored to the clinical circumstances[123-129]
2. Use of appropriate combinations of techniques has a synergistic effect on reduction of blood loss[130-133]

B. Surgical Techniques to Minimize Blood Loss

1. Meticulous hemostasis and operative technique
   a. Rigorous hemostasis using combination of techniques[134-142]
      (1) Least traumatic surgical approach (e.g., consider an approach that avoids operating through known or suspected adhesions). Well-planned operative exposure through avascular tissue planes[143,144]
      (2) Atraumatic tissue handling
      (3) Knowledge of common aberrant vasculature
      (4) Expeditious and fastidious control of hemorrhage
      (5) Mechanical occlusion (ligation, vascular clips, clamps, tacks, balloons)[145-151]
      (6) Vascular isolation[152-156] (e.g., Pringle maneuver)
      (7) Venovenous bypass[157]
   b. Intraoperative positioning of patient[158,159]
      (1) Avoid venous compression
   c. Tourniquets[160,161]
2. Minimize duration of surgery
   a. Reduced operating time may decrease intraoperative blood loss[162,163]
   b. Consider enlarged surgical team
   c. Review and rehearse procedures[164]
   d. Ensure availability of equipment and instruments necessary to perform the procedure expeditiously and to manage contingencies
3. Staged surgery for complex procedures[165-169]
   a. Planned reoperation (e.g., high blood loss surgery, trauma)[170]
   b. Consider temporary packing and wound closure for nonsurgical bleeding

C. Prophylactic Angiographic Embolization

1. Preoperative embolization[171-179]

D. Hemostatic Surgical Instruments

1. Electrocautery/electrosurgery[180,181]
2. Ultrasonic scalpel[182,183]
3. Argon beam coagulator[184-188]
4. Radiofrequency thermal ablation[189-191]
5. Water-jet dissector[192-194]
6. Microwave devices[195-197]
7. Laser[198,199]

E. Minimally Invasive Approaches

1. Endoscopic/laparoscopic surgery[200-204]
2. Endoluminal techniques[205-207]
3. Cryosurgery[208-210]
4. Precision radiation therapy
   a. Stereotactic radiosurgery[211] (e.g., linear accelerator)
   b. Conformal and Intensity Modulated Radiation Therapy (IMRT)[212]
   c. Brachytherapy[213]

F. Pharmacological Enhancement of Hemostasis[214,215]

1. Systemic hemostatic agents
   a. Tranexamic acid[216-223]
   b. Aprotinin[224-231] (when available for clinical use)
      Note: Administer a test dose[232]
   c. Epsilon-aminocaproic acid[233]
   d. Vasopressin[234,235]
   e. Conjugated estrogens (IV)[236-238]
   f. Octreotide (somatostatin)[239-241]

Notes:

1. Antifibrinolytics may be administered prophylactically in patients at high risk of bleeding or to patients with excessive postoperative bleeding.[242]
2. Aprotinin has been reported to decrease bleeding in patients treated with aspirin before surgery.[243-245]
3. In postoperative or trauma patients, pharmacological hemostatic agents should be considered when bleeding is generalized or the bleeding site is not accessible. Do not defer surgery if active bleeding cannot be controlled medically.

2. Augment clotting factor activity
   a. Desmopressin[246-252]
      Notes:
      1. Desmopressin has been reported to decrease bleeding in patients treated with aspirin or NSAIDs before surgery.[253,254]
      2. Intra- or postoperative desmopressin may decrease blood loss *in patients with otherwise normal hemostatic function* by increasing serum levels of factor VIII and von Willebrand factor and increasing platelet adhesion in a dose-dependent manner.[255-258]
      3. Desmopressin is also used to treat the prolonged bleeding time and platelet dysfunction associated with uremia to assist in the maintenance of hemostasis during surgical procedures and postoperatively.[259]

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4. Desmopressin causes a transient dose-dependent increase in plasminogen activator activity. Avoid excessive dose. Also, there is a tendency toward lessening of response with repeat administration within 48 hours.
5. Desmopressin has been used with epsilon-aminocaproic acid or tranexamic acid without adverse effects.[260]

b. Vitamin K[261,262] (prophylactic)

Notes:

1. Preoperative prophylactic administration of vitamin K increases levels of vitamin K-dependent coagulation factors.
2. Consider postoperative parenteral vitamin K.[263]
3. Administration of antibiotics may adversely affect absorption of oral vitamin K.

c. Recombinant factor VIIa (r-FVIIa)[264-269]

Notes:

1. Consider use of r-FVIIa in patients with congenital bleeding disorders or abnormal platelet function.[270-272]
2. Consider use of r-FVIIa in patients with thrombocytopenia or acquired platelet defects *with otherwise normal coagulation mechanisms* who are bleeding at sites with limited possibilities for mechanical hemostasis.[273-279]
3. Consider use of r-FVIIa in patients with bleeding due to DIC.[280]

d. Clotting factor replacement therapy

(1) Clotting factors VIIa, VIII, IX are available as recombinant products

e. Cryoprecipitate[281]

3. Topical/Local hemostatic agents

a. Tissue adhesives[282-284]

b. Fibrin glue[285-293]

c. Fibrin gel or platelet gel[294,295] (See also ***4.K.***)

d. Collagen hemostat (Avitene®, Instat®)[296,297]

e. Topical thrombin or thrombin-soaked packing[298,299]

f. Oxidized cellulose hemostat (Surgicel®, Oxycel®)

g. Gelatin foam/sponges (Gelfoam®, Surgifoam®)

h. Calcium alginate[300-303] (Algosteril®, Kaltostat®)

Note: Topical hemostatic agents can stop or reduce capillary bleeding when the bleeding site is identifiable and accessible.

4. Topical/Local vasoconstrictors

a. Induce local vasoconstriction by infiltration with epinephrine[304,305] or sympathomimetic amines

b. Phenylephrine[306]

c. Topical cocaine[307,308]

G. Normothermia/Preservation of Coagulation

1. Maintain normothermia

a. Hypothermia may increase blood loss due to platelet dysfunction and impairment of coagulation protein function[309-314]

b. Maintain a high ambient room temperature. Employ preinduction, intraoperative, and postoperative patient warming. Keep covered as much as possible. Consider monitoring core temperature[315]

c. Consider forced-air warming (applied to head, neck, shoulders) to maintain core temperature and decrease vasodilator requirements[316,317]

d. Warm all intravenous fluids and blood returned from autotransfusion unit[318]

e. Hypothermia may predispose to coagulopathy and bleeding and is associated with vasoconstriction and hypertension, impaired immune response to infections, dehiscence, hemodynamic instability, and shivering (associated with increased oxygen consumption)[319-323]

2. Consider controlled therapeutic hypothermia in certain clinical settings (e.g., cardiac surgery, neurosurgery) to decrease tissue oxygen requirements and protect against cerebral or myocardial ischemia[324-326]

3. Individualize and optimize heparinization and protamine reversal for cardiac procedures; avoid standard dosing[327,328]

a. Weight-based dosing protocols for heparin are often unreliable due to patients' widely variable response to heparin, variable clearance rates during surgery, and drug interactions

b. Consider use of heparin-bonded circuits for CPB[329-333]

H. Controlled Hypotensive Anesthesia

1. Induce and control optimum level of deliberate hypotension[334-338] (e.g., hepatic surgery,[339,340] orthopedic,[341] pediatric,[342,343] spinal,[344] urologic[345])

2. The higher the expected blood loss, the greater the indications for use of controlled hypotension in combination with other blood conservation techniques (e.g., erythropoietin, blood salvage)[346-350]

3. Individualize approach according to the type of surgery being performed and the presence of any preexisting medical conditions

a. Relative contraindications to controlled hypotension include uncontrolled hypertension, coronary artery disease, cerebral vascular disease, severe pulmonary disease, renal disease, hepatic disease, pregnancy, hypovolemia

4. Hypotensive epidural anesthesia has been safely used in elderly patients with comorbid conditions, including low cardiac output due to ventricular dysfunction[351,352]

5. Some agents used to induce hypotension (e.g., nitroglycerine, sodium nitroprusside) may transiently inhibit platelet aggregation,[353,354] but the clinical consequences may not be significant in patients with normal platelet function

I. Other Anesthetic Considerations

1. Normovolemic anemia is generally well tolerated (See **7.**)

2. Consider continuous high FiO_2 in patients with oxygen transport limitations

3. Regional/epidural anesthesia[355-360]

Note: Consistent reduction of blood loss has not been observed with the use of regional or general anesthesia. Regardless of the choice of anesthesia (regional, narcotic, etc.), the anesthetic technique must be well-planned and executed so as to minimize blood loss (e.g., positioning, ventilation, controlled hypotension).

4. Control intraoperative blood pressure and avoid intraoperative hypertension, especially in vascular operations[361,362]

a. Cardiovascularly compromised patients may tolerate a moderate reduction in blood pressure. Maintain coronary flow by ensuring adequate volume support

J. Cell Salvage/Autotransfusion

1. Intraoperative blood salvage[363-374]

a. Blood cell salvage can provide autologous blood that is immediately available in the event of rapid blood loss[375,376]

b. In oncologic surgery with use of blood salvage,[377] consider leukocyte depletion filters[378-380] alone or in combination with irradiation[381,382]

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c. If there is risk of bacterial contamination (e.g., bowel injury), consider preoperative and/or postoperative systemic antibiotic prophylaxis. Consider addition of antibiotic to anticoagulant/saline solution[383]

d. With precautions, risk of amniotic fluid embolism is rare when blood salvage is employed in obstetric surgery[384]

K. Component Sequestration

1. Autologous single- or multicomponent intraoperative pheresis/sequestration[385-388]
2. Platelet-rich plasma[389,390]
3. Plateletpheresis[391,392]

L. Intraoperative Hemodilution

1. Acute Normovolemic (Isovolemic) Hemodilution (ANH)[393-399]
   a. The efficacy of ANH is proportional to the amount of blood withdrawn. ANH may be more effective when 1000 mL or more of autologous blood is withdrawn at the commencement of surgery (See ***1.F.2.***)
   b. If intravascular volume is maintained, blood pressure and heart rate may remain nearly unchanged[400,401]
   c. Blood withdrawn at the commencement of surgery is reinfused during or after surgery, as needed, to maintain the desired post-ANH hemoglobin concentration
   d. ANH has been used in selected patients with cardiac disease[402-405] but should be used with caution in conjunction with anesthetic agents having a negative inotropic effect.[406,407] Additional vigilance and monitoring may be necessary in patients with hepatic or renal dysfunction or cardiovascular, cerebrovascular, or pulmonary disease
   e. ANH is safe and effective in small children[408-410]
2. Acute Hypervolemic Hemodilution (AHH)[411-415]
   a. During AHH, asanguineous fluid is infused at the beginning of surgery to achieve a reduction in the hematocrit
   b. Compared to ANH, AHH has higher oxygen transport capacity and peripheral oxygen delivery and is well tolerated[416]
   c. Although AHH may be less effective than ANH for blood conservation, it may provide a greater margin of safety in older surgical patients[417-419]

Notes:

1. Hemodilution may be employed alone or in conjunction with other blood conservation methods such as preoperative erythropoietin, controlled hypotension, or cell salvage.[420,421] To optimize blood conservation, hemodilution should be a component of an integrated surgical blood management program.[422]
2. During surgical hemodilution, moderate anemia is generally well tolerated due to control of blood volume. Recommendations regarding minimum hemoglobin levels in the literature are generally in the context of acute blood loss.
3. In cardiac surgery, there is evidence that limited bypass prime volume, reduced-caliber tubing, and limited hemodilution can significantly decrease allogeneic blood transfusion.[423,424] Consider "primeless pump" to maintain higher intraoperative hematocrit.[425] Alternatively, consider use of ultrafiltration. (See ***4.M.***)

M. Hemofiltration/Hemoconcentration

1. Consider use of ultrafiltration devices instead of centrifugation to conserve platelets, coagulation factors, and plasma proteins[426-428]
   a. Consider use of ultrafiltration in addition to cell salvage to avoid the discard of plasma from cell salvage equipment[429]
2. After cardiopulmonary bypass, concentrate residual oxygenator contents and reinfuse to patient
3. In cardiac surgery for infants and children, consider a combination of smaller bypass circuits, intraoperative blood salvage, antifibrinolytic agents, greater tolerance of anemia, and modified ultrafiltration[430]

5. POSTOPERATIVE MANAGEMENT

A. Close Surveillance for Blood Loss

1. Monitor patient frequently to identify and quantify any bleeding or changes in coagulation status to facilitate prompt intervention
2. Signs/symptoms of blood loss include:[431]
   a. Pain, wound swelling, or firmness at surgical site and surrounding areas
   b. Hemodynamic instability
   c. Fluid status

   Note: A common cause of poor response to fluid therapy is continued hemorrhage. Maintain a high index of suspicion of bleeding when a patient shows evidence of hypovolemia despite reasonable hydration.
   d. Vital signs and clinical examination (e.g., dizziness, nausea, thirst, dyspnea, tachycardia, tachypnea, diaphoresis, change in mental status, shock)
   e. Decreasing serial hemoglobin/hematocrit (individualize tests according to clinical circumstances; minimal blood samples)
   f. Decreasing serial CVP measurements
   g. Tube drainage
3. Diagnosis of bleeding[432,433]
   a. Consider site(s) of bleeding:
      (1) Bleeding from only one site (e.g., the operative wound) is likely a localized defect in surgical hemostasis
      (2) Diffuse bleeding may suggest a generalized problem of hemostasis (e.g., oozing from mucosal membranes, IV sites, widespread petechiae, purpura, large ecchymosis, hematuria)

   Notes:

   1. Relatively normal hemostasis test results in the setting of excessive bleeding would indicate a surgical source rather than coagulopathy.
   2. Oozing may be caused by a hemostatic plug formation problem (e.g., due to platelet dysfunction or dilutional thrombocytopenia).

   b. Review history of recent drug ingestion (e.g., aspirin and aspirin-containing compounds, NSAIDs, anticoagulants/antiplatelet agents, some antibiotics, self-medication)
4. Continuous low-level blood loss (e.g., oozing) could become significant if permitted for a prolonged period of time

B. Prompt Arrest of Bleeding

1. Hemostatic pharmacological interventions
   a. Systemic hemostatic agents[434-436] (See ***4.F.1.***)
   b. Clotting factor augmentation (See ***4.F.2.***)
   c. Topical/Local hemostatic agents (See ***4.F.3.***)
2. Angiographic embolization[437] (See ***6.A.8.***)
3. Immediate return to OR to control hemorrhage
   a. Clinical experience and consideration of clinical circumstances allow the anesthesiologist, in consultation with the surgeon, to assess and diagnose whether postoperative bleeding is excessive and requires immediate reoperation

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C. Postoperative Blood Salvage[438-446]

Note: For the rapidly bleeding patient, consider cell salvage as a temporary measure until the patient can be promptly returned to the operating room for surgical hemostasis.

D. Hemostasis/Coagulation Management[447]

1. Individualized neutralization of heparin[448-450]
2. Consider monitoring coagulation and platelet function using point-of-care viscoelastic analysis (e.g., thromboelastogram, Sonoclot) to optimize hemostasis management, assess platelet function, differentiate mechanical versus hemostatic bleeding, identify hypercoagulable and heparin-resistant patients, and screen for hyperfibrinolysis
3. Maintain normothermia (See ***4.G.***)

E. Judicious Fluid Therapy

1. Active rigorous fluid management in the immediate postoperative period to minimize hemodilution, sustain adequate perfusion and vital organ function; avoid hypertension[451-453] (See ***3.A.***)
   a. Tissue perfusion may be assessed by blood gas measurements, patient alertness, urine output
2. Maintain normovolemia in the hemodynamically stable patient[454]

F. Control of Blood Pressure/Avoidance of Hypertension

1. Consider tolerating moderate hypotension in a bleeding patient (e.g., mean arterial pressure (MAP) of 60-70 mm Hg in a normotensive patient) while taking measures to arrest bleeding
2. Use appropriate positioning and optimum ventilation techniques

G. Erythropoietin Therapy (See ***1.D.***3.)

H. Judicious Prophylaxis of Thromboembolism

1. Using clinical judgment, individualize timing, dosage, and duration of anticoagulation according to risk of bleeding and thromboembolism.[455,456] Avoid routine prophylaxis
   a. Maintain close clinical and laboratory monitoring for any anticoagulated patient to reduce bleeding risk
   b. Consider use of low-dose, low-molecular-weight heparin
   c. Patients at high risk for bleeding as well as for thrombosis and who may also require emergency surgery require treatment with short-acting anticoagulants that can be monitored with conventional methods (e.g., heparin, lepirudin)
2. If there is evidence of ongoing bleeding, discontinue, substitute, or reduce dosage of anticoagulant or antiplatelet agent
3. Consider use of compression devices, foot pumps, or vena cava filters in patients at increased risk of bleeding and thrombosis where use of heparin is contraindicated[457-459]

I. Judicious Use of Analgesics

1. Consider adverse effects of medications and drug interactions (e.g., platelet dysfunction, thrombocytopenia)
2. Some NSAIDs may be more likely to increase postoperative bleeding after certain procedures[460]

J. Prophylaxis of Infection

K. Prophylaxis of Upper Gastrointestinal Hemorrhage (See ***2.C.***)

L. Nutritional Support[461]

6. MANAGEMENT OF ACUTE BLEEDING AND SHOCK

In an actively bleeding trauma patient, arrest of external and internal hemorrhage must be the first management priority. Secondarily, employ moderate fluid underresuscitation in the presence of uncontrolled hemorrhage. Minimize time at the scene and in the emergency department. Appropriate resources (e.g., surgical personnel, autotransfusion devices) should be mobilized expeditiously. With multiple personnel, it is possible to perform assessment, control of hemorrhage, and fluid resuscitation simultaneously. Consider using a combination of measures to arrest blood loss (e.g., pharmacological and mechanical). Avoid treatment delays through advance planning, good organization, and well-rehearsed systematic management protocols.

A. Stop the Blood Loss

1. Direct pressure, elevation, pressure points, pressure dressings
2. Consider tourniquets
3. Pharmacological hemostatic agents[462-464] (See ***4.F.***)
4. Employ diagnostic methods that yield rapid results (e.g., ultrasound)[465-470] and facilitate timely decision-making
5. Tolerate hypotension (See ***6.B.***)
6. Prompt surgery for patients with active bleeding[471,472] (See ***4.B.***3.)
   a. Modified operative approach for rapid control of bleeding[473-478]
   b. "Damage control" strategy[479-486] (See notes below.)
   c. For pelvic fractures, consider early stabilization (e.g., external fixation)[487-489] or use of anti-shock garment (tamponade effect)[490]
   d. Minimally invasive devices (e.g., endoscopy for GI bleeding)[491-493]
7. Autotransfusion/blood salvage[494-500] (See ***4.J.***)
   a. Blood that collects in the thoracic or abdominal cavity following blunt or penetrating trauma can be autotransfused using drainage devices
   b. With appropriate precautions, autotransfusion of enteric-contaminated blood has been performed without sequelae[501,502]
8. Emergency arterial embolization[503-510]
   a. Consider prompt angiographic embolization for bleeding patients where surgical repair may release the tamponade effect and possibly result in severe blood loss[511]
   b. Consider angiographic embolization as part of nonoperative management for bleeding patients who are hemodynamically stable

Notes:

1. Avoid delay. Prompt control of hemorrhage should be the first objective.[512]
2. Consider "damage control" strategy for multiple injuries associated with hemodynamic compromise: Brief initial laparotomy and rapid control of major vascular injuries, control of contamination, use of temporizing measures (e.g., packing) to restore a survivable physiology, and planned reoperation for staged definitive surgical repair. This requires early recognition of a patient's physiological limits and prompt modification of the duration and scope of surgery.
3. Consider precautions to avoid bleeding sequelae related to removal of packing.[513,514]

B. Treat Shock

1. Trendelenburg/shock position (patient supine with head lower than legs)

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2. Judicious fluid resuscitation/individualized volume replacement (See ***3.A.***)
   a. In the presence of uncontrolled hemorrhage, consider moderate underresuscitation (MAP of 55-70 mm Hg) sufficient to sustain tissue perfusion until hemostasis is secured[515-525] (not for patients with head injuries)
      (1) In the presence of uncontrolled hemorrhage, aggressive fluid resuscitation or use of anti-shock garments to elevate arterial or venous blood pressure to the normal range may increase the rate of bleeding and dislodge an effective thrombus[526-530]
      (2) Colloid resuscitation may provide more rapid and effective correction of intravascular volume deficits and avoid peripheral edema
   b. Avoid rapid infusion rates[531]
   c. Use warmed fluids
      (1) Infusion of unwarmed fluids may cause hypothermia and coagulopathy
   d. Consider intraosseous (IO) route for pediatric or adult patients if difficulty is encountered in promptly establishing adequate intravenous access[532,533]

C. Maximize Oxygenation of Circulating Blood

1. Airway management, administration of oxygen, treatment of pulmonary injuries (See ***3.***)

D. Maintain Normothermia

1. Active patient warming[534-537] (See ***4.G.***)
2. Warming of intravenous fluids, body-cavity lavage, and airway

Note: Therapeutic hypothermia may be indicated in rare cases.[538]

E. Early Initiation of Erythropoietin Therapy

1. High-dose recombinant erythropoietin (r-HuEPO) to decrease duration of anemia[539-543]
   a. Critically ill patients may be unable to mount an erythropoietic response to acute anemia or respond to endogenous EPO[544,545]
2. Supplementary IV iron[546-549]

F. Management of Severe Acute Anemia[550]

1. Maximize oxygen delivery (See ***3.***)
   a. Maintain normovolemia (See ***7.B.***)
   b. Ensure adequate cardiac output
2. Minimize iatrogenic blood loss (See ***2.A.***)
3. Minimize oxygen demand (See ***3.C.***)

G. Antibiotic Prophylaxis

1. Decisions regarding prophylactic antibiotic administration should take into consideration the number of organs injured, the degree of contamination, and the presence of colon injury[551,552]
2. Prompt and appropriate wound management to prevent infection[553] (especially fecal contamination)

H. Prevention of Thromboembolism

1. For multiple trauma patients at high risk of thromboembolism (for whom anticoagulants are contraindicated due to bleeding and mechanical prophylaxis is not possible because of their injuries), consider inferior vena cava filters and close surveillance for evidence of bleeding

I. Early Transfer When Necessary

1. Consider making transfer arrangements in advance if appropriate skills and facilities are not available locally

7. PHYSIOLOGICAL RESPONSE TO ANEMIA

A. Compensatory Mechanisms[554]

1. Increased cardiac output (heart rate and stroke volume)
2. Redistribution of blood flow to augment the coronary and cerebral (vital organ) perfusion
3. Increased tissue oxygen extraction[555,556]
4. Decreased oxygen affinity of hemoglobin
   a. Oxygen delivery to tissues is increased due to a rightward shift of the oxyhemoglobin dissociation curve as a result of a rise in 2,3-DPG levels

Notes:

1. Adaptive mechanisms in chronic and acute anemia differ.
2. Under conditions of normovolemic anemia, decreased blood viscosity results in decreased vascular resistance and increased venous return and cardiac output.
3. Decreased blood viscosity may lower the risk of thrombosis.

B. Tolerance of Normovolemic Anemia

1. Moderate levels of normovolemic anemia are well tolerated by critically ill patients with coexisting disease[557-560]
2. Profound intraoperative normovolemic hemodilution has been reported to be well tolerated in children[561]
3. Hemodilution to a hematocrit of 15% has been reported to be well tolerated in anesthetized adult patients[562-564]
4. Studies in healthy resting adults show good oxygen delivery and tolerance of normovolemic anemia to hemoglobin levels of 45 g/L[565,566]

Notes:

1. In a study of 8,787 elderly hip fracture patients undergoing surgical repair, anemia of 80 g/L appeared to have no effect on mortality even among those with cardiovascular disease.[567]
2. The "10/30" transfusion threshold is arbitrary and outdated. The efficacy of RBC transfusion has not been demonstrated in an appropriately controlled, prospective study.[568-570] The data preclude any scientific conclusion in support of a safe hemoglobin concentration or transfusion trigger.[571,572]
3. The compensatory mechanisms permitting tolerance of normovolemic anemia may be affected by several factors necessitating other measures to ensure adequate oxygen delivery:
   (1) left ventricular dysfunction and drug therapy (e.g., beta-adrenergic or calcium channel blockade),
   (2) certain pharmacological agents, such as anesthetics, hypnotics, and neuromuscular blocking drugs,
   (3) intraoperative conditions (e.g., hypothermia).

C. Effects of Storage on Red Cells

1. Impaired oxygen-carrying capacity of hemoglobin due to lower levels of 2,3-DPG in red blood cells. This may be reversible within 24-48 hours[573,574]
2. Decreased deformability of RBCs. This may adversely affect tissue oxygen delivery in sepsis and septic shock[575,576]
3. Decreased oxygen delivery due to impaired microvascular flow and/or formation of microaggregates in stored blood. This may impair microcirculatory oxygenation in sepsis and shock[577]

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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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