

194. Thomas DK. Hypoglycaemia in children before operation: its incidence and prevention. *Br J Anaesth.* 1974;46(1):66–68.
195. Berry F. Practical aspects of fluid and electrolyte therapy. In: Berry F, ed. *Anesthetic Management of Difficult and Routine Pediatric Patients*. New York: Churchill Livingstone; 1986:107–135.
196. Murat I, Dubois M-C. Perioperative fluid therapy in pediatrics. *Pediatric Anesthesia.* 2008;18(5):363–370.
197. Phillips S, Daborn AK, Hatch DJ. Preoperative fasting for paediatric anaesthesia. *Br J Anaesth.* 1994;73(4):529–536.
198. Bailey AG, McNaull PP, Jooste E, Tuchman JB. Perioperative crystalloid and colloid fluid management in children: where are we and how did we get here? *Anesth Analg.* 2010;110(2):375–390.
199. Welborn LG, McGill WA, Hannallah RS, Nisselson CL, Ruttimann UE, Hicks JM. Perioperative blood glucose concentrations in pediatric outpatients. *Anesthesiology.* 1986;65(5):543–547.
200. Sümpelmann R, Becke K, Brenner S, Breschan C, Eich C, Höhne C, et al. Perioperative intravenous fluid therapy in children: guidelines from the Association of the Scientific Medical Societies in Germany. *Pediatric Anesthesia.* 2017;27(1):10–18.
201. McNab S, Ware RS, Neville KA, Choong K, Coulthard MG, Duke T, et al. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. *Cochrane Database Syst Rev.* 2014;(12):CD009457.
202. Holliday MA, Ray PE, Friedman AL. Fluid therapy for children: facts, fashions and questions. *Arch Dis Child.* 2007;92(6):546–550.
203. Kashani A, Landaverde C, Medici V, Rossaro L. Fluid retention in cirrhosis: pathophysiology and management. *QJM.* 2008;101(2):71–85.
204. Sola-Vera J, Miñana J, Ricart E, Planella M, González B, Torras X, et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. *Hepatology.* 2003;37(5):1147–1153.
205. Stravitz RT, Kramer AH, Davern T, Shaikh AOS, Caldwell SH, Mehta RL, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med.* 2007;35(11):2498–2508.
206. Ganzevoort W, Rep A, Bonsel GJ, Fetter WPF, van Sonderen L, De Vries JJP, et al. A randomised controlled trial comparing two temporising management strategies, one with and one without plasma volume expansion, for severe and early onset pre-eclampsia. *BJOG.* 2005;112(10):1358–1368.
207. Duley L, Williams J, Henderson-Smart DJ. Plasma volume expansion for treatment of women with pre-eclampsia. *Cochrane Database Syst Rev.* 2000;2:CD001805.
208. Thornton CE, von Dadelszen P, Makris A, Tooher JM, Ogle RF, Hennessy A. Acute pulmonary oedema as a complication of hypertension during pregnancy. *Hypertens Pregnancy.* 2011;30(2):169–179.
209. The management of hypertensive disorders during pregnancy. NICE clinical guideline 107. Manchester, UK: National Institute for Health and Clinical Excellence; 2010.
210. Thornton C, Hennessy A, von Dadelszen P, Nishi C, Makris A, Ogle R. An international benchmarking collaboration: measuring outcomes for the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can.* 2007;29(10):794–800.
211. Wijayatilake DS, Shepherd SJ, Sherren PB. Updates in the management of intracranial pressure in traumatic brain injury. *Curr Opin Anaesthesiol.* 2012;(5):540–547.
212. Ryu JH, Walcott BP, Kahle KT, Sheth SA, Peterson RT, Nahed BV, et al. Induced and sustained hypernatremia for the prevention and treatment of cerebral edema following brain injury. *Neurocrit Care.* 2013.
213. Fletcher JJ, Bergman K, Blostein PA, Kramer AH. Fluid balance, complications, and brain tissue oxygen tension monitoring following severe traumatic brain injury. *Neurocrit Care.* 2010;13(1):47–56.
214. Velat GJ, Kimball MM, Mocco JD, Hoh BL. Vasospasm after aneurysmal subarachnoid hemorrhage: review of randomized controlled trials and meta-analyses in the literature. *World Neurosurg.* 2011;76(5):446–454.
215. Sen J, Belli A, Albon H, Morgan L, Petzold A, Kitchen N. Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. *Lancet Neurol.* 2003;2(10):614–621.
216. Tummala RP, Sheth RN, Heros RC. Hemodilution and fluid management in neurosurgery. *Clin Neurosurg.* 2006;53:238–251.
217. van der Jagt M. Fluid management of the neurological patient: a concise review. *Critical Care.* 2016;20:126.
218. Van Aken HK, Kampmeier TG, Ertmer C, Westphal M. Fluid resuscitation in patients with traumatic brain injury: what is a SAFE approach? *Curr Opin Anaesthesiol.* 2012;25(5):563–565.
219. Levett D, Vercueil A, Grocott M. Resuscitation fluids in trauma 1: why give fluid and how to give it. *Trauma.* 2006;8(1):47–53.
220. Harris T, Thomas GOR, Brohi K. Early fluid resuscitation in severe trauma. *BMJ.* 2012;345:e5752.
221. Johansson PI, Oliveri RS, Ostrowski SR. Hemostatic resuscitation with plasma and platelets in trauma. *J Emerg Trauma Shock.* 2012;5(2):120–125.
222. Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess.* 2013;17(10):1–79.
223. Brain Trauma Foundation, Neurological Surgeons, Brain Trauma Foundation; American Association of. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma.* 2007;24(suppl 1):S1–S106.
224. Sigurdsson GH. Perioperative fluid management in microvascular surgery. *J Reconstr Microsurg.* 1995;11(1):57–65.
225. Disa JJ, Polvora VP, Pusic AL, Singh B, Cordeiro PG. Dextran-related complications in head and neck microsurgery: do the benefits outweigh the risks? A prospective randomized analysis. *Plast Reconstr Surg.* 2003;112(6):1534–1539.
226. Shetty PS, Boyce H, Chisholm D. Anaesthesia for onco-plastic reconstructive surgery. *Curr Anaesth Crit Care.* 2009;20(1):18–21.
227. Ojima H, Kuwano H, Kato H, Miyazaki T, Nakajima M, Sohda M, et al. Relationship between cytokine response and temporary ventilation during one-lung ventilation in esophagectomy. *Hepatogastroenterology.* 2007;54(73):111–115.
228. Michelet P, D'Journo X-B, Roch A, Doddoli C, Marin V, Papazian L, et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. *Anesthesiology.* 2006;105(5):911–919.
229. Low D, Kunz S, Schembre D, Otero H, Malpass T, Hsi A, et al. Esophagectomy—it's not just about mortality anymore: standardized perioperative clinical pathways improve outcomes in patients with esophageal cancer. *J Gastrointest Surg.* 2007;11(11):1395–1402.
230. Kita T, Mammoto T, Kishi YK. Fluid management and postoperative respiratory disturbances in patients with transthoracic esophagectomy for carcinoma. *J Clin Anesth.* 2002;14(4):252–256.
231. Neal JM, Wilcox RT, Allen HW, Low DE. Near-total esophagectomy: the influence of standardized multimodal management and intraoperative fluid restriction. *Reg Anesth Pain Med.* 2003;28(4):328–334.
232. Tandon S, Batchelor A, Bullock R, Gascoigne A, Griffin M, Hayes N, et al. Peri-operative risk factors for acute lung injury after elective oesophagectomy. *Br J Anaesth.* 2001;86(5):633–638.
233. Wei S, Tian J, Song X, Chen Y. Association of perioperative fluid balance and adverse surgical outcomes in esophageal cancer and esophagogastric junction cancer. *Ann Thorac Surg.* 2008;86(1):266–272.
234. Jones RM, Moulton CE, Hardy KJ. Central venous pressure and its effect on blood loss during liver resection. *Br J Surg.* 1998;85(8):1058–1060.
235. Redai I, Emond J, Brentjens T. Anesthetic considerations during liver surgery. *Surg Clin North Am.* 2004;84(2):401–411.
236. Moore J, McLeod A. Anaesthesia for gynaecological oncology surgery. *Curr Anaesth Crit Care.* 2009;20(1):8–12.
237. Shenoy S, Ward P, Wigmore T. Surgical management of urological malignancy: anaesthetic and critical care considerations. *Curr Anaesth Crit Care.* 2009;20(1):22–27.
238. Rabey PG. Anaesthesia for renal transplantation. *BJA CEPD Reviews.* 2001;1(1):24–27.
239. De Gasperi A, Narcisi S, Mazza E, Bettinelli L, Pavani M, Perrone L, et al. Perioperative fluid management in kidney transplantation: is volume overload still mandatory for graft function? *Transplant Proc.* 2006;38(3):807–809.
240. Schmid S, Jungwirth B. Anaesthesia for renal transplant surgery: an update. *Eur J Anaesthesiol.* 2012;29(12):552–558.
241. Calixto Fernandes MH, Schricker T, Magder S, Hatzakorzian R. *Perioperative Fluid Management in Kidney Transplantation: A Black Box.* Crit Care [Internet]; 2018. [cited 2018 Apr 30];22. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5784708/>.

242. Fabbroni D, Bellamy M. Anaesthesia for hepatic transplantation. *Continuing Education in Anaesthesia, Critical Care & Pain*. 2006;6(5):171–175.
243. Froghi F, Koti R, Gurusamy K, Mallett S, Thorburn D, Selvès L, et al. Cardiac output Optimisation following Liver Transplant (COLT) trial: study protocol for a feasibility randomised controlled trial. *Trials* [Internet]. 2018 Mar 7 [cited 2018 Apr 30];19. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5842525/>.
244. Jones JG, Wardrop CA. Measurement of blood volume in surgical and intensive care practice. *Br J Anaesth*. 2000;84(2):226–235.
245. Chumlea WC, Guo SS, Zeller CM, Reo NV, Siervogel RM. Total body water data for white adults 18 to 64 years of age: the Fels Longitudinal Study. *Kidney Int*. 1999;56(1):244–252.
246. Baarsma R, Hof P, Zijlstra WG, Zock JP, Okken A. Measurement of total bodywater volume with deuterated water in newborn infants. *Biol Neonate*. 1992;62:108–112, 2–3.
247. Ellis KJ, Shypailo RJ, Abrams SA, Wong WW. The reference child and adolescent models of body composition. A contemporary comparison. *Ann N Y Acad Sci*. 2000;904:374–382.
248. Campbell I. Physiology of fluid balance. *Ann Intensive Care*. 2009;10(12):593–596.
249. Hoffer LJ, Hamadeh MJ, Robitaille L, Norwich KH. Human sulfate kinetics. *Am J Physiol Regul Integr Comp Physiol*. 2005;289(5):R1372–1380.
250. Hall JE. The body fluid compartments. In: *Guyton and Hall Textbook of Medical Physiology*. 12th ed. Philadelphia: WB Saunders; 2010:285–300.
251. Grădinaru I, Ghiciuc C-M, Popescu E, Nechifor C, Mândreci I, Nechifor M. Blood plasma and saliva levels of magnesium and other bivalent cations in patients with parotid gland tumors. *Magnes Res*. 2007;20(4):254–258.
252. Sewón LA, Karjalainen SM, Söderling E, Lapinleimu H, Simell O. Associations between salivary calcium and oral health. *J Clin Periodontol*. 1998;25(11 Pt 1):915–919.
253. Lentner. Units of Measurement, Body Fluids, Composition of the Body, Nutrition. In: *Geigy Scientific Tables*. 8th ed. Basle: Ciba-Geigy Ltd; 1981.
254. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anaesthesia*. 2013;68(1):79–90.
255. Rasmussen HS, Videbaek R, Melchior T, Aurup P, Cintin C, Pedersen NT. Myocardial contractility and performance capacity after magnesium infusions in young healthy persons: a double-blind, placebo-controlled, cross-over study. *Clin Cardiol*. 1988;11(8):541–545.
256. Sugimoto J, Romani AM, Valentin-Torres AM, Luciano AA, Ramirez Kitchen CM, Funderburg N, et al. Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism. *J Immunol*. 2012;188(12):6338–6346.
257. Li F-Y, Chaigne-Delalande B, Kanelloupolou C, Davis JC, Matthews HF, Douek DC, et al. Signaling role for Mg²⁺ revealed by immunodeficiency due to loss of MagT1. *Nature*. 2011;475(7357):471–476.
258. Soar J, Perkins GD, Abbas G, Alfonzo A, Barelli A, Bierens JJLM, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation*. 2010;81(10):1400–1433.

KEY POINTS

- The presence of a significant acid-base abnormality often signals a sinister underlying problem.
- All acid-base abnormalities result from alterations in the dissociation of water.
- Only three factors independently affect acid-base balance—the arterial partial pressure of carbon dioxide (PaCO_2), the strong ion difference (SID), and the total concentration of weak acids (A_{TOT}).
- Respiratory acidosis and alkalosis are caused by hypercarbia and hypocarbia, respectively.
- Metabolic acidosis is caused by decreased SID or increased A_{TOT} . Decreased SID results from accumulation of metabolic anions (shock, ketoacidosis, and renal failure), hyperchloremia, and free water excess. Increased A_{TOT} results from hyperphosphatemia.
- Metabolic alkalosis is caused by increased SID or decreased A_{TOT} . SID increases due to sodium gain, chloride loss, or free water deficit. A_{TOT} decreases in hypoalbuminemia and hypophosphatemia. This is particularly common in critical illness.
- Most acid-base disorders are treated by reversal of the cause.

Introduction—Why Is Acid-Base Balance Important?

Blood gas and pH analyses have been the most robust laboratory and bedside tools for identifying and monitoring critical illness since the advent of modern medicine. There is good reason to believe that understanding acid-base chemistry will continue to be important for physicians for decades to come.¹

The human body is composed principally of water, partitioned into intracellular and extracellular compartments. The electrolyte composition of each of these spaces is tightly controlled to maintain homeostasis. Alterations in the relative concentrations of electrolytes and of carbon dioxide (CO_2) impact the tendency of water to auto-ionize into its component parts: hydrogen and hydroxyl ions.² Alterations in the water, gas, and electrolyte composition of the fluid compartments manifest as changes in the chemistry profile of body water and acid-base balance.

The hydrogen ion concentration is conventionally measured as pH (literally the “power of hydrogen”), the negative logarithmic value of its concentration. Deviations in extracellular pH away from the resting value of 7.4 have long been associated with acute and critical illness. Such deviations are known as “acid-base abnormalities.”³ All acid-base abnormalities result from changes in the local concentration of strong ions, weak acids, and CO_2 .^{2,4,5}

This chapter first looks at the basic science behind acid-base abnormalities. Subsequently, we explore the detection and treatment of acid-base conundrums, with specific reference to perioperative medicine and critical care.

What Are Acids and Bases?

The concept of acids and bases is relatively new in medicine,⁶ and arose with the development of laboratory science in the early part of the 20th century. However, as early as 1831, O’Shaughnessy identified loss of “carbonate of soda” from the blood as a fundamental disturbance in patients dying of cholera.⁷ This led directly to the development of crystalloid replacement therapy for hypovolemic shock. In 1909, L.J. Henderson coined the term “acid-base” balance.⁸ He was able to define this process in terms of carbonic acid equilibrium. Henderson’s work was later refined by Hasselbalch in 1916.⁹ Their method described acid-base balance in terms of the hydration equation for CO_2 :¹⁰



$$\text{pH} = \text{pK}_a + \log [\text{HCO}_3^-] / [\text{H}_2\text{CO}_3]$$

$$\begin{aligned} [\text{Total CO}_2] &= [\text{HCO}_3^-] + [\text{Dissolved CO}_2] \\ &+ [\text{Carbamino CO}_2] + [\text{H}_2\text{CO}_3] \end{aligned}$$

$$\approx \text{P}_{\text{CO}_2} \times 0.03 \text{ mmol CO}_2/\text{L/mm Hg}$$

So, substituting into the foregoing equation:

$$\text{pH} = 6.1 + \log [\text{HCO}_3^-] / \text{P}_{\text{CO}_2} \times 0.03$$

This is the Henderson-Hasselbalch equation.

The introduction of this concept into clinical practice became possible with the development of volumetric CO_2 analysis by Van Slyke and others in 1919.¹¹ This led to

60 years of research and interest in CO_2 and its derivative, bicarbonate, as the principle agents that impact acid-base chemistry, despite the knowledge in the 1920s of the importance of chloride in acid-base equilibria.¹²

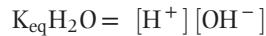
An understanding of acid-base chemistry in the human body requires familiarity with physical chemistry. Because the body contains a large quantity of water, the physical properties of water have enormous implication for maintenance of homeostasis. Water is a simple triatomic molecule. Its chemical formula is H_2O and its structural formula is $\text{H}-\text{O}-\text{H}$. The charge distribution of each covalent bond is unequal, and the molecule has a polar conformation and an $\text{H}-\text{O}-\text{H}$ bond angle of 105 degrees. Water molecules attract and form hydrogen bonds with one another. Consequently, water has a high surface tension, a low vapor pressure, a high specific heat capacity, a high heat of vaporization, and a high boiling point.

Water molecules are in continual motion. Occasionally a collision generates sufficient energy to transfer a proton from one water molecule to another. Thus, water is always slightly dissociated into a negatively charged hydroxyl (OH^-) ion and a positively charged hydronium (H_3O^+) ion. Conventionally, this self-ionization of water is written as follows:

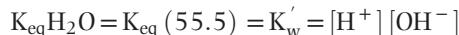


The symbol H^+ is convenient because, although protons dissociating from water have many aliases (such as H_3O^+ and H_3O_4^+), most physicians and chemists refer to them as hydrogen ions.

The self-ionization of water is minuscule. In pure water at 25°C, the $[\text{H}^+]$ and $[\text{OH}^-]$ are 1.0×10^{-7} mmol/L. The tendency for water to dissociate into its component parts is represented by the expression



The molarity of water is extremely high—55.5 M (“there is a lot of water in water”). As the concentration of water and the K_{eq} are constants, the ion-product dissociation constant (pKa) for water can be expressed as follows:



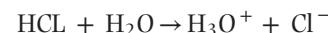
The implication is that the product of the concentrations of hydroxyl and hydrogen is constant, so when there is an increase in the concentration of hydrogen ions, there is a concomitant decrease in the concentration of hydroxyl ions, and vice versa.

Pure water is considered neutral because the relative concentrations of hydrogen and hydroxyl are equal at 1.0×10^{-7} mmol/L. A solution is considered *acidic* if the concentration of hydrogen ions exceeds that of hydroxyl ions ($[\text{H}^+] > 1.0 \times 10^{-7}$ mmol/L, $[\text{OH}^-] < 1.0 \times 10^{-7}$ mmol/L). A solution is considered *alkaline* if the hydroxyl ion concentration exceeds the hydrogen ion concentration.

In 1903, Svante Arrhenius (1859-1927) established the foundations of acid-base chemistry. In an aqueous solution, an Arrhenius acid is any substance that delivers a hydrogen ion into the solution.⁵ A base is any substance that delivers a hydroxyl ion into the solution. Because of its high dielectric

constant, water is a highly ionizing solution. Therefore, substances with polar bonds will dissociate into their component parts (dissolve) in water. Brønsted and Lowry (BL) independently advanced this concept using slightly different terminology: an acid is a proton donor, a base a proton acceptor. Water itself is amphoteric and can act as either an acid or as a base. Thus, when hydrochloric acid (HCl) is dissolved in water, chloride, the acid, donates a proton to water, the base. Similarly, when potassium hydroxide (KOH) is dissolved in water, potassium, the base, receives a hydrogen ion from water, the acid or proton donor.

The degree of dissociation of substances in water determines whether they are strong acids or strong bases. Lactic acid, which has an ion pKa of 3.4, is completely dissociated at physiologic pH, and is a strong acid. Conversely, carbonic acid, which has a pKa of 6.4, is incompletely dissociated, and is a weak acid. Similarly, ions such as sodium (Na^+), potassium (K^+), and chloride (Cl^-), which do not easily bind other molecules, are considered *strong ions*—they exist free in solution. As each Na^+ delivers a hydroxyl moiety into extracellular fluid (ECF), it is functionally a base, as are all cations. As each Cl^- delivers a hydrogen moiety into ECF, it is functionally an acid, as are all anions. The hydrogen and hydroxyl ions delivered in this way bind to one another, forming water molecules, and relatively few free hydrogen or hydroxyl ions remain free in solution.



In this reaction, hydrogen chloride acts as a BL acid and water as a BL base.



In this reaction, water acts as a BL acid and sodium as a BL base.



Because of electrical neutrality, the hydrogen and hydroxyl ions delivered by chloride and sodium become water.

In summary, all acid-base reactions in the human body relate to the presence of charged particles within an aqueous environment. In the following section, how the components of ECF influence the acid-base status of the body, as measured by clinicians, is discussed. This is followed by an explanation of different acid-base abnormalities, and the tools used to identify them. These approaches are neither distinct from one another nor scientifically incompatible.

What Determines the Acidity or Alkalinity of a Solution?

Because all acid-base reactions are based on the principles of physical chemistry, three simple rules must be followed:²

1. *Electrical neutrality:* in aqueous solutions, in any compartment, the sum of all the positive charged ions must equal the sum of all the negative charged ions.

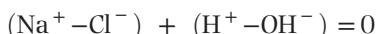
2. *Dissociation equilibria*: the dissociation equilibria of all incompletely dissociated substances, as derived from the law of mass action, must be satisfied at all times.
3. *Mass conservation*: the amount of a substance in a given compartment remains constant unless it is added, removed, generated, or destroyed. Therefore, the total concentration of an incompletely dissociated substance is the sum of concentrations of its dissociated and undissociated forms.

To determine the acid-base status of a fluid, all substances to which these rules could be applied must be accounted for. Fundamentally this involves counting up all the charges (and hence hydrogen and hydroxyl ions) delivered by strong cations (bases) and strong anions (acids), weak acid buffers, and CO_2 .¹³ A discussion of key groups follows.

STRONG IONS

The first group of ions, the strong ions, dissociate completely. The most abundant strong ions in the extracellular space are Na^+ and Cl^- . Other important strong ions include K^+ , sulfate (SO_4^{2-}), magnesium (Mg^{2+}), and calcium (Ca^{2+}). These are occasionally referred to as “mineral” acids or bases because they cannot be metabolized.⁶ Organic acids are generated from metabolism and accumulate when there is metabolic dysfunction—such as kidney failure, splanchnic hypoperfusion, or hormonal deficiency.

In a solution containing strong ions, created, for example, using specified concentrations of sodium hydroxide (NaOH) and HCl, the hydrogen ion concentration can be calculated by solving for electric neutrality:



This creates two separate simultaneous equations¹⁴:

$$\text{H}^+ = \sqrt{K_w' + \frac{([\text{Na}^+] - [\text{Cl}^-])^2}{4} - \frac{([\text{Na}^+] - [\text{Cl}^-])}{2}}$$

and

$$\text{OH}^- = \sqrt{K_w' + \frac{([\text{Na}^+] - [\text{Cl}^-])^2}{4} + \frac{([\text{Na}^+] - [\text{Cl}^-])}{2}}$$

These equations tell us that hydrogen and hydroxyl concentrations are determined by the K_w' (water pKa), and the difference in charge between Na^+ and Cl^- . Because the former is constant, in this system $([\text{Na}^+] - [\text{Cl}^-])$ must determine $[\text{H}^+]$ and $[\text{OH}^-]$. Given that the concentration of both Na^+ and Cl^- are known, the net positive charge minus net negative charge can be quantified. It is the *strong ion difference* (SID).¹⁴ Logically, in any solution, the sum total of the charges imparted by strong cations minus the charges from strong anions will represent the SID. SID independently influences hydrogen ion concentration (Fig. 48.1). In human ECF, SID is always positive.

$$\text{SID} = ([\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}]) - ([\text{Cl}^-] + [\text{A}^-]) = 40 - 44 \text{ mEq/L}$$

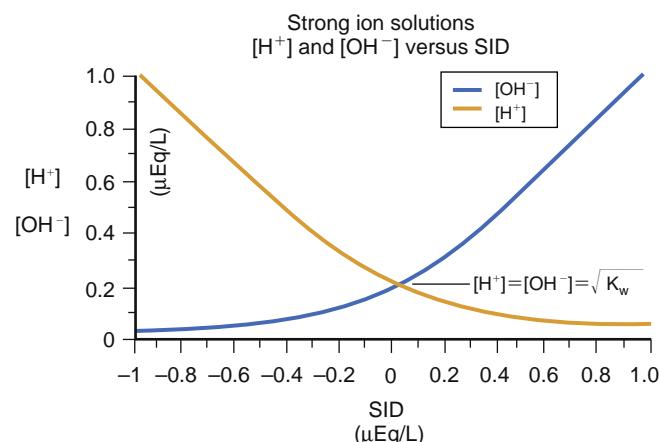


Fig. 48.1 Effect of Changes in the Strong Ion Difference (SID) on Hydrogen and Hydroxyl Ion Concentration. (Modified from Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol*. 1983;61:1444–1461.)

Hydroxyl ions almost always exceed hydrogen ions quantitatively in solution. The relationship between SID and $[\text{H}^+]$ is nonlinear in these conditions. Any change in SID will change both $[\text{H}^+]$ and $[\text{OH}^-]$ concentrations. Because of the K_w' , this relationship is inverse: as $[\text{H}^+]$ increases, $[\text{OH}^-]$ decreases (see Fig. 48.1). SID is an independent variable, and $[\text{H}^+]$ and $[\text{OH}^-]$ are dependent, meaning that the addition of hydrogen ions alone (without strong corresponding anions) cannot influence the pH of the solution.

WEAK ACID “BUFFER” SOLUTIONS

The degree of water dissociation, and thus the hydrogen ion concentration, is also influenced by charges derived from weak acids. These acids are partially dissociated compounds whose degree of dissociation is determined by the prevailing temperature and pH. The predominant molecules in this group are albumin and phosphate. Stewart used the term A_{TOT} to represent the total concentration of weak anions or acids that influence acid-base balance.²

The acid HA will only partly dissociate, represented by the equilibrium

$$[\text{H}^+] \times [\text{A}^-] = K_A \times [\text{HA}]$$

K_A is the weak acid pKa. If we assume that HA and A^- play no further part in this reaction (the law of mass conservation), the amount of A^- present in the solution must equal the amount initially present, so:

$$[\text{HA}] + [\text{A}^-] = [\text{A}_{\text{TOT}}]$$

where $[\text{A}_{\text{TOT}}]$ is the total weak acid concentration.

In order to calculate the effect of weak acid dissociation on $[\text{H}^+]$, we must take into account water dissociation and electrical neutrality:

$$[\text{H}^+] + [\text{OH}^-] = K_w' \text{ (water dissociation).}$$

$$[\text{SID}] + [\text{H}^+] - [\text{A}^-] - [\text{OH}^-] = 0 \text{ (electrical neutrality).}$$

These four simultaneous equations determine the $[H^+]$ in this solution containing strong ions and weak acids. SID and A_{TOT} are independent variables. K_w' and K_A are constants. Consequently, the other variables $[HA]$, $[H^+]$, $[OH^-]$, and $[A^-]$ must adjust to satisfy the foregoing equations. They are dependent variables.

CARBON DIOXIDE

Along with strong ions and weak bases, ECF contains CO_2 . The concentration of CO_2 in ECF is determined by tissue production and alveolar ventilation. CO_2 , when in solution, exists in four forms: CO_2 (denoted $CO_2[d]$), carbonic acid (H_2CO_3), bicarbonate ions (HCO_3^-), and carbonate ions CO_3^{2-} .

The concentration of $CO_2(d)$ is determined by the solubility coefficient of CO_2 (SCO_2), which depends on body temperature, PCO_2 , and other factors. Several equilibrium equations can be derived from the hydration of CO_2 :

$$[CO_2(d)] = [SCO_2] \times Pco_2$$

The tendency for CO_2 to hydrate to H_2CO_3 , and subsequently dissociate to H^+ and HCO_3^- , is reflected by the equation:

$$[CO_2(d)] \times [OH^-] = K_1 \times [HCO_3^-]$$

These equations can be combined together and with water equilibrium to the following:

$$[H^+] \times [HCO_3^-] = K_c \times pCO_2$$

HCO_3^- also dissociates to release hydrogen ions and carbonate, the equilibrium reaction which is represented by this equation:

$$[H^+] \times [CO_3^{2-}] = K_3[HCO_3^-]$$

FACTORS INDEPENDENTLY INFLUENCING WATER DISSOCIATION

Now that we have looked at the different factors that may influence the concentration of hydrogen ions in a solution—strong ions, weak acids, and CO_2 —we can combine the derived equations to a solve for $[H^+]$:

1. Water dissociation equilibrium:

$$[H^+] \times [OH^-] = K_w'$$

2. Weak acid dissociation equilibrium:

$$[H^+] \times [A^-] = K_A \times [HA]$$

3. Conservation of mass for weak acids:

$$[HA] + [A^-] = [A_{TOT}]$$

4. HCO_3^- formation equilibrium:

$$[H^+] \times [HCO_3^-] = K_c \times pCO_2$$

5. Carbonate ion formation equilibrium:

$$[H^+] \times [CO_3^{2-}] = K_3 \times [HCO_3^-]$$

6. Electrical neutrality:

$$[SID] + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$$

There are six independent simultaneous equations, and just six unknown, dependent variables determined by them: $[HA]$, $[A^-]$, $[HCO_3^-]$, $[CO_3^{2-}]$, $[OH^-]$, and $[H^+]$. There are three known independent variables: $[SID]$, $[A_{TOT}]$, and PCO_2

Solving the equations for $[H^+]$:

$$[SID] + [H^+] - K_c \times Pco_2 / [H^+] - K_A \times [A_{TOT}] / (K_A + [H^+]) - K_3 \times K_c Pco_2 / [H^+]^2 - K_w' / [H^+] = 0$$

In other words, $[H^+]$ is a function of SID , A_{TOT} , PCO_2 , and a number of constants. All other variables, most notably $[H^+]$, $[OH^-]$, and $[HCO_3^-]$ are dependent and cannot independently influence acid-base balance.

Acid-Base Abnormalities

The value of the physical chemistry (“Stewart”) approach is that it allows us to use a simple model for understanding acid-base disturbances, as all abnormalities can be explained in terms of SID , A_{TOT} , or PCO_2 .^{2,14} Traditionally, acid-base disturbances have been classified as resulting from either alterations in arterial carbon dioxide ($PaCO_2$) tension (respiratory acidosis or alkalosis) or alterations in blood chemistry (metabolic acidosis or alkalosis).¹⁶ This remains a useful classification, although it must be remembered that respiratory or metabolic abnormalities rarely occur independent of one another.

RESPIRATORY ACID-BASE ABNORMALITIES

Respiratory Alkalosis

The normal $PaCO_2$ is 40 mm Hg (5.3 kPa). Respiratory alkalosis occurs when there is an acute decrease in $PaCO_2$ as a result of hyperventilation. Acute respiratory alkalosis is characterized by a $pH > 7.45$, a low $PaCO_2$, and a low HCO_3^- . A simple rule of thumb for this reaction is as follows:

Acute respiratory alkalosis:

$$\Delta HCO_3^- = 0.2 \Delta PaCO_2$$

The hyperventilating patient will present with symptoms and signs of vasoconstriction: lightheadedness, visual disturbances, dizziness, and hypocalcemia from increased binding of calcium to albumin. The hypocalcemia is caused by an increase in the available negative charge on albumin in alkaline states. Acute hypocalcemia is associated with paresthesia and tetany. In anesthesia practice, patients may hyperventilate preoperatively as a consequence of anxiety, and postoperatively secondary to pain, agitation, or a full bladder. More commonly, hyperventilation results from poor mechanical ventilation strategy and may result in significant systemic and, in particular, cerebral vasoconstriction. Therapeutic hyperventilation is no longer used to treat intracranial hypertension because of significant concerns regarding cerebral hypoperfusion and ischemia.

Respiratory Acidosis

Respiratory acidosis occurs when there is an acute rise in PaCO_2 usually associated with respiratory failure. This may result from problems with

- Central ventilator control—such as toxicity from anesthetic agents, benzodiazepines, or opioids, stroke, spinal cord injury;
- Peripheral ventilator control—such as myasthenia gravis, poliomyelitis, polymyopathy, or neuromuscular blockade;
- Ventilation-perfusion mismatch—associated with pneumothorax, pleural effusion, atelectasis, pneumonia, or pulmonary edema.

Clinically, patients have signs of CO_2 retention: cyanosis, vasodilatation, and narcosis.

Respiratory acidosis causes a rapid increase in $[\text{H}^+]$. Compensation for hypercarbia is slow, requiring increased urinary excretion of Cl^- ,⁸ and pH falls rapidly. A concomitant increase in the plasma HCO_3^- occurs and reflects a higher total CO_2 load. In the mid-1960s, Brackett, Cohen, and Schwartz elegantly described the relative changes in HCO_3^- in response to acute and chronic elevations in PaCO_2 , providing us with extremely useful “rules of thumb”:¹⁷

In acute hypercarbia, the bicarbonate concentration of plasma rises slowly

- An increase in PaCO_2 by 10 mm Hg (1.3 kPa) results in an increase in HCO_3^- by 1 mmol/L (1 mEq/L)

A patient returning to the intensive care unit from the operating room who has been under ventilation for several hours may be hypercapnic, for example, with a PaCO_2 of 80 mm Hg (10.5 kPa). Using this rule, the expected HCO_3^- will be 28 mmol/L (Table 48.1).

In chronic respiratory failure, the total CO_2 load in the body increases substantially, reflected by relatively high levels of plasma HCO_3^- . There is a concomitant fall in plasma chloride, reflecting compensation for elevated levels of carbonic acid.

In chronic respiratory acidosis:

- $\Delta\text{H}^+ (\text{nEq/L}) = 0.8 (\Delta\text{PCO}_2)$
- An increase in PaCO_2 by 10 mm Hg (1.3 kPa) will increase plasma $[\text{HCO}_3^-]$ by 3 mmol/L (3 mEq/L)

A patient returning to the intensive care unit from the operating room, ventilated to a PaCO_2 of 40 mm Hg (5.3 kPa) but with high total CO_2 , secondary to chronic respiratory failure (for example, from COPD), may fail to liberate from mechanical ventilation, due to acute metabolic alkalosis. Using the “rule” the patient’s preoperative total CO_2 of 33 mEq/L (mmol/L) will indicate a baseline PaCO_2 of 70 mm Hg (9.3 kPa) for that patient (see Table 48.1).

For anesthesiologists, who routinely administer mechanical ventilation to patients with various levels of CO_2 retention, it is important to consider goals for both arterial and end tidal carbon dioxide (etCO_2) in the operating room. This should also include consideration of the impact of drugs,

TABLE 48.1 Changes in Bicarbonate HCO_3^- and PaCO_2 in Acute and Chronic Hypercarbia

ACUTE HYPERCARBIA		
Measured Bicarbonate	Expected PaCO_2 in Acute Respiratory Failure	
$\text{HCO}_3^- \text{ mEq/L or mmol/L}$	$\text{PaCO}_2 \text{ mm Hg}$	$\text{PaCO}_2 \text{ kPa}$
24	40	5.3
25	50	6.6
26	60	8.0
27	70	9.3
28	80	10.5
29	90	11.8
30	100	13

CHRONIC HYPERCARBIA		
Measured Bicarbonate	Expected PaCO_2 in Chronic Respiratory Failure	
$\text{HCO}_3^- \text{ mEq/L or mmol/L}$	$\text{PaCO}_2 \text{ mm Hg}$	$\text{PaCO}_2 \text{ kPa}$
24	40	5.3
27	50	6.6
30	60	8.0
33	70	9.3
36	80	10.5
39	90	11.8
42	100	13

such as opioids and benzodiazepines, on respiratory function and on the effect of intravenous fluids on overall acid-base dynamics. For example, both isotonic saline (0.9%) solution and Ringer’s Lactate (or Hartmann’s) solution will cause progressive increase in extracellular chloride in a dose-dependent manner. This does not occur with truly balanced solutions such as Plasmalyte-148 or Normosol-R. In theory, this may impact postoperative $\text{CO}_2\text{-HCO}_3^-$ homeostasis and respiratory function.

In critical illness, in particular in patients with acute respiratory distress syndrome (ARDS), there is general consensus among intensivists that aggressive mechanical ventilation to normalize pH and PaCO_2 is more harmful than “permissive” hypercapnia. Data support that such an approach—a “lung protective” strategy—is well tolerated,^{18,19} and may indeed be beneficial.²⁰

METABOLIC ACID-BASE DISTURBANCES

Metabolic acid-base disturbances are caused by abnormalities of extracellular water and electrolyte composition and serum protein levels. Using the terminology described above, metabolic acid-base abnormalities are caused by alterations in the SID or A_{TOT} , or both. An increase in the SID causes alkalemia; a decrease in the SID causes acidemia. The alteration may be caused by a change in the total or relative concentration of strong ions. For example, a decrease in the SID (i.e., more anions relative to cations)

TABLE 48.2 Classification of Primary Acid-Base Abnormalities

Abnormalities	Acidosis	Alkalosis
Respiratory	Increased PCO ₂	Decreased PCO ₂
Metabolic		
ABNORMAL SID		
Caused by water excess or deficit	Water excess = dilutional ↓ SID + ↓ [Na ⁺]	Water deficit = contraction ↑ SID ↑ [Na ⁺]
Caused by electrolytes	Chloride excess	Chloride deficit
Chloride (measured)	↓ SID ↑ [Cl ⁻]	↑ SID + ↓ [Cl ⁻]
Other (unmeasured) anions, such as lactate and keto acids	↓ SID ↑ [UMA ⁻]	—
ABNORMAL A_{TOT}		
Albumin [Alb]	↑ [Alb] (rare)	↓ [Alb]
Phosphate [Pi]	↑ [Pi]	

[Alb], Concentration of serum albumin; A_{TOT}, to represent the total concentration of weak ions; [Cl⁻], concentration of chloride ions; [Na⁺], concentration of sodium ions; PCO₂, partial pressure of carbon dioxide; [Pi], concentration of inorganic phosphate; SID, strong ion difference; [UMA⁻], unmeasured anions; ↑, increased; ↓, decreased.

(Modified from Fenc V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. *Am J Respir Crit Care Med*. 2000;162:2246–2251.)

causes acidosis; this may occur because of a net increase in anions: mineral acids such as chloride or organic acids lactate or ketones (organic acids can be metabolized). In addition, SID can fall due to an increase in the volume of distribution of the same quantity of ions (Table 48.2). A useful rule of thumb is that for every 1 mEq/L fall in the SID, there is a 1 mEq/L fall in the [HCO₃⁻] from baseline (although the “normal” level varies with respiratory function; see Table 48.1)—and this approach is widely used to characterize metabolic acidosis. Likewise, for every 1 mEq/L increase in the SID, there is a 1 mEq/L increase in the [HCO₃⁻] from baseline—and this approach is widely used to characterize metabolic alkalosis. Note that, in all scenarios, [HCO₃⁻] is a dependent variable—dependent on changes in SID or A_{TOT}.

Metabolic acidosis is of clinical significance for two reasons: pathologies arising from the acidosis itself and pathologies arising from the cause of the acidosis. Acidosis is associated with alterations in transcellular ion pumps and increased ionized calcium. The result is vasodilation, diminished muscular performance (particularly myocardial), and arrhythmias. The oxyhemoglobin dissociation curve shifts rightward to increase oxygen offload into the tissues. Rapid-onset metabolic acidosis may be associated with profound hypotension, cardiac arrhythmias, and death. The malignancy of the acidosis is strongly related to the underlying disease process; lactic acidosis caused by circulatory shock is more malevolent than hyperchloremic acidosis.¹³ The body is hyperresponsive to acidosis. Increasing hydrogen ion content in cerebrospinal fluid activates the respiratory center to stimulate respiration. Alveolar ventilation increases, reducing arterial CO₂ content, hence reducing the total body [H⁺]. Bicarbonate concentration simultaneously falls, due to buffering activity, and due to the reduction in total

CO₂. As a result, the blood pH falls less in metabolic acidosis compared with respiratory acidosis.

Metabolic alkalosis rarely occurs as a result of acute illness. Symptoms and signs of metabolic alkalosis include widespread vasoconstriction, lightheadedness, tetany, and paresthesia. The main compensatory mechanism is hypoventilation that may delay weaning from mechanical ventilation in critically ill patients.

In normal ECF, the SID is 40 to 44 mEq/L, this positive charge being balanced principally by weak acids (without which the pH of blood would be 11.9). Anything that increases the SID will increase the relative concentration of cations to anions and alkalinize the solution. Anything that decreases the SID will decrease the relative concentration of cations to anions and will acidify the solution. Hence, if the extracellular compartment volume is expanded with free water (no electrolytes), the components of the system are diluted, with relatively more dilution of more abundant moieties (sodium rather than chloride); the result is a reduction in SID and “dilutional acidosis.” This is rarely seen in clinical practice, due to the renal water clearance. Conversely, if free water is removed from the ECF, for example from increased evaporative losses, there is an increase in the relative concentration of charged moieties, and this concentration effects more abundant ions and compounds (sodium rather than chloride). The SID increases and the patient develops a “contraction alkalosis” (see Table 48.2). This is commonly seen in clinical practice, in particular following the administration of loop diuretics that have a greater impact on water removal over salt.

In hospital medicine, “normal saline” (NaCl 0.9%—NS), containing 154 mEq (3.5 g) of sodium and 154 mEq (5.5 g) of chloride, is commonly used. The SID of this solution is 0. As each liter of fluid delivers relatively more chloride than sodium (as the baseline proportions in ECF are 1.4:1—SID 40), progressive hyperchloremia results. This reduces SID and results in “hyperchloremic acidosis.”²¹

Any process that removes chloride without sodium, such as vomiting or aggressive nasogastric suctioning with a loss of HCl, causes metabolic alkalosis (hypochloremic alkalosis) due to an increase in SID. The alkalosis is caused by chloride loss, which obeys the law of conservation of mass (i.e., there is a finite quantity available in the ECF), not hydrogen ions, whose source—water—is unlimited. Severe diarrhea, which is associated with loss of both potassium and sodium, reduces the SID, and is associated with metabolic acidosis. Aggressive use of diuretics causes a net loss of free water over sodium and chloride and causes contraction alkalosis.

The most significant form of metabolic acidosis is associated with a net gain of “unmeasured” (organic—that is electrolytes not conventionally measured on serum chemistry analysis) anions and, consequently, a decreased SID.

1. In dysoxia, liver dysfunction, and, in particular, states of severe stress, lactate is produced, reducing the SID and causing acidosis
2. In out-of-control diabetes (ketoacidosis) or during starvation or liver disease, β-hydroxybutyrate and acetacetate are produced, reducing SID and causing acidosis
3. In severe renal failure, Cl⁻, SO₄²⁻, PO₄³⁻ (“fixed renal acids”), and various other metabolic intermediaries are not excreted, causing acidosis.

The total weak acid pool, principally serum albumin and phosphate, is also an important determinant of acid-base status. Hyperphosphatemia has long been associated with the acidosis of renal failure. Hypoalbuminemia is common in critical care. Hypoalbuminemia decreases A_{TOT} and is associated with metabolic alkalosis.^{22,23} There is a strong association between hypoalbuminemia and severity of critical illness. Albumin deficits result from four different homeostatic changes: reprioritization of hepatic protein production favoring production of acute phase reactants and limiting albumin synthesis; capillary leak with loss of albumin into the interstitium; breakdown of pre-existing albumin so that its constituent amino acids can be used for protein synthesis; and replacement of plasma with protein-free fluids.

The impact of hypoalbuminemia on acid-base balance has been grossly underestimated. Stewart's original theory has been subsequently modified by Fencl and Figge.²⁴ The serum albumin concentration is the core negative charge offsetting the net positive charge of the SID.²² Consequently, the presence of hypoalbuminemia may mask the detection of acidosis²⁵ caused, for example, by unmeasured anions (UMA), when using conventional tools of acid-base chemistry: pH, bicarbonate, base deficit, and the anion gap (AG).²⁶ Indeed, the presence of hypoalbuminemia has significant implications, not least for its association with adverse outcomes.²⁷ Hyperalbuminemia is very unusual; in cholera, when associated with hemoconcentration, it results in acidosis.²⁸

Regulation of Acid-Base Balance

Extracellular hydrogen ion concentration appears to be tightly controlled by the body. In all probability this regulation reflects a need to prevent rapid changes in extracellular electrochemical balance from interfering with the function of transcellular ion pumps. To prevent fluctuation a variety of intracellular and extracellular buffering systems have evolved. A *buffer* is a solution of two or more chemicals that minimizes changes in pH in response to the addition of an acid or base. Ideally, a buffer has a pK_a that is equal to the pH, and an ideal body buffer has a pK_a between 6.8 and 7.2. Most biologically salient buffers are weak acids.

It is valuable to view control of hydrogen ion concentration in terms of volatile and metabolic acids (mineral and organic). The major source of acid in the body is the volatile acid CO_2 , which produces 12,500 mEq of H^+ a day, mostly excreted by the lungs. In contrast, only 20 to 70 mEq of hydrogen ion-promoting anions are excreted daily thru the kidney. Volatile acid is principally buffered by hemoglobin (Hb). Deoxygenated Hb is a strong base and there would be a huge rise in the pH of venous blood if Hb did not bind the hydrogen ions produced in oxidative metabolism.

Carbon dioxide easily passes through cell membranes. Within the erythrocyte CO_2 combines with H_2O , under the influence of the enzyme carbonic anhydrase, to form H_2CO_3 , which ionizes to hydrogen and bicarbonate. Hydrogen ions bind to histidine residues on deoxyhemoglobin (the "Haldane" effect), and bicarbonate is actively pumped out of the cell. Chloride moves inward to maintain electro-neutrality (the chloride shift) and to ensure the continued

production of carbonic acid. CO_2 is also buffered directly by Hb (carbaminohemoglobin) and by plasma proteins (carbamino proteins). Venous blood contains 1.68 mmol/L extra CO_2 over arterial blood: 65% as HCO_3^- and H^+ bound to Hb, 27% as carbaminohemoglobin (CO_2 bound to Hb), and 8% dissolved.

When respiratory failure occurs, the principal CO_2 buffering system, Hb, becomes overwhelmed, leading to the rapid development of acidosis. In response, the kidney excretes an increased chloride load, using NH_4^+ , a weak cation, for electrochemical balance. Thus ECF osmolality is maintained. This process is conventionally referred to as "metabolic compensation." Chronic respiratory acidosis is associated with increase in total body CO_2 content, reflected principally by an increase in serum bicarbonate (see Table 48.1). Hypercapnia is associated with a progressive increase in CSF bicarbonate, reflecting an overall increase in total CO_2 load. Compensation for this hypercarbia is a reduction in CSF chloride²⁹ and an increase in CSF SID.³⁰⁻³² This is probably controlled by active transport mechanisms across the blood-brain barrier or at the level of the choroid plexus and can be blocked by furosemide and acetazolamide.³³⁻³⁶ The result is a rightward shift in the PCO_2 response curve: the respiratory center responds to hypercarbia by increasing respiratory drive at a higher PCO_2 level than under normal conditions.

Bicarbonate is a dependent variable that increases or decreases with PCO_2 .³⁷ The rate of conversion of CO_2 to HCO_3^- is dependent on carbonic anhydrase activity and occurs slowly. Thus, it is possible to mathematically determine whether a rise in $PaCO_2$ is acute or longstanding (see Table 48.1). Metabolic acid is buffered principally by increased alveolar ventilation, producing respiratory alkalosis, and extracellular weak acids. These weak acids include plasma proteins, phosphate, and bicarbonate. The bicarbonate buffering system (92% of plasma buffering and 13% overall) is probably the most important extracellular buffer. The pK_a of bicarbonate is relatively low (6.1), but the system derives its importance from the enormous quantity of CO_2 present in the body. The coupling of bicarbonate and H_2O produces CO_2 , which is then excreted through the lungs, increasing alveolar ventilation. Physicians must be aware of the importance of this compensatory mechanism. For example, anesthetized or critically ill patients on controlled mechanical ventilation lose the capacity to regulate their own PCO_2 . Consequently, the combination of acute metabolic and respiratory acidosis can cause a devastating reduction in pH.

The major effect of the kidney on acid-base balance relates to renal handling of sodium and chloride ions. As dietary intake of sodium and chloride is roughly equal, the kidney excretes a net chloride load, using NH_4^+ , a weak cation, to electrochemically neutralize urinary chloride.³⁸

In metabolic acidosis, the kidneys preferentially excrete chloride. In metabolic alkalosis, chloride is retained and sodium and potassium are excreted. The presence of bicarbonate in the urine reflects the need to maintain electrical neutrality. Abnormalities in the renal handling of chloride may be responsible for several inherited acid-base disturbances. In renal tubular acidosis, there is inability to excrete Cl^- in proportion to Na^+ .³⁹ The diagnosis can be made by observing a hyperchloremic metabolic acidosis, with

inappropriately low levels of Cl^- in the urine: the urinary SID is positive. If the urinary SID is negative, the process is not of renal origin. Similarly, pseudohypoaldosteronism appears to be due to high reabsorption of chloride.⁴⁰ Bartter syndrome is caused by a mutation in the gene encoding the chloride channel—CLCNKB—that regulates the Na-K-2Cl cotransporter (NKCC2).⁴¹

The other causes of hyperchloremic metabolic acidosis are gastrointestinal losses (diarrhea, small bowel or pancreatic drainage), parenteral nutrition, excessive administration of saline, and the use of carbonic anhydrase inhibitors.

Analytic Tools Used in Acid-Base Chemistry

Acid-base balance is a core component of the clinical evaluation of the acutely and critically ill. Arterial blood gas (ABG) analysis provides immediate information on the status of the patient's respiratory system and whether or not a state of acidosis or alkalosis is present. By applying a variety of empiric rules, the information contained in an ABG is often sufficient to allow one to identify the presence, cause, and progression of a disease. The diagnostic sensitivity of blood gas analysis is augmented when a blood chemistry panel, glucose and lactate, and blood and urinary ketones measurements are added.

Several different approaches to acid-base balance are in widespread use.⁴² These can be described as descriptive, based on changes in the Henderson Hasselbalch equation; semi-quantitative, based on calculations and nomograms; or quantitative, based on physical chemistry. These may be used interchangeably—and I would suggest that there is no best or worst approach, merely different methods of analyzing the data. The descriptive approach utilizes the inter-relationship between PaCO_2 and $[\text{HCO}_3^-]$ to detect and diagnose acid-base abnormalities. An extension of this is the anion gap (AG). The semi-quantitative approach includes the buffer base (BB) concept, the standardized base excess (BE), and the base-deficit gap (BDG). The quantitative approach utilizes SID and A_{TOT} and is quantified using the strong ion gap (SIG).

Over time, quantitative analyses are likely to dominate the clinical approach to acid-base chemistry. Many of the early approaches were developed at a time when only total CO_2 levels could be measured. Indeed, the continued popularity of the AG is curious given that serum lactate and blood ketones can now be easily measured at the bedside.

THE DESCRIPTIVE (CO_2 -BICARBONATE [BOSTON]) APPROACH

Schwartz, Brackett, Relman, and colleagues at Tufts University in Boston developed the most popular descriptive approach to acid-base chemistry in the 1960s. Their formulation uses acid-base maps and the mathematical relationship between CO_2 tension and plasma bicarbonate (or total CO_2), derived from the Henderson-Hasselbalch equation, to classify acid-base disturbances in terms of two independent variables: PaCO_2 and $[\text{HCO}_3^-]$.^{43,44} To validate

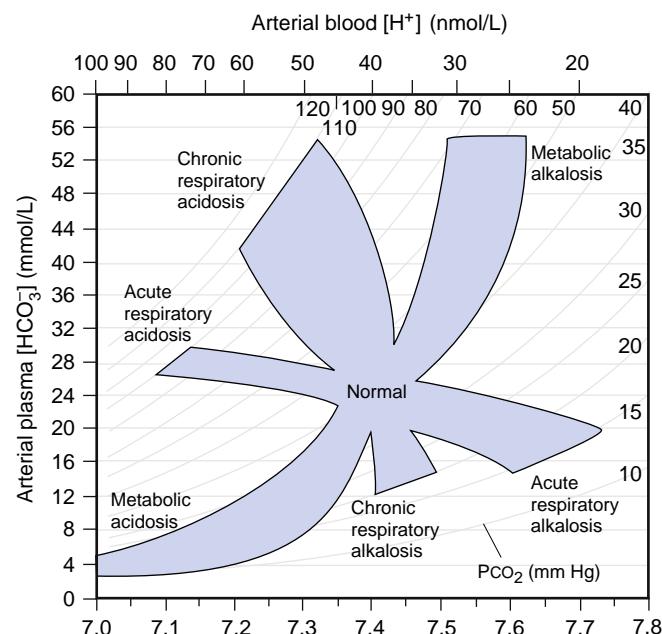


Fig. 48.2 Acid-Base Nomogram Using the Boston Approach. Different acid-base disturbances can be distinguished based on the relative values of PCO_2 and $[\text{HCO}_3^-]$. (Modified from Brenner BM, Rector FC. *The Kidney*. 3rd ed. Philadelphia, PA: WB Saunders; 1986:473.)

this approach, a number of patients with known acid-base disturbances, at steady states of compensation, were evaluated. The degree of compensation, relative to what was considered normal, was measured for each disease state. The investigators were able to describe six primary states of acid-base imbalance, using linear equations or maps, relating hydrogen ion concentration to PCO_2 for respiratory disturbances, and PCO_2 to $[\text{HCO}_3^-]$ concentration for metabolic disturbances (Fig. 48.2). For any given acid-base disturbance, an expected $[\text{HCO}_3^-]$ concentration was determined. These were then compiled into a series of mathematical rules (see Table 48.1 and Box 48.1). For most simple disturbances, this is a reasonable approach. As discussed above, in acute respiratory acidosis, the $[\text{HCO}_3^-]$ will increase by 1 mmol/L (mEq/L) for every 10 mm Hg (1.3 kPa) elevation in PaCO_2 above 40 mm Hg (5.3 kPa). In chronic respiratory acidosis, the $[\text{HCO}_3^-]$ will increase by 3 mEq/L for every 10 mm Hg (1.3 kPa) elevation in PaCO_2 above 40 mm Hg (5.3 kPa).

In acute metabolic acidosis, the $[\text{HCO}_3^-]$ falls by 1 mEq/L for every 1 mEq/L in strong anions. The respiratory center is activated, resulting in a predictable fall in the PaCO_2 . This was neatly characterized by Winters in a pediatric population in 1967 and remains robust.⁴⁵ In acute metabolic acidosis, the PaCO_2 (in mm Hg) falls predictably, using the $1.5 \times [\text{HCO}_3^-] + 8$ rule. For example, if the $[\text{HCO}_3^-]$ is 12 mmol/L (mEq/L), then the expected PaCO_2 is $1.5 \times 12 + 8 = 26$ mm Hg. If the PaCO_2 is higher than this, then compensation is inadequate and there is a concomitant respiratory problem (for example, ketoacidosis in the presence of a respiratory tract infection). Winters also described expected compensation using the BE approach (see next section): for every 1 mEq/L reduction in the BE the PaCO_2 is expected to fall by 1 mm Hg—otherwise “compensation” is inadequate.

BOX 48.1 The Descriptive (CO₂-HCO₃⁻) Approach to Acid-Base

Respiratory Disorders

Acute Respiratory Acidosis

$$\text{Expected } [\text{HCO}_3^-] = 24 + [(\text{measured PaCO}_2 - 40)/10]$$

Chronic Respiratory Acidosis

$$\text{Expected } [\text{HCO}_3^-] = 24 + 4 [(\text{measured PaCO}_2 - 40)/10]$$

Acute Respiratory Alkalosis

$$\text{Expected } [\text{HCO}_3^-] = 24 - 2 [(\text{40} - \text{measured PaCO}_2)/10]$$

Chronic Respiratory Alkalosis

$$\text{Expected } [\text{HCO}_3^-] = 24 - 5 [(\text{40} - \text{measured PaCO}_2)/10] \text{ (range: } \pm 2\text{)}$$

Metabolic Disorders

Metabolic Acidosis

$$\text{Expected PaCO}_2 = 1.5 \times [\text{HCO}_3^-] + 8 \text{ (range: } \pm 2\text{)}$$

Metabolic Alkalosis

$$\text{Expected PaCO}_2 = 0.7 \times [\text{HCO}_3^-] + 20 \text{ (range: } \pm 5\text{)}$$

In metabolic alkalosis, in order to restore pH to homeostatic levels, it is necessary to retain carbonic acid, and hypoventilation occurs, ultimately resulting in increased [HCO₃⁻]. The expected PaCO₂ equals 0.7 × [HCO₃⁻] + 20 (in mm Hg). So if a patient has a [HCO₃⁻] of 34 mEq/L (mmol/L), then the PaCO₂ should be 44 mm Hg.

Using these maps, equations, and rules, physicians can determine the nature of most respiratory and metabolic acid-base disturbances and in a manner that is usually accurate. Although there is a mathematical relationship in place, alterations in [H⁺] and [HCO₃⁻] do not reflect cause and effect. For example, chronic hypoventilation is associated with an increase in PCO₂ and [HCO₃⁻]. Many physicians have incorrectly assigned the increase in [HCO₃⁻] as compensation for raised PCO₂. It is not. The increased HCO₃⁻ concentration reflects increased total CO₂ in the body.

Although the PCO₂-HCO₃⁻ approach is relatively accurate for most disturbances, and is particularly useful for respiratory problems, there are several inherent pitfalls, particularly in relation to the metabolic component. First, the approach is not as simple as it seems, requiring the clinician to refer to confusing maps or to learn formulas and perform mental arithmetic. Second, the system neither explains nor accounts for many of the complex acid-base abnormalities seen in perioperative and critically ill patients, such as those with acute acidosis in the setting of hypoalbuminemia, free water deficit or excess, hyperchloremia, hyperphosphatemia, or concurrent metabolic acidosis and alkalosis.

ANION GAP APPROACH

The most widely used tool for investigating metabolic acidosis is the AG, developed by Emmett and Narins in 1977.⁴⁶ It is based on the law of electrical neutrality. It is entirely consistent with the physical chemistry approach, described

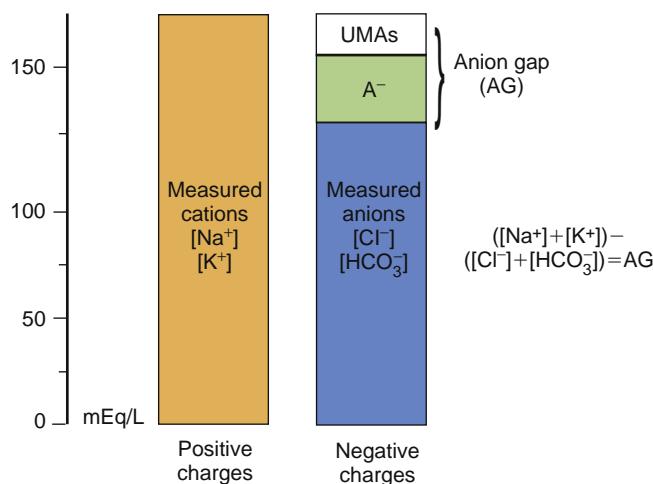


Fig. 48.3 The Anion Gap Represents the Difference in Charge Between Measured Cations and Measured Anions. The missing negative charge is made up of weak acids (A⁻), such as albumin and phosphate, and strong unmeasured anions (UMAs), such as lactate.

in the next section, and is usually used alongside the Boston approach to acid-base. Again, the system is based on data that were not easily available or known at the time of publication: the contribution to electrical neutrality ascribed to weak acids (phosphate and albumin) and UMA. The sum of the difference in charge of the common extracellular ions reveals an unaccounted for “gap” of -10 to -12 mEq/L. There are three widely used variants of the AG (Fig. 48.3), depending on whether or not potassium and lactate are included:

$$\text{Anion gap (simple)} = ([\text{Na}^+] - [\text{Cl}^-] + [\text{HCO}_3^-]) = 12 \text{ to } 14 \text{ mEq/L}$$

$$\text{Anion gap (conventional)} = ([\text{Na}^+] + [\text{K}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])) = 14 \text{ to } 18 \text{ mEq/L}$$

$$\text{Anion gap (modern)} = ([\text{Na}^+] + [\text{K}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-] + [\text{lactate}^-])) = 14 \text{ to } 18 \text{ mEq/L}$$

If the patient develops a metabolic acidosis, and the gap widens to, for example, >20 mEq/L, then the acidosis is caused by UMA (usually renal acids or ketones). If the gap does not widen, then the anions are being measured, and the acidosis has been caused by hyperchloremia (bicarbonate cannot independently influence acid-base status) or lactate (if used). While this is a useful tool, it is weakened by the assumption of what is or is not a “normal gap”.⁴⁷ The AG frequently underestimates the extent of the metabolic disturbance.²⁶ The majority of critically ill patients are hypoalbuminemic, and many are also hypophosphatemic. Consequently, the gap may be normal in the presence of UMA. This has been extensively studied by Fencl and Figge, who have provided us with a variant known as the “corrected AG”.²⁶

$$\text{Anion gap corrected (for albumin)} = \text{calculated anion gap} + 0.25 (\text{normal albumin}^* - \text{observed albumin g/L})$$

*which may vary between populations/labs; if g/dL used the factor is 2.5.

In this corrected form the AG accurately quantifies metabolic acidosis, and it is useful in discriminating an acidosis due to UMA from one reflecting hyperchloremia, in a previously healthy patient (e.g., in acute trauma). Moviat and colleagues have demonstrated that the AG corrected for albumin accurately detects complex acid-base abnormalities in intensive care.⁴⁸

Another version of the AG is the delta AG (delta ratio DR—Box 48.2), an approach that has successfully predicted adverse outcomes in critical illness.⁴⁹ Simply, if the AG is normal, or unchanged, and the bicarbonate level falls,

then the delta ratio will be less than 0.4, and a hyperchloremic acidosis is present. A DR between 1 and 2 is what one would expect from metabolic acidosis due to UMA or lactate. If the ratio is greater than 2, mixed acid-base abnormalities are present. Although on the surface, this process is relatively simple, it assumes that the clinician knows the normal AG and bicarbonate for that particular patient. In addition, it does not result in a clear diagnosis other than hyperchloremia.

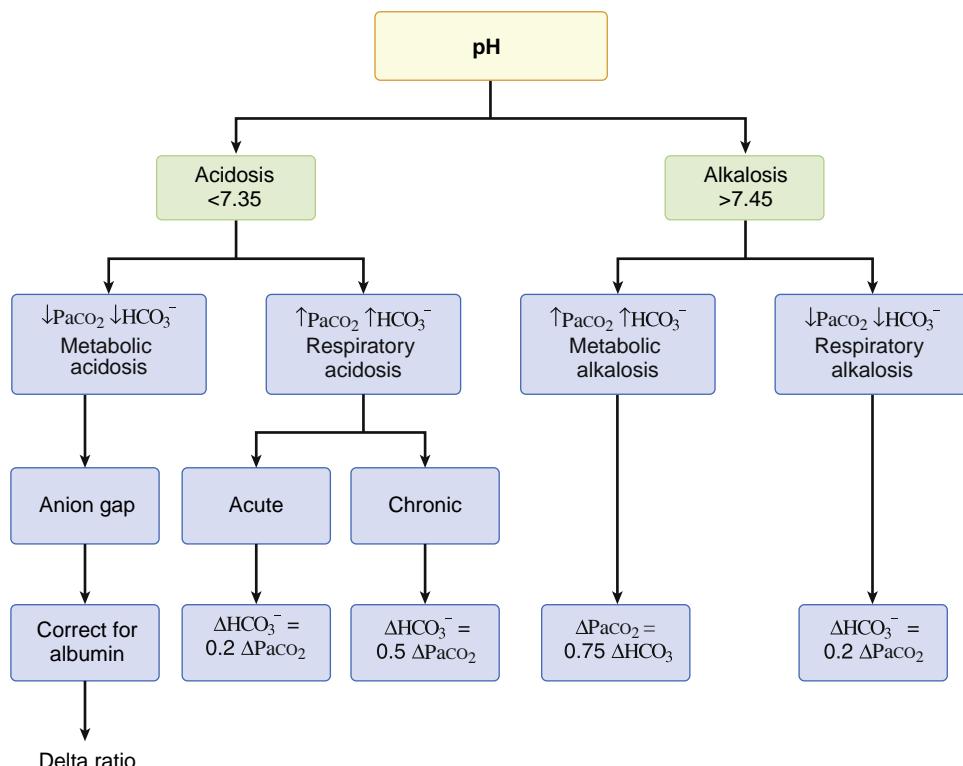
Fig. 48.4 is a decision tree that uses this descriptive approach to acid-base.

BOX 48.2 The Delta Anion Gap (Delta Ratio)

$$\begin{aligned}\text{Delta ratio} &= \Delta \text{Anion gap} / \Delta [\text{HCO}_3^-] \text{ or } \uparrow \text{anion gap} / \downarrow [\text{HCO}_3^-] \\ &= \frac{\text{Measured anion gap} - \text{Normal anion gap}}{\text{Normal } [\text{HCO}_3^-] - \text{Measured } [\text{HCO}_3^-]} \\ &= \frac{(\text{AG} - 12)}{(24 - [\text{HCO}_3^-])}\end{aligned}$$

THE SEMI-QUANTITATIVE (BASE DEFICIT/EXCESS [COPENHAGEN] APPROACH

In metabolic acidosis, the addition of UMA to the ECF results in a net gain of one hydrogen ion for each anion. This is buffered, principally by bicarbonate, such that each anion gained results in an equivalent fall in the bicarbonate concentration. Thus, the change in the bicarbonate concentration from baseline should reflect the total quantity of net



Delta ratio	Clinical assessment
<0.4	Hyperchloremic normal AG acidosis
<1	High AG and normal AG acidosis
1 to 2	Pure anion gap acidosis Lactic acidosis: average value 1.6 DKA more likely to have a ratio closer to 1 because of urine ketone loss
>2	High AG acidosis and concurrent metabolic alkalosis or preexisting compensated respiratory acidosis

Fig. 48.4 The Descriptive (“Boston”) Approach to Acid-Base Balance. DKA, Diabetic ketoacidosis; AG, Anion gap.

anions gained. Adherents to the descriptive approach to acid-base refer to this as the “delta” bicarbonate. However, this is problematic, as it does not separate out the effect of CO_2 metabolism on the $[\text{HCO}_3^-]$.

In 1948, Singer and Hastings⁵⁰ proposed that changes in the whole blood BB could be used to quantify the metabolic component independent of Henderson-Hasselbalch. The BB represented the sum of the bicarbonate and the non-volatile buffer ions (essentially the serum albumin, phosphate, and Hb). Applying the law of electrical neutrality, the BB was forced to equal the electrical charge difference between strong (fully dissociated) ions. Thus, normally $\text{BB} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$. Alterations in BB represented changes in strong ion concentrations (which could not be easily measured in 1948). BB increases in the presence of a metabolic alkalosis and decreases in metabolic acidosis. The major drawback of BB measurements is the potential for changes in buffering capacity associated with alterations in Hb concentration and pH.

Following the development of sophisticated electrodes for measuring CO_2 tension in Copenhagen in the early 1950s,⁵¹ Astrup and Jorgensen developed the standard bicarbonate—the bicarbonate concentration at 37°C and at a PaCO_2 of 40 mm Hg (5.3 kPa).⁵² Building upon this work, Siggaard-Anderson and Astrup⁵³ recognized that PCO_2 and $[\text{HCO}_3^-]$ were not independent variables. As a result, they derived the BE as a measure that could differentiate respiratory from metabolic acid-base disturbances. As defined, the BE is the amount of strong acid (strong anion) or base (strong cation) required to return the pH to 7.4, assuming that PCO_2 is constant at 40 mm Hg (5.3 kPa) and that the temperature is 37°C.⁵⁴ Like the Boston group, the Siggaard-Anderson data were derived from observations on a large population of patients. The investigators carefully titrated known amounts of acid or base to blood maintained by tonometry at various PaCO_2 values and a wide range of hemoglobin concentration at 37°C. These studies led to the development of an alignment nomogram (Fig. 48.5 and Table 48.3) that allowed for the determination of BE from a single measurement of pH, PaCO_2 , and Hb concentration at 37°C. Current algorithms for computing the BE are derived from the Van Slyke equation (1977).⁵⁵

$$\text{BE} = \frac{(\text{HCO}_3^- - 24.4 + [2.3 \times \text{Hb} + 7.7]) \times (\text{pH} - 7.4)}{[\text{pH} - 7.4] \times (1 - 0.023 \times \text{Hb})}$$

The most commonly used estimation of BE uses just the bicarbonate and pH by the following equation:

$$\text{BE} = 0.93 \times ([\text{HCO}_3^-] - 24.4 + 14.83 \times [\text{pH} - 7.4])$$

There is a very high level of agreement between this calculation and the empirical data that were used to construct the original nomogram. The calculation is accurate *in vitro*, but not *in vivo* because of the dynamic buffering activity of Hb within the acid-base paradigm of gas and electrolyte exchange. Moreover, weak acids such as phosphate and albumin also contribute to nonbicarbonate buffering. Hence the following formula is now used to calculate the standard base excess (SBE) or the BE of ECF:

$$\text{SBE} = \frac{((\text{HCO}_3^- \text{ actual mEq/L}) - 24.8 + (16.2 \times (\text{pH} - 7.40)))}{16.2}$$

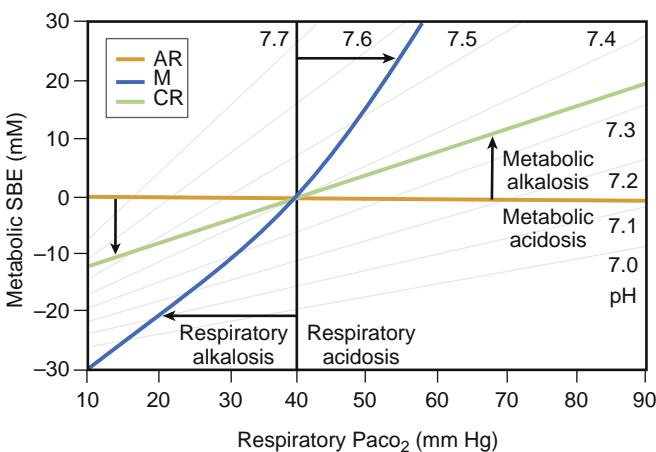


Fig. 48.5 Acid-Base Nomogram Using the Copenhagen Approach as Revised by Schlichtig. The various acid-base disturbances can be distinguished based on PCO_2 and base deficit or excess, here referred to as standard base excess (SBE). Arrows represent changes as the body compensates for acute acidosis or alkalosis. AR, Acute respiratory acidosis or alkalosis; CR, chronic respiratory acidosis or alkalosis; M, metabolic acidosis or alkalosis. (From Schlichtig R, Grogono AW, Severinghaus JW. Human Paco_2 and standard base excess compensation for acid-base imbalance. *Crit Care Med*. 1998;26:1173–1179.)

TABLE 48.3 Changes in Standard Base Deficit or Excess in Response to Acute and Chronic Acid-Base Disturbances

Disturbance	SBDE vs. PaCO_2
Acute respiratory acidosis	$\Delta \text{BDE} = 0$
Acute respiratory alkalosis	$\Delta \text{BDE} = 0$
Chronic respiratory acidosis	$\Delta \text{BDE} = 0.4 \Delta \text{PaCO}_2$
Metabolic acidosis	$\Delta \text{PaCO}_2 = \Delta \text{BDE}$
Metabolic alkalosis	$\Delta \text{PaCO}_2 = 0.6 \Delta \text{BDE}$

Δ , Change in value; BDE , base deficit or excess; PaCO_2 , partial pressure of arterial carbon dioxide.

Modified from Narins RB, Emmett M. Simple and mixed acid-base disorders: a practical approach. *Medicine (Baltimore)*. 1980;59:161–187.

The value of 16.2 mEq/L approximates all of the nonbicarbonate buffers in ECF (albumin, phosphate, and mean ECF Hb). It is likely that Siggaard-Andersen overestimated the impact of Hb as an extracellular buffer and underestimated the uptake and release of chloride into erythrocytes in the peripheries and lungs respectively.⁵⁶

Although various descriptions of this approach to acid-base chemistry refer to the BE—and that term is reported on blood gas forms, when a negative base excess (1-BE) is reported—the correct terminology refers to it as the *base deficit*.⁵⁷ For simplicity, in the following discussion, I will refer to the BE, keeping in mind that it may be positive (metabolic alkalosis) or negative (metabolic acidosis).

Application of simple mathematical rules allows for use of the BE in each of the common acid-base disturbances (Box 48.3 and Fig. 48.6). For example, in acute respiratory acidosis or alkalosis, BE does not change. Conversely, in acute metabolic acidosis, the magnitude of change of the PaCO_2 (in millimeters of mercury) is the same as that of the BE (in mmol/L or mEq/L).

BOX 48.3 Calculation of the Base Excess Gap^{12,58,59}

$$BE_{NaW} (\text{water and sodium effect}) = 0.3 ([Na^{+}_{\text{meas}}] - 140) \text{ mEq/L}$$

$$BE_{Cl} (\text{chloride effect}) = 102 - [Cl^{-} \text{ effective}] \text{ (mEq/L)}$$

$$BE_{Pi} (\text{phosphate effect}) = (0.309 \times (pH - 0.47)) \times Pi \text{ mEq/L}$$

$$BE_{\text{prot}} (\text{protein effect}) = (42 - [\text{Albumin g/L}]) \times (0.148 \times pH - 0.818)$$

$$BE_{\text{calc}} = BE_{NaW} + BE_{Cl} + BE_{PO4} + BE_{\text{prot}}$$

$$BE_{\text{Gap}} = BE_{\text{calc}} - BE_{\text{actual}} - [\text{lactate mEq/L}]$$

A Simplified Calculation of the Base Excess Gap⁶⁰

$$BE_{NaCl} = ([Na^{+}] - [Cl^{-}]) - 38$$

$$BE_{\text{Alb}} = 0.25 (42 - \text{albumin g/L})$$

$$BE_{NaCl} - BE_{\text{Alb}} = BDE_{\text{calc}}$$

$$BE_{\text{actual}} - BE_{\text{calc}} - [\text{lactate}] = BEG = \text{the effect of unmeasured anions or cations}$$

*This approach involves calculating the base deficit excess for sodium, chloride, and free water (BE_{NaCl}), and that for albumin (BE_{Alb}). The result is the calculated BE (BE_{calc}). This is subtracted from the measured BE to find the BE gap.

There has been considerable discussion over the past 60 years about the merits and demerits of the BE, as compared to the $\text{CO}_2\text{-HCO}_3^-$ system. In reality, there is little difference between the two; both equations and nomograms were derived from patient data and abstracted backward. Calculations use bicarbonate as measured on a blood gas analyzer. Consequently, for most patients, either approach is relatively accurate but may be misleading because they do not allow the clinician to distinguish between, for example, acidosis due to lactate or chloride, or alkalosis due to dehydration or hypoalbuminemia. These measures may miss the presence of an acid-base disturbance entirely; for example, a hypoalbuminemic (metabolic alkalosis) critically ill patient with a lactic acidosis (metabolic acidosis) may have a normal range pH, bicarbonate, and BE. This lack of precision may lead to inappropriate or inadequate therapy.

Changes in the BE occur secondary to alterations in the relative concentrations of sodium, chloride, free water, albumin, phosphate, and UMA. By calculating the contribution of the individual components of the BE it is possible to identify: (1) contraction alkalosis, (2) hypoalbuminemic alkalosis, (3) hyperchloremic acidosis, (4) dilution acidosis (if indeed it exists), and (5) acidosis secondary to UMA. This approach, which can be labelled the base-deficit gap, has been proposed by Gilfix and Magder (see Box 48.3)⁵⁸ and simplified subsequently by Balasubramanyan and associates⁵⁹ and Story and associates.⁶⁰ The BDG should mirror the SIG (below) the corrected AG.

The simplified calculation as proposed by Story et al. is very easy to calculate at the bedside and in the majority of situations (see Box 48.3) replicates the more complex calculations originally proposed by Gilfix and Magder.⁵⁸

STEWART APPROACH

A more accurate reflection of true acid-base status can be derived using the Stewart or physical chemical approach, subsequently updated by Fencl.^{5,15} This approach is based on the concept of electrical neutrality, a small advance from the AG. There exists, in plasma, a SIDa $[(Na^{+} + Mg^{2+} + Ca^{2+} = K^{+}) - (Cl^{-} + A^{-})]$ of 40 to 44 mEq/L, balanced by the negative charge on bicarbonate and A_{TOT} (the BB—SIDe). There is a small difference between SIDa (apparent SID) and BB (SIDe—effective SID) that represents a SIG and quantifies the amount of UMA present (Fig. 48.7).

$$\text{SIDa (apparent SID)} = ([Na^{+}] + [K^{+}] + [Mg^{2+}] + [Ca^{2+}]) - [Cl^{-}]$$

$$\text{SIDe (effective)} = [HCO_3^{-}] + [\text{charge on albumin}] + [\text{charge on Pi}] \text{ (in mmol/L)}$$

Weak acids' degree of ionization is pH dependent, so one must calculate for this:

$$[\text{alb}^{-}] = [\text{alb g/L}] \times (0.123 \times pH - 0.631)$$

$$Pi \text{ (mmol/L)} = [PO_4] \times (0.309 \times pH - 0.469)$$

$$\text{Strong Ion Gap (SIG)} = \text{SIDa} - \text{SIDe}$$

Unfortunately, the SIG may not represent unmeasured strong anions but only all anions that are unmeasured. For example, if a patient has been resuscitated with gelatin, his/her SIG will increase. Further, SID changes quantitatively in absolute and relative terms when there are changes in plasma water concentration. Fencl has addressed this by correcting the chloride concentration for free water ($Cl^{-\text{corr}}$) using the following equation⁵:

$$[Cl^{-}]_{\text{corr}} = [Cl^{-}]_{\text{observed}} \times ([Na^{+}]_{\text{normal}} / [Na^{+}]_{\text{observed}}).$$

This corrected chloride concentration may then be inserted into the SIDa equation above. Similarly, the derived value for UMA can also be corrected for free water by substituting UMA for Cl^{-} in the above equation.²⁵ In a series of nine normal subjects, Fencl estimated the "normal" SIG as $8 \pm 2 \text{ mEq/L}$.²⁵

Calculation of SIG is cumbersome. The data required are more extensive and thus more expensive than other approaches and there is much confusion about the normal range of SIG. It is unclear, in standard clinical practice, that SIG has any advantage over AGc (which is SIG without calcium, magnesium, and phosphate—which usually cancel out each other's charges).

In all likelihood no single number will ever allow us to make sense of complex acid-base disturbances. Fencl²⁵ has suggested that, rather than focusing on AG or BDE, physicians should address each blood gas in terms of all alkalinizing and acidifying effects: respiratory acidosis/alkalosis, the presence or absence of abnormal SID (due to

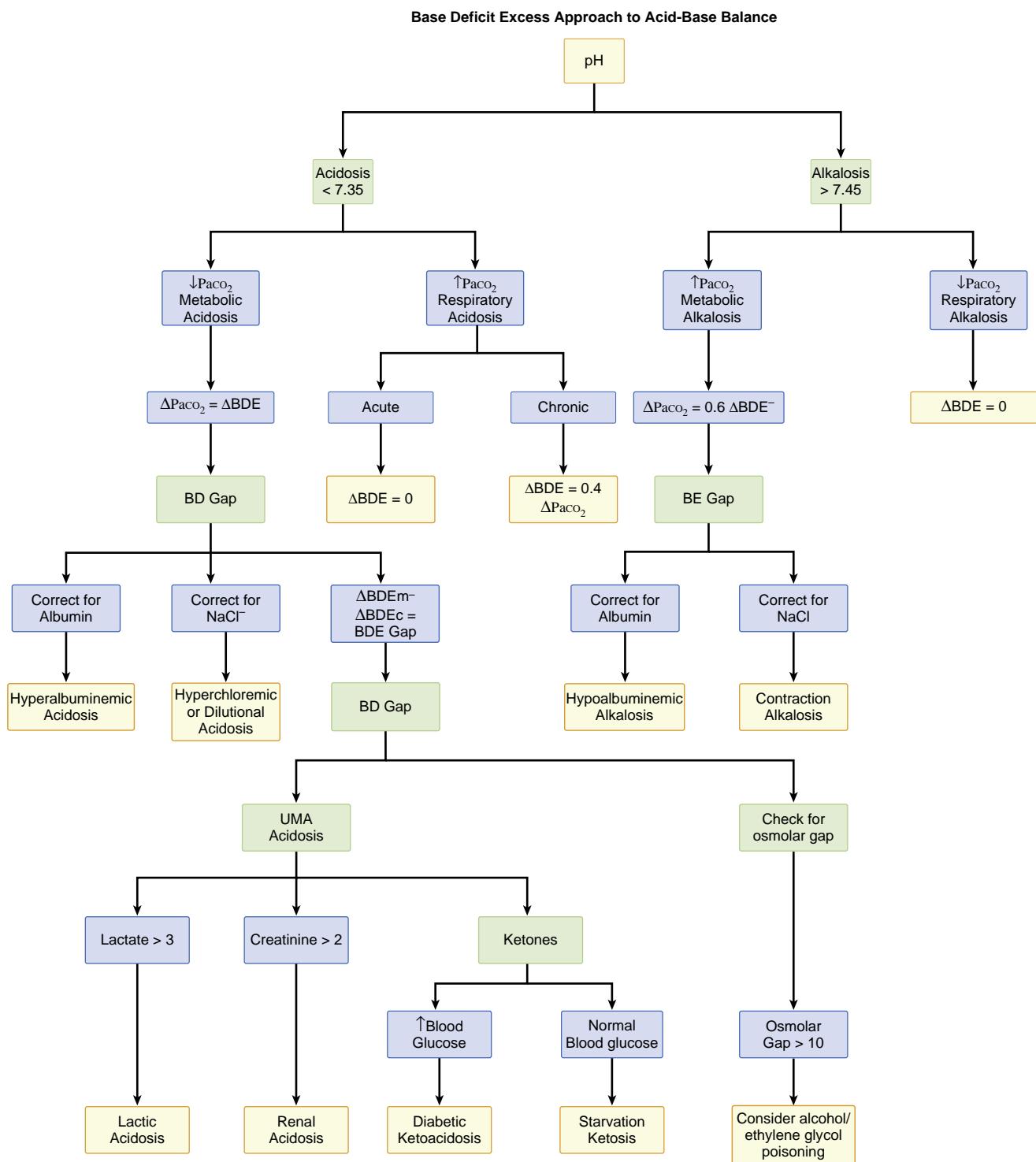


Fig. 48.6 The Semi-Quantitative (“Copenhagen”) Approach to Acid-Base Balance. BD, Base deficit; BE, base excess; BDE_m, measured base deficit or excess; BDE_c, Base deficit or excess corrected for albumin, sodium, chloride, and free water (see Box 48.3); UMA, unmeasured anions; lactate in mmol/L, creatinine in mg/dL, osmolar gap in mOsm.

water excess/deficit, measured electrolytes, or unmeasured electrolytes), and abnormal A_{TOT} . Consider the following patient, described by Fencl²⁵ (data in mEq/L unless otherwise stated):

Na 117, Cl 92, Ca 3.0, Albumin 6.0 g/L
K 3.9, Mg 1.4, Pi 0.6 mmol/L

ABG: pH 7.33, PCO₂ 30 mm Hg, HCO₃ 15

Derived values would be:

AG 13, AG_{corrected} 23, BE -10, SID 18, Cl_{corrected} 112, UMA_{corrected} 18.

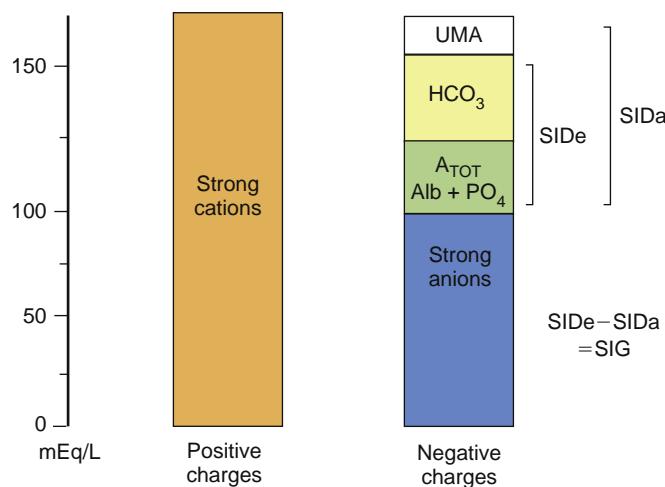


Fig. 48.7 The Strong Ion Gap: SID Apparent is the Sum of ATOT plus $[HCO_3^-]$. SID effective is the real SID. The difference between the two is made up of unmeasured anions (UMA). SID, Strong ion difference; SIG, strong ion gap.

Using traditional methodology, one would describe this as a nongap metabolic acidosis and look for causes of bicarbonate wasting such as renal tubular acidosis or gastrointestinal losses. The degree of respiratory alkalosis is appropriate for the degree of acidosis ($\Delta BD = \Delta PCO_2$). However, the Fencl-Stewart approach reveals a much more complex situation. SID is reduced to 18 mEq/L, caused by free water excess, UMA, and, surprisingly, hyperchloremia (see the corrected chloride). However, the degree of acidosis does not mirror the metabolic disturbance because of the alkalinizing force of hypoalbuminemia. The corrected AG mirrors the change in SID, but this alteration is grossly underestimated by the base deficit. This patient has a dilutional acidosis, a hyperchloremic acidosis, and a lactic acidosis!

In conclusion, for the majority of patients presenting to the emergency room or operating suite who have been previously healthy, the use of tools such as the base deficit or AG to assess metabolic disturbances remains reasonable, particularly if corrected for albumin. However, for critically ill patients, the most effective method of interpreting acid-base conundrums involves unraveling simultaneous acidifying and alkalinizing processes and using calculations to distinguish between the various forces at play. Unfortunately, a clinician's ability to interpret such information is dependent on the amount of available data. A simple blood gas alone may camouflage a significant acid-base disturbance.

In the next section, we will look at the causes of many commonly seen acid-base disturbances in different clinical settings.

Acid-Base Problems in Perioperative and Critical Care Medicine

RESPIRATORY ACIDOSIS AND ALKALOSIS

In perioperative medicine respiratory acid-base abnormalities are an uncommon complication of prolonged spontaneous breathing under anesthesia, inadequate mechanical

TABLE 48.4 Acid-Base Disturbances Commonly Seen Perioperatively

Disorder	Cause
Respiratory acidosis	Hypoventilation; narcosis, incomplete reversal of neuromuscular blockade
Respiratory alkalosis	Hyperventilation; anxiety, pain
Metabolic acidosis due to unmeasured anions (widened gap acidosis)	Hypoperfusion—lactic acidosis; diabetic ketoacidosis; renal failure
Metabolic acidosis due to measured anions (non-gap hyperchloremic acidosis)	Hyperchloremia—"normal" saline and saline-containing fluids; renal tubular acidosis; bladder reconstructions
Metabolic acidosis due to free water excess (hyponatremia, dilution acidosis)	Hypotonic fluid administration; sodium loss—diarrhea; administration of hyperosmolar fluids—mannitol, alcohol, hyperproteinemia
Metabolic alkalosis	Hyperventilation of patient with history of CO_2 retention (COPD); sodium gain (sodium bicarbonate, massive blood transfusion); chloride loss—nasogastric suctioning

ventilation (both acute respiratory acidosis) or excessive mechanical ventilation (respiratory alkalosis) (Table 48.4). Acute respiratory acidosis results from hypoventilation or increased dead space ventilation. Patients may manifest respiratory distress characterized by respiratory acidosis in the recovery room PACU or surgical ICU. Assessment begins with an examination of the patient's breathing pattern (Fig. 48.8): slow shallow breathing indicates impaired respiratory drive, rapid shallow breathing suggests chest wall or lung pathology, and obstructed breathing signifies airway obstruction. Blood gas analysis of acute respiratory acidosis will reflect a dramatic fall in pH, an elevated $PaCO_2$, and a slight rise in HCO_3^- (by 1 mEq/L [mmol/L] for every 10 mm Hg [or 1.2 kPa] rise in $PaCO_2$). The BE should be zero. Respiratory acidosis as a complication of anesthesia is relatively common—excessive sedation (particularly opioids), partial neuromuscular blockade, intraoperative hypoventilation, pneumothorax, etc. It may also complicate CO_2 insufflation during laparoscopy—the patients' minute ventilation should be dynamically adjusted intraoperatively to maintain $etCO_2$ levels near baseline.

For patients with COPD (or other causes of chronic respiratory failure), it is worthwhile, preoperatively, to calculate the baseline $PaCO_2$ on a patient from the total CO_2 on blood chemistry panel. As discussed earlier, the total CO_2 (HCO_3^-) rises by 3 mEq/L (mmol/L) for every 10 mm Hg (1.3 kPa) rise in $PaCO_2$. A patient, for example, with a baseline total CO_2 of 33 mEq/L (mmol/L) would be expected to have a baseline $PaCO_2$ of 70 mm Hg (9.3 kPa). For intraoperative management, the $etCO_2$ should be maintained, if the patient is undergoing mechanical ventilation, between 3 and 5 mm Hg (0.5–1 kPa) of baseline (the $PaCO_2$ - $etCO_2$ gradient increases with age and non-supine positioning).

If the patient is hypoventilating, perioperatively, the pH falls, the $PaCO_2$ rises, but the rise in the total CO_2 (HCO_3^-) is lower than expected. If this patient's $PaCO_2$, postoperatively, is 90 mm Hg (12 kPa) and the total CO_2 (HCO_3^-) is

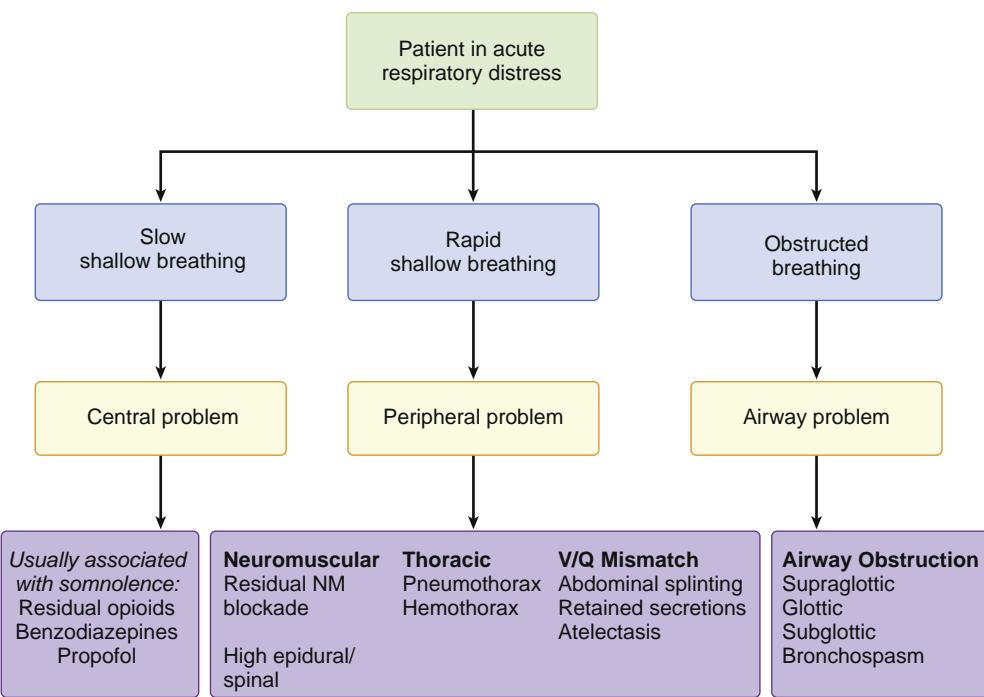


Fig. 48.8 Using the Breathing Pattern to Determine the Cause of Acute Respiratory Distress and Respiratory Acidosis.

35 mmol/L (mEq/L), then the patient has acute or chronic respiratory acidosis. This problem may be compounded by the patient's lack of pulmonary reserve and the negative impact on the respiratory center by opioids and other anesthetic agents. Consideration should be given to administration of noninvasive ventilation to restore PaCO_2 to what is normal for that patient.

In emergency medicine and critical illness, respiratory acidosis complicates a wide variety of pathologies. Most commonly, these cause a problem of the patient "can't breathe"—a neuromuscular or anatomical problem—or the patient "won't breathe"—a central nervous system pathology. The latter includes neurologic injury (stroke, spinal cord injury, botulism, tetanus, and toxic suppression of the respiratory center [opioids, barbiturates, benzodiazepines]). Patients "can't breathe" due to a variety of neuromuscular disorders (Guillain-Barré syndrome, myasthenia gravis), flail chest, hydro-hemo-pneumo-thorax, pulmonary edema, and pneumonia. Failure to ventilate, as manifest by respiratory acidosis, may result from abdominal hypertension and abdominal compartment syndrome, where diaphragmatic excursion is impeded by high intra-abdominal pressures, often with associated oliguria and hypotension.

Acute respiratory alkalosis is caused by hyperventilation, either due to anxiety or pain, central respiratory stimulation (as occurs early in salicylate poisoning), or excessive artificial ventilation. In acute respiratory alkalosis the pH is above 7.45, the PaCO_2 below 40 mm Hg (5.3 kPa), and the $[\text{HCO}_3^-]$ falls by 2 mEq/L (mmol/L) for every 10 mm Hg (1.3 kPa) fall in PaCO_2 . There is no change in the BE. So, if a patient has a PaCO_2 of 30 mm Hg, the $[\text{HCO}_3^-]$ should be 22 mEq/L (mmol/L).

Acute respiratory alkalosis usually accompanies acute metabolic acidosis, in which case the reduction in PCO_2

from baseline (usually 40 mm Hg) is equal to the magnitude of the base deficit (see Table 48.3). The fall in bicarbonate, from baseline, is significantly greater than that seen in primary respiratory alkalosis, due to the consumption of bicarbonate as extracellular buffer (the $[\text{HCO}_3^-]$ falls 1 mEq/L for every 1 mEq/L gain in strong anions). For example, in a patient with a lactic acidosis whose lactate is 10 mEq/L, the BE should be -10, the $[\text{HCO}_3^-]$ 10 mEq/L (mmol/L) lower than baseline, and the PCO_2 30 mm Hg. If the PCO_2 is higher than expected, then there is a concomitant problem with the respiratory apparatus. An example would be a multi-trauma patient, where massive blood loss leads to lactic acidosis and a flail chest causes respiratory acidosis.

Metabolic Acidosis and Alkalosis

METABOLIC ACIDOSIS

Acute metabolic acidosis is caused by an alteration in SID or A_{TOT} . SID is changed by an alteration in the relative quantity of strong anions to strong cations. Anions, mineral or organic, can be gained, as occurs with lactic-, renal-, keto-, and hyperchloremic acidosis, or cation can be lost, as occurs with severe diarrhea or renal tubular acidosis.

Acute metabolic acidosis is characterized by a pH of < 7.35 and a fall in both PaCO_2 and $[\text{HCO}_3^-]$ below the patient's baseline. For patients without COPD or chronic CO_2 retention, this represents a PaCO_2 < 40 mm Hg (5.3 kPa) and a $[\text{HCO}_3^-]$ below 24 mEq/L (mmol/L); there is a negative BE (base deficit) whose magnitude represents the net strong anion gain. This simple approach indicates that an acidosis is present, and that it is metabolic in origin. To further investigate the acidosis, one or more of the

analytical tools described above may be employed. The most widely used tool is the AG, which should be adjusted for albumin. This differentiates hyperchloremic acidosis from acidosis caused by other measured and UMA. In the setting of metabolic acidosis, where possible, these anions should be directly measured—lactate, ketones, phosphate, albumin or surrogate markers of anion accumulation—serum creatinine and the osmolar gap. Causes of metabolic acidosis that are commonly encountered by anesthesiologists are discussed below.

LACTIC ACIDOSIS

The presence of lactic acidosis is an excellent marker of acute critical illness, the magnitude of which often reflects the degree of hyperlactatemia. Lactic acidosis occurs when the production of lactate in the body is greater than the liver's capacity to clear it—there is a problem of overproduction or inadequate clearance.

Lactic acid is produced physiologically as a degradation product of glucose metabolism. In nature it exists as two isoforms: L-lactate which is produced by the human body and is measured by blood gas analyzers, and D-lactate which can only be produced by fermentation by bacteria. The formation of L-lactate (lactate) from pyruvate is catalyzed by lactate dehydrogenase. Lactate is used as a “buffer” in isotonic fluids, principally lactated Ringer's solution and Hartmann's solution; these contain a racemic mixture of both D and L lactate at a concentration of 14 mmol/L each.

Under normal conditions, the ratio of lactate to pyruvate ratio is less than 20:1. In anaerobic conditions, for example following vigorous exercise, lactate levels increase dramatically, and high levels of circulating lactate are frequently interpreted as evidence of increased glycolytic activity. However, lactate is often produced under aerobic conditions. Activation of β -adrenergic receptors in skeletal muscle by stress (increased circulating catecholamines) or exogenous infusion (epinephrine/norepinephrine infusions) increases [lactate], resulting in aerobic glycolysis. Lactate is metabolized to pyruvate and then into glucose (gluconeogenesis) in the liver and subsequently to CO_2 and H_2O (the Cori cycle). Hence the lactate in Ringer's lactate (or Hartmann's) solution is considered to be a source of bicarbonate. This is only the case if the liver is capable of handling the lactate load.

Plasma lactate and arterial pH should be measured early in any critically ill patient—it is now a diagnostic component of the definition of septic shock.⁶¹ A lactate concentration > 2 mEq/L (mmol/L) is clinically significant and a level of 5 mEq/L (mmol/L) in the presence of metabolic acidosis is severe.⁶² Isolated hyperlactatemia in the absence of acidosis is of unclear clinical significance.⁶³

Traditionally, lactic acidosis has been described as taking one of two forms: type 1 (may also be termed type A, global inadequate oxygen delivery) is seen in hypovolemic/hemorrhagic shock while type 2 (type B) occurs despite normal global oxygen delivery and tissue perfusion. Lactic acidosis may also develop in situations where there is significant regional hypoperfusion. Examples include bowel ischemia, where lactate is produced in large quantity due to glycolysis despite global oxygen delivery that is normal. Type 2 lactic

acidosis is associated with any state in which circulating catecholamines (endogenous or exogenous) are in excess. Examples include simple exercise and the hyperinflammatory state of trauma or sepsis. Type 2 lactic acidosis may also be seen in cyanide poisoning (associated with sodium nitroprusside), with biguanides (metformin, which blocks hepatic gluconeogenesis), and in hypercatabolic diseases such as lymphoma, leukemia, AIDS, or diabetic ketoacidosis (DKA). In critical illness, type 1 and type 2 lactic acidosis frequently coexist.

It is universally accepted that lactic acidosis is a sensitive marker of disease severity.⁶⁴ Persistence of lactic acidosis strongly predicts poor outcomes in acute illness.⁶⁵⁻⁶⁷ Rapid clearance (i.e., reduced plasma concentration presumably due to reduced production and increased metabolism) of lactate has been associated with improved outcomes.^{68,69} It remains controversial whether it is possible to institute therapy that improves outcomes and simultaneously increases lactate clearance. Simplistically, improved overall perfusion consequent of blood or isotonic fluid administration should reduce glycolysis and reduce lactate production, increasing hepatic blood flow and increasing metabolism. However, not all patients who are under-resuscitated are hyperlactatemic, and probably the minority of patients who are hyperlactatemic are under-resuscitated. Although fluid resuscitation with the goal of normalizing serum lactate may be associated with improved outcomes, excessive or late fluid resuscitation increases mortality.⁷⁰ It is important to note that, following fluid bolus, plasma lactate rapidly falls, perhaps due to hemodilution, and then falls slowly, at 10% to 20% per hour, due to rate-limited hepatic clearance. If plasma lactate does not fall, fluid resuscitation should be discontinued.⁷¹

The presence of evidence of good overall oxygen delivery and normal consumption, as measured by cardiac output monitors and mixed venous oxygen saturation, in lactic acidosis is not reassuring. Indeed, bowel ischemia may be indicated by otherwise unexplained lactic acidosis, and the availability heuristic associated with sepsis may result in delayed diagnosis and inappropriate fluid resuscitation (Fig. 48.9).

Metformin is associated with severe lactic acidosis, a phenomenon that appears more likely when the patient has liver dysfunction, is dehydrated, is in heart failure, has suffered acute kidney injury (AKI), or is septic.⁷² The mechanism of harm is unknown, although metformin is thought to impair oxidative metabolism in hepatocyte mitochondria, and block gluconeogenesis. Renal impairment appears to be a significant risk factor. The patient presenting with metformin-associated lactic acidosis frequently looks reasonably well, despite serum lactate that may exceed 10 mmol/L. There is no specific treatment except for withdrawal of the drug, gentle rehydration, and patience.

D-lactate-induced acidosis can occur, typically in patients with short bowel syndrome and bacterial overgrowth. It manifests as a widened AG acidosis where no other potential source of metabolic acid is identified. Crucially, point-of-care blood gas analyzers do not measure D-lactate. However, many laboratories are able to measure the molecule, and this test should be considered in a high-risk patient (post major abdominal surgery) with unexplained acidosis.

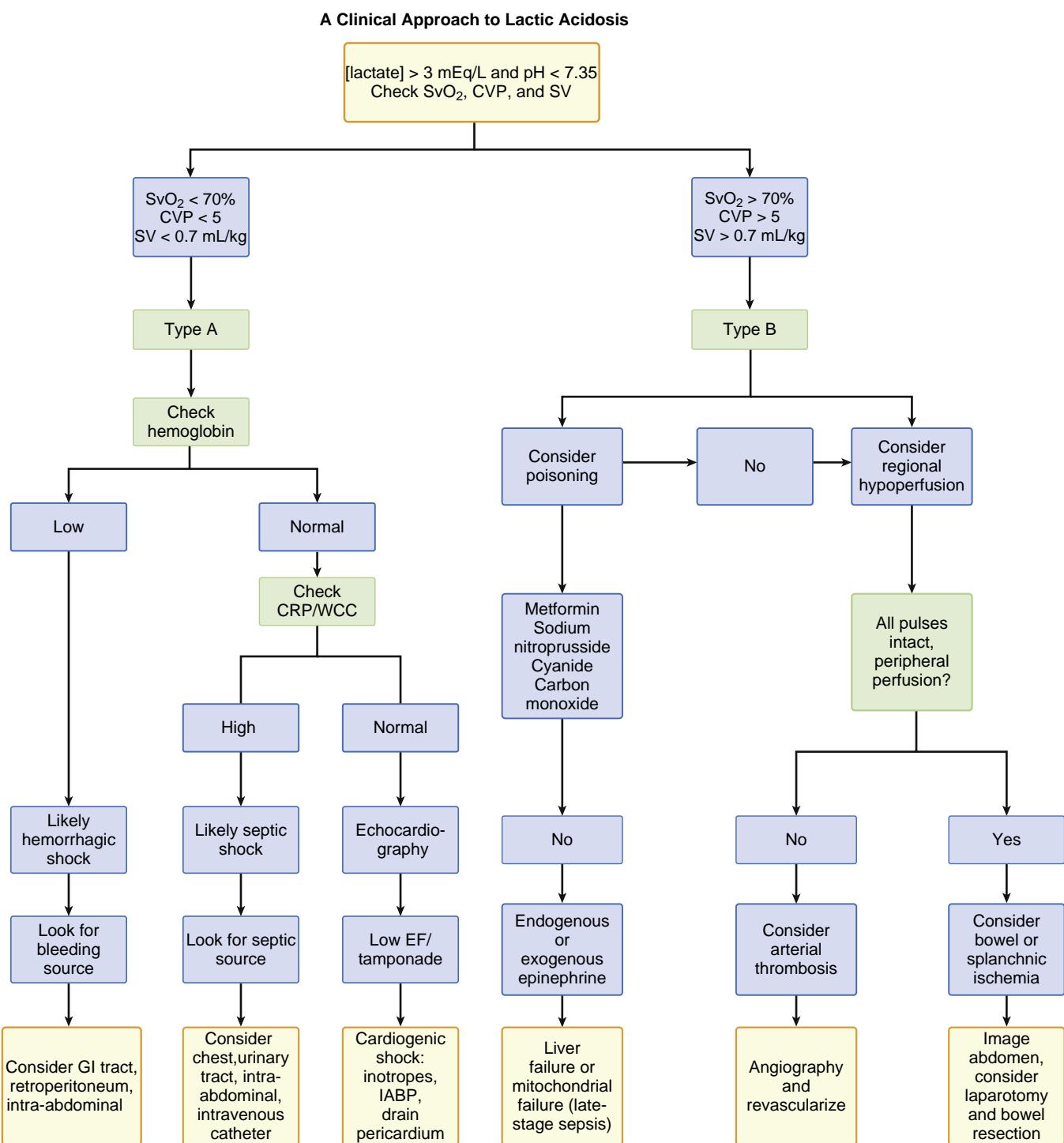


Fig. 48.9 Evaluation of a Patient with Lactic Acidosis. CRP, C-Reactive protein; CVP, central venous pressure; EF, ejection fraction; GI, gastrointestinal; IABP, intra-aortic balloon counterpulsation; SV, stroke volume; SvO_2 , mixed venous oxygen saturation; WCC, white cell count.

Ketoacidosis

Ketone bodies—acetone (<2%), acetoacetate (20%), and 3- β -hydroxybutyrate (β OHb) (78%)—are normal by-products of fat metabolism. They are produced when fatty acids are metabolized by the liver, when glucose is unavailable as an energy source. During ketogenesis, acetoacetate

is generated from acetyl co-enzyme A. This either enters mitochondria to be converted to β OHb or it spontaneously decarboxylates to acetone. Ketones are transported by blood to the tissues, in particular the brain, where they are used as energy sources. Under normal dietary conditions, ketones are undetectable in blood and urine. However, in situations where fat becomes the primary source of energy

(for example in starvation or low-carbohydrate diets), ketones can be measured in blood (principally β OHb) and urine (principally acetoacetate). In a variety of clinical situations, such as prolonged starvation, alcoholism, alcoholic- or obesity-related steatohepatitis, and, most commonly, insulin deficiency (diabetes mellitus), a dramatic increase in circulating ketones occurs. As these are strong anionic compounds, ketones reduce SID, resulting in metabolic acidosis. When this occurs in type-1 diabetes (T1D), it is known as diabetic ketoacidosis (DKA).

DKA may be the first manifestation of T1D, or may result from poor glycemic control or specific stress triggers, such as infection, trauma, or surgery. Typically there is an imbalance between the relative quantity of insulin and glucose-promoting hormones (cortisol, epinephrine, and glucagon). Blood glucose increases, exceeding the renal reabsorption threshold. This results in glycosuria, osmotic diuresis, dehydration, and the vicious cycle of activation of stress hormones. This leads to increased metabolism of fatty acids and, in the absence of insulin, or consequent of severe insulin resistance, there is unrestrained oxidation of fatty acids to ketones in the liver. Regardless of the cause, there is usually elevated blood glucose, significant dehydration, and depletion of potassium, phosphorous, and magnesium.

The diagnosis of DKA is relatively simple. Usually there is a clear history of either diabetes or polyuria and polydipsia: the patient presents to the emergency room with hyperglycemia and glycosuria, and, usually, positive urinary ketones. Ketoacidosis is confirmed by performing ABG analysis. Every hospital has a protocol for the management of DKA. Insulin is administered by an infusion (with or without an initial bolus). This may be a weight-based fixed-rate infusion (0.1 units of insulin per kilo per hour) or more traditional infusion based on blood glucose.⁷³ The patient is resuscitated with several liters of isotonic crystalloid (usually isotonic saline [0.9%] solution), and when blood glucose falls within a “controlled” range, intravenous dextrose is administered. Insulin suppresses ketone production. Glucose is required to assist ketone metabolism, which can take some time. Two major mistakes are made in the management of DKA. Administration of 0.9% NaCl results in an entirely predictable hyperchloremic acidosis; this may or may not be harmful but may be perceived incorrectly as persistence of ketoacidosis. A small study that compared NS with Plasmalyte-148 (a balanced salt solution [BSS]) reported that patients receiving the balanced solution instead of NS had more rapid resolution of metabolic acidosis, less hyperchloremia, improved blood pressure profile, and greater urinary output.⁷⁴

The second error is very important for anesthesiologists. As noted above, the majority of ketones in the body are in the form of β OHb. These can only be identified by measuring “blood” ketones. Urinary ketone sticks measure only acetoacetate.⁷⁵ The absence of ketones in the urine does not eliminate the diagnosis of ketoacidosis (particularly if it is not associated with diabetes). Blood ketones are easily measured using handheld devices (although these may be hard to find in hospitals due to the current disenfranchisement of point-of-care testing). Interestingly, as β OHb must be metabolized to acetoacetate, urinary ketones may actually increase during the time that the whole body ketone load is falling and ketosis is resolving.

Patients presenting for emergency surgery may have multiple simultaneous acid-base abnormalities, and physicians often miss ketoacidosis due to availability bias—the presence of elevated lactate may result in search satisficing—and a major metabolic abnormality is missed.⁷⁶ Despite fluid resuscitation and source control, the acidosis may not resolve. This in turn may lead to inappropriate therapy such as renal replacement therapy (RRT) and sodium bicarbonate administration, neither of which are of any value in ketoacidosis. All forms of ketoacidosis require insulin therapy and, eventually, glucose administration. Ketoacidosis of non-diabetic origin may take many hours, and occasionally days, to resolve.

Renal Acidosis

The kidney excretes water and a variety of metabolic byproducts, principally derived from proteins. The kidney also excretes surplus electrolytes, some of which are strong ions, including chloride, sulfate, formate, urate citric acid cycle metabolites (fumarate, citrate), and phosphate. These accumulate in AKI and cause “renal acidosis.” Early in AKI, hyperchloremia is the principle source of acidosis; subsequently, 50% to 60% of acidosis is caused by UMA and up to 30% is associated with hyperphosphatemia.⁷⁷ Fifty percent of patients with AKI in critical illness have a normal AG.⁷⁷

AKI, in perioperative medicine, may accompany hypotension, hypovolemia, renal hypoperfusion (from aortic cross clamping or intraabdominal hypertension), rhabdomyolysis, sepsis, or urinary obstruction. Irrespective of the cause, patients develop oliguria, volume overload, and hyperkalemia secondary to metabolic acidosis.

The identification of metabolic acidosis in AKI is key to the diagnosis, severity, and therapeutic strategy in AKI. Although serum creatinine is the most widely used marker of renal function, isolated readings are unhelpful. Fluid resuscitation can artificially lower the creatinine concentration, by dilution; diuresis can artificially elevate it. Metabolic acidosis, particularly in the presence of hyperkalemia with elevated creatinine, should always prompt the clinician to determine the extent of renal acidosis. This is not easy. Hyperchloremia typically accompanies renal acidosis, but isotonic saline solution is frequently administered to patients with elevated creatinine under the mistaken belief that patients are less likely to develop hyperkalemia compared with BSSs.⁷⁸ A study of anephric patients undergoing renal transplantation demonstrated that patients treated with NS were more acidotic and hyperkalemic than patients treated with lactated Ringer’s solution.⁷⁸ Hyperphosphatemia is a minor contributor to renal acidosis, and currently no tests are available to clinically identify the UMA, except by a process of exclusion. Hence, renal acidosis is usually diagnosed by identifying a widened AG, base deficit gap, or SIG, and excluding ketones and lactate. Usually the key decision step regarding RRT involves uncontrolled hyperkalemia. Renal acidosis can be temporarily controlled by administration of sodium bicarbonate (assuming the patient can clear CO_2), by increasing the SID. This may be necessary if the risk of delaying surgery exceeds the risk of delaying RRT. Note, however, in critical illness, delaying RRT was associated with a 4.7% increase in mortality at 90 days.⁷⁹

Hyperchloremic Acidosis

Hyperchloremia has been a known cause of metabolic acidosis since the dawn of acid-base chemistry,¹² but due to difficulty in measuring serum Cl⁻ during most of the 20th century, hyperchloremia was largely ignored until recent decades. The extracellular space contains 110 to 130 g of salt. For a 70 kg male (ECF volume 18 L), this is approximately 58 g of Na⁺ (3.22 g/L) and 65 g (3.62 g/L) of Cl⁻. The average American ingests approximately 3 g or more of salt (NaCl) each day (2.3 g is recommended). To maintain the normal ratio of Na⁺ to Cl⁻ (1.4:1 approximately), the body needs to excrete 30% more Cl⁻ than Na⁺, and this is one of the major excretory roles of the kidney. This approximates to 15 to 20 mmol of Cl⁻ excretion per day; to maintain electrical neutrality Cl⁻ is excreted with ammonium (NH₄⁺), a byproduct of nitrogen metabolism. In renal failure, Cl⁻ accumulates, and this is often the cause of the early metabolic acidosis associated with AKI. For decades, it has been hypothesized that elevated circulating levels of Cl⁻, usually as a consequence of intravenous administration, may actually be nephrotoxic, due, presumably, to increased metabolic demands on the kidney. One liter of isotonic saline solution (0.9%, normal saline, NS) contains 9 g of salt, 3.5 g Na⁺, and 5.5 g Cl⁻ (154 mmol/L of each). For a eucloremic patient (the human body does not store chloride, unlike, for example, calcium), this means that if 1 L of NaCl 0.9% is administered, most or all of the Cl⁻ must be excreted—an 8- to 10-fold increase in metabolic load for the kidney. Moreover, as NS has a SID of 0, elevated serum chloride is usually associated with a non-AG (hyperchloremic) metabolic acidosis.⁸⁰

Hyperchloremic acidosis is a complication of renal tubular acidosis, which is caused by a defect in chloride excretion. The urine is relatively alkaline. Hyperchloremia also occurs when ureters have been re-implanted in the bowel after, for example, cystectomy, and excreted chloride is reabsorbed.

Are hyperchloremia and hyperchloremic acidosis clinically significant? As a cause of acidosis, hyperchloremia is less sinister than other causes: in a study of critically ill patients with various acid-base disorders, mortality was highest for lactic acidosis (56%); for SIG acidosis it was 39% and for hyperchloremic acidosis 29% ($P < .001$).⁸¹ Nevertheless, hyperchloremia may result in clinically significant organ dysfunction. An observational study of 31,000 surgical patients comparing intravenous saline to intravenous BSS demonstrated significant outcome differences, favoring BSS.⁸² Complications enhanced by the use of normal saline included postoperative infections, blood transfusions, and kidney injury requiring dialysis.

A hyperchloremic state may be associated with nephrotoxicity; saline infusion has been associated with reduced renal blood flow, renal vasoconstriction, reduced glomerular filtration, and splanchnic hypoperfusion.⁸³ In a relatively large before-and-after cohort study of patients treated in an Australian ICU, the use of chloride-rich fluids was associated with a 3.7% absolute increase in the risk for need in RRT relative to BSS.⁸⁴

Two large randomized controlled trials looked at the use of isotonic saline solution versus BSS in emergency medicine patients⁸⁵ and critically ill patients.⁸⁶ Although the

volume of fluid administered intravenously was relatively low, certainly in comparison with perioperative patients, in both studies there was approximately a 1% increase in renal complications. Whether this effect scales up with larger volumes will presumably be the subject of further study and meta-analysis.

NS solution, originally introduced by Hamburger in the 19th century and labelled “normal” due to flawed research, has been the most widely used intravenous fluid for over a century, despite minimal research demonstrating its clinical efficacy and safety.⁸⁷ As mounting research demonstrates that this particular fluid may be harmful, and with a variety of other balanced solutions available for clinical practice, the role of NS in perioperative medicine is highly questionable.

Perioperative Metabolic Alkalosis

Perioperative metabolic alkalosis is usually of iatrogenic origin. Overventilation of patients with chronic respiratory failure results in acute metabolic alkalosis because the presence of chronic compensatory alkalosis associated with chloride loss in urine has not been taken into account (Fig. 48.10). More frequently, metabolic alkalosis is associated with increased SID due to sodium gain. This abnormality results from the administration of fluids in which sodium is buffered by weak ions, citrate (in blood products), acetate (in parenteral nutrition), and, of course, bicarbonate. It is important to recognize that buffer ions such as citrate, acetate, gluconate, and lactate are, under normal conditions, rapidly cleared by the liver and do not contribute to acid-base balance. Sodium and chloride obey the law of conservation of mass. Sodium gain is “chloride sensitive” alkalosis, treated by administration of net loads of chloride—0.9% NaCl, potassium chloride, calcium chloride, and, occasionally, hydrogen chloride. It is important to correct chloride-sensitive alkalosis, as the normal compensatory measure is hypoventilation, increasing PaCO₂, which may lead to CO₂ narcosis and failure to liberate from mechanical ventilation.

Large volumes of BSSs are likely to cause metabolic alkalosis, due to dilution of A_{TOT} (principally hypoalbuminemia), a process that is curtailed when using lactated Ringer’s solution (Hartmann’s) due to lower SID (20 mEq/L). The acquired hypoalbuminemic alkalosis is of undetermined clinical significance.

Another cause of metabolic alkalosis in perioperative patients reflects loss of chloride-rich fluids from the gastrointestinal tract. Gastric juice contains HCl, which, when lost as a result of continuous suctioning or vomiting, obeys the law of conservation of mass and leads to alkalosis.

Perioperative fluid therapy remains highly controversial. Isotonic fluids are usually administered due to fear of cerebral edema associated with stress-induced water retention. However, this results in large amounts of solute, in particular sodium and chloride, accumulating in the extravascular space. Acquired hypernatremia is associated with adverse clinical outcomes and is very difficult to treat.⁸⁸ BSSs appear safer than NS, but large-volume administration of these resuscitation fluids are also associated with worse outcomes.⁸⁹

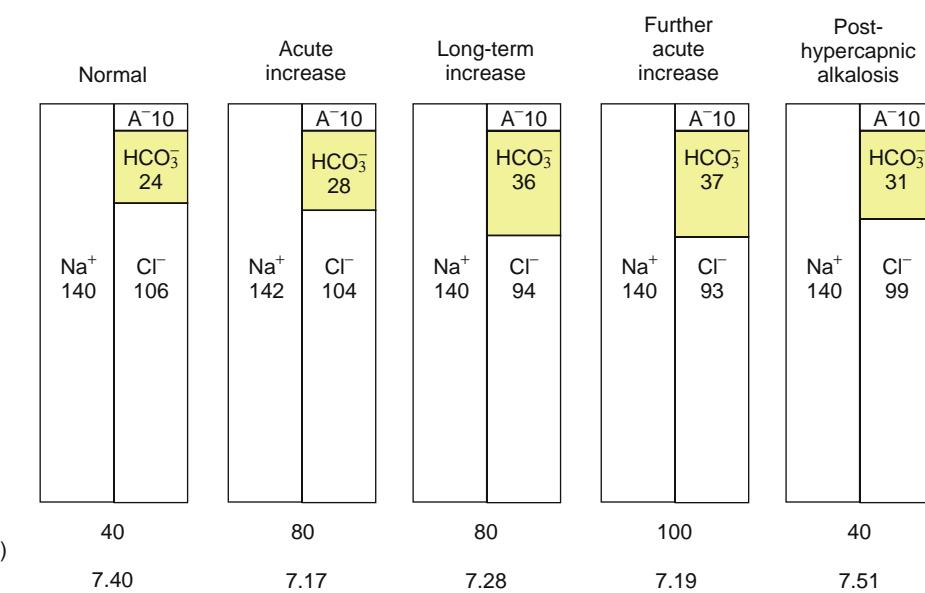


Fig. 48.10 Changes in Acid-Based and Electrolyte Composition in Patients With Respiratory Acidosis. Left to right, the panels depict normal acid-base status; adaptation to an acute rise in the partial pressure of arterial carbon dioxide (PaCO_2) to 80 mm Hg; adaptation to a long-term rise in PaCO_2 to 80 mm Hg; superimposition of an acute further increment in PaCO_2 (to a level of 100 mm Hg) in the same patient; and post-hypercapnic alkalosis resulting from an abrupt reduction in PaCO_2 to the level of 40 mm Hg in the same patient. A^- denotes unmeasured plasma anions, and the numbers within the bars give ion concentrations in millimoles per liter. (Modified from Adrogue HJ, Madias NE. Management of life-threatening acid-base disorders. First of two parts. *N Engl J Med*. 1998;338[1]:26-34.)

ACID-BASE DISTURBANCES IN CRITICAL ILLNESS

Critically ill patients may have many confounding acid-base disturbances that are not evident when only a single quantitative measure, such as base deficit, is employed. Patients will frequently have perturbations of PCO_2 , SID, and A_{TOT} , and significant pathology may be overlooked due to apparently normal blood gas results.⁹⁰

The most common single disturbance in acid-base chemistry in critically ill patients is hypoalbuminemia.²⁴ This abnormality is ubiquitous and causes a metabolic alkalosis of unpredictable magnitude. Hypoalbuminemia may mask significant alterations in SID, for example lactic or renal acidosis. Therefore, when the AG is used in critically ill patients it should be corrected for albumin.²⁶ Similarly, the use of base deficit to predict lactate is unreliable in critical illness, particularly in patients undergoing secondary deterioration.²⁵ Further, prolonged respiratory failure, with associated hypercarbia, leads to additional metabolic alkalosis due to chloride loss in urine (see Fig. 48.10)⁹¹ Kidney injury is associated with accumulation of metabolic by-products, phosphate, renal anions, chloride, and other UMA, leading initially to metabolic acidosis. However, late polyuric renal failure may be associated with significant contraction alkalosis, due to loss of sodium, potassium, and free water.

Critically ill patients are vulnerable to significant changes in SID and free water. Nasogastric suctioning causes chloride loss, diarrhea leads to sodium and potassium deficits. Surgical drains placed in tissue beds may remove fluids with varying electrolyte concentrations (the pancreatic bed, for example, secretes fluid rich in sodium). Fever, sweating, evaporation from denuded tissue, and inadequately humidified ventilator circuits all can lead to large-volume insensible loss and contraction alkalosis.

Infusions administered to patients may be responsible for unrecognized alterations in serum chemistry. Many antibiotics, for example piperacillin-tazobactam, are diluted in sodium-rich solutions. Others, such as vancomycin, are administered in large volumes of free water (5% dextrose). Lorazepam is diluted in propylene glycol, large volumes of which will cause metabolic acidosis similar to that seen with ethylene glycol.⁹²

Continuous renal replacement therapy (CRRT) is used in critical illness to hemofilter and hemodialysis patients who are hemodynamically unstable. Rocktaschel⁹³ and colleagues have demonstrated that CRRT resolved the acidosis of acute renal failure by removing strong ions and phosphate. However, in the presence of hypoalbuminemia, use of dialysis to correct a metabolic acidosis may unmask a metabolic alkalosis due to hypoalbuminemia. CRRT is not an effective treatment for lactic acidosis or ketoacidosis.

Other seemingly innocuous therapies may cause significant disturbances to acid-base balance. Loop diuretics, such as furosemide, are often administered to critically ill patients. These agents preferentially excrete water over electrolytes and provoke a contraction alkalosis. Similarly, carbonic anhydrase inhibitors such as acetazolamide may be used to treat patients with hypochloremic metabolic alkalosis or respiratory alkalosis by decreasing the plasma SID. This effect is completely explained by the increased renal excretion ratio of sodium to chloride, resulting in an increase in serum chloride.⁹⁴

Neurosurgical patients are vulnerable to a variety of acid-base disturbances as a result of osmotherapy or from disturbances caused by brain injury. Most commonly, NS solution is administered to these patients and results in hyperchloremic acidosis.⁹⁵ Diabetes insipidus (DI) is a frequent complication of severe head injury, particularly when the patient is progressing toward brain death. DI is caused

by damage to the pituitary and/or the hypothalamus and results in a loss of antidiuretic hormone (ADH) secretion. Absent ADH, the kidney is unable to concentrate the urine and a massive diuresis follows. The disorder is characterized by an increase in plasma osmolality in the presence of a low urinary osmolality. DI will typically manifest as a contraction alkalosis. The treatment is hormonal replacement with either vasopressin or desmopressin.

TREATING ACID-BASE DISTURBANCES

In general, in acute illness and perioperative medicine, acid-base disturbances are clinical indicators of disease processes that are more harmful than hydrogen ion abnormalities themselves. Correcting the pH is usually unlikely to resolve the problem, except in certain circumstances, such as hyperkalemia in AKI, where acidosis is the major cause of the problem.

The treatment of acid-base abnormalities is determined by whether the acids, in particular, are organic or mineral acids. Organic acids can be metabolized, excreted, or dialyzed from the body. Diabetic and nondiabetic ketoacidosis are treated primarily with insulin, intravenous fluid, and glucose. The ketoacids causing metabolic acidosis are metabolized by the liver. AKI is treated with dialysis and ultrafiltration, which directly removes UMA. Surprisingly, there are no clear guidelines regarding the optimal timing of initiation of RRT,^{79,96} particularly in the perioperative period.⁹⁷

For decades, sodium bicarbonate (NaHCO_3^-) has been used to "correct" acidosis. The sodium component, as a strong anion, widens the SID and is alkalinizing. Simultaneously, the bicarbonate moiety provides buffer for hydrogen ions, generating CO_2 , which is presumably excreted from the body by increased alveolar ventilation. In respiratory failure, sodium bicarbonate will worsen respiratory acidosis despite increased SID. CO_2 also enters cells and may cause intracellular acidosis, the clinical significance of which is unclear.⁹⁸

NaHCO_3^- is commonly used to treat hyperchloremic acidosis. For patients with renal tubular acidosis, this involves long-term treatment with sodium bicarbonate tablets and chloride restriction. In acquired hyperchloremic acidosis, intravenous sodium bicarbonate corrects the base deficit,⁹⁹ but the benefit is unclear. The major drawbacks of NaHCO_3^- therapy include sodium and volume overload, metabolic alkalosis, hypertension, and hypocalcemia.

Sodium bicarbonate therapy has been extensively studied in lactic acidosis and circulatory shock.¹⁰⁰ A recent randomized trial of 389 critically ill patients with metabolic acidosis compared the administration of 4.2% (hypertonic) NaHCO_3^- to keep pH above 7.3, up to a maximum of 1000 mL in the first 24 hours, versus no intervention.¹⁰¹ Although there were no differences in the primary outcome—28-day mortality—the patients who received NaHCO_3^- had a lower incidence of AKI and requirement for RRT. It is unclear why there was a reduction in the need for RRT. Perhaps the reduction in acidosis delayed the decision to start RRT and resulted in the intervention being avoided completely,⁹⁶ or reversal of acidosis reduced vasopressor requirement and improved kidney blood flow; but this is merely speculation. Previous meta-analyses have failed to demonstrate benefit from NaHCO_3^- therapy,¹⁰²

presumably due to the paucity of available research. Until larger multicenter trials have been conducted, NaHCO_3^- therapy should be used with caution for treatment of metabolic acidosis, due to circulatory shock or ketoacidosis. It is also unlikely that NaHCO_3^- therapy benefits perioperative patients at risk for postoperative kidney failure.¹⁰³

Metabolic alkalosis is rarely seen in elective perioperative care. It is most likely encountered when unmasked by overventilation of patients who chronically retain CO_2 . Minute ventilation should be reduced. Critically ill patients may have metabolic alkalosis due to chloride deficit, free water deficit, or hypoalbuminemia. Contraction alkalosis is treated by correcting the free water deficit using the formula below:

$$\text{Free water deficit} = 0.6 \times \text{patient's weight in kg} \\ \times (\text{patient's sodium}/140 - 1)$$

Hypochloremic alkalosis should be treated by correcting the chloride deficit using NS or LR.

There is no evidence that correcting hypoalbuminemia is of clinical benefit for the majority of patients.¹⁰⁴ Respiratory alkalosis usually results from anxiety or pain. Short-term therapy, such as CO_2 rebreathing, should be followed by treating the underlying problem—for example with opioids or benzodiazepines.

Hypercarbic acidosis may be encountered in the perioperative period due to deliberate¹⁰⁵ or inadvertent hyperventilation. It is also associated with elevated dead space ventilation as seen in ARDS. In general, acute respiratory acidosis is well tolerated and can be easily reversed by increasing minute ventilation. However, in ARDS, a high tidal volume and transpulmonary pressures result in ventilator induced lung injury (VILI) and increased mortality.¹⁰⁶ Consequently, hypercarbia must be tolerated by the physician and patient ("permissive hypercarbia") or CO_2 removed by an extracorporeal circuit.¹⁰⁷

Summary

Much of the confusion regarding acid-base chemistry relates to the attempt to apply observational approaches, such as that of Henderson-Hasselbalch and Schwartz and Brackett, to the entire spectrum of pathophysiologic processes. The use of physical chemistry principles has permitted easier explanation of acid-base balance, and tools to apply to a wide variety of clinical situations. This does not suggest that the "traditional" approach is incorrect, merely that it looks at a mirror image of that proposed by Stewart, Fencl, and others. All acid-base disorders can be explained in terms of SID, A_{TOT} , and PCO_2 . This is important to anesthesiologists, who may significantly impact acid-base balance with our choice of fluids and mechanical ventilation strategy.

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References

1. Berend K, et al. *N Engl J Med*. 2014;371:1434.
2. Stewart PA. *Can J Physiol Pharmacol*. 1983;61:1444.
3. Gomez H, Kellum JA. *Crit Care Clin*. 2015;31:849.
4. Adrogue HJ, Madias NE. *Am J Kidney Dis*. 2016;68:793.
5. Fencl V, Leith DE. *Respir Physiol*. 1993;91:1.
6. Aiken CGA. *JCDR*. 2013;7:2038.
7. Moon JB. *N Engl J Med*. 1967;276:283.
8. Henderson LJ. *Ergebn Physiol*. 1909;8:254.
9. Hasselbalch KA. *Biochem Z*. 1916;78:112.
10. Sirker AA, et al. *Anaesthesia*. 2002;57:348.
11. Van Slyke DD. *Proc Natl Acad Sci USA*. 1921;7:229.
12. Henderson LH. Blood as a physicochemical system. *J Biol Chem*. 1921;46:411.
13. Corey HE. *Kidney Int*. 2003;64:777.
14. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol*. 1983;61:1444–1461.
15. Deleted in proofs.
16. Severinghaus JW. *Anesthesiology*. 1976;45:539.
17. Brackett NC, Cohen JJ, Schwartz WB. Carbon dioxide titration curve of normal man. *N Engl J Med*. 1965;272:6–12.
18. Hickling KG. *Respir Care Clin North Am*. 2002;8:155.
19. Laffey JG, Kavanagh BP. *Lancet*. 1999;354:1283.
20. Contreras M, et al. *Crit Care Med*. 2012;40:2622.
21. Scheingraber S, et al. *Anesthesiology*. 1999;90:1265.
22. Figge J, et al. *J Lab Clin Med*. 1992;120:713.
23. Story DA, et al. *Br J Anaesth*. 2004;92:54.
24. Figge J, et al. *J Lab Clin Med*. 1991;117:453.
25. Fencl V, et al. *Am J Respir Crit Care Med*. 2000;162:2246.
26. Figge J, et al. *Crit Care Med*. 1998;26:1807.
27. Goldwasser P, Feldman J. *J Clin Epidemiol*. 1997;50:693.
28. Wang F, et al. *N Engl J Med*. 1986;315:1591.
29. Bleich HL, et al. *J Clin Invest*. 1964;43:11.
30. Kazemi H, Johnson DC. *Physiol Rev*. 1986;66:953.
31. Bondoli A, et al. *Resuscitation*. 1981;9:99.
32. Javaheri S, et al. *Am J Respir Crit Care Med*. 1994;150:78.
33. Johnson DC, et al. *Respir Physiol*. 1984;56:301.
34. Johnson DC, et al. *J Appl Physiol*. 1987;63:1591.
35. Smith QR, Johanson CE. *Brain Res*. 1991;562:306.
36. Javaheri S. *J Appl Physiol*. 1987;62:1582.
37. Narins R, Emmett M. *Medicine (Baltimore)*. 1980;59:161.
38. Kellum JA. *Diagnosis and Treatment of Acid Base Disorders, Textbook of Critical Care Medicine*. 4th ed. Shoemaker, ed. Saunders; 2000: 839–853.
39. Rodriguez-Soriano J. *Pediatr Nephrol*. 2000;14:1121.
40. Choate KA, et al. *Proc Natl Acad Sci U S A*. 2003;100:663.
41. Shaer AJ. *Am J Med Sci*. 2001;322:316.
42. Kellum JA. *Crit Care*. 2005;9:500.
43. Schwartz WB, et al. *J Clin Invest*. 1965;44:291.
44. Brackett NC, et al. *N Engl J Med*. 1965;272:6.
45. Albert MS. *Ann Intern Med*. 1967;66:312.
46. Emmett M, Narins RG. *Medicine (Baltimore)*. 1977;56:38.
47. Salem MM, Mujais SK. *Arch Intern Med*. 1992;152:1625.
48. Moviat M, et al. *Crit Care*. 2003;7:R41.
49. Lipnick MS, et al. *Crit Care Med*. 2013;41:49.
50. Singer RB, Hastings AB. *Medicine (Baltimore)*. 1948;10:242.
51. Severinghaus JW. The invention and development of blood gas analysis apparatus. *Anesthesiology*. 2002;97:253.
52. Jorgensen K. *Scand J Clin Lab Invest*. 1957;9:122.
53. Astrup P, Siggard-Andersen O. *Adv Clin Chem*. 1963;69:1.
54. Wooten EW. *J Appl Physiol*. 2003;95:2333.
55. Siggard-Andersen O. *Scand J Clin Lab Invest Suppl*. 1977;37:15.
56. Prange HD, et al. *J Appl Physiol*. 2001;91(1985):33.
57. Siggard-Andersen O. *Scand J Clin Lab Invest*. 1971;27:239.
58. Gilfix BM, et al. *J Crit Care*. 1993;8:187.
59. Balasubramanyan N, et al. *Crit Care Med*. 1999;27:1577.
60. Story DA, et al. *Br J Anaesth*. 2004;92:54.
61. Singer M, et al. *JAMA*. 2016;315:801.
62. Fall PJ, Szerlip HM. *J Intensive Care Med*. 2005;20:255.
63. Lee SW, et al. *Emerg Med J*. 2008;25:659.
64. Mikkelsen ME, et al. *Crit Care Med*. 2009;37:1670.
65. Abramson D, et al. *J Trauma*. 1993;35:584.
66. Arnold RC, Shapiro NI, et al. *Shock*. 2009;32:35.
67. McNelis J, et al. *Am J Surg*. 2001;182:481.
68. Jones AE, et al. *JAMA*. 2010;303:739.
69. Jansen TC, et al. *Am J Respir Crit Care Med*. 2010;182:752.
70. Liu V, et al. *Ann Am Thorac Soc*. 2013;10:466.
71. Bakker J, et al. *Intensive Care Med*. 2016;42:472.
72. DeFronzo R, et al. *Metabolism*. 2016;65:20.
73. Tran TTT, et al. *Front Endocrinol*. 2017;8:106.
74. Chua HR, et al. *J Crit Care*. 2012;27:138.
75. Brewster S. *Practical Diabetes*. 2017;34:13.
76. Saposnik G, et al. *BMC Med Inform Decis Mak*. 2016;16:138.
77. Rocktaeschel J, et al. *Crit Care*. 2003;7:R60.
78. O'Malley, et al. *Anesth Analg*. 2005;100:1518.
79. Zarbock A. *JAMA*. 2016;315(20):2190.
80. Myles PS, et al. *World J Surg*. 2017;41:2457.
81. Gunnerson KJ, et al. *Crit Care*. 2006;10:R22.
82. Shaw AD, et al. *Ann Surg*. 2012;255:821.
83. Wilkes NJ, et al. *Anesth Analg*. 2001;93:811.
84. Yunos NJ. *JAMA*. 2012;308:1566.
85. Self WH, et al. *N Engl J Med*. 2018;378:819.
86. Semler MW, et al. *N Engl J Med*. 2018;378:829.
87. Awad S. The history of 0.9% saline. *Clin Nutr*. 2008;27(2):179.
88. Tsipotis E, et al. *Am J Med*. 2018;131:72.
89. Simoes CM, et al. *BMC Anesthesiol*. 2018;18:49.
90. Moviat M, et al. *Crit Care Med*. 2008;36:752.
91. Adrogue HJ, et al. *Kidney Int*. 1984;(25):591.
92. Tayar J, et al. *N Engl J Med*. 2002;346:1253.
93. Rocktaeschel J, et al. *Int J Artif Organs*. 2003;26:19.
94. Moviat M, Pickkers P, et al. *Crit Care*. 2006;10:R14.
95. Lima MF, et al. *J Neurosurg Anesthesiol*. 2018.
96. Gaudry S, et al. *N Engl J Med*. 2016;375:122.
97. Romagnoli S, et al. *Nephron*. 2018;1.
98. Swenson ER. *Anesthesiology*. 2018;128:873.
99. Rehm M, Finsterer U. *Anesth Analg*. 2003;96:1201.
100. Forsythe SM, Schmidt GA. *Chest*. 2000;117:260.
101. Jaber S, et al. *Lancet*. 2018;392:31.
102. Velissaris D, et al. *Crit Care Res Pract*. 2015;2015:605830.
103. McGuinness SP, et al. *Crit Care Med*. 2013;41:1599.
104. Caironi P, et al. *N Engl J Med*. 2014;370:1412.
105. Lyons C, Callaghan M. *Anaesthesia*. 2017;72:1379.
106. Slutsky AS, Ranieri VM. *N Engl J Med*. 2013;369:2126.
107. Barrett NA, Camporota L. *Crit Care Resusc*. 2017;19(suppl 1):62.

References

1. Berend K, de Vries APJ, Gans ROB. Physiological approach to assessment of acid base disturbances. *N Engl J Med.* 2014;371:1434–1445.
2. Stewart PA. Independent and dependent variables of acid-base control. *Respir Physiol.* 1978;33:9–26.
3. Gomez H, Kellum JA. Understanding acid base disorders. *Crit Care Clin.* 2015;31:849–860.
4. Adrogue HJ, Madias NE. Assessing acid-base status: physiologic versus physicochemical approach. *Am J Kidney Dis.* 2016;68:793–802.
5. Fencl V, Leith DE. Stewart's quantitative acid-base chemistry: applications in biology and medicine. *Respir Physiol.* 1993;91:1–916.
6. Aiken CGA. History of medical understanding and misunderstanding of acid base balance. *JCDR.* 2013;7:2038–2041.
7. Moon JB. Sir William Brooke O'Shaughnessy—the foundations of fluid therapy and the Indian telegraph service. *N Engl J Med.* 1967;276:283–284.
8. Henderson LJ. Das gleichgewicht zwischen sauren und bases im tierischen organismus. *Ergebn Physiol.* 1909;8:254–325.
9. Hasselbalch KA. Die berechnung der wasserstoffzahl des blutes aus der freien und gebundenen kohlensäure desselben, und die sauerstoffbindung des blutes als funktion der wasserstoffzahl. *Biochem Z.* 1916;78:112–144.
10. Sirker AA, Rhodes A, Grounds RM, Bennett ED. Acid-base physiology: the 'traditional' and the 'modern' approaches. *Anaesthesia.* 2002;57:348–356.
11. Van Slyke DD. An apparatus for determination of the gases in blood and other solutions. *Proc Natl Acad Sci U S A.* 1921;7:229–231.
12. Henderson LH. Blood as a physicochemical system. *J Biol Chem.* 1921;46:411–419.
13. Corey HE. Stewart and beyond: new models of acid-base balance. *Kidney Int.* 2003;64:777–787.
14. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol.* 1983;61:1444–1461.
15. Deleted in proofs.
16. Severinghaus JW. Acid-base balance nomogram—a Boston-Copenhagen detente. *Anesthesiology.* 1976;45:539–541.
17. Brackett NC, Cohen JJ, Schwartz WB. Carbon dioxide titration curve of normal man. *N Engl J Medicine.* 1965;272:6–12.
18. Hickling KG. Permissive hypercapnia. *Respir Care Clin N Am.* 2002;8:155–169. v.
19. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill—too little of a good thing? *Lancet.* 1999;354:1283–1286.
20. Contreras M, Ansari B, Curley G, et al. Hypercapnic acidosis attenuates ventilation-induced lung injury by a nuclear factor-KB dependent mechanism. *Crit Care Med.* 2012;40(9):2622–2630.
21. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology.* 1999;90:1265–1270.
22. Figge J, Mydosh T, Fencl V. Serum proteins and acid-base equilibria: a follow-up. *J Lab Clin Med.* 1992;120:713–719.
23. Story DA, Morimatsu H, Bellomo R. Strong ions, weak acids and base excess: a simplified Fencl-Stewart approach to clinical acid-base disorders. *Br J Anaesth.* 2004;92:54–60.
24. Figge J, Rossing TH, Fencl V. The role of serum proteins in acid-base equilibria. *J Lab Clin Med.* 1991;117:453–467.
25. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. *Am J Respir Crit Care Med.* 2000;162:2246–2251.
26. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. *Crit Care Med.* 1998;26:1807–1810.
27. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. *J Clin Epidemiol.* 1997;50:693–703.
28. Wang F, Butler T, Rabbani GH, Jones PK. The acidosis of cholera. Contributions of hyperproteinemia, lactic acidemia, and hyperphosphatemia to an increased serum anion gap. *N Engl J Med.* 1986;315:1591–1595.
29. Bleich HL, Berkman PM, Schwartz WB. The response of cerebrospinal fluid composition to sustained hypercapnia. *J Clin Invest.* 1964;43:11–18.
30. Kazemi H, Johnson DC. Regulation of cerebrospinal fluid acid-base balance. *Physiol Rev.* 1986;66:953–1037.
31. Bondoli A, Magalini SI, de AC, et al. Changes in plasma and cerebrospinal fluid electrolytes in hypercapnia. *Resuscitation.* 1981;9:99–102.
32. Javaheri S, Corbett W, Wagner K, Adams JM. Quantitative cerebrospinal fluid acid-base balance in acute respiratory alkalosis. *Am J Respir Crit Care Med.* 1994;150:78–82.
33. Johnson DC, Frankel HM, Kazemi H. Effect of furosemide on cerebrospinal fluid composition. *Respir Physiol.* 1984;56:301–308.
34. Johnson DC, Singer S, Hoop B, Kazemi H. Chloride flux from blood to CSF: inhibition by furosemide and bumetanide. *J Appl Physiol.* 1987;63:1591–1600.
35. Smith QR, Johanson CE. Chloride efflux from isolated choroid plexus. *Brain Res.* 1991;562:306–310.
36. Javaheri S. Effects of acetazolamide on cerebrospinal fluid ions in metabolic alkalosis in dogs. *J Appl Physiol.* 1987;62:1582–1588.
37. Narins R, Emmett M. Simple and mixed acid-base disorders: a practical approach. *Medicine (Baltimore).* 1980;59:161–187.
38. Kellum JA. *Diagnosis and Treatment of Acid Base Disorders, Textbook of Critical Care Medicine.* 4th ed. Shoemaker, ed. Saunders; 2000: 839–853.
39. Rodriguez-Soriano J. New insights into the pathogenesis of renal tubular acidosis—from functional to molecular studies. *Pediatr Nephrol.* 2000;14:1121–1136.
40. Choate KA, Kahle KT, Wilson FH, Nelson-Williams C, Lifton RP. WNK1, a kinase mutated in inherited hypertension with hyperkalemia, localizes to diverse Cl⁻-transporting epithelia. *Proc Natl Acad Sci U S A.* 2003;100:663–668.
41. Shaer AJ. Inherited primary renal tubular hypokalemic alkalosis: a review of Gitelman and Bartter syndromes. *Am J Med Sci.* 2001;322:316–332.
42. Kellum JA. Reunification of acid-base physiology. *Critical Care.* 2005;9:500–507.
43. Schwartz WB, Brackett NC, Cohen JJ. The response of extracellular hydrogen ion concentration to graded degrees of chronic hypercapnia: the physiologic limits of the defense of pH*. *Eur J Clin Invest.* 1965;44:291–301.
44. Brackett NC, Cohen JJ, Schwartz WB. Carbon dioxide titration curve of normal man. *N Engl J Med.* 1965;272:6–12.
45. Albert MS, Dell RB, Winters RW. Quantitative displacement of acid-base equilibrium in metabolic acidosis. *Ann Intern Med.* 1967;66:312–322.
46. Emmett M, Narins RG. Clinical use of the anion gap. *Medicine (Baltimore).* 1977;56:38–54.
47. Salem MM, Mujais SK. Gaps in the anion gap. *Arch Intern Med.* 1992;152:1625–1629.
48. Moviat M, van HF, van der HH. Conventional or physicochemical approach in intensive care unit patients with metabolic acidosis. *Crit Care.* 2003;7:R41–R45.
49. Lipnick MS, Braun AB, Cheung JT, Gibbons FK, Christopher KB. The difference between critical care initiation anion gap and prehospital admission anion gap is predictive of mortality in critical illness. *Crit Care Med.* 2013;41:49–59.
50. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. *Medicine.* 1948;10:242.
51. Severinghaus JW. The invention and development of blood gas analysis apparatus. *Anesthesiology.* 2002;97:253–256.
52. Jorgensen K, Astrup P. Standard bicarbonate, its clinical significance, and a new method for its determination. *Scand J Clin Lab Invest.* 1957;9:122–132.
53. Astrup P, Siggaard-Andersen O. Micromethods for measuring acid-base values of blood. *Adv Clin Chem.* 1963;69:1–28.
54. Wooten EW. Calculation of physiological acid-base parameters in multicompartment systems with application to human blood. *J Appl Physiol.* 2003;95:2333–2344.
55. Siggaard-Andersen O. The van Slyke equation. *Scand J Clin Lab Invest Suppl.* 1977;37:15–20.
56. Prange HD, Shoemaker JL, Westen EA, Horstkotte DG, Pinshow B. Physiological consequences of oxygen-dependent chloride binding to hemoglobin. *J Appl Physiol.* 2001;91(1985):33–38.
57. Siggaard-Andersen O. An acid-base chart for arterial blood with normal and pathophysiological reference areas. *Scand J Clin Lab Invest.* 1971;27:239–245.
58. Gilfix BM, Bique M, Magder S. A physical chemical approach to the analysis of acid-base balance in the clinical setting. *J Crit Care.* 1993;8:187–197.

59. Balasubramanyan N, Havens PL, Hoffman GM. Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. *Crit Care Med.* 1999;27:1577–1581.
60. Story DA, Morimatsu H, Bellomo R. Strong ions, weak acids and base excess: a simplified Fencl-Stewart approach to clinical acid-base disorders. *Br J Anaesth.* 2004;92:54–60.
61. Singer M, Deutschman CS, Seymour C. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA.* 2016;315:801–810.
62. Fall PJ, Szerlip HM. Lactic acidosis: from sour milk to septic shock. *Intensive Care Med.* 2005;20:255–271.
63. Lee SW, Hong YS, Park DW, et al. Lactic acidosis not hyperlactatemia as a predictor of inhospital mortality in septic emergency patients. *Emerg Med J.* 2008;25:659–665.
64. Mikkelsen ME, Miltiades AN, Gaiesti DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med.* 2009;37:1670–1677.
65. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. *J Trauma.* 1993;35:584–588.
66. Arnold RC, Shapiro NI, Jones AE, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock.* 2009;32(1):35–39.
67. McNelis J, Marini CP, Jurkiewicz A, et al. Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. *Am J Surg.* 2001;182:481–485.
68. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA.* 2010;303:739–746.
69. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. LACTATE study group. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med.* 2010;182:752–761.
70. Liu V, Morehouse JW, Soule J, Whippy A, Escobar GJ. Fluid volume, lactate values, and mortality in sepsis patients with intermediate lactate values. *Ann Am Thorac Soc.* 2013;10:466–473.
71. Bakker J, de BD, Hernandez G. Lactate-guided resuscitation saves lives: we are not sure. *Intensive Care Med.* 2016;42:472–474.
72. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: current perspectives on causes and risk. *Metabolism.* 2016;65:20–29.
73. Tran TTT, Pease A, Wood AJ, et al. Review of evidence for adult diabetic ketoacidosis management protocols. *Front Endocrinol.* 2017;8:106.
74. Chua HR, Venkatesh B, Stachowski E, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *J Crit Care.* 2012;27:138–145.
75. Brewster S, Curtis L, Poole R. Urine versus blood ketones. *Practical Diabetes.* 2017;34:13–15.
76. Saposnik G, Redelmeier D, Ruff CC, Tobler PN. Cognitive biases associated with medical decisions: a systematic review. *BMC Med Inform Decis Mak.* 2016;16:138.
77. Rocktaschel J, Morimatsu H, Uchino S, et al. Acid-base status of critically ill patients with acute renal failure: analysis based on Stewart-Figge methodology. *Crit Care.* 2003;7:R60.
78. O'Malley CM, Frumento RJ, Hardy MA, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg.* 2005;100:1518–1524. table.
79. Zarbock A. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA.* 2016;315(20):2190–2199.
80. Myles PS, Andrews S, Nicholson J, Lobo DN, Mythen M. Contemporary approaches to perioperative IV fluid therapy. *World J Surg.* 2017;41:2457–2463.
81. Gunnerson K, Saul M, He S, Kellum J. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Crit Care.* 2006;10:R22.
82. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to plasma-lyte. *Ann Surg.* 2012;255(5):821–829.
83. Wilkes NJ, Woolf R, Mutch M, et al. The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. *Anesth Analg.* 2001;93:811–816.
84. Yunos N. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA.* 2012;308:1566–1572.
85. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically ill adults. *N Engl J Med.* 2018;378:819–828.
86. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med.* 2018;378:829–839.
87. Awad S. The history of 0.9% saline. *Clin Nutr.* 2008;27(2):179–188.
88. Tsipotis E, Price LL, Jaber BL, Madias NE. Hospital-associated hypernatremia spectrum and clinical outcomes in an unselected cohort. *Am J Med.* 2018;131:72–82.
89. Simoes CM, Carmona MJC, Hajjar LA, et al. Predictors of major complications after elective abdominal surgery in cancer patients. *BMC Anesthesiol.* 2018;18:49.
90. Moviat M, Terpstra AM, Ruitenberg W, Kluijtmans LAJ, Pickkers P, van der Hoeven JG. Contribution of various metabolites to the “unmeasured” anions in critically ill patients with metabolic acidosis. *Crit Care Med.* 2008;36:752.
91. Adrogue HJ, Eknayan G, Suki WK. Diabetic ketoacidosis: role of the kidney in the acid-base homeostasis re-evaluated. *Kidney Int.* 1984;25:591–598.
92. Tayar J, Jabbour G, Saggi SJ. Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam. *N Engl J Med.* 2002;346:1253–1254.
93. Rocktaschel J, Morimatsu H, Uchino S, Ronco C, Bellomo R. Impact of continuous veno-venous hemofiltration on acid-base balance. *Int J Artif Organs.* 2003;26:19–25.
94. Moviat M, Pickkers P, van der Voort PHJ, van der Hoeven JG. Acetazolamide-mediated decrease in strong ion difference accounts for the correction of metabolic alkalosis in critically ill patients. *Crit Care.* 2006;10:R14.
95. Lima MF, Neville IS, Cavalheiro S, Bourguignon DC, Pelosi P, Malbouisson LMS. Balanced crystalloids versus saline for perioperative intravenous fluid administration in children undergoing neurosurgery: a randomized clinical trial. *J Neurosurg Anesthesiol.* 2018.
96. Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med.* 2016;375:122–133.
97. Romagnoli S, Ricci Z, Ronco C. Perioperative acute kidney injury: prevention, early recognition, and supportive measures. *Nephron.* 2018;1–6.
98. Swenson ER. Does aerobic respiration produce carbon dioxide or hydrogen ion and bicarbonate? *Anesthesiology.* 2018;128:873–879.
99. Rehm M, Finsterer U. Treating intraoperative hyperchloremic acidosis with sodium bicarbonate or tris-hydroxymethyl aminomethane: a randomized prospective study. *Anesth Analg.* 2003;96(4):1201–1208.
100. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. *Chest.* 2000;117:260–267.
101. Jaber S, Paugam C, Futier E, et al. Sodium bicarbonate therapy for patients with severe metabolic acidemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. *Lancet.* 2018;392:31–40.
102. Velissaris D, Karamouzos V, Ktenopoulos N, Pierrakos C, Karanikolas M. The use of sodium bicarbonate in the treatment of acidosis in sepsis: a literature update on a long term debate. *Crit Care Res Pract.* 2015;2015:605830.
103. McGuinness SP, Parke RL, Bellomo R, Van Haren FM, Bailey M. Sodium bicarbonate infusion to reduce cardiac surgery-associated acute kidney injury: a phase II multicenter double-blind randomized controlled trial. *Crit Care Med.* 2013;41:1599–1607.
104. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med.* 2014;370:1412–1421.
105. Lyons C, Callaghan M. Apnoeic oxygenation with high-flow nasal oxygen for laryngeal surgery: a case series. *Anaesthesia.* 2017;72:1379–1387.
106. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med.* 2013;369:2126–2136.
107. Barrett NA, Camporota L. The evolving role and practical application of extracorporeal carbon dioxide removal in critical care. *Crit Care Resusc.* 2017;19(suppl 1):62–67.

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KEY POINTS

- Blood transfusion is safer now than at any other time in history. Advances in donor screening, improved testing, automated data systems, and changes in transfusion medicine practices account for these increases in safety.
- Although the overall condition of the patient is of prime importance, hemoglobin (Hb) values remain a primary component for transfusion decisions with the use of either a restrictive or liberal strategy. In general, a transfusion trigger of 6 to 8 g/dL Hb (restrictive strategy) can be tolerated by patients.
- Preoperative anemia is an independent, and potentially modifiable, risk factor for postoperative morbidity and mortality.
- The term *patient blood management* has become synonymous with appropriate transfusion strategy.
- The addition of plasma and sometimes platelets to packed red blood cells (PRBCs) is described by the term *transfusion ratios*. For example, 2 units of plasma with 1 unit of platelets with 1 unit of PRBCs would be 2:1:1.
- Infectivity of blood is no longer a major cause of transfusion-related morbidity and mortality. Transfusion-related acute lung injury is the leading cause of transfusion-related mortality.
- Fresh whole blood has gained renewed interest as a choice in patients with major blood loss and related coagulopathy (see also [Chapter 50](#)).
- Although storage lesions of red blood cells increase over time, there is no evidence that blood stored for short periods compared with moderately long periods of time contributes to worse clinical outcomes. However, as newer solutions extend the shelf-life of blood, this may need continued evaluation, particularly in high-risk groups.

Transfusion of human-derived blood products is one of the most common procedures in modern medicine, often proving life-saving. In a recent analysis of electronic medical records from hospitals in the United States, blood transfusion occurred for 12.5% of hospitalized inpatient encounters, with red blood cells (RBCs) being the most commonly transfused component, followed by platelets and plasma.¹ Transfusion is not without risk, and the anesthesiologist must weigh the risks and benefits of providing or withholding transfusion therapy for individual patients in specific clinical settings. This chapter focuses on the physiology and pathology of transfusion medicine with particular attention to the acquisition, processing, storage, indication for, and risk of blood therapy in the perioperative period.

Evolution and Recent History of Blood Transfusion Therapy

THE 1960S

Transfusion medicine has undergone enormous changes in the last 60 years, but the consensus of whether to use whole blood, its components, or both has vacillated every decade

or so. In the 1960s, most blood given was in the form of whole blood, whereas fresh frozen plasma (FFP) was available for the treatment of coagulopathies.^{2,3}

THE 1970S THROUGH THE 1980S

Transfusion therapy was characterized in this period by “giving the patient only the component of blood that was needed.” Component transfusion therapy rather than whole blood transfusion was the standard of care. For example, if the patient was anemic, only packed red blood cells (PRBCs) would be transfused, or if thrombocytopenia existed, only platelet concentrates would be given. Caution regarding administration of blood transfusions increased during this time period in part because of concern regarding the infectivity of blood (e.g., hepatitis and human immunodeficiency virus [HIV]). Furthermore, individual clinical decisions regarding blood transfusions were and continue to be monitored by local hospital transfusion committees (as required by regulatory agencies of various countries including the United States). These committees have the responsibility of monitoring the individual and institutional transfusion practices by evaluating clinical appropriateness of transfusion triggers.⁴

1990S THROUGH THE 2000S

With improved screening techniques for HIV and other blood-borne pathogens during this decade, the incidence of blood transfusion-related infectious disease transmission decreased 10,000-fold. The focus of blood product safety now shifted to *noninfectious serious hazards of transfusion*.⁵ These hazards include hemolytic transfusion reactions, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO), to name a few. With an increased awareness of the potential morbidity and mortality associated with blood product administration, research focused on the concept of liberal versus restrictive blood transfusion strategy. Attention now turned to balancing the threats posed by two independent (yet related) risk factors of patient outcome—anemia and transfusion.

Although the strategy of specific component therapy was still prominent, the concept of reconstituted “whole blood” was introduced during this decade. Led by trauma hospitals and the military, FFP and platelets were transfused along with PRBCs, resulting in a transfusion ratio that was similar to that of whole blood.^{6,7} Because the concept of transfusing components that reconstitute whole blood rouses the prior practice of transfusing whole blood, that concept is being reexamined⁸ again in the literature and may yet prove beneficial in patients with life-threatening bleeding.^{9,10}

2010 TO THE PRESENT

The 2010s saw a shift away from simply correcting anemia and coagulopathy, to a more patient-centered, multi-pronged approach to transfusion medicine. As a result, the term *patient blood management (PBM)* has become synonymous with modern, evidence-based transfusion medicine.¹¹ The Society for the Advancement of Blood Management defines PBM as “the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome.”¹² PBM recognizes transfusions are but a temporary solution to an often complex, multifactorial process that requires attention to the underlying cause of anemia.¹³

Integration of PBM into clinical pathways has reduced the reliance on allogenic blood product transfusion as the only means to avoid anemia and likely explains the continued decrease in transfusions noted in U.S. hospitals over the last decade.¹⁴ In a recent retrospective analysis, implementation of a PBM system with a reduced transfusion threshold from 8 g/dL to 7 g/dL Hb in orthopedic surgical patients reduced the use of erythrocytes by 32% while improving clinical outcomes. Most notably, patients 65 years and older demonstrated the most improved clinical outcomes, including 30-day readmission rates.¹⁵ Comprehensive PBM programs also can include evaluation of preoperative anemia, clinical decision support, educational efforts, improved surgical techniques, and blood conservation strategies.

PBM in many countries has been facilitated by computerized data systems¹⁶ and supply guidelines.¹⁷ A limitation of most of the PBM publications is that they describe mostly nonbleeding, anemic patients and the decision to initiate transfusion. Very little information addresses what

guidelines should be used for repetitive transfusions. The anesthesia provider offers insight into these issues and can provide guidance as to how PBM fits into the perioperative clinical environment.

Blood Procurement

SOURCE OF DONORS

Significant global disparities exist regarding access to “safe” blood, or blood that is properly collected and tested. According to World Bank definitions, low- and middle-income countries collect 53% of all blood donations worldwide, yet represent 81% of the world’s population. In addition, the prevalence of transfusion-transmissible infections in blood donations from low- and middle-income countries is significantly higher than those from high-income countries, yet low-income countries have less access to basic quality screening procedures.¹⁸ Another issue, particularly in low-income countries, is incentivized donors. The World Health Organization’s (WHO) decision-making body, the World Health Assembly, has issued resolutions and consensus statements that emphasize the need for all member states to develop national blood systems based on voluntary, unpaid donations as a means to ensure a safe, secure, and sufficient supply of blood products.¹⁹ Some experts have suggested that offering economic incentives or rewards to donors should be seriously considered,²⁰ because limited empirical research exists to support the assumption that incentivized donations, including noncash incentives, either improve recruitment of donors or pose a risk to blood product safety.²¹ However, the WHO strongly defends voluntary nonremunerated blood donation as a vehicle to a safer blood supply and increased donor participation.²²

In the United States, the Food and Drug Administration’s (FDA) Center for Biologics Evaluation and Research provides the regulatory oversight for blood banks and donation centers, with most voluntarily obtaining accreditation from the AABB (formerly, American Association of Blood Banks). In Europe, the European Commission sets standards for blood products and their components in the European Blood Directive (Directive 2002/98/EC). These regulatory and professional societies set standards with regard to the donation, collection, testing, processing, storage, and distribution of products.

In the United States, those over the age of 16 and who weigh at least 110 pounds are eligible for screening for potential blood donation. Vital signs are assessed, including temperature, heart rate, and blood pressure. Hb levels are measured, with minimum cutoffs of 13 g/dL for men and 12.5 g/dL for women. Blood is collected either as whole blood and separated by centrifugation or by apheresis, in which only specific components are collected while other components are returned to the donor. An outline of the separation scheme by which various blood components are derived is shown in Fig. 49.1. Apheresis is particularly helpful in donors with blood type AB, as they represent a rare blood type yet serve as the universal plasma donor. As recipients, patients with blood type AB rarely require AB specific blood, as they can be transfused with any type of red cell. Therefore, if plasma is collected from AB donors while

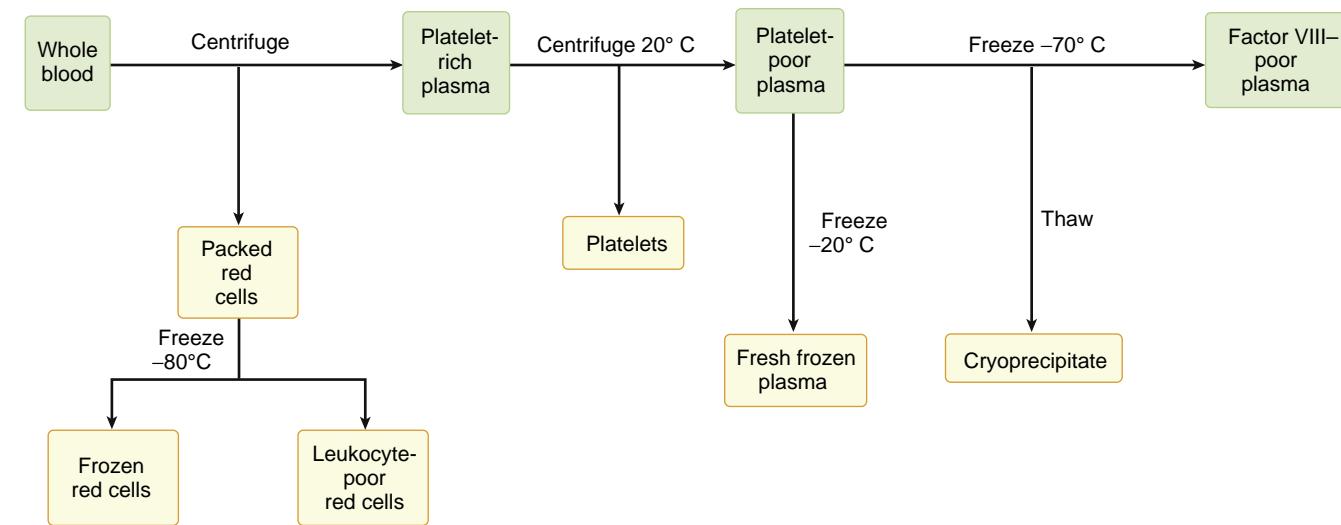


Fig. 49.1 Scheme for separation of whole blood for component therapy.

red cells are immediately returned, this may allow for more frequent plasma donation from this small but vitally important group of donors.

TRANSFUSION-TRANSMISSIBLE INFECTIONS

Donor screening attempts to reduce the risk of a transfusion-transmissible disease and to protect the donor from an adverse reaction due to donation. Deferment based on medical history includes those considered to be in high-risk categories for potential transmission of an infectious agent, including those with a significant travel history, history of injection drug use, recent tattoos, or men who have had sex with men (MSM) in the previous 12 months. The latter deferment category has been controversial in recent years, given the changing epidemiology of the HIV epidemic and improved screening methods. In this population, some advocate for reducing the time interval between potential exposure and donation to 3 months.²³

The use of more sensitive screening tests in conjunction with changes in transfusion medicine practices have made infectious risks quite rare. The FDA requires blood products to be tested for hepatitis B and C, HIV (types 1 and 2), human T-lymphotropic virus (HTLV; types 1 and 2), and *treponema pallidum* (syphilis), West Nile virus, and Zika virus. Testing is recommended for *Trypanosoma cruzi* (Chagas disease) for first-time donors. Historically, the FDA has published tables on the risks for infectivity, Table 49.1 but because the rates are so infrequent, the last tables published were for data from 2011.

Several blood-safety changes made between the years of 1982 and 2008 have decreased the risk for disease transmission by allogenic blood so that the demand for autologous blood has declined as well. The West Nile virus story illustrates how rapidly our blood banks can respond. In 2002, West Nile virus caused the largest outbreak of arboviral encephalitis ever recorded in the United States (i.e., approximately 4200 patients). Twenty-three cases of transfusion-transmitted infections resulted in seven deaths. In 2003, testing became available that now makes that infection very rare (see Table 49.1). The FDA's response to the 2015 to 2016 Zika virus outbreak was similarly swift—the blood supply was immediately shifted from areas with low risk of infections to areas of known infection; authorization for screening tests was issued

TABLE 49.1 Percentage Risk of Transfusion-Transmitted Infection With a Unit of Screened Blood in the United States

Infection	Risk	Window Period (Days)
Human immunodeficiency virus-1 and -2	1:1,476,000	5-6
Human T-lymphotropic virus (HTLV-II)	1:2,993,000	51
Cytomegalovirus (CMV)	Infrequent with leukocyte-reduced components	
Hepatitis C virus (HCV)	1:1,149,000	3-4
Hepatitis B virus (HBV)	1: 280,000	24
Hepatitis A virus (HAV00)	1:1,000,000	
Bacteria red blood cells	1:1,000 with septic reaction in 1:500,000	
Pheresis platelets (with early aerobic culture)		
Parasites: Babesia and malaria	<1:4,000,000	7-14
West Nile virus (WNV)	1/1,100,000	?
Acute hemolytic transfusion reactions	1:38,000-1:70,000	

Data from AABB: *AABB Technical Manual*, 17th ed. 2011, AABB; and Fiebig ER, Busch MP. Infectious risks of transfusions. In: Spiess BD, Spence RK, Shander A, eds. *Perioperative Transfusion Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2006.

within months, and universal screening with a qualitative nucleic acid test (NAT) for the detection of Zika virus ribonucleic acid (RNA) was mandated.²⁴

The changes in blood transfusion testing can be appreciated when comparing tests used in 1998 (Box 49.1) with those used in 2018 (Table 49.2). The use of nucleic acid technology has decreased the window of infectivity (i.e., time from being infected to a positive test result), which is a major reason for the decrease in infectivity with hepatitis, HIV, West Nile virus, and Zika virus.

BOX 49.1 Infectious Disease Testing for Blood Transfusions

1. Discontinue serum alanine aminotransferase testing
2. Hepatitis C antibody testing
3. Antibody to hepatitis B core antigen
4. Human immunodeficiency virus (HIV) type 1
5. HIV-2
6. HIV Ag (p24 antigen)
7. Human T-cell lymphotropic virus (HTLV) types 1 and 2
8. Serologic test for syphilis

Modified from National Institutes of Health, Consensus Development Panel on Infectious Disease Testing for Blood Transfusions. Infectious disease testing for blood transfusions. *JAMA*. 1995;274:1374–1379.

TABLE 49.2 Tests Used for Detecting Infectious Agents in All Units of Blood: 2018

Virus	Genetic Testing	Antibody To
Human immunodeficiency virus (HIV)	Nucleic acid technology	HIV-1, HIV-2
Hepatitis C virus (HCV)	Nucleic acid technology	HCV
Hepatitis B virus (HBV)	Nucleic acid technology	Anti-HBc, HBsAg
Human T-cell lymphotropic, virus (HTLV)		HTLV-1, HTLV-2
West Nile virus	Nucleic acid technology	
Zika virus	Nucleic acid technology	

Posttransfusion Hepatitis

When blood transfusions became a reality in the 1940s, viral hepatitis was recognized as a major complication. The concern is primarily with hepatitis B, C, and, rarely, D, which are parenterally transmitted viruses. Before 1985, the overall incidence of posttransfusion hepatitis ranged from a low of 3% to a high of 19%, depending on the institution and the location (e.g., donors from large cities have a more frequent incidence of the hepatitis virus). In most areas, the incidence of hepatitis has ranged from 3% to 10%. Ninety percent of posttransfusion hepatitis is caused by the hepatitis C virus. Fewer than a third of these patients develop jaundice.²⁵ To determine their ultimate fate, Tong and colleagues²⁵ monitored 131 patients with chronic posttransfusion hepatitis C for several years and found the following incidence of signs, symptoms, and conditions:

- Fatigue (67%)
- Hepatomegaly (67%)
- Chronic hepatitis (23%)
- Chronic active hepatitis (51%)
- Hepatocellular carcinoma (11%)

It was found that 20 patients had died of the following:

- Complications of cirrhosis (8 patients)
- Hepatocellular carcinoma (11 patients)
- Chronic active hepatitis-pneumonia (1 patient)

Even today, patients with hepatitis C and apparent recovery from the acute infection may go on to develop cirrhosis and hepatocellular carcinoma. Several antiviral therapies, such as Mavyret (glecaprevir-pibrentasvir), Harvoni (ledipasvir-sofosbuvir), Epclusa (sofosbuvir-velpatasvir), and Vosevi (sofosbuvir-velpatasvir-voxilaprevir), now exist that may stop progression and even cure infection from certain genotypes of hepatitis C. However, any person who has ever tested positive for hepatitis B or hepatitis C, at any age, is currently ineligible to donate blood.²⁶

Cytomegalovirus

Asymptomatic chronic infection with cytomegalovirus (CMV), a double-stranded DNA virus belonging to the herpesviridae family, is common enough in healthy adults that some view CMV as normal flora. Infection with the CMV virus is limited to humans, requires contact with the body fluids of a previously infected individual, survives best within cells, and persists in its latent form in the monocytes of people with antibody evidence of previous exposure infection. Fortunately, the primary concern is recipients who are at risk because of pregnancy (multiple), immaturity, or immunosuppression. CMV seroconversion usually occurs in subsets of patients receiving multiple transfusions. CMV causes a heterophil antibody-negative response that closely resembles infectious mononucleosis in many respects. An infectious mononucleosis-like syndrome that can occur 1 to 2 months after open-heart surgery is known as the *postperfusion syndrome* or *posttransfusion mononucleosis*.²⁷ The evidence for transmission of CMV is most convincing when the recipient changes from a seronegative state before transfusion to a seropositive state accompanied by the mononucleosis-like illness several weeks after transfusion.

Transfusion-transmitted CMV can cause significant clinical problems in certain patient populations, such as premature neonates, allograft recipients, and patients post splenectomy.²⁸ To prevent infection in high-risk populations, use of leukocyte-reduced blood, use of frozen deglycerolized RBCs, and screening for CMV antibody negative donors have been recommended (see the section on leukoreduction and irradiation of blood transfusions). Wilhelm and associates²⁹ concluded that it is not necessary to provide blood products from CMV-seronegative donors for most patients who receive blood transfusions, because the risk for seroconversion is approximately 0.14% overall, or 0.38% per unit of seropositive donor blood. They do recommend continuing to use CMV-seronegative blood to prevent CMV infection in preterm and newborn infants. Plasma components, such as FFP and cryoprecipitate, and leukoreduced components from seropositive donors are considered to be CMV safe.

Zika Virus

More recently, transfusion-transmissible Zika virus infection has been of concern.³⁰ Transmitted by mosquitos, Zika virus infection is associated with Guillain-Barre syndrome³¹ and microcephaly in newborns whose mothers were infected during pregnancy.³² Although these manifestations of Zika virus infection are striking, 80% of infected persons are asymptomatic, and thus pose a potential threat to the blood supply. As a result, the FDA issued guidance that all donations collected in the United States be tested for Zika virus using NAT.³³

TABLE 49.3 Infectious Diseases Theoretically Transmissible by Blood Transfusion for Which No Test Is Available: 2004

Disease	Risk
Malaria	<1 million in the United States
Severe acute respiratory syndrome (SARS)	Unknown
Variant Creutzfeldt-Jakob disease	Three potential cases in the United Kingdom

Other Transfusion-Associated Infectious Diseases

Although many other infectious diseases can theoretically be transmitted by blood transfusion, only a few are of real concern. They include *Yersinia enterocolitica* infection, syphilis, malaria, Chagas disease, variant Creutzfeldt-Jakob disease, parvovirus B19, and severe acute respiratory syndrome (SARS; Table 49.3).

During the late 1980s, Tripple and colleagues³⁴ described seven cases of fatal transfusion-associated *Y. enterocolitica* sepsis. These investigators also reviewed the literature and found 26 cases of gram-negative bacterial sepsis with whole blood or PRBCs. *Y. enterocolitica* is a bacterium that can cause mostly mild gastrointestinal problems. However, in severe cases, sepsis and death can occur. Unfortunately, storage of blood at 4°C in phosphate buffer enhances its growth.

Fortunately, posttransfusion syphilis is unlikely because the infective agent cannot survive during storage at 1°C to 6°C. Platelet concentrates are the blood component most likely to be implicated because they commonly are stored at room temperature.

Posttransfusion malaria has never been a significant cause of blood recipient morbidity. Nevertheless, malaria can occur, especially if blood donors at risk for harboring parasites are not excluded. Consequently, blood banks thoroughly question donors for history of travel or migration from areas where malaria is endemic.

Even though there are no cases of variant Creutzfeldt-Jakob disease from blood transfusions, the virus can be transmitted by blood in animal models and stringent donor policies based on travel and residence in England or other countries in Europe are in place.

Like malaria, there are other infectious agents that can transmit disease through blood transfusions, but there are no available blood testing methods for these cases (see Table 49.3). Without a specific diagnostic test, screening with restrictive donor criteria is used. For example, in 2003 in the United States, donors with suspected SARS or who traveled to certain countries in Southeast Asia would not be accepted.

BIOCHEMICAL CHANGES IN STORED BLOOD

Units of blood collected from donors are usually separated into components (e.g., RBCs, plasma, cryoprecipitate, and platelets; see Fig. 49.1). Citrate phosphate dextrose adenine-1 (CPDA-1) is an anticoagulant preservative that is used for blood stored at 1°C to 6°C. Citrate prevents clotting by binding Ca^{2+} . Phosphate serves as a buffer, and

dextrose is a red cell energy source, allowing the RBCs to continue glycolysis and maintain sufficient concentrations of high-energy nucleotides (adenosine triphosphate [ATP]) to ensure continued metabolism and subsequent viability during storage. The addition of adenine prolongs storage time by increasing the survival of RBCs, allowing them to resynthesize the ATP needed to fuel metabolic reactions. This extends the storage time from 21 to 35 days.³⁵ Without adenine, RBCs gradually lose their ATP and their ability to survive after transfusion. Finally, storage at 1°C to 6°C assists preservation by reducing the rate of glycolysis approximately 40 times the rate at body temperature.

The shelf life of PRBCs can be extended to 42 days when AS-1 (Adsol), AS-3 (Nutricel), or AS-5 (Optisol) is used.^{36,37} Adsol contains adenine, glucose, mannitol, and sodium chloride (NaCl). Nutricel contains glucose, adenine, citrate, phosphate, and NaCl. Optisol contains only dextrose, adenine, NaCl, and mannitol. On a national level, 85% of RBCs are collected in AS-1. In Europe, a solution similar to AS-1 containing saline, adenine, glucose, and mannitol is used. As of 2015, the FDA approved a new additive solution, AS-7, which increases storage time to at least 56 days; however, the solution is not yet commercially available in the United States.³⁸

The hematocrit (Hct) of the transfused product depends on the storage method. When CPDA is the anticoagulant used, the Hct is greater than 65%, because most of the plasma is removed, and the resulting volume is approximately 250 mL. When AS-1 is used, most of the plasma is also removed, but 100 mL of storage solution is added, resulting in an Hct of 55% to 60% and volume of 310 mL.³⁹ The duration of storage is set by U.S. federal regulation and is based on the requirement that at least 70% of the transfused RBCs remain in circulation for 24 hours after infusion.

During storage of whole blood and PRBCs, a series of biochemical reactions occur that alter the biochemical makeup of blood and account for some of the complications. Collectively, these are known as *red cell storage lesions* and may be responsible for the organ injury associated with red cell transfusion. During storage, RBCs metabolize glucose to lactate; hydrogen ions accumulate, and plasma pH decreases, while increases in oxidative damage to lipids and proteins are noted. The storage temperature of 1°C to 6°C inhibits the sodium-potassium pump, resulting in a loss of potassium ion (K^+) from the cells into the plasma and a gain of intracellular sodium.⁴⁰ Although K^+ concentrations appear elevated in 35-day stored RBC concentrates, the total plasma volume in the concentrates is only 70 mL, so total K^+ is not markedly elevated. Over time, there are progressive decreases in RBC concentrations of ATP, nitric oxide (NO), and 2,3-diphosphoglycerate (2,3-DPG).

The osmotic fragility of RBCs increases during storage, and some cells undergo lysis, resulting in increased plasma Hb levels. In addition, deformability of RBCs appears impaired in patients who receive allogenic blood cell transfusion, potentially resulting in micro-occlusive events.⁴¹ Frank and associates⁴² studied the blood of patients undergoing posterior spinal fusion surgery and found that increased duration of blood storage was associated with decreased RBC deformability, which was not "readily" reversible after transfusion. They speculated that these deformed cells may be defective in delivering oxygen (O_2) to

TABLE 49.4 Properties of Whole Blood and Packed Red Cell Concentrates Stored in CPDA-1

Variable	DAYS OF STORAGE		
	0	35 (Whole Blood)	35 (Packed Cells)
pH	7.55	6.73	6.71
Plasma hemoglobin (mg/dL)	0.50	46.00	246.00
Plasma potassium (mEq/L)	4.20	17.20	76.00
Plasma sodium (mEq/L)	169.00	153.00	122.00
Blood dextrose (mg/dL)	440.00	282.00	84.00
2,3-Diphosphoglycerate (μ M/mL)	13.20	1.00	1.00
Percent survival*	—	79.00	71.00

*Percent recovery of O_2 -tagged red blood cells at 24 h.
CPDA-1, Citrate phosphate dextrose adenine-1.

the cells and concluded that both the “age of blood storage” and “amount” of blood given should be considered when giving blood (Table 49.4).

CHANGES IN OXYGEN TRANSPORT

RBCs are transfused primarily to increase transport of O_2 to tissues. Theoretically, an increase in the circulating red cell mass will produce an increase in O_2 uptake in the lungs and a corresponding increase in O_2 delivery to tissues, but RBC function may be impaired during preservation, making it difficult for them to release O_2 to the tissues immediately after transfusion.

The O_2 dissociation curve is determined by plotting the partial pressure of O_2 (P_{O_2}) in blood against the percentage of Hb saturated with O_2 (Fig. 49.2). As Hb becomes more saturated, the affinity of Hb for O_2 also increases. This is reflected in the sigmoid shape of the curve, which indicates that a decrease in the arterial partial pressure of oxygen (P_{aO_2}) makes considerably more O_2 available to the tissues. Shifts in the O_2 dissociation curve are quantitated by the P_{50} , which is the partial pressure of O_2 at which Hb is half saturated with O_2 at $37^\circ C$ and pH 7.4. A low P_{50} indicates a left shift in the O_2 -dissociation curve and an increased affinity of Hb for O_2 . The leftward shift of the curve indicates that a lower than normal O_2 tension saturates Hb in the lung, but the subsequent release of O_2 to the tissues is more difficult, as it occurs at a lower than normal capillary O_2 tension compared with an unshifted curve. In other words, the increased affinity of Hb for O_2 makes it more difficult for Hb to release O_2 to hypoxic tissues. This leftward shift is likely a result of decreased levels of 2,3-DPG in stored RBCs, which can remain low for up to 3 days posttransfusion.⁴³

Many of the advances in blood processing and storage are centered on the material of the collections and storage containers.⁴⁴ Innovative methods of storing blood are being developed. For example, storing blood in an electrostatic field of 500 to 3000 V decreases hemolysis and attenuates the decrease in pH associated with prolonged storage.⁴⁵ Current blood collection and storage systems are made of disposable plastic; these materials must have properties compatible with collection, processing, storage,

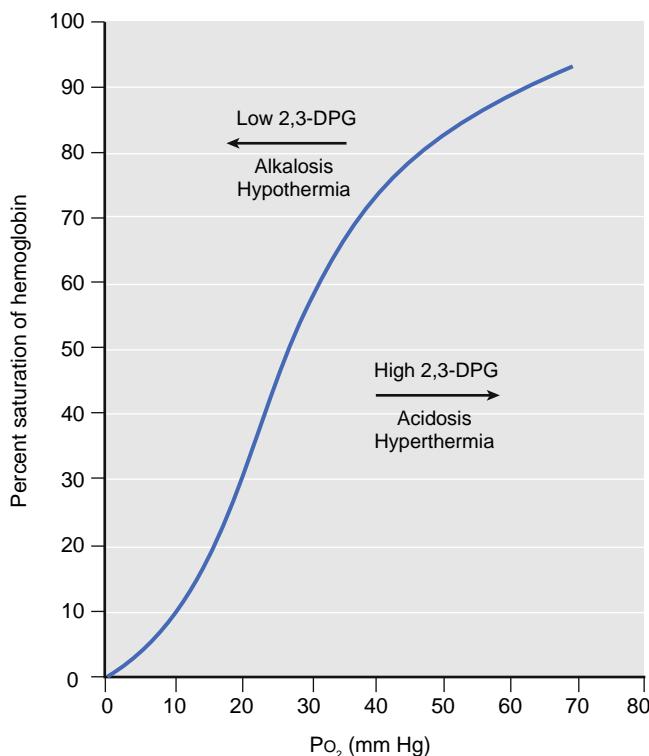


Fig. 49.2 Factors that shift the oxygen dissociation curve. **2,3-DPG, 2,3-Diphosphoglycerate.** (From Miller RD. The oxygen dissociation curve and multiple transfusions of ACD blood. In: Howland WS, Schweizer O, eds. *Management of Patients for Radical Cancer Surgery: Clinical Anesthesia Series*. Vol. 9. Philadelphia: FA Davis; 1972:43.)

and administration. Polyvinylchloride (PVC) with use of different plasticizers is commonly used because it is nontoxic, has flexibility, mechanical strength, water impermeability, resistance to temperature extremes for sterilization and freezing, compatibility with blood components, and selective permeability for cellular gas exchange.

Recent animal data suggest that red cells in stored blood can be rejuvenated with solutions of inosine prior to administration, reversing storage lesions and mitigating the potential for organ damage. This could be a promising technique to restore ATP and 2,3-DPG levels, while reducing a recipient's immune response and transfusion-associated organ injury.⁴⁶ However, small clinical trials in humans demonstrating clinical benefit are lacking.⁴⁷ Larger trials are ongoing.

CLINICAL IMPLICATIONS: DURATION OF BLOOD STORAGE

The fact that blood can be stored for 42 days is a mixed blessing. The obvious advantage is the increased availability of blood, but the clinical evidence regarding safety has not been consistent, reflecting the difficulty of conducting a systematic study of patients in varied clinical settings. For decades, many clinicians have tried to establish a firm relationship between the 2,3-DPG levels associated with stored blood and patient outcome. In 1993, Marik and Sibbald⁴⁸ found that the administration of blood that had been stored for more than 15 days decreased intramucosal pH, suggesting that splanchnic ischemia had occurred. In addition, an

increased incidence of postoperative pneumonia in cardiac patients has been associated with the use of older blood.⁴⁹ Yet prolonged storage of blood was not associated with increased morbidity after cardiac surgery.⁵⁰ Purdy and colleagues⁵¹ found that patients who received 17-day-old blood (range, 5-35 days) versus 25-day-old blood (range, 9-36 days) had higher survival rates. Koch and colleagues⁵² concluded that giving erythrocytes (PRBCs) older than 14 days was associated with an increased risk for postoperative complications, along with reduced short-term and long-term survival in patients undergoing coronary artery bypass surgery. This article also had an accompanying editorial that concluded, “to the extent possible, newer blood might be used in clinical situations that seem to call for it.”⁵³ In addition, a meta-analysis concluded that older stored blood is associated with an increased risk for death.⁵⁴

However, there is equal data arguing the contrary, and other researchers have not arrived at a clear conclusion and recommended more studies. Weiskopf and associates⁵⁵ performed studies in healthy volunteers who were evaluated by a standard computerized neuropsychologic test 2 days and 1 week after acute isovolumic anemia was induced. When correcting the anemia, they concluded that erythrocytes stored for 3 weeks are as efficacious as those stored for 3.5 hours. Spahn⁴ wrote an accompanying editorial agreeing with Weiskopf and associates⁵⁵ and, furthermore, postulated that 2,3-DPG levels may not be the key factor in determining the delivery of O₂ (i.e., 2,3-DPG levels are reduced in older blood, but the blood still delivers O₂). Cata and associates⁵⁶ also concluded that no change in outcome occurred in patients undergoing radical prostatectomy and receiving older blood. Saager and colleagues⁵⁷ also found no relationship between duration of blood storage and mortality in nearly 7000 patients undergoing noncardiac surgery.

Since the publication of the eighth edition of this text, several randomized control trials evaluating the influence of the duration of blood storage have been published. In 2016, Heddle and colleagues⁵⁸ published results from the INFOMR trial, a large, pragmatic, randomized controlled trial enrolling adult hospitalized patients in six centers from four countries. Patients were randomized to receive either blood that had been stored for the shortest duration (mean duration of storage 13 days) versus blood stored for the longest duration (mean duration of storage 23 days). Only patients with A and O blood types were included as the less common blood types could not achieve an appropriate difference in mean duration of storage. More than 20,000 patients were included in the primary analysis. No significant differences in mortality were noted between the two groups. In prespecified high-risk categories, including patients undergoing cardiovascular surgery, patients admitted to the intensive care unit (ICU), and those with cancer, the results remained the same.

Similarly, the results of the recent RECESS trial published in 2015⁵⁹ revealed similar mortality rates among those transfused with blood stored less than 10 days (median storage time 7 days) compared with those transfused with blood stored for more than 21 days (median storage time 28 days). Changes in preoperative to 7 days postoperative Multiple Organ Dysfunction Score (MODS) were similar between the two groups, as well. Finally, two randomized

controlled trials in critically ill adults evaluating the age of transfused blood on mortality and other outcomes, such as new bloodstream infections, duration of mechanical ventilation, and the use of renal replacement therapy, failed to demonstrate differences between groups transfused with fresher blood compared with those transfused with older blood.^{60,61}

These recent randomized controlled trials demonstrate the safety and noninferiority of “older” versus “younger” blood, but the complete answer may still need further data. First, the measures of outcome may be insufficiently sensitive to detect important and meaningful clinical outcomes. Many studies use mortality as their primary outcome measure. Although this is obviously a critical benchmark, it may not be sensitive enough to detect clinical differences regarding the safe or optimal length of time for the storage of blood. Important adverse clinical outcomes could occur without a change in mortality per se (e.g., duration of hospitalization, cardiovascular events, quality of life, neurocognitive decline). Second, these studies compare moderately young with moderately old blood. Ethical and logistical issues preclude a trial comparing “very” young and “very” old blood or even comparing moderately aged blood to very old blood (e.g., stored for 35-42 days).⁶²⁻⁶⁴ Because the quality of blood decreases with length of storage, increased morbidity with exposure to more aged red cells is physiologically plausible, but the debate regarding the effectiveness of a blood transfusion and its duration of storage continues. More prospective studies are likely required.

Blood Component Therapy: Indications for Transfusion

A major advance in the field of blood banking has been the development of blood component therapy. The basic philosophy is that patients are best treated by administration of the specific fraction of blood that they lack. This concept has presented problems to the surgical team, who often desire the physiologic effects of whole blood.

ALLOGENEIC (HOMOLOGOUS) BLOOD

PRBCs contain the same amount of Hb as whole blood, but much of the plasma has been removed. The Hct value of PRBCs is approximately 60% (Table 49.5). Other than severe hemorrhage, most indications for RBCs can be effectively treated with PRBCs, conserving the plasma and the components for other patients (see Fig. 49.1). Many blood banks have conscientiously followed this principle, and whole blood is not available or only available in trauma centers or by special arrangement.

The administration of PRBCs is facilitated by utilizing crystalloid or colloid as a carrier; however, not all crystalloids are suitable. Solutions containing Ca²⁺ may precipitate clotting. Lactated Ringer solution is not recommended for use as a diluent or carrier for PRBCs because of the Ca²⁺ (Table 49.6), although several experimental studies found lactated Ringer solution and normal saline to be equally acceptable.^{65,66} A more important factor may be whether the diluent is hypotonic with respect to plasma. In hypotonic solutions, the RBCs will swell and eventually lyse.

TABLE 49.5 Metabolic Characteristics of Packed Red Blood Cells

Value	Packed Red Blood Cells
Hematocrit (%)	57
pH	6.79
pCO ₂ (mm Hg)	79
Bicarbonate (mmol/L)	11
Plasma sodium (mmol/L)	126
Plasma potassium (mmol/L)	20.5
Glucose (mmol/L)	24
Lactic acid (mmol/L)	9.4

From Sumplemann R, Schürholz T, Thorns E, et al. Acid-base, electrolyte and metabolite concentration in packed red blood cells for major transfusion in infants. *Paediatr Anaesth*. 2001;11:169–173.

TABLE 49.6 Compatibility of Blood With Intravenous Solutions

Blood to Intravenous Solution (1:1 Ratio)	HEMOLYSIS AT 30 MIN	
	Room Temperature	37°C
5% Dextrose in water	1+	4+
Plasmanate*	1+	3+
5% Dextrose in 0.2% saline	0	3+
5% Dextrose in 0.45% saline	0	0
5% Dextrose in 0.9% saline	0	0
0.9% Saline	0	0
Normosol-R, pH 7.4 [†]	0	0
Lactated Ringer solution	0 (clotted)	0 (clotted)

*Cutter Laboratories, Berkeley, CA.

[†]Abbott Laboratories, Chicago, IL.

Solutions that cause hemolysis are listed in Table 49.6. Recommended solutions compatible with packed erythrocytes are 5% dextrose in 0.45% saline, 5% dextrose in 0.9% saline, 0.9% saline, and Normosol-R with a pH of 7.4.

RBC transfusions are given to increase O₂-carrying capacity. Increasing intravascular volume in the absence of significant anemia is not an indication for blood transfusion because volume can be augmented with administration of intravascular fluids that are not derived from human blood (e.g., crystalloids). As such, a sole Hb value should not be the only basis for a transfusion decision. It should be the overall status of the patient that prompts transfusion therapy (e.g., hemodynamics, organ perfusion and oxygen delivery, and anticipated surgical needs).⁶⁷ Even so, the Hb value has become the basis for many transfusion strategies. It is the prime criterion for defining restrictive versus liberal transfusion strategies.

When a patient is hemorrhaging, the goals should be to restore and maintain intravascular volume, cardiac output, and organ perfusion to normal levels. By using crystalloids, colloids, or both to treat hypovolemia, normovolemic dilutional anemia may be created. Increasing

cardiac output enhances O₂ delivery to the tissues only to a limited extent. In fact, during normovolemic anemia, Mathru and colleagues⁶⁸ found inadequate splanchnic and preportal O₂ delivery and consumption when the Hb level decreased to 5.9 g/dL. Although the current PBM emphasis is on fewer or even avoidance of blood transfusions, clearly an Hb value exists below which a blood transfusion should be given.

The basis for using the Hb or Hct value as the initial consideration for defining transfusion requirements followed a 1988 National Institutes of Health (NIH) Consensus Conference that concluded that otherwise healthy patients with Hb value more than 10 g/dL rarely require perioperative blood transfusions, whereas patients with acute anemia with a Hb value of less than 7 g/dL frequently require blood transfusions.⁶⁹ They also recognized that patients with chronic anemia (as in renal failure) might tolerate an Hb concentration of less than 6 to 7 g/dL. Amazingly, despite many studies, publications, and debates, the fundamental guidelines have not changed substantially in the 30 plus years since this conference.

An excellent editorial by LeManach and Syed⁷⁰ outlines key questions that should be considered regarding transfusion triggers, including what we need to learn and the role of databases. Of prime importance is identifying the variables that predict the need for erythrocyte transfusion and the approach that can most accurately estimate the impact of transfusions. Many studies use death rate as their main indicator. Although clearly an important indicator, there are additional obvious factors in between the extremes of life and death, including vital signs, key laboratory values, and other indicators used in critical care units. Several groups working with patients in ICUs have attempted to define the point at which blood transfusions should be given by measures of tissue oxygenation and hemodynamics (e.g., increase in O₂ consumption in response to added O₂ content).^{71–73} The O₂ extraction ratio has been recommended as an indicator for transfusions;⁷⁴ however, this technique requires invasive monitoring, and the results were not dramatic between groups who were or were not transfused. No specific measure can consistently predict when a patient will benefit from a blood transfusion. The ultimate determination of the Hb or Hct value at which blood should be given is a clinical judgment based on many factors, such as cardiovascular status, age, anticipated additional blood loss, arterial oxygenation, mixed venous O₂ tension, cardiac output, and intravascular blood volume (Table 49.7).

ADDITIONAL BLOOD TRANSFUSIONS

To determine whether subsequent units of blood are indicated after the initial administration, the overall condition of the patient and the clinical situation need to be reassessed. The following key components of information to consider include:

1. Measurement and trend of vital signs
2. Measurement of blood loss and assessment of anticipated blood loss
3. Quantitation of intravenous fluids given
4. Determination of Hb concentration
5. Surgical concerns.

TABLE 49.7 American College of Surgeons Classes of Acute Hemorrhage

Factors	Class I	Class II	Class III	Class IV
Blood loss (mL)	750	750-1500	1500-2000	2000 or more
Blood loss (% blood volume)	15	15-30	30-40	40 or more
Pulse (beats/min)	100	100	120	140 or higher
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respirations per minute	14-20	20-30	30-40	35
Urine output (mL/h)	30	20-30	5-10	Negligible
Central nervous system: mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (3-1 rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

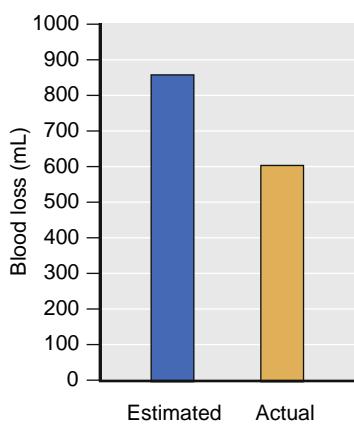


Fig. 49.3 Discrepancy between estimated and actual blood loss. (From Stovener J. Anesthesiologists vastly overstate bleeding. *Anesthesiology News*, May 14, 2012.)

Measurement of Blood Loss

Measuring blood loss is obviously important when assessing the need for both the initial and subsequent blood transfusions (see Table 49.7). A standard approach includes a combination of visualization and gravimetric measurements based on weight differences between dry and blood-soaked gauze pads. A study in patients undergoing spine surgery found that anesthesiologists tended to overestimate blood loss by as much as 40% (Fig. 49.3). On the other hand, optical scanners tended to underestimate blood loss compared with the standard gravimetric calculations.⁷⁵ The accuracy of measurements is not uniformly consistent and no “gold standard” for blood loss quantification exists.

Predicting surgical blood loss is also an important component to intraoperative transfusion medicine. As part of the WHO preoperative guidelines to improve the safety of patients undergoing surgery, the anesthesiologist must consider the possibility of a large-volume blood loss prior to the induction of anesthesia.⁷⁶ In a prospective trial evaluating both surgeons’ and anesthesiologists’ ability to predict the estimated blood loss prior to incision, members of both these medical professions underestimated the blood loss by greater than 500 mL in 10% of intermediate or major surgeries, which potentially placed those patients at risk for being without adequate intravenous access or appropriate resuscitative volume.⁷⁷

Determination of Hemoglobin Concentration

While transfusion decisions depend on many clinical factors, the blood Hb value is an important measurement that is fraught with confounding variables. With regard to measurement of blood loss, clinical investigators at Duke University emphasized that “interpretation of intermittent measurements of Hb levels is often complicated by fluid shifts, intravenous volume infusions, and actual transfusions,”⁷⁸ yet these values are critical to transfusion decisions.

Continuous blood Hb monitoring has become available on a noninvasive basis using spectrophotometric finger technology (Masimo SpHb, Masimo, Irvine, CA). Numerous studies have been performed in a variety of clinical situations with emphasis on assessment of blood loss and/or the need for transfusions. Although measurements are relatively accurate (i.e., SpHb correlate within 1.0-1.5 g/dL with laboratory Hb measurements), the appearance of inaccurate values is not uncommon.^{79,80} SpHb appears to perform worse in patients with moderately to severely low Hb levels or in patients being actively resuscitated.^{81,82}

Accuracy also depends on finger blood flow and temperature. The monitor displays a value for perfusion index (PI), which can be helpful in assessing the accuracy of the SpHb value. The accuracy of SpHb can be improved with a PI greater than 4% to 5%. A bupivacaine digital nerve block decreases the number of inaccurate values and increases the number of accurate values for several hours.^{83,84} Although not specifically studied, warming the finger should also increase the PI and, therefore, the accuracy of SpHb.

SpHb monitoring can still be valuable even though its accuracy is not consistent. Observation of the trend is often recommended to help clinicians detect a changing Hb level when it is suspected to be stable. For example, Giraud and colleagues⁸⁵ concluded that SpHb is less invasive and less accurate than other measurements but provides valuable data on a continuous basis. They then concluded that none of the results would have led to transfusion errors as identified by the American Society of Anesthesiologists (ASA) Task Force on Perioperative Blood Transfusion and Adjuvant Therapies’ practice guidelines. If the SpHb value suddenly changes 1 or 2 g/dL, the reasons for this change should be explored, even if the absolute value is satisfactory. For example, if the SpHb reading is 11 g/dL, but rapidly decreases to 9.5 g/dL, the clinical situation needs to be reassessed. Although an attractive concept and possibly

accurate, more definitive studies are necessary.⁸⁶ SpHb could become very valuable with transfusion decision making in the future.⁸⁷

Invasive point-of-care testing, such as HemoCue (HCue; Hemocue America, Brea, CA), provides a quick and efficient method to accurately determine Hb value. This point-of-care test allows for the determination of Hb levels at the bedside in less than 5 minutes. If the person performing the test is properly trained, HCue measurements are extremely accurate.^{80,85} Several other point-of-care Hb tests exist, including RapidLab (Siemens, Malvern, PA) and I-Stat (Abbot Inc, Princeton, NJ). Comparative testing of these three modalities demonstrates favorable intertest reliability.⁸⁸

Preoperative Anemia

Preoperative anemia (i.e., low Hb value in women <12 g/dL; in men <13 g/dL) is a common comorbidity among patients undergoing major surgery with an incidence up to 40% and is an independent risk factor for increased perioperative mortality,⁸⁹ and postoperative acute kidney injury (AKI).⁹⁰ In patients with a moderate to high risk of significant blood loss (defined as >500 mL), the Hb value ideally should be obtained 3 to 8 weeks prior to surgery.⁹¹ This provides sufficient time for the patient to undergo iron therapy or to correct nutritional deficiencies. Erythropoiesis-stimulating agents, especially intravenously administrated iron therapy, may be beneficial for treatment of preoperative anemia. The concept of treating anemia preoperatively as a means to decrease the need for intraoperative transfusions is widely accepted. For example, intravascular iron therapy in patients undergoing abdominal surgery significantly increased preoperative Hb levels, reduced the need for transfusion, and shortened hospital length of stay.⁹² PREVENTT, a large phase III randomized controlled trial investigating preoperative intravenous iron therapy, is ongoing to further characterize this intervention. Oral therapy, if given with sufficient time preoperatively and tolerated by the patient, may be just as effective at correcting the anemia as intravenous therapy.⁹³

Erythropoiesis-stimulating agents (ESAs), such as darbepoetin alfa, act by stimulating red cell progenitor cells in the bone marrow and inducing erythropoiesis. They are frequently prescribed for patients with anemia who have end-stage renal disease or who are undergoing chemotherapy treatment to increase their Hb levels and reduce the incidence of transfusion. The evidence has been mixed on the utility and safety of ESAs as a means to increase Hb levels and decrease transfusions in various perioperative patient populations. This may be a result of the heterogeneity of study protocols. A more recent randomized controlled trial in patients undergoing cardiac surgery found a decreased incidence of transfusion in patients with preoperative anemia who were treated with a single dose of erythropoietin administered 2 days prior to surgery.⁹⁴ Although no difference in adverse events was noted, the study was underpowered, leaving the question of safety due to the association of ESAs with hypertension and thrombotic events unanswered.⁹⁵

If limited preoperative time is available, Karkouti and associates⁹⁶ suggested that prophylactic erythrocyte transfusion should be used to reduce perioperative anemia. This suggestion met with controversy, and many editorials and

letters to the editor were written supporting⁹⁷ and condemning⁹⁸ such an approach. Recent retrospective data suggest that preoperative transfusion, even in severely anemic patients, offers no benefit and may be an independent predictor of complications in some patients.⁹⁹

Liberal Versus Restrictive Transfusion Strategy

The terminology of liberal versus restrictive has become completely indoctrinated into the transfusion therapy vocabulary. Several medical and surgical organizations have provided documents regarding their own definition of liberal and restrictive approaches. Some of these organizations include the American Association of Blood Banks,¹⁰⁰ International Conference on Transfusion Outcomes Group,⁶ and Surgical Hip Fracture Repair (FOCUS).¹⁰¹ In fact, many of these studies were supported by the NIH, which is an indication of how important this topic is for patient care.

Liberal versus restrictive transfusion strategy is based on the Hb value when a transfusion decision is made. A restrictive policy is the administration of blood transfusion when the Hb value is 7 to 8 g/dL or less. In contrast, a liberal policy is the administration of blood transfusion when the Hb value is 9 to 10 g/dL or greater. Many studies have been performed in multiple clinical situations, with varying patient conditions and acuity. The most recent randomized controlled studies continue to show no benefit to a liberal strategy compared with a restrictive strategy. One conclusion is that if no clinical advantages are associated with the liberal transfusion policy, perhaps the restrictive approach should be used. Certainly, fewer transfusion reactions would be expected with the restrictive approach.¹⁰¹

How liberal should the transfusion trigger be in critically ill patients? Some critical care physicians have suggested that administration of blood transfusions is related to the incidence of ventilator-assisted pneumonia¹⁰² and nosocomial infections.¹⁰³ Although this possibility cannot be excluded, these are complicated outcomes with many confounding variables. Despite the difficulty with identifying a specific transfusion trigger, Ely and Bernard¹⁰⁴ have generally confirmed the conclusions discussed earlier: better outcomes have not consistently occurred with liberal transfusion triggers (i.e., 9.0 to 10.0 g/dL).^{105,106} Subsequent editorials have leaned toward a lower transfusion trigger even for critically ill patients.^{107,108}

Recent data from prospective, randomized controlled trials in high-risk cardiac surgery patients and critically ill patients with septic shock continue to show the noninferiority of restrictive transfusion thresholds.^{109,110} In addition, a meta-analysis of randomized trials of liberal versus restrictive transfusion approaches concluded, "restrictive strategies may decrease the incidence of healthcare-associated infections."¹¹¹

Perhaps a one-value, one-size-fits-all approach to a liberal versus restrictive transfusion strategy is too simplistic of an approach for transfusion decision making. In an editorial, Beattie and Wijeysundera⁶⁷ advocated for a more context-specific approach to appropriate transfusion triggers. That is, the transfusion trigger for an otherwise healthy young adult patient should be different than that for an elderly patient with significant cardiovascular comorbidities. The American College of Surgeons attempted to categorize patient characteristics and blood loss as a basis for transfusion decisions (see Table 49.7). Small aggregate

data support this theory of customized transfusion thresholds, but the results have yet to be proven in a prospective, randomized trial.¹¹² Hb values are important, but the overall condition of the patient may be of prime importance.

In addition to a dichotomized one-size-fits-all approach, the liberal versus restrictive strategy associated with PBM has some additional limitations. This strategy primarily addresses the indications for administering an initial unit of blood.¹¹³ Most of this strategy is directed toward anemia in stable patients who are not actively bleeding. It does not describe what the indications for administration of subsequent units of blood should be. The need for repetitive transfusions in a bleeding patient is not addressed in the liberal versus restrictive discussion. Yet it is a very important topic for anesthesia providers. Patients with active bleeding, especially those with cardiovascular disease, should probably be subjected to a more liberal transfusion strategy.¹¹⁴

General Conclusions

The emphasis on Hb levels for transfusion decisions needs some caution. There can be variability from one patient to another regarding the need for increased O₂-carrying capacity via blood transfusions. Also, an individual patient's Hb level may vary markedly in the perioperative period independent of and in addition to transfusions of RBCs. During acute bleeding, Hb values are only slightly decreased initially because the intravascular volume has not been repleted and the Hb level has not been diluted.¹¹⁴ The development of more sensitive indicators of tissue oxygenation (e.g., intramucosal pH) may provide indicators for transfusion in the future. As concluded by Weiskopf,¹¹⁵ "we merely await advances in technology that will enable us to measure directly the value of concern and thereby free us from arguments over which surrogate (e.g., hemoglobin) to measure and what value indicates the need for augmented oxygen delivery." Although Weiskopf wrote this opinion in 1998, surrogate indicators are still used for transfusion decisions today.

In the presence of incomplete data, the ASA's 2015 updated practice guidelines offer these recommendations:¹¹⁶

1. Transfusion is rarely indicated when the Hb concentration is more than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute.
2. A restrictive transfusion strategy (Hb <8 g/dL) should be employed to reduce the patient's transfusion requirements and decrease the potential harmful effects of transfusions.
3. Multimodal protocols and algorithms should be employed to reduce intraoperative blood loss and transfusion requirements. These pathways include point-of-care testing to direct care.
4. The use of a single Hb trigger for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation is not recommended.
5. When appropriate, intraoperative and postoperative blood recovery, acute normovolemic hemodilution (ANH), and measures to decrease blood loss (i.e., deliberate hypotension and pharmacologic drugs) may be beneficial.

PLATELET CONCENTRATES

Platelet concentrates are obtained either as pooled concentrates from 4 to 6 whole-blood donations or as apheresis concentrates obtained from one donor.¹¹⁷ If platelets are stored at room temperature, they can be used up to 7 days after collection with constant and gentle agitation. Bacterial contamination, mainly from platelet concentrates, is the third leading cause of transfusion-related deaths (Table 49.8), although the incident rate has steadily declined over the last 15 years.¹¹⁸ In a report of 10 contaminated platelet transfusions between 1982 and 1985, half were platelets stored for 5 days or more. A prospective analysis from 1987 to 1990 resulted in seven cases of sepsis in patients receiving platelets for thrombocytopenia secondary to bone marrow failure.¹¹⁹ Because the use of multidonor platelet products stored for 5 days results in an incidence of sepsis five times higher than use of those stored for 4 days, shorter storage times are being emphasized. In studies that actively survey transfused platelets,¹²⁰ a rate of bacterial contamination has been identified of approximately 1 per 2500 units (Table 49.9). Twenty-five percent of the patients exposed to contaminated platelet products developed a septic transfusion reaction, although these cases were only identified by active surveillance. Prior to this study, septic transfusion reactions associated with platelet transfusions were reported at a rate of 1 per 100,000 transfused platelets,¹²¹ suggesting this is likely an underreported event.¹²¹

TABLE 49.8 Transfusion-Related Fatalities in the United States, 2012 Through 2016

Complication	FY 2012-2015 (Number)	FY 2012-2015 (Percent)	FY 2016 (Number)	FY 2016 (Percent)
Anaphylaxis	6	4	5	12
Contamination	14	10	5	12
HTR (ABO)	10	7	4	9
HTR (non-ABO)	18	13	1	2
Hypotensive Reaction	2	1	1	2
TACO	37	26	19	44
TRALI	56	39	8	19

TACO, Transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

From Fatalities reported to FDA following blood collection and transfusion: annual summary for fiscal year 2016. These reports are available online at <https://www.fda.gov/media/111226/download>

TABLE 49.9 History of Platelet Concentrates Shelf Life in Relationship to Key Events

Year	Shelf Life	Practical Shelf Life*
1984-1986	7 days	6-7 days [†]
1986-1999	5 days	3 days [‡]
1999-2004	5 days	3 days [§]
2004-present	5 days	2.5-3 days

*Days that platelet concentrates are actually available to clinicians.

[†]Reports of bacterial contamination.

[‡]Nucleic acid technology testing, centralized blood donor testing.

[§]Bacterial detection implemented.

At present, platelet concentrates are routinely tested for bacteria and are the only blood product stored at room temperature.¹²² For any patient who develops a fever within 6 hours after receiving platelets, sepsis from platelets should be considered.

Indications for the use of platelets are somewhat difficult to define. The most recent guidelines published in 2015 by the ASA Task Force on Perioperative Blood Management¹¹⁶ provide the following recommendations regarding management for platelet transfusions:

1. Monitor platelet count, except in situations of massive transfusion.
2. Monitor platelet function, if available.
3. Consider use of desmopressin in patients with excessive bleeding or suspected platelet dysfunction.
4. Platelet transfusion may be indicated despite an adequate platelet count if there is known or suspected platelet dysfunction (e.g., cardiopulmonary bypass, bleeding, recent use of antiplatelet therapy, congenital platelet dysfunction).
5. Prophylactic platelet transfusion is rarely indicated in surgical or obstetric patients when the platelet count is greater than $100 \times 10^9/\text{L}$ and is usually indicated when the platelet count is less than $50 \times 10^9/\text{L}$. The determination of whether patients with intermediate platelet counts ($50-100 \times 10^9/\text{L}$) require therapy should be based on the patient's risk for bleeding.

Many institutions have strict thresholds targeted to the patient's condition that outline the minimum platelet count needed for the categories of (1) prophylaxis, (2) periprocedural (based on type of procedure), and (3) active bleeding. In the first category, a required platelet count may be $10 \times 10^9/\text{L}$ in patients receiving chemotherapy.¹²³ In the second category, patients undergoing bone marrow biopsy or lumbar puncture should have platelet counts between 20 and $30 \times 10^9/\text{L}$. For neurosurgery, a platelet count of $100 \times 10^9/\text{L}$ may be targeted. Such thresholds are often guided by professional societies. The American Society of Regional Anesthesia and Pain Medicine guidelines also include recommendations in the setting of therapy that may alter platelet function.¹²⁴ A clinician's institution will likely have precise platelet recommendations for most procedures.

Patients with severe thrombocytopenia ($<20 \times 10^9/\text{L}$) and clinical signs of bleeding usually require platelet transfusion. However, patients may have very low platelet counts (much lower than $20 \times 10^9/\text{L}$) and not have clinical bleeding. These patients probably do not need platelet transfusions (Table 49.10). The recent PATCH trial evaluated patients receiving antiplatelet therapy who presented with intracerebral hemorrhage (ICH).¹²⁵ Such patients often receive platelet transfusions due to concern about the irreversible inhibition of platelet function and the high risk of morbidity and mortality associated with ICH. Study participants were excluded if their Glasgow Coma Scale score was less than 8 or if their treatment plan included expected surgical intervention within the first 24 hours of presentation. Platelet transfusion increased the risk of death or dependence at 3 months and the risk of a serious adverse event during the hospital stay compared with standard medical therapy without transfusion. Although this study excluded patients who were deemed surgical candidates

TABLE 49.10 Correlation Between Platelet Count and Incidence of Bleeding

Platelet Count (cells/mm ³)	Total No. Patients	No. Patients With Bleeding
>100,000	21	0
75,000-100,000	14	3
50,000-75,000	11	7
<50,000	5	5

Data from Miller RD, Robbins TO, Tong MJ, et al. Coagulation defects associated with massive blood transfusions. *Ann Surg*. 1971;174:794.

at presentation, even in this high-risk patient population, platelet transfusions are not indicated unless there is active bleeding.

When possible, ABO-compatible platelets should be used. The need to use them, however, is not well documented, and specific testing is difficult. Aggregation cannot be used for matching, because platelets cause clumping. The platelet membrane has immunoglobulins, and any additional deposit of recipient antibodies is difficult to detect. Despite the fact that platelets can be destroyed by antibodies directed against class I human leukocyte antigen (HLA) proteins on their membranes and by antibodies against ABO antigens, platelets will continue to be chosen without regard to antigen systems for the majority of patients.¹²⁶ ABO-incompatible platelets produce very adequate hemostasis.

The effectiveness of platelet transfusions is difficult to monitor. Under ideal circumstances, one platelet concentrate usually produces an increase of approximately 7 to $10 \times 10^9/\text{L}$ at 1 hour after transfusion in the 70-kg adult. Ten units of platelet concentrates are required to increase the platelet count by $100 \times 10^9/\text{L}$. However, many factors, including splenomegaly, previous sensitization, fever, sepsis, and active bleeding, may lead to decreased survival and decreased recovery of transfused platelets.

Other various different types of platelet concentrates have been proposed, including leukocyte-depleted platelets and ultraviolet-irradiated platelets. The use of these products is reviewed by Kruskall.¹²⁷

FRESH FROZEN PLASMA

FFP is the most frequently used plasma product. It is processed shortly after donation, generally frozen within 8 hours or 24 hours (PF24). It contains all the plasma proteins, particularly factors V and VIII, which gradually decline during the storage of blood. PF24 is comparable to FFP, except for a slight reduction in factor V and approximately 25% decrease in factor VIII.^{128,129} Thawed plasma is stored at 1 °C to 6 °C for up to 5 days. The use of FFP carries with it the same inherent risks that are observed with the use of any blood product, such as sensitization to foreign proteins.

Although FFP is a reliable solution for intravascular volume replacement in cases of acute blood loss, alternative therapies are equally satisfactory and considerably safer. The risks of FFP administration include TRALI, TACO, and allergic or anaphylactic reactions.

In 2015 the ASA Task Force recommended the following guidelines regarding the administration of FFP:

1. Prior to the administration of FFP, coagulation studies should be obtained when feasible.
2. For the correction of coagulopathy when the international normalized ratio (INR) is greater than 2, in the absence of heparin.
3. For the correction of coagulopathy due to coagulation deficiencies in patients transfused with more than one blood volume (approximately 70 mL/kg) when coagulation studies cannot be easily or quickly obtained.
4. Replacement of known coagulation factor deficiencies with associated bleeding, disseminated intravascular coagulation (DIC), or both, when specific components are not available.
5. Reversal of warfarin anticoagulation when severe bleeding is present and prothrombin complex concentrations are not available.

FFP or plasma is often given to critical care patients before insertion of an intravascular catheter. Hall and associates¹³⁰ studied 1923 patients admitted to 29 ICUs in the United Kingdom who underwent intravascular catheterization. They compared patients who did and did not receive FFP. Chronic liver disease and more abnormal coagulation tests increased the frequency of patients receiving FFP, but the severity of the prothrombin time (PT) alone was not a factor. Whether prophylactic FFP should be given in this situation is not well defined. In 2015, Muller and associates¹³¹ published results from a randomized, open-label trial of prophylactic FFP use prior to an invasive procedure in critically ill patients with an INR of 1.5 to 3. The trial ended before reaching target enrollment, because of slow recruitment. The occurrence of bleeding did not differ between the two groups, but the trial may not have had enough power to distinguish a statistical significance between groups. Also, an INR reduction below 1.5 only occurred in 54% of patients in the intervention group.

In an effort to “expedite” the availability of plasma for patients who require massive transfusions, some trauma centers keep thawed plasma readily available. In one study, patients with severe trauma who had already received 1 unit of RBCs and plasma were then divided into two groups, one of which immediately received 4 units of thawed plasma. The patients who received the plasma had a reduction in overall blood product use and 30-day mortality.¹³² More recently, Sperry and colleagues¹³³ randomized prehospital injured patients in flight transport who were at risk for hemorrhage to standard of care versus empiric administration of 2 units FFP. By 3 hours, Kaplan-Meier curves revealed early separation of the two groups, favoring empiric administration of FFP in the prehospital setting that persisted until their prespecified end point of 30 days following randomization.

CRYOPRECIPITATE

Cryoprecipitate is prepared when FFP is thawed, and the precipitate is reconstituted. The product contains factor VIII:C (i.e., procoagulant activity), factor VIII:vWF (i.e., von Willebrand factor), fibrinogen, factor XIII, and fibronectin, which is a glycoprotein that may play a role in reticuloendothelial clearance of foreign particles and bacteria from

the blood. All other plasma proteins are present in only trace amounts in cryoprecipitate.

Cryoprecipitate is frequently administered as ABO compatible; however, this probably is not very important because the concentration of antibodies in cryoprecipitate is extremely low. Cryoprecipitate may contain RBC fragments, and cryoprecipitate prepared from Rh-positive donors can possibly sensitize Rh-negative recipients to the Rh antigen. Cryoprecipitate should be administered through a filter and as rapidly as possible. The rate of administration should be at least 200 mL/h, and the infusion should be completed within 6 hours of thawing.

According to the 2015 ASA Task Force on Perioperative Blood Management,¹¹⁶ transfusion of cryoprecipitate is rarely indicated when the fibrinogen levels are greater than 150 mg/dL in nonobstetric patients. The following indications were provided regarding the administration of cryoprecipitate:

1. When testing of fibrinogen activity reveals evidence for fibrinolysis
2. When fibrinogen concentrations are less than 80 to 100 mg/dL in patients experiencing excessive bleeding
3. Obstetrical patients who are experiencing excessive bleeding despite a measured fibrinogen concentration greater than 150 mg/dL
4. In patients undergoing massive transfusion when the timely assessment of fibrinogen concentrations cannot be determined
5. In patients with congenital fibrinogen deficiencies and when possible, in consultation with the patient's hematologist
6. In bleeding patients with von Willebrand disease types 1 and 2A who fail to respond to desmopressin or vWF/FVIII concentrates (or if not available)
7. In bleeding patients with von Willebrand disease types 2B, 2M, 2N, and 3 who fail to respond to vWF/FVIII concentrates (or if concentrates are not available)

Fibrin glue may be used by surgeons to create local hemostasis. It is prepared in a manner similar to that of cryoprecipitate. With added thrombin, it is applied locally to the surgical site. The efficacy of this product has been difficult to demonstrate in clinical trials.

MASSIVE TRANSFUSION AND TRANSFUSION RATIOS

The transition from administration of whole blood to component therapy in the 1970s created new challenges in transfusion medicine, especially in patients undergoing trauma or any type of surgery associated with significant blood loss. FFP was not usually required as a separate component with the administration of whole blood, and significant thrombocytopenia usually occurred only after 15 to 20 units of blood.⁵ With the change from whole blood to PRBCs, the incidence of coagulopathies increased, especially in units responsible for trauma patients. Rather than basing transfusion decisions on clinical judgment or laboratory tests, the concept of developing ratios of FFP and/or platelet concentrates with PRBCs evolved. For example, a 1:1:1 ratio would be transfusion of 1 unit of plasma, and one-sixth unit of platelets to 1 unit of RBCs. A 1:1:2 ratio

would be transfusion of 1 unit of plasma, and one-sixth unit of platelets to every 2 units of RBCs. The convention of one-sixth unit of platelets results from the common allocation of platelet products in 1 unit (apheresis) from a single donor or 1 pool (pooled) from six donors in a “six pack.” In review of the literature, ratios may be expressed as plasma/platelets/RBCs or RBCs/plasma/platelets.

Holcomb and associates¹³⁴ concluded that increased platelet ratios were associated with improved survival after massive blood transfusions. Subsequently, Kornblith and associates¹³⁵ concluded that the laboratory clotting profile of 1:1:1 plasma/platelets/RBC was significantly more hemostatic when examining activity of factors II, V, VII, VIII, IX, and X; antithrombin III, as well as protein C and higher fibrinogen levels when compared with a 1:1:2 ratio. Results of the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study supported this idea. With data from 10 U.S. level-I trauma centers, the conclusion of the study¹³⁶ was that higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients who received transfusions of at least 3 units of blood products during the first 24 hours after admission.¹³⁶ Among survivors at 24 hours, the subsequent risk for death by day 30 was not associated with plasma or platelet ratios. When comparing groups of patients with similar Injury Severity Scores, only a survival benefit was seen in ratios with high plasma to RBC resuscitation. However, no additional morbidity benefit of 1:1 over 1:2 ratios was identified.¹³⁷

More recently in the randomized control trial Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) study, Holcomb and associates¹³⁸ found that among patients with severe trauma and major bleeding, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio versus a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days.

These aggressive uses of FFP, platelets, and other blood products have only been shown to be beneficial in response to coagulopathies from massive blood transfusions. Aggressive plasma administration to other transfused patients was associated with an increased rate of serious complications, including acute respiratory distress syndrome (ARDS) and organ dysfunction.¹²⁶ A retrospective study showed that a higher FFP-PRBC ratio was associated with the need for advanced interventional procedures in patients with post-partum hemorrhage.¹³⁹

Synthetic Oxygen-Carrying Substances

HB-BASED OXYGEN CARRIERS

Various other substances that carry or facilitate the transport of O₂ have been made. Oxygen therapeutics are labeled as Hb-based O₂ carriers (HBOCs). HBOCs have advantages over human blood of not requiring type and crossmatch and not transmitting infectious viruses, typical characteristics of most synthetic blood products (Table 49.11).

Two approaches have dominated attempts to develop synthetic blood. The first approach uses linear binding kinetics, unlike the nonlinear binding of Hb. The most notable is the

TABLE 49.11 Comparison of General Synthetic Blood With Allogeneic Blood

Parameter	Synthetic	Allogeneic
Oxygen delivery	Rapid and consistent	Dependent on 2,3-DPG
Risk for disease transmission	None	See Table 49.2
Storage	Room temperature	Refrigeration
	Stable efficacy	Loss of efficacy
Shelf life	1-3 year	42 days
Preparation	Ready to use	Crossmatch
Compatibility	Universal	Type specific
Duration of action	1-3 days	60-90 days

2,3-DPG, 2,3-Diphosphoglycerate.

perfluorochemical emulsion called Fluosol-DA. Fluosol-DA was initially approved by the FDA for perfusion of ischemic tissues in the setting of percutaneous coronary intervention.¹⁴⁰ However, it had little use because it carried O₂ only when the Pao₂ was more than 300 mm Hg.¹⁴¹ Fluosol was withdrawn from the market in 1994. Another perfluoro compound, perfluorooctyl bromide, carries three to four times more O₂, has a longer half-life, and presumably fewer problems than are associated with Fluosol-DA, but it is not available on the market.¹⁴²

Most HBOCs modify the Hb molecule from humans, animals, or recombinant technology. Original efforts required Hb to be stroma free to prevent nephrotoxicity. The stroma-free Hb needed to be modified to have a favorable O₂ affinity (i.e., decreased O₂ affinity/right shift in the O₂ dissociation curve) and to extend its relatively short intravascular half-life. A variety of approaches have been used, including crosslinking, pyridoxylation and polymerization, and conjugation and encapsulation to accomplish this. Stroma-free Hb causes severe arteriolar vasoconstriction of microvascular structures from NO scavenging, which is not beneficial for organ perfusion. A human recombinant hemoglobin (rHb 1.1) was made in *Escherichia coli* and functions as normal Hb in terms of O₂-carrying capacity, but it, too, was plagued by microvascular vasoconstriction. Although a subsequent iteration, rHbg 2.0, minimized NO scavenging and caused little arteriolar vasoconstriction when compared with rHb 1.1 and diaspirin crosslinked Hb,^{143,144} vasoconstriction may still prove to be their ultimate downfall.

Most clinical trials have shown increased use of allogeneic blood transfusions;¹⁴⁵ however, the outcome of the HBOCs have been similar: failure in clinical trials due to increased adverse events. Natanson and colleagues¹⁴⁶ performed a cumulative meta-analysis on 16 trials involving 5 different products and 3711 patients. They concluded that there was a significant increased risk for myocardial infarction and death when HBOCs were given, an outcome that was found among all the technologies (e.g., cross-linked, polymerized, or conjugated). An accompanying editorial concluded that a 30% increased risk for death and a three-fold increase in the risk for myocardial infarction should preclude any additional studies.¹⁴⁷

Several HBOCs are available clinically under the FDA's Expanded Access (compassionate use) program. HBOC-201 hemoglobin glutamer-250 (bovine), Hemopure (Biopure Corporation) is developed from ultrapurified bovine RBCs that have been glutaraldehyde polymerized. It has a higher P_{50} (i.e., 43 instead of 26 mm Hg), which means that it may deliver O_2 to the tissues at least as well, if not better, than human RBCs.¹⁴⁸ A recent case series reported three cases of HBOC-201, under the FDA's Expanded Access to patients in severe sickle cell crisis (SCC) with multiorgan failure, who refused RBCs (Jehovah's Witnesses) or for whom compatible RBCs were not available.¹⁴⁹ A recent case report described use of bovine pegylated carboxyhemoglobin (Sanguinate) in a Jehovah's Witness with a lymphoproliferative disorder, gastrointestinal bleeding, and resultant severe anemia who was bridged to hemostatic interventions.¹⁵⁰ For now, HBOCs are likely to be reserved for situations in which RBC transfusion is not an option or as a bridge to stabilizing therapy.

Autologous Blood

Autologous blood transfusion constitutes three distinct procedures (1) preoperative autologous donation (PAD), (2) acute normovolemic hemodilution (ANH), and (3) intraoperative and postoperative blood salvage. Although the advantages and disadvantages vary with each technique, autologous transfusion aims to decrease the incidence and severity of complications associated with allogenic transfusions and conserve the supply of banked blood. Autologous blood may also be an acceptable solution in patients with rare blood phenotypes or alloantibodies.¹⁵¹

PREOPERATIVE AUTOLOGOUS DONATION

It is assumed that preoperative autologous blood transfusion is safer than allogeneic blood, mainly because of the decreased risk for transfusion-transmissible infections, such as HIV and hepatitis C. However, as blood safety has improved with a marked decrease in infectivity from allogeneic blood, the difference in safety compared with autologous blood is much less. Not surprisingly, the proportion of autologous blood collected has significantly decreased since the peak in the mid-1990s.¹⁵²

To be eligible, the AABB requires that most donor's Hb be no less than 11 g/dL prior to donation. Repeated donations should be separated by a week with 72 hours between the last donation and the time of surgery. The latter recommendation is to ensure restoration of intravascular volume and appropriate testing and preparation of the donated blood.¹⁵³ At 72 hours postdonation, while intravascular volume may be restored, red cell mass is not. According to the Hemoglobin and Iron Recovery Study (HEIRS), recovery of 80% red cell mass varies from 25 to more than 168 days.¹⁵⁴ On average, for those who undergo PAD, Hb is 1.1 g/dL less than those who do not donate preoperatively. In a meta-analysis incorporating data from multiple surgical patient populations, while PAD decreased the absolute risk of receiving allogenic blood by 44%, the risk of receiving a transfusion from any source (i.e., allogenic or PAD), increased by 24%, which questions the procedure's use as a transfusion-sparing practice.¹⁵⁵

BOX 49.2 Contradictions to Participation in Autologous Blood Donation Programs

1. Evidence of infection and risk of bacteremia
2. Scheduled surgery to correct aortic stenosis
3. Unstable angina
4. Active seizure disorder
5. Myocardial infarction or cerebrovascular accident within 6 months of donation
6. High-grade left main coronary artery disease
7. Cyanotic heart disease
8. Uncontrolled hypertension

Donation itself is not without risk. In a study of American Red Cross donors, PAD was associated with nearly 12 times the postdonation hospitalization rate as allogenic donors.¹⁵⁶ The criteria for autologous donation are less stringent than those for allogenic donors, as historically 15% of autologous donors do not meet safety criteria for allogenic donation.¹⁵⁷ As such, certain patient populations are poor candidates for PAD because of their underlying comorbidities. These populations include patients with severe cardiopulmonary disease (e.g., severe aortic stenosis, recent myocardial infarction, or cerebrovascular event) and those with bacteremia (Box 49.2).

ACUTE NORMOVOLEMIC HEMODILUTION

ANH is a procedure initiated before the start of significant blood loss, by which the anesthesiologist removes whole blood from a patient while simultaneously restoring intravascular volume with either crystalloid (3 mL/1 mL of blood removed) or colloid (1 mL/1 mL of blood removed) solutions to maintain adequate hemodynamics. Blood is collected in standard blood bags containing citrate anticoagulant and maintained at room temperature in the operating room for up to 8 hours or at 4°C for 24 hours. Bleeding that occurs following ANH sheds a lower percentage of RBCs per unit of total blood volume lost, constituting the presumed major benefit of this procedure.¹⁵⁸

When major bleeding has stopped or when clinically appropriate, the sequestered blood is then reinfused into the patient in the reverse order of collection because the first unit collected has the highest concentration of coagulation factors and platelets and the highest Hb level.¹⁵⁹ Although some providers advocate that stored blood be gently agitated to preserve platelet function, most practitioners do not do this, and no formal recommendations exist requiring this procedure. Reassuringly, no differences in thromboelastography (TEG) measurements have been noted between samples agitated during storage compared with those left stationary.¹⁶⁰

The amount of blood saved by ANH is both of a function of the postdilutional Hb achieved and the amount of blood volume lost intraoperatively, the latter hopefully occurring after the blood salvage. Patients undergoing minimal ANH—less than 15% of a patient's blood volume—would only save 100 mL of RBCs, equaling 0.5 units of PRBCs. However, increasing the ANH to target postdilutional Hct of 28% in the setting of 2600 mL blood loss resulted in savings of 215 mL of RBC compared with blood loss without prior hemodilution (Fig. 49.4).¹⁶¹

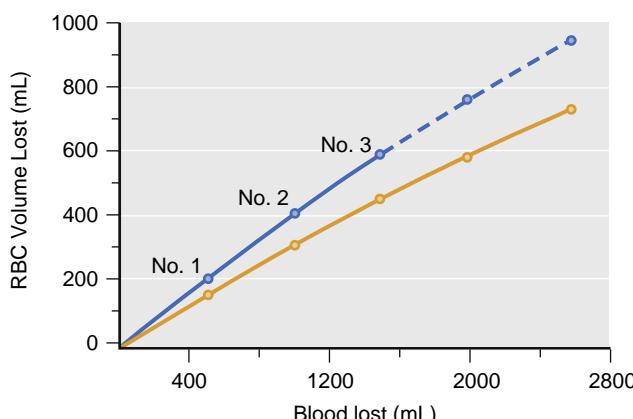


Fig. 49.4 The relationship between whole blood volume (*mL*) lost (abscissa) and red blood cell (RBC) volume lost (*ordinate*) in a 100-kg patient undergoing hemodilution: RBC volume lost with 2800 mL whole blood intraoperatively after hemodilution of 1500 mL whole blood (*solid blue line*); RBC volume lost with 2800 mL whole blood lost during hemodilution at each of three 500 mL volumes (*solid orange line*); cumulative RBC volume lost intraoperatively, derived for 2800 mL whole blood lost if hemodilution had not been performed (*blue dashed line*). A net of 215 mL reduction in RBC volume lost with hemodilution is illustrated by the divergence of the two curves. (From Goodnough LT, Grishaber JE, Monk TG, et al. Acute preoperative hemodilution in patients undergoing radical prostatectomy: a case study analysis of efficacy. *Anesth Analg*. 1994;78:932–937, with permission.)

Although larger volumes of hemodilution provide the largest benefit in terms of RBC mass saved and allogenic transfusions avoided,¹⁶² retrospective data suggest that even mild ANH may help to improve outcomes.¹⁶³ Prospective, randomized trials demonstrate ANH as a means to decrease transfusion requirements in multiple types of surgeries, including hip replacement,¹⁶⁴ hepatic resection,¹⁶⁵ and vascular surgery.¹⁶⁶ A recent meta-analysis evaluated 29 randomized controlled trials involving 1252 patients undergoing ANH (and 1187 controls) during cardiac surgery.¹⁶⁷ They found patients who underwent ANH were transfused less frequently than those in the control groups, receiving on average three-fourths fewer allogenic blood units than those in the control groups. Not surprisingly, patients undergoing ANH experienced less postoperative blood cell mass loss with a mean loss of 388 mL in the ANH groups and 450 mL in the control groups. Another meta-analysis demonstrated similar findings in a broader patient population that included multiple surgical specialties, but the findings were criticized due to the heterogeneity of the studies included and the potential for publication bias, which would likely overestimate any true benefit.¹⁶⁸ ANH has also been shown to decrease the need for other component therapy, because the removal of whole blood also removes and stores platelets and plasma.¹⁶² In cardiac surgery specifically, ANH may protect the sequestered blood from the effects of cardiopulmonary bypass and the platelet dysfunction that occurs.¹⁶⁹

Decisions regarding the use of ANH should be made with consideration given to the patient's vital signs, Hct, blood volume, and the estimation of surgical blood loss and risk of transfusion (Box 49.3). ANH is not without potential risk. A recent study in porcine animal models demonstrated significant adverse effects of ANH transfusions particularly in the adult compared with infant animal models. These effects

BOX 49.3 Criteria for Selection of Patients for Acute Normovolemic Hemodilution

1. Likelihood of transfusion exceeding 10% (i.e., blood requested for crossmatch according to a maximum surgical blood order schedule)
2. Preoperative Hb of at least 12 g/dL
3. Absence of clinically significant coronary, pulmonary, renal, or liver disease
4. Absence of severe hypertension
5. Absence of infection and risk of bacteremia

included the development of bronchoconstriction and acute lung injury as a result of extravasation of fluid and deterioration of cardiopulmonary hemodynamics.¹⁷⁰ Similarly, in dog models, ANH to a Hct of 30% demonstrated decreased oxygen delivery to the kidneys with preserved delivery to other organs, including the heart, brain, and spinal cord, suggesting ANH may place the kidneys at risk.¹⁷¹ Most studies evaluating ANH have focused on a reduction in RBC mass loss and the use of allogenic blood cell transfusions as the primary outcomes. Fewer studies have reported favorable findings with respect to end-organ damage in patients treated with ANH compared with those not treated, but studies in the future should look more closely at these important outcomes.¹⁶²

INTRAOPERATIVE CELL SALVAGE

The term *intraoperative blood collection* or *cell salvage* describes the technique of collecting, processing, and reinfusing blood lost by a patient during surgery. It is a perioperative blood conservation technique to reduce use of allogenic blood and the risks associated with allogeneic blood exposure. It may be acceptable for use in patients that do not consent to allogeneic or preoperative autologous blood transfusions, such as Jehovah's Witnesses. This technique should be discussed with such patients and acceptability should be determined on a case-by-case basis.¹⁷²

The AABB continues to recommend the following general indications for cell salvage use in their 2016 guidelines:¹⁷³

1. Anticipated blood loss is 20% or more than the patient's estimated blood volume.
2. Crossmatch-compatible blood is unobtainable.
3. Patient is unwilling to accept allogeneic blood but will consent to receive blood from intraoperative blood salvage.
4. The procedure is likely to require more than one unit of RBCs.

Cell salvage involves the collection of blood from the surgical field through a specialized double-lumen suction tubing that delivers anticoagulant, commonly heparin or citrate, to the tip of the suction catheter (Fig. 49.5). This prevents suctioned blood from clotting within the collection system. Blood from the surgical field is collected in a reservoir until enough fluid accumulates for processing. Processing involves specialized centrifugation that causes the lower density plasma and anticoagulant fluid to rise up and separate from the higher density RBCs, which are collected at the bottom of a conical- or cylindrical-shaped bowl. In general,

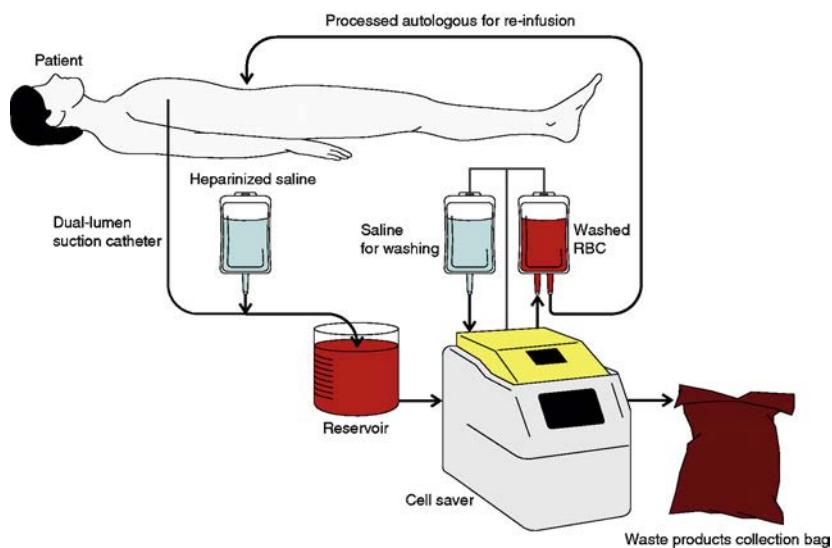


Fig. 49.5 Diagram of the setup of a standard cell salvage circuit. RBC, Red blood cell. (From Ashworth A, Klein A. Cell salvage as part of a blood conservation strategy in anaesthesia. *Br J Anaesth.* 2010;105[4]:401–416. <https://doi.org/10.1093/bja/aeq244>.)

500 to 700 mL of collected blood is required for processing to produce 225 to 250 mL of salvaged saline-suspended PRBCs with a Hct of 50% to 60%.¹⁷⁴ At this point, the salvaged PRBCs are ready for immediate or delayed transfusion. Microaggregate filters (40 µm) are most often employed during reinfusion because recovered and processed blood may contain tissue debris, small blood clots, or bone fragments. Some systems are able to continually process blood and can provide the equivalent of 12 units/h of banked blood to a massively bleeding patient.¹⁷⁵

The oxygen transport properties and survival of recovered RBCs appears to be equivalent to those of stored allogeneic RBCs. Levels of 2,3-DPG appear to be present at near normal levels in salvaged blood compared with stored allogenic blood cells, which have up to 90% reduction in 2,3-DPG levels.⁴³ Similarly, the P50 of salvaged blood is similar to that of fresh venous blood drawn from the same patient and significantly higher than that of 2-week old banked blood, suggesting better oxygen-offloading capabilities.¹⁷⁶ RBC deformability also appears improved compared with PRBCs.⁴¹

Some practical considerations for cell recovery programs are listed in (Box 49.4). If collected under aseptic conditions with a saline-wash device and if properly labeled, blood may be stored at room temperature for up to 4 hours or at 1°C to 6°C for up to 24 hours, provided storage at 1°C to 6°C is begun within 4 hours of ending the collection.¹⁷³ The allowable interval of room temperature storage is shorter for recovered blood (4 hours) than for ANH blood (8 hours). Storage times are the same for recovered blood regardless of whether unwashed or washed.

Reinfusion of salvaged blood is not without risk (Box 49.5).¹⁷⁷ Air embolism is a serious, potentially fatal problem, but this risk is now mitigated with newer systems that do not allow for the system's direct connection to the patient's intravenous tubing. Collection systems that neither concentrate nor wash shed blood before reinfusion increase the risk of adverse effects. Shed blood has undergone varying degrees of coagulation or fibrinolysis and hemolysis, and infusion of large volumes of washed or unwashed

BOX 49.4 Practical Considerations for Intraoperative Cell Recovery, Storage, and Reinfusion

1. If not transfused immediately, units collected from a sterile operating field and processed with a device for intraoperative blood collection that washes with 0.9% saline should be stored under one of the following conditions before initiation of transfusion:
 - a. At room temperature for up to 4 h after terminating collection
 - b. At 1°C–6°C for up to 24 h, provided storage at 1°C–6°C is begun within 4 h of ending the collection
2. Transfusion of blood collected intraoperatively by other means should begin within 6 h of initiating the collection.
3. Each unit collected intraoperatively should be labeled with the patient's first name, last name, and hospital identification number; the date and time of initiation of collection and of expiration; and the statement "For Autologous Use Only."
4. If stored in the blood bank, the unit should be handled like any other autologous unit.
5. The transfusion of shed blood collected under postoperative or posttraumatic conditions should begin within 6 h of initiating the collection.

blood has been associated with disseminated intravascular coagulation (DIC).¹⁷⁸ In general, blood collected at low flow rates or during slow bleeding from patients who are not systemically anticoagulated will have undergone coagulation and fibrinolysis and will not contribute to hemostasis on reinfusion. The high suction pressure and surface skimming during aspiration and the turbulence or mechanical compression that occurs in roller pumps and plastic tubing make some degree of hemolysis inevitable.¹⁷⁹ Patients exhibit a level of plasma-free hemoglobin that is usually higher than after allogeneic transfusion. High concentrations of free hemoglobin can be nephrotoxic to patients and free hemoglobin causes severe arteriolar vasoconstriction of microvascular structures from NO scavenging.¹⁸⁰ However, the clinical importance of this phenomenon in

BOX 49.5 Types of Adverse Reactions That May Be Seen With Blood Transfusion from Intraoperative Cell Salvage

Hypervolemia
Bacterial contamination
Hypotension
Nonimmune hemolysis
Immune hemolysis
Febrile nonhemolytic reactions
Allergic reactions
Disseminated intravascular coagulation
Coagulopathies
Air embolus
Reactions secondary to reinfusion of anticoagulants or other contaminants
Nonspecific temperature increases, chills, skin flushing, etc.

From Domen R. Adverse reactions associated with autologous blood transfusion: evaluation and incidence at a large academic hospital. *Transfusion*. 1998;38:296–300. <https://doi.org/10.1046/j.1537-2995.1998.38398222875.x>

intraoperative cell salvage has not been established. Many programs limit the quantity of recovered blood that may be reinfused without processing. To minimize hemolysis, the vacuum level should ordinarily not exceed 150 mm Hg, although higher levels of suction may occasionally be needed during periods of rapid bleeding. One study found that vacuum settings as high as 300 mm Hg could be used, when necessary, without causing excessive hemolysis.¹⁸¹

Positive bacterial cultures from recovered blood are sometimes observed, but clinical infection is rare¹⁸² and may be mitigated with the use of a leukocyte filter in the system¹⁸³. Intraoperative collection is contraindicated when certain procoagulant materials (e.g., topical collagen) are applied to the surgical field because systemic activation of coagulation may result. Other instances that may preclude use of cell salvage include: use of parenterally incompatible chemicals (e.g., chlorhexidine, betadine, hydrogen peroxide) in the surgical field, and use of hypotonic solutions in the surgical field, which may lyse red blood cells.

Clinical Studies

As with PAD and ANH, collection and recovery of intraoperative autologous blood should undergo scrutiny with regard to both safety and efficacy.¹⁸⁴ A meta-analysis of 75 studies evaluating the utility for cell salvage to minimize allogeneic blood transfusion found that cell salvage reduced the need for allogeneic blood transfusion in adult-elective surgeries by 38%.¹⁸⁵ The greatest benefit was seen in orthopedic procedures but cardiac surgery patients also benefited. On average, intraoperative blood salvage saved an average of 0.68 units of allogenic banked blood. Of note, two randomized controlled trials published in 2014 of patients undergoing hip and knee arthroplasty with either preoperative hemoglobin concentration between 10 to 13 g/dL or more than 13 g/dL failed to show cell salvage as an effective means to reduce allogenic blood requirements.^{186,187} However, both studies combined intraoperative and postoperative cell salvage and did not separate

TABLE 49.12 Procedures Where Intraoperative Cell Salvage May Be Indicated

General Surgery	Hepatic resection
	Splenectomy
Neurosurgery	Basilar Aneurysm
Transplant Surgery	Liver transplant
	Kidney transplant
Cardio/Thoracic	Cardiac transplant/VAD implant
	Pulmonary transplant
	Coronary artery bypass grafting
	Cardiac valve repair/replacement
	Aortic arch Aneurysm
	Thoracic trauma
Vascular	Aortic Aneurysm repair
	Femoral bypass grafting
Orthopedic	Total shoulder replacement
	Total hip replacement or revision
	Bilateral knee replacement
	Open reduction/internal fixation pelvic or long bone fracture
	Multilevel spine surgery
Urology	Nephrectomy
	Radical prostatectomy
Gynecology	Hysterectomy
Obstetrics	Placenta accreta, increta, or percreta

Adapted from Esper SA, Waters JH. Intra-operative cell salvage: a fresh look at the indications and contraindications. *Blood Transfus*. 2011;9(2):139–147.

patients who received one technique (or both techniques) from those who received another.

In some cases, the value of blood salvage may not be in terms of patient outcome or reduction of transfusion requirements, but instead in cost savings. The value of intraoperative blood collection was recently demonstrated for high-risk cesarean surgeries but not for routine procedures.¹⁸⁸ A list of surgeries where intraoperative cell salvage may be indicated are provided in Table 49.12. As comprehensive PBM pathways continue to evolve and improve patient outcomes, future studies regarding the efficacy and cost-effectiveness of cell salvage will be needed.

POSTOPERATIVE CELL SALVAGE

Postoperative blood collection denotes the recovery of blood from surgical drains followed by reinfusion, with or without processing.¹⁶⁶ In some programs, postoperative shed blood is collected into sterile canisters and reinfused, without processing, through a microaggregate filter. Recovered blood is dilute, is partially hemolyzed, and may contain high concentrations of cytokines. For these reasons, most programs set an upper limit on the volume (e.g., 1400 mL) of unprocessed blood that can be reinfused. If transfusion of blood has not begun within 6 hours of initiating the

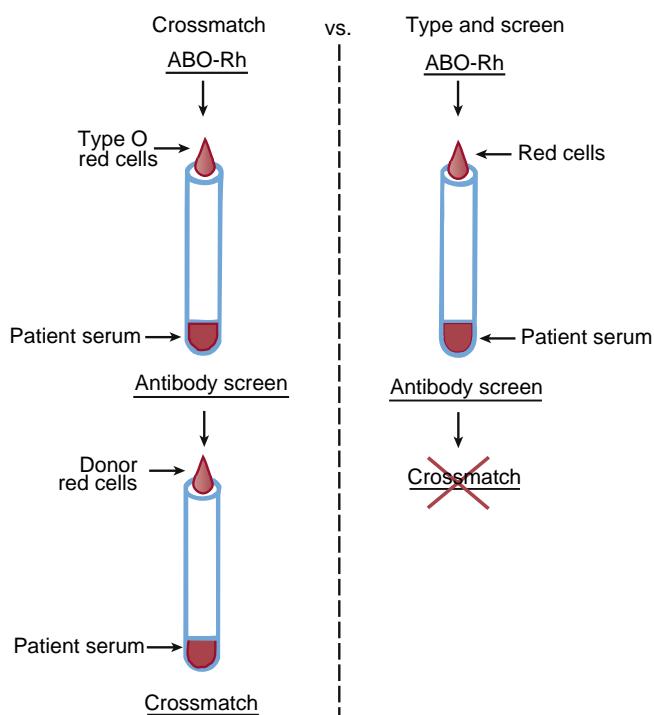


Fig. 49.6 Outline of the tests used for a crossmatch. The X over the word crossmatch means that the crossmatch is not included in the type and screen.

collection, the blood must be discarded. Although this technique gained popularity for total joint arthroplasties, the technique is being used less frequently because of a number of factors, including improved PBM programs, lack of evidence for effectiveness, and care pathways that lead to earlier hospital discharge.¹⁷⁴

Compatibility Testing

GENERAL PRINCIPLES

The ABO-Rh type, antibody screen, and crossmatch are frequently referred to as compatibility tests. These tests were designed to demonstrate harmful antigen-antibody interactions *in vitro* so that harmful *in vivo* antigen-antibody interactions can be prevented. Donor blood used for emergency transfusion of type-specific blood must be screened for hemolytic anti-A and/or anti-B antibodies, and Rh antibodies. Similarly, recipient blood must also undergo ABO-Rh typing, as well as testing for unexpected antibodies. Once this has been completed, proper selection of donor blood requires a crossmatch to test for compatibility between recipient blood and donor blood (Fig. 49.6). All approved blood banks have redundant processes in place to ensure that the patient receives the correct unit of blood. Most will require a second confirmatory specimen drawn on a separate occasion from the first type and screen to reduce the risk of a crossmatch error and a hemolytic blood transfusion reaction.¹⁸⁹

ABO-RH TYPING

Determination of the patient's correct blood type is exceedingly important because the most serious and tragic

TABLE 49.13 ABO Compatibility Testing

Blood Group	RED CELLS TESTED WITH		SERUM TESTED WITH	
	Anti-A	Anti-B	A Cells	B Cells
A	+	-	-	+
B	-	+	+	-
AB	+	+	-	-
O	-	-	+	+

TABLE 49.14 Donor Blood Groups That Patients Can Receive

Donor	Recipient
O	O, A, B, AB
A	A, AB
B	B, AB
AB	AB

reactions are usually caused by accidental transfusion of ABO-incompatible blood. In fact, 15% of all transfusion-related deaths are related to hemolytic reactions due to antibody incompatibility.¹⁹⁰ These reactions result from naturally occurring antibodies (i.e., anti-A and anti-B), which activate complement and lead to rapid intravenous hemolysis. Anti-A or anti-B antibodies are formed whenever the individual lacks either or both of the A and B antigens. ABO typing is performed by testing RBCs for the A and B antigens and the serum for the A and B antibodies before transfusion (Table 49.13).

The second most important testing is that for the Rh(D) antigen. Antigen D is very common, and, except for the A and B antigens, the one most likely to produce immunization. Of Rh(D)-negative recipients, 60% to 70% of patients given Rh(D)-positive blood produce anti-D antibodies. Anti-D antibodies may also be formed in the Rh(D)-negative parturient. Approximately 85% of individuals possess the D antigen and are classified as Rh(D) positive; the remaining 15%, who lack the D antigen, are classified as Rh(D) negative. Transfusion of Rh(D)-positive blood to a Rh(D)-negative patient with Rh(D) antibodies may produce a hemolytic transfusion reaction. Table 49.14 identifies compatible donor/recipient blood types.

ANTIBODY SCREENING

Antibody screens are performed to identify unexpected RBC alloantibodies. The patient's serum is combined with commercially supplied RBCs that are specifically selected due to their expression of RBC antigens for which clinically significant alloantibodies are formed.¹⁹¹ The reagent RBCs are type O so they do not react to anti-A or anti-B antibodies that may be present in the patient's serum. Alloantibodies are typically immunoglobulin (Ig)G, and thus do not readily produce agglutination *in vitro*, but do so *in vivo*. As a result, an indirect antiglobulin test (formerly an indirect Coombs test) is undertaken to evaluate for the presence of IgG alloantibodies. The patient's serum is combined with the reagent RBCs with an additive that promotes binding of

antibodies to the RBCs. The mixture is incubated at 37°C, washed and mixed with reagent containing antibodies to IgG and complement. The reagent binds to any IgG attached to the RBCs, crosslinking the RBCs and producing agglutination in vitro. If the test is positive, follow-up testing must be undertaken to identify the target antigen.

The screen for unexpected antibodies is also used on donor serum and is performed shortly after withdrawal of blood from the donor. It is necessary to screen donor serum for unexpected antibodies to prevent their introduction into the recipient's serum.

Daratumumab, a human monoclonal antibody targeting the CD38 glycoprotein was recently approved for the treatment of multiple myeloma, and has been noted to interfere with antibody screening. The drug binds to CD38 expressed on reagent RBCs, leading to a potentially false positive result.¹⁹² Treatment of reagent RBCs with dithiothreitol negates the interference but also leads to denaturing Kell antigens; therefore, K⁻ RBC units should be allocated in this circumstance unless the patient is known to be K⁺.¹⁹³ As immunotherapeutic agents and their indications expand, anesthesiologists should be aware of their implications to antibody screening to allow for appropriate testing to avoid delays in the allocation of blood products.¹⁹⁴

CROSSMATCHING

A crossmatch is a trial transfusion within a test tube in which donor RBCs are mixed with recipient serum to detect a potential for transfusion reaction. The full crossmatch can be completed in 45 to 60 minutes and is performed in three phases: an immediate spin (IS) phase, an incubation phase, and an indirect antiglobulin phase.

First, the IS phase is conducted at room temperature and is a check against errors in ABO typing. It detects ABO incompatibilities and those caused by naturally occurring antibodies in the MN, P, and Lewis systems, but is insensitive to the presence of other RBC alloantibodies. This takes 1 to 5 minutes to complete. In the setting of a negative antibody screen or during emergency situations when an abbreviated crossmatching process is required, this step may serve as the sole confirmatory process to eliminate reactions that may result from human errors in ABO-Rh typing alone. Blood given after this test is more than 99% safe in terms of avoiding incompatible transfusion reactions caused by unexpected antibodies.¹⁹⁵

Next, the incubation and indirect globulin or "indirect Coombs" phases primarily detect antibodies in the Rh system and other non-ABO blood group systems.¹⁹⁶ This two-step process involves incubation of the test tube at 37°C in albumin or low-ionic strength salt solution, which aids in the detection of incomplete antibodies or antibodies able to attach to a specific antigen (i.e., sensitization) but are unable to cause agglutination in a saline suspension of RBCs. An incubation period of 30 to 45 minutes in albumin and 10 to 20 minutes in low-ionic strength salt solution in this phase is of sufficient duration to allow antibody binding to cells so that incomplete antibodies missed in this phase can be detected in the subsequent antiglobulin phase. The RBCs are centrifuged, resuspended, and observed for hemolysis and agglutination. The RBCs are then washed and resuspended in solution to remove unbound immunoglobulins.

Antiglobulin sera is added to the test tubes. The antihuman antibodies present in the sera become attached to the antibody on the RBCs, causing agglutination. This antiglobulin phase detects most incomplete antibodies in the blood group systems, including the Rh, Kell, Kidd, and Duffy blood group systems.

The incubation and antiglobulin phases are important because the antibodies appearing in these phases are capable of causing serious hemolytic reactions. Except for hemolytic reactions involving anti-A and anti-B, reactions caused by antibodies appearing in the immediate phase are frequently less severe as many are naturally occurring, present in low titers, and not reactive at physiologic temperatures.

ELECTRONIC CROSMATCH

In previously transfused or pregnant patients, only 1 patient in 100 may have an irregular antibody other than the anti-A and anti-B antibodies. However, some of these irregular antibodies are reactive only at temperatures below 30°C and therefore are insignificant in most transfusions. Others that are reactive at approximately 30°C can produce serious reactions if the transfused cells contain the appropriate antigen. In order of probable significance, anti-Rh(D), Kell, C, E, and Kidd are the most common of clinically significant antibodies. If the correct ABO and Rh blood type is given, the possibility of transfusing incompatible blood is less than 1 in 1000. ABO-Rh typing alone results in a 99.8% chance of a compatible transfusion, the addition of an antibody screen increases the safety to 99.94%, and a crossmatch increases this to 99.95%.¹⁹⁷ Complete transfusion testing for compatibility between donor and recipient blood ensures optimal safety and therapeutic effect of transfused blood, but the process is time-consuming and costly.

Once a serologic crossmatch is complete, blood is allocated and set aside for that patient for up to 72 hours. If unused, the product is returned to circulation for other potential recipients. This practice leads to the loss of use for that blood product and increases the chance for outdated of unused products. Eliminating the serologic crossmatch and replacing it with a type and screen followed by a computerized or electronic crossmatch improves the efficiency of the blood banking system, while maintaining, if not improving, patient safety.¹⁹⁸ According to FDA guidance in the United States, a computerized match requires that software determine if incompatibility exists between donor and recipient. Decisions are made based on two separate ABO/Rh typing results from separate specimens from both the donor and the recipient. Under usual perioperative circumstances, measuring the two results from a single specimen should be avoided, as a major cause of ABO errors is a mislabeled specimen.¹⁹⁹ Mislabeled of specimens occurs with an incidence of more than 7 per 1000 specimens with "wrong blood in tube" occurring at a rate of 0.4 instances per 1000 specimens.²⁰⁰ Interestingly, in this study by Novis and associates, the incident error rate did not decrease between the years of 2007 and 2015, despite the institution of barcode scanning.

A clinically significant current or previously detected positive antibody screen excludes the use of the electronic crossmatch and a serologic crossmatch should be performed.²⁰¹

Patients with a history of a clinically significant antibody despite a current negative antibody screen should continue to be excluded from the electronic crossmatch. The concern is that low titers of circulating antibodies can produce a falsely negative antibody screen.²⁰²

The type and screen without the serologic crossmatch does not protect against reactions caused by antibodies reactive against lower incidence antigens. These are antigens not represented on the screening cells but present on the donor RBCs. In general, antibodies that are not detected in the type and screen are weakly reactive antibodies that do not result in serious hemolytic transfusion reactions. In a study of 13,950 patients, Oberman and associates²⁰³ discovered only eight “clinically significant” antibodies after complete crossmatch that were not detected during the antibody screening. The antibodies were all in lower titer and were believed to be unlikely to cause serious hemolytic reactions.

Maximal Surgical Blood Order Schedule

In the 1960s and 1970s, the number of crossmatched units ordered for certain surgical procedures frequently far exceeded the number actually transfused. This led to blood being set aside and potential outdatedness. To better quantify this problem, the crossmatch-to-transfusion (C/T) ratio has been used. If the C/T ratio is high, a blood bank is burdened with keeping a large blood inventory, using excessive personnel time, and having a high incidence of outdated units. Sarma²⁰⁴ recommended that for surgical procedures in which the average number of units transfused per case is less than 0.5, determination of the ABO-Rh type and a screen of the patient serum for unexpected antibodies (type and screen) should be used. This would be in lieu of a complete crossmatch for patients with negative antibody screens. More recently, Dexter and associates²⁰⁵ established that using the estimated blood loss reported in an anesthesia information system is more efficacious at predicting the need for transfusions. Their data indicated that for surgical procedures with less than 50 mL expected blood loss, a type and screen is not required.

To increase the rate of use and lower the C/T ratio, blood banks attempt to decrease the emphasis on crossmatching of blood through such programs as the maximal surgical blood order schedule (MSBOS).²⁰⁶ Ideally, blood banks aim to maintain C/T ratio of less than 2.²⁰⁷ The MSBOS consists of a list of surgical procedures and the maximal number of units of blood that the blood bank will crossmatch for each procedure. This schedule is based on the blood transfusion experience for surgical cases in a hospital. Each hospital's MSBOS is unique to that practice. The implementation of the MSBOS resulted in a decrease of blood unit expiration from 6.5% to 4.5% at the University of Michigan.²⁰⁸ Subsequently, patients were categorized into one of three groups: (1) requiring a crossmatch, (2) requiring a type and screen, or (3) no sample required. Preoperative blood orders decreased by 38% with a C/T ratio that decreased by 27%. However, the authors noted the rate of emergency release RBC units increased from 2.2 to 3.1 patients per 1000, but 60% of those patients requiring emergency release blood

were undergoing emergency surgery. Of the patients in the “no sample required” category, only a marginal increase of 0.4 to 1 per 1000 patients requiring emergency release blood was noted.²⁰⁹

Instead of the blood bank examining the next day's surgical schedule and allocating blood as described in the previous paragraph, now information technology systems have the capability of displaying the surgical schedule along with the MSBOS's recommendation regarding blood preparation. The night before, the blood bank examines the surgical schedule and MSBOS recommendations to see whether blood is needed. The blood bank also uses the MSBOS information to see if additional testing should be performed. Missing tests are communicated to the primary team so that appropriate orders can be placed.

Emergency Transfusion

In many situations, urgent need for blood occurs before completion of compatibility testing (ABO-Rh typing, antibody screen, or crossmatch; see also [Chapter 66](#), which describes transfusion challenges in patients who require surgery and anesthesia after injury from trauma). In essence, for those situations that do not allow time for complete testing, an abbreviated format for testing can be used or uncrossmatched group O blood can be allocated. The procedures described in the following paragraphs aim to provide the potentially life-saving blood product, while minimizing the risk for acute, intravascular hemolytic transfusion reactions.

TYPE-SPECIFIC, PARTIALLY CROSMATCHED BLOOD

When using uncrossmatched blood, it is best to obtain at least an ABO-Rh typing and an immediate-phase crossmatch. This incomplete crossmatch is accomplished by adding the patient's serum to donor RBCs at room temperature, centrifuging it, and then reading it for macroscopic agglutination. This takes 1 to 5 minutes and eliminates serious hemolytic reactions resulting from errors that may occur in ABO typing. Only a few unexpected antibodies outside the ABO systems are detected, such as those directed against antigens in the MN, P, and Lewis systems, most of which are not clinically significant.

TYPE-SPECIFIC, UNCROSMATCHED BLOOD

For proper use of type-specific blood, the ABO-Rh type must be determined during the patient's hospitalization. Reports of blood type from patients, relatives, outside medical records may be inaccurate. For those who have never been exposed to foreign RBCs, most ABO type-specific transfusions are successful. Caution should be used for patients who have previously received transfusions or have been pregnant. Historically, in the military, type-specific uncrossmatched blood has been used in emergencies with no serious consequence. In the civilian setting, using 1 year's experience with 56 patients, uncrossmatched, type-specific blood for emergency transfusion produced no adverse effects.²¹⁰ The investigators concluded that although the use of

uncrossmatched blood is usually safe, the potential for serious reaction still exists, and they cautioned against its indiscriminate use. For those who have previously been exposed to RBC antigens, transfusion of the ABO-Rh type-specific, uncrossmatched blood may be more hazardous.

TYPE O RH-NEGATIVE (UNIVERSAL DONOR), UNCROSSMATCHED BLOOD

Type O blood lacks A and B antigens and consequently cannot be hemolyzed by anti-A or anti-B antibodies in the recipient's plasma (see [Tables 49.13 and 49.14](#)). Type O blood can be used for transfusions when typing or cross-matching is not available. However, some type O donors produce high titers of hemolytic IgG, IgM, anti-A, and anti-B antibodies. High titers of these hemolysins in donor units are capable of causing destruction of A or B RBCs of a non-type O recipient. Type O Rh-negative, uncrossmatched PRBCs should be used in preference to type O Rh-negative whole blood because packed erythrocytes have smaller volumes of plasma and are almost free of hemolytic anti-A and anti-B antibodies. If type O Rh-negative whole blood is to be used, the blood bank must supply type O blood that is previously determined to be free of hemolytic anti-A and anti-B antibodies.

Some hospitals have an emergency-release pack of uncrossmatched O negative RBCs. This blood usually can be provided in approximately 5 minutes for urgent situations. Also available in some hospitals is a massive transfusion protocol (MTP), which provides 4 units uncrossmatched O negative RBCs, 4 units thawed AB plasma, and 1 unit of platelet concentrates. Use of MTP blood is determined by physician judgment, but that decision is reviewed after the emergency situation. Although uncrossmatched blood appropriately causes great concern, the risks for complication appear to be quite infrequent.²¹¹ Boisen and associates describe only a 0.1% occurrence of detectable hemolysis in the transfusion of 10,916 uncrossmatched units in 2906 patients.²¹² Also, in patients transfused with uncrossmatched blood with antigens for which they are later found to have antibodies against, only 7 out of 262 patients experienced hemolytic reactions.²¹³

If emergency transfusion of more than 2 units of type O Rh-negative, uncrossmatched whole blood is used, the patient cannot be switched to his or her blood type (A, B, or AB) once that is determined. Switching could cause major intravascular hemolysis of donor RBCs because of high titers of transfused anti-A and anti-B. Continued use of O Rh-negative whole blood results only in minor hemolysis of recipient RBCs and hyperbilirubinemia. The patient must not be transfused with his or her correct blood type until the blood bank determines that the transfused anti-A and anti-B has decreased to levels that permit safe transfusion of type-specific blood.

Fresh Whole Blood

The definition of fresh whole blood is based on storage time, which varies widely in the literature.²¹⁴ Some investigators²¹⁵ define fresh blood as blood stored at 1°C to 6°C within 8 hours after collection and used within 24 hours,

while other investigators define it as fresh if it has been stored less than 48 hours at 2°C to 5°C. The degree to which fresh blood regains its various functions is directly related to the length of storage and whether it has been cooled. The longer blood is stored, the less effective it becomes, especially regarding coagulation. Whole blood stored for 24 hours at 4°C has less hemostatic effects than blood stored for less than 6 hours because of decreased platelet aggregability.²¹⁶ Whole blood that has been typed and crossmatched, but not cooled, retains most of the factors of normal *in vivo* blood. The difference between 1 hour and 2 days of storage can be tremendous and may impact clinical outcomes.

Numerous studies have examined the use and safety of fresh whole blood, particularly by the U.S. military in Iraq and Afghanistan.²¹⁷ Whole blood has been a component of transfusion for over 70 years.⁹ Experience in Vietnam showed that typed and crossmatched warm whole blood was extremely effective in treating the coagulopathy from massive transfusions.^{2,3,218}

Complications

COAGULATION ABNORMALITIES

Major trauma or blood loss will initiate a cascade of coagulation abnormalities, including a consumptive coagulopathy from tissue hypoperfusion as manifested by increased protein C levels.²¹⁹ This coagulopathy is caused by a combination of factors, of which the most important are the dilution of coagulation factors by volume administration (e.g., crystalloid, colloid, PRBC), and the duration of hypotension and hypoperfusion. Various protocols have been developed for approaches to massive blood transfusion administration ([Fig. 49.7](#)). Patients who have adequate perfusion and are not hypotensive for a long period (e.g., 1 hour or less) may tolerate administration of multiple units of blood without developing a coagulopathy. The patient who is hypotensive and has received many units of RBCs will develop a coagulopathy that resembles DIC. When such bleeding occurs, the differential diagnosis is dilutional thrombocytopenia, deficiency of factors V and VIII, a DIC-like syndrome, or a transfusion reaction. Clinical signs include oozing into the surgical field, hematuria, gingival bleeding, petechia, bleeding from venipuncture sites, and ecchymosis.

THROMBOCYTOPENIA

Thrombocytopenia is defined as a platelet count less than $150 \times 10^9/L$ or more than 50% decrease compared with the previous measurement. Clinical bleeding usually does not occur during surgery until platelet counts are less than $50 \times 10^9/L$ and for spontaneous bleeding until platelet counts are less than $10 \times 10^9/L$.²²⁰ Independent of whether whole blood or PRBCs are given, few viable platelets exist in a unit of blood stored for more than 24 hours. For whole blood stored at 4°C, platelets are damaged sufficiently to be readily trapped and absorbed by the reticuloendothelial system soon after infusion. Even platelets that are not immediately stored have a reduced survival time.

Thrombocytopenia can trigger a hemorrhagic diathesis in a patient who has received multiple units of bank blood.

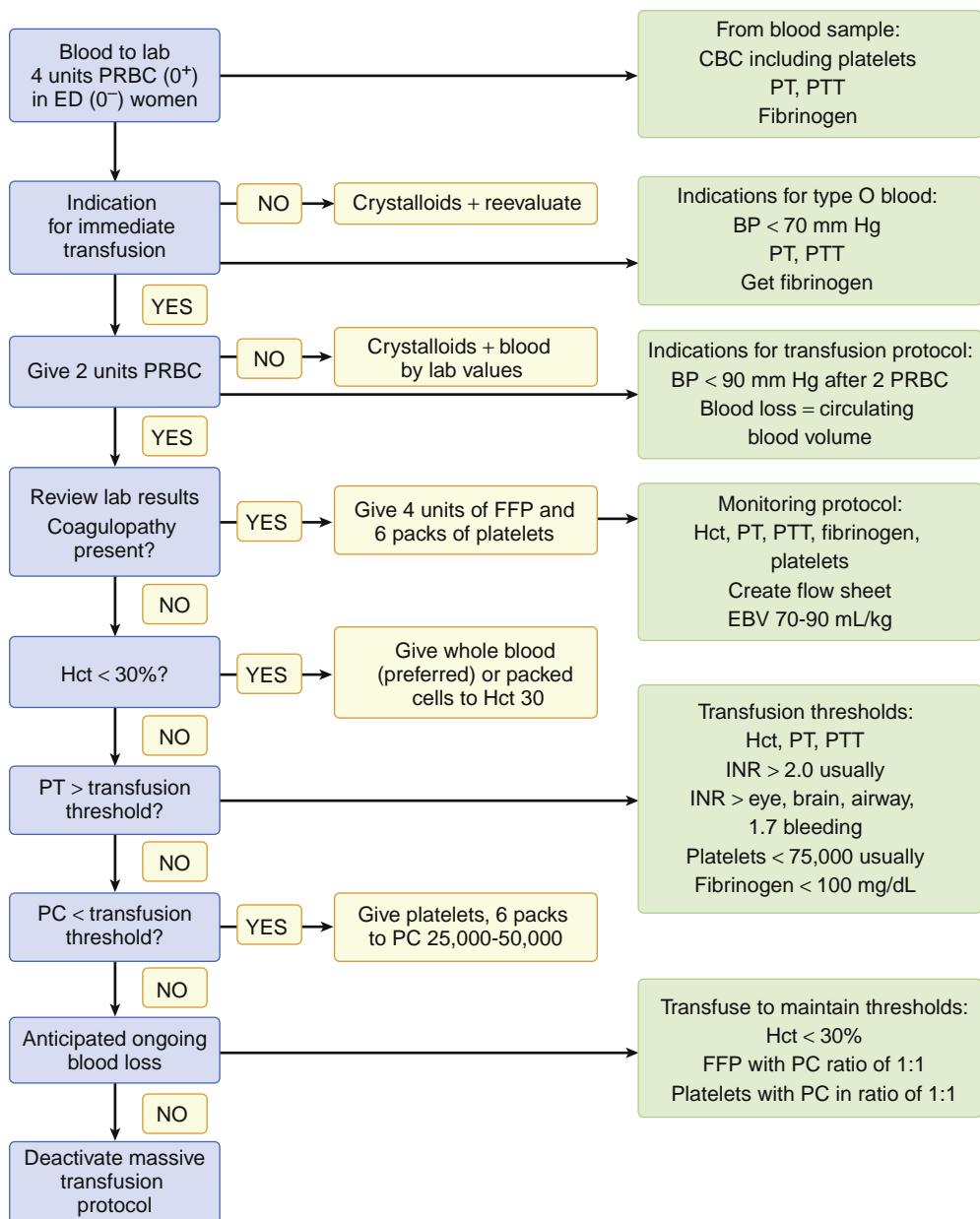


Fig. 49.7 This algorithm for diagnosing and treating a massive transfusion was modified from the massive transfusion protocol used at the San Francisco General Hospital. This protocol suggests how to approach a patient with major blood loss. *BP*, Blood pressure; *CBC*, complete blood cell count; *EBV*, effective blood volume; *ED*, emergency department; *FFP*, fresh frozen plasma; *Hct*, hematocrit; *INR*, international normalized ratio; *PC*, platelet count; *PRBCs*, packed red blood cells; *PT*, prothrombin time; *PTT*, partial thromboplastin time.

Platelet counts decreased to less than $100 \times 10^9/\text{L}$ when 10 to 15 units of blood were given to acutely wounded, previously healthy soldiers.²¹⁹ Miller and colleagues² found that platelet counts less than $75 \times 10^9/\text{L}$ are a reasonably accurate guide as to when patients will develop a bleeding problem from dilutional thrombocytopenia (see Table 49.10). One trauma group suggests that a higher than normal platelet count may be required in severely injured trauma patients²²² to maintain adequate hemostasis because damaged capillaries require platelets to “plug the holes.” The military and trauma hospitals tend to follow transfusion ratios and do not follow strict platelet thresholds for transfusion.

Several investigators^{223,224} have questioned the role of dilutional thrombocytopenia in the coagulopathy of

massively transfused patients. They point out that the platelet count rarely decreases to as low a level as would be predicted from dilution alone (Fig. 49.8). It may be that platelets are released into the circulation from the spleen and bone marrow but that some of the platelets present function poorly. Patients with chronic thrombocytopenia or leukemia often do not have a hemorrhagic diathesis with a platelet count lower than $15 \times 10^9/\text{L}$. For unexplained reasons, patients with an acute induced thrombocytopenia (e.g., from blood transfusions) develop a hemorrhagic diathesis at a much higher platelet count than patients with chronic thrombocytopenia (e.g., idiopathic thrombocytopenic purpura).

Most would agree that platelets should not be given to treat laboratory evidence of thrombocytopenia unless

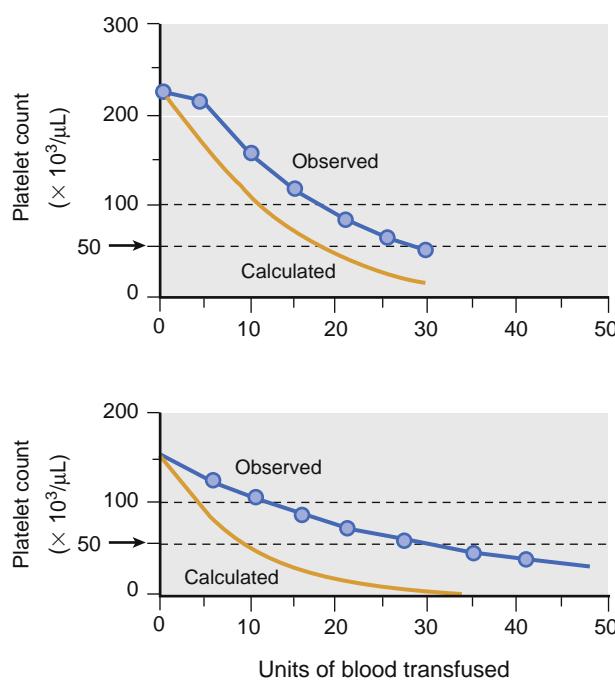


Fig. 49.8 Mean platelet counts after massive transfusions in relation to number of units of blood transfused. Observed versus predicted values calculated on the basis of 2 blood exchange models. (From Myllylä G. New transfusion practice and haemostasis. *Acta Anaesthesiol Scand Suppl*. 1988;89:76.)

clinical coagulopathy is also present. Treating laboratory numbers without correlation with the clinical status is fundamentally contrary to good medical practice. When the platelet count is less than 50 to $70 \times 10^9/L$, coagulation is likely impaired due to a combination of dilutional thrombocytopenia and DIC. In many cases, certainly with a concomitant medical condition (e.g., DIC, sepsis), the platelet count as a result of dilutional thrombocytopenia cannot be predicted,²²⁵ nor can the actual impact on clinical bleeding. This is just one of the reasons why efficacy of blood product administration is often difficult to assess. Growing use of point-of-care viscoelastic tests such as tTEG and rotational thromboelastometry instead of platelet count to guide hemostatic therapy is becoming more common.²²⁶

LOW LEVELS OF FIBRINOGEN AND FACTORS V AND VIII

Considerable attention has been paid to the decreases in blood fibrinogen concentrations that occur during blood loss and blood replacement, likely due to the availability of a lyophilized fibrinogen concentrate for clinical use. Fibrinogen supplementation was previously provided by administration of FFP and cryoprecipitate. Levy and colleagues²²⁷ provided an excellent scholarly review of fibrinogen and hemostasis and concluded that fibrinogen is critical for effective clot formation, and its monitoring and supplementation as the treatment of major bleeding should be recognized. Many prospective studies of fibrinogen supplementation in acquired bleeding report that it is the most effective method of supplementation, and a comprehensive safety profile of fibrinogen concentrate is beginning to appear.

Factors V and VIII may also be affected during storage and significant transfusion.²²⁸ These factors decrease to 50% and 30% of normal, respectively, in whole blood after 21 days of storage²²⁹ and are not present in units of PRBCs. By 35 days of storage, factor V and factor VIII fall further to approximately 20% activity of normal.²³⁰

Administration of FFP, which contains all the factors, has been recommended. However, this practice is of questionable benefit because only 5% to 20% of factor V and 30% of factor VIII are needed for adequate hemostasis during surgery, and even during massive blood transfusion, factors V and VIII rarely decrease below those levels.

DISSEMINATED INTRAVASCULAR COAGULATION-LIKE SYNDROME

The coagulation system consists of clotting and fibrinolytic mechanisms. The function of the former is to prevent excessive blood loss, and that of the latter is to ensure circulation within the vasculature. With this DIC-like syndrome, the clotting system is deranged, leading to disseminated fibrin deposition, which renders the blood unclottable. The deposited fibrin may severely alter the microcirculation and lead to ischemic necrosis in various organs, particularly the kidney. Table 49.15 displays the interchange between various medical conditions and their impact on various measures of the coagulation system.²³¹

The specific reasons for the development of DIC syndrome are usually not apparent. However, hypoxic acidotic tissues with stagnant blood flow probably release tissue thromboplastin directly or through the protein C pathway.²¹⁹ The release of tissue plasminogen activator from damaged tissue may cause fibrinolysis. The coagulation system is activated by tumor necrosis factor and endotoxins, resulting in consumption of factors I, II, V, and VIII, and platelets. In an attempt to counteract the hypercoagulable state, the fibrinolytic system is activated to lyse the excessive fibrin. If enough thromboplastin lodges in the circulating blood, the result is massive focal necrosis or more generalized activation of the coagulation system.

DIAGNOSIS AND TREATMENT OF A HEMORRHAGIC DIATHESIS AFTER BLOOD TRANSFUSIONS

Although treatment is more likely to be successful when the cause of the bleeding problem has been identified, precise diagnosis is often difficult. In addition to clinical examination of the patient, various coagulation laboratory tests may be helpful. One traditional approach has been to obtain a blood sample for platelet count, PTT, and plasma fibrinogen level; observation of a clot for size, stability, and lysis; and observation of the plasma for evidence of hemolysis. If the PTT is 1.5 times normal or more and other tests are normal, the bleeding is probably a result of very low levels of factors V and VIII. This can be treated with FFP or with cryoprecipitate (Fig. 49.9).

Whether platelets are administered in the form of fresh blood, platelet-rich plasma, or platelet concentrates depends on intravascular volume replacement requirements, personal preference, and availability of laboratory personnel. Fresh blood (<6 hours old) supplies the

TABLE 49.15 Laboratory Findings in Various Platelet and Coagulation Disorders in the Intensive Care Unit

Condition	Prothrombin Time	Activated Partial Thromboplastin	Fibrinogen Level	D-Dimer Level	Bleeding Time	Platelet Count	Findings on Blood Smear
Vitamin K deficiency or use of vitamin K antagonist	Prolonged	Normal or mildly prolonged	Normal	Unaffected	Unaffected	Unaffected	
Aspirin or thienopyridines	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Liver failure							
Early stage	Prolonged	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected	
End stage	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	
Uremia	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
DIC	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	Fragmented red cells
TPP	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Very low	Fragmented red cells
Hyperfibrinolysis	Prolonged	Prolonged	Low	Very high	Possibly prolonged	Unaffected	

DIC, Disseminated intravascular coagulation; TPP, thrombotic thrombocytopenic purpura.

From Hunt BJ. Bleeding and coagulopathies in critical care. *N Engl J Med*. 2014;370:847–859.

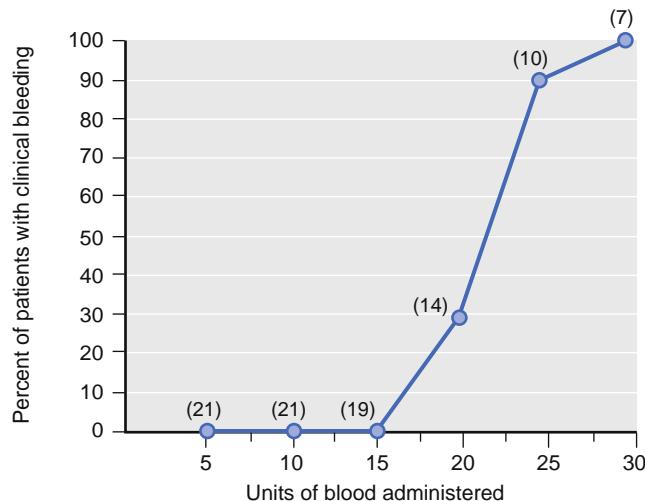


Fig. 49.9 Correlation between units of blood administered and percent of patients who had a hemorrhagic diathesis. The numbers in parentheses represent the number of patients at each data point. (From Miller RD. Transfusion therapy and associated problems. *Reg Refresher Courses Anesthesiol*. 1973;1:101.)

largest number of platelets per donation. More than 80% of the platelets can be given by platelet-rich plasma, which has half of the volume of a unit of blood. However, because most blood banks only have components, platelet concentrates are frequently recommended. Platelet concentratestes are contained in a 50-mL unit and provide approximately 70% of the platelets in a unit of blood. In a 70-kg person, approximately 10 units of platelet concentrates are required to increase the platelet count by $10 \times 10^9/L$ in absence of a consumptive process. Although logistically difficult to obtain, fresh blood is extremely effective in treating transfusion-induced coagulopathies. Lavee and associates²³² found that 1 unit of fresh whole blood was as effective as, if not superior to, 8 to 10 platelet units.

Determining the plasma fibrinogen level is useful because this coagulation factor does not decrease in whole blood. If the in vivo plasma fibrinogen level is low (<150 mg/dL), it is not a result of a dilutional coagulopathy and strongly suggests DIC or a DIC-like syndrome. DIC is likely with thrombocytopenia, hypofibrinogenemia, and lysis of clot.²²⁸ With much less plasma, dilution of certain coagulation values may be more profound with the use of PRBCs rather than whole blood. With use of PRBCs, fibrinogen levels decreased significantly in contrast to use of whole blood, in which fibrinogen levels remained unchanged unless DIC is present (Fig. 49.10).²³³

An algorithm for the evaluation and initial therapy of a patient with a suspected coagulopathy is given in Fig. 49.11 (see also the section on blood transfusions, pharmacology, and hemostasis).

Citrate Intoxication and Hyperkalemia

Citrate intoxication leads to hypocalcemia, dysrhythmia, and hypotension due to the sequestration of ionized calcium by citrate. The probability of citrate intoxication is increased in pediatric populations²³⁴ and in the setting of hyperventilation, liver disease, and liver transplantation. Infusion of more than 1 unit of blood every 10 minutes can lead to decreasing ionized Ca^{2+} levels. Even at these rates of infusion, ionized calcium levels do not decrease enough to cause bleeding. Citrate reactions in the setting of apheresis for donation of blood components, however, are more common and in one study occurred in more than 5% of donations.²³⁵

Similar to citrate intoxication, hyperkalemia as a result of transfusion is relatively rare. Although hyperkalemia is occasionally reported,^{234,236} large amounts of blood must be given. Even though serum K^+ levels may be as high as 19 to 50 mEq/L in blood stored for 21 days,²³⁷ the net gain of K^+ is

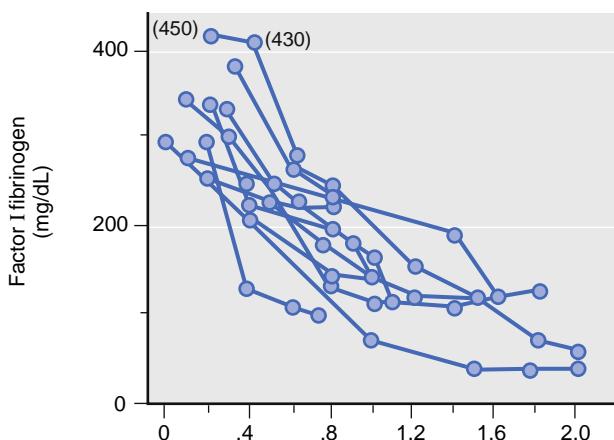


Fig. 49.10 Decreases in fibrinogen level as blood volume is replaced with Adsol-packed red blood cells and crystalloid solutions. Each patient is represented by a solid line. (From Murray DJ, Olson J, Strauss R, et al. Coagulation changes during packed red cell replacement of major blood loss. *Anesthesiology*. 1988;69:839.)

approximately only 10 mEq/L when the loss of K^+ via blood loss is taken into account. For clinically significant hyperkalemia to occur, banked blood must be given at a rate of 120 mL/minute or more. Although still rare, hyperkalemia can occur more frequently in patients with impaired renal function.²³⁸

Temperature

Administration of blood that has been stored at 4°C can decrease the recipient's temperature and should be avoided if possible due to complications from hypothermia. Hypothermia can interfere with the coagulation process. Even small decreases in body temperature can significantly impair coagulation factors and platelet function.²³⁹ If the temperature decreases to less than 30°C, ventricular irritability and cardiac arrest may occur. Shivering from even mild hypothermia increases metabolic demands and is counterproductive to tissue perfusion, especially in settings where anemia or hypoperfusion is contributing to tissue ischemia.²⁴⁰

Workup and Initial Therapy for Coagulopathy

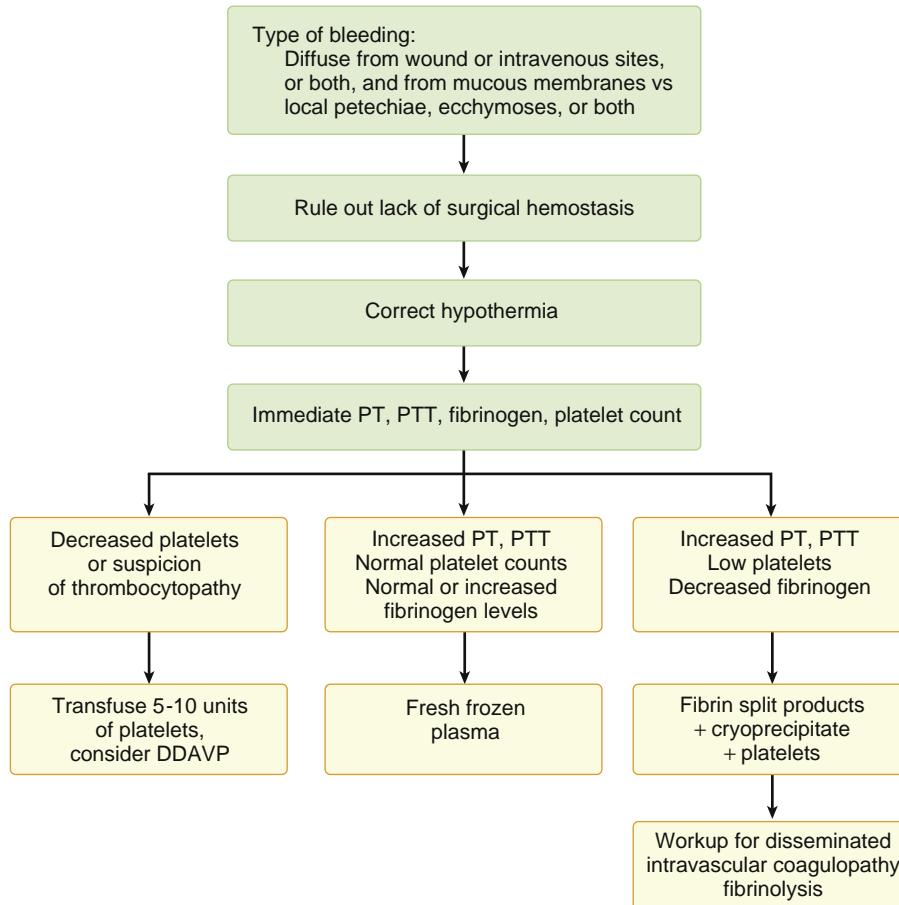


Fig. 49.11 Algorithm for the evaluation and initial therapy of a patient with suspected perioperative coagulopathy. The evaluation is based on the clinical scenario and is affected by the type and location of injury, the amount of fluid administered, and the age and body temperature of the patient. DDAVP, 1-Deamino-8-D-arginine vasopressin, a vasopressin analogue also known as desmopressin acetate; PT, prothrombin time; PTT, partial thromboplastin time. (Modified from Habibi S, Corrison DB, McDermott JC, et al. Trauma and massive hemorrhage. In: Muravchick S, Miller RD, eds. *Atlas of Anesthesia: Subspecialty Care*. New York: Churchill Livingstone; 1998.)

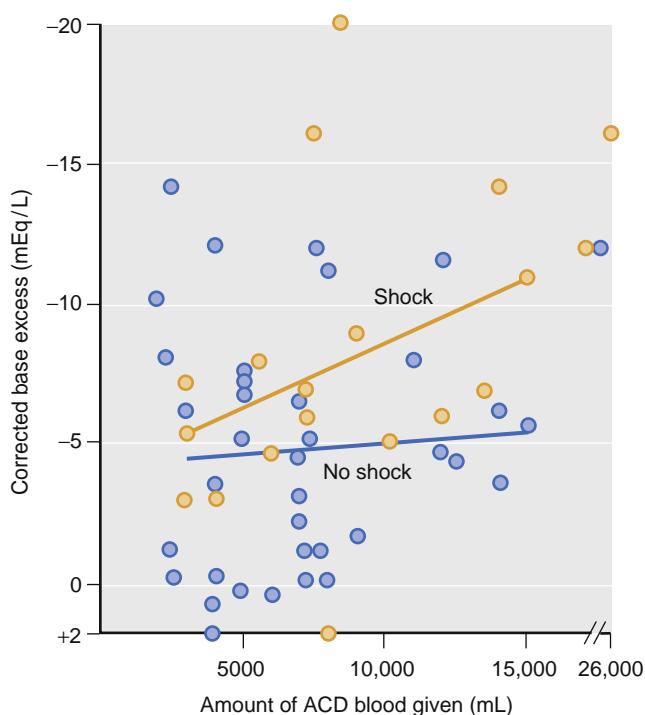


Fig. 49.12 Correlation between the amount of blood administered (milliliters) and intraoperative base excess. ACD, Acid citrate dextrose. (From Miller RD, Tong MJ, Robbins TO. Effects of massive transfusion of blood on acid-base balance. *JAMA*. 1971;216:1762.)

Maintaining a patient's normal temperature is considered to be increasingly important. Decreases in body temperature can be prevented by warming the blood to body temperature before transfusing. Perhaps the safest and most common method of warming blood is to pass it through plastic coils or plastic cassettes in a warm water (37°C - 38°C) bath or warming plates. These heat exchangers should have upper (e.g., 43°C) and lower (e.g., 33°C) temperature limits.

Acid-Base Abnormalities

The pH of most storage media is very acidic (e.g., pH 5.5 for CPD). When this solution is added to a unit of freshly drawn blood, the pH of the blood immediately decreases from 7.4 to 7.1. As a result of accumulation of lactic and pyruvic acids by RBC metabolism and glycolysis, the pH of bank blood continues to decrease to approximately 6.9 after 21 days of storage. A large portion of the acidosis can be accounted for by the carbon dioxide partial pressure (PCO_2) of 150 to 220 mm Hg. PCO_2 is high mainly because the plastic container of blood does not provide an escape mechanism for carbon dioxide. With adequate ventilation in the recipient, the high PCO_2 should be of little consequence.

Even when the PCO_2 is returned to 40 mm Hg, a metabolic acidosis can be still present in blood (see Table 49.4). The metabolic acid-base response to blood transfusion can be quite variable (Fig. 49.12).²⁴¹ The empirical administration of sodium bicarbonate is not indicated because of these unpredictable acid-base changes, but administration should be guided by analyses of arterial blood gases.²⁴² Blood transfusions provide citrate, which can lead to the

endogenous generation of bicarbonate. In some patients, this leads to a significant incidence of metabolic alkalosis after blood transfusions.²⁴²

Transfusion Reactions

HEMOLYTIC TRANSFUSION REACTION

One of the most catastrophic transfusion reactions is intravascular hemolysis. Intravascular hemolysis occurs when there is a direct attack on transfused donor cells by recipient antibody and complement. Such a reaction can occur from infusion of as little as 10 mL of blood.²⁴³ If properly treated, death is rare.²⁴⁴ However, prevention of renal failure and DIC is crucial. Hemolytic transfusion reactions involving extravascular RBC destruction are generally less serious than those of the intravascular variety. In these cases, recipient antibody coats but does not immediately hemolyze the transfused RBCs and destruction occurs primarily in the reticuloendothelial system.

Since 1975, the FDA has required that all fatal reactions occurring in blood recipients or donors be reported within 24 hours by telephone or within 7 days in writing by all FDA-registered transfusion services. From 1976 to 1985, 328 deaths were reported and analyzed.²⁴⁵ Of these deaths, 159 were acute hemolytic reactions and 23 from delayed reactions. Of the 159 deaths from acute hemolytic reactions, 137 were caused by errors involving ABO incompatibility. More than half of these errors occurred after the blood had been issued by the blood bank and were committed by practitioners administering blood products to the patient in the operating room, emergency department, ICU, or ward. In 2011, the incidence of an acute hemolytic transfusion reaction resulting from ABO incompatibility was 1:1200 to 1:190,000.²⁴⁶ The incidence of hemolytic transfusion reactions is sufficient enough that The Joint Commission²⁴⁴ requires peer-review programs to reduce transfusion errors and complications. Specifically, two patient identifiers and confirmation of the correct blood product are required before a blood product can be given. New technologies are being used to facilitate a decreased incidence of transfusion-related errors such as barcode scanning of blood prior to administration.

Signs and Symptoms

The classic signs and symptoms (Table 49.16) of a hemolytic transfusion reaction—chills, fever, chest and flank pain, and nausea—are masked by anesthesia. Under general anesthesia, hemoglobinuria, bleeding diathesis, or hypotension may be the only clue. The presenting sign is usually hemoglobinuria. As little as 50 mL of incompatible blood may exceed the binding capacity of haptoglobin, which is a protein that can bind approximately 100 mg of Hb/100 mL of plasma. Usually, free hemoglobin circulates as a complex with haptoglobin, which is cleared by the reticuloendothelial system (Fig. 49.13). A sample of plasma that contains 2 mg/dL of Hb is faintly pink or light brown. When the level of Hb reaches 100 mg/dL, the plasma is red. When the level of plasma Hb reaches 150 mg/dL, hemoglobinuria occurs. In general, the quantity of the free Hb in the plasma correlates with the volume of incompatible blood transfused.

TABLE 49.16 Frequency and Signs and Symptoms of Hemolytic Transfusion Reactions in 40 Patients

Sign or Symptom	No. Patients
Fever	19
Fever and chills	16
Chest pain	6
Hypotension	6
Nausea	2
Flushing	2
Dyspnea	2
Hemoglobinuria	1

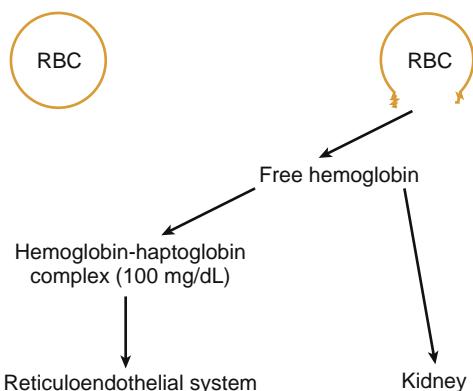


Fig. 49.13 Schematic representation of the effect on hemolyzed erythrocytes (RBC) due to the administration of incompatible blood.

Complement activation also causes release of various substances, including histamines and vasoactive amines. The symptoms can be so alarming that cessation of blood is indicated, even if Hb is not seen in plasma. Laboratory tests that should be performed if a hemolytic transfusion reaction is suspected include serum haptoglobin, plasma and urine Hb, bilirubin, and direct antiglobulin determinations. The direct antiglobulin test can confirm the presence of hemolytic transfusion reaction because it shows that antibody is attached to transfused donor RBCs.

Treatment

Although several consequences of intravascular hemolysis are possible, the renal and coagulation systems are affected the most. The cause of acute renal failure from intravascular hemolysis is likely due to precipitation of Hb in the form of acid hematin in the distal tubule causing mechanical tubular blockage. The magnitude of the precipitation probably is inversely related to the pH and volume of urine flow. Therapy should be directed toward maintaining urinary output in excess of 75 mL/h by generous administration of intravenous fluids and diuretics. One approach is summarized in **Box 49.6** and includes the administration of crystalloids to maintain adequate intravascular volume while initially administering mannitol. If this is ineffective, the dose of mannitol may be increased or the use of more potent diuretics, such as furosemide may be required to maintain adequate urinary output. Alkalization of the urine to prevent precipitation of acid hematin in the distal tubules is of

BOX 49.6 Steps in the Treatment of a Hemolytic Transfusion Reaction

1. Stop the transfusion.
2. Maintain the urine output at a minimum of 75-100 mL/h by the following methods:
 - a. Administer fluids intravenously and possibly mannitol
 - b. Administer furosemide if intravenous fluids and mannitol are ineffective
3. Alkalize the urine
4. Assay urine and plasma hemoglobin concentrations.
5. Determine platelet count, prothrombin time, partial thromboplastin time, and serum fibrinogen level.
6. Return unused blood to blood bank for repeat crossmatch.
7. Send patient's blood and urine sample to blood bank for examination.
8. Prevent hypotension to ensure adequate renal blood flow.

questionable value but is easy and therefore recommended. DIC commonly occurs with hemolytic transfusion reactions, probably because RBC stroma is severed, releasing erythrocytin, which activates the intrinsic system of coagulation and leads to fibrin formation. Subsequently, platelets and factors I, II, V, and VII are consumed. As soon as a hemolytic transfusion reaction is recognized, platelet count, PT, and PTT should be obtained to provide baseline values with which subsequent laboratory values can be compared. Hypotension during a hemolytic transfusion reaction may result from activation of the kallikrein system.²⁴⁷

DELAYED HEMOLYTIC TRANSFUSION REACTION (IMMUNE EXTRAVASCULAR REACTION)

An immediate hemolytic transfusion reaction often is a dramatic event because the concentration of the antibody is high enough to cause immediate and appreciable RBC destruction. In many cases of hemolytic transfusion reaction, the transfused donor cells may survive initially, but after a variable delay (2-21 days), they are hemolyzed.²⁴⁸ This type of reaction occurs mainly in recipients sensitized to RBC antigens by previous blood transfusions or pregnancy. As a result, this delayed reaction is more common in females with a known disposition for alloimmunization. These delayed hemolytic transfusion reactions occur when the level of antibody at the time of transfusion is too low to be detected. RBC destruction occurs only when the level of antibody is increased after a secondary stimulus (i.e., anamnestic response). These delayed reactions are often manifested only by a decrease in the posttransfusion Hct. Jaundice and hemoglobinuria can occur in these patients and can cause some impairment in renal function, but only rarely do they lead to death. Unlike immediate reactions, antibodies most commonly involved in delayed hemolytic reactions are those in the Rh and Kidd systems rather than the ABO system. Although improved blood-banking procedures have decreased the incidence of immediate hemolytic transfusion reactions, the delayed hemolytic reaction may not be preventable, because pretransfusion testing is unable to detect very low levels of antibody present in potential blood recipients.

The surgical team should include in their differential diagnosis a delayed hemolytic transfusion reaction in any patient who has an unexplained decrease in Hb 2 to 21 days

after a transfusion, even without obvious manifestation of hemolysis. This is especially important in a postoperative patient when the decrease in Hb may be attributed to postoperative bleeding and lead to a return to the operative room for additional surgery.

TRANSFUSION-RELATED ACUTE LUNG INJURY

When a blood transfusion is implicated as the cause of ARDS, it is classified as TRALI. From 2012 to 2016, TRALI was the most common cause of transfusion-related mortality reported to the FDA¹¹⁸ (see Table 49.8). Although it is underdiagnosed and underreported,²⁴⁹⁻²⁵¹ the incidence of TRALI varies from 1.3% to 3%, depending on the surgical procedures. In addition, larger transfused blood volumes appear to be associated with an increased incidence.²⁵² TRALI occurs in the absence of excessive intravascular volume and cardiac failure²⁵³ and manifests as noncardiogenic pulmonary edema. Symptoms and signs usually appear within 6 hours after transfusion with a clear temporal relationship to the transfusion.²⁴⁹ Fever, dyspnea, fluid in the endotracheal tube, and severe hypoxia are typical. During anesthesia, a persistent decrease of oxygen saturation can herald its insidious onset. Although the chest radiograph reveals pulmonary edema, excessive circulatory volume (i.e., left atrial hypertension) is not present. All blood components, especially FFP, are implicated as inciting factors. The only specific therapy is to stop the transfusion and institute supportive measures. The blood bank should be notified to provide blood components from a different donor and to quarantine all units from the donor in question. All records should be reexamined, and the results of the patient's HLA testing should be evaluated if possible. Although most patients recover within 96 hours, TRALI remains the leading cause of transfusion-related death.

Identified risk factors include higher interleukin-8 (IL-8) levels, liver surgery, chronic alcohol abuse, shock, higher peak airway pressures while being mechanically ventilated, smoking, and positive fluid-balance.²⁵⁴ As far as blood products are concerned, receipt of plasma or whole blood from female donors, especially multiparous donors, was identified as the most common risk factor. The decreased use of plasma from female donors has markedly reduced the incidence of TRALI.

TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD

Unlike TRALI, TACO refers to an excessive administration volume of blood leading to pulmonary edema with evidence for increased left-sided cardiac filling pressures (e.g., elevated B-type natriuretic peptide/protein, elevated central venous pressure, new or worse left heart failure). TRALI and TACO have overlapping clinical findings and can be easily confounded (Table 49.17). In 2016 the FDA noted an increase in the case fatalities attributable to TACO, perhaps as a result of the increased reporting and improved understanding of the two entities.¹¹⁸

Recently, a retrospective analysis demonstrated a decreasing incident rate—with a rate of 5.5% in 2004 and 3% in 2011.^{254a} Reasons for the decline are unclear but may be related to a more restrictive transfusion practice, thus limiting the exposure of a patient to potential volume overload;

TABLE 49.17 Comparison of definitions of TACO and TRALI per CDC Guidelines.

TACO	TRALI
<p>New onset or exacerbation of 3 or more of the following within 6 h of cessation of transfusion:</p> <ul style="list-style-type: none"> ■ Acute respiratory distress (dyspnea, cough, orthopnea) ■ Elevated brain natriuretic peptide (BNP) ■ Elevated central venous pressure (CVP) ■ Evidence of left heart failure ■ Evidence of positive fluid balance ■ Radiographic evidence of pulmonary edema 	<p>No evidence of acute lung injury prior to transfusion AND ALI onset during or within 6 h of cessation of transfusion AND Hypoxemia defined by any of these methods</p> <ul style="list-style-type: none"> ■ $\text{PaO}_2/\text{FiO}_2$ less than or equal to 300 mm Hg ■ Oxygen saturation less than 90% on room air ■ Other clinical evidence AND Radiographic evidence of bilateral infiltrates without evidence of left atrial hypertension (i.e., circulatory overload)

Adapted from the CDC, National Healthcare Safety Network Biovigilance Component. Hemovigilance Surveillance Protocol v2.5.2. April 2018.

although this latter statement is purely conjecture and not supported by the findings of Clifford and associates. Besides volume transfused, other risk factors included advancing age and intraoperative fluid balance. Interestingly, leukoreduction may play a role in the reduced incidence of TACO, suggesting additional mechanisms of this entity's pathophysiology.²⁵⁵ Diuretics may be helpful, but in both cases supportive measures such as lung protective ventilation should be instituted.

NONHEMOLYTIC TRANSFUSION REACTIONS

Nonhemolytic reactions to blood transfusions usually are not serious and are categorized into febrile or allergic. The most common adverse reactions to blood transfusions are febrile reactions. The symptoms consist of chills, fever, headache, myalgia, nausea, and nonproductive cough occurring shortly after a blood transfusion and are caused by pyrogenic cytokines and intracellular contents released by donor leukocytes. Use of leukoreduced blood has lowered the incidence of febrile reactions.²⁵⁶ Less frequently, the patient may have other symptoms such as hypotension, chest pain, vomiting, and dyspnea. Even pulmonary infiltrations with radiographic evidence of pre hilar nodule formation and lower lung infiltrates along with overt pulmonary edema have been reported.²⁵⁶ A direct antiglobulin test readily differentiates a hemolytic reaction from a febrile reaction because this test rules out the attachment of antibody to transfused donor RBCs. More serious complications may need to be ruled out (e.g., hemolytic or septic reactions), which may also be associated with fever and chills. No clear consensus exists on whether the transfusion should be terminated when a febrile reaction occurs.^{257,258}

Allergic reactions can be minor, anaphylactoid, or anaphylactic. An anaphylactoid reaction is clinically similar to anaphylaxis, but it is not mediated by IgE. Most allergic transfusion reactions are minor and caused by the presence of foreign protein in the transfused blood. The most common symptom is urticaria associated with itching. Occasionally, the patient has facial swelling. The transfusion usually does

not need to be discontinued. Antihistamines are used to relieve the symptoms of the allergic reaction. Infrequently, a more severe form of allergic reaction involving anaphylaxis occurs in which the patient has dyspnea, hypotension, laryngeal edema, chest pain, and shock. These are anaphylactic reactions caused by the transfusion of IgA to patients who are IgA deficient and have formed anti-IgA. This type of reaction does not involve red cell destruction and occurs very rapidly, usually after the transfusion of only a few milliliters of blood or plasma. Patients who experience anaphylactic reactions should be given transfusions with washed RBCs so that all traces of donor IgA have been removed or with blood that lacks the IgA protein.

OTHER ADVERSE EFFECTS OF BLOOD TRANSFUSION

Transfusion-Associated Graft-Versus-Host Disease

Transfusion-associated graft-versus-host disease (GVHD) is caused by engraftment of donor lymphocytes from transfused blood products, initiating an immune reaction against recipient tissues. Severely immunocompromised patients are at risk. Also, directed donations from first- or second-degree relatives are at risk because transfused lymphocytes with shared HLA haplotypes cannot be recognized and eliminated.²⁵⁹ A generalized rash, leukopenia, and thrombocytopenia occur. Sepsis and death usually result. Irradiation of blood can prevent transfusion-associated GVHD from occurring, although one case reported it occurring despite leukocyte filtering.²⁶⁰

Transfusion-Related Immunomodulation

Homologous (allogeneic) blood transfusion exerts a nonspecific immunosuppressive action on the recipient. More than 150 clinical studies have tried to relate allogeneic blood transfusions to recurrence of resected cancers, postoperative infections, and virus activation, with the conclusion that adverse effects may be caused by transfusion-related immunomodulation. Although the conclusions of these studies are contradictory and inconclusive, universal leukocyte reduction of RBCs is moving forward.^{261,262}

OTHER NONINFECTIOUS RISKS OF BLOOD TRANSFUSIONS

Table 49.18 lists some of the less common noninfectious risks of blood transfusions.

1. Microchimerism: Chimerism refers to more than one cell line in an individual organism. Specifically, donor lymphocytes may persist in a patient. The outcome of patients with microchimerism is not known.
2. Posttransfusion purpura: This refers to recipient alloantibodies attacking donor platelet antigens and is treated with intravenous immunoglobulin.
3. Hypotensive transfusion reactions: Activation of the coagulation pathway activates production of bradykinin and allergic reactions.
4. Transfusion-related AKI.
5. Alloimmunization: Only 2% to 8% of recipients who are chronically transfused develop RBC alloantibodies.⁵
6. HLA alloimmunization and human platelet antigen (HPA) alloimmunization: HLA alloimmunization refers

to patients whose platelet counts become refractory to transfusions because of antibodies directed against HLA class I antibodies. HPA alloimmunization is platelet refractoriness from antibodies against platelet antigens (HPA antibodies).

7. Iron overload: This complication is the result of chronic transfusion therapy. Iron begins to deposit into vital organs. In the absence of adequate chelation of iron, fatal liver or heart dysfunction, or both, can occur.
8. Adverse ocular reaction: In 1997, 112 cases of bilateral conjunctival erythema occurred within 24 hours of transfusion. The Centers for Disease Control and Prevention (CDC) studied 49 other cases in 1997 and 1998 and concluded that they were toxic reactions to a chemical or material used in the blood collection filtration system, most likely a leukocyte-reducing filter system.²⁶³

Leukoreduction and Irradiation of Blood Transfusions

GENERAL CONSIDERATIONS

Universal leukoreduction has been implemented because of some anticipated benefits. The chances of a febrile reaction can be reduced, especially in patients who are already alloimmunized from pregnancy. The risk for HLA alloimmunization from blood transfusions can be reduced, minimizing refractoriness to platelet transfusions, and the risk for CMV can be reduced. Leukoreduction can also decrease transmission of variant Creutzfeldt-Jakob disease, leukocyte-induced immunomodulation, and even postoperative mortality. In 2001, the case for and against universal leukoreduction was debated.^{264,265} As of 2004, these anticipated benefits were not confirmed, despite numerous studies attempting to do so,²⁶⁶ but a “may help, won’t hurt” approach has been used to justify universal leukoreduction.²⁶⁴

IRRADIATED BLOOD PRODUCTS

Blood products are irradiated to prevent the proliferation of donor T lymphocytes in blood, which are the immediate cause of transfusion-associated GVHD.²⁶⁷ Fewer than one per million transfusions result in transfusion-associated GVHD, but this disease has a fatality rate greater than 90%. Only cellular products (RBCs, platelets, and granulocytes), but not noncellular products (thawed frozen plasma and cryoprecipitate), need be irradiated. Indications for irradiation include:

1. Fetal recipients of intrauterine transfusions
2. Infants younger than 4 months of age
3. Critically ill children
4. Children younger than 1 year of age undergoing extracorporeal membrane oxygenation/extracorporeal cardiac life support
5. Recipients of cellular components known to be from a blood relative
6. Recipients of cellular components whose donor is selected for HLA compatibility
7. Recipients who have undergone marrow or peripheral blood progenitor cell transplantation

TABLE 49.18 Noninfectious Hazards of Transfusion

Transfusion Reaction	Incidence (per 10 ⁵ Transfusions)	Etiology	Therapy	Prevention
Febrile	All components: 70-6800	Storage-generated proinflammatory cytokines Patient antileukocyte antibodies bind to donor leukocytes	Stop transfusing Give antipyretics Supportive care	Prestorage leukoreduction
TACO	All components: 16.8-8000 Practice-dependent	Circulatory overload Patients with cardiac or renal disease, infants, and the critically ill are at increased risk	Stop transfusing Give diuretics Oxygen	Identify patients at high risk Transfuse slowly
TRALI	Erythrocytes: 10-20 Platelets/plasma: 50-100	Passive transfusion of donor antibodies Storage-generated toxic lipids	Supportive care	Remove high-risk donors from the donor pool
Allergic	All components: 3000 mild, 2 anaphylactic	Mild reactions: Transfusion of soluble antigens in donor plasma Anaphylaxis: IgA deficiency or other recipient protein deficiency	Stop transfusing ASA monitors Large-bore IV access Epinephrine Antihistamines Supportive care	Pretransfusion antihistamine use remains common practice despite limited evidence
Hemolytic	Erythrocytes: 1.1-9.0	Donor antibodies bind to patient erythrocytes Patient antibodies bind to donor erythrocytes	Stop transfusing Repeat matching Supportive care Treat DIC	Standard operating procedures
TRIM	Unknown	The mechanism is unknown but may depend on the presence of donor leukocytes	Treat complications (e.g., infection, malignancy)	Prestorage leukocyte reduction may be beneficial, but this approach is controversial
Microchimerism	All components: 5000-10,000 massive transfusion	Permanent residence of donor cells in recipient	Unknown	Unknown
Posttransfusion purpura	All components: 2	Recipient alloantibodies attack donor platelet antigens	IVIG	Avoid units positive for implicated HPA antigens in patients with a history of PTP
Hypotensive	Unknown	Production of kinins by the activation of the contact system Patients on ACE inhibitors are at increased risk	Stop transfusing ASA monitors Large-bore IV access Supportive care	Avoid the use of negatively charged leukocyte reduction filters
Graft-versus-host	Varies by patient population	Transfusion into immunocompromised host Transfusion of donor cells closely matching HLA type	No consensus exists Consider bone marrow transplant	Gamma irradiation of cellular products

ACE, Angiotensin converting enzyme; ASA, American Society of Anesthesiologists; DIC, disseminated intravascular coagulation; HLA, human leukocyte antigen; HPA, human platelet alloantigen; IgA, immunoglobulin A; IV, intravenous; IVIG, intravenous immunoglobulin; PTP, posttransfusion purpura; TACO, transfusion associated circulatory overload; TRALI, transfusion-related acute lung injury; TRIM, transfusion-related immunomodulation.

Reprinted from Hillyer CD, Silberstein LE, Ness PM, et al. *Blood Banking and Transfusion Medicine: Basic Principles and Practice*. 2nd ed. Philadelphia: Elsevier; 2007:678-679.

Irradiation is not necessary for patients undergoing routine nonmyeloablative chemotherapy for solid tumors and solid organ transplant patients receiving routine posttransplant immunosuppressive therapy.

Informed Consent

Before any transfusion is given, informed consent should be obtained from the patient or guardian. What constitutes consent varies across the United States and is still changing. If a patient is injured by a transfusion administered without a valid consent, damages may be recovered even though the defendant did everything properly.¹⁴⁶ Many years ago, the *Paul Gann Blood Safety Act* was passed in California. This law mandated that patients be informed of the risks of blood transfusions and of any alternatives. The changes in transfusion medicine should

lead to additional education for clinicians who administer blood products to ensure they are compliant with current laws and regulations. Local hospital transfusion medicine committees can provide clinicians with such information.

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References

- Karafin MS, et al. *Transfusion*. 2017;57(12):2903–2913.
- Miller RD, et al. *Ann Surg*. 1971;174:794.
- Miller RD. *Anesthesiology*. 2009;110:1412–1416.
- Spahn DR. *Anesthesiology*. 2006;104:905.
- Hendrickson JE, Hillyer CD. *Anesth Analg*. 2009;108:759–769.
- Shander A, et al. *Transfus Med Rev*. 2011;25:232–246.
- Lelubre C, et al. *Transfusion*. 2009;49:1384.
- Yazer MH, et al. *J Trauma Acute Care Surg*. 2016;81:21.
- Miller RD. *Anesth Analg*. 2013;116:1392.
- Spinella PC, Cap AP. *Curr Opin Hematol*. 2016;23:536.
- Desai N, et al. *Anesth Analg*. 2018;127:1211.
- Society for the Advancement of Blood Management. *A Guide to Patient Blood Management*; 2016. <https://www.sabm.org/wp-content/uploads/2018/08/Guide-to-PBM-2016.pdf>. Accessed 28 March 2019.
- Shander A, Goodnough LT. *Annals of Internal Med*. 2019;170:125–126.
- Ellingson KD, et al. *Transfusion*. 2017;57(suppl 2):1588–1598.
- Gupta PB, et al. *Anesthesiology*. 2018;129:1082.
- Mukhtar SA, et al. *Anaesth Intensive Care*. 2013;41:207.
- Liesbacher K, et al. *AnästhesiIntensivmed*. 2013;54:295.
- WHO. *Global Status Report on Blood Safety and Availability* 2016. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.
- WHO Expert Group. *Vox Sang*. 2012;103:337–342.
- Lacetera N, et al. *Science*. 2013;342:692.
- Chell K, et al. *Transfusion*. 2018;58:242–254.
- Dhingra N. *Science*. 2013;342:691–692.
- Haire B, et al. *Transfusion*. 2018;58:816–822.
- <https://www.fda.gov/%20EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm>. Accessed 10 December 2018.
- Tong MJ, et al. *N Engl J Med*. 1995;332:1463–1466.
- Centers for Disease Control and Prevention. Hepatitis C FAQs for the Public. <https://www.cdc.gov/hepatitis/hcv/cfaq.htm>. Accessed 16 March 2019.
- Preiksaitis VK, et al. *J Med Virol*. 1985;15:283–290.
- Preiksaitis JK, et al. *J Infect Dis*. 1988;157:523–529.
- Wilhelm JA, et al. *J Infect Dis*. 1986;154:169–171.
- Goodnough LT, Marques MB. *Anesthesia Analg*. 2017;124:282.
- Peterson LR, et al. *N Engl J Med*. 2016;374:1552–1563.
- Schuler-Faccini L, et al. *MMWR Morb Mortal Wkly Rep*. 2016;65:59–62.
- U.S. Food and Drug Administration. *Revised recommendations for reducing the risk of Zika virus transmission by blood and blood components*; 2018. <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf>. Accessed 8 November 2018.
- Tripple MA, et al. *Transfusion*. 1990;30:207–213.
- Moore GL, et al. *Transfusion*. 1981;21:135–137.
- Valeri CR. *N Engl J Med*. 1985;312:377–378.
- Lovric VA, et al. *Vox Sang*. 1985;49:181–186.
- Cancelas JA, et al. *Transfusion*. 2015;55:491–498.
- Kleinman S, et al. *UpToDate*. <https://www.uptodate.com/contents/practical-aspects-of-red-blood-cell-transfusion-in-adults-storage-processing-modifications-and-infusion>. Accessed Feb 7, 2019.
- Nagababu E, et al. *Transfusion*. 2016;56:1101–1111.
- Salaria ON, et al. *Anesth Analg*. 2014;118:1179–1187.
- Frank SM, et al. *Anesth Analg*. 2013;116:975–981.
- Scott AV, et al. *Anesth Analg*. 2016;122:616–623.
- Tsoi W. *VOXS*. 2016;11:49–54.
- Nishiyama T, Hayashi D. *J Anesth*. 2007;21:42–46.
- Wozniak MJ, et al. *Anesthesiology*. 2018;128:375–385.
- Wozniak MJ, et al. *Br J Anaesth*. 2017;118:689–698.
- Marik PE, Sibbald WJ. *JAMA*. 1993;269:3024–3029.
- Vamvakas EC, Carven JH. *Transfusion*. 1999;39:701–710.
- Leal-Noval SR, et al. *Anesthesiology*. 2003;98:815–822.
- Purdy RF, et al. *Can J Anaesth*. 1997;44:1256–1261.
- Koch CG, et al. *N Engl J Med*. 2008;358:1229–1239.
- Adamson JW. *N Engl J Med*. 2008;358:1295–1296.
- Wang D, et al. *Transfusion*. 2012;52:1184–1195.
- Weiskopf RB, et al. *Anesthesiology*. 2006;104:911–920.
- Cata JP, et al. *Mayo Clin Proc*. 2011;86:120–127.
- Saager L, et al. *Anesthesiology*. 2013;118:51–58.
- Heddle NM, et al. *N Engl J Med*. 2016;375:1937.
- Steiner ME, et al. *N Engl J Med*. 2015;372:1419.
- Cooper DJ, et al. *N Engl J Med*. 2017;377:1858.
- Lacroix J, et al. *N Eng J Med*. 2015;372:1410.
- Garraud O. *J Thoracic Dis*. 2017;9:E146–E148.
- Tobian A, et al. *N Eng J Med*. 2016;375:1995–1997.
- Goel R, et al. *Transfusion*. 2016;56:1690–1698.
- Cull DL, et al. *Surg Gynecol Obstet*. 1991;173:9–12.
- Albert K, et al. *Can J Anaesth*. 2009;56:352–356.
- Beattie WS, Wijeysundera DN. *Anesthesiology*. 2016;125(1):11–13.
- Mathru M, et al. *Anesthesiology*. 2006;105:37.
- Consensus conference. *JAMA*. 1988;260:2700–2703.
- Le Manach Y, Syed S. *Anesthesiology*. 2012;117:1153–1155.
- Corwin HL, et al. *Chest*. 1995;108:767–771.
- Hébert PC, et al. *JAMA*. 1995;273:1439–1444.
- Bishop MH, et al. *J Trauma*. 1995;38:780–787.
- Frank SM, et al. *Anesthesiology*. 2012;117:99–106.
- McNamara D. *Anesthesiology News* 32. 2012.
- World Alliance for Patient Safety. *WHO Guidelines for Safe Surgery*; 2008.
- Solon JG, et al. *J Eval Clin Prac*. 2013;19:100–105.
- Stovener J. *Anesthesiology News* 14. 2012.
- Berkow L, et al. *Anesth Analg*. 2011;113:1396–1402.
- Miller RD, et al. *Anesth Analg*. 2011;112:858–863.
- Xu T, et al. *Crit Care Med*. 2016;44:e344–e352.
- Bridges E, et al. *Shock*. 2016;46:55–60.
- Miller RD, et al. *J Anesth*. 2012;26:845–850.
- Miller RD, et al. *Anesth Analg*. 2014;118:766–771.
- Giraud B, et al. *Br J Anaesth*. 2013;111:946–954.
- Barker SJ, et al. *Anesth Analg*. 2016;122:565–572.
- Frasca D, et al. *Anaesthesia*. 2015;70:803–809.
- Kolotiniuk NV, et al. *J Cardiothor Vasc Anesthesia*. 2018;32:1638–1641.
- Musallam KM, et al. *Lancet*. 2011;3278:1396–1407.
- Karkouti K, et al. *Can J Anesth*. 2015;62:377–384.
- Kozek-Langenecker SA, et al. *Eur J Anaesthesiology*. 2017;34:332–395.
- Froessler B, et al. *Ann Surg*. 2016;264:41–46.
- Keeler BD, et al. *Br J Surg*. 2017;104:214–221.
- Weltert L, et al. *Transfusion*. 2015;55:1644–1654.
- Unger EF, et al. *N Engl J Med*. 2010;362:189–192.
- Karkouti K, et al. *Anesthesiology*. 2011;115:523–530.
- Goodnough LT, Shander A. *Anesth Analg*. 2013;116:15–34.
- Levy JH. *Anesthesiology*. 2011;114:1016–1018.
- Papageorge CM, et al. *Surgery*. 2017;161:1067–1075.
- Carson JL, et al. *JAMA*. 2016;316:2025–2035.
- Carson JL, et al. *N Engl J Med*. 2011;365:2453–2462.
- Shorr AF, et al. *Crit Care Med*. 2004;32:666–674.
- Taylor RW, et al. *Crit Care Med*. 2006;34:2302–2308.
- Ely EW, Bernard GR. *N Engl J Med*. 1999;340:467–468.
- Hébert PC, Ferguson DA. *JAMA*. 2002;288:1525–1526.
- Vincent JL, et al. *JAMA*. 2002;288:1499–1507.
- Walsh TS, McClelland DBL. *Br J Anaesth*. 2003;90:719–722.
- McCrossan L, Masterson G. *Br J Anaesth*. 2002;88:6–9.
- Mazer CD, et al. *N Eng J Med*. 2017;377:2133–2144.
- Holst LB, et al. *N Engl J Med*. 2014;371:1381–1391.
- Rohde HM, et al. *JAMA*. 2014;311:1317–1326.
- Hovaguimian F, Myles PS. *Anesthesiology*. 2016;125:46–61.
- Villanueva C, et al. *N Engl J Med*. 2013;368:11–21.
- Laine L. *N Engl J Med*. 2013;368:75–76.
- Weiskopf RB. *Transfusion*. 1998;38:517–521.
- American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Practice Guidelines for Perioperative Blood Management*. *Anesthesiology*. 2015;122:241.
- Thiel T, et al. *New Engl J Med*. 2013;368:487–489.
- <https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM59-8243.pdf>. Accessed 22 March 2019.
- Morrow JF, et al. *JAMA*. 1991;266:255–258.
- Hong H, et al. *Blood*. 2016;127:496.
- Benjamin RJ. *Blood*. 2016;127:380.
- Dunne WM, et al. *Transfusion*. 2005;45:1138–1142.
- Rebulla R, et al. *N Engl J Med*. 1997;337:1870–1875.
- Horlocker TT, et al. *Reg Anesth Pain Med*. 4th ed. 2018;43:263–309.
- Baharoglu MI, et al. *Lancet*. 2016;387:2605.
- Teixeira PG, et al. *J Trauma*. 2009;66:693–697.
- Kruskall MS. *N Engl J Med*. 1997;337:1914–1915.
- Scott E, et al. *Transfusion*. 2009;49:1584–1591.
- Cardigan R, et al. *Transfusion*. 2005;45:1342–1348.
- Hall DP, et al. *Br J Anaesthesia*. 2012;109:919–927.
- Muller MC, et al. *Transfusion*. 2015;55:26.
- Radwan ZA, et al. *JAMA*. 2013;148:170–175.

133. Sperry JL, et al. *N Engl J Med*. 2018;379:315.
134. Holcomb JB, et al. *J Trauma*. 2011;71:S315–S317.
135. Kornblith LZ, et al. *J Trauma Acute Care Surg*. 2014;77:818.
136. Holcomb JB, et al. *JAMA Surg*. 2013;148:127–136.
137. Bhangu A, et al. *Injury*. 2013;44:1693–1699.
138. Holcomb JB, et al. *JAMA*. 2015;313(5):471–482.
139. Pasquier P, et al. *Anesth Analg*. 2013;116:155–161.
140. Kerins DM. *Am J Med Sci*. 1994;307:218.
141. Tremper KK, et al. *N Engl J Med*. 1982;307:277–283.
142. Spahn DR, et al. *Anesthesiology*. 2002;97:1338–1349.
143. Hermann J, et al. *Anesthesiology*. 2007;107:273–280.
144. Crawford MW, et al. *Anesthesiology*. 2007;107:281–287.
145. Wahr JA. *Anesth Analg*. 2002;94:799–808.
146. Natanson C, et al. *JAMA*. 2008;299:2304–2312.
147. Fergusson DA, McIntyre SL. *JAMA*. 2008;299:2324–2326.
148. Levy J. *Expert Opin Biol Ther*. 2003;3:509–517.
149. Davis JM, et al. *Transfusion*. 2018;58:132.
150. DeSimone, RA, et al. 2018; 58:2297-2300.
151. Goodnough LT, et al. *Transfusion*. 2003;43:668.
152. Vassallo R, et al. *Transfusion Med Reviews*. 2015;29:268–275.
153. AABB. *Standards for Blood Banks and Transfusion Services*. 29th ed. Bethesda MD: AABB Press; 2014.
154. Kiss JE, et al. *JAMA*. 2015;313:575–583.
155. Henry DA, et al. *Cochrane Database Syst Rev*. 2002;(2):CD003602.
156. Popovsky MA, et al. *Transfusion*. 1995;35:734–737.
157. AuBuchon JP, et al. *Transfusion*. 1991;31:513–517.
158. Messmer K, et al. *Eur Surg Res*. 1986;18:254–263.
159. Goodnough LT, et al. *Transfusion*. 1998;38:473–476.
160. Lu SY, et al. *Anesth Analg*. 2014;118:264–268.
161. Goodnough LT, et al. *Anesth Analg*. 1994;78:932–937.
162. Goldberg J, et al. *Ann Thoracic Surg*. 2015;100:1581–1587.
163. Zhou Z, et al. *BMC Anesthesiology*. 2017;17:13.
164. Roberts, et al. *Am J Surg*. 1991;162:477.
165. Jarnagin, et al. *Ann Surg*. 2008;248:360.
166. De Haan, et al. *Ann Thoracic Surg*. 1995;59:901.
167. Barile L, et al. *Anesth Analg*. 2017;124:743.
168. Sniecinski RM, Mascha EJ. *Anesth Analg*. 2017;124:726.
169. Sebastian R, et al. *PedAnesth*. 2017;27:85–90.
170. Albu G, et al. *Anesth Analg*. 2018;126:995.
171. Crystal GJ. *J Cardiothorac Vasc Anesth*. 2015;29:320–327.
172. Kisilevsky AE, et al. *J Clin Anesth*. 2016;35:434–440.
173. AABB. *Standards for Perioperative Autologous Blood Collection and Administration*. 7th ed. AABB; 2016.
174. Sikorski RA, et al. *Vox Sanguinis*. 2017;112:499–510.
175. Williamson KR, Taswell HF. *Transfusion*. 1991;31:662.
176. Li, et al. *J Cardiothoracic Surg*. 2015;10:126.
177. Domen RE. *Transfusion*. 1998;38:296.
178. Konig G, et al. *Transfus Altern Transfus Med*. 2012;12:78–87.
179. Yazer MH, et al. *Transfusion*. 2008;48:1188–1191.
180. Tsai AG, et al. *Blood*. 2006;108(10):3603–3610.
181. Gregoretti S. *Transfusion*. 1996;36:57.
182. Bell K, et al. *Transfusion Med*. 1992;2:295.
183. Waters JH, et al. *Anesthesiology*. 2003;99(3):652–655.
184. Esper SA, Waters JH. *Blood Transfusion Med*. 2011;9:139.
185. Carless PA, et al. *Cochrane Database Syst Rev*. 2010;(3):CD001888.
186. So-Osman C, et al. *Anesthesiology*. 2014;120:839–851.
187. So-Osman, et al. *Anesthesiology*. 2014;120:852–860.
188. Lim G, et al. *Anesthesiology*. 2018;128:328–337.
189. Gilsch C, et al. *BMJ Open Quality*. 2018;7:e000270.
190. Hendrickson JE, et al. *Transfusion Med Rev*. 2014;28:137–144.
191. American Society of Anesthesiologists. *Transfusion Practices: Questions and Answers*. 3rd ed. Chicago: American Society of Anesthesiologists; 1998:8–9.
192. Chapuy CI, et al. *Transfusion*. 2015;55:1545–1554.
193. Chapuy CI, et al. *Transfusion*. 2016;56:2964–2972.
194. Murphy MF. *N Eng J Med*. 2016;375(3):295–296.
195. Boyd PR, et al. *Am J Clin Pathol*. 1980;74:694–699.
196. Coombs RR, et al. *Br J Exp Pathol*. 1945;26:255–266.
197. Walker RH. In: Polesky HF, Walker RH, eds. *Safety and Transfusion Practices*. Skokie, Ill: College of American Pathologists; 1982:79.
198. Butch SH, et al. *Transfusion*. 1994;34:105–109.
199. Daurat A, et al. *Transfus Clin Biol*. 2017;24:47–51.
200. Novis DA, et al. *Arch Pathol Lab Med*. 2017;141:255–59.
201. U.S. Food and Drug Administration. *Guidance for Industry: Computer Crossmatch*. April 2011.
202. Mazepa MA. *Am J Clin Pathol*. 2014;141:618–624.
203. Oberman AJ, et al. *Transfusion*. 1978;18:137–141.
204. Sarma DP. *JAMA*. 1980;243:1536–1538.
205. Dexter F, et al. *Anesthesiology*. 2012;116:768–778.
206. Friedman BA. *Transfusion*. 1979;19:268–278.
207. Krier DB. *Am J Med Qual*. 1996;11:68–72.
208. Frank SM, et al. *Anesthesiology*. 2013;118:1286–1297.
209. Frank SM, et al. *Anesthesiology*. 2014;121:501–509.
210. Gervin AS, Fischer RP. *J Trauma*. 1984;24:327–331.
211. Mulay SB, et al. *Transfusion*. 2013;53:1416–1420.
212. Boisen et al. *Anesthesiology*. 2015;122:191–195.
213. Goodell PP, et al. *Am J Clin Pathol*. 2010;134:202–206.
214. Fergusson DA, et al. *JAMA*. 2012;308:1443–1451.
215. Spinella PC, et al. *Anesth Analg*. 2012;115:571–578.
216. Weiskopf RB. *Anesthesiology*. 2012;116:518–521.
217. Auten JD, et al. *J Trauma Acute Care Surg*. 2015;79:790–611.
218. Erber WN, et al. *Med J Aust*. 1996;165:11–13.
219. Brohi K, et al. *Ann Surg*. 2007;245:812–818.
220. Kaufman RM, et al. *Ann Intern Med*. 162:205–213.
221. Deleted in proofs.
222. Brown LM, et al. *J Trauma*. 2011;71(suppl 3):S337–S342.
223. Counts RB, et al. *Ann Surg*. 1979;190:91–99.
224. Reed RL, et al. *Ann Surg*. 1986;203:40–48.
225. Wang HL, et al. *J Intensive Care Med*. 2013;28:268–280.
226. Gorlinger K, et al. *Br J Anaesth*. 2012;110:222–230.
227. Levy JH, et al. *Anesth Analg*. 2012;114:261–274.
228. Miller RD. *Anesthesiology*. 1973;39:82–93.
229. Hondon JA, et al. *TANZ J Surg*. 1982;52:265–269.
230. Simon TL. *Plasma Ther Transfus Technol*. 1988;9:309–315.
231. Hunt BJ. *N Engl J Med*. 2014;370:847–859.
232. Lavee J, et al. *J Thorac Cardiovasc Surg*. 1989;97:204–212.
233. Murray DJ, et al. *Anesthesiology*. 1988;69:839–845.
234. Parshuram CS, Jaffe AR. *Pediatr Crit Care Med*. 2003;4:65–68.
235. Robillard P, Grégoire Y. *Comparison of vasovagal and citrate reaction rates in donors according to type of apheresis procedure*. Abstract Presented at American Association of Blood Banks. 09 October 2017.
236. Linko K, Tigerstedt I. *Acta Anaesthesiol Scand*. 1984;28:220–221.
237. Kleinman S. Red blood cell transfusion in adults: Storage, specialized modifications, and infusion parameters. *UpToDate*. Available at: www.uptodate.com/contents/red-blood-cell-transfusion-in-adults-storage-specialized-modifications-and-infusion-parameters?Accessed April 14, 2013.
238. Smith HM, et al. *Anesth Analg*. 2008;106:1062–1069.
239. Van Poucke S, et al. *Thromb J*. 2014;12(1):31.
240. De Witte J, Sessler D. *Anesthesiology*. 2002;96(2):467–484.
241. Miller RD, et al. *JAMA*. 1971;216:1762–1765.
242. Collins JA, et al. *Ann Surg*. 1971;173:6–18.
243. Seyfried H, Walewska I. *World J Surg*. 1987;11:25–29.
244. Linden JV, et al. *Transfusion*. 2000;40:1207–1213.
245. Capon SM, Sacher RA. *J Intensive Care Med*. 1989;4:100–111.
246. AABB Technical Manual. 17th ed. AABB; 2011.
247. Lopas H. *Am J Physiol*. 1973;225:372–379.
248. Schoneville H, et al. *Transfusion*. 2006;46:630–635.
249. Toy P, et al. *Crit Care Med*. 2005;33:721–726.
250. Zhou L, et al. *Transfusion*. 2005;45:1056–1063.
251. Kleinman S, et al. *Transfusion*. 2004;44:774–789.
252. Clifford L, et al. *Anesthesiology*. 2015;122:12–20.
253. Triuli DJ. *Anesth Analg*. 2009;108:770–776.
254. Toy P, et al. *Blood*. 2012;119:1757–1767.
- 254a. Clifford L, et al. *Anesthesiology*. 2015;122:21–28.
255. Blumberg, et al. *Transfusion*. 2010;50:2738–2744.
256. King KE, et al. *Transfusion*. 2004;44:25–29.
257. Oberman HA. *Transfusion*. 1994;34:353–355.
258. Widman FK. *Transfusion*. 1994;34:356–358.
259. Ohto H, Anderson KC. *Trans Med Rev*. 1996;10:31–43.
260. Hayashi H, et al. *Anesthesiology*. 1992;79:1419–1421.
261. Vamvakas EC. *Transfus Altern Transfus Med*. 2002;4:48–52.
262. Youssef LA, Spitalnik SL. *Curr Opin Hematol*. 2017;24(6): 551–557.
263. Centers for Disease Control and Prevention. *JAMA*. 1998;279:576–578.
264. Corwin HL, AuBuchon JP. *JAMA*. 2003;289:1993–1995.
265. Vamvakas EC, Blajchman MA. *Transfusion*. 2001;41:691–712.
266. Hébert PC, et al. *JAMA*. 2003;289:1941–1949.
267. American Association of Blood Banks Technical Manual. 19th ed. AABB; 2017.
268. Kleinman S, et al. *Transfus Med Rev*. 2003;17:120–162.

References

1. Karafin MS, Bruhn R, Westlake M, et al. Demographic and epidemiologic characterization of transfusion recipients from four US regions: evidence from the REDS-III recipient database. *Transfusion*. 2017;57(12):2903–2913. <https://doi.org/10.1111/trf.14370>.
2. Miller RD. Coagulation defects associated with massive blood transfusions. *Ann Surg*. 1971;174:794–801.
3. Miller RD. Massive blood transfusions and coagulopathies: impact of vietnam military data on modern transfusion medicine. *Anesthesiology*. 2009;110:1412–1416.
4. Spahn DR. Physiologic transfusion triggers. *Anesthesiology*. 2006;104:905–906.
5. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. *Anesth Analg*. 2009;108:759–769.
6. Shander A, Fink A, Javidroozi M, et al. Appropriateness of allogeneic red blood cell transfusion: the international consensus conference on transfusion outcomes. *Transfus Med Rev*. 2011;25:232–246.
7. Lelubre C, Piagnelli M, Vincent JL. Association between duration of storage of transfused red blood cells and morbidity and mortality in adult patients: myth or reality? *Transfusion*. 2009;49:1384–1394.
8. Yazer MH, Jackson B, Sperry JL, et al. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. *J Trauma Acute Care Surg*. 2016;81:21–26.
9. Miller RD. Fresh whole blood and the Vietnam military conflict. *Anesth Analg*. 2013;116:1392–1393.
10. Spinella PC, Cap AP. Whole blood: back to the future. *Curr Opin Hematol*. 2016;23:536–542.
11. Desai N, Schofield N, Richards T. Perioperative patient blood management to improve outcomes. *Anesth Analg*. 2018;127:1211–1220.
12. Society for the Advancement of Blood Management. *A Guide to Patient Blood Management*; 2016. <https://www.sabm.org/wp-content/uploads/2018/08/Guide-to-PBM-2016.pdf>
13. Shander A, Goodnough LT. From tolerating anemia to treating anemia. *Annals of Internal Med*. 2019;170:125–126.
14. Ellingson KD, Sapiano MRP, Haass K. Continued decline in blood collection and transfusion in the United States-2015. *Transfusion*. 2017;57(suppl 2):1588–1598.
15. Gupta PB, DeMario VM, Amin RM, et al. Patient blood management program improves blood use and clinical outcomes in orthopedic surgery. *Anesthesiology*. 2018;129:1082–1091.
16. Mukhtar SA, Leahy MF, Koay K, et al. Effectiveness of a patient blood management data system in monitoring blood use in Western Australia. *Anaesth Intensive Care*. 2013;41:207–215.
17. Liebscher K, Huschke H, Hammer T. Computer-aided creation of a blood supply guideline. *Anaesth Intensivmed*. 2013;54:295–300.
18. WHO. *Global Status Report on Blood Safety and Availability 2016*. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.
19. WHO Expert Group. Expert consensus statement on achieving self-sufficiency in safe blood and blood products, based on voluntary non-remunerated blood donation (VNRBD). *Vox Sang*. 2012;103:337–342.
20. Lacetera N, Macis M, Slonim R. In defense of WHO's blood donation policy: response. *Science*. 2013;342:692.
21. Chell K, Davison TE, Masser B, Jensen K. A systematic review of incentives in blood donation. *Transfusion*. 2018;58:242–254.
22. Dhingra N. In defense of WHO's blood donation policy. *Science*. 2013;342:691–692.
23. Haire B, Whitford K, Kaldor JM. Blood donor deferral for men who have sex with men: still room to move. *Transfusion*. 2018;58:816–822.
24. <https://www.fda.gov/%20EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm485199.htm>. Accessed 10 December 2018.
25. Tong MJ, El-Farra NS, Reikes AR, et al. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med*. 1995;332:1463–1466.
26. Centers for Disease Control and Prevention. Hepatitis C FAQs for the Public. <https://www.cdc.gov/hepatitis/hcv/cfaq.htm>. Accessed 16 March 2019.
27. Preiksaitis VK, Grumet FC, Smith WK, et al. Transfusion-acquired cytomegalovirus infection in cardiac surgery patients. *J Med Virol*. 1985;15:283–290.
28. Preiksaitis JK, Brown L, McKenzie M. The risk of cytomegalovirus infection in seronegative transfusion recipients not receiving exogenous immunodepression. *J Infect Dis*. 1988;157:523–529.
29. Wilhelm JA, Matter L, Schopfer K. The risk of transmitting cytomegalovirus to patients receiving blood transfusions. *J Infect Dis*. 1986;154:169–171.
30. Goodnough LT, Marques MB. Current status of pharmacologic therapies in patient blood management. *Anesthesia Analg*. 2017;124:282.
31. Peterson LR, et al. Zika Virus. *N Engl J Med*. 2016;374:1552–1563
32. Schuler-Faccini L, et al. Possible association between Zika virus infection and microcephaly - Brazil, 2015. *MMWR Morb Mortal Wkly Rep*. 2016;65:59–62.
33. U.S. Food and Drug Administration. *Revised recommendations for reducing the risk of Zika virus transmission by blood and blood components*; 2018. <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf>. Accessed 8 November 2018.
34. Tripple MA, Bland JJ, Murphy MJ, et al. Sepsis associated with transfusion of red cells contaminated with yersinia enterocolitica. *Transfusion*. 1990;30:207–213.
35. Moore GL, Peck CC, Sohmer PR, et al. Some properties of blood stored in CPDA-1 solution. *Transfusion*. 1981;21:135–137.
36. Valeri CR. Measurement of viable ADSOL-preserved human red cells. *N Engl J Med*. 1985;312:377–378.
37. Lovric VA, Archer GT, Wisdom L, et al. Thirty-five-day modified red cells and 7-day stored platelet concentrates from triple bags of identical PVC formation. *Vox Sang*. 1985;49:181–186.
38. Cancelas JA, et al. Additive solution-7 reduces the red blood cell cold storage lesion. *Transfusion*. 2015;55:491–498.
39. Kleinman S, et al. Practical aspects of red blood cell transfusion in adults: storage, processing, modifications, and infusion. *UpToDate*. <https://www.uptodate.com/contents/practical-aspects-of-red-blood-cell-transfusion-in-adults-storage-processing-modifications-and-infusion>. Accessed Feb 7, 2019.
40. Nagababu E, et al. Oxidative stress and rheologic properties of stored red blood cells before and after transfusion to surgical patients. *Transfusion*. 2016;56:1101–1111.
41. Salaria ON, et al. Impaired red blood cell deformability after transfusion of stored allogeneic blood but not autologous salvaged blood in cardiac surgery patients. *Anesth Analg*. 2014;118:1179–1187.
42. Frank SM, Abazyan B, Ono M, et al. Decreased erythrocyte deformability after transfusion and the effects of erythrocyte storage duration. *Anesth Analg*. 2013;116:975–981.
43. Scott AV, et al. 2,3-Diphosphoglycerate concentrations in autologous salvaged versus stored red blood cells and in surgical patients after transfusion. *Anesth Analg*. 2016;122:616–623.
44. Tsoi W. Advances in blood storage bags and preservative solutions. *VOXUS*. 2016;11:49–54.
45. Nishiyama T, Hayashi D. Electrostatic field can preserve red blood cells in stored blood preparations. *J Anesth*. 2007;21:42–46.
46. Wozniak MJ, et al. A comparison of red cell rejuvenation versus mechanical washing for the prevention of transfusion-associated organ injury in swine. *Anesthesiology*. 2018;128:375–385.
47. Wozniak MJ, et al. Randomized trial of red cell washing for the prevention of transfusion-associated organ injury in cardiac surgery. *Br J Anaesth*. 2017;118:689–698.
48. Marik PE, Sibbald WJ. Effects of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA*. 1993;269:3024–3029.
49. Vamvakas EC, Carven JH. Transfusion and postoperative pneumonia in coronary artery bypass surgery: effect of the length of storage of transfused red cells. *Transfusion*. 1999;39:701–710.
50. Leal-Naval SR, Jara-Lopez I, Garcia-Garmendia JL, et al. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. *Anesthesiology*. 2003;98:815–822.
51. Purdy RF, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. *Can J Anaesth*. 1997;44:1256–1261.
52. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*. 2008;358:1229–1239.
53. Adamson JW. New blood, old blood, or no blood? *N Engl J Med*. 2008;358:1295–1296.

54. Wang D, Sun J, Solomon SB, et al. Transfusion of older stored blood and risk of death: a meta-analysis. *Transfusion*. 2012;52:1184–1195.
55. Weiskopf RB, Feiner J, Hopf H, et al. Fresh blood and aged stored blood equally efficacious in immediately reversing anemia-induced brain oxygenation deficits in humans. *Anesthesiology*. 2006;104:911–920.
56. Cata JP, Klein EA, Hoeltge GA, et al. Blood storage duration and biochemical recurrence of cancer after radical prostatectomy. *Mayo Clin Proc*. 2011;86:120–127.
57. Saager L, Turan A, Fiqueroa PI, et al. Erythrocyte storage duration is not associated with increased mortality in noncardiac surgical patients: a retrospective analysis of 6,994 patients. *Anesthesiology*. 2013;118:51–58.
58. Heddle NM, et al. Effect of short-term vs. long-term blood storage on mortality after transfusion. *N Engl J Med*. 2016;375:1937.
59. Steiner ME, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med*. 2015;372:1419.
60. Cooper DJ, et al. Age of red cells for transfusion and outcomes in critically ill adults. *N Engl J Med*. 2017;377:1858.
61. Lacroix J, et al. Age of transfused blood in critically ill adults. *N Engl J Med*. 2015;372:1410.
62. Garraud O. Effect of “old” versus “fresh” transfused red blood cells on patients’ outcome: probably more complex than appears. *J Thoracic Dis*. 2017;9:E146–E148.
63. Tobian A, et al. Red cells - aging gracefully in the blood bank. *New Engl J Med*. 2016;375:1995–1997.
64. Goel R, et al. Red blood cells stored 35 days or more are associated with adverse outcomes in high-risk patients. *Transfusion*. 2016;56:1690–1698.
65. Cull DL, Lally KP, Murphy KD. Compatibility of packed erythrocytes and Ringer’s lactate solution. *Surg Gynecol Obstet*. 1991;173:9–12.
66. Albert K, Vlymen J, James P, Parlow J. Ringer’s lactate is compatible with the rapid infusion of AS-3 preserved packed red blood cells. *Can J Anaesth*. 2009;56:352–356.
67. Beattie WS, Wijeyesundara DN. Approaching a safe last resort: triggers for perioperative blood transfusion. *Anesthesiology*. 2016;125(1):11–13.
68. Mathru M, Solanki DR, Woodson LC, et al. Oxygen consumption is impaired during acute normovolemic anemia. *Anesthesiology*. 2006;105:37.
69. Consensus conference. Perioperative red blood cell transfusion. *JAMA*. 1988;260:2700–2703.
70. Le Manach Y, Syed S. Erythrocyte transfusion: remedy or poison? *Anesthesiology*. 2012;117:1153–1155.
71. Corwin HL, Parsonnet KC, Gettinger A. RBC transfusion in the ICU: is there a reason? *Chest*. 1995;108:767–771.
72. Hébert PC, Wells G, Marshall J, et al. Canadian critical care trials group: transfusion requirements in critical care: a pilot study. *JAMA*. 1995;273:1439–1444.
73. Bishop MH, Shoemaker WC, Appel PL, et al. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. *J Trauma*. 1995;38:780–787.
74. Frank SM, Savage WJ, Rothschild JA, et al. Variability in blood and blood component utilization as assessed by an anesthesia information management system. *Anesthesiology*. 2012;117:99–106.
75. McNamara D. Tablet-Based Technology Gauges Surgical Blood Loss. *Anesthesiology News* 32; 2012.
76. World Alliance for Patient Safety. *WHO Guidelines for Safe Surgery*; 2008.
77. Solon JG, et al. Safe surgery: how accurate are we at predicting intraoperative blood loss? *J Eval Clin Pract*. 2013;19:100–105.
78. Stovener J. Anesthesiologists vastly overstate bleeding. *Anesthesiology News*. 2012;14.
79. Berkow L, Rotolo S, Mirski E. Continuous noninvasive hemoglobin monitoring during complex spinal surgery. *Anesth Analg*. 2011;113:1396–1402.
80. Miller RD, Ward TA, Shibuski SC, et al. A comparison of three methods of hemoglobin monitoring in patients undergoing spine surgery. *Anesth Analg*. 2011;112:858–863.
81. Xu T, et al. Evaluation of noninvasive hemoglobin monitoring in surgical critical care patients. *Crit Care Med*. 2016;44:e344–e352.
82. Bridges E, et al. Noninvasive continuous hemoglobin monitoring in combat casualties: a pilot study. *Shock*. 2016;46:55–60.
83. Miller RD, Ward TA, McColloch CE, et al. Does a digital regional nerve block improve the accuracy of noninvasive hemoglobin monitoring? *J Anesth*. 2012;26:845–850.
84. Miller RD, Ward TA, McColloch CE, et al. A comparison of lidocaine and bupivacaine digital nerve blocks on noninvasive continuous hemoglobin monitoring in a randomized trial in volunteers. *Anesth Analg*. 2014;118:766–771.
85. Giraud B, Frasca D, Debaene B, et al. Comparison of haemoglobin measurement methods in the operating theatre. *Br J Anaesth*. 2013;111:946–954.
86. Barker SJ, et al. Continuous noninvasive hemoglobin monitoring: a measured response to a critical review. *Anesth Analg*. 2016;122:565–572.
87. Frasca D, et al. Continuous monitoring of haemoglobin concentration after in-vivo adjustment in patients undergoing surgery with blood loss. *Anaesthesia*. 2015;70:803–809.
88. Kolotiniuk NV, et al. Measures of blood hemoglobin and hematocrit during cardiac surgery: comparison of three point-of-care devices. *J Cardiothor Vasc Anesthesia*. 2018;32:1638–1641.
89. Musallam KM, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet*. 2011;3278:1396–1407.
90. Karkouti K, et al. Interrelationship of preoperative anemia, intraoperative anemia, and red blood cell transfusion as potentially modifiable risk factors for acute kidney injury in cardiac surgery: a historical multicentre cohort study. *Can J Anesth*. 2015;62:377–384.
91. Kozek-Langenecker SA, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. *Eur J Anaesthesiology*. 2017;34:332–395.
92. Froessler B, et al. The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: a randomized controlled trial. *Ann Surg*. 2016;264:41–46.
93. Keeler BD, et al. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. *Br J Surg*. 2017;104:214–221.
94. Weltert L, et al. A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: results of a prospective single-blind randomized controlled trial. *Transfusion*. 2015;55:1644–1654.
95. Unger EF, Thompson AM, Blank MJ, Temple R. Erythropoiesis-stimulating agents—time for a reevaluation. *N Engl J Med*. 2010;362:189–192.
96. Karkouti K, Wijeyesundara DN, Yau TM, et al. Risk influence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients. *Anesthesiology*. 2011;115:523–530.
97. Goodnough LT, Shander A. Current status of pharmacologic therapies in patient blood management. *Anesth Analg*. 2013;116:15–34.
98. Levy JH. Hemoglobin-based oxygen carriers for reversing hypotension and shock: “NO” Way, “NO” How? [Editorial]. *Anesthesiology*. 2011;114:1016–1018.
99. Papageorge CM, et al. Preoperative blood transfusion is a predictor of worse short-term postoperative outcomes after colectomy. *Surgery*. 2017;161:1067–1075.
100. Carson JL, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA*. 2016;316:2025–2035.
101. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med*. 2011;365:2453–2462.
102. Shorr AF, Duh MS, Kelly KM. Red blood cell transfusion and ventilator-associated pneumonia: a potential link? *Crit Care Med*. 2004;32:666–674.
103. Taylor RW, O’Brien J, Trottier SJ. Red blood cell transfusions and nosocomial infections in critically ill patients. *Crit Care Med*. 2006;34:2302–2308.
104. Ely EW, Bernard GR. Transfusions in critically ill patients. *N Engl J Med*. 1999;340:467–468.
105. Hébert PC, Fergusson DA. Red blood cell transfusions in critically ill patients. *JAMA*. 2002;288:1525–1526.
106. Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA*. 2002;288:1499–1507.
107. Walsh TS, McClelland DBL. When should we transfuse critically ill and perioperative patients with known coronary artery disease? *Br J Anaesth*. 2003;90:719–722.

108. McCrossan L, Masterson G. Blood transfusion in critical illness. *Br J Anaesth.* 2002;88:6–9.
109. Mazer CD, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med.* 2017;377:2133–2144.
110. Holst LB, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med.* 2014;371:1381–1391.
111. Rohde HM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA.* 2014;311:1317–1326.
112. Hovaguimian F, Myles PS. Restrictive versus liberal transfusion strategy in the perioperative and acute care settings: a context-specific systematic review and meta-analysis of randomized controlled trials. *Anesthesiology.* 2016;125:46–61.
113. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med.* 2013;368:11–21.
114. Laine L. Blood transfusion for gastrointestinal bleeding. *N Engl J Med.* 2013;368:75–76.
115. Weiskopf RB. Do we know when to transfuse red cells to treat acute anemia? *Transfusion.* 1998;38:517–521.
116. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management. *Anesthesiology.* 2015;122:241.
117. Thiel T, Heddle N, Greinacher A. Donor exposures in recipients of pooled platelet concentrates. *New Engl J Med.* 2013;368:487–489.
118. <https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM59-8243.pdf>. Accessed 22 March 2019.
119. Morrow JF, Braine HG, Kickler TS, et al. Septic reactions to platelet transfusions. *JAMA.* 1991;266:255–258.
120. Hong H, et al. Detection of septic transfusion reactions to platelet transfusions by active and passive surveillance. *Blood.* 2016;127:496.
121. Benjamin RJ. Transfusion-related sepsis: a silent epidemic. *Blood.* 2016;127:380.
122. Dunne WM, Case LK, Isgriggs L. In-house validation of the BACTEC 9240 blood culture system for detection of bacterial contamination in platelet concentrates. *Transfusion.* 2005;45:1138–1142.
123. Rebulla R, et al. The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. Gruppo Italiano Malattie Ematologiche Maligne Dell'adulto. *N Engl J Med.* 1997;337:1870–1875.
124. Horlocker TT, Vandermeulen E, Kopp SL, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). *Reg Anesth Pain Med.* 2018;263–309.
125. Baharoglu MI, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *Lancet.* 2016;387:2605.
126. Teixeira PG, Inaba K, Shulman I, et al. Impact of plasma transfusion in massively transfused trauma patients. *J Trauma.* 2009;66:693–697.
127. Kruskall MS. The perils of platelet transfusions. *N Engl J Med.* 1997;337:1914–1915.
128. Scott E, Puca K, Heraly J, et al. Evaluation and comparison of coagulation factor activity in fresh-frozen plasma and 24-hour plasma at thaw and after 120 hours of 1 to 6°C storage. *Transfusion.* 2009;49:1584–1591.
129. Cardigan R, Lawrie AS, Mackie IJ. The quality of fresh-frozen plasma produced from whole blood stored at 4°C overnight. *Transfusion.* 2005;45:1342–1348.
130. Hall DP, Lone NI, Watson DM, et al. Factors associated with prophylactic plasma transfusion before vascular catheterization in non-bleeding critically ill adults with prolonged prothrombin time: a case-control study. *Br J Anaesthesia.* 2012;109:919–927.
131. Muller MC, et al. Transfusion of fresh-frozen plasma in critically ill patients with a coagulopathy before invasive procedures: a randomized clinical trial (CME). *Transfusion.* 2015;55:26.
132. Radwan ZA, Bai Y, Matijevic N, et al. An emergency department thawed plasma protocol for severely injured patients. *JAMA.* 2013;148:170–175.
133. Sperry JL, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *New Engl J Med.* 2018;379:315.
134. Holcomb JB, Wade CE, Trauma Outcomes Group, et al. Defining present blood component transfusion practices in trauma patients: papers from the Trauma Outcomes Group. *J Trauma.* 2011;71:S315–S317.
135. Kornblith LZ, Howard BM, Cheung CK, et al. The whole is greater than the sum of its parts: hemostatic profiles of whole blood variants. *J Trauma Acute Care Surg.* 2014;77:818.
136. Holcomb JB, del Junco DJ, Fox EE, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg.* 2013;148:127–136.
137. Bhangu A, Nepogodiev D, Doughty H, et al. Meta-analysis of plasma to red blood cell ratios and mortality in massive blood transfusions for trauma. *Injury.* 2013;44:1693–1699.
138. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the proppr randomized clinical trial. *JAMA.* 2015;313(5):471–482.
139. Pasquier P, Gayat E, Rackelboom T, et al. An observational study of the fresh frozen plasma: red blood cell ratio in postpartum hemorrhage. *Anesth Analg.* 2013;116:155–161.
140. Kerins DM. Role of the perfluorocarbon Fluosol-DA in coronary angioplasty. *Am J Med Sci.* 1994;307:218.
141. Tremper KK, Friedman AE, Levine EM, et al. The preoperative treatment of severely anemic patients with perfluorochemical oxygen transport fluid, Fluosol-DA. *N Engl J Med.* 1982;307:277–283.
142. Spahn DR, Waschke KF, Standl T, et al. Use of perflubron emulsion to decrease allogeneic blood transfusion in high blood-loss non-cardiac surgery: results of a European phase 3 study. *Anesthesiology.* 2002;97:1338–1349.
143. Hermann J, Corso C, Messmer KF. Resuscitation with recombinant hemoglobin rHb 2.0 in a rodent model of hemorrhagic shock. *Anesthesiology.* 2007;107:273–280.
144. Crawford MW, Shichor T, Engelhardt T. The novel hemoglobin-based oxygen carrier HRC 101 improves survival in murine sickle cell disease. *Anesthesiology.* 2007;107:281–287.
145. Wahr JA. The use of bovine hemoglobin glutamer-250 (Hemopure) in surgical patients: results of a multicenter, randomized, single-blinded trial. *Anesth Analg.* 2002;94:799–808.
146. Natanson C, Kern SJ, Lurie P, et al. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis. *JAMA.* 2008;299:2304–2312.
147. Fergusson DA, McIntyre SL. The future of clinical trials evaluating blood substitutes. *JAMA.* 2008;299:2324–2326.
148. Levy J. The use of haemoglobin glutamer-250 (HBOC-201) as an oxygen bridge in patients with acute anaemia associated with surgical blood loss. *Expert Opin Biol Ther.* 2003;3:509–517.
149. Davis JM, El-Haj N, Shah NN, et al. Use of the blood substitute HBOC-201 in critically ill patients during sickle crisis: a three-case series. *Transfusion.* 2018;58:132.
150. DeSimone RA, Berlin DA, Avecilla ST, Goss CA. Investigational use of PEGylated carboxyhemoglobin bovine in a Jehovah's Witness with hemorrhagic shock. *Transfusion.* 2018;58:2297–2300.
151. Goodnough LT, et al. Bloodless medicine: clinical care without allogeneic blood transfusion. *Transfusion.* 2003;43:668.
152. Vassallo R, et al. Preoperative autologous blood donation: waning indications in an era of improved blood safety. *Transfusion Med Reviews.* 2015;29:268–275.
153. AABB. *Standards for Blood Banks and Transfusion Services.* 29th ed. Bethesda MD: AABB Press; 2014.
154. Kiss JE, et al. Oral iron supplementation after blood donation: a randomized clinical trial. *JAMA.* 2015;313:575–583.
155. Henry DA, et al. Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev.* 2002;(2):CD003602.
156. Popovsky MA, et al. Severe outcomes of allogeneic and autologous blood donation: frequency and characterization. *Transfusion.* 1995;35:734–737.
157. AuBuchon JP, et al. The safety of preoperative autologous blood donation in the nonhospital setting. *Transfusion.* 1991;31:513–517.
158. Messmer K, et al. Present state of intentional hemodilution. *Eur Surg Res.* 1986;18:254–263.
159. Goodnough LT, et al. Acute normovolemic hemodilution should replace the preoperative donation of autologous blood as a method of autologous-blood procurement. *Transfusion.* 1998;38:473–476.
160. Lu SY, et al. Stationary versus agitated storage of whole blood during acute normovolemic hemodilution. *Anesth Analg.* 2014;118:264–268.

161. Goodnough LT, Grishaber JE, Monk TG, et al. Acute preoperative hemodilution in patients undergoing radical prostatectomy: a case study analysis of efficacy. *Anesth Analg*. 1994;78:932–937.
162. Goldberg J, et al. Greater volume of acute normovolemic hemodilution may aid in reducing blood transfusions after cardiac surgery. *Am Thorac Surg*. 2015;100:1581–1587.
163. Zhou Z, et al. Mild volume acute normovolemic hemodilution is associated with lower intraoperative transfusion and postoperative pulmonary infection in patients undergoing cardiac surgery -- a retrospective, propensity matching study. *BMC Anesthesiology*. 2017;17:13.
164. Roberts, et al. Autotransfusion of unwashed mediastinal shed blood fails to decrease banked blood requirements in patients undergoing aortocoronary bypass surgery. *Am J Surg*. 1991;162:477.
165. Jarnagin, et al. A prospective randomized trial of acute normovolemic hemodilution compared to standard intraoperative management in patients undergoing major hepatic resection. *Ann Surg*. 2008;248:360.
166. DeHaan, et al. Retransfusion of suctioned blood during cardiopulmonary bypass impairs hemostasis. *Ann Thoracic Surg*. 1995;59:901.
167. Barile L, et al. Acute normovolemic hemodilution reduces allogeneic red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis of randomized trials. *Anesth Analg*. 2017;124:743.
168. Sniecienski RM, Mascha EJ. Acute normovolemic hemodilution: picking more apples and oranges. *Anesth Analg*. 2017;124:726.
169. Sebastian R, et al. Revisiting acute normovolemic hemodilution and blood transfusion during pediatric cardiac surgery: a prospective observational study. *Paediatr Anaesth*. 2017;27:85–90.
170. Albu G, et al. Cardiorespiratory alterations following acute normovolemic hemodilution in a pediatric and an adult porcine model: a prospective interventional study. *Anesth Analg*. 2018; 126:995.
171. Crystal GJ. Regional tolerance to acute normovolemic hemodilution: evidence that the kidney may be at greatest risk. *J Cardiothorac Vasc Anesth*. 2015;29:320–327.
172. Kisilevsky AE, et al. Spine tumor resection among patients who refuse blood product transfusion: a retrospective case series. *J Clinical Anesthesia*. 2016;35:434–440.
173. AABB. *Standards for Perioperative Autologous Blood Collection and Administration*. 7th ed. AABB; 2016.
174. Sikorski RA, et al. Autologous blood salvage in the era of patient blood management. *Vox Sanguinis*. 2017;112:499–510.
175. Williamson KR, Taswell HF. Intraoperative blood salvage: a review. *Transfusion*. 1991;31:662.
176. Li, et al. Oxygen carrying capacity of salvaged blood in patients undergoing off-pump coronary artery bypass grafting surgery: a prospective observational study. *J Cardiothoracic Surg*. 2015;10:126.
177. Domen RE. Adverse reactions associated with autologous blood transfusion: evaluation and incidence at a large academic hospital. *Transfusion*. 1998;38:296.
178. Konig G, et al. Washing and filtering of cell-salvaged blood - does it make autotransfusion safer? *Transfus Altern Transfus Med*. 2012;12:78–87.
179. Yazer MH, et al. A comparison of hemolysis and red cell mechanical fragility in blood collected with different cell salvage suction devices. *Transfusion*. 2008;48:1188–1191.
180. Tsai AG, Cabrales P, Manjula BN, et al. Dissociation of local nitric oxide concentration and vasoconstriction in the presence of cell-free hemoglobin oxygen carriers. *Blood*. 2006;108(10):3603–3610.
181. Gregoretti S. Suction-induced hemolysis at various vacuum pressures: implications for intraoperative blood salvage. *Transfusion*. 1996;36:57.
182. Bell K, et al. A controlled trial of intra-operative autologous transfusion in cardiothoracic surgery measuring effect on transfusion requirements and clinical outcome. *Transfusion Med*. 1992;2:295.
183. Waters JH, Tuohy MJ, Hobson DF, Procop G. Bacterial reduction by cell salvage washing and leukocyte depletion filtration. *Anesthesiology*. 2003;99(3):652–655.
184. Esper SA, Waters JH. Intra-operative cell salvage: a fresh look at the indications and contraindications. *Blood Transfus Med*. 2011; 9:139.
185. Carless PA, Henry DA, Moxey AJ, et al. Cell salvage for minimizing perioperative allogeneic blood transfusion. *J Cardiothorac Vasc Anesth*. 2010;3:CD001888.
186. So-Osman C, et al. Patient blood management in elective total hip- and knee-replacement surgery (Part 1): a randomized controlled trial on erythropoietin and blood salvage as transfusion alternatives using a restrictive transfusion policy in erythropoietin-eligible patients. *Anesthesiology*. 2014;120:839–851.
187. So-Osman, et al. Patient blood management in elective total hip- and knee-replacement surgery (part 2): a randomized controlled trial on blood salvage as transfusion alternative using a restrictive transfusion policy in patients with a preoperative hemoglobin above 13 g/dL. *Anesthesiology*. 2014;120:852–860.
188. Lim G, et al. Cost-effectiveness analysis of intraoperative cell salvage for obstetric hemorrhage. *Anesthesiology*. 2018;128:328–337.
189. Gilsch C, et al. Evaluation of a two-sample process for prevention of ABO mists transfusions in a high volume academic hospital. *BMJ Open Quality*. 2018;7:e000270.
190. Hendrickson JE, et al. Red blood cell alloimmunization mitigation strategies. *Transfusion Med Rev*. 2014;28:137–144.
191. American Society of Anesthesiologists. *Transfusion Practices: Questions and Answers*. 3rd ed. Chicago: American Society of Anesthesiologists; 1998:8–9.
192. Chapuy CI, et al. Resolving the daratumumab interference with blood compatibility testing. *Transfusion*. 2015;55:1545–1554.
193. Chapuy CI, et al. International validation of a dithiothreitol (DTT)-based method to resolve the daratumumab interference with blood compatibility testing. *Transfusion*. 2016;56:2964–2972.
194. Murphy MF. Interference of new drugs with compatibility testing for blood transfusion. *N Eng J Med*. 2016;375(3):295–296.
195. Boyd PR, Sheedy KC, Henry JB. Type and screen: use and effectiveness in elective surgery. *Am J Clin Pathol*. 1980;74:694–699.
196. Coombs RR, Mourant AE, Race RR. A new test for the detection of weak and incomplete Rh agglutinins. *Br J Exp Pathol*. 1945;26:255–266.
197. Walker RH. What is a clinically significant antibody? In: Polesky HF, Walker RH, eds. *Safety and Transfusion Practices*. Skokie, Ill: College of American Pathologists; 1982:79.
198. Butch SH, et al. Electronic verification of donor-recipient compatibility: the computer crossmatch. *Transfusion*. 1994;34:105–109.
199. Daurat A, et al. Evaluation of the non-compliance with grouping guidelines which may lead to "wrong blood in tube", an observational study and risk factor analysis. *Transfus Clin Biol*. 2017;24:47–51.
200. Novis DA, et al. Blood bank specimen mislabeling: a College of American Pathologists Q-Probes Study of 41,333 blood bank specimens in 30 institutions. *Arch Pathol Lab Med*. 2017;141:255–259.
201. U.S. Food and Drug Administration. *Guidance for industry: Computer crossmatch (Computerized analysis of the compatibility between the donor's cell type and the recipient's serum or plasma type)* April 2011.
202. Mazepa MA. Pathology consultation on electronic crossmatch. *Am J Clin Pathol*. 2014;141:618–624.
203. Oberman AJ, Barnes BA, Friedman BA. The risk of abbreviating the major crossmatch in urgent or massive transfusion. *Transfusion*. 1978;18:137–141.
204. Sarma DP. Use of blood in elective surgery. *JAMA*. 1980;243:1536–1538.
205. Dexter F, Ledolet J, Davis E, et al. Systematic criteria for type and screen based on procedure's probability of erythrocyte transfusion. *Anesthesiology*. 2012;116:768–778.
206. Friedman BA. An analysis of surgical blood use in United States hospitals with application to the maximum surgical blood order schedule. *Transfusion*. 1979;19:268–278.
207. Krier DB. Transfusion-to-cross-match community comparison data. *Am J Med Qual*. 1996;11:68–72.
208. Frank SM, et al. Optimizing preoperative blood ordering with data acquired from an anesthesia information management system. *Anesthesiology*. 2013;118:1286–1297.
209. Frank SM, et al. Reducing unnecessary preoperative blood orders and costs by implementing an updated institution-specific maximum surgical blood order schedule and a remote electronic blood release system. *Anesthesiology*. 2014;121:501–509.
210. Gervin AS, Fischer RP. Resuscitation of trauma patients with type-specific uncrossmatched blood. *J Trauma*. 1984;24:327–331.
211. Mulay SB, et al. Risks and adverse outcomes associated with emergency-release red blood cell transfusion. *Transfusion*. 2013;53:1416–1420.
212. Boisen, et al. Pretransfusion testing and transfusion of uncrossmatched erythrocytes. *Anesthesiology*. 2015;122:191–195.
213. Goodell PP, et al. Risk of hemolytic transfusion reactions following emergency-release RBC transfusion. *Am J Clin Pathol*. 2010;134:202–206.

214. Fergusson DA, Hébert P, Hogal DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. *JAMA*. 2012;308:1443–1451.
215. Spinella PC, Reddy HL, Jaffe JS, et al. Fresh whole blood use for hemorrhagic shock: preserving benefit while avoiding complications. *Anesth Analg*. 2012;115:571–578.
216. Weiskopf RB. Reconstruction deconstructed blood for trauma. *Anesthesiology*. 2012;116:518–521.
217. Auten JD, et al. The safety of early fresh, whole blood transfusion among severely battle injured at US Marine Corps forward surgical care facilities in Afghanistan. *J Trauma Acute Care Surg*. 2015;79:790–611.
218. Erber WN, Tan J, Grey D, et al. Use of unrefrigerated fresh whole blood in massive transfusion. *Med J Aust*. 1996;165:11–13.
219. Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion. *Ann Surg*. 2007;245:812–818.
220. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 162:205–213.
221. Deleted in proofs.
222. Brown LM, Call MS, Knudson MM, et al. A normal platelet count may not be enough: the impact of admission platelet count on mortality and transfusion in severely injured trauma patients. *J Trauma*. 2011;71(suppl 3):S337–S342.
223. Counts RB, Haisch C, Simon TL, et al. Hemostasis in massively transfused trauma patients. *Ann Surg*. 1979;190:91–99.
224. Reed RL, Heimback DM, Counts RB, et al. Prophylactic platelet administration during massive transfusion. *Ann Surg*. 1986;203:40–48.
225. Wang HL, Aguilera C, Knopf KB, et al. Thrombocytopenia in the intensive care unit. *J Intensive Care Med*. 2013;28:268–280.
226. Gorlinger K, Dirkmann D, Solomon C, et al. Fast interpretation of thromboelastometry in non-cardiac surgery: reliability in patients with hypo-, normo-, and hypercoagulability. *Br J Anaesth*. 2012;110:222–230.
227. Levy JH, Szlam F, Tanaka KA, et al. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. *Anesth Analg*. 2012;114:261–274.
228. Miller RD. Complications of massive blood transfusions. *Anesthesiology*. 1973;39:82–93.
229. Hondon JA, Russell WJ, Duncan BM, Lloyd JV. The stability of coagulation factors in stored blood. *ANZ J Surg*. 1982;52:265–269.
230. Simon TL. Changes in plasma coagulation factors during blood storage. *Plasma Ther Transfus Technol*. 1988;9:309–315.
231. Hunt BJ. Bleeding and coagulopathies in critical care. *N Engl J Med*. 2014;370:847–859.
232. Lavee J, Martinowitz U, Mohr R, et al. The effect of transfusion of fresh whole blood versus platelet concentrates after cardiac operations. *J Thorac Cardiovasc Surg*. 1989;97:204–212.
233. Murray DJ, Olson J, Strauss R, et al. Coagulation changes during packed red cell replacement of major blood loss. *Anesthesiology*. 1988;69:839–845.
234. Parshuram CS, Jaffe AR. Prospective study of potassium-associated acute transfusion events in pediatric intensive care. *Pediatr Crit Care Med*. 2003;4:65–68.
235. Robillard P, Grégoire Y. Comparison of *vasovagal and citrate reaction rates in donors according to type of apheresis procedure*. Abstract Presented at American Association of Blood Banks. 09 October 2017
236. Linko K, Tigerstedt I. Hyperpotassemia during massive blood transfusions. *Acta Anaesthesiol Scand*. 1984;28:220–221.
237. Kleinman, Steven. Red blood cell transfusion in adults: Storage, specialized modifications, and infusion parameters. *UpToDate*. Available at: www.uptodate.com/contents/red-blood-cell-transfusion-in-adults-storage-specialized-modifications-and-infusion-parameters? Accessed April 14, 2013.
238. Smith HM, Farrow SJ, Ackerman JD, et al. Cardiac arrests associated with hyperkalemia during red blood cell transfusion: a case series. *Anesth Analg*. 2008;106:1062–1069.
239. Van Poucke S, Stevens K, Marcus AE, Lancé M. Hypothermia: effects on platelet function and hemostasis. *Thromb J*. 2014;12(1):31.
240. De Witte J, Sessler D. Perioperative shivering: physiology and pharmacology. *Anesthesiology*. 2002;96(2):467–484.
241. Miller RD, Tong MJ, Robbins TO. Effects of massive transfusion of blood on acid-base balance. *JAMA*. 1971;216:1762–1765.
242. Collins JA, Simmons RL, James PM, et al. The acid-base status of seriously wounded combat casualties. I. Resuscitation with stored blood. *Ann Surg*. 1971;173:6–18.
243. Seyfried H, Walewska I. Immune hemolytic transfusion reactions. *World J Surg*. 1987;11:25–29.
244. Linden JV, Wagner K, Voytovich AE, et al. Transfusion errors in New York State: an analysis of 10 years' experience. *Transfusion*. 2000;40:1207–1213.
245. Capon SM, Sacher RA. Hemolytic transfusion reactions: a review of mechanisms, sequelae, and management. *J Intensive Care Med*. 1989;4:100–111.
246. AABB *Technical Manual*. 17th ed. AABB; 2011.
247. Lopas H. Immune hemolytic transfusion reactions in monkeys: activation of the kallikrein system. *Am J Physiol*. 1973;225:372–379.
248. Schonewille H, van de Watering LMG, Brand A. Additional red blood cell alloantibodies after blood transfusions in nonhematologic alloimmunized patient cohort: is it time to take precautionary measures? *Transfusion*. 2006;46:630–635.
249. Toy P, Popovsky MA, Abraham E, et al. Transfusion-related acute lung injury: definition and review. *Crit Care Med*. 2005;33:721–726.
250. Zhou L, Giacherio D, Cooling L, et al. Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. *Transfusion*. 2005;45:1056–1063.
251. Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion*. 2004;44:774–789.
252. Clifford L, et al. Characterizing the epidemiology of postoperative transfusion-related acute lung injury. *Anesthesiology*. 2015;122:12–20.
253. Triuli DJ. Transfusion-related acute lung injury: current concepts for the clinician. *Anesth Analg*. 2009;108:770–776.
254. Toy P, Gajic P, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. *Blood*. 2012;119:1757–1767.
- 254a. Clifford L, et al. Characterizing the epidemiology of perioperative transfusion-associated circulatory overload. *Anesthesiology*. 2015;122:21–28.
255. Blumberg, et al. An association between decreased cardiopulmonary complications (transfusion-related acute lung injury and transfusion-associated circulatory overload) and implementation of universal leukoreduction of blood transfusions. *Transfusion*. 2010;50:2738–2744.
256. King KE, Shirey S, Thoman SK, et al. Universal leukoreduction decreases the incidence of febrile nonhemolytic transfusion reactions to RBCs. *Transfusion*. 2004;44:25–29.
257. Oberman HA. Controversies in transfusion medicine: should a febrile transfusion response occasion the return of the blood component to the blood bank? *Transfusion*. 1994;34:353–355.
258. Widman FK. Controversies in transfusion medicine: should a febrile transfusion response occasion the return of the blood component to the blood bank? *Transfusion*. 1994;34:356–358.
259. Ohto H, Anderson KC. A survey of transfusion-associated graft-versus-host disease in immunocompetent recipients. *Trans Med Rev*. 1996;10:31–43.
260. Hayashi H, Nishiuchi T, Tamura H, et al. Transfusion-associated graft-versus-host disease caused by leukocyte-filtered stored blood. *Anesthesiology*. 1992;79:1419–1421.
261. Vamvakas EC. Transfusion-related immunomodulation. *Transfus Altern Transfus Med*. 2002;4:48–52.
262. Youssef LA, Spitalnik SL. Transfusion-related immunomodulation: a reappraisal. *Curr Opin Hematol*. 2017;24(6):551–557.
263. Centers for Disease Control and Prevention. Adverse ocular reactions following transfusion: United States 1997–1998. *JAMA*. 1998;279:576–578.
264. Corwin HL, AuBuchon JP. Is leukoreduction of blood components for everyone? *JAMA*. 2003;289:1993–1995.
265. Vamvakas EC, Blajchman MA. Universal WBC reduction: a case for and against. *Transfusion*. 2001;41:691–712.
266. Hébert PC, Fergusson DA, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA*. 2003;289:1941–1949.
267. American Association of Blood Banks *Technical Manual*. 19th ed. AABB; 2017.
268. Kleinman S, Chan P, Robillard P. Risks associated with transfusion of cellular blood components in Canada. *Transfus Med Rev*. 2003;17:120–162.

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KEY POINTS

- Normal hemostasis is a balance between generation of a localized hemostatic clot and uncontrolled thrombus formation.
- The extrinsic pathway of coagulation begins with exposure of blood plasma to tissue factor and represents the initiation phase of plasma-mediated hemostasis.
- The intrinsic pathway amplifies and propagates the hemostatic response to maximize thrombin generation.
- The common pathway generates thrombin, forms fibrin, and crosslinks fibrin strands to produce an insoluble fibrin clot.
- Routine preoperative coagulation testing of all surgical patients is costly and lacks predictive value for detection of hemostatic abnormalities. Testing should be based on the preoperative history and physical examination and the planned surgery.
- Antiplatelet agents and anticoagulants are used to reduce the formation of blood clots in the setting of coronary or cerebral atherosclerosis or after vascular thrombosis.
- Thrombolytic therapy is used to break up or dissolve blood clots.
- Procoagulant drugs (antifibrinolytics, factor replacements, prothrombin complex concentrate) help control blood loss during surgery.
- Perioperative management of patients who require chronic anticoagulation or antiplatelet therapy involves balancing the risk of surgical bleeding against the risk of developing postoperative thromboembolism.

Introduction

Hemostasis is an ordered enzymatic process involving cellular and biochemical components that function to preserve the integrity of the circulatory system after injury. The ultimate goal of this process is to limit blood loss secondary to vascular injury, maintain intravascular blood flow, and promote revascularization after thrombosis. As such, normal physiologic hemostasis is a constant balance between procoagulant pathways responsible for generation of a stable localized hemostatic clot and counter-regulatory mechanisms inhibiting uncontrolled thrombus propagation or premature thrombus degradation. Vascular endothelium, platelets, and plasma coagulation proteins play equally important roles in this process. Derangements in this delicate system can lead to excessive bleeding or pathologic thrombus formation. This chapter will examine normal and abnormal hemostasis, mechanisms to monitor coagulation, medications to manipulate coagulation, and management options for the perioperative anticoagulated patient.

Normal Hemostasis

Vascular endothelial injury—mechanical or biochemical—leads to platelet deposition at the injury site, a process often referred to as primary hemostasis. Although this initial platelet

plug may prove adequate for a minor injury, control of more significant bleeding necessitates stable clot formation incorporating crosslinked fibrin—a process mediated by activation of plasma clotting factors and often referred to as secondary hemostasis. Although the terms primary and secondary hemostasis remain relevant for descriptive and diagnostic purposes, advances in understanding cellular and molecular processes underlying hemostasis suggest a far more complex interplay between vascular endothelium, platelets, and plasma-mediated hemostasis than is reflected in this model.¹

VASCULAR ENDOTHELIAL ROLE IN HEMOSTASIS

In order to maintain blood flow throughout the circulatory system, the vascular endothelium employs several strategies to inhibit unprovoked thrombus formation. Healthy endothelial cells possess antiplatelet, anticoagulant, and profibrinolytic effects to inhibit clot formation.² The negatively charged vascular endothelium repels platelets, and endothelial cells produce potent platelet inhibitors such as prostacyclin (prostaglandin I₂) and nitric oxide (NO).^{3,4} An adenosine diphosphatase (CD39) expressed on the surface of vascular endothelial cells also serves to block platelet activation via degradation of adenosine diphosphate (ADP), a potent platelet activator.⁵ Given these endogenous antiplatelet effects, quiescent platelets normally do not adhere to healthy vascular endothelial cells.

The vascular endothelium also plays a pivotal anticoagulant role through expression of several inhibitors of plasma-mediated hemostasis. Endothelial cells increase activation of protein C, an anticoagulant, via surface glycoprotein thrombomodulin (TM), which acts as a cofactor for thrombin-mediated activation of protein C, making its activation 1000 times faster. Endothelial cells also increase endothelial cell protein C receptor, which further enhances protein C activation by an additional 20-fold.⁶ Endothelial-bound glycosaminoglycans, such as heparan sulfate, function to accelerate the protease activity of antithrombin (AT), which degrades factors IXa, Xa, and thrombin.⁷ Endothelial cells also produce tissue factor pathway inhibitor (TFPI), which inhibits the procoagulant activity of factor Xa as well as the TF-VIIa complex.⁸ Finally, the vascular endothelium synthesizes tissue plasminogen activator (t-PA), which is responsible for activating fibrinolysis, a primary counter-regulatory mechanism limiting clot propagation.

Despite these natural defense mechanisms to inhibit thrombus generation, a variety of mechanical and chemical stimuli may shift the balance such that the endothelium instead promotes clot formation. Damage to vascular endothelial cells exposes the underlying extracellular matrix (ECM), which contains collagen, von Willebrand factor (vWF), and other platelet-adhesive glycoproteins.^{9,10} Platelets bind to and are activated by exposure to ECM components. Exposure of tissue factor, constitutively expressed by fibroblasts in the ECM, activates plasma-mediated coagulation pathways to generate thrombin and fibrin clot.¹¹ Certain cytokines (i.e., interleukin-1, tumor necrosis factor, and γ -interferon) and hormones (i.e., desmopressin acetate [DDAVP] or endotoxin) induce prothrombotic changes in vascular endothelial cells by increasing synthesis and expression of vWF, tissue factor, and plasminogen activator inhibitor-1 (PAI-1), and down-regulating normal anti-thrombotic cellular and biochemical pathways.^{12,13} Finally, thrombin, hypoxia, and high fluid shear stress can also induce prothrombotic vascular endothelial changes such as increased synthesis of PAI-1. This associated inhibition of fibrinolysis has been implicated in the prothrombotic state and high incidence of venous thrombosis after surgery.^{14,15}

PLATELETS AND HEMOSTASIS

Platelets contribute a critical role in hemostasis. Derived from bone marrow megakaryocytes, nonactivated platelets circulate as discoid anuclear cells with a lifespan of 8 to 12 days.¹⁶ Under normal conditions, approximately 10% of platelets are consumed to support vascular integrity with $1.2-1.5 \times 10^{11}$ new platelets formed daily.¹⁷ The platelet membrane is characterized by numerous receptors and a surface-connected open canalicular system serving to increase platelet membrane surface area and provide rapid communication between the platelet interior and exterior environment.¹⁸ Under normal circumstances, platelets do not bind the vascular endothelium. However, when injury occurs, platelets contribute to hemostasis by adhering to the damaged vasculature, aggregating with one another to form a platelet plug, and facilitating generation of fibrin crosslinks to stabilize and reinforce the plug. Initially, upon exposure of the ECM, platelets undergo a series of biochemical and physical alterations characterized by three major

phases: adhesion, activation, and aggregation. Exposure of subendothelial matrix proteins (i.e., collagen, vWF, fibronectin) allows for platelet adhesion to the vascular wall. vWF proves particularly important as a bridging molecule between ECM collagen and platelet glycoprotein Ib/factor IX/factor V receptor complexes.¹⁹ Absence of either von Willebrand disease (vWF) or glycoprotein Ib/factor IX/factor V receptors (Bernard-Soulier syndrome) results in a clinically significant bleeding disorder.

In addition to promoting their adhesion to the vessel wall, the platelet interaction with collagen serves as a potent stimulus for the subsequent phase of thrombus formation, termed platelet activation. The generation of thrombin resulting from exposure of tissue factor, functions as a second pathway for platelet activation. Platelets contain two specific types of storage granules: α granules and dense bodies.¹⁸ α granules contain numerous proteins essential to hemostasis and wound repair, including fibrinogen, coagulation factors V and VIII, vWF, platelet-derived growth factor, and others. Dense bodies contain the adenine nucleotides ADP and adenosine triphosphate, as well as calcium, serotonin, histamine, and epinephrine. During the activation phase, platelets release granular contents, resulting in recruitment and activation of additional platelets and propagation of plasma-mediated coagulation.²⁰ During activation, platelets undergo structural changes to develop pseudopod-like membrane extensions and to release physiologically active microparticles, which serve to dramatically increase platelet membrane surface area. Redistribution of platelet membrane phospholipids during activation exposes newly activated glycoprotein platelet surface receptors and phospholipid binding sites for calcium and coagulation factor activation complexes, which is critical to propagation of plasma-mediated hemostasis.¹

During the final phase of platelet aggregation, activators released during the activation phase recruit additional platelets to the site of injury. Newly active glycoprotein IIb/IIIa receptors on the platelet surface bind fibrinogen, thereby promoting cross-linking and aggregation with adjacent platelets.²⁰ The importance of these receptors is reflected by the bleeding disorder associated with their hereditary deficiency, Glanzmann thrombasthenia.

PLASMA-MEDIATED HEMOSTASIS

Plasma-mediated hemostasis was originally described as a cascade or waterfall sequence of steps involving the serial activation of enzymes and cofactors to accelerate and amplify fibrin generation by thrombin.²¹ Trace plasma proteins, activated by exposure to tissue factor or foreign surfaces, initiate this series of reactions culminating in conversion of soluble fibrinogen to insoluble fibrin clot.²² Thrombin generation, the “thrombin burst,” represents the key regulatory step in this process. Thrombin not only generates fibrin but also activates platelets and mediates a host of additional processes affecting inflammation, mitogenesis, and even down-regulation of hemostasis.²³

Traditionally, the coagulation cascade describing plasma-mediated hemostasis has been depicted as extrinsic and intrinsic pathways, both of which culminate in a common pathway in which fibrin generation occurs.²⁴ This cascade model has proven to be an oversimplification,

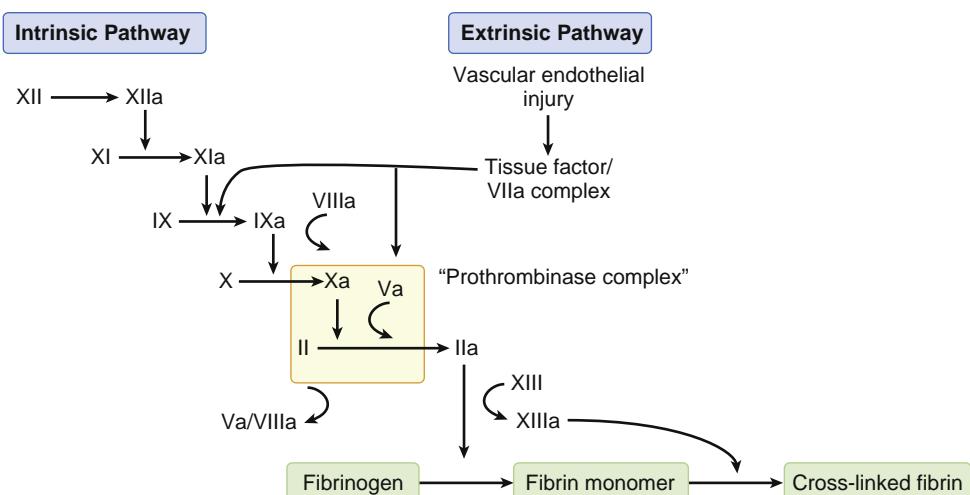


Fig. 50.1 Depiction of the Classic Coagulation Cascade Incorporating Extrinsic and Intrinsic Pathways of Coagulation. (From Slaughter TF. The coagulation system and cardiac surgery. In: Estafanous FG, Barasch PG, Reves JG, eds. *Cardiac Anesthesia: Principles and Clinical Practice*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001: 320, with permission.)

as it does not fully reflect *in vivo* hemostasis. For instance, individuals with deficiencies in the intrinsic pathway (factor XII, prekallikrein, or high molecular weight kininogen) exhibit prolongations of the activated partial thromboplastin time (aPTT), but do not actually experience an increased bleeding risk. Nevertheless, the cascade model remains a useful descriptive tool for organizing discussions of plasma-mediated hemostasis (Fig. 50.1). Coagulation factors are, for the most part, synthesized by the liver and circulate as inactive proteins termed zymogens. The somewhat confusing nomenclature of the classic coagulation cascade derives from the fact that inactive zymogens were identified using Roman numerals assigned in order of discovery. As the zymogen is converted to an active enzyme, a lower-case letter "a" is added to the Roman numeral identifier. For example, inactive prothrombin is referred to as factor II and active thrombin is identified as factor IIa. Some numerals were subsequently withdrawn or renamed as our understanding of the coagulation pathway evolved.

The cascade characterizes a series of enzymatic reactions in which inactive precursors—zymogens—undergo activation to amplify the overall reaction. Each stage of the cascade requires assembly of membrane-bound activation complexes, each composed of an enzyme (activated coagulation factor), substrate (inactive precursor zymogen), cofactor (accelerator or catalyst), and calcium.²⁵ Assembly of these activation complexes occurs on platelet or microparticle phospholipid membranes that localize and concentrate reactants. Coagulation factor activation slows dramatically in the absence of these phospholipid membrane anchoring sites. This requirement functionally confines clot formation to sites of injury.

Extrinsic Pathway of Coagulation

The extrinsic pathway of coagulation is now understood to represent the initiation phase of plasma-mediated hemostasis and begins with exposure of blood plasma to tissue factor.²⁶ Tissue factor is prevalent in subendothelial tissues surrounding the vasculature. Under normal conditions, the vascular endothelium minimizes contact between

tissue factor and plasma coagulation factors. After vascular injury, small concentrations of factor VIIa circulating in plasma form phospholipid-bound activation complexes with tissue factor, factor X, and calcium to promote conversion of factor X to Xa.²² Additionally, the tissue factor/factor VIIa complex also activates factor IX of the intrinsic pathway, further demonstrating the key role of tissue factor in initiating hemostasis.²⁷

Intrinsic Pathway of Coagulation

Classically, the intrinsic or contact activation system was described as a parallel pathway for thrombin generation initiated by factor XII activation after contact with negatively charged surfaces such as glass, dextran sulfate, or kaolin. However, the rarity of bleeding disorders resulting from contact activation factor deficiencies led to our current understanding of the intrinsic pathway as an amplification system to propagate thrombin generation initiated by the extrinsic pathway.²⁸ Recent cell-based models of coagulation suggest that thrombin generation by way of the extrinsic pathway is limited by a natural inhibitor, TFPI,²⁹ but the small quantities of thrombin generated do activate factor XI and the intrinsic pathway. The intrinsic pathway then subsequently amplifies and propagates the hemostatic response to maximize thrombin generation (Fig. 50.2). Although factor XII may be activated by foreign surfaces (i.e., cardiopulmonary bypass [CPB] circuits or glass vials), the intrinsic pathway plays a minor role in the initiation of hemostasis. Proteins of the intrinsic pathway may, however, contribute to inflammatory processes, complement activation, fibrinolysis, kinin generation, and angiogenesis.²⁸

Common Pathway of Coagulation

The final pathway, common to both extrinsic and intrinsic coagulation cascades, depicts thrombin generation and subsequent fibrin formation. Signal amplification results from activation of factor X by both intrinsic (FIXa, FVIIIa, Ca²⁺) and extrinsic (tissue factor, FVIIa, Ca²⁺) tenase complexes. The tenase complexes in turn facilitate formation of the

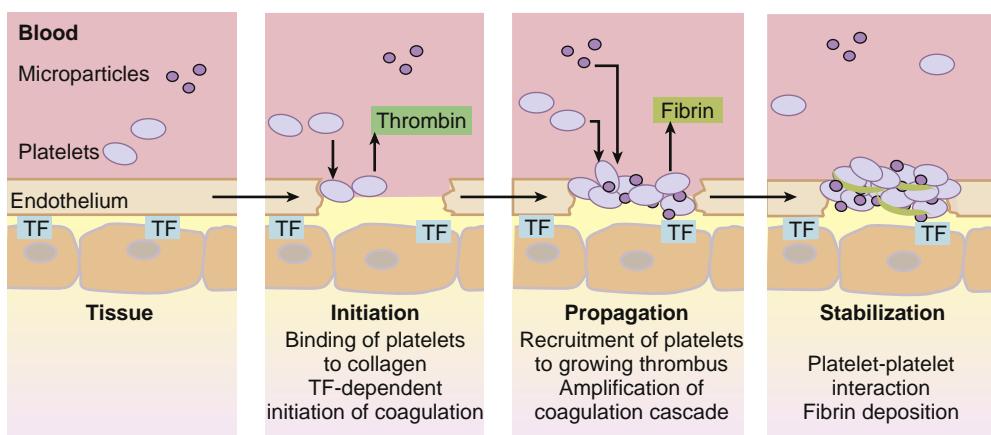


Fig. 50.2 Clot Formation at Vascular Injury Site. Vascular injury exposes subendothelial tissue factor (TF) initiating plasma-mediated hemostasis via the extrinsic pathway. The intrinsic pathway further amplifies thrombin and fibrin generation. Platelets adhere to exposed collagen to undergo activation, resulting in recruitment and aggregation of additional platelets. (From Mackman N, Tilley RE, Key NS. Role of extrinsic pathway of blood coagulation in hemostasis and thrombosis. *Arterioscler Thromb Vasc Biol*. 2007;27:1687-1693, with permission.)

prothrombinase complex (FXa, FII [prothrombin], FVa [cofactor], and Ca^{2+}), which mediates a surge in thrombin generation from prothrombin.³⁰ Thrombin proteolytically cleaves fibrinopeptides A and B from fibrinogen molecules to generate fibrin monomers, which polymerize into fibrin strands to form clot.³⁰ Finally, factor XIIIa, a transglutaminase activated by thrombin, covalently crosslinks fibrin strands to produce an insoluble fibrin clot resistant to fibrinolytic degradation.³¹

Both fibrinogen and factor XIII have been implicated in acquired bleeding disorders. Reduced concentrations of either protein may promote excess postoperative hemorrhage and transfusion requirements. Recent availability of plasma concentrates for both fibrinogen and factor XIII suggest the potential for randomized controlled trials to determine efficacy of these biologics in treatment of acquired coagulopathies.³²

Thrombin generation remains the key enzymatic step regulating hemostasis. Not only does thrombin activity mediate conversion of fibrinogen to fibrin, but it also has a host of other actions. It activates platelets and factor XIII, converts inactive cofactors V and VIII to active conformations, activates factor XI and the intrinsic pathway, up-regulates expression of tissue factor, stimulates vascular endothelial expression of PAI-1 to down-regulate fibrinolytic activity, and suppresses uncontrolled thrombosis through activation of protein C.³³

Intrinsic Anticoagulant Mechanisms

Once activated, regulation of hemostasis proves essential to limit clot propagation beyond the injury site. One simple, yet important, anticoagulant mechanism derives from flowing blood and hemodilution. The early platelet and fibrin clot proves highly susceptible to disruption by shear forces from flowing blood. Blood flow further limits localization and concentration of both platelets and coagulation factors such that a critical mass of hemostatic components may fail to coalesce.^{30,34} However, later in the clotting process, more robust counter-regulatory mechanisms are necessary to limit clot propagation. Four major counter-regulatory pathways have been identified that appear particularly crucial for down-regulating hemostasis: fibrinolysis, TFPI, the protein C system, and serine protease inhibitors (SERPINS).

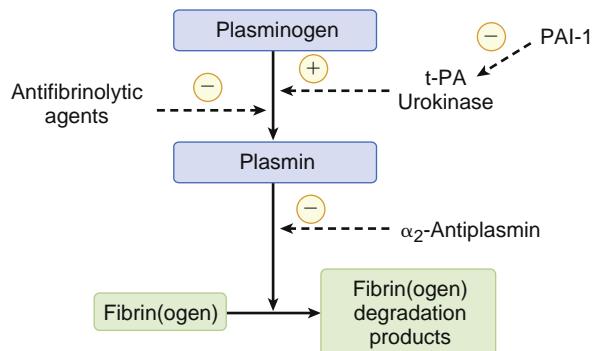


Fig. 50.3 Principal Mediators of Fibrinolysis. Dashed lines depict sites of action for promoters and inhibitors of fibrinolysis. PAI, Plasminogen activator inhibitor; t-PA, tissue plasminogen activator. (From Slaughter TF. The coagulation system and cardiac surgery. In: Estafanous FG, Barasch PG, Reves JG, eds. *Cardiac Anesthesia: Principles and Clinical Practice*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:320, with permission.)

The fibrinolytic system comprises a cascade of amplifying reactions culminating in plasmin generation and proteolytic degradation of fibrin and fibrinogen. As with the plasma-mediated coagulation cascade, inactive precursor proteins are converted to active enzymes, necessitating a balanced system of regulatory controls to prevent excessive bleeding or thrombosis (Fig. 50.3). The principal enzymatic mediator of fibrinolysis is the serine protease, plasmin, which is generated from plasminogen.³⁵ In vivo, plasmin generation is most often accomplished by release of t-PA or urokinase from the vascular endothelium. Activity of t-PA and urokinase is accelerated in the presence of fibrin, which limits fibrinolysis to areas of clot formation. Factor XIIa and kallikrein of the intrinsic pathway also contribute to fibrinolysis through activation of plasminogen after exposure to foreign surfaces.³⁶ Fortunately, fibrinolytic activity is limited by the rapid inhibition of free plasmin. In addition to enzymatic degradation of fibrin and fibrinogen, plasmin inhibits hemostasis by degrading essential cofactors V and VIII and reducing platelet glycoprotein surface receptors essential to adhesion and aggregation.³⁷ Fibrin degradation products also possess mild anticoagulant properties.

TFPI and factor Xa form phospholipid membrane-bound complexes that incorporate and inhibit tissue factor/factor VIIa complexes.³⁸ This inhibition leads to downregulation of the extrinsic coagulation pathway.³⁹ As TFPI rapidly extinguishes tissue factor/VIIa activity, the critical role of the intrinsic pathway to continued thrombin and fibrin generation becomes apparent.²⁸

The protein C system proves particularly important in down-regulating coagulation through inhibition of thrombin and the essential cofactors Va and VIIIa. After binding to TM, thrombin's procoagulant function decreases and instead its ability to activate protein C is augmented.⁴⁰ Protein C, complexed with the cofactor protein S, degrades both cofactors Va and VIIIa. Loss of these critical cofactors limits formation of tenase and prothrombinase activation complexes essential to formation of factor Xa and thrombin, respectively. Additionally, once bound to TM, thrombin is rapidly inactivated and removed from circulation, providing another mechanism by which the protein C pathway down-regulates hemostasis.⁴⁰

The most significant SERPINs regulating hemostasis include AT and heparin cofactor II. AT inhibits thrombin, as well as factors IXa, Xa, XIa, and XIIa.⁴¹ Heparin binds AT causing a conformational change that accelerates AT-mediated inhibition of targeted enzymes. Heparin cofactor II is a more recently discovered SERPIN that inhibits thrombin alone.⁴² Although the precise physiologic role for heparin cofactor II remains unclear, when bound by heparin, its inhibitory activity is dramatically increased.

Disorders of Hemostasis

EVALUATION OF BLEEDING DISORDERS

The perioperative period presents significant challenges to the hemostatic system; therefore, identification and correction of hemostatic disorders can be of vital importance. Unfortunately, assessment of bleeding risk continues to be a challenge and the optimal methods for preoperative evaluation remain controversial. Although routine preoperative coagulation testing of all surgical patients may seem prudent, such an approach is costly and lacks predictive value for detection of hemostatic abnormalities. Standard coagulation tests such as the prothrombin time (PT) and aPTT were designed as diagnostic tests to be used when a bleeding disorder is suspected based on clinical evaluation. As a result, when used as screening tests, these *in vitro* assays are limited in their ability to reflect the *in vivo* hemostatic response.⁴³ For example, because of the nature of establishing normal value ranges for these tests, 2.5% of healthy individuals will have abnormal PT or aPTT values. Meanwhile, those with mild hemophilia A, vWD, and factor XIII deficiency may experience clinically significant bleeding despite having normal values on standard testing.⁴⁴ Consequently, a carefully performed bleeding history remains the single most effective predictor of perioperative bleeding.

A thorough history should focus on prior bleeding episodes.⁴⁵ In particular, patients should be asked whether they have experienced excessive bleeding after hemostatic challenges such as dental extractions, surgery, trauma, or childbirth and whether blood transfusions or reoperation

were required to control the bleeding. Common presentations suggestive of a bleeding disorder may include frequent epistaxis necessitating nasal packing or surgical intervention. Oral surgery and dental extractions prove particularly good tests of hemostasis because of increased fibrinolytic activity on the mucous membranes of the oral cavity. Women with platelet disorders or vWD may experience menorrhagia, and postpartum hemorrhage commonly occurs in those with underlying disorders of hemostasis.⁴⁶ A history of spontaneous nontraumatic hemorrhage proves particularly concerning when associated with hemarthroses or deep muscle bleeding. Identification of a bleeding disorder at an early age or in family members suggests an inherited condition. A careful medication history including direct questions relating to consumption of aspirin and nonsteroidal antiinflammatory drugs (NSAIDs), as well as supplements such as ginkgo and vitamin E.⁴⁷ Finally, inquiries regarding coexisting diseases should be included (i.e., renal, hepatic, thyroid, and bone marrow disorders and malignancy).

For most patients, a thoughtfully conducted bleeding history will eliminate the need for preoperative laboratory-based coagulation testing. Should the preoperative history or physical examination reveal signs or symptoms suggestive of a bleeding disorder, further laboratory testing is indicated. Preoperative coagulation screening tests may be indicated, despite a negative history, in cases in which the planned surgery is commonly associated with significant bleeding (i.e., CPB). Finally, preoperative testing may prove justified in settings in which the patient is unable to provide an adequate preoperative bleeding history. Should evidence of a bleeding disorder be detected, underlying etiologies should be clarified if possible before proceeding with surgery.

INHERITED BLEEDING DISORDERS

Von Willebrand Disease

Inherited disorders of hemostasis include those involving platelet quantity and function, coagulation factor deficiencies, or disorders of fibrinolytic pathways. Among these inherited bleeding disorders, vWD is the most common and is characterized by quantitative or qualitative deficiencies of vWF resulting in defective platelet adhesion and aggregation.⁴⁸ Affecting up to 1% of the population, vWD is categorized into three main types (types 1, 2, and 3), with most cases demonstrating an autosomal dominant inheritance pattern.⁴⁹ Types 1 and 3 lead to varying quantitative vWF deficiencies, while type 2 encompasses four subtypes expressing qualitative defects that affect vWF function. Under normal conditions, vWF plays a critical role in platelet adhesion to the ECM and prevents degradation of factor VIII by serving as a carrier molecule.⁵⁰ Classically, patients with vWD describe a history of easy bruising, recurrent epistaxis, and menorrhagia, which are characteristic of defects in platelet-mediated hemostasis. In more severe cases (i.e., type 3 vWD), concomitant reductions in factor VIII may lead to serious spontaneous hemorrhage, including hemarthroses.

Routine coagulation studies are generally not helpful in the diagnosis of vWD, as the platelet count and PT will be normal in most patients and the aPTT may demonstrate

mild-to-moderate prolongation depending on the level of factor VIII reduction.⁵¹ Instead, initial screening tests involve measurement of vWF levels (vWF antigen) and vWF platelet binding activity in the presence of the ristocetin cofactor, which leads to platelet agglutination. Measurable reductions in factor VIII activity may occur in severe cases.⁵² Increasingly, platelet function tests have replaced bleeding times in assessing for vWD.^{53,54} Mild cases of vWD often respond to DDAVP, which results in the release of vWF from endothelial cell. Use of vWF:factor VIII concentrates (Humate-P, CSL Behring, King of Prussia, PA) may be indicated in the perioperative period if there is a significant bleeding history.⁵⁵

Hemophilias

Although less common than vWD, the hemophilias merit consideration given their diverse clinical presentation. Hemophilia A, factor VIII deficiency, and hemophilia B, factor IX deficiency, are both X-linked inherited bleeding disorders most frequently presenting in childhood as spontaneous hemorrhage involving joints, deep muscles, or both. Hemophilia A occurs with an incidence of 1:5000 males and hemophilia B in 1:30,000 males. While most cases are inherited, nearly one third of cases represent new mutations with no family history.⁵⁶ The severity of the disease depends on an individual's baseline factor activity level.⁵⁷ In mild cases, patients with hemophilia may not be identified until later in life, often after unexplained bleeding with surgery or trauma. Classically, laboratory testing in patients with hemophilia reveals prolongation of the aPTT, whereas the PT, bleeding time, and platelet count remain within normal limits. However, a normal aPTT may also be seen in mild forms of hemophilia; therefore, specific factor analyses need to be performed to confirm the diagnosis and determine the severity of the factor deficiency. In most cases, perioperative management of patients with hemophilia A or B necessitates consultation with a hematologist and administration of recombinant or purified factor VIII or factor IX concentrates, respectively.⁵⁸ Mild cases of hemophilia A may be treated with desmopressin. An increasingly common complication of hemophilia, particularly in the case of hemophilia A, has been the development of alloantibodies directed against the factor VIII protein.⁵⁹ Administration of factor VIII concentrates will fail to control bleeding in patients with high-titer antibodies. Several approaches to reduce bleeding in these patients include: substitution of porcine factor VIII, administration of activated (FEIBA, Shire Inc., Lexington, MA) or non-activated prothrombin complex concentrates (PCCs), or treatment with recombinant factor VIIa (NovoSeven, Novo Nordisk Inc., Bagsvaerd, Denmark).⁶⁰

ACQUIRED BLEEDING DISORDERS

Drug Induced

Medications represent the most significant cause of acquired coagulopathy in perioperative patients. In addition to anticoagulants such as heparin and warfarin, the increasing number of direct oral anticoagulants (DOACs) and antiplatelet drugs have further complicated perioperative management. An understanding of the effect of these agents and strategies for reversal can be critical to reduce

bleeding complications during urgent and emergent procedures. Additionally, there are several classes of medications that may unintentionally increase bleeding risk due to side effects, primarily via platelet inhibition. β -Lactam antibiotics impair platelet aggregation that can result in clinically significant bleeding in patients with higher baseline risk.⁶¹ Nitroprusside,⁶² nitroglycerin,⁶³ and NO⁶⁴ also result in decreased platelet aggregation and secretion. Similarly, selective-serotonin reuptake inhibitors, such as paroxetine, decrease platelet serotonin storage, which inhibits platelet aggregation and may have clinical consequences in individuals with preexisting coagulopathies.⁶⁵ These medications should be considered in patients with an otherwise unexplained coagulopathy.

Liver Disease

Hemostatic defects associated with hepatic failure prove complex and multifactorial. Severe liver disease impairs synthesis of coagulation factors, produces quantitative and qualitative platelet dysfunction, and impedes clearance of activated clotting and fibrinolytic proteins. The liver is the primary site for the production of procoagulant factors including fibrinogen, prothrombin (factor II), factors V, VII, IX, X, XI, XII, as well as the anticoagulants protein C and S, and AT. Laboratory findings commonly associated with liver disease include a prolonged PT and possible prolongation of the aPTT, suggesting that these individuals are at increased risk of bleeding. However, the abnormal values only reflect the decrease in procoagulant factors and do not account for the concomitant decrease in anticoagulant factors.⁶⁶ As a result, patients with chronic liver disease are thought to have a rebalanced hemostasis and actually generate amounts of thrombin equivalent to healthy individuals.⁶⁷

Similarly, thrombocytopenia from splenic sequestration is often observed in patients with liver disease and portal hypertension⁶⁸ and is accompanied by platelet dysfunction due to increased production of endothelial NO and prostacyclin resulting in platelet inhibition.⁶⁹ Despite these alterations, increases in vWF commonly observed in these patients may serve to restore platelet function. Also, levels of the plasma metalloprotease ADAMTS13, responsible for cleaving vWF multimers, are decreased in chronic liver disease and result in high circulating levels of large vWF multimers that promote platelet aggregation.⁷⁰ This increase in vWF may in part correct for thrombocytopenia and platelet dysfunction but also can result in a prothrombotic state and increased clotting risk.

Fibrinolysis of formed clot is also aberrant in patients with liver disease. Normally, fibrin clot is degraded by plasmin, which is converted to its active form by t-PA and urokinase plasminogen activator (u-PA). Excessive fibrinolysis is prevented by thrombin-activatable fibrinolysis inhibitor (TAFI), which blocks activation of plasmin from plasminogen. TAFI is synthesized by the liver and as levels are decreased in patients with chronic liver disease, it was believed that such individuals are at increased bleeding risk due to hyperfibrinolysis.⁷¹ However, levels of PAI-1, a SERPIN of t-PA and u-PA, are also increased in liver disease, which may in actuality normalize fibrinolysis.⁷²

In summary, procoagulant and anticoagulant hemostatic mechanisms are rebalanced in patients with chronic

liver disease, but this balance is easily disrupted and these patients are at risk for both bleeding and inappropriate clotting.⁷³ Traditional coagulation testing does not correlate with bleeding risk in these patients, which has led to studies looking at the use of viscoelastic coagulation testing using thromboelastography (TEG) or rotational thromboelastometry (ROTEM) as a means of assessing functional coagulation and guiding perioperative blood product transfusion and administration of antifibrinolytic agents.^{73,74}

Renal Disease

Platelet dysfunction commonly occurs in association with chronic renal failure and uremia, as reflected by a prolonged bleeding time and propensity for bleeding associated with surgery or trauma. The underlying mechanisms are multifactorial but have mostly been attributed to decreased platelet aggregation and adhesion to injured vessel walls. Impaired adhesion is likely due to defects of the glycoprotein IIb/IIIa, which facilitates platelet binding of fibrinogen and vWF.^{75,76} Additionally, accumulation of guanidinosuccinic acid and the resulting increase in endothelial NO synthesis further decreases platelet responsiveness.⁷⁷ Red blood cell (RBC) concentration has also been speculated to contribute to platelet dysfunction, as correction of anemia results in shortened bleeding times, presumably related to the role of RBCs in causing platelet margination along the vessel wall under laminar flow conditions.⁷⁸ Both dialysis and correction of anemia have been reported to shorten bleeding times in patients with chronic renal failure. Treatment of platelet dysfunction related to chronic renal disease includes transfusion of cryoprecipitate (rich in vWF) or administration of desmopressin (0.3 µg/kg), which stimulates release of vWF from endothelial cells.⁷⁹ Additionally, conjugated estrogens (0.6 mg/kg intravenously for 5 days) have been demonstrated to shorten bleeding times,⁸⁰ perhaps via decreased generation of NO.⁸¹

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a pathologic hemostatic response to tissue factor/factor VIIa complex that leads to excessive activation of the extrinsic pathway, which overwhelms natural anticoagulant mechanisms and generates intravascular thrombin. Numerous underlying disorders may precipitate DIC, including trauma, amniotic fluid embolus, malignancy, sepsis, or incompatible blood transfusions.⁸² Most often, DIC presents clinically as a diffuse bleeding disorder associated with consumption of coagulation factors and platelets during widespread microvascular thrombotic activity, which results in multiorgan dysfunction. Laboratory findings typical of DIC include reductions in platelet count; prolongation of the PT, aPTT, and thrombin time (TT); and elevated concentrations of soluble fibrin and fibrin degradation products. However, DIC is both a clinical and laboratory diagnosis; hence, laboratory data alone do not provide sufficient sensitivity or specificity to confirm a diagnosis.⁸³ For example, chronic DIC states have been identified with relatively normal screening coagulation tests accompanied by elevated concentrations of soluble fibrin and fibrin degradation products.⁸⁴ Management of DIC requires management of the underlying condition precipitating hemostatic activation. Otherwise, treatment is mostly supportive and includes

selective blood component transfusions to replete coagulation factors and platelets consumed in the process. The use of anticoagulants such as heparin remains controversial with recommendations that its use be limited to conditions with the highest thrombotic risk.⁸⁵ Antifibrinolytic therapy generally is contraindicated in DIC, owing to the potential for catastrophic thrombotic complications.⁸⁶

CARDIOPULMONARY BYPASS-ASSOCIATED COAGULOPATHY

Institution of CPB by directing blood flow through an extracorporeal circuit causes significant perturbations to the hemostatic system. Initial priming of the bypass circuit results in hemodilution and thrombocytopenia.⁸⁷ Adhesion of platelets to the synthetic surfaces of the bypass circuit further decreases platelet counts and contributes to platelet dysfunction.⁸⁸ During CPB, expression of platelet surface receptors important for adhesion and aggregation (GPIb, GPIb/IIIa) are downregulated and the number of vWF-containing α granules are decreased, thereby impairing platelet function.⁸⁹ Furthermore, induced hypothermia during CPB results in reduced platelet aggregation and plasma-mediated coagulation by decreasing clotting factor production and enzymatic activity.⁹⁰ Hyperfibrinolysis may also occur as a result of CPB, supporting the use of antifibrinolytic drugs to decrease intraoperative blood loss.⁹¹

TRAUMA-INDUCED COAGULOPATHY

Uncontrolled hemorrhage is a frequent cause of trauma-related deaths. Coagulopathy in this setting may be due to acidosis, hypothermia, and hemodilution from resuscitation; however, an independent acute coagulopathy is also experienced by these individuals.⁹² Termed trauma-induced coagulopathy (TIC) or acute traumatic coagulopathy, this process involves disordered hemostasis and increased fibrinolysis observed early after injury.⁹³ The anticoagulant effect of activated protein C (APC) is thought to play a primary role in TIC by decreasing thrombin generation via inhibition of factor Va and VIIIa and promoting fibrinolysis through inhibition of PAI-1. The relevance of APC in the development of TIC is supported by the association of hypoperfusion and increasing injury severity with increased levels of APC activity.⁹⁴ Hypoperfusion is thought to be the stimulus for APC activation.⁹⁵ Additionally, degradation of the endothelial glycocalyx (EG), a gel-like matrix lining the vascular endothelium, is linked to factors associated with trauma, including tissue damage, hypoperfusion, elevated catecholamines, and inflammation. The EG has anticoagulant properties and contains proteoglycans such as syndecan-1, hyaluronic acid, heparan sulfate, and chondroitin sulfate which are shed during endothelial injury. Shedding of proteoglycans results in an “autoheparinization” phenomenon that contributes to TIC. Markers of EG degradation have been found to be associated with inflammation, coagulopathy, and increased mortality in trauma patients.⁹⁶

Although platelet counts appear to be normal, platelet dysfunction contributes to increased bleeding in TIC. Significant platelet hypofunction in response to various agonists, including ADP, arachidonic acid, and collagen, has

BOX 50.1 Hypercoagulable States and Risk for Perioperative Thrombosis

High Risk

Heparin-induced thrombocytopenia
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Antiphospholipid antibody syndrome

Moderate Risk

Factor V Leiden genetic polymorphism
Prothrombin G20210A genetic polymorphism
Hyperhomocysteinemia
Dysfibrinogenemia
Postoperative prothrombotic state
Malignancy
Immobilization

been observed acutely in trauma patients prior to resuscitation.^{97,98} It is hypothesized that trauma patients experience “platelet exhaustion” as a result of activation from widespread release of ADP from injured tissues. This diffuse activation renders platelets unresponsive to subsequent stimulation.⁹⁸ Platelet insensitivity to ADP is also associated with increased susceptibility of clots to tPA-mediated fibrinolysis.⁹⁹ The importance of early treatment to reduce hyperfibrinolysis in trauma is supported by the findings of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) trial, which demonstrated a mortality benefit from early administration of tranexamic acid (TXA).^{100,101}

PROTHROMBOTIC STATES

Thrombophilia, a propensity for thrombotic events, commonly manifests clinically in the form of venous thrombosis (frequently deep venous thrombosis [DVT] of the lower extremity).¹⁰² As with bleeding disorders, thrombophilia may result from inherited or acquired conditions (Box 50.1). The pathogenesis of thrombosis is thought to be due to Virchow’s triad (blood stasis, endothelial injury, and hypercoagulability).⁹ In the majority of cases, a risk factor or precipitating event is identified; however, a single factor generally does not result in clinically significant thrombosis.¹⁰³ Instead, multiple factors act synergistically to increase risk.¹⁰⁴ For example, thrombotic complications often occur after surgery or during pregnancy in association with obesity, underlying malignancy, or an inherited thrombophilia.¹⁰⁵ Random screening of asymptomatic patients for thrombotic risk has not proven cost effective or clinically efficacious.^{106,107} As with bleeding disorders, a history focusing on prior thrombotic events, family history of thrombosis, and concurrent drug therapy offers greater predictive value than random screening.

INHERITED THROMBOTIC DISORDERS

Improvements in biochemical and molecular testing have dramatically improved our understanding of blood coagulation and the prevalence of prothrombotic disorders.¹⁰⁸

Because of more specific testing, an inheritable thrombotic predisposition is identified in as many as 50% of patients presenting with venous thromboembolism.¹⁰⁹ The most common inherited prothrombotic conditions include single point mutations in genes for factor V (factor V Leiden) or prothrombin (prothrombin G20210A). In the case of the factor V Leiden, the mutation results in APC resistance whereby the essential cofactor Va is no longer susceptible to APC-mediated degradation. This simple alteration in balance between hemostasis and the APC counter-regulatory system induces a prothrombotic condition present in approximately 5% of the Caucasian population.¹¹⁰ In the case of the prothrombin gene mutation, increased prothrombin concentrations in plasma generate a hypercoagulable state. Less common inherited forms of thrombophilia include deficiencies of AT, protein C, or protein S.¹⁰⁸ Inherited forms of thrombophilia are characterized by highly variable penetrance affected by blood type, sex, and other confounding variables. Environmental factors such as oral contraceptive use, pregnancy, immobility, infection, surgery, or trauma greatly affect the incidence of thrombosis in those with an inherited predisposition.¹¹¹ In the absence of coexisting precipitating conditions, presence of a family history, test abnormality suggesting thrombophilia, or history of thrombosis, risks associated with long-term preventive anticoagulation may outweigh potential benefits.¹⁰⁶ After a thrombotic complication, however, these patients most often are managed with life-long anticoagulation.

ACQUIRED THROMBOTIC DISORDERS

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) describes an acquired autoimmune disorder characterized by venous or arterial thromboses, or both, and recurrent pregnancy loss. This syndrome may occur in association with autoimmune disorders such as systemic lupus erythematosus or rheumatoid arthritis, or it may occur in isolation. APS results from development of autoantibodies directed against phospholipid-binding proteins, which affect the coagulation system and is associated with up to 10% of cases of DVT and 6% of pregnancy-associated morbidity.¹¹² Characteristically, APS results in mild prolongation of the aPTT and positive testing for lupus anticoagulant, anticardiolipin or anti-β2-glycoprotein I antibodies.¹¹³ Antibodies associated with APS interfere with phospholipids common to many laboratory-based tests of coagulation. Despite the prolonged aPTT, APS poses no increased bleeding risk but rather increases the potential for thrombosis. Isolated prolongation of an aPTT in a preoperative patient merits consideration of the diagnosis of APS. Patients with this syndrome who have experienced a thrombotic complication are at increased risk for recurrent thrombosis and most often are managed by life-long anticoagulation.¹¹⁴

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) describes an autoimmune-mediated drug reaction occurring in as many as 5% of patients receiving heparin therapy. Patients with HIT experience a mild-to-moderate thrombocytopenia. As opposed to other drug-induced thrombocytopenias, HIT

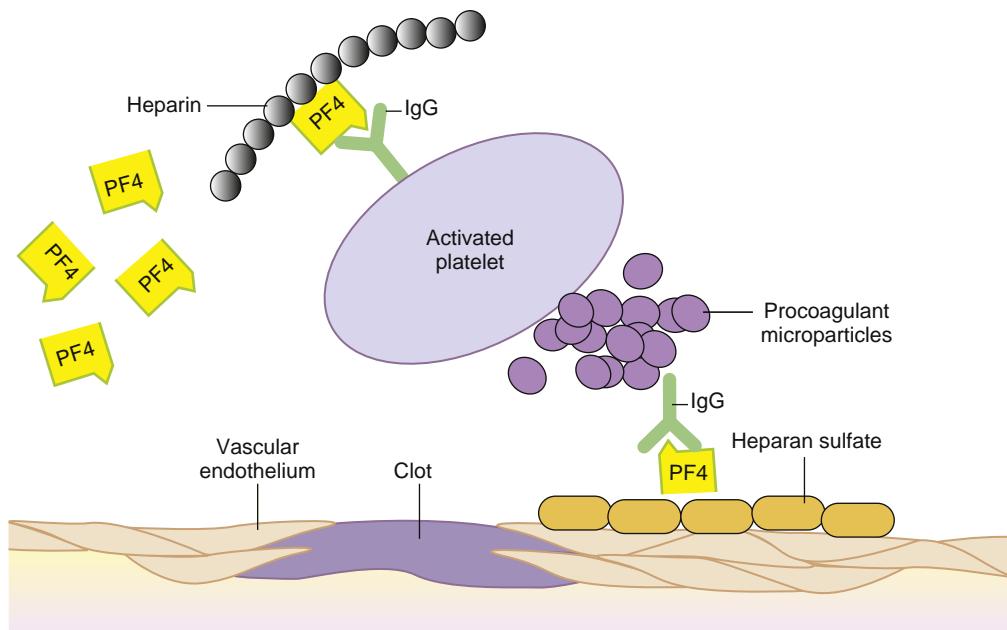


Fig. 50.4 Mechanisms Underlying Thrombosis in Heparin-Induced Thrombocytopenia. Immune complexes composed of heparin, platelet factor 4 (PF4), and antibodies bind to platelet surface Fc_γ receptors to activate platelets. PF4/heparin immune complexes further activate vascular endothelium, monocytes, and macrophages to increase tissue factor expression. IgG, Immunoglobulin G. (From Slaughter TF, Greenberg CS. Heparin-associated thrombocytopenia and thrombosis: Implications for perioperative management. *Anesthesiology*. 1997;87:669, with permission.)

results in platelet activation and potential for venous and arterial thromboses.¹¹⁵ Evidence suggests that HIT is mediated by immune complexes (composed of immunoglobulin G [IgG] antibody, platelet factor 4 [PF4], and heparin) that bind platelet Fc_γ receptors to activate platelets. Anti-PF4/heparin antibodies may “activate” vascular endothelium, monocytes, and macrophages by up-regulating tissue factor expression (Fig. 50.4). Risk factors for development of HIT include patient population, gender, and heparin formulation used. Women are at increased risk of HIT (odds ratio [OR] 2.37; 95% CI 1.37–4.09) as are surgical patients compared to medical patients (OR 3.25; 95% CI 1.98–5.35).¹¹⁶ Given the high doses of heparin administered during cardiac surgery with CPB, these patients have a higher incidence of anti-PF4 antibody development (up to 50%); however, the incidence of HIT in this population appears to be similar to other surgical groups.¹¹⁷ Use of unfractionated heparin (UFH) carries a greater risk of HIT development than low-molecular-weight heparin (LMWH) (absolute risk 2.6% vs. 0.2%).¹¹⁸ Patients developing HIT during heparin therapy experience substantially increased risk for thrombosis (OR 20:40, absolute risk 30% to 75%).¹¹⁵

HIT manifests clinically as thrombocytopenia occurring 5 to 14 days after initiating heparin therapy. With prior heparin exposure, thrombocytopenia or thrombosis may occur within 1 day. A diagnosis of HIT should be entertained for any patient experiencing thrombosis or thrombocytopenia (absolute or relative $\geq 50\%$ reduction in platelet count) during or after heparin administration. Although HIT remains a clinical diagnosis, HIT antibodies testing should be undertaken to confirm the diagnosis. The enzyme-linked immunosorbent assay (ELISA) is sensitive, but not as specific as the serotonin release assay (SRA), because the SRA indicates heparin-induced platelet activation. For many intensive care patients, a positive ELISA test

does not lead to a positive SRA, which means these patients are unlikely to have HIT.¹¹⁹

In cases where HIT is suspected, heparin must be discontinued immediately (including UFH, LMWH, heparin-bonded catheters, heparin flushes). Alternative nonheparin anticoagulation must be administered concurrently. In most cases, a direct thrombin inhibitor (DTI, e.g., bivalirudin, lepirudin, or argatroban) is substituted for heparin until adequate prolongation of the international normalized ratio (INR) can be achieved with warfarin. Initiation of warfarin alone is contraindicated for HIT treatment because the initial decreased synthesis of proteins C and S enhances the patient’s prothrombotic state. Platelet transfusions should be held unless the patient is severely thrombocytopenic ($<20 \times 10^9/L$) with signs of bleeding. Use of DOACs (e.g., rivaroxaban, apixaban, dabigatran, edoxaban) is being investigated.¹²⁰

Typically, PF4/heparin immune complexes are cleared from the circulation within 3 months. If possible, patients experiencing HIT should avoid future exposure to UFH; however, several reports describe subsequent limited perioperative reexposure to UFH after laboratory testing to ensure absence of PF4/heparin immune complexes. If titers remain high, treatment with plasmapheresis for rapid antibody clearance is an alternative plan, but risks and benefits should be discussed with the hematologists.¹²¹ Otherwise, bivalirudin, the shortest acting DTI, is the alternative agent for anticoagulation while on CPB.

MONITORING COAGULATION

Traditionally, perioperative coagulation monitoring has focused on (1) preoperative testing to identify patients at increased risk for perioperative bleeding and (2) intraoperative monitoring of heparin therapy during cardiac and

vascular surgery. The ideal test for perioperative coagulation should be simple to perform, accurate, reproducible, diagnostically specific, and cost effective. No current coagulation monitor meets these expectations; however, integrating results from multiple forms of monitoring may provide valuable diagnostic insight into perioperative coagulopathies.

COMMON LABORATORY-BASED MEASURES OF COAGULATION

Prothrombin Time

The PT assesses the integrity of the extrinsic and common pathways of plasma-mediated hemostasis. It measures time required in seconds for clot formation to occur after mixing a sample of patient plasma with tissue factor (thromboplastin) and calcium. It is sensitive to deficiencies in fibrinogen, and factors II, V, VII, or X. As three of these factors have vitamin K-dependent synthesis (factors II, VII, and X), the PT assay has been used to monitor anticoagulation with vitamin K antagonists (VKAs) such as warfarin. The thromboplastin reagent, derived from animal or recombinant sources, can vary in its ability to bind factor VII and initiate coagulation, which limits interlaboratory comparisons. Given the importance of monitoring PT results for patients on long-term warfarin therapy, the INR was introduced as a means of normalizing PT results among different laboratories.¹²²

Thromboplastin reagents are tested against an international recombinant standard and assigned an international sensitivity index (ISI) based on the results. The INR subsequently is calculated as $INR = (\text{patient PT}/\text{standard PT})^{\text{ISI}}$, in which the standard PT represents the geometric mean of multiple normal samples from the testing laboratory. Institution of the INR substantially reduced interlaboratory variations. The PT is more sensitive at detecting decreases in factors VII and X than levels of fibrinogen and factors II and V; however, due to variations in thromboplastin reagents, factor levels as low as 40% to 50% may not prolong the PT.¹²³

Any prolongation of the PT should be assessed further with mixing studies to determine whether delayed clot formation is attributable to a coagulation factor deficiency or an inhibitor (e.g., antiphospholipid antibody, fibrin degradation products). The mixing study is performed by mixing the patient's plasma sample with "normal" donor plasma. In the case of a coagulation factor deficiency, time to clot formation will correct whereas time to clot formation will not correct in the presence of an inhibitor.

Activated Partial Thromboplastin Time

The aPTT assesses integrity of the intrinsic and common pathways of plasma-mediated hemostasis. It measures the time required in seconds for clot formation to occur after mixing a sample of patient plasma with phospholipid, calcium, and an activator of the intrinsic pathway of coagulation (e.g., celite, kaolin, silica, or ellagic acid). The aPTT is more sensitive to deficiencies in factors VIII and IX than other factors in the intrinsic and common pathways. In most cases, coagulation factor levels below 30% to 40% of normal are detectable; however, aPTT reagents vary in their sensitivity to factor concentrations and may not be

prolonged until levels drop below 15% for some factors.¹²⁴ Additionally, as there is no reference standard reagent for the aPTT analogous to the INR for PT, individual institutions must set their own normal ranges and aPTT values cannot be compared between laboratories.

Monitoring anticoagulation during cardiac and vascular surgery remains necessary given the widely acknowledged pharmacokinetic and pharmacodynamic response to heparin. Patient-specific factors affecting response to heparin include age, weight, intravascular volume, and concentrations of AT, heparin cofactor II, PF4, and other heparin-binding proteins. Therefore, patients experience widely divergent anticoagulant responses to identical weight-based doses of heparin. In situations where heparin therapy must be initiated in patients with a baseline aPTT prolongation (lupus anticoagulant or factor inhibitors), alternative tests such as anti-factor Xa activity or heparin level measurements must be used.

Anti-Factor Xa Activity

The anti-factor Xa activity assay or factor Xa inhibition test is being used with increasing frequency to monitor heparin anticoagulation instead of, or in addition to, the aPTT assay. The assay involves combining patient plasma with reagent factor Xa and an artificial substrate that releases a colorimetric signal after factor Xa cleavage, thereby providing a functional assessment of heparin anticoagulant effect.¹²⁵ While aPTT values can be affected by several patient factors such as coagulation factor deficiencies, factor inhibitors, or the presence of lupus anticoagulant, measurement of the heparin-bound AT inhibition of factor Xa activity is not influenced by these variables. Anti-factor Xa testing can also be used to measure the effect of other anticoagulants such as LMWH, fondaparinux, and factor Xa inhibitors. As with the aPTT assay, the anti-factor Xa test lacks adequate standardization, and activity levels vary based on the type of assay used, and patient population assayed.¹²⁶ Furthermore, significant discordance between aPTT and anti-factor Xa results can be observed in hospitalized patients receiving heparin therapy.¹²⁷ Data supporting the use of anti-factor Xa over aPTT is sparse; however, it may be helpful to use anti-factor Xa testing in combination with the aPTT to monitor both heparin effect and generalized coagulation status, respectively.

Platelet Count and Bleeding Time

The platelet count remains a standard component in screening for coagulation abnormalities. Automated platelet counts are performed in bulk using either optical-based or impedance-based measurements. Recommendations regarding optimal platelet counts prove somewhat arbitrary, but platelet counts exceeding 100,000 μL commonly are associated with normal hemostasis. Abnormally low platelet counts merit further assessment, including a visual platelet count from a blood smear. Sample hemodilution and platelet clumping are common etiologies for falsely low platelet counts.

With the growth of point-of-care platelet function monitors, the bleeding time has declined in popularity. Limitations of the bleeding time include poor reproducibility, time needed to perform the test, and potential for scarring. Furthermore, the bleeding time is affected by numerous

confounding variables, including skin temperature, skin thickness, age, ethnicity, anatomic test location, and a host of other factors.¹²⁸ In general, the bleeding time is not predictive of bleeding and for that reason its use as a preoperative screening test to assess bleeding risk is not recommended.¹²⁹

COMMON POINT-OF-CARE MEASURES OF COAGULATION

Although laboratory-based measures of coagulation remain the mainstay of preoperative coagulation testing, increasing availability of sensitive and specific point-of-care coagulation monitoring may soon offer opportunities to direct blood component and hemostatic drug therapy more specifically without delays inherent to standard laboratory testing. Commercially available point-of-care tests applicable in the perioperative setting may be considered in four broad categories: (1) functional measures of coagulation that measure the intrinsic ability of blood to generate clot, (2) heparin concentration monitors, (3) viscoelastic measures of coagulation, and (4) platelet function monitors.

Activated Clotting Time

The activated clotting time (ACT), described by Hattersley in 1966 as a variation of the Lee-White whole blood clotting time, employs a contact activation initiator, typically celite (diatomaceous earth) or kaolin, to accelerate clot formation and reduce time for assay completion.¹³⁰ Current commercial ACT monitors automate clot detection. One of the more widely available ACT monitors uses a glass test tube containing a small magnet (Hemochron Response Whole Blood Coagulation System, ITC, Edison, NJ). After adding sample blood, the tube is placed into the analyzer and the tube is rotated slowly at 37°C, allowing the magnet to maintain contact with a proximity detection switch. As fibrin clot forms, the magnet becomes entrapped and dislodged from the detection switch, thereby triggering an alarm to signal completion of the ACT. Another ACT device uses a “plumb bob” flag assembly that is raised and released repeatedly to settle in the sample vial containing blood and contact activator (Hepcon HMS Plus, Medtronic, Minneapolis, MN). With clot formation, the flag descent slows, which triggers an optical detector and sets off an alarm to signal completion of the ACT.

The ACT in normal individuals is 107 ± 13 seconds. Because the ACT measures clot formation by way of intrinsic and common pathways, heparin and other anticoagulants prolong time to clot formation. The ACT proves somewhat resistant to platelet dysfunction and thrombocytopenia. ACT testing remains a popular perioperative coagulation monitor because of its simplicity, low cost, and linear response at high heparin concentrations. Limitations of ACT monitoring include lack of sensitivity at low heparin concentrations and poor reproducibility.¹³¹ Further limitations of the ACT include artefactual prolongation of results with hemodilution or hypothermia, and values beyond 600 seconds exceed the linear response range for the assay. Although duplicate measurements improve results, newer electrochemically based ACT analyzers (i-STAT, Abbott, Princeton, NJ) improve reproducibility such that single ACT determinations may prove adequate.

Heparin Concentration Measurement

Protamine titration remains the most popular point-of-care method for determining heparin concentration in perioperative settings. Protamine, a strongly basic polycationic protein, directly inhibits heparin in a stoichiometric manner. In other words, 1 mg of protamine will inhibit 1 mg (~100 units) of heparin, thereby forming the basis for protamine titration as a measure of heparin concentration. As increasing concentrations of protamine are added to a sample of heparin-containing blood, time to clot formation decreases until the point at which the protamine concentration exceeds heparin concentration to delay clot formation. If a series of blood samples with incremental doses of protamine are analyzed, the sample in which the protamine and heparin concentrations are most closely matched will clot first. This methodology allows for an estimate of heparin concentration. Assuming that the heparin-protamine titration curve for an individual patient remains constant throughout the operative period, protamine titration methods may estimate heparin doses required to achieve a desired plasma heparin concentration or the protamine dose needed to reverse a given heparin concentration in blood.¹³² Current point-of-care heparin concentration monitoring employs automated measurement techniques (Hepcon HMS Plus, Medtronic, Minneapolis, MN). The advantages of measuring heparin concentration include sensitivity for low heparin concentrations as well as relative insensitivity to hemodilution and hypothermia. A major limitation of heparin concentration monitoring is failure to assess directly for an anticoagulant effect. For example, consider a patient with a homozygous deficiency of AT; in this case, heparin concentration determination alone would fail to identify the lack of anticoagulant effect after heparin administration.

Viscoelastic Measures of Coagulation

Initially developed in the 1940s, viscoelastic measures of coagulation have undergone a resurgence in popularity. The unique aspect of viscoelastic monitors lies in their ability to measure the entire spectrum of clot formation in whole blood from early fibrin strand generation through clot retraction and fibrinolysis. The early TEG developed by Hartert in 1948 has evolved into two independent viscoelastic monitors: the modern TEG (TEG 5000 Thromboelastograph Hemostasis Analyzer System, Haemoscope, Braintree, MA) and ROTEM (TEM Systems, Durham, NC).¹³³ In the case of the TEG 5000, a small (0.35-mL) sample of whole blood is placed into a disposable cuvette within the instrument. The cuvette is maintained at a temperature of 37°C and continuously rotates around an axis of approximately 5 degrees. A sensor “piston” attached by a torsion wire to an electronic recorder is lowered into the blood within the cuvette. Addition of an activator, most often kaolin or celite, initiates clot formation. As the fibrin-platelet plug evolves, the piston becomes enmeshed within the clot, transferring rotation of the cuvette to the piston, torsion wire, and electronic recorder.¹³⁴

Although variables derived from the TEG tracing do not coincide directly with laboratory-based tests of coagulation, the TEG depicts characteristic abnormalities in clot formation and fibrinolysis. Various parameters describing clot formation and lysis are identified and measured by the TEG.

For example, the R value (reaction time) measures time to initial clot formation. The R value may be prolonged by a deficiency of one or more plasma coagulation factors or inhibitors such as heparin. Maximum amplitude provides a measure of clot strength and may be decreased by either qualitative or quantitative platelet dysfunction or decreased fibrinogen concentration. The α angle and K (BiKoatugulierung or coagulation) values measure rate of clot formation and may be prolonged by any variable slowing clot generation such as a plasma coagulation factor deficiency or heparin anticoagulation. Modification of clotting activators may be incorporated to assess platelet or fibrin contributions to clot strength.

In a somewhat analogous manner, ROTEM measures viscoelastic changes in a sample of whole blood subjected to coagulation activation. Specific activators differ from that of the TEG with resulting quantitative measures termed (1) coagulation time (seconds), (2) α angle (clot formation time; seconds), (3) maximal clot firmness (MCF; millimeter), and (4) lysis time (LT; second) (Fig. 50.5 on TEG in attached file).

In contrast to TEG and ROTEM, an alternative viscoelastic measure of coagulation (Sonoclot Analyzer, Sienco Inc., Arvada, CO) immerses a rapidly vibrating probe into a 0.4-mL sample of blood. As clot formation proceeds, impedance to probe movement through the blood increases to generate an electrical signal and characteristic clot signature. The analyzer signature may be used to derive the ACT and to provide information regarding clot strength and presence of fibrinolysis.

Viscoelastic monitors generate characteristic diagrams by translating mechanical resistance to sensor movement within a sample of whole blood to an electronic waveform subject to quantitative analysis.¹³³ One of the more common applications for viscoelastic monitoring has been real-time detection of excess fibrinolysis during liver transplantation or cardiac surgery. Evidence suggests that viscoelastic monitoring may prove beneficial in differentiating surgically related bleeding from that due to a coagulopathy. When used as one component of a diagnostic algorithm, both TEG and ROTEM have been demonstrated to reduce blood administration.^{135,136} More widespread application of viscoelastic monitoring has been hindered by lack of specificity associated with abnormal findings and qualitative assay interpretation.¹³⁷ Digital automation of these instruments has simplified interpretation and improved reproducibility.

Platelet Function Monitors

Assessment of platelet function has proved challenging for several reasons. Historically, tests of platelet function are costly, time consuming, and technically demanding. Platelet dysfunction may occur as a result of diverse inherited or acquired disorders affecting surface receptors involved in adhesion or aggregation, storage granules, internal activation pathways, phospholipid membranes, or other mechanisms.¹³⁸ Lack of standardized quality controls necessitates use of local donor blood to establish normal control ranges. Complicating assessment further is the fact that platelets are highly susceptible to activation or desensitization during sample collection, transport, storage, and processing.

The technique for platelet aggregometry was developed in the 1960s and soon became the gold standard

for assessment of platelet function.¹³⁹ The classic method involves centrifugation of patient blood to obtain platelet-rich plasma, which is then analyzed in a cuvette at 37°C placed between a light source and photocell. Addition of platelet agonists such as ADP, epinephrine, collagen, and ristocetin, stimulates platelet aggregation, which in turn results in a decrease in turbidity of the solution and an increase in light transmission. Patterns based upon the kinetics and amplitude of response to these various agonists are associated with specific platelet disorders and aid in diagnosis.¹⁴⁰ In an effort to decrease the labor required to prepare the platelet rich plasma solution as well as to include the effect of RBCs and plasma proteins on platelet function, a technique for whole blood aggregometry was developed.¹⁴¹ Whole blood aggregometry uses platinum electrodes onto which platelets adhere. Platelet aggregation induced by agonists results in increased adhesion of aggregates to the electrodes, raising the impedance which is measured over time. A multichannel system (Multiplate Analyzer, Roche Diagnostics, Indianapolis, IN) is available and is used to diagnose platelet dysfunction as well as monitor anti-platelet therapy.¹⁴² Flow cytometry employing fluorescent-labeled antibodies provides another sensitive method for quantitating platelet activation, responsiveness, and surface receptor availability.¹⁴³ Despite representing standards of care, these measurements remain technically challenging, costly, and time-consuming laboratory-based assays.

Although viscoelastic measures of coagulation (i.e., TEG or ROTEM) may detect platelet dysfunction, the sensitivity and specificity are limited. Incorporation of a platelet mapping assay into TEG provides a method for viscoelastic measurement of drug-induced platelet inhibition with reasonable correlation to optical aggregometry.¹³⁴

Fortunately, an increasing array of platelet function assays specifically designed as point-of-care instruments are becoming available.¹⁴⁰ As a measure of primary hemostasis, a platelet function analyzer (PFA-100, Siemens, Tarrytown, NY) increasingly has replaced the bleeding time in assessment of hemostasis. The PFA-100 incorporates high-shear conditions to simulate small vessel injury in the presence of either ADP or epinephrine, both potent platelet activators.¹⁴⁴ Time to clot-mediated aperture occlusion is reported as closure time. The PFA-100 has proven effective in detecting vWD and aspirin-mediated platelet dysfunction. This instrument, as a component of a standardized screening protocol, reduces time to identify and classify platelet dysfunction. Limitations of the PFA-100 include interference by thrombocytopenia and hemodilution.

Many other different point-of-care platelet function testing devices are on the market today. It is important to keep in mind that monitors from different manufacturers measure differing aspects of platelet-mediated or plasma-mediated hemostasis. When using different instruments, results may vary from "severe" platelet dysfunction to "no platelet dysfunction" in a single sample of blood. Before adopting any point-of-care monitoring, an understanding of the quality assurance requirements, test methodology, and concomitant strengths and weaknesses are essential to inform patient care. Also, in considering any point-of-care coagulation testing, it must be recognized that results will not necessarily mirror those reported from laboratory-based

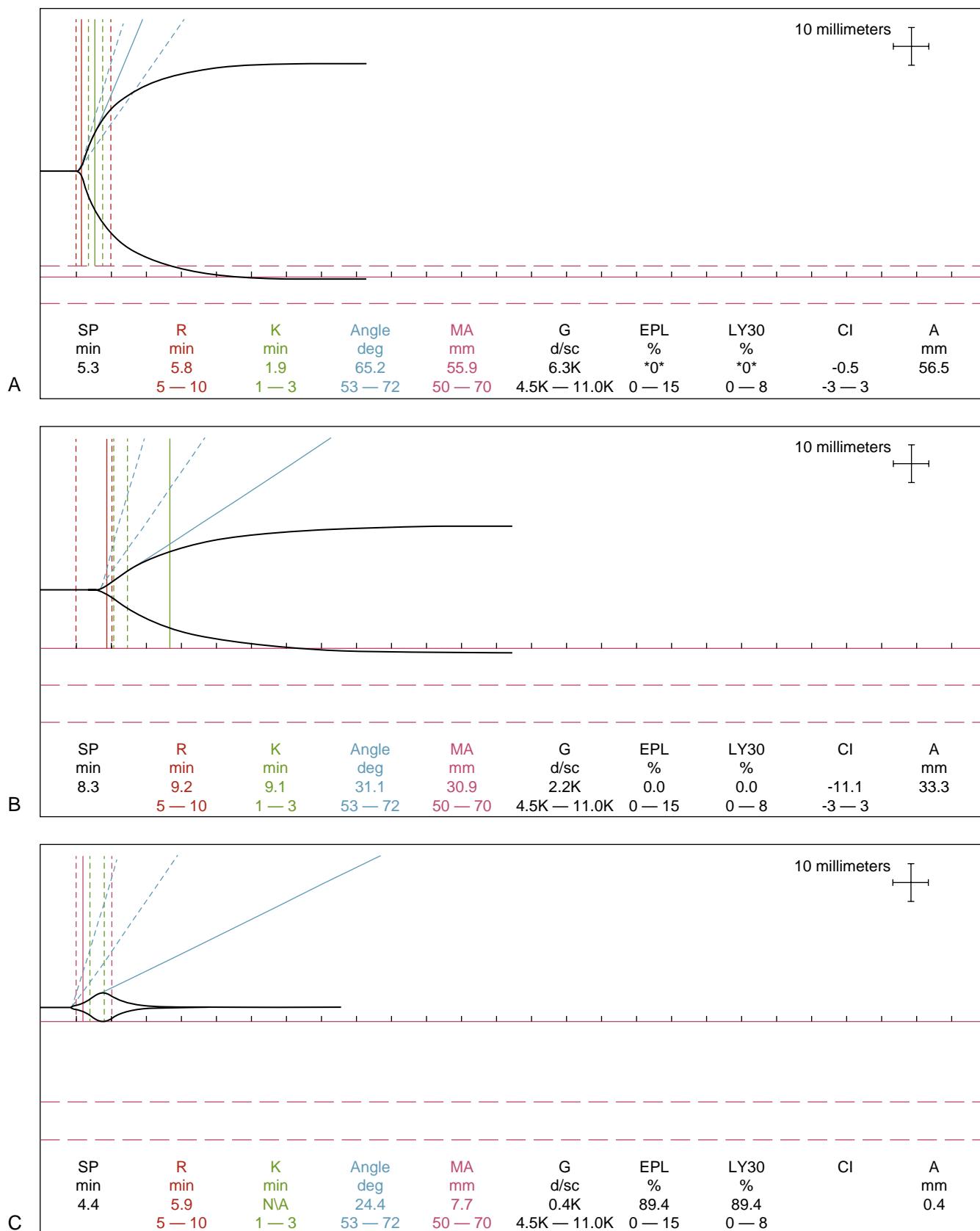


Fig. 50.5 Thromboelastographs from kaolin-activated samples analyzed using a TEG 5000 system depicting (A) normal coagulation, (B) hypofibrinogenemia, and (C) hyperfibrinolysis.

testing because of differences between using whole blood samples for testing as opposed to plasma or processed platelets. Reagent sensitivities can vary across manufacturers and lots. Hopefully, further advances in point-of-care coagulation monitoring will offer the opportunity for clinicians to make informed, bedside decisions about transfusion therapy and hemostatic drug administration to minimize perioperative bleeding and adopt effective patient blood management practices.

Antithrombotics, Thrombolytics, and Procoagulant Drugs

In the following sections, we will briefly review some common medications used to decrease or increase clot formation and then examine perioperative management strategies to reverse anticoagulants. This is not intended to be an exhaustive list of all FDA-approved drugs, so only more commonly used medications are discussed here.

Starting with antithrombotic drugs, these drugs are usually used to reduce the formation of blood clots in the setting of coronary or cerebral atherosclerosis or after vascular thrombosis. They can be further subdivided into antiplatelet agents and anticoagulants (Table 50.1).

ANTIPLATELET AGENTS

Antiplatelet agents inhibit thrombus formation by inhibiting platelet aggregation and/or adhesion to clot or damaged endothelium. Depending on the drug, they can work either reversibly or irreversibly. Most common antiplatelet agents can be divided into: (1) cyclooxygenase (COX) inhibitors, (2) P2Y12 receptor antagonists, and (3) platelet GPIIb/IIIa antagonists, although there are several other classes available such as phosphodiesterase inhibitors, protease-activated receptor-1 antagonists, adenosine reuptake inhibitors, and thromboxane inhibitors.

Cyclooxygenase Inhibitors

Aspirin and NSAIDS are the two primary members of this class. There are two forms of the cyclooxygenase enzyme: COX-1 and COX-2. COX-1 maintains the integrity of the gastric lining and renal blood flow and initiates the formation of thromboxane A₂ (Tx_A₂), which is important for platelet aggregation. COX-2 is responsible for synthesizing the prostaglandin mediators in pain and inflammation.

Aspirin

Aspirin is a non-selective and irreversible COX inhibitor. It acetylates a serine residue on COX-1 and prevents the production of Tx_A₂ in platelets.¹⁴⁵ COX-2, which leads to antiinflammatory and analgesic effects, is 170 times less sensitive than COX-1 to aspirin so only at high doses can aspirin irreversibly inhibit both COX-1 and COX-2.¹⁴⁶ Because platelets are anuclear, they are unable to synthesize new COX-1 once aspirin has irreversibly inhibited the enzyme. Consequently, despite its short half-life of approximately 15 to 20 minutes, aspirin's inhibitory effect persists through the platelet lifespan of 7 to 10 days.¹⁴⁷

The recovery of platelet function after aspirin depends on platelet turnover. Generally, megakaryocytes generate

TABLE 50.1 Common Classes of Antithrombotics, Thrombolytics, and Procoagulants

Category	Subcategory	Generic Drug Names
Antiplatelet agents	Cyclooxygenase inhibitors	Aspirin, NSAIDS
	P2Y12 receptor antagonists	Ticlopidine, clopidogrel, prasugrel, cangrelor, and ticagrelor
Anticoagulants	Platelet GPIIb/IIIa antagonists	Abciximab, eptifibatide, and tirofiban
	Vitamin K antagonists	Warfarin
Thrombolytics	Heparin	UFH, LMWH, fondaparinux
	Direct thrombin inhibitors	Argatroban, bivalirudin (IV) Desirudin (SQ) Dabigatran (PO)
	Factor Xa inhibitors	Rivaroxaban, apixaban, edoxaban
Antifibrinolytics	Fibrin-specific agents	Alteplase, reteplase, tenecteplase
	Non-fibrin-specific agents	Streptokinase
Factor Replacements	Lysine analogs	Tranexamic acid, epsilon-aminocaproic acid
	Recombinant Factor VIIa	
	Factor VIII-vWF	
Fibrinogen concentrates	Prothrombin complex concentrates	3-factor PCC; 4-factor PCC, activated PCC, FEIBA

FEIBA, Factor VIII Bypass Activity; IV, intravenous; LMWH, low-molecular-weight heparin; NSAIDS, nonsteroidal antiinflammatory drugs; PCC, prothrombin complex concentrate; PO, per os, by mouth; SQ, subcutaneous; UFH, unfractionated heparin; vWF, von Willebrand factor.

10% to 12% of platelets daily, so near normal hemostasis is expected in 2 to 3 days after the last dose of aspirin with typical platelet turnover. High platelet turnover diseases, which result from increased production (e.g., essential thrombocythemia) or increased consumption (e.g., inflammation), may require more frequent than once daily aspirin dosing.¹⁴⁸ Immediate reversal of aspirin for emergencies can be achieved with platelet transfusions.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Most NSAIDS are nonselective, reversible COX inhibitors and therefore provide antipyretic, analgesic, and antiplatelet aggregation effects.¹⁴⁹ Platelet function normalizes 3 days after discontinuing the use of NSAIDS. Selective COX-2 antagonists such as celecoxib were introduced in the late 1990s to provide antiinflammatory, analgesic, and

antipyretic activity without the gastrointestinal complications,¹⁵⁰ but clinical trials with selective COX-2 antagonists have reported increased risks for cardiovascular complications.¹⁵¹ COX-2 specific inhibitors do not affect platelet function because platelets do not express COX-2. The increased cardiovascular risk is thought to be due to inhibition of PGI₂ without inhibition of TXA₂, thus tipping the balance toward thrombosis. Current recommendations are to use COX-2 inhibitors only when necessary for pain and then with the lowest effective dose possible after weighing the risks and benefits.¹⁵²

P2Y12 RECEPTOR ANTAGONISTS

These drugs (ticlopidine, clopidogrel, prasugrel, cangrelor, and ticagrelor) interfere with platelet function by inhibiting the P2Y12 receptor, which inhibits platelet adhesion and aggregation by preventing the expression of GPIIb/IIIa on the surface of activated platelets.¹⁵³ Ticlopidine, clopidogrel, and prasugrel are members of a class known as thienopyridines, and are pro-drugs requiring hepatic metabolism to generate the active metabolite that then irreversibly inactivates the ADP-binding site of the P2Y12 receptor.¹⁵⁴ Ticagrelor and cangrelor are reversible inhibitors.

Clopidogrel (Plavix) is the most commonly prescribed agent in this class. Platelet functions normalize 7 days after discontinuing clopidogrel and 14 to 21 days after discontinuing ticlopidine. Because clopidogrel is a pro-drug and requires CYP2C19 for activation, it has wide interindividual variability in inhibiting ADP-induced platelet function. Although many factors may be involved in this variability, genetic polymorphism of CYP2C19 along with ABCB1, which affects the intestinal permeability and oral bioavailability of clopidogrel, are thought to play a significant role.¹⁵⁵ Patients treated with clopidogrel who have decreased CYP2C19 and ABCB1 activity were shown to have increased risk of major cardiovascular events.¹⁵⁶ The FDA put a black box warning on clopidogrel to make patients and healthcare providers aware that CYP2C19-poor metabolizers, representing up to 14% of patients, are at high risk of treatment failure and that genotype testing may be helpful prior to drug initiation.¹⁵⁷

Ticagrelor binds to the P2Y12 receptor at a different site than the thienopyridines, and causes a conformational change of the receptor.¹⁵⁸ While ticagrelor needs to undergo metabolism to an active metabolite, both the parent drug and the active metabolite have anti-platelet effects.¹⁵⁹ Genetic polymorphisms do not appear to be clinically relevant for this drug.¹⁶⁰ Because it is much shorter acting than clopidogrel, ticagrelor must be dosed twice daily, which may be of benefit prior to surgery.

The newest drug in this group is cangrelor. It is the only one available for intravenous administration, and like ticagrelor, it changes the conformation of the P2Y12 receptor, resulting in inhibition of ADP-induced platelet aggregation.¹⁵⁸ It received FDA approval in 2015 for adult patients undergoing percutaneous coronary intervention (PCI). This drug has the fastest onset of action (seconds), and platelet function normalizes within 60 minutes after drug discontinuation.¹⁶¹ This rapid onset may allow for bridging therapy in patients with drug-eluting stents who require surgery.

GLYCOPROTEIN IIB/IIIA INHIBITORS

Glycoprotein IIb/IIIa inhibitors (GPI) (abciximab, eptifibatide, and tirofiban) work to prevent platelet aggregation by decreasing the binding of fibrinogen and vWF to glycoprotein IIb/IIIa receptors on the surface of activated platelets.¹⁶² They are given intravenously in order to: (1) stop ongoing arterial thrombosis or (2) eliminate excessive platelet reactivity in diseased vessels so that occlusive thrombi and restenosis do not occur. Their use was highly touted in the past with balloon angioplasty where acute closure was a feared complication. Now with the introduction of stents and P2Y12 receptor antagonists, GPI have become less popular in routine PCI because of the associated bleeding risk and their use is only recommended in a subset of patients with high risk angiographic features or those not loaded adequately with dual antiplatelet agents.¹⁶³ Although abciximab has a short plasma half-life (approximately 10 minutes), its effects on platelet function can be seen for much longer, even after the infusion has been stopped. One rare, but serious side effect to be aware of, abciximab can produce thrombocytopenia immediately after drug administration in a small proportion of patients. Mild thrombocytopenia (platelet count $<100 \times 10^9/L$) developed more frequently in patients treated with the drug than control subjects (4.2% vs. 2.0%; $P < .001$).¹⁶⁴

ANTICOAGULANTS

Vitamin K Antagonists

Warfarin, the most frequently used oral VKA in the United States, inhibits the vitamin K-dependent carboxylation of coagulation factors II, VII, IX, and X and proteins C and S. Warfarin is highly effective in reducing the risk of venous and arterial thromboemboli, and is still the anticoagulant of choice for patients with valvular atrial fibrillation and mechanical heart valves despite the popularity and increased utilization of DOACs for nonvalvular atrial fibrillation.¹⁶⁵

Warfarin has a long half-life (40 hours) and the complete anticoagulant effect can take 3 to 4 days to emerge because of the long half-lives of the preexisting coagulation factors. Prothrombin (factor II) has the longest half-life (~60 hours). Factor VII and protein C have the shortest half-lives (3-6 hours).¹⁶⁶ Because of this long initiation period, patients at high risk for thromboembolism must be bridged with another anticoagulant (usually UFH or LMWH) until the target INR is achieved. Also, early reductions in the anticoagulant protein C can cause an imbalance toward a hypercoagulable state if warfarin is started alone, resulting in thrombosis or warfarin-induced skin necrosis.

Warfarin is monitored using the INR, and the therapeutic range for warfarin anticoagulation is generally an INR of 2.0 to 3.0, except for patients with mechanical heart valves, where higher values are necessary (INR 2.5-3.5). The INR is not calibrated to evaluate non-warfarin deficiencies such as liver disease and should not be used to evaluate therapeutic effects of other anticoagulants. Warfarin has a very narrow therapeutic window and can be easily affected by drug-drug interactions and patient variability. The need for frequent laboratory monitoring makes warfarin a difficult drug for patients to maintain compliance and the reported

time in therapeutic range is only about $65\% \pm 20\%$ in patients with atrial fibrillation.¹⁶⁷

Warfarin's pharmacology can be affected by genetic variations in the metabolism of the drug (CYP2C9) and in the production of a vitamin K epoxide reductase enzyme (VKORC1), which reduces vitamin K after it has been oxidized. Recent meta-analyses of randomized trials found that pharmacogenetics testing for polymorphisms unfortunately did not reduce rates of bleeding or thromboembolism.¹⁶⁸ Current recommendations are to only perform pharmacogenetics testing in patients who consistently have INRs outside the therapeutic range or who have an adverse event while on therapy.¹⁶⁹

Unfractionated Heparin

UFH can be isolated from porcine or bovine intestines and is a mixture of different length polysaccharides with a high molecular weight (mean molecular weight around 15,000 daltons or 35-45 polysaccharide units).¹⁷⁰ UFH binds to AT and indirectly inhibits thrombin (factor IIa) and factor Xa. Benefits of heparin are its short half-life and full reversibility with protamine. Heparin does not have any fibrinolytic activity, so it will not lyse an existing clot.

Full-dose heparin for cardiac surgery is administered as an intravenous bolus of 300 to 400 U/kg. An ACT greater than 400 to 480 seconds is usually considered safe for initiation of CPB. Patients may be resistant to UFH if they have a hereditary deficiency of AT or an acquired deficiency of AT from prolonged heparin administration. The incidence of heparin resistance during CPB is reported at approximately 21%.¹⁷¹ Simply increasing the dose of heparin in patients with an AT deficiency is often not effective. For these patients, treatment should be with fresh frozen plasma (FFP) transfusions or AT concentrate, which will replenish AT levels and restore heparin response.¹⁷² Other causes of heparin resistance can be due to increased heparin clearance, increased levels of heparin-binding proteins, or elevations of fibrinogen and factor VIII levels.

Low Molecular Weight Heparin and Fondaparinux

LMWH, produced by cleaving UFH into shorter fragments (mean molecular weight approximately 4000 daltons, approximately 15 saccharide units)¹⁷³ and fondaparinux, a synthetic pentasaccharide (mean molecular weight 1700 daltons) of the AT binding region of heparin, act more specifically via AT to inhibit factor Xa. LMWH and fondaparinux do not affect the aPTT assay, and coagulation testing is usually not needed. Anti-factor Xa activity levels may be necessary in patients who may have unpredictable drug levels (e.g., renal failure, pregnancy, and body weight less than 50 kg or more than 80 kg).

LMWH has a longer half-life than heparin and can be administered subcutaneously either once or twice daily. LMWH is primarily excreted by the kidney, so its half-life is prolonged in patients with renal failure. Approximately 25% to 50% of LMWH molecules contain 18 or more saccharide units and can inhibit factor Xa and thrombin, while the remaining 50% to 75% of LMWH molecules contain <18 saccharide units and only inhibit factor Xa.¹⁷⁴ Protamine requires more than 14 saccharide units in the heparin molecule for interaction.¹⁷⁵ Therefore, protamine is only partially effective in reversing LMWH. It does not

completely abolish the anti-Xa activity, but it may neutralize the higher molecular weight fractions of LMWH.

Fondaparinux has a much longer half-life (17-21 hours) and can be dosed daily.

Because it is only 5 saccharide units, protamine is not effective for reversing fondaparinux.¹⁷⁶ Because antigen formation by the PF4/heparin complex requires a polysaccharide chain of at least 8 to 10 saccharides, fondaparinux-associated HIT is unlikely to occur,¹⁷⁷ and only eight cases of possible fondaparinux-associated HIT have been reported in the literature.¹⁷⁸ Currently, fondaparinux is not FDA approved for use in HIT, but there is considerable positive anecdotal experience in the literature (e.g., decreased bleeding risk) when compared with DTIs.¹⁷⁹

Direct Thrombin Inhibitors

DTIs bind directly to thrombin and do not require a cofactor such as antithrombin to exert their effect. All DTIs inhibit thrombin in its free (soluble) and fibrin-bound (insoluble) states, unlike heparin, which only has effect on free thrombin. Other advantages over heparin include: lack of binding to other plasma proteins that leads to a more predictable anticoagulant effect, and no concern for developing an immune-mediated thrombocytopenia.

Hirudin is a naturally occurring anticoagulant found in leeches, while argatroban and bivalirudin are synthetic agents. Argatroban, with a half-life of 45 minutes, is the preferred DTI in patients with renal insufficiency because it is eliminated by the liver. It reversibly binds to the active site on thrombin. Argatroban is FDA approved for the prophylaxis and treatment of thrombosis and for PCI anticoagulation in patients with HIT. Clinical effects are usually monitored with aPTT or ACT in the operating room. Dosing goals are to maintain an aPTT 1.5 to 3 times baseline. Because argatroban prolongs thrombin-dependent coagulation, the PT and INR will be prolonged as well, which can complicate transition to warfarin therapy for long-term anticoagulation.¹⁸⁰

Bivalirudin, a 20-amino acid synthetic analogue of hirudin, is a reversible DTI, and is metabolized by proteolytic cleavage and hepatic metabolism.¹⁸¹ It has the shortest half-life among the intravenous DTIs and is the drug of choice for patients with both renal and hepatic dysfunction, although dose adjustments are still necessary. In studies, bivalirudin has been shown to have better efficacy in preventing primary outcomes with lower bleeding rates when compared with UFH for percutaneous transluminal coronary angioplasty for unstable or postinfarction angina,¹⁸² and for use as an alternative to heparin in patients with HIT undergoing PCI.¹⁸³

Desirudin was approved in 2010 and is the only DTI available for subcutaneous administration. An early, small, open label study (16 patients) showed that desirudin may be a potentially cost-effective alternative to argatroban for patients with suspected HIT.¹⁸⁴ Desirudin also has more predictable pharmacokinetics, and dosage adjustments and aPTT monitoring may be unnecessary in patients with a creatinine clearance greater than 30 mL/min.¹⁸⁵

Direct Oral Anticoagulants

Several new oral anticoagulants have been introduced into the market over the past 10 years. These new drugs have more predictable pharmacokinetics and pharmacodynamics

and fewer drug-drug interactions, allowing them to be dosed without daily laboratory monitoring. The drawback has been the lack of specific antidotes for anticoagulation reversal, but this is slowly changing with the introduction of idarucizumab.

Most DOACs are approved for prevention of venous thromboembolism after hip or knee replacement surgery, treatment and secondary prevention of venous thromboembolism, and prevention of stroke in nonvalvular atrial fibrillation. Many are also being studied for use in secondary prevention of coronary events after acute coronary syndrome, prevention of thrombosis in elective PCI, and prevention of thrombus formation on mechanical heart valves. The results from early preclinical trials have been positive and encourage further randomized trials, so increased impact of these agents in the future is expected.¹⁸⁶ The DOACs have a shorter half-life than warfarin and have demonstrated noninferior efficacy to warfarin. A meta-analysis of phase II and phase III randomized clinical trials comparing DOACs with VKAs in patients with atrial fibrillation showed that use of DOACs was associated with a significant reduction in major bleeding (Relative risk [RR] 0.86, 95% CI 0.72-1.02) and a significantly decreased risk of intracranial hemorrhage (RR 0.46, 95% CI 0.39-0.56).¹⁸⁷

Dabigatran (Pradaxa), an oral DTI, was the first new anti-thrombotic agent approved for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation since warfarin. When given at a dose of 150 mg twice daily, dabigatran was shown to reduce the risk of stroke while having a similar bleeding risk as warfarin at an INR of 2.0 to 3.0.¹⁸⁸ Although the bleeding risk is similar, the bleeding profile does differ between the two drugs. Dabigatran increases the risk of major gastrointestinal bleeding but lowers the risk of intracranial bleeding when compared with warfarin.¹⁸⁹ Dabigatran is predominantly eliminated by the kidneys, so the dose should be reduced in patients with a creatinine clearance less than 30 mL/min.

Monitoring of dabigatran therapy is difficult because the perfect laboratory test does not exist. The aPTT does not become linear until dabigatran concentrations are quite high (>200 ng/mL).¹⁹⁰ The TT is very sensitive to dabigatran, so while it is useful to detect any presence of the drug, it cannot be used to quantify the amount of drug present.¹⁹¹ If available, dilute TT or ecarin clotting time are both linear at clinically relevant dabigatran concentrations and are the tests of choice if monitoring is necessary.¹⁹²

Direct Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) are agents whose activity is directed against the active site of factor Xa. Factor Xa inhibitors have been associated with fewer strokes and embolic events, fewer intracranial hemorrhages, and lower all-cause mortality compared with warfarin.¹⁹³ A comparison of apixaban versus warfarin in patients with atrial fibrillation showed a reduction in stroke risk along with a significant reduction in major bleeding.¹⁹⁴ The anti-factor Xa assays are the tests best suited for monitoring the effects of the direct Xa inhibitors, but assays must be individually calibrated for each drug.¹⁹²

THROMBOLYTICS

Thrombolytic therapy is used to break up or dissolve blood clots. These medications are most commonly used during

acute myocardial infarctions, strokes, massive pulmonary embolus, arterial thromboembolism, and venous thrombosis. Thrombolytics may be given through an intravenous line systemically or directly to the site of the blockage. Most thrombolytic agents are serine proteases that work by converting plasminogen to plasmin. Plasmin then lyses the clot by breaking down fibrinogen and fibrin. Fibrinolytic agents are divided into two categories: (1) fibrin-specific agents and (2) non-fibrin-specific agents. Fibrin-specific agents are alteplase (tPA), reteplase, and tenecteplase. They theoretically produce less plasminogen conversion in the absence of fibrin and result in less fibrinogen depletion. Non-fibrin-specific agents (e.g., streptokinase) catalyze systemic fibrinolysis. Streptokinase, produced by beta-hemolytic streptococci, is highly antigenic and can cause immunologic sensitization and allergic reactions, particularly with repeat administration even several years after previous exposure.¹⁹⁵ Streptokinase is not widely used in the United States but is still used internationally because of its lower cost.

t-PAs are both thrombolytics and anticoagulants because as mentioned earlier, fibrinolysis generates increased amounts of circulating fibrin degradation products, which inhibit platelet aggregation. Surgery or puncture of non-compressible vessels is contraindicated within a 10-day period after the use of thrombolytic drugs.

Time is usually of the essence when administering these drugs. Medical providers should quickly obtain a history and physical exam, review absolute and relative contraindications, (Table 50.2), order relevant laboratory tests, request necessary consultations, and proceed with decision making. Many studies have investigated the use of thrombolytics in acute pulmonary embolus, ST-elevation myocardial infarction (STEMI), and ischemic stroke. Thrombolytics are indicated in the setting of hemodynamic instability due to acute pulmonary embolus.¹⁹⁶ A meta-analysis in patients with massive pulmonary embolism found that systemic thrombolytic therapy decreased the composite endpoint of death and recurrent thromboembolism (9.4% vs. 19%, odds ratio 0.45, 95% CI 0.22-0.92).¹⁹⁷ Primary PCI is the preferred treatment for patients with acute STEMI if it can be performed by an experienced operator within 2 hours from presentation to the emergency department, but fibrinolytic therapy remains an important modality in hospitals with limited primary PCI

TABLE 50.2 Absolute and Relative Contraindications for Thrombolytics

Absolute Contraindications	Relative Contraindications
Vascular lesions	Ischemic stroke >3 months prior
Severe, uncontrolled hypertension (SBP > 185 or DBP > 110)	Active peptic ulcer
Recent cranial surgery or trauma	Current use of anticoagulant drugs
Brain tumor	Pregnancy
Ischemic stroke <3 months prior	Prolonged/traumatic CPR <3 weeks prior
Active bleeding	Major surgery <3 weeks prior

CPR, Cardiopulmonary resuscitation; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

availability. Early thrombolysis was associated with a lower mortality rate. When compared between less than 2 hours versus greater than 4 hours from time of symptom presentation to thrombolysis administration, 30-day mortality was decreased with earlier administration (5.5% vs. 9%).¹⁹⁸ For stroke care, the primary goal is to restore blood flow to ischemic regions in order to reduce stroke-related disability and mortality. Alteplase is the recommended therapy for treatment of acute ischemic stroke if treatment can be initiated within 4.5 hours of symptom onset.¹⁹⁹ Mechanical thrombectomy should still be considered even if thrombolysis has been administered for ischemic stroke.

PROCOAGULANT DRUGS

Anesthesiologists may use procoagulant drugs for individuals at risk of bleeding to help control blood loss during surgery. These drugs can be divided into two different classes: antifibrinolytics and factor replacements. (see Table 50.1).

Antifibrinolytics

There are two types of antifibrinolytics, the lysine analogs, epsilon-aminocaproic acid (EACA) and TXA, and a SERPIN, aprotinin. Aprotinin was removed from the US market due to concerns of renal and cardiovascular toxicity and is now only available in Europe and Canada. The lysine analogs act by competitively inhibiting the binding site on plasminogen, leading to inhibition of plasminogen activation as well as preventing plasminogen binding of fibrin, therefore impairing fibrinolysis.²⁰⁰ TXA has been more thoroughly studied than EACA, but aside from subtle differences, both agents appear to have similar efficacy and have been shown to decrease perioperative blood loss.

TXA has been studied in the large CRASH-2 trial of patients admitted after trauma and was associated with a reduction in all-cause mortality (14.5% vs. 16%, $P = .0035$), including the risk of death due to bleeding (4.9% vs. 5.8%, $P = .0077$), without an increase in vascular occlusive events.¹⁰⁰ Subgroup analysis of the CRASH-2 data showed that early treatment (≤ 1 hour) after traumatic injury significantly reduced the risk of death due to bleeding events in the TXA group (RR 0.68; 95% CI, 0.57-0.82; $P < .0001$). RR was also lower 0.79 (95% CI, 0.64-0.97; $P = .03$) if TXA was administered between 1 and 3 hours; however, treatment after 3 hours seemed to increase death due to bleeding, with a RR of 1.44 (95% CI, 1.12-1.84; $P = .004$).¹⁰¹

Aside from trauma, there are also trials studying use of TXA in cardiac surgery, orthopedic surgery, neurosurgery, hepatic surgery, and obstetric and gynecology surgery. The World Maternal Antifibrinolytic Trial (WOMAN) found that administration of TXA reduced death due to bleeding in women with postpartum hemorrhage, especially if given within 3 hours of birth, and was not associated with an increase in adverse effects.²⁰¹ In a recent meta-analysis in surgical patients, TXA reduced the probability of receiving a blood transfusion by a third (risk ratio 0.62; 95% CI, 0.58-0.65; $P < .001$).²⁰² Fewer deaths occurred in the TXA group (risk ratio 0.61; 95% CI, 0.38-0.98; $P = .04$), but the effect of TXA on myocardial infarction (risk ratio 0.68; 95% CI, 0.43-1.09; $P = .11$), stroke (risk ratio 1.14; 95% CI, 0.65-2.00; $P = .65$), deep vein thrombosis (risk ratio 0.86; 95% CI, 0.53-1.39; $P = .54$), and pulmonary embolism

(risk ratio 0.61; 95% CI, 0.25-1.47; $P = .27$) was inconclusive. A Cochrane review also found that TXA significantly reduced blood transfusions by 39%; however, TXA was not associated with decreased mortality in all surgeries in their analysis.²⁰³

Overall, the lysine analogs (TXA and EACA) appear to be inexpensive and low risk adjunctive agents that should be considered for use in major surgery or critical bleeding. The rate of thrombosis does not appear to be elevated, but further studies are necessary before this can be definitively concluded. In terms of side effects, there is a reported dose-response relationship of high-dose TXA and seizures in patients undergoing cardiac surgery.²⁰⁴ The reported mechanism is TXA binding to GABA_A receptors, subsequently blocking GABA_A-mediated inhibition in the central nervous system.²⁰⁵

Factor Replacements

Recombinant Factor VIIa. Recombinant factor VIIa (rFVIIa) increases the generation of thrombin via the intrinsic and extrinsic pathways to enhance hemostasis. The drug was originally FDA approved for use in hemophilia patients. It binds to tissue factor at the site of vessel injury and to the surface of the activated platelet, leading to activation of factor X. Both mechanisms result in a “burst” of thrombin and fibrin generation, which leads to clot formation. The half-life of rFVIIa is only 2 to 2.5 hours, so the initial dose may require repeating until the bleeding is controlled.

Successful use of rFVIIa in hemophilia patients with inhibitors generated a great deal of interest in the drug's ability to enhance hemostasis in hemorrhaging patients without a preexisting coagulation disorder. This off-label use of rFVIIa had been quite varied, and included patients with intracranial hemorrhage,^{206,207} trauma,^{208,209} and traumatic brain injury,²¹⁰ and patients undergoing cardiac surgery²¹¹ and liver transplantation.^{212,213} While treatment with rFVIIa reduced the progression of the hematoma following intracranial hemorrhage and reduced the risk of acute respiratory distress syndrome (risk reduction, -0.05; 95% CI, -0.02 to -0.08) in trauma patients, mortality or functional outcomes were not improved in any patient subset.²¹¹

As the off-label use of rFVIIa increased, there were more troubling reports of arterial and venous thromboses. A review studying the safety of off-label rFVIIa reported a higher rate of arterial thromboembolic events with the use of rFVIIa compared with placebo (5.5% vs. 3.2%, $P = .003$), and an increased observed rate for coronary events (2.9% vs. 1.1%, $P = .002$).²¹⁴ This rate was noted to be increased with age (for patients aged 65-74 years, OR 2.12; 95% CI: 0.95-4.71 and for those ≥ 75 years, OR 3.02, 95% CI: 1.22-7.48), as well as higher doses. Considering that no randomized controlled trial has been able to demonstrate a significant benefit in terms of intensive care stay, hospital stay, or mortality, guidelines currently recommend that rFVIIa no longer be used for the off-label indications of prevention and treatment of bleeding in patients without hemophilia.²¹⁵ Each clinician will have to weigh the risk of thromboembolic events against the benefit for the refractory bleeding patient where the “last ditch” use of rFVIIa in massive hemorrhage has not been formally assessed.

Prothrombin Complex Concentrate. PCCs are commercially available purified concentrates containing varying amounts of vitamin K-dependent coagulation factors. Three-factor PCCs differ from 4-factor PCCs in that they do not contain significant amounts of factor VII. Most of the factors are preserved in the inactive state, with the aim of decreasing thrombogenic risk; however, FEIBA is a 4-factor PCC that contains activated factor VII. The products may also contain coagulation inhibitors such as heparin, AT, protein C, and protein S to mitigate the thrombotic risk by providing more balanced replacement of procoagulant factors and anticoagulant proteins.

While PCCs are derived from human plasma, they are treated with at least one viral reduction process, reducing the risk of transfusion-transmitted infection and the lower administration volume decreases the risk of transfusion-associated circulatory overload (TACO).²¹⁶ While PCCs appear to be safe and have low risk of thrombosis, there is accumulating evidence that the level of factor II and its balance with the coagulation inhibitors may be the important key.²¹⁷

Fibrinogen Concentrate. Fibrinogen concentrate is produced from pooled human plasma, but viral inactivation steps are incorporated into the manufacturing. It can be used to correct hypofibrinogenemia with the goals of reducing coagulopathy, bleeding, and transfusion requirements. Fibrinogen concentrate offers benefits over FFP and cryoprecipitate in terms of standardized fibrinogen content, low infusion volume, and faster time to administration due to rapid reconstitution. Alternatively, cryoprecipitate and FFP are cheaper, and they also provide additional procoagulant factors that could be beneficial during massive bleeding. In a recent meta-analysis, seven randomized controlled trials showed a significant reduction in bleeding and transfusion requirements with the use of fibrinogen concentrates, but data on mortality were lacking and there was significant heterogeneity among the trials.²¹⁸ While the data are inconclusive, some hospitals have incorporated fibrinogen concentrate into algorithms based on viscoelastic coagulation tests with the goal of reducing transfusion requirements.

Perioperative Management of Anticoagulation

The perioperative management of patients who require chronic anticoagulation or antiplatelet therapy involves balancing the risk of surgical bleeding against the risk of developing postoperative thromboembolism. Patients should be evaluated with enough time prior to elective surgery to perform these necessary risk assessments and make management decisions regarding discontinuation and reinstitution of anticoagulation or antiplatelet therapy.

VITAMIN K ANTAGONISTS

For patients taking VKAs, the current recommendation is to stop VKAs 5 days prior to surgery for those who are at low risk for perioperative thromboembolism (Table 50.3). VKAs should be restarted 12 to 24 hours postoperatively if there is adequate hemostasis. For patients at high risk of

TABLE 50.3 Perioperative Thromboembolism Risk Stratification

Risk	Indication
High	Mechanical heart valve
	Rheumatic valvular heart disease
	CHADS score ≥ 5
	VTE within 3 months or h/o VTE when VKAs are discontinued
Moderate	CHADS score of 3 or 4
	VTE between 3 and 12 months or h/o recurrence
	Active cancer
Low	CHADS score 0-2
	VTE > 12 months prior and no other risk factors

CHADS, Congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, prior stroke; VKA, vitamin K antagonists; VTE, venous thromboembolism.

thromboembolism, bridging anticoagulation with UFH or LMWH after discontinuation of VKAs should occur. The difficulty arises in defining a plan for patients who are at moderate risk. No definitive evidence exists, so the approach chosen should be based on individual patient and surgical risk factors.²¹⁹

HEPARINS

For those patients receiving bridging therapy with UFH, the infusion should be stopped 4 to 6 hours prior to surgery²²⁰ and resumed without a bolus dose no sooner than 12 hours postoperatively. In surgeries with high postoperative bleeding risk, resumption of UFH should be delayed 48 to 72 hours until adequate hemostasis has been achieved. In patients receiving bridging therapy with LMWH, the last dose of LMWH should be administered 24 hours prior to surgery and dosing should be resumed 24 hours postoperatively in low bleeding risk surgery and delayed until 48 to 72 hours postoperatively for surgeries with high bleeding risk.²¹⁹

ASPIRIN

For patients receiving aspirin therapy, risk assessment is based on (1) the patient's risk of a perioperative cardiovascular event; (2) whether the surgery is a minor procedure, major procedure, or cardiac procedure; and (3) the timing and type of stent placement for those patients who have undergone recent PCI. Low-dose aspirin (acetylsalicylic acid, ASA) has been shown to reduce the risk of stroke and myocardial infarction by 25% to 30%,^{221,222} and studies report significant increased risk with the withdrawal of low-dose aspirin because of a platelet rebound phenomenon that leads to increased thrombus stability, improved fibrin crosslinking, and decreased fibrinolysis.²²³ The decision to discontinue low-dose aspirin must weigh the risks of bleeding versus the benefits of cardiovascular risk reduction. Studies suggest that perioperative aspirin use may lead to a small increase in the risk for major bleeding (2.9% vs. 2.4%, $P = .04$),^{222,224} but continuation of perioperative aspirin may confer a significant reduction in myocardial infarction and other major cardiovascular events (1.8% vs. 9.0%, $P = .02$).²²⁵

Recommendations currently are to continue aspirin for patients who are at moderate to high risk for cardiovascular events requiring noncardiac surgery and only stop aspirin use 7 to 10 days prior to surgery for patients at low risk for cardiovascular events.²²⁶ Patients who are having minor procedures (e.g., minor dental, dermatologic procedures, or cataract surgery) and are on aspirin for the secondary prevention of cardiovascular disease should continue taking it in the perioperative period.

Patients with coronary stents presenting for surgery are problematic because of the concerns for in-stent thrombosis that can occur with stopping antiplatelet therapy. Surgery should be delayed if possible for at least 6 weeks after bare-metal stent placement and for at least 6 months after drug-eluting stent placement.²²⁷ If surgery is required before this time has passed, dual anti-platelet therapy should be continued unless the risk of bleeding is thought to outweigh the risk of stent thrombosis.

Many studies have examined management of aspirin therapy perioperatively; however, there is much less data for management of clopidogrel in the perioperative setting. In most clinical situations, aspirin provides benefit that outweighs the bleeding risk and should be continued unless the patient is undergoing intracranial procedures, transurethral prostatectomy, intraocular procedures, or surgeries with extremely high bleeding risk.²²⁸ The data are inconclusive about use of bridging therapy for patients with coronary stents who require noncardiac surgery. For patients with a very high risk of stent thrombosis, bridging therapy with intravenous, reversible glycoprotein inhibitors or a reversible intravenous P2Y12 inhibitor have been

suggested, but concomitant parenteral anticoagulation therapy is not recommended.

NEURAXIAL ANESTHESIA AND ANTICOAGULATION

In addition to surgical bleeding risk assessment, many patients who are on anticoagulant or antiplatelet therapy can potentially benefit from neuraxial anesthetics. Management of perioperative anticoagulation is becoming increasingly more complex with the advent of the DOACs and the number of patients who are now receiving chronic anticoagulation. There is a lack of randomized controlled trials showing safety in the timing of surgical procedures and regional anesthesia because a broad clinical experience with these drugs along with neuraxial techniques does not exist. Most guidelines in the literature are based exclusively on the pharmacokinetics and pharmacodynamics of these drugs.²²⁹ These guidelines and recommendations will continue to be updated as evidence emerges on the bleeding risk and pharmacologic profiles of the newer anticoagulants. In the absence of concrete data, many hospital committees are setting local practice guidelines (Table 50.4). Early preoperative assessment of patients receiving anticoagulation and a multidisciplinary team approach between the patient, primary care physician, surgeon, anesthesiologist, and hematologist is essential to ensure the perioperative safety of these patients. Continued research on thromboembolic events and bleeding risk in the setting of these novel therapies is needed before official recommendations can be made regarding management.

TABLE 50.4 UCSF Guidelines for the Use of Antithrombotic Agents in the Setting of Neuraxial Procedures

Anticoagulant	Minimum Time Between the Last Dose and When Neuraxial Catheter can Occur	Minimum Time After Catheter Placement to Drug Start	Minimum Time Between Last Dose of Drug and Catheter Removal	Minimum Time Between Neuraxial Catheter Removal and When Next Dose can be Given
NSAIDs/ASA	No restrictions for catheter placement or removal			
Heparin SQ BID	No restrictions for catheter placement or removal			
Heparin SQ TID	4 h	2 h	4 h	2 h
Lovenox qD	12 h	6 h	12 h	4 h
Warfarin	5 days and INR < 1.5	Contraindicated while catheter in place		2 h
Clopidogrel	7 days	Contraindicated while catheter in place		2 h
Ticlodipine	14 days	Contraindicated while catheter in place		2 h
Dabigatran	5 days	Contraindicated while catheter in place		6 h
Rivaroxaban	3 days	Contraindicated while catheter in place		6 h
Apixaban	3 days	Contraindicated while catheter in place		6 h
Abciximab	48 h	Contraindicated while catheter in place		2 h
Eptifibatide	8 h	Contraindicated while catheter in place		2 h
Alteplase*	10 days	Contraindicated while catheter in place		10 days

*Full dose for stroke or myocardial infarction. No time restrictions for catheter placement or removal with low dose (2 mg) for catheter clearance. ASA, acetylsalicylic acid; BID, two times a day; INR, international normalized ratio; NSAIDs, nonsteroidal antiinflammatory drugs; qD, once a day; SQ, subcutaneous; TID, three times a day. Adapted from UCSF Guidelines for the use of antithrombotic agents in the setting of neuraxial procedures and Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (third edition). *Reg Anesth Pain Med*. 2010; 35:64–101.

Emergent Reversal of Anticoagulants

VITAMIN K ANTAGONISTS

The incidence of VKA-associated major bleeding is between 1.1% and 8.1% per year depending on the study design.^{230,231} Some of these patients will require warfarin reversal for bleeding and other patients will require warfarin reversal prior to emergency surgery. Four-factor PCCs as opposed to three-factor PCCs are now the drug of choice for emergent reversal of oral VKA in place of FFP or rFVIIa,²³² but PCCs only provide a transient correction due to the short half-life of these factors relative to the long half-life of warfarin. Concomitant administration of vitamin K is required to restore carboxylation of the vitamin K dependent factors (VKDFs) by the liver and provide a more sustained correction after the factors in the PCC infusion have been metabolized. Intravenous administration of vitamin K gives a more rapid response than subcutaneous or oral administration.²³³ The dose required depends on the clinical situation and the need to be able to re-establish anticoagulation after surgery. For instance, lower doses (3 mg) may allow for warfarin reversal during the acute event, while avoiding warfarin resistance if rapid re-establishment of a therapeutic INR is required.²³⁴

Rapid reversal of VKA with FFP is difficult and often unrealistic. Time to thaw ABO-compatible units is a concern, but the large volume required to raise the VKDF by 50% is often untenable, especially in a patient population prone to pulmonary, renal, and cardiac disease.²³⁵ There are also concerns for transmission of viral diseases, and transfusion-related complications such as volume overload, TACO, and lung injury (transfusion-related acute lung injury). In a recent randomized controlled trial using 4-factor PCC

to reverse VKA prior to surgery or invasive interventions, effective hemostasis was higher (90% PCC vs. 75% FFP), fluid overload was lower (3% PCC vs. 13% FFP), and thromboembolic events were similar compared with patients who received FFP (7% PCC vs. 8% FFP).²³⁶

DIRECT THROMBIN INHIBITORS

There are no direct reversal agents for intravenous DTIs; however, their half-lives are relatively short, so time and supportive medical care are often sufficient to manage their anticoagulant effect in acute clinical situations. For the DOACs, idarucizumab, a specific antidote for dabigatran, is a humanized antibody fragment that binds to dabigatran with an affinity 350 times greater than thrombin. The drug received FDA approval in 2015 and can completely reverse the anticoagulant effect of dabigatran in minutes.²³⁷ Andexanet alfa, a recombinant derivative of factor Xa, was developed to reverse the factor Xa inhibitors by acting as a decoy. It has a higher affinity for factor Xa inhibitors than intrinsic factor Xa. The drug was recently approved by the FDA for patients who present with an acute hemorrhage while receiving apixaban or rivaroxaban. The indication currently does not cover edoxaban, or enoxaparin.^{238,239}

EMERGING AGENTS

There are additional reversal agents in development that may be approved by the FDA soon. Ciraparantag (PER977), a small, synthetic, water-soluble, cationic molecule, binds and neutralizes UFH, LMWH, fondaparinux, dabigatran, and factor Xa inhibitors through hydrogen bonding and charge-charge interactions. Phase I trials have been completed in healthy volunteers.²⁴⁰ Common anticoagulants and possible reversal agents for emergencies are listed for reference in Table 50.5.

TABLE 50.5 Common Anticoagulants Along with the Required Laboratory Monitoring and Possible Reversal Agents for Emergencies

Antithrombotic Agent	Drug Name	Stop Before Procedure	Monitoring	Reversal Agents
Antiplatelet agents	ASA	7 days	None	Platelet transfusion
	P2Y12 receptor antagonists	7-14 days		
	GPIIb/IIIa antagonists	24-72 h		
Vitamin K antagonists	Warfarin	2-5 days	PT, INR	PCC, FFP, vitamin K
Heparins	Unfractionated heparin (UFH)(IV)	6 h	aPTT	Protamine
	Low-molecular weight heparin (LMWH)	12-24 h	None required, but fXa levels can monitor levels	Partially reversed by protamine
Pentasaccharide	Fondaparinux	3 days (prophylactic dosing)	None required, but fXa levels can monitor levels	None
Direct thrombin inhibitors	Argatroban, Bivalirudin	4-6 h 3 h	aPTT or ACT	None
	Dabigatran	2-4 days (longer if renal impairment)	None required, thrombin time can monitor levels	Idarucizumab
FXa inhibitors	Rivaroxaban, Apixaban, Edoxaban	2-3 days 2-3 days 2-3 days	None required, but fXa levels can monitor levels	Andexanet alfa for rivaroxaban and apixaban

ACT, activated clotting time; aPTT, activated partial thromboplastin time; ASA, acetylsalicylic acid; FFP, fresh frozen plasma; INR, international normalized ratio; IV, intravenous; PCC, prothrombin complex concentrate; PT, prothrombin time.

Conclusion

The coagulation system remains exceedingly complex, but an understanding of the fundamental principles of hemostasis will allow the anesthesia provider to identify patients at risk of bleeding preoperatively, and safely manage blood loss and treat acquired coagulopathy both intraoperatively and postoperatively. Given the abundance of different anti-thrombotic and anticoagulant medications, perioperative management is becoming increasingly challenging. Early preoperative assessment of patients receiving anticoagulation and a multidisciplinary team approach between the patient, primary care physician, hematologist, surgeon, and anesthesiologist is essential to ensure the perioperative safety of these patients.

 Complete references available online at expertconsult.com.

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References

1. Furie B, et al. *N Engl J Med*. 2008;359(9):938–949.
2. van Hinsbergh VW, et al. *Semin Immunopathol*. 2012;34(1):93–106.
3. Moncada S, et al. *Nature*. 1976;263(5579):663–665.
4. Broekman MJ, et al. *Blood*. 1991;78(4):1033–1040.
5. Marcus AJ, et al. *J Clin Invest*. 1997;99(6):1351–1360.
6. Esmen CT, et al. *Semin Thromb Hemost*. 2006;32(suppl 1):49–60.
7. Mertens G, et al. *J Biol Chem*. 1992;267(28):20435–22043.
8. Wood JP, et al. *Blood*. 2014;123(19):2934–2943.
9. Wolberg AS, et al. *Anesth Analg*. 2012;114(2):275–285.
10. Chiu JJ, et al. *Physiol Rev*. 2011;91(1):327–387.
11. Stern D, et al. *Proc Natl Acad Sci U S A*. 1985;82(8):2523–2527.
12. Margetic S. *Biochem Med (Zagreb)*. 2012;22(1):49–62.
13. Van De Craen B, et al. *Thromb Res*. 2012;130(4):576–585.
14. Achneck HE, et al. *Vascular*. 2008;16(suppl 1):S6–13.
15. Kassis J, et al. *Blood*. 1992;80(7):1758–1764.
16. Broos K, et al. *Thromb Res*. 2012;129(3):245–249.
17. Hanson SR, et al. *Blood*. 1985;66(5):1105–1109.
18. Broos K, et al. *Blood Rev*. 2011;25(4):155–167.
19. Wu YP, et al. *Arterioscler Thromb Vasc Biol*. 2000;20(6):1661–1667.
20. Brass L. *Hematology Am Soc Hematol Educ Program*. 2010;2010:387–396.
21. Macfarlane RG. *Nature*. 1964;202:498–499.
22. Hoffman. *J Thromb Thrombolysis*. 2003;16(1-2):17–20.
23. Coughlin SR. *J Thromb Haemost*. 2005;3(8):1800–1814.
24. Schenone M, et al. *Curr Opin Hematol*. 2004;11(4):272–277.
25. Mann KG, et al. *Blood Cells Mol Dis*. 2006;36(2):108–117.
26. Furie B, et al. *N Engl J Med*. 1992;326(12):800–806.
27. Osterud B, et al. *Proc Natl Acad Sci U S A*. 1977;74(12):5260–5264.
28. Renne T. *Semin Immunopathol*. 2012;34(1):31–41.
29. Hoffman M. *Blood Rev*. 2003;17(suppl 1):S1–5.
30. Furie B, et al. *J Thromb Haemost*. 2007;5(suppl 1):12–17.
31. Pisano JJ, et al. *Science*. 1968;160(3830):892–893.
32. Levy JH, et al. *Transfusion*. 2013;53(5):1120–1131.
33. Crawley JT, et al. *J Thromb Haemost*. 2007;5(suppl 1):95–101.
34. Barshtein G, et al. *Expert Rev Cardiovasc Ther*. 2007;5(4):743–752.
35. Kolev K, et al. *Thromb Haemost*. 2003;89(4):610–621.
36. Woodruff RS, et al. *J Thromb Thrombolysis*. 2011;32(1):9–20.
37. Andrews RK, et al. *Arterioscler Thromb Vasc Biol*. 2007;27(7):1511–1520.
38. Crawley JT, et al. *Arterioscler Thromb Vasc Biol*. 2008;28(2):233–242.
39. Broze GJ, et al. *Proc Natl Acad Sci U S A*. 1987;84(7):1886–1890.
40. Esmen CT. *Chest*. 2003;123(2):268–328.
41. Perry DJ. *Blood Rev*. 1994;8(1):37–55.
42. Tollefson DM, et al. *J Biol Chem*. 1982;257(5):2162–2169.
43. Segal JB, et al. *Transfusion*. 2005;45(9):1413–1425.
44. Chee YL, et al. *Br J Haematol*. 2008;140(5):496–504.
45. Greaves M, et al. *J Thromb Haemost*. 2007;5(suppl 1):167–174.
46. Sadler JE. *Annu Rev Med*. 2005;56:173–1791.
47. Dinehart SM, et al. *Dermatol Surg*. 2005;31(7 Pt 2):819–826. discussion 26.
48. Leebeek FW, et al. *N Engl J Med*. 2016;375(21):2067–2080.
49. Rodeghiero F, et al. *Blood*. 1987;69(2):454–459.
50. Brinkhous KM, et al. *Proc Natl Acad Sci U S A*. 1985;82(24):8752–8756.
51. Lippi G, et al. *Blood Coagul Fibrinolysis*. 2007;18(4):361–364.
52. Roberts JC, et al. *Int J Lab Hematol*. 2015;37(suppl 1):11–17.
53. Posan E, et al. *Thromb Haemost*. 2003;90(3):483–490.
54. Castaman G, et al. *Br J Haematol*. 2010;151(3):245–251.
55. Miesbach W, et al. *Thromb Res*. 2015;135(3):479–484.
56. Kasper CK, et al. *Haemophilia*. 2007;13(1):90–92.
57. Franchini M, et al. *J Thromb Haemost*. 2010;8(3):421–432.
58. Srivastava A, et al. *Haemophilia*. 2013;19(1):e1–47.
59. Franchini M, et al. *Blood*. 2008;112(2):250–255.
60. Hoffman M, et al. *J Thromb Haemost*. 2012;10(8):1478–1485.
61. Sattler FR, et al. *Am J Surg*. 1988;155(5A):30–39.
62. Hines R, et al. *Anesthesiology*. 1989;70(4):611–615.
63. Schafer AI, et al. *Blood*. 1980;55(4):649–654.
64. Hogman M, et al. *Lancet*. 1993;341(8861):1664–1665.
65. Hergovich N, et al. *Clin Pharmacol Ther*. 2000;68(4):435–442.
66. Tripodi A, et al. *N Engl J Med*. 2011;365(2):147–156.
67. Tripodi A, et al. *Hepatology*. 2005;41(3):553–558.
68. Afshar N, et al. *J Hepatol*. 2008;48(6):1000–1007.
69. Lisman T, et al. *J Hepatol*. 2002;37(2):280–287.
70. Lisman T, et al. *Hepatology*. 2006;44(1):53–61.
71. Leebeek FW, et al. *Semin Thromb Hemost*. 2015;41(5):474–480.
72. Lisman T, et al. *Gastroenterology*. 2001;121(1):131–139.
73. Forkin KT, et al. *Anesth Analg*. 2018;126(1):46–61.
74. Yates SG, et al. *Transfusion*. 2016;56(4):791–798.
75. Benigni A, et al. *Am J Kidney Dis*. 1993;22(5):668–676.
76. Gawaz MP, et al. *J Am Soc Nephrol*. 1994;5(1):36–46.
77. Noris M, et al. *Blood*. 1999;94(8):2569–2574.
78. Turitto VT, et al. *Science*. 1980;207(4430):541–543.
79. Kim JH, et al. *Ann Hematol*. 2015;94(9):1457–1461.
80. Liu YK, et al. *Lancet*. 1984;2(8408):887–890.
81. Zojja C, et al. *Lab Invest*. 1991;65(4):479–483.
82. Gando S, et al. *Nat Rev Dis Primers*. 2016;2:16037.
83. Toh CH, et al. *Ann Lab Med*. 2016;36(6):505–512.
84. Thachil J. *Anesthesiology*. 2016;125(1):230–236.
85. Kitchens CS. *Hematology Am Soc Hematol Educ Program*. 2009; 240–246.
86. Levi M, et al. *Br J Haematol*. 2009;145(1):24–33.
87. Woodman RC, et al. *Blood*. 1990;76(9):1680–1697.
88. Gluszko P, et al. *Am J Physiol*. 1987;252(3 Pt 2):H615–621.
89. Harker LA, et al. *Blood*. 1980;56(5):824–834.
90. Weidman JL, et al. *Anesthesiology*. 2014;120(4):1009–1014.
91. Brown JR, et al. *Circulation*. 2007;115(22):2801–2813.
92. Brohi K, et al. *J Trauma*. 2003;54(6):1127–1130.
93. Chang R, et al. *Blood*. 2016;128(8):1043–1049.
94. Cohen MJ, et al. *Ann Surg*. 2012;255(2):379–385.
95. Brohi K, et al. *Ann Surg*. 2007;245(5):812–818.
96. Johansson PI, et al. *Ann Surg*. 2011;254(2):194–200.
97. Kutcher ME, et al. *J Trauma Acute Care Surg*. 2012;73(1):13–19.
98. Wohlauer MV, et al. *J Am Coll Surg*. 2012;214(5):739–746.
99. Moore HB, et al. *J Thromb Haemost*. 2015;13(10):1878–1887.
100. CRASH Trial collaborators, et al. *Lancet*. 2010;376(9734):23–32.
101. CRASH Trial collaborators, et al. *Lancet*. 2011;377(9771):1096–1101. 101 e1–e2.
102. Esmen CT, et al. *Blood Rev*. 2009;23(5):225–229.
103. Piazza G, et al. *Circulation*. 2010;121(19):2146–2150.
104. Spencer FA, et al. *J Gen Intern Med*. 2006;21(7):722–727.
105. Douketis J, et al. *BMJ*. 2011;342:d813.
106. Middeldorp S. *Hematology Am Soc Hematol Educ Program*. 2011;2011:150–155.

107. Wu O, et al. *Health Technol Assess*. 2006;10(11):1–110.
108. Dahlback B. *Blood*. 2008;112(1):19–27.
109. Heit JA. *Am J Hematol*. 2012;87(suppl 1):S63–67.
110. Ridker PM, et al. *JAMA*. 1997;277(16):1305–1307.
111. Goldhaber SZ, et al. *J Am Coll Cardiol*. 2010;56(1):1–7.
112. Andreoli L, et al. *Arthritis Care Res (Hoboken)*. 2013;65(11):1869–1873.
113. Giannakopoulos B, et al. *Blood*. 2009;113(5):985–994.
114. Lim W, et al. *JAMA*. 2006;295(9):1050–1057.
115. Kelton JG, et al. *Blood*. 2008;112(7):2607–2616.
116. Warkentin TE, et al. *Blood*. 2006;108(9):2937–2941.
117. Warkentin TE, et al. *Blood*. 2000;96(5):1703–1708.
118. Martel N, et al. *Blood*. 2005;106(8):2710–2715.
119. Berry C, et al. *J Am Coll Sur*. 2011;213(1):10–17.
120. Warkentin TE, et al. *Blood*. 2017;130(9):1104–1113.
121. Welsby IJ, et al. *Anesth Analg*. 2010;110(1):30–35.
122. Poller L. *J Thromb Haemost*. 2004;2(6):849–860.
123. Massignon D, et al. *Thromb Haemost*. 1996;75(4):590–594.
124. Burns ER, et al. *Am J Clin Pathol*. 1993;100(2):94–98.
125. Teien AN, et al. *Thromb Res*. 1976;8(3):413–416.
126. Ignjatovic V, et al. *Thromb Res*. 2007;120(3):347–351.
127. Price EA, et al. *Ann Pharmacother*. 2013;47(2):151–158.
128. Rodgers RP, et al. *Semin Thromb Hemost*. 1990;16(1):1–20.
129. Lind SE. *Blood*. 1991;77(12):2547–2552.
130. Hattersley PG. *JAMA*. 1966;196(5):436–440.
131. Paniccia R, et al. *Anesthesiology*. 2003;99(1):54–59.
132. Enriquez LJ, et al. *Br J Anaesth*. 2009;103(suppl 1):i14–22.
133. Ganter MT, et al. *Anesth Analg*. 2008;106(5):1366–1375.
134. Bolliger D, et al. *Transfus Med Rev*. 2012;26(1):1–13.
135. Shore-Lesserson L, et al. *Anesth Analg*. 1999;88(2):312–319.
136. Weber CF, et al. *Anesthesiology*. 2012;117(3):531–547.
137. Bolliger D, et al. *Semin Thromb Hemost*. 2017;43(4):386–396.
138. Hayward CP. *Blood Rev*. 2011;25(4):169–173.
139. Born GV. *Nature*. 1962;194:927–929.
140. Harrison P. *Br J Haematol*. 2000;111(3):733–744.
141. Cardinal DC, et al. *J Pharmacol Methods*. 1980;3(2):135–158.
142. Jambor C, et al. *Anesth Analg*. 2011;113(1):31–39.
143. Panzer S, et al. *Vox Sang*. 2011;101(1):1–9.
144. Kundu SK, et al. *Semin Thromb Hemost*. 1995;21(suppl 2):106–112.
145. Roth GJ, et al. *J Clin Invest*. 1975;56(3):624–632.
146. Mitchell JA, et al. *Proc Natl Acad Sci U S A*. 1993;90(24).
147. Costello PB, et al. *Arthritis Rheum*. 1982;25(5):550–555.
148. Pascale S, et al. *Blood*. 2012;119(15):3595–3603.
149. Diaz-Gonzalez F, et al. *Eur J Immunol*. 2015;45(3):679–686.
150. Silverstein FE, et al. *JAMA*. 2000;284(10):1247–1255.
151. Solomon SD, et al. *N Engl J Med*. 2005;352(11):1071–1080.
152. Coxib and Traditional NSAID Trialists' (CNT) Collaboration. *Lancet*. 2013;382(9894):769–779.
153. Ferri N, et al. *Drugs*. 2013;73(15):1681–1709.
154. Savi P, et al. *Thromb Haemost*. 2000;84(5):891–896.
155. Taubert D, et al. Impact of P-glycoprotein on clopidogrel absorption. *Clin Pharmacol Ther*. 2006;80(5):486–501.
156. Mega JL, et al. *Lancet*. 2010;376(9749):1312–1319.
157. Mega JL, et al. *JAMA*. 2010;304(16):1821–1830.
158. Wallentin L. *Eur Heart J*. 2009;30(16):1964–1977.
159. Floyd CN, et al. *Clin Pharmacokinet*. 2012;51(7):429–442.
160. Wallentin L, et al. *Lancet*. 2010;376(9749):1320–1328.
161. Akers WS, et al. *J Clin Pharmacol*. 2010;50(1):27–35.
162. Subban V, et al. *Indian Heart J*. 2013;65(3):260–263.
163. Hanna EB, et al. *JACC Cardiovasc Interv*. 2010;3(12):1209–1219.
164. Dasgupta H, et al. *Am Heart J*. 2000;140(2):206–211.
165. Yates SG, et al. *J Thromb Haemost*. 2015;13(suppl 1):S180–186.
166. Benzon HT, et al. *Anesthesiology*. 2010;112(2):298–304.
167. Pokorney SD, et al. *Am Heart J*. 2015;170(1):141–148.
168. Stergiopoulos K, et al. *JAMA Intern Med*. 2014;174(8):1330–1338.
169. Shaw K, et al. *Ther Drug Monit*. 2015;37(4):428–436.
170. Johnson EA, et al. *Carbohydr Res*. 1976;51(1):119–127.
171. Ranucci M, et al. *Perfusion*. 2002;17(3):199–204.
172. Finley A, et al. *Anesth Analg*. 2013;116(6):1210–1222.
173. Li G, et al. *Anal Chem*. 2014;86(13).
174. Hirsh J, et al. *Circulation*. 1998;98(15):1575–1582.
175. Harenberg J, et al. *Thromb Res*. 1985;38(1):11–20.
176. van Veen JJ, et al. *Blood Coagul Fibrinolysis*. 2011;22(7):565–570.
177. Greinacher A, et al. *Thromb Haemost*. 1995;74(3):886–892.
178. Bhatt VR, et al. *Eur J Haematol*. 2013;91(5):437–441.
179. Schindewolf M, et al. *J Am Coll Cardiol*. 2017;70(21):2636–2648.
180. Hursting MJ, et al. *Clin Appl Thromb Hemost*. 2005;11(3):279–287.
181. Robson R, et al. *Clin Pharmacol Ther*. 2002;71(6):433–439.
182. Bittl JA, et al. *Am Heart J*. 2001;142(6):952–959.
183. Mahaffey KW, et al. *J Invasive Cardiol*. 2003;15(11):611–616.
184. Boyce SW, et al. *Am J Ther*. 2011;18(1):14–22.
185. Nafziger AN, et al. *J Clin Pharmacol*. 2010;50(6):614–622.
186. Lee CJ, et al. *Br J Clin Pharmacol*. 2011;72(4):581–592.
187. Dentali F, et al. *Circulation*. 2012;126(20):2381–2391.
188. Connolly SJ, et al. *N Engl J Med*. 2009;361(12):1139–1151.
189. Wallentin L, et al. *Lancet*. 2010;376(9745):975–983.
190. Garcia D, et al. *J Thromb Haemost*. 2013;11(2):245–252.
191. Miyares MA, et al. *Am J Health Syst Pharm*. 2012;69(17):1473–1484.
192. Tripodi A. 2013;121(20):4032–4035.
193. Bruins Slot KM, et al. *JAMA*. 2014;311(11):1150–1151.
194. Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992.
195. Squire IB, et al. *Eur Heart J*. 1999;20(17):1245–1252.
196. Kearon C, et al. *Chest*. 2012;141(suppl 2):e419S–e96S.
197. Wan S, et al. *Circulation*. 2004;110(6):744–749.
198. Boersma E, et al. *Lancet*. 1996;348(9030):771–775.
199. Powers WJ, et al. *Stroke*. 2015;46(10):3020–3035.
200. Astedt B, et al. *Scand J Gastroenterol Suppl*. 1987;137:22–25.
201. WOMAN Trial Collaborators. *Lancet*. 2017;389(10084):2105–2116.
202. Ker K, et al. *BMJ*. 2012;344:e3054.
203. Henry DA, et al. *Cochrane Database Syst Rev*. 2011;(3):CD001886.
204. Manji RA, et al. *Can J Anaesth*. 2012;59(1):6–13.
205. Lecker I, et al. *Can J Anaesth*. 2012;59(1):1–5.
206. Mayer SA, et al. *N Engl J Med*. 2005;352(8):777–785.
207. Mayer SA, et al. *N Engl J Med*. 2008;358(20):2127–2137.
208. Boffard KD, et al. *J Trauma*. 2005;59(1):8–15; discussion -8.
209. Hauser CJ, et al. *J Trauma*. 2010;69(3):489–500.
210. Narayan RK, et al. *Neurosurgery*. 2008;62(4):776–786.
211. Yank V, et al. *Ann Intern Med*. 2011;154(8):529–540.
212. Lodge JP, et al. *Liver Transpl*. 2005;11(8):973–979.
213. Planinsic RM, et al. *Liver Transpl*. 2005;11(8):895–900.
214. Levi M, et al. *N Engl J Med*. 2010;363(19):1791–1800.
215. Lin Y, et al. *Transfus Med*. 2012;22(6):383–394.
216. Sorensen B, et al. *Crit Care*. 2011;15(1):201.
217. Dusel CH, et al. *Blood Coagul Fibrinolysis*. 2004;15(5):405–411.
218. Lunde J, et al. *Acta Anaesthesiol Scand*. 2014;58(9):1061–1074.
219. Douketis JD, et al. *Chest*. 2012;141(suppl 2):e326S–e50S.
220. Hirsh J, et al. *Chest*. 2004;126(suppl 3):188S–203S.
221. Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324(7329):71–86.
222. Burger W, et al. *J Intern Med*. 2005;257(5):399–414.
223. Lordkipanidze M, et al. *Pharmacol Ther*. 2009;123(2):178–186.
224. Pulmonary Embolism Prevention Trial Collaborative Group. *Lancet*. 2000;355(9212):1295–1302.
225. Oscarsson A, et al. *Br J Anaesth*. 2010;104(3):305–312.
226. Biondi-Zoccai GG, et al. *Eur Heart J*. 2006;27(22):2667–2674.
227. Levine GN, et al. *J Am Coll Cardiol*. 2016;68(10):1082–1115.
228. Valgimigli M, et al. *Eur Heart J*. 2018;39(3):213–260.
229. Horlocker TT, et al. *Reg Anesth Pain Med*. 2010;35(1):64–101.
230. Palareti G, et al. *Lancet*. 1996;348(9025):423–428.
231. Levine MN, et al. *Chest*. 1992;102(suppl 4).
232. Sarode R, et al. *Circulation*. 2013;128(11):1234–1243.
233. Dezee KJ, et al. *Arch Intern Med*. 2006;166(4):391–397.
234. Burbury KL, et al. *Br J Haematol*. 2011;154(5):626–634.
235. Hickey M, et al. *Circulation*. 2013;128(4):360–364.
236. Goldstein JN, et al. *Lancet*. 2015;385(9982):2077–2087.
237. Pollack CV, et al. *N Engl J Med*. 2015;373(6):511–520.
238. Connolly SJ, et al. *N Engl J Med*. 2016;375(12):1131–1341.
239. Connolly SJ, et al. *N Engl J Med*. 2019;Feb 7. [Epub ahead of print].
240. Ansell JE, et al. *Thromb Haemost*. 2017;117(2):238–245.

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References

1. Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med*. 2008;359(9):938–949. <https://doi.org/10.1056/NEJMra0801082>. Published Online First: 2008/08/30.
2. van Hinsbergh VW. Endothelium—role in regulation of coagulation and inflammation. *Semin Immunopathol*. 2012;34(1):93–106. <https://doi.org/10.1007/s00281-011-0285-5>. Published Online First: 2011/08/17.
3. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature*. 1976;263(5579):663–665. Online First: 1976/10/21.
4. Broekman MJ, Eiroa AM, Marcus AJ. Inhibition of human platelet reactivity by endothelium-derived relaxing factor from human umbilical vein endothelial cells in suspension: blockade of aggregation and secretion by an aspirin-insensitive mechanism. *Blood*. 1991;78(4):1033–1040. Online First: 1991/08/15.
5. Marcus AJ, Broekman MJ, Drosopoulos JH, et al. The endothelial cell ecto-ADPase responsible for inhibition of platelet function is CD39. *J Clin Invest*. 1997;99(6):1351–1360. <https://doi.org/10.1172/JCI119294>. Published Online First: 1997/03/15.
6. Esmon CT. Inflammation and the activated protein C anticoagulant pathway. *Semin Thromb Hemost*. 2006;32(suppl 1):49–60. <https://doi.org/10.1055/s-2006-939554>. Published Online First: 2006/05/05.
7. Mertens G, Cassiman JJ, Van den Berghe H, Vermeylen J, David G. Cell surface heparan sulfate proteoglycans from human vascular endothelial cells. Core protein characterization and antithrombin III binding properties. *J Biol Chem*. 1992;267(28):20435–22043. Online First: 1992/10/05.
8. Wood JP, Ellery PE, Maroney SA, Mast AE. Biology of tissue factor pathway inhibitor. *Blood*. 2014;123(19):2934–2943. <https://doi.org/10.1128/blood-2013-11-512764>. Published Online First: 2014/03/13.
9. Wolberg AS, Aleman MM, Leiderman K, Machlus KR. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. *Anesth Analg*. 2012;114(2):275–285. <https://doi.org/10.1213/ANE.0b013e31823a088c>. Published Online First: 2011/11/23.
10. Chiu JJ, Chien S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. *Physiol Rev*. 2011;91(1):327–387. <https://doi.org/10.1152/physrev.00047.2009>. Published Online First: 2011/01/21.
11. Stern D, Nawroth P, Handley D, Kisiel W. An endothelial cell-dependent pathway of coagulation. *Proc Natl Acad Sci U S A*. 1985;82(8):2523–2527. Online First: 1985/04/01.
12. Margetic S. Inflammation and haemostasis. *Biochem Med (Zagreb)*. 2012;22(1):49–62. Online First: 2012/03/06.
13. Van De Craen B, Declerck PJ, Gils A. The biochemistry, physiology and pathological roles of PAI-1 and the requirements for PAI-1 inhibition in vivo. *Thromb Res*. 2012;130(4):576–585. <https://doi.org/10.1016/j.thromres.2012.06.023>. Published Online First: 2012/07/18.
14. Achneck HE, Sileshi B, Lawson JH. Review of the biology of bleeding and clotting in the surgical patient. *Vascular*. 2008;16(suppl 1):S6–S13. Online First: 2008/03/01.
15. Kassis J, Hirsh J, Podor TJ. Evidence that postoperative fibrinolytic shutdown is mediated by plasma factors that stimulate endothelial cell type I plasminogen activator inhibitor biosynthesis. *Blood*. 1992;80(7):1758–1764. Online First: 1992/10/01.
16. Broos K, De Meyer SF, Feys HB, Vanhoorelbeke K, Deckmyn H. Blood platelet biochemistry. *Thromb Res*. 2012;129(3):245–249. <https://doi.org/10.1016/j.thromres.2011.11.002>. Published Online First: 2011/11/29.
17. Hanson SR, Slichter SJ. Platelet kinetics in patients with bone marrow hypoplasia: evidence for a fixed platelet requirement. *Blood*. 1985;66(5):1105–1109. Online First: 1985/11/01.
18. Broos K, Feys HB, De Meyer SF, Vanhoorelbeke K, Deckmyn H. Platelets at work in primary hemostasis. *Blood Rev*. 2011;25(4):155–167. <https://doi.org/10.1016/j.blre.2011.03.002>. Published Online First: 2011/04/19.
19. Wu YP, Vink T, Schiphorst M, et al. Platelet thrombus formation on collagen at high shear rates is mediated by von Willebrand factor-glycoprotein Ib interaction and inhibited by von Willebrand factor-glycoprotein IIb/IIIa interaction. *Arterioscler Thromb Vasc Biol*. 2000;20(6):1661–1667. Online First: 2000/06/10.
20. Brass L. Understanding and evaluating platelet function. *Hematology Am Soc Hematol Educ Program*. 2010;2010:387–396. <https://doi.org/10.1182/asheducation-2010.1.387>. Published Online First: 2011/01/18.
21. Macfarlane RG. An enzyme cascade in the blood clotting mechanism, and its function as a biochemical amplifier. *Nature*. 1964;202:498–499. Online First: 1964/05/02.
22. Hoffman M. Remodeling the blood coagulation cascade. *J Thromb Thrombolysis*. 2003;16(1-2):17–20. <https://doi.org/10.1023/B:THRO.0000014588.95061.28>. Published Online First: 2004/02/05.
23. Coughlin SR. Protease-activated receptors in hemostasis, thrombosis and vascular biology. *J Thromb Haemost*. 2005;3(8):1800–1814. <https://doi.org/10.1111/j.1538-7836.2005.01377.x>. Published Online First: 2005/08/17.
24. Schenone M, Furie BC, Furie B. The blood coagulation cascade. *Curr Opin Hematol*. 2004;11(4):272–277. Online First: 2004/08/18.
25. Mann KG, Brummel-Ziedins K, Orfeo T, Butenas S. Models of blood coagulation. *Blood Cells Mol Dis*. 2006;36(2):108–117. <https://doi.org/10.1016/j.bcmd.2005.12.034>. Published Online First: 2006/02/28.
26. Furie B, Furie BC. Molecular and cellular biology of blood coagulation. *N Engl J Med*. 1992;326(12):800–806. <https://doi.org/10.1056/NEJM199203193261205>. Published Online First: 1992/03/19.
27. Osterud B, Rapaport SI. Activation of factor IX by the reaction product of tissue factor and factor VII: additional pathway for initiating blood coagulation. *Proc Natl Acad Sci U S A*. 1977;74(12):5260–5264. Online First: 1977/12/01.
28. Renne T. The procoagulant and proinflammatory plasma contact system. *Semin Immunopathol*. 2012;34(1):31–41. <https://doi.org/10.1007/s00281-011-0288-2>. Published Online First: 2011/08/23.
29. Hoffman M. A cell-based model of coagulation and the role of factor VIIa. *Blood Rev*. 2003;17(suppl 1):S1–S5. Online First: 2003/12/31.
30. Furie B, Furie BC. In vivo thrombus formation. *J Thromb Haemost*. 2007;5(suppl 1):12–17. <https://doi.org/10.1111/j.1538-7836.2007.02482.x>. Published Online First: 2007/08/01.
31. Pisano JJ, Finlayson JS, Peyton MP. Cross-link in fibrin polymerized by factor 13: epsilon-(gamma-glutamyl)lysine. *Science*. 1968;160(3830):892–893. Online First: 1968/05/24.
32. Levy JH, Greenberg C. Biology of factor XIII and clinical manifestations of factor XIII deficiency. *Transfusion*. 2013;53(5):1120–1131. <https://doi.org/10.1111/j.1537-2995.2012.03865.x>. Published Online First: 2012/08/30.
33. Crawley JT, Zanardelli S, Chion CK, Lane DA. The central role of thrombin in hemostasis. *J Thromb Haemost*. 2007;5(suppl 1):95–101. <https://doi.org/10.1111/j.1538-7836.2007.02500.x>. Published Online First: 2007/08/01.
34. Barshtein G, Ben-Ami R, Yedgar S. Role of red blood cell flow behavior in hemodynamics and hemostasis. *Expert Rev Cardiovasc Ther*. 2007;5(4):743–752. <https://doi.org/10.1586/14779072.5.4.743>. Published Online First: 2007/07/04.
35. Kolev K, Machovich R. Molecular and cellular modulation of fibrinolysis. *Thromb Haemost*. 2003;89(4):610–621. Online First: 2003/04/02.
36. Woodruff RS, Sullenger B, Becker RC. The many faces of the contact pathway and their role in thrombosis. *J Thromb Thrombolysis*. 2011;32(1):9–20. <https://doi.org/10.1007/s11239-011-0578-5>. Published Online First: 2011/03/16.
37. Andrews RK, Karunakaran D, Gardiner EE, Berndt MC. Platelet receptor proteolysis: a mechanism for downregulating platelet reactivity. *Arterioscler Thromb Vasc Biol*. 2007;27(7):1511–1520. <https://doi.org/10.1161/ATVBAHA.107.141390>. Published Online First: 2007/04/28.
38. Crawley JT, Lane DA. The haemostatic role of tissue factor pathway inhibitor. *Arterioscler Thromb Vasc Biol*. 2008;28(2):233–242. <https://doi.org/10.1161/ATVBAHA.107.141606>. Published Online First: 2007/10/24.
39. Broze GJ, Miletich JP. Isolation of the tissue factor inhibitor produced by HepG2 hepatoma cells. *Proc Natl Acad Sci U S A*. 1987;84(7):1886–1890. Online First: 1987/04/01.
40. Esmon CT. The protein C pathway. *Chest*. 2003;124(suppl 3):26S–32S. Online First: 2003/09/13.

41. Perry DJ. Antithrombin and its inherited deficiencies. *Blood Rev.* 1994;8(1):37–55. Online First: 1994/03/01.
42. Tollesen DM, Majerus DW, Blank MK. Heparin cofactor II. Purification and properties of a heparin-dependent inhibitor of thrombin in human plasma. *J Biol Chem.* 1982;257(5):2162–2169. Online First: 1982/03/10.
43. Segal JB, Dzik WH. Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion.* 2005;45(9):1413–1425. <https://doi.org/10.1111/j.1537-2995.2005.00546>. xpublished Online First: 2005/09/01.
44. Chee YL, Crawford JC, Watson HG, Greaves M. Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. British Committee for Standards in Haematology. *Br J Haematol.* 2008;140(5):496–504. <https://doi.org/10.1111/j.1365-2141.2007.06968>. xpublished Online First: 2008/02/16.
45. Greaves M, Watson HG. Approach to the diagnosis and management of mild bleeding disorders. *J Thromb Haemost.* 2007;5(suppl 1):167–174. <https://doi.org/10.1111/j.1538-7836.2007.02495>. xpublished Online First: 2007/08/01.
46. Sadler JE. New concepts in von Willebrand disease. *Annu Rev Med.* 2005;56:173–1791. <https://doi.org/10.1146/annurev.med.56.082103.104713>. Published Online First: 2005/01/22.
47. Dinehart SM, Henry L. Dietary supplements: altered coagulation and effects on bruising. *Dermatol Surg.* 2005;31(7 Pt 2):819–826. discussion 26. Online First: 2005/07/21.
48. Leebeek FW, Eikenboom JC. Von Willebrand's Disease. *N Engl J Med.* 2016;375(21):2067–2080. <https://doi.org/10.1056/NEJMra1601561>. Published Online First: 2016/12/14.
49. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood.* 1987;69(2):454–459. Online First: 1987/02/01.
50. Brinkhous KM, Sandberg H, Garris JB, et al. Purified human factor VIII procoagulant protein: comparative hemostatic response after infusions into hemophilic and von Willebrand disease dogs. *Proc Natl Acad Sci U S A.* 1985;82(24):8752–8756. Online First: 1985/12/01.
51. Lippi G, Franchini M, Poli G, Salvagno GL, Montagnana M, Guidi GC. Is the activated partial thromboplastin time suitable to screen for von Willebrand factor deficiencies? *Blood Coagul Fibrinolysis.* 2007;18(4):361–364. <https://doi.org/10.1097/MBC.0b013e32810fd872>. Published Online First: 2007/05/03.
52. Roberts JC, Flood VH. Laboratory diagnosis of von Willebrand disease. *Int J Lab Hematol.* 2015;37(suppl 1):11–17. <https://doi.org/10.1111/ijlh.12345>. Published Online First: 2015/05/16.
53. Posan E, McBane RD, Grill DE, Motsko CL, Nichols WL. Comparison of PFA-100 testing and bleeding time for detecting platelet hypo-function and von Willebrand disease in clinical practice. *Thromb Haemost.* 2003;90(3):483–490. <https://doi.org/10.1160/TH03-02-0111>. Published Online First: 2003/09/06.
54. Castaman G, Tosetto A, Goedeve A, et al. The impact of bleeding history, von Willebrand factor and PFA-100(R) on the diagnosis of type 1 von Willebrand disease: results from the European study MCMIDM-1VWD. *Br J Haematol.* 2010;151(3):245–251. <https://doi.org/10.1111/j.1365-2141.2010.08333>. xpublished Online First: 2010/08/27.
55. Miesbach W, Krekeler S, Wolf Z, Seifried E. Clinical use of Haemate(R) P in von Willebrand disease: a 25-year retrospective observational study. *Thromb Res.* 2015;135(3):479–484. <https://doi.org/10.1016/j.thromres.2014.12.017>. Published Online First: 2015/01/18.
56. Kasper CK, Lin JC. Prevalence of sporadic and familial haemophilia. *Haemophilia.* 2007;13(1):90–92. <https://doi.org/10.1111/j.1365-2516.2006.01397>. xpublished Online First: 2007/01/11.
57. Franchini M, Favaloro EJ, Lippi G. Mild hemophilia A. *J Thromb Haemost.* 2010;8(3):421–432. <https://doi.org/10.1111/j.1538-7836.2009.03717>. xpublished Online First: 2009/12/10.
58. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia.* 2013;19(1):e1–47. <https://doi.org/10.1111/j.1365-2516.2012.02909>. xpublished Online First: 2012/07/11.
59. Franchini M, Lippi G. Acquired factor VIII inhibitors. *Blood.* 2008;112(2):250–255. <https://doi.org/10.1182/blood-2008-03-143586>. Published Online First: 2008/05/09.
60. Hoffman M, Dargaud Y. Mechanisms and monitoring of bypassing agent therapy. *J Thromb Haemost.* 2012;10(8):1478–1485. <https://doi.org/10.1111/j.1538-7836.2012.04793>. xpublished Online First: 2012/05/29.
61. Sattler FR, Weitekamp MR, Sayegh A, Ballard JO. Impaired hemostasis caused by beta-lactam antibiotics. *Am J Surg.* 1988;155(5A):30–39. Online First: 1988/05/31.
62. Hines R, Barash PG. Infusion of sodium nitroprusside induces platelet dysfunction in vitro. *Anesthesiology.* 1989;70(4):611–615. Online First: 1989/04/01.
63. Schafer AI, Alexander RW, Handin RI. Inhibition of platelet function by organic nitrate vasodilators. *Blood.* 1980;55(4):649–654. Online First: 1980/04/01.
64. Hogman M, Frostell C, Arnberg H, Hedenstierna G. Bleeding time prolongation and NO inhalation. *Lancet.* 1993;341(8861):1664–1665. Online First: 1993/06/26.
65. Hergovich N, Aigner M, Eichler HG, Entlicher J, Drucker C, Jilma B. Paroxetine decreases platelet serotonin storage and platelet function in human beings. *Clin Pharmacol Ther.* 2000;68(4):435–442. <https://doi.org/10.1067/mcp.2000.110456>. Published Online First: 2000/11/04.
66. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med.* 2011;365(2):147–156. <https://doi.org/10.1056/NEJMra1011170>. Published Online First: 2011/07/15.
67. Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology.* 2005;41(3):553–558. <https://doi.org/10.1002/hep.20569>. Published Online First: 2005/02/24.
68. Afshai N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. *J Hepatol.* 2008;48(6):1000–1007. <https://doi.org/10.1016/j.jhep.2008.03.009>. Published Online First: 2008/04/25.
69. Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. *J Hepatol.* 2002;37(2):280–287. Online First: 2002/07/20.
70. Lisman T, Bongers TN, Adelmeijer J, et al. Elevated levels of von Willebrand Factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology.* 2006;44(1):53–61. <https://doi.org/10.1002/hep.21231>. Published Online First: 2006/06/27.
71. Leebeek FW, Rijken DC. The fibrinolytic status in liver diseases. *Semin Thromb Hemost.* 2015;41(5):474–480. <https://doi.org/10.1055/s-0035-1550437>. Published Online First: 2015/06/07.
72. Lisman T, Leebeek FW, Mosnier LO, et al. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. *Gastroenterology.* 2001;121(1):131–139. Online First: 2001/07/05.
73. Forkin KT, Colquhoun DA, Nemergut EC, Huffmyer JL. The coagulation profile of end-stage liver disease and considerations for intraoperative management. *Anesth Analg.* 2018;126(1):46–61. <https://doi.org/10.1213/ANE.0000000000002394>. Published Online First: 2017/08/11.
74. Yates SG, Gavva C, Agrawal D, Sarode R. How do we transfuse blood components in cirrhotic patients undergoing gastrointestinal procedures? *Transfusion.* 2016;56(4):791–798. <https://doi.org/10.1111/trf.13495>. Published Online First: 2016/02/16.
75. Benigni A, Boccardo P, Galbusera M, et al. Reversible activation defect of the platelet glycoprotein IIb-IIIa complex in patients with uremia. *Am J Kidney Dis.* 1993;22(5):668–676. Online First: 1993/11/01.
76. Gawaz MP, Dobos G, Spath M, Schollmeyer P, Gurland HJ, Mujais SK. Impaired function of platelet membrane glycoprotein IIb-IIIa in end-stage renal disease. *J Am Soc Nephrol.* 1994;5(1):36–46. Online First: 1994/07/01.
77. Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? *Blood.* 1999;94(8):2569–2574. Online First: 1999/10/09.
78. Turitto VT, Weiss HJ. Red blood cells: their dual role in thrombus formation. *Science.* 1980;207(4430):541–543. Online First: 1980/02/01.
79. Kim JH, Baek CH, Min JY, Kim JS, Kim SB, Kim H. Desmopressin improves platelet function in uremic patients taking antiplatelet agents who require emergent invasive procedures. *Ann Hematol.* 2015;94(9):1457–1461. <https://doi.org/10.1007/s00277-015-2384-1>. Published Online First: 2015/05/03.
80. Liu YK, Kosfeld RE, Marcum SG. Treatment of uraemic bleeding with conjugated oestrogen. *Lancet.* 1984;2(8408):887–890. Online First: 1984/10/20.

81. Zoja C, Noris M, Corna D, et al. L-arginine, the precursor of nitric oxide, abolishes the effect of estrogens on bleeding time in experimental uremia. *Lab Invest*. 1991;65(4):479–483. Online First: 1991/10/01.
82. Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. *Nat Rev Dis Primers*. 2016;2:16037. <https://doi.org/10.1038/nrdp.2016.37>. Published Online First: 2016/06/03.
83. Toh CH, Alhamdi Y, Abrams ST. Current pathological and laboratory considerations in the diagnosis of disseminated intravascular coagulation. *Ann Lab Med*. 2016;36(6):505–512. <https://doi.org/10.3343/alm.2016.36.6.505>. Published Online First: 2016/09/01.
84. Thachil J. Disseminated Intravascular Coagulation: a Practical Approach. *Anesthesiology*. 2016;125(1):230–236. <https://doi.org/10.1097/ALN.0000000000001123>. Published Online First: 2016/04/01.
85. Kitchens CS. Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). *Hematology Am Soc Hematol Educ Program*. 2009;240–246. <https://doi.org/10.1182/asheducation-2009.1.240>. Published Online First: 2009/12/17.
86. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol*. 2009;145(1):24–33. <https://doi.org/10.1111/j.1365-2141.2009.07600.x> Published Online First: 2009/02/19.
87. Woodman RC, Harker LA. Bleeding complications associated with cardiopulmonary bypass. *Blood*. 1990;76(9):1680–1697. Online First: 1990/11/01.
88. Gluszko P, Rucinski B, Musial J, et al. Fibrinogen receptors in platelet adhesion to surfaces of extracorporeal circuit. *Am J Physiol*. 1987;252(3 Pt 2):H615–H621. <https://doi.org/10.1152/ajpheart.1987.252.3.H615>. Published Online First: 1987/03/11.
89. Harker LA, Malpass TW, Branson HE, Hessel EA 2nd, Slichter SJ. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective alpha-granule release. *Blood*. 1980;56(5):824–834. Online First: 1980/11/01.
90. Weidman JL, Shook DC, Hilberath JN. Cardiac resuscitation and coagulation. *Anesthesiology*. 2014;120(4):1009–1014. <https://doi.org/10.1097/ALN.0000000000000086>. Published Online First: 2013/12/04.
91. Brown JR, Birkmeyer NJ, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation*. 2007;115(22):2801–2813. <https://doi.org/10.1161/CIRCULATIONAHA.106.671222>. Published Online First: 2007/05/30.
92. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. *J Trauma*. 2003;54(6):1127–1130. <https://doi.org/10.1097/01.TA.0000069184.82147.06>. Published Online First: 2003/06/19.
93. Chang R, Cardenas JC, Wade CE, Holcomb JB. Advances in the understanding of trauma-induced coagulopathy. *Blood*. 2016;128(8):1043–1049. <https://doi.org/10.1182/blood-2016-01-636423>. Published Online First: 2016/07/07.
94. Cohen MJ, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. *Ann Surg*. 2012;255(2):379–385. <https://doi.org/10.1097/SLA.0b013e318235d9e6>. Published Online First: 2011/12/03.
95. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion? modulated through the protein C pathway? *Ann Surg*. 2007;245(5):812–818. <https://doi.org/10.1097/01.sla.0000256862.79374.31>. Published Online First: 2007/04/26.
96. Johansson PI, Stensballe J, Rasmussen LS, Ostrowski SR. A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. *Ann Surg*. 2011;254(2):194–200. <https://doi.org/10.1097/SLA.0b013e318226113d>. Published Online First: 2011/07/21.
97. Kutcher ME, Redick BJ, McCreery RC, et al. Characterization of platelet dysfunction after trauma. *J Trauma Acute Care Surg*. 2012;73(1):13–19. <https://doi.org/10.1097/TA.0b013e318256deab>. Published Online First: 2012/06/30.
98. Wohlauer MV, Moore EE, Thomas S, et al. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. *J Am Coll Surg*. 2012;214(5):739–746. <https://doi.org/10.1016/j.jamcoll-surg.2012.01.050>. Published Online First: 2012/04/24.
99. Moore HB, Moore EE, Chapman MP, et al. Viscoelastic measurements of platelet function, not fibrinogen function, predicts sensitivity to tissue-type plasminogen activator in trauma patients. *J Thromb Haemost*. 2015;13(10):1878–1887. <https://doi.org/10.1111/jth.13067>. Published Online First: 2015/08/11.
100. CRASH Trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32. [https://doi.org/10.1016/S0140-6736\(10\)60835-5](https://doi.org/10.1016/S0140-6736(10)60835-5). Published Online First: 2010/06/18.
101. CRASH Trial collaborators, Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377(9771):1096–1101. [https://doi.org/10.1016/S0140-6736\(11\)60278-X](https://doi.org/10.1016/S0140-6736(11)60278-X). 101e1-2 Published Online First: 2011/03/29.
102. Esmon CT. Basic mechanisms and pathogenesis of venous thrombosis. *Blood Rev*. 2009;23(5):225–229. <https://doi.org/10.1016/j.blre.2009.07.002>. Published Online First: 2009/08/18.
103. Piazza G, Goldhaber SZ. Venous thromboembolism and atherosclerosis: an integrated approach. *Circulation*. 2010;121(19):2146–2150. <https://doi.org/10.1161/CIRCULATIONAHA.110.951236>. Published Online First: 2010/05/19.
104. Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med*. 2006;21(7):722–727. <https://doi.org/10.1111/j.1525-1497.2006.00458.x>. Published Online First: 2006/07/01.
105. Douketis J, Tosoletti A, Marcucci M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. *BMJ*. 2011;342:d813. <https://doi.org/10.1136/bmj.d813>. Published Online First: 2011/02/26.
106. Middeldorp S. Is thrombophilia testing useful? *Hematology Am Soc Hematol Educ Program*. 2011;2011:150–155. <https://doi.org/10.1182/asheducation-2011.1.150>. Published Online First: 2011/12/14.
107. Wu O, Robertson L, Twaddle S, et al. Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. *Health Technol Assess*. 2006;10(11):1–110. Online First: 2006/04/06.
108. Dahlback B. Advances in understanding pathogenic mechanisms of thrombophilic disorders. *Blood*. 2008;112(1):19–27. <https://doi.org/10.1182/blood-2008-01-077909>. Published Online First: 2008/06/25.
109. Heit JA. Predicting the risk of venous thromboembolism recurrence. *Am J Hematol*. 2012;87(suppl 1):S63–S67. <https://doi.org/10.1002/ajh.23128>. Published Online First: 2012/03/01.
110. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. *JAMA*. 1997;277(16):1305–1307. Online First: 1997/04/23.
111. Goldhaber SZ. Risk factors for venous thromboembolism. *J Am Coll Cardiol*. 2010;56(1):1–7. <https://doi.org/10.1016/j.jacc.2010.01.057>. Published Online First: 2010/07/14.
112. Andreoli L, Chighizola CB, Banzato A, Pons-Estel GJ, Ramire de Jesus G, Erkan D. Estimated frequency of antiphospholipid antibodies in patients with pregnancy morbidity, stroke, myocardial infarction, and deep vein thrombosis: a critical review of the literature. *Arthritis Care Res (Hoboken)*. 2013;65(11):1869–1873. <https://doi.org/10.1002/acr.22066>. Published Online First: 2013/07/19.
113. Giannakopoulos B, Passam F, Ioannou Y, Krilis SA. How we diagnose the antiphospholipid syndrome. *Blood*. 2009;113(5):985–994. <https://doi.org/10.1182/blood-2007-12-129627>. Published Online First: 2008/08/30.
114. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA*. 2006;295(9):1050–1057. <https://doi.org/10.1001/jama.295.9.1050>. Published Online First: 2006/03/02.
115. Kelton JG, Warkentin TE. Heparin-induced thrombocytopenia: a historical perspective. *Blood*. 2008;112(7):2607–2616. <https://doi.org/10.1182/blood-2008-02-078014>. Published Online First: 2008/09/24.
116. Warkentin TE, Sheppard JA, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood*. 2006;108(9):2937–2941. <https://doi.org/10.1182/blood-2005-11-012450>. Published Online First: 2006/07/22.

117. Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood*. 2000;96(5):1703–1708. Online First: 2000/08/29.
118. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood*. 2005;106(8):2710–2715. <https://doi.org/10.1182/blood-2005-04-1546>. Published Online First: 2005/06/30.
119. Berry C, Tcherniantchouk O, Ley EJ, et al. Overdiagnosis of heparin-induced thrombocytopenia in surgical ICU patients. *J Am Coll Sur*. 2011;213(1):10–17. <https://doi.org/10.1016/j.jamcollsurg.2011.04.002>. discussion 7–8. published Online First: 2011/05/03.
120. Warkentin TE, Pai M, Linkins LA. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. *Blood*. 2017;130(9):1104–1113. <https://doi.org/10.1182/blood-2017-04-778993>. Published Online First: 2017/06/25.
121. Welsby IJ, Um J, Milano CA, Ortel TL, Arepally G. Plasmapheresis and heparin reexposure as a management strategy for cardiac surgical patients with heparin-induced thrombocytopenia. *Anesth Analg*. 2010;110(1):30–35. <https://doi.org/10.1213/ANE.0b013e3181c3c1cd>. Published Online First: 2009/11/26.
122. Poller L. International normalized ratios (INR): the first 20 years. *J Thromb Haemost*. 2004;2(6):849–860. <https://doi.org/10.1111/j.1538-7836.2004.00775>. xpublished Online First: 2004/05/14.
123. Massignon D, Moulisma M, Bondon P, et al. Prothrombin time sensitivity and specificity to mild clotting factor deficiencies of the extrinsic pathway: evaluation of eight commercial thromboplastins. *Thromb Haemost*. 1996;75(4):590–594. Online First: 1996/04/01.
124. Burns ER, Goldberg SN, Wenz B. Paradoxical effect of multiple mild coagulation factor deficiencies on the prothrombin time and activated partial thromboplastin time. *Am J Clin Pathol*. 1993;100(2):94–98. Online First: 1993/08/01.
125. Teien AN, Lie M, Abildgaard U. Assay of heparin in plasma using a chromogenic substrate for activated factor X. *Thromb Res*. 1976;8(3):413–416. Online First: 1976/03/01.
126. Ignatovic V, Summerhayes R, Gan A, et al. Monitoring unfractionated heparin (UFH) therapy: which anti-factor Xa assay is appropriate? *Thromb Res*. 2007;120(3):347–351. <https://doi.org/10.1016/j.thromres.2006.10.006>. Published Online First: 2006/11/23.
127. Price EA, Jin J, Nguyen HM, Krishnan G, Bowen R, Zehnder JL. Discordant aPTT and anti-Xa values and outcomes in hospitalized patients treated with intravenous unfractionated heparin. *Ann Pharmacother*. 2013;47(2):151–158. <https://doi.org/10.1345/aph.1R635>. Published Online First: 2013/02/07.
128. Rodgers RP, Levin J. A critical reappraisal of the bleeding time. *Semin Thromb Hemost*. 1990;16(1):1–20. <https://doi.org/10.1055/s-2007-1002658>. Published Online First: 1990/01/01.
129. Lind SE. The bleeding time does not predict surgical bleeding. *Blood*. 1991;77(12):2547–2552. Online First: 1991/06/15.
130. Hattersley PG. Activated coagulation time of whole blood. *JAMA*. 1966;196(5):436–440. Online First: 1966/05/02.
131. Paniccia R, Fedi S, Carbonetto F, et al. Evaluation of a new point-of-care celite-activated clotting time analyzer in different clinical settings. The i-STAT celite-activated clotting time test. *Anesthesiology*. 2003;99(1):54–59. Online First: 2003/06/27.
132. Enriquez LJ, Shore-Lesserson L. Point-of-care coagulation testing and transfusion algorithms. *Br J Anaesth*. 2009;103(suppl 1):i14–i22. <https://doi.org/10.1093/bja/aep318>. Published Online First: 2009/12/17.
133. Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesth Analg*. 2008;106(5):1366–1375. <https://doi.org/10.1213/ane.0b013e31816b367>. Published Online First: 2008/04/19.
134. Bolliger D, Seeberger MD, Tanaka KA. Principles and practice of thromboelastography in clinical coagulation management and transfusion practice. *Transfus Med Rev*. 2012;26(1):1–13. <https://doi.org/10.1016/j.tmrv.2011.07.005>. Published Online First: 2011/08/30.
135. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg*. 1999;88(2):312–319. Online First: 1999/02/11.
136. Weber CF, Gorlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology*. 2012;117(3):531–547. <https://doi.org/10.1097/ALN.0b013e318264c644>. published Online First: 2012/08/24.
137. Bolliger D, Tanaka KA. Point-of-care coagulation testing in cardiac surgery. *Semin Thromb Hemost*. 2017;43(4):386–396. <https://doi.org/10.1055/s-0037-1599153>. published Online First: 2017/03/31.
138. Hayward CP. Diagnostic evaluation of platelet function disorders. *Blood Rev*. 2011;25(4):169–173. <https://doi.org/10.1016/j.blre.2011.03.004>. published Online First: 2011/04/19.
139. Born GV. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature*. 1962;194:927–929. Online First: 1962/06/09.
140. Harrison P. Progress in the assessment of platelet function. *Br J Haematol*. 2000;111(3):733–744. Online First: 2000/12/21.
141. Cardinal DC, Flower RJ. The electronic aggregometer: a novel device for assessing platelet behavior in blood. *J Pharmacol Methods*. 1980;3(2):135–158. Online First: 1980/02/01.
142. Jambor C, von Pape KW, Spannagl M, Dietrich W, Giebel A, Weisser H. Multiple electrode whole blood aggregometry, PFA-100, and in vivo bleeding time for the point-of-care assessment of aspirin-induced platelet dysfunction in the preoperative setting. *Anesth Analg*. 2011;113(1):31–39. <https://doi.org/10.1213/ANE.0b013e31821acddc>. published Online First: 2011/04/27.
143. Panzer S, Jilma P. Methods for testing platelet function for transfusion medicine. *Vox Sang*. 2011;101(1):1–9. <https://doi.org/10.1111/j.1423-0410.2011.01467>. xpublished Online First: 2011/06/15.
144. Kundu SK, Heilmann EJ, Sio R, Garcia C, Davidson RM, Ostgaard RA. Description of an in vitro platelet function analyzer—PFA-100. *Semin Thromb Hemost*. 1995;21(suppl 2):106–112. Online First: 1995/01/01.
145. Roth GJ, Majerus PW. The mechanism of the effect of aspirin on human platelets. I. Acetylation of a particulate fraction protein. *J Clin Invest*. 1975;56(3):624–632. <https://doi.org/10.1172/JCI108132>. published Online First: 1975/09/01.
146. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci U S A*. 1993;90(24):11693–11697 Online First: 1993/12/15].
147. Costello PB, Green FA. Aspirin survival in human blood modulated by the concentration of erythrocytes. *Arthritis Rheum*. 1982;25(5):550–555. Online First: 1982/05/01.
148. Pascale S, Petrucci G, Dragani A, et al. Aspirin-insensitive thromboxane biosynthesis in essential thrombocythemia is explained by accelerated renewal of the drug target. *Blood*. 2012;119(15):3595–3603. <https://doi.org/10.1182/blood-2011-06-359224>. published Online First: 2012/01/12].
149. Diaz-Gonzalez F, Sanchez-Madrid F. NSAIDs: learning new tricks from old drugs. *Eur J Immunol*. 2015;45(3):679–686. <https://doi.org/10.1002/eji.201445222>. published Online First: 2014/12/20].
150. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study*. *JAMA*. 2000;284(10):1247–1255. Online First: 2000/09/09].
151. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med*. 2005;352(11):1071–1080. <https://doi.org/10.1056/NEJMoa050405>. published Online First: 2005/02/17].
152. Coxib and Traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769–779. [https://doi.org/10.1016/S0140-6736\(13\)60900-9](https://doi.org/10.1016/S0140-6736(13)60900-9). published Online First: 2013/06/04].
153. Ferri N, Corsini A, Bellosta S. Pharmacology of the new P2Y12 receptor inhibitors: insights on pharmacokinetic and pharmacodynamic properties. *Drugs*. 2013;73(15):1681–1709. <https://doi.org/10.1007/s40265-013-0126-z>. published Online First: 2013/10/12].

154. Savi P, Pereillo JM, Uzabiaga MF, et al. Identification and biological activity of the active metabolite of clopidogrel. *Thromb Haemost*. 2000;84(5):891–896. Online First: 2000/12/29.
155. Taubert D, von Beckerath N, Grimberg G, et al. Impact of P-glycoprotein on clopidogrel absorption. *Clin Pharmacol Ther*. 2006;80(5):486–501. <https://doi.org/10.1016/j.cpt.2006.07.007>. Published Online First: 2006/11/23.
156. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet*. 2010;376(9749):1312–1319. [https://doi.org/10.1016/S0140-6736\(10\)61273-1](https://doi.org/10.1016/S0140-6736(10)61273-1). Published Online First: 2010/08/31.
157. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304(16):1821–1830. <https://doi.org/10.1001/jama.2010.1543>. Published Online First: 2010/10/28.
158. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J*. 2009;30(16):1964–1977. <https://doi.org/10.1093/eurheartj/ehp296>. Published Online First: 2009/07/28.
159. Floyd CN, Passacquale G, Ferro A. Comparative pharmacokinetics and pharmacodynamics of platelet adenosine diphosphate receptor antagonists and their clinical implications. *Clin Pharmacokinet*. 2012;51(7):429–442. <https://doi.org/10.2165/11630740-000000000-00000>. Published Online First: 2012/05/10.
160. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet*. 2010;376(9749):1320–1328. [https://doi.org/10.1016/S0140-6736\(10\)61274-3](https://doi.org/10.1016/S0140-6736(10)61274-3). Published Online First: 2010/08/31.
161. Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhubl SR. Pharmacokinetics and pharmacodynamics of a bolus and infusion of canagrelor: a direct, parenteral P2Y12 receptor antagonist. *J Clin Pharmacol*. 2010;50(1):27–35. <https://doi.org/10.1177/0091270009344986>. Published Online First: 2009/09/26.
162. Subban V, Sarat Chandra K. Glycoprotein IIb/IIIa inhibitors—do we still need them? *Indian Heart J*. 2013;65(3):260–263. <https://doi.org/10.1016/j.ihj.2013.04.032>. Published Online First: 2013/07/03.
163. Hanna EB, Rao SV, Manoukian SV, Saucedo JF. The evolving role of glycoprotein IIb/IIIa inhibitors in the setting of percutaneous coronary intervention strategies to minimize bleeding risk and optimize outcomes. *JACC Cardiovasc Interv*. 2010;3(12):1209–1219. <https://doi.org/10.1016/j.jcin.2010.09.015>. Published Online First: 2011/01/15.
164. Dasgupta H, Blankenship JC, Wood GC, Frey CM, Demko SL, Menapace FJ. Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis. *Am Heart J*. 2000;140(2):206–211. <https://doi.org/10.1067/mhj.2000.107554>. Published Online First: 2000/08/05.
165. Yates SG, Sarode R. New strategies for effective treatment of vitamin K antagonist-associated bleeding. *J Thromb Haemost*. 2015;13(suppl 1):S180–S186. <https://doi.org/10.1111/jth.12970>. Published Online First: 2015/07/08.
166. Benzon HT, Avram MJ, Benzon HA, Kirby-Nolan M, Nader A. Factor VII levels and international normalized ratios in the early phase of warfarin therapy. *Anesthesiology*. 2010;112(2):298–304. <https://doi.org/10.1097/ALN.0b013e3181ca6cfc>. Published Online First: 2010/01/26.
167. Pokorney SD, Simon DN, Thomas L, et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J*. 2015;170(1):141–148, 8 e1. <https://doi.org/10.1016/j.ahj.2015.03.017>. Published Online First: 2015/06/22.
168. Stergiopoulos K, Brown DL. Genotype-guided vs clinical dosing of warfarin and its analogues: meta-analysis of randomized clinical trials. *JAMA Intern Med*. 2014;174(8):1330–1338. <https://doi.org/10.1001/jamainternmed.2014.2368>. Published Online First: 2014/06/18.
169. Shaw K, Amstutz U, Kim RB, et al. Clinical practice recommendations on genetic testing of CYP2C9 and VKORC1 variants in warfarin therapy. *Ther Drug Monit*. 2015;37(4):428–436. <https://doi.org/10.1097/FTD.0000000000000192>. Published Online First: 2015/07/18.
170. Johnson EA, Mulloy B. The molecular-weight range of mucosal-heparin preparations. *Carbohydr Res*. 1976;51(1):119–127. Online First: 1976/10/01.
171. Ranucci M, Isgro G, Cazzaniga A, et al. Different patterns of heparin resistance: therapeutic implications. *Perfusion*. 2002;17(3):199–204. <https://doi.org/10.1191/0267659102pf562oa>. Published Online First: 2002/05/23.
172. Finley A, Greenberg C. Review article: heparin sensitivity and resistance: management during cardiopulmonary bypass. *Anesth Analg*. 2013;116(6):1210–1222. <https://doi.org/10.1213/ANE.0b013e31827e4e62>. Published Online First: 2013/02/15.
173. Li G, Steppich J, Wang Z, et al. Bottom-up low molecular weight heparin analysis using liquid chromatography-Fourier transform mass spectrometry for extensive characterization. *Anal Chem*. 2014;86(13):6626–6232. <https://doi.org/10.1021/ac501301v>. Published Online First: 2014/06/07.
174. Hirsh J. Low-molecular-weight heparin : a review of the results of recent studies of the treatment of venous thromboembolism and unstable angina. *Circulation*. 1998;98(15):1575–1582. Online First: 1998/10/14.
175. Harenberg J, Gnasso A, de Vries JX, Zimmermann R, Augustin J. Inhibition of low molecular weight heparin by protamine chloride in vivo. *Thromb Res*. 1985;38(1):11–20. Online First: 1985/04/01.
176. van Veen JJ, Maclean RM, Hampton KK, et al. Protamine reversal of low molecular weight heparin: clinically effective? *Blood Coagul Fibrinolysis*. 2011;22(7):565–570. <https://doi.org/10.1097/MBC.0b013e3283494b3c>. Published Online First: 2011/10/01.
177. Greinacher A, Alban S, Dummel V, Franz G, Mueller-Eckhardt C. Characterization of the structural requirements for a carbohydrate based anticoagulant with a reduced risk of inducing the immunological type of heparin-associated thrombocytopenia. *Thromb Haemost*. 1995;74(3):886–892. Online First: 1995/09/01.
178. Bhatt VR, Aryal MR, Shrestha R, Armitage JO. Fondaparinux-associated heparin-induced thrombocytopenia. *Eur J Haematol*. 2013;91(5):437–441. <https://doi.org/10.1111/ejh.12179>. Published Online First: 2013/08/03.
179. Schindewolf M, Steindl J, Beyer-Westendorf J, et al. Use of Fondaparinux off-label or approved anticoagulants for management of heparin-induced thrombocytopenia. *J Am Coll Cardiol*. 2017;70(21):2636–2648. <https://doi.org/10.1016/j.jacc.2017.09.1099>. Published Online First: 2017/11/25.
180. Hursting MJ, Lewis BE, Macfarlane DE. Transitioning from argatroban to warfarin therapy in patients with heparin-induced thrombocytopenia. *Clin Appl Thromb Hemost*. 2005;11(3):279–287. Online First: 2005/07/15.
181. Robson R, White H, Aylward P, Frampton C. Bivalirudin pharmacokinetics and pharmacodynamics: effect of renal function, dose, and gender. *Clin Pharmacol Ther*. 2002;71(6):433–439. <https://doi.org/10.1067/mcp.2002.124522>. Published Online First: 2002/06/28.
182. Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J*. 2001;142(6):952–959. Online First: 2001/11/22.
183. Mahaffey KW, Lewis BE, Wildermann NM, et al. The anticoagulant therapy with bivalirudin to assist in the performance of percutaneous coronary intervention in patients with heparin-induced thrombocytopenia (ATBAT) study: main results. *J Invasive Cardiol*. 2003;15(11):611–616. Online First: 2003/11/11.
184. Boyce SW, Bandyk DF, Bartholomew JR, Frame JN, Rice L. A randomized, open-label pilot study comparing desirudin and argatroban in patients with suspected heparin-induced thrombocytopenia with or without thrombosis: PREVENT-HIT Study. *Am J Ther*. 2011;18(1):14–22. <https://doi.org/10.1097/MJT.0b013e3181f65503>. Published Online First: 2010/11/17.
185. Nafziger AN, Bertino JS. Desirudin dosing and monitoring in moderate renal impairment. *J Clin Pharmacol*. 2010;50(6):614–622. <https://doi.org/10.1177/009127009350626>. Published Online First: 2009/11/17.
186. Lee CJ, Ansell JE. Direct thrombin inhibitors. *Br J Clin Pharmacol*. 2011;72(4):581–592. <https://doi.org/10.1111/j.1365-2125.2011.03916.x>. Published Online First: 2011/01/19.

187. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Agno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation*. 2012;126(20):2381–2391. <https://doi.org/10.1161/CIRCULATIONAHA.112.115410>. Published Online First: 2012/10/17.
188. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–1151. <https://doi.org/10.1056/NEJMoa0905561>. Published Online First: 2009/09/01.
189. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376(9745):975–983. [https://doi.org/10.1016/S0140-6736\(10\)61194-4](https://doi.org/10.1016/S0140-6736(10)61194-4). Published Online First: 2010/08/31.
190. Garcia D, Barrett YC, Ramacciotti E, Weitz JI. Laboratory assessment of the anticoagulant effects of the next generation of oral anti-coagulants. *J Thromb Haemost*. 2013;11(2):245–252. <https://doi.org/10.1111/jth.12096>. Published Online First: 2012/12/12.
191. Miyares MA, Davis K. Newer oral anticoagulants: a review of laboratory monitoring options and reversal agents in the hemorrhagic patient. *Am J Health Syst Pharm*. 2012;69(17):1473–1484. <https://doi.org/10.2146/ajhp110725>. Published Online First: 2012/08/18.
192. Tripodi A. The laboratory and the direct oral anticoagulants. *Blood*. 2013;121(20):4032–4035. <https://doi.org/10.1182/blood-2012-12-453076>. Published Online First: 2013/04/09.
193. Bruins Slot KM, Berge E. Factor Xa inhibitors vs warfarin for preventing stroke and thromboembolism in patients with atrial fibrillation. *JAMA*. 2014;311(11):1150–1151. <https://doi.org/10.1001/jama.2014.1403>. Published Online First: 2014/03/20.
194. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992. <https://doi.org/10.1056/NEJMoa1107039>. Published Online First: 2011/08/30.
195. Squire IB, Lawley W, Fletcher S, et al. Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. *Eur Heart J*. 1999;20(17):1245–1252. <https://doi.org/10.1053/euhj.1999.1528>. Published Online First: 1999/08/24.
196. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e419S–e96S. <https://doi.org/10.1378/chest.11-2301>. Published Online First: 2012/02/15.
197. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation*. 2004;110(6):744–749. <https://doi.org/10.1161/01.CIR.0000137826.09715>. Published Online First: 2004/07/21.
198. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet*. 1996;348(9030):771–775. [https://doi.org/10.1016/S0140-6736\(96\)02514-7](https://doi.org/10.1016/S0140-6736(96)02514-7). Published Online First: 1996/09/21.
199. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(10):3020–3035. <https://doi.org/10.1161/STR.0000000000000074>. Published Online First: 2015/07/01.
200. Astedt B. Clinical pharmacology of tranexamic acid. *Scand J Gastroenterol Suppl*. 1987;137:22–25. Online First: 1987/01/01.
201. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389(10084):2105–2116. [https://doi.org/10.1016/S0140-6736\(17\)30638-4](https://doi.org/10.1016/S0140-6736(17)30638-4). Published Online First: 2017/05/01.
202. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ*. 2012;344:e3054. <https://doi.org/10.1136/bmj.e3054>. Published Online First: 2012/05/23.
203. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev*. 2011;(3):CD001886. <https://doi.org/10.1002/14651858.pub4>published Online First: 2011/03/18.
204. Manji RA, Grocott HP, Leake J, et al. Seizures following cardiac surgery: the impact of tranexamic acid and other risk factors. *Can J Anaesth*. 2012;59(1):6–13. <https://doi.org/10.1007/s12630-011-9618-z>. Published Online First: 2011/11/09.
205. Lecker I, Orser BA, Mazer CD. “Seizing” the opportunity to understand antifibrinolytic drugs. *Can J Anaesth*. 2012;59(1):1–5. <https://doi.org/10.1007/s12630-011-9621-4>. Published Online First: 2011/11/05.
206. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352(8):777–785. <https://doi.org/10.1056/NEJMoa042991>. Published Online First: 2005/02/25.
207. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358(20):2127–2137. <https://doi.org/10.1056/NEJMoa0707534>. Published Online First: 2008/05/16.
208. Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma*. 2005;59(1):8–15; discussion 8. Online First: 2005/08/13.
209. Hauser CJ, Boffard K, Dutton R, et al. Results of the CONTROL trial: efficacy and safety of recombinant activated factor VII in the management of refractory traumatic hemorrhage. *J Trauma*. 2010;69(3):489–500. <https://doi.org/10.1097/TA.0b013e3181edf36e>. Published Online First: 2010/09/15.
210. Narayan RK, Maas AI, Marshall LF, et al. Recombinant factor VIIa in traumatic intracerebral hemorrhage: results of a dose-escalation clinical trial. *Neurosurgery*. 2008;62(4):776–786. <https://doi.org/10.1227/01.neu.0000316898.78371>; discussion 86–8. 74published Online First: 2008/05/23.
211. Yank V, Tuohy CV, Logan AC, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med*. 2011;154(8):529–540. <https://doi.org/10.7326/0003-4819-154-8-201104190-00004>. Published Online First: 2011/04/20.
212. Lodge JP, Jonas S, Jones RM, et al. Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl*. 2005;11(8):973–979. <https://doi.org/10.1002/lt.20470>. Published Online First: 2005/07/22.
213. Planinsic RM, van der Meer J, Testa G, et al. Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl*. 2005;11(8):895–900. <https://doi.org/10.1002/lt.20458>. Published Online First: 2005/07/22.
214. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med*. 2010;363(19):1791–1800. <https://doi.org/10.1056/NEJMoa1006221>. Published Online First: 2010/11/05.
215. Lin Y, Moltzan CJ, Anderson DR. National Advisory Committee on Blood and Blood Products. The evidence for the use of recombinant factor VIIa in massive bleeding: revision of the transfusion policy framework. *Transfus Med*. 2012;22(6):383–394. <https://doi.org/10.1111/j.1365-3148.2012.01164>. xpublished Online First: 2012/05/29.
216. Sorensen B, Spahn DR, Innerhofer P, Spannagl M, Rossaint R. Clinical review: prothrombin complex concentrates—evaluation of safety and thrombogenicity. *Crit Care*. 2011;15(1):201. <https://doi.org/10.1186/cc9311>. Published Online First: 2011/02/25.
217. Dusel CH, Grundmann C, Eich S, Seitz R, Konig H. Identification of prothrombin as a major thrombogenic agent in prothrombin complex concentrates. *Blood Coagul Fibrinolysis*. 2004;15(5):405–411. Online First: 2004/06/19.
218. Lunde J, Stensballe J, Wikkelsø A, Johansen M, Afshari A. Fibrinogen concentrate for bleeding—a systematic review. *Acta Anaesthesiol Scand*. 2014;58(9):1061–1074. <https://doi.org/10.1111/aas.12370>. Published Online First: 2014/07/26.
219. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl 2):e326S–e50S <https://doi.org/10.1378/chest.11-2298>. Published Online First: 2012/02/15.

220. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(suppl 3):188S–203S. https://doi.org/10.1378/chest.126.3_suppl.188S. Published Online First: 2004/09/24.
221. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71–86. Online First: 2002/01/12.
222. Burger W, Chemnitius JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention—cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation—review and meta-analysis. *J Intern Med*. 2005;257(5):399–414. <https://doi.org/10.1111/j.1365-2796.2005.01477.x>. Published Online First: 2005/04/20.
223. Lordkipanidze M, Diodati JG, Pharand C. Possibility of a rebound phenomenon following antiplatelet therapy withdrawal: a look at the clinical and pharmacological evidence. *Pharmacol Ther*. 2009;123(2):178–186. <https://doi.org/10.1016/j.pharmthera.2009.03.019>. Published Online First: 2009/05/12.
224. Pulmonary Embolism Prevention Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;355(9212):1295–1302. Online First: 2000/04/25.
225. Oscarsson A, Gupta A, Fredrikson M, et al. To continue or discontinue aspirin in the perioperative period: a randomized, controlled clinical trial. *Br J Anaesth*. 2010;104(3):305–312. <https://doi.org/10.1093/bja/aeq003>. Published Online First: 2010/02/13.
226. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J*. 2006;27(22):2667–2674. <https://doi.org/10.1093/eurheartj/ehl334>. Published Online First: 2006/10/21.
227. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68(10):1082–1115. <https://doi.org/10.1016/j.jacc.2016.03.513>. Published Online First: 2016/04/03.
228. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39(3):213–260. <https://doi.org/10.1093/eurheartj/ehx419>. Published Online First: 2017/09/10.
229. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35(1):64–101. Online First: 2010/01/08.
230. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian study on complications of oral anti-coagulant therapy. *Lancet*. 1996;348(9025):423–428. Online First: 1996/08/17.
231. Levine MN, Hirsh J, Landefeld S, Raskob G. Hemorrhagic complications of anticoagulant treatment. *Chest*. 1992;102(suppl 4):352S–63S. Online First: 1992/10/01.
232. Sarode R, Milling TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients with vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation*. 2013;128(11):1234–1243. <https://doi.org/10.1161/CIRCULATIONAHA.113.002283>. Published Online First: 2013/08/13.
233. Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'Malley PG. Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med*. 2006;166(4):391–397. <https://doi.org/10.1001/391>. Published Online First: 2006/03/01.
234. Burbury KL, Milner A, Snooks B, Jupe D, Westerman DA. Short-term warfarin reversal for elective surgery—using low-dose intravenous vitamin K: safe, reliable and convenient*. *Br J Haematol*. 2011;154(5):626–634. <https://doi.org/10.1111/j.1365-2141.2011.08787.x>. Published Online First: 2011/07/15.
235. Hickey M, Gatien M, Taljaard M, Aujnaranin A, Giulivi A, Perry JJ. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. *Circulation*. 2013;128(4):360–364. <https://doi.org/10.1161/CIRCULATIONAHA.113.001875>. Published Online First: 2013/06/19.
236. Goldstein JN, Refaai MA, Milling TJ, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet*. 2015;385(9982):2077–2087. [https://doi.org/10.1016/S0140-6736\(14\)61685-8](https://doi.org/10.1016/S0140-6736(14)61685-8). Published Online First: 2015/03/03.
237. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511–520. <https://doi.org/10.1056/NEJMoa1502000>. Published Online First: 2015/06/23.
238. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;Feb 7. <https://doi.org/10.1056/NEJMoa1814051> [Epub ahead of print].
239. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375(12):1131–1341. <https://doi.org/10.1056/NEJMoa1607887>. Published Online First: 2016/08/31.
240. Ansell JE, Bakrhu SH, Laulicht BE, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. *Thromb Haemost*. 2017;117(2):238–245. <https://doi.org/10.1160/TH16-03-0224>. Published Online First: 2016/11/18.

CHRISTOPH STEIN and ANDREAS KOPF

KEY POINTS

- The normal physiology of neuronal function, receptors, and ion channels is altered by persistent pain.
- Because of the large number of sources and manifestation of chronic pain, classification must include cancer-related, neuropathic, inflammatory, arthritis, and musculoskeletal pain.
- Interdisciplinary management of chronic pain must include specialists in psychology, physical therapy, occupational therapy, neurology, and anesthesiology.
- Drugs used for chronic pain are multiple and include opioids, nonsteroidal antiinflammatory drugs and antipyretic analgesics, serotonin receptor ligands, antiepileptics, antidepressants, topical analgesics (e.g., nonsteroidal antiinflammatory drugs, capsaicin, local anesthetics, opioids), and adjuvants such as local anesthetics, α_2 -agonists, baclofen, botulinum toxin, antiemetics, laxatives, novel drugs such as cannabinoids, and ion channel blockers.
- Interventional management of chronic pain includes the use of diagnostic blocks, therapeutic blocks, continuous catheter techniques (peripheral, epidural, intrathecal), and stimulation techniques such as acupuncture, transcutaneous electrical nerve stimulation, and spinal cord stimulation.
- Perioperative management of patients with chronic pain involves the following: the use of opioid and nonopioid analgesics; evaluation for dependence, addiction, and pseudoaddiction; and practical considerations.

Introduction

PHYSIOLOGICAL CHANGES IN PERSISTENT PAIN

Excitatory Mechanisms

Pain may be roughly divided into two broad categories: physiologic and pathologic pain. Physiologic (acute, nociceptive) pain is an essential early warning sign that usually elicits reflex withdrawal and thereby promotes survival by protecting the organism from further injury. In contrast, pathologic (e.g., neuropathic) pain is an expression of the maladaptive operation of the nervous system; it is pain as a disease.¹ Physiologic pain is mediated by a sensory system consisting of primary afferent neurons, spinal interneurons and ascending tracts, and several supraspinal areas. Trigeminal and dorsal root ganglia (DRG) give rise to high-threshold A δ - and C-fibers innervating peripheral tissues (skin, muscles, joints, viscera). These specialized primary afferent neurons, also called nociceptors, transduce noxious stimuli into action potentials and conduct them to the dorsal horn of the spinal cord (Fig. 51.1). When peripheral tissue is damaged, primary afferent neurons are sensitized or directly activated (or both) by a variety of thermal, mechanical, and/or chemical stimuli. Examples are protons, sympathetic amines, adenosine triphosphate (ATP), glutamate, neuropeptides (calcitonin gene-related peptide, substance P), nerve growth factor, prostanoids, bradykinin, proinflammatory cytokines, and chemokines.² Many of these agents lead to opening (gating) of cation channels in the neuronal membrane. Such

channels include the capsaicin-, proton-, and heat-sensitive transient receptor potential vanilloid 1 (TRPV1), or the ATP-gated purinergic P2X₃ receptor. Gating produces an inward current of Na⁺ and Ca⁺⁺ ions into the peripheral nociceptor terminal. If this depolarizing current is sufficient to activate voltage-gated Na⁺ channels (e.g., Na_v1.8), they too will open, further depolarizing the membrane and initiating a burst of action potentials that are then conducted along the sensory axon to the dorsal horn of the spinal cord.^{2,3}

Transmission of input from nociceptors to spinal neurons that project to the brain is mediated by direct monosynaptic contact or through multiple excitatory or inhibitory interneurons. The central terminals of nociceptors contain excitatory transmitters such as glutamate, substance P, and neurotrophic factors that activate postsynaptic N-methyl-D-aspartate (NMDA), neurokinin (NK₁), and tyrosine kinase receptors, respectively. Repeated nociceptor stimulation can sensitize both peripheral and central neurons (activity-dependent plasticity). In spinal neurons such a progressive increase of output in response to persistent nociceptor excitation has been termed “wind-up.” Later, sensitization can be sustained by transcriptional changes in the expression of genes coding for various neuropeptides, transmitters, ion channels, receptors, and signaling molecules (transcription-dependent plasticity) in both nociceptors and spinal neurons. Important examples include the NMDA receptor, cyclooxygenase-2 (COX-2), Ca⁺⁺ and Na⁺ channels, cytokines and chemokines expressed by neurons and/or glial cells.^{2,3} In addition, physical rearrangement of neuronal

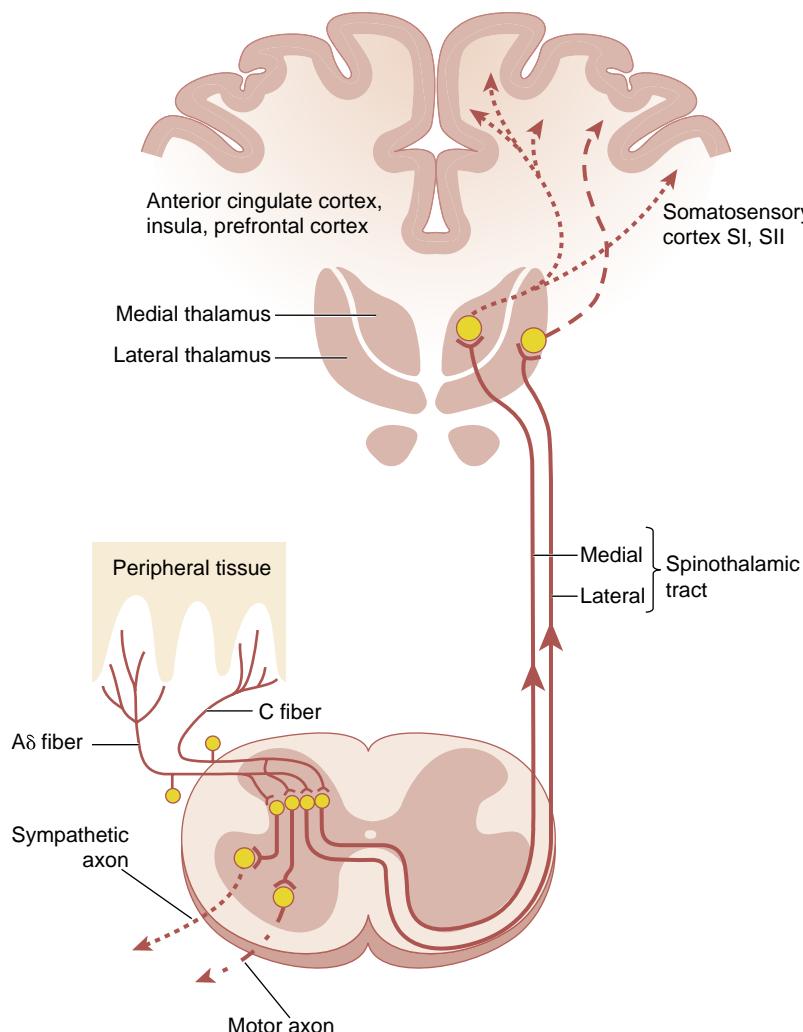


Fig. 51.1 Nociceptive pathways. For details see text. (Adapted from Brack A, Stein C, Schaible HG. Periphere und zentrale Mechanismen des Entzündungsschmerzes. In: Straub RH, ed. *Lehrbuch der klinischen Pathophysiologie komplexer chronischer Erkrankungen*. vol. 1. Göttingen: Vandenhoeck & Ruprecht; 2006:183–192.²⁰³)

circuits by apoptosis, nerve growth, and sprouting occurs in the peripheral and central nervous system.¹ Both induction and maintenance of central sensitization are critically dependent on the peripheral drive by nociceptors, indicating that therapeutic interventions targeting such neurons may be particularly effective, even in chronic pain syndromes.^{3,4}

Inhibitory Mechanisms

Concurrent with the events just described, powerful endogenous mechanisms counteracting pain unfold. This was initially proposed in the “gate control theory of pain” in 1965⁵ and has since been corroborated and expanded by experimental data. In 1990, a “peripheral gate” was discovered at the source of pain generation by demonstrating that immune cell-derived opioid peptides can block the excitation of nociceptors carrying opioid receptors within injured tissue⁶ (Fig. 51.2). This represented the first example of many subsequently described neuro-immune interactions relevant to pain.^{7–11} Inflammation of peripheral tissue leads to increased expression, axonal transport, and enhanced G-protein coupling of opioid receptors in DRG neurons as well as enhanced permeability of the perineurium. These phenomena are dependent on sensory neuron electrical activity, production of

proinflammatory cytokines, and the presence of nerve growth factor within the inflamed tissue. In parallel, opioid peptide-containing immune cells extravasate and accumulate in the inflamed tissue.^{9,11} These cells upregulate the gene expression of opioid precursors and the enzymatic machinery for their processing into functionally active peptides. In response to stress, catecholamines, corticotropin-releasing factor, cytokines, chemokines, or bacteria, leukocytes secrete opioids, which then activate peripheral opioid receptors and produce analgesia by inhibiting the excitability of nociceptors, the release of excitatory neuropeptides, or both (see Fig. 51.2).^{9,11,12} The clinical relevance of these mechanisms has been shown in studies demonstrating that patients with knee joint inflammation express opioid peptides in immune cells and opioid receptors on sensory nerve terminals within synovial tissue.¹³ After knee surgery, pain and analgesic consumption was enhanced by blocking the interaction between the endogenous opioids and their receptors with intraarticular naloxone,¹⁴ and was diminished by stimulating opioid secretion.¹⁵

In the spinal cord, inhibition is mediated by the release of opioids, γ -aminobutyric acid (GABA), or glycine from interneurons, which activate presynaptic opioid- or GABA-receptors (or both) on central nociceptor terminals

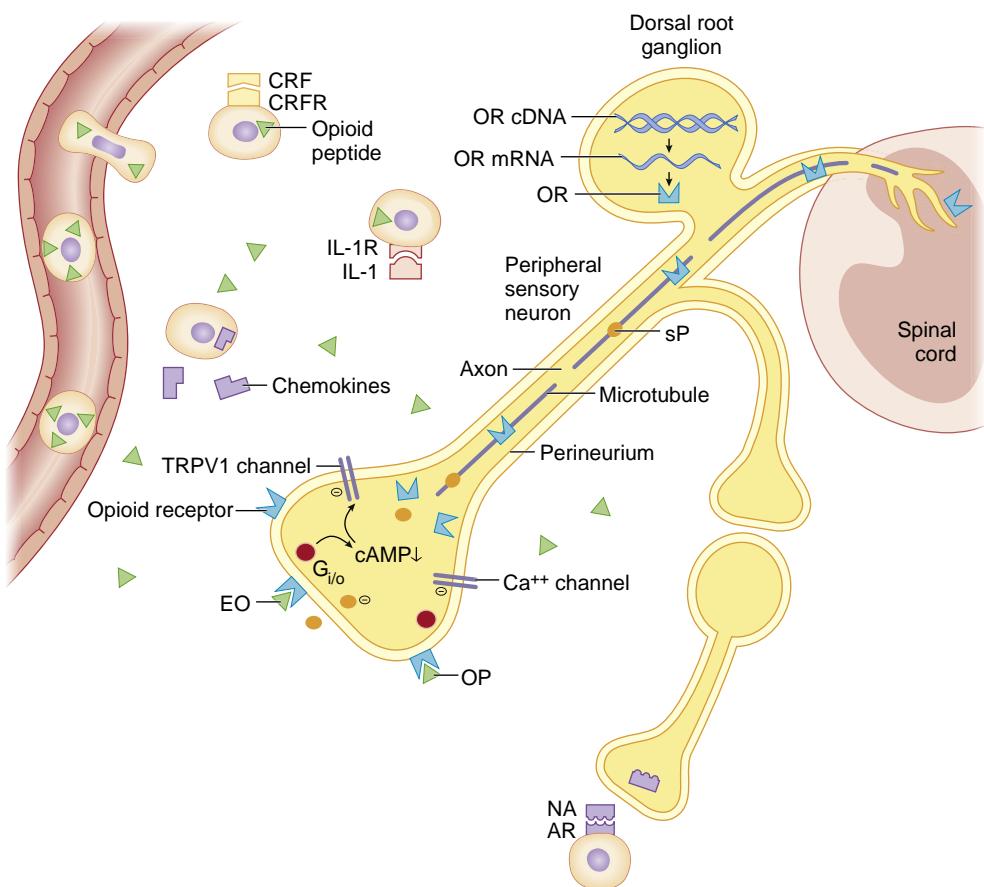


Fig. 51.2 Endogenous antinociceptive mechanisms within peripheral injured tissue. Opioid peptide-containing circulating leukocytes extravasate upon activation of adhesion molecules and chemotaxis by chemokines. Subsequently, these leukocytes are stimulated by stress or releasing agents to secrete opioid peptides. For example, corticotropin-releasing factor (CRF), interleukin-1 β (IL-1), and noradrenaline (NA, released from postganglionic sympathetic neurons) can elicit opioid release by activating their respective CRF receptors (CRFR), IL-1 receptors (IL-1R), and adrenergic receptors (AR) on leukocytes. Exogenous opioids (EO) or endogenous opioid peptides (OP, green triangles) bind to opioid receptors (OR) that are synthesized in dorsal root ganglia and transported along intraaxonal microtubules to peripheral (and central) terminals of sensory neurons. The subsequent inhibition of ion channels (e.g., TRPV1, Ca⁺⁺) (see Fig. 64.3 and text) and of substance P (sP) release results in antinociceptive effects. (Adapted from Stein C, Machelska H. Modulation of peripheral sensory neurons by the immune system: implications for pain therapy. *Pharmacol Rev*. 2011;63:860-881.⁹)

to reduce excitatory transmitter release. In addition, the opening of postsynaptic K⁺ or Cl⁻ channels by opioids or GABA, respectively, evokes hyperpolarizing inhibitory potentials in dorsal horn neurons. During ongoing nociceptive stimulation spinal interneurons upregulate gene expression and the production of opioid peptides.^{16,17} Powerful descending inhibitory pathways from the brainstem also become active by operating mostly through noradrenergic, serotonergic, and opioid systems. Key regions are the periaqueductal grey and the rostral ventromedial medulla, which then projects along the dorsolateral funiculus to the dorsal horn.^{2,18} The integration of signals from excitatory and inhibitory neurotransmitters with cognitive, emotional, and environmental factors (see later) eventually results in the central perception of pain. When the intricate balance between biologic, psychological, and social factors becomes disturbed, chronic pain can develop.^{19,20}

Translation of Basic Research

Basic research on pain continues at a rapid pace but translation into clinical applications has been difficult.^{4,21} Many obstacles have been discussed, including overinterpretation of data, reporting bias toward neglecting negative results,

inadequate animal models, flawed study design, genetic and species differences.^{4,21-23} Notwithstanding, animal studies are indispensable, continue to be improved, and have successfully predicted adverse side effects of drug candidates.^{22,23} For ethical reasons, many models are restricted to days or weeks, while human chronic pain can last for months or years. Therefore, animal models may be more cautiously termed as reflecting “persistent” pain.^{21,23} Brain imaging is an area of intense research and numerous studies have investigated changes in patients with various pain syndromes. However, such studies have not yet provided reproducible findings specific for a disease or a pathophysiological basis for individual syndromes.²² Neuroimaging can only detect alterations associated with nociceptive processes whereas clinical pain encompasses a much more complex subjective experience that critically relies on self-evaluation. Thus, although recent data have provided valuable information on pain neurophysiology, current imaging techniques cannot provide an objective proxy, biomarker, or predictor for clinical pain.^{24,25} Genetics is another budding scientific field. However, with the possible exception of the metabolic enzyme CYP2D6, pharmacogenetics is not expected to serve as a guide to individualized (“personalized”) clinical pain therapy any time soon.^{22,26-29}

CLINICAL DEFINITIONS, PREVALENCE, AND CLASSIFICATION OF CHRONIC PAIN

Definitions

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”³⁰ This classification further states that pain is always subjective and that it is a sensation in parts of the body. At the same time, it is unpleasant and therefore also has emotional/psychological components. Aside from malignant disease, many people report chronic pain in the absence of tissue damage or any likely pathophysiologic cause. There is usually no way to distinguish their experience from that due to tissue damage. If patients regard their experience as pain or if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain.³¹ Nociception is neurophysiological activity in peripheral sensory neurons (nociceptors) and higher nociceptive pathways and is defined by the IASP as the “neural process of encoding noxious stimuli.” Nociception is not synonymous to pain. Chronic pain is defined as “extending in duration beyond the expected temporal boundary of tissue injury and normal healing, and adversely affecting the function or well-being of the individual” by the American Society of Anesthesiologists.³² The IASP subcommittee on taxonomy defined it in 1986 as “pain without apparent biological value that has persisted beyond the normal tissue healing time usually taken to be three months.”

Prevalence

Beyond these general definitions there exists no common understanding about the characteristics of the chronic pain patient. This may be one reason why estimates of prevalence differ greatly from one publication to another. Heterogeneous populations, the occurrence of undetected comorbidity, different definitions of chronic pain, and different approaches to data collection have resulted in estimates from 20% to 60%. Some surveys indicate a more frequent prevalence among women and the elderly. Chronic pain has enormous socioeconomic costs due to the need for healthcare services, disability compensation, lost workdays, and related expenses.^{31,33,34}

Classification

There is a tradition to distinguish between malignant (related to cancer and its treatment) and nonmalignant (e.g., neuropathic, musculoskeletal, inflammatory) chronic pain. Nonmalignant chronic pain is frequently classified into inflammatory (e.g., arthritic), musculoskeletal (e.g., low back pain), headaches, and neuropathic pain (e.g., postherpetic neuralgia, phantom pain, complex regional pain syndrome, diabetic neuropathy, human immunodeficiency virus-associated neuropathy). Frequent symptoms of neuropathic pain include spontaneous lancinating, shooting, or burning pain; hyperalgesia; and allodynia.³⁵ Cancer pain can originate from invasion of the tumor into tissues innervated by primary afferent neurons (e.g., pleura, peritoneum) or directly into a peripheral nerve plexus. In the latter, neuropathic symptoms may be predominant. Pain may be underestimated by medical staff and family members,

resulting in poor pain control.³¹ Many treatments for cancer are associated with severe pain. For example, cytoreductive radiotherapy or chemotherapy frequently causes painful oral mucositis, especially in patients with bone marrow transplantation.³⁶

Biopsychosocial Concept of Chronic Pain

Chronic pain is characterized by the complex interaction of biologic (tissue damage), psychological (cognition, memory, conditioning), and environmental/social factors (attention, reinforcement). Studies have shown that multimodal pain management programs rooted in this concept can lead to reduced pain, increased activity, and improved daily functioning.³⁷ Therefore, it is of utmost importance to screen patients with ongoing pain for risk factors. Special attention should be paid to patients presenting with limited mobility, lack of motivation, depression, anger, anxiety, and fear of reinjury, which hamper the return to normal work or recreational activities. Such patients may become preoccupied with pain and somatic processes, which may disrupt sleep and cause irritability and social withdrawal. Other cognitive factors such as patients' expectations or beliefs (e.g., perceived inability to control the pain) influence psychosocial and physical functioning. Pain behavior such as limping, medication intake, or avoidance of activity is subject to operant conditioning; that is, it responds to reward and punishment. For example, pain behavior may be positively reinforced by attention from a spouse or healthcare provider (e.g., by inadequate use of nerve blocks or medications). Conversely, such behavior can be extinguished when it is disregarded and incremental activity is reinforced by social attention and praise.¹⁹ Respondent learning mechanisms (i.e., classical conditioning) may also contribute to chronicity.²⁰ Other issues often coexist, such as substance abuse problems, family dysfunction, and conflicts with legal or insurance systems. Consequently, care seeking is an integral feature of the pain experience, and excessive use of the healthcare system ensues. The interplay between these biologic, psychological, and social factors results in the persistence of pain and illness behaviors.^{19,20} Treating only one aspect of this complex syndrome (“monomodal” therapy) is obviously insufficient. The biopsychosocial concept was first described by Engel in 1959³⁸ but its implementation into daily practice has been tardy, especially concerning chronic pain patients.^{39,40} This concept helps to understand why chronic pain may exist without obvious physical cause or why pathologic somatic findings may remain unnoticed by the patient. Interestingly, the experience and regulation of social and physical pain may share a common neuroanatomic basis.⁴¹ In a multimodal approach, pain management simultaneously addresses physical, psychological, and social skills and underscores the patients' active responsibility to regain control over life by improving function and well-being.^{20,37,42} Methods usually include (among others) cognitive-behavioral therapy, physical exercise, and medication management. Cognitive-behavioral therapy aims to correct maladaptive cognitive and behavioral patterns, such as catastrophizing and fear-avoidance-beliefs. It encourages patients to take a proactive versus passive role in their healing process, and to experience life mindfully through defusion, acceptance, and committed action.^{43,44} Functional restoration includes

occupational and physical therapy to help the patient gain confidence in physical activity. Activation per se seems to be more important than specific therapeutic techniques. Social support can affect pain intensity and mood by addressing employment and retirement issues as well as other concerns such as financial and legal disputes.

INTERDISCIPLINARY MANAGEMENT OF CHRONIC PAIN

The anesthesiologist John J. Bonica was the first to appreciate the need for a multidisciplinary approach to chronic pain. His early experiences in and after World War II convinced Bonica that complex pain problems could be more effectively treated when different disciplines contribute their specialized knowledge and skills to the common goal of making a correct diagnosis and developing the most effective therapeutic strategy. The first multidisciplinary facility was put into practice at the Tacoma General Hospital, followed by the University of Washington in 1960. From 1970 through 1990, the number of pain management facilities continued to increase in North America and Europe, mostly directed by anesthesiologists. Such comprehensive pain centers should have personnel and facilities to evaluate and treat the biomedical, psychosocial, and occupational aspects of chronic pain and to educate and teach medical students, residents, and fellows. Guidelines for characteristics of pain treatment facilities have been published by the IASP.⁴⁵ Interdisciplinary and multimodal management results in increased physical and psychosocial function, reduced health care use, and vocational rehabilitation. Such programs offer the most efficacious and cost-effective, evidence-based treatment of chronic nonmalignant pain.^{37,40} Treatment without an interdisciplinary approach is inadequate and may lead to misdiagnoses. For example, overlooking psychological processes in a presumed discogenic back pain, or overlooking a somatic etiology in a presumed “psychogenic” pain disorder may lead to the wrong conclusions.⁴⁶ Moreover, conventional monomodal approaches such as pharmacotherapy alone only perpetuate the expensive, futile, and endless search for medical solutions.^{40,42} A prominent example is the recent “opioid epidemic” with inadequate opioid medication as a monomodal therapy of chronic noncancer pain, which has significantly delayed appropriate diagnostic and therapeutic management.⁴⁷ The “current opioid misuse measure” questionnaire may be a useful tool to detect inadequate opioid medication.⁴⁸

The core team usually comprises a pain management physician (often an anesthesiologist with subspecialty training but could also be a physical medicine and rehabilitation physician or psychiatrist with appropriate training), a psychologist, a physical therapist, and an occupational therapist. Depending on the local circumstances, administrators, social workers, pain nurses, and/or pharmacists can also be involved. The initial screening of the patient by members of the core team determines what other specialists will be needed for a complete assessment. After this evaluation, the patient is presented to the entire core team and a comprehensive treatment plan is developed. This plan is tailored to the patient’s needs, abilities, and expectations, with a focus on achieving measurable treatment goals

established with the patient. For some patients, education and medical management may suffice, whereas for others, an intensive full-day outpatient or inpatient rehabilitation program over several weeks may be needed. Early stratification of the management according to the patient’s prognosis (low, medium, or high risk for persistent disability because of pain) results in significantly higher clinical and cost effectiveness.⁴⁹ To foster patient compliance, an open discussion of treatment goals with regard to the patient’s expectations is essential. Many patients expect the complete resolution of pain and the return to full function, a goal that may not be achievable. More realistic options are some reduction of pain, improvement of physical function, and/or return to work. Mood, sleep, active coping skills, and social functioning may also be improved.^{50,51} Thus, rehabilitation rather than cure is the most appropriate therapeutic option.⁴⁰

Psychology

The role of the psychologist includes the initial assessment and treatment approaches such as education, cognitive-behavioral therapy, and relaxation training. Assessment of the patient addresses the sensory, affective, cognitive, behavioral, and occupational dimensions of the pain problem. This includes an extensive biographic history and behavioral analysis along with the use of questionnaires. Most questionnaires include scoring systems for pain intensity (e.g., numerical or visual analog scales), but pain behavior (e.g., West-Haven-Yale Multidimensional Pain Inventory), multidimensional pain quality, cognitive coping, fear (e.g., State-Trait-Anxiety-Inventory), depression, and other associated symptoms are far more relevant. Indications for psychological pain management are relevant somatization, depressive disorders, inadequate coping, drug abuse, and high levels of pain behavior reinforced by the environment (e.g., family members). A key factor is motivational change for acceptance of the complex therapeutic program.⁵² Some types of pain syndromes, such as chronic headache, inflammatory rheumatic pain, or unspecific back pain may specifically benefit from behavioral therapy.^{20,40} This usually means a complete change of view for the patient, from a purely passive recipient of curative treatment to an active, self-reliant approach to functional restoration, vocational rehabilitation, and reduced healthcare use despite pain. Thus, pain reduction alone is no longer the focus of therapy.^{37,40}

Physical Therapy

The role of the physical therapist includes initial evaluation of the musculoskeletal system, assessment of the patient’s workplace and home, education in active physical coping skills, and management of the physical rehabilitation process. An intensive exercise program emphasizing the patient’s responsibility for self-management is an integral part of comprehensive programs for chronic nonmalignant pain.^{37,40,53} Improving fitness, mobility, and posture counteracts the effects of disuse and complements behavioral treatment. The physical therapist encourages the adoption of regular exercise into daily life, facilitates repeated exposure to movement as much as possible despite pain, and reinforces education in the biopsychosocial model of pain management. Different techniques of exercise such as muscle conditioning and aerobics are efficacious in improving