

of spontaneous circulation, always should receive precedence over sodium bicarbonate because effective circulation is the most powerful therapy for patients with acidosis.

The treatment for patients with metabolic acidosis with buffers, such as sodium bicarbonate, remains a subject of discussion and research that is balanced between two perspectives. On one hand is the observation that the circulatory status of acidemic patients may improve with infusion of bicarbonate. On the other hand is the concern that carbon dioxide generated by the reaction of acid protons with the bicarbonate anion can permeate freely across cell membranes and generate acid equivalents through carbonic anhydrase-catalyzed hydrolysis:



Thus, the administration of sodium bicarbonate may potentially worsen intracellular acidosis of myocardial cells or cells of the central nervous system. However, a study using ^{31}P nuclear magnetic resonance spectroscopy to probe brain pH demonstrated that sodium bicarbonate did ameliorate the progressive central nervous system acidosis seen during cardiopulmonary resuscitation and that blood and cerebral pH paralleled each other.³¹

Current recommendations state that sodium bicarbonate may be used in cases of prolonged cardiac arrest after effective ventilation is ensured and epinephrine plus chest compressions have been provided. Administration also may be considered when shock is associated with documented metabolic acidosis. The initial dosage is 1 mEq/kg (1 mL/kg of 8.4% solution) by the IV or IO routes. It should not be administered by the ET route. A dilute (0.5 mEq/mL) solution may be used in neonates because of concerns of intraventricular hemorrhage related to the hyperosmolarity of the 8.4% solution. Subsequent doses should be guided by blood gas analysis. If unavailable, subsequent doses may be considered every 10 minutes of continued arrest.

Sodium bicarbonate administration may have several adverse effects. Resulting metabolic alkalosis causes a leftward shift of the oxyhemoglobin dissociation curve increasing the affinity of hemoglobin for oxygen and reducing delivery of oxygen to tissues. Hypernatremia and hyperosmolarity may result from sodium bicarbonate administration. An increased incidence of hypernatremia but not alkalosis is seen when patients resuscitated with sodium bicarbonate are compared with those resuscitated without.³ The hyperosmolarity of 8.4% (i.e., 1 mEq/mL) sodium bicarbonate has been related to intraventricular hemorrhage in sick neonates. Acute intracellular shifts of potassium and decreased ionized calcium concentration may result from sodium bicarbonate administration, and decreases in fibrillation threshold and impairment of cardiac function have been observed.

Despite the intuitive belief that a pH close to 7.4 would make the heart more readily resuscitable, little clinical data support this belief.³⁰ A recent double-blind, controlled trial in which 502 adults with ventricular fibrillation or asystole were randomized to receive a buffer solution or normal saline showed that the buffer had no effect on survival.³² A recent review of clinical articles confirmed the importance of ventilation and circulation in the resolution of acidosis secondary to cardiac arrest.¹¹⁶ Studies based on animal models have yielded conflicting results.^{12, 35, 57, 119, 121}

The possible exacerbation of intracellular acidosis by carbon dioxide produc-

tion from sodium bicarbonate has led to examination of non-carbon dioxide producing buffers, such as carbicarb and tromethamine. Carbicarb is an equimolar mixture of sodium bicarbonate and sodium carbonate and is considered to consume, rather than produce, carbon dioxide. Despite the theoretic advantage, studies generally have shown no difference. In canine models comparing sodium bicarbonate with carbicarb, no difference was shown in return of spontaneous circulation between buffers and between the buffered animals and controls. Acidosis was equally corrected in both groups that received buffers^{12, 35}; however, in a model of hypoxic lactic acidosis without cardiac arrest, carbicarb administration resulted in significant improvement in cardiac index compared with sodium bicarbonate or sodium chloride.³⁵

Controversy still exists concerning the role of sodium bicarbonate. Some of the most recently published work suggests an adjunctive role in prolonged arrest; however, adequate ventilation and circulation clearly are the most important parts of treating the acidosis of patients with cardiac arrest.

Atropine

Pharmacology. Atropine is a parasympatholytic drug that accelerates sinus and atrial pacemakers, improves conduction through the AV node, and reduces cardiac vagal tone. It is a muscarinic receptor antagonist that competitively blocks the binding of acetylcholine to muscarinic cholinergic receptors at various neuroeffector sites of smooth muscle, cardiac muscle, and gland cells in peripheral ganglia and in the central nervous system. Although the dominant cardiac response is tachycardia, the heart rate often decreases transiently, particularly when small doses are administered. This paradoxical effect was once thought to be caused by central vagal stimulation, but the effect has been demonstrated for muscarinic receptor antagonists that do not enter the brain. Data suggest that the decreased heart rate may result from blockade of M1 receptors on postganglionic parasympathetic neurons, which relieves the inhibitory effects of synaptic acetylcholine on release of transmitter.³³ Larger dosages of atropine cause progressively increasing tachycardia by blocking vagal effects at the M2 receptor in the sinoatrial nodal pacemaker. The resting heart rate is increased by approximately 35 to 40 beats per minute in young men given 2 mg atropine. The influence of atropine is most noticeable in healthy young adults in whom vagal tone is considerable. In infancy and old age, even large doses of atropine may not increase the heart rate.

Adequate doses of atropine can abolish many types of reflex vagal cardiac slowing and even asystole, including bradycardia from inhalation of irritant vapors, stimulation of the carotid sinus, eyeball pressure, peritoneal stimulation, and injection of contrast material during cardiac catheterization. It also prevents or abolishes bradycardia or asystole caused by choline esters, acetylcholinesterase inhibitors, or other parasympathomimetic drugs, as well as cardiac arrest from stimulation of the vagus.

Elimination of vagal influence on the heart by atropine may facilitate AV conduction. Atropine shortens functional refractory period of the AV node and can increase ventricular rates in patients with atrial fibrillation or flutter. In some cases of second-degree heart block (e.g., Wenckebach AV block), in which vagal activity is an etiologic factor, atropine may decrease the degree of

blockage. In some patients with complete heart block, the idioventricular rate may be accelerated by atropine.

Atropine has a half-life of 3.5 ± 1.5 hours, a volume of distribution of 2.0 ± 1.1 L/kg, and a clearance of 8 ± 4 mL/min/kg. Hepatic metabolism accounts for metabolism of approximately half of a dose, with the remainder excreted unchanged in the urine.⁵⁶ Atropine causes mydriasis. It does not abolish pupillary reactivity. Fixed and dilated pupils should not be attributed to atropine.⁵⁷

Clinical Indications. Atropine is used to treat patients with symptomatic bradycardia, to prevent or treat vagally mediated bradycardia accompanying intubation attempts, and to treat patients with the uncommon occurrence of symptomatic bradycardia with AV block. Most bradycardic events in infants and children result from hypoxia. Therefore, oxygen and ventilatory support through bag-valve-mask and ET intubation are the primary therapies. Moreover, persistent symptomatic bradycardia may be treated more effectively with epinephrine, which provides inotropic and chronotropic support. Whether atropine is useful in asystole or pulseless electric activity is unclear. When atropine in incremental doses was compared with placebo in a canine model of asphyxia-induced pulseless electric activity, no difference in rate of return of spontaneous circulation was observed. Moreover, the rate of return of spontaneous circulation decreased with increasing atropine dosages.²⁸

The recommended atropine dosage is 0.02 mg/kg, with a minimum dosage of 0.1 mg (to avoid the paradoxical decrease in heart rate seen at low dosages) and a maximum single dose of 0.5 mg for children and 1.0 mg for adolescents. The dose may be repeated after 5 minutes for a maximum total dosage of 1.0 mg for children and 2.0 mg for adolescents. Complete vagolysis usually is obtained at these higher dosages, and additional atropine is not of any benefit. Atropine may be administered by the IV, IO, or ET route. No information is available on the absorption of atropine by the ET route. It is reasonable that the IV dosage be increased two to three times and diluted to a volume of 3 mL to 5 mL for ET administration. Alternatively, the drug could be administered through a suction catheter inserted into the bottom of the ET tube. In both circumstances, administration should be followed by several positive-pressure breaths. Atropine may block bradycardia secondary to hypoxia when administered to block the vagotonic effects associated with intubation or bronchoscopy. For this reason, careful attention must be paid to observing the patient and using pulse oximetry in these procedures.

Glucose

Glucose is a simple, readily available, and often overlooked agent in pediatric resuscitation. Critically ill infants or children are at increased risk for hypoglycemia. Moreover, symptoms of hypoglycemia, such as pallor, cool extremities and poor perfusion, and diaphoresis, mimic those of shock. In the haste to resuscitate with isotonic crystalloids, such as normal saline or Ringer's lactate, or to push epinephrine and start therapy with dopamine, it is easy to forget checking the serum glucose and administering dextrose. Therefore, a rapid bedside glucose test should be performed on critically ill infants or young children with cardiorespiratory instability.

Glucose is administered in a dosage of 0.5 to 1.0 g/kg IV. A maximum

concentration of 25% dextrose in water (D25W) should be infused by peripheral vein. Because it is supplied as 50% dextrose in water, glucose must be diluted 1:1 with sterile water before peripheral vein administration. Dilution results in a volume of 2 to 4 mL/kg.

ANTIARRHYTHMIA THERAPY

Bradycardia and asystole are much more common presentations of pediatric cardiac arrest than are ventricular fibrillation or ventricular tachycardia. These rhythms occur, however, so a brief discussion of pharmacologic arrhythmia management in the setting of cardiac arrest resuscitation is warranted. The immediate and definitive therapy for ventricular fibrillation and pulseless ventricular tachycardia is defibrillation or cardioversion. Defibrillation should not be delayed for a trial of pharmacologic therapy in patients who are pulseless or in severe shock. Metabolic, electrolyte, and toxicologic disorders, such as hypocalcemia, hypokalemia, or hyperkalemia, and tricyclic antidepressant ingestions, are more common causes of ventricular arrhythmia in children than myocardial infarction as seen in adults. Correction of metabolic and electrolyte irregularities and toxin-specific interventions should be the primary means of managing these dysrhythmias.

Supraventricular tachycardia (SVT) is a relatively common dysrhythmia in children. Although not usually life threatening in its initial presentation, if SVT continues unabated, it eventually leads to worsening heart failure, metabolic acidosis, and ultimately cardiac arrest, which is a special concern in young infants in whom the clinical recognition of abnormal rhythm is difficult because of vagueness of symptoms. A comprehensive review of SVT in children recently has been published.⁵⁸

Adenosine

The treatment for patients with SVT in unstable patients is synchronized cardioversion at a starting dosage of 0.5 J/kg. Many patients are hemodynamically stable on presentation, however, which gives opportunity for pharmacologic intervention. Adenosine is now in widespread use for the management of SVT. Other agents that are used and effective include verapamil, digoxin, esmolol, and procainamide.

Adenosine is an endogenous nucleoside that functions by acutely slowing AV node conduction. It probably accomplishes this task by direct action on AV node G protein-coupled adenosine receptors. It also inhibits the electrophysiologic effects of increased intracellular cyclic adenosine monophosphate (AMP) which occurs with sympathetic stimulation. Adenosine also causes arterial and coronary vasodilation.^{21,59} The initial dosage is 0.1 mg/kg, which should be administered by a rapid IV push. Rapid infusion maximizes the concentration of drug that reaches the heart and compensates for adenosine's extremely short half-life, present approximately 10 seconds. Adenosine is eliminated by carrier-mediated uptake, which occurs in most cell types, including the endothelium,

and subsequent metabolism by adenosine deaminase. When administered by peripheral IV, a 3-mL to 5-mL bolus of fluid should follow to accelerate delivery of the agent to the heart. When available, central venous administration is preferable. The brief half-life has made the risk for severe side effects tolerable. Brief periods of sinus arrest are common with administration and are the means by which it works. Other reported side effects include atrial fibrillation, episodes of apnea, bronchospasm, accelerated ventricular rhythm, wide complex tachycardia, chest discomfort, and flushing. In the presence of aminophylline, an agent that increases cyclic AMP and may antagonize adenosine receptors, adenosine may be ineffective. Larger dosages of adenosine may overcome the initial inhibition caused by aminophylline, but the SVT may recur because of the brief half-life of adenosine. If an initial dose of adenosine does not work, the dosage should be doubled and repeated immediately. A maximum dose is unclear, but 350 $\mu\text{g/kg}$ in infants and children and between 12 mg and 20 mg in adults have been reported.^{23, 29}

Lidocaine and Bretylium

Ventricular fibrillation is seen in less than 10% of pediatric cardiac arrests. A metabolic or toxicologic cause of ventricular arrhythmia always should be considered. When a ventricular arrhythmia requires specific drug therapy, lidocaine is the primary drug to use, with bretylium tosylate as a second choice. Lidocaine suppresses ventricular ectopy and raises the fibrillation threshold. It is a sodium channel blocker, and, as such, is classified as a type Ib antiarrhythmic. By decreasing the slope of phase 4 depolarization of the cardiac pacemaker cell action potential, it decreases automaticity and increases the threshold for excitability.²⁷

Lidocaine is recommended for treatment for patients with ventricular fibrillation after several unsuccessful defibrillation attempts and to prevent recurrence of fibrillation after successful conversion from ventricular fibrillation. The dosage is 1.0 mg/kg by the IV, IO, or ET routes. Before ET administration, the dose of lidocaine should be diluted in 3 mL to 5 mL of fluid. The elimination half-life is 120 minutes^{28, 31} and represents hepatic metabolism. The therapeutic plasma concentration is 1.5 to 5.0 $\mu\text{g/mL}$. The initial plasma lidocaine concentration drops rapidly, with a half-life of approximately 8 minutes, representing distribution from the central compartment to peripheral tissues. Lidocaine efficacy depends on maintenance of therapeutic plasma concentration in the central compartment. Therefore, a single dose may result in transient suppression of arrhythmia, but the arrhythmia may recur as the drug distributes and the central compartment concentration decreases. Thus, there is a requirement for multiple loading doses and institution of a continuous infusion. Immediately after a 1-mg/kg loading dose, therapy with a continuous infusion of 20 to 50 $\mu\text{g/kg/min}$ should be started. The clearance is decreased in congestive heart failure, cirrhosis, postcardiopulmonary bypass surgery, and obesity. Dosage should be reduced when these conditions are present. Patients with plasma levels greater than 6 $\mu\text{g/mL}$ may begin to manifest signs of toxicity. Toxic effects include central nervous system agitation with partial and generalized seizures, tremor,

dysarthria, altered level of consciousness, and nystagmus. Excessive dosages cause myocardial depression and circulatory collapse.

Information about bretylium tosylate in pediatrics is limited. In contradistinction to lidocaine, which blocks sodium channels, bretylium tosylate is a quaternary ammonium salt that prolongs cardiac action potentials and interferes with norepinephrine re-uptake by sympathetic neurons. It may function as a potassium channel blocker. It is excreted essentially unchanged in the urine.

Bretylium may be used in treating ventricular fibrillation refractory to defibrillation and lidocaine and ventricular tachycardia resistant to lidocaine and cardioversion. The recommended dosage is 5 mg/kg by IV push, which can be increased to 10 mg/kg and defibrillation repeated. Continuous infusions of 1 to 2 mg/min have been used in adults. Because of interference with norepinephrine re-uptake, bretylium may induce an initial increase in heart rate, blood pressure, or even frequency of ventricular extrasystoles. With prolonged use, hypotension may develop because of continued inhibition of norepinephrine re-uptake and eventual depletion of norepinephrine stores.

CARDIOVASCULAR SUPPORT IN THE POSTRESUSCITATION PERIOD

The cardiovascular system of pediatric patients resuscitated from cardiac arrest usually requires support with inotropes and occasionally vasopressors. In this section, the pharmacology of epinephrine, dopamine, and dobutamine is reviewed in the context of this role. The pharmacology of these agents has been reviewed in detail.³² Table 2 describes the preparation of infusions and generally used dosage ranges.

Epinephrine

The pharmacology and pharmacokinetics of epinephrine have been reviewed in the context of cardiac arrest resuscitation. Epinephrine is used to treat

Table 2. MEDICATIONS DELIVERED BY CONTINUOUS INFUSION

Drug	Preparation	Infusion Rate	Usual Dosage Range
Epinephrine, Isoproterenol	0.6 $\times$ body weight (kg), added to diluent to make 100 mL	1 mL/hr delivers 0.1 $\mu\text{g/kg/min}$	0.05–1.0 $\mu\text{g/kg/min}$
Dopamine, dobutamine	6 $\times$ body weight (kg), added to diluent to make 100 mL	1 mL/hr delivers 1.0 $\mu\text{g/kg/min}$	Dopamine 0.5–2.0 $\mu\text{g/kg/min}$ (renal), 2.0–15 $\mu\text{g/kg/min}$ (inotropic), > 15 $\mu\text{g/kg/min}$ (pressor) Dobutamine 2.0–20 $\mu\text{g/kg/min}$
Lidocaine	60 $\times$ body weight (kg), added to diluent to make 100 mL	1 mL/hr delivers 10 $\mu\text{g/kg/min}$	20–50 $\mu\text{g/kg/min}$

patients with shock associated with myocardial dysfunction, and, as such, is the drug of choice for treating patients with hypotension following successful treatment of cardiac arrest. Shock following an episode of hypoxemia or ischemia is usually cardiogenic⁷⁶ and may respond to epinephrine infusion. Epinephrine is most likely to be useful when hypotension exists in the context of a low cardiac index and stroke index. At low infusion rates (i.e., 0.05 to 0.1 $\mu\text{g/kg/min}$), systemic vascular resistance decreases slightly, and heart rate, cardiac output, and systolic blood pressure increase somewhat. At intermediate infusion rates, α_1 -adrenergic activation is important but is balanced by the improved cardiac output and activation of vascular β_2 -receptors. Although epinephrine constricts renal and cutaneous arterioles, renal function and skin perfusion may improve. Very high infusion rates (i.e., more than 1–2 $\mu\text{g/kg/min}$) are associated with significant α_1 -adrenergic-mediated vasoconstriction; blood flow to individual organs is compromised, and the associated increase in afterload may further impair myocardial function. In a study involving adult patients in septic shock, one group observed that stepwise infusion of epinephrine was associated with linear increases in cardiac rate, mean arterial pressure, cardiac index, left ventricular stroke work index, oxygen consumption, and oxygen delivery. In that study, neither pulmonary nor systemic vascular resistances were affected by epinephrine infusion.⁷⁷

Preparation and Administration

Epinephrine should be infused into a central vein, if possible. At the low infusion volumes often used for infants and children, available infusion pumps produce cyclic variations in fluid-delivery rate. These may be of sufficient magnitude to cause oscillations in hemodynamic response.¹⁰⁰ In infants and small children, therefore, epinephrine and other vasoactive compounds should be administered by a syringe pump.

Adverse Effects

Intravenous overdosage of epinephrine is immediately life-threatening. Manifestations include myocardial infarction, ventricular tachycardia, extreme hypertension (as much as 400/300), cerebral hemorrhage, seizures, renal failure, and pulmonary edema. Bradycardia also has been observed.⁸⁴

Manifestations of acute overdosage are treated symptomatically, if they persist. β -receptor antagonists, such as propranolol, are contraindicated. Hypertension is treated with short-acting antihypertensives (i.e., nitroprusside).

Hypokalemia is produced by epinephrine infusion caused by stimulation of β_2 -adrenergic receptors that are linked to sodium-potassium-ATPase located in skeletal muscle. Infusion of 0.1 $\mu\text{g/kg/min}$ lowered serum potassium by 0.8 mEq/L.²¹ Hyperglycemia results from α -adrenergic-mediated suppression of insulin release.

Epinephrine is an α_1 -adrenergic agonist, and infiltration into local tissues or intra-arterial injection may produce severe vasospasm and tissue injury. Concurrent activation of β_2 receptors by epinephrine limits vasospasm, and local injury to tissue is less common than with either norepinephrine or dopamine.

Dopamine

Although epinephrine is the drug of choice for myocardial dysfunction and shock in the postresuscitation period, dopamine may be used in patients with less severe shock and hypotension.

Basic Pharmacology

In the enzymatic pathway leading from tyrosine to epinephrine, decarboxylation transforms L-dopa to dopamine. Dopamine is a central neurotransmitter and also is found in sympathetic nerve terminals and in the adrenal medulla, where it is the immediate precursor of norepinephrine. In healthy individuals, plasma levels of dopamine are in the range of 50 to 100 pg/mL.

Dopamine stimulates dopamine (D_1 and D_2) receptors located in the brain and in vascular beds in the kidney, mesentery, and coronary arteries. It also stimulates α -receptors and β -receptors, although the affinity of the compound for these receptors is lower. D_2 -receptors are coupled through G_i protein to adenylate cyclase. The increase in cAMP produced by their activation evokes vasodilation, which increases blood flow to these organs and may enhance renal solute and water excretion. Dopamine also modulates release of aldosterone and prolactin (D_2 -receptors), which also may affect renal solute clearance.^{25, 102, 103}

In healthy adult volunteers, infusion rates between 1 and 10 $\mu\text{g/kg/min}$ increased stroke volume and cardiac output without major effect on heart rate or blood pressure. Low infusion rates augment renal sodium excretion; intermediate rates (i.e., 10 $\mu\text{g/kg/min}$) produce chronotropic and inotropic effects, and still higher infusion rates increase vascular resistance.^{8, 46, 122} Renal blood flow, glomerular filtration rate, and sodium excretion are maintained or increase during dopamine infusion in patients with poor cardiac output. It is often stated that infants display reduced sensitivity to dopamine; however, the evidence of this view is not conclusive. Some experimental evidence shows diminished sensitivity to dopamine in infants; however, this finding is limited to studies in immature animals.^{8, 78} A contrary observation was made by Padbury and coworkers,⁸⁷ who measured cardiac output in a group of infants and found that mean blood pressure increased at doses of 0.5 to 1 $\mu\text{g/kg/min}$, whereas heart rate increased beyond 2 to 3 $\mu\text{g/kg/min}$. Cardiac output and stroke volume increased before heart rate, and systemic vascular resistance did not change within the range of dopamine infusion rates (0.5–8 $\mu\text{g/kg/min}$).

Low infusion rates of dopamine frequently are used to augment renal function during critical illness.^{104, 113} Although evidence shows that low-dose dopamine may promote salt excretion and urine flow rate, data do not conclude that the chances of renal failure are thereby reduced.

Pharmacokinetics

Plasma dopamine clearance ranges from 60 to 80 mL/kg/min in normal adults.⁵¹ The half-life has not been reliably determined but probably is in the range of 2 to 4 minutes. Clearance is lower in patients with renal or hepatic

disease.^{11, 12} Age has a striking effect on clearance of dopamine, and clearance in children younger than 2 years of age is approximately twice as rapid as it is in older children (82 versus 46 mL/kg/min).¹¹ This observation has been confirmed: in a recent study, Allen and colleagues¹ demonstrated that during the first 20 months of age, the clearance of infused dopamine decreases by almost 50%, with an additional 50% decrease from ages 1 to 12 years. This pharmacokinetic difference, rather than a difference in receptors or myocardial sensitivity, may account for the observation that infants require and tolerate higher infusion rates. The pharmacokinetics of dopamine and other cardiovascular drugs have been reviewed.¹⁰

Clinical

Dopamine is an effective inotropic and vasopressor agent in neonates and infants with a variety of conditions associated with circulatory failure, including hyaline membrane disease, asphyxia, sepsis syndrome, and cyanotic congenital heart disease.¹⁰⁰⁻¹¹¹

Although little formal data are available concerning use of dopamine in critically ill children, clinicians use dopamine to enhance renal function and exploit its inotropic and vasopressor properties. Dopamine is less likely to produce severe tachycardia or dysrhythmias than epinephrine or isoproterenol.

Following volume repletion, dopamine is indicated in the context of moderately severe degrees of distributive shock (e.g., sepsis or hypoxia-ischemia) or cardiogenic shock. It is also indicated in the absence of hypotension, when clinical signs or hemodynamic measurements suggest a state of compensated shock or inadequate peripheral perfusion. Dopamine is not the agent of choice when an elevated cardiac output exists, a markedly reduced systemic vascular resistance and profound hypotension. This pattern is observed in patients with septic shock and suggests use of a vasopressor, such as norepinephrine. Dopamine is also not the drug of choice to treat hypotension associated with major reductions in cardiac index (e.g., $< 2\text{--}2.5\text{ L/min/m}^2$). Epinephrine is more appropriate. Children with primary myocardial disease not complicated by frank hypotension benefit from more selective inotropic agents, such as dobutamine, milrinone, or amrinone. Infusion rates of dopamine needed to improve signs of severe myocardial dysfunction may be associated with troublesome tachycardia or dysrhythmia and may increase myocardial oxygen consumption disproportionately to myocardial perfusion.

To treat patients with shock associated with hypotension, therapy is initiated with an infusion rate of 5 to 10 $\mu\text{g/kg/min}$. The rate of infusion is increased in steps of 2 to 5 $\mu\text{g/kg/min}$, guided by evidence of improved blood flow (e.g., skin temperature, capillary refill, sensorium, and urine output) and by restoration of a blood pressure that is appropriate for age. Infusion rates of more than 25 to 30 $\mu\text{g/kg/min}$ of dopamine are not customary, even if they maintain a normal blood pressure. At infusion rates of this magnitude, the effect on blood pressure is likely to represent an increase in systemic vascular resistance (α -adrenergic activation) rather than cardiac output.

Adverse Effects

Dopamine administration produces mainly cardiovascular toxicity, including tachycardia, hypertension, and dysrhythmia. The effect of dopamine on

myocardial oxygen balance is better than it is for isoproterenol but not as good as for dobutamine, amrinone, and milrinone.^{7, 10, 78}

Dopamine depresses the ventilatory response to hypoxemia and hypercarbia by as much as 60%.¹²⁰ Dopamine and other β -agonists decrease Pao_2 by interfering with hypoxic vasoconstriction. In one study, dopamine increased shunt in patients with adult respiratory distress syndrome from 27% to 40%.⁶¹ Dopamine can cause or worsen limb ischemia, gangrene of distal parts and entire extremities, and extensive loss of skin.⁶¹ Infusion rates as low as 1.5 $\mu\text{g/kg/min}$ have been responsible for limb loss.^{2, 45, 46} The presence of an arterial catheter also increases the possibility of limb ischemia. Because dopamine promotes release of norepinephrine from synaptic terminals and also is converted to norepinephrine *in vivo*, it is more often associated with limb ischemia than are other adrenergic compounds. Extravasation of dopamine should be treated immediately with local infiltration with a solution of phentolamine (Regitine) (5 to 10 mg in 15 mL of normal saline) administered with a fine hypodermic needle.

Preparation and Administration

Dopamine is administered by central venous catheter to avoid the risk of skin injury caused by extravasation. In an emergency, dopamine may be administered through an IO needle.⁶⁵

Dobutamine

Clinical Pharmacology

In adults with congestive heart failure, dobutamine produces a 50% to 80% increase in cardiac output, which is almost entirely caused by improvement in stroke volume. Left atrial pressure decreases and systemic vascular resistance decreases or remains the same. Heart rate increases little, if at all. Although renal function is not directly affected by dobutamine, renal function and urine output may improve as the increase in cardiac output fosters relaxation of sympathetic tone and improved perfusion. Dobutamine is a dilator of the pulmonary vasculature.⁶⁶

In one small study, dobutamine infusion (10 $\mu\text{g/kg/min}$) was associated with increases in cardiac output (30%), blood pressure (17%), and heart rate (7%). The threshold plasma concentrations for these increases were 13 ng/mL, 23 ng/mL, and 65 ng/mL, demonstrating that dobutamine is a relatively selective inotrope with little effect on heart rate at customary infusion rates.⁵² Somewhat greater thresholds for improved cardiac output were observed in a second group of children⁷⁹ and in infants,⁷⁸ but in all studies, dobutamine improved cardiac contractility without substantially altering heart rate unless high infusion rates were used.

Pharmacokinetics

The half-life is approximately 2 minutes in adults, and the volume of distribution is 0.2 L/kg. Congestive heart failure increases the volume of distribution.

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bution. In adults, the clearance is approximately 2 L/m²/min. Typical clearance values in children are 70 to 100 mL/kg/min. Infusions in the range used clinically yield plasma dobutamine concentrations from approximately 50 ng/mL to 160 to 190 ng/mL in children⁵² and adults.⁵⁴ The principal route of elimination is methylation by COMT, followed by hepatic glucuronidation and excretion into urine and bile. Dobutamine also is cleared from the plasma by non-neuronal uptake (uptake-2). Some investigators have reported nonlinear elimination kinetics, but other data suggest that the kinetics of dobutamine can be adequately described by a simple first-order (linear) model.¹⁰⁶

Clinical

In adults, dobutamine produces improvement in various conditions associated with poor myocardial performance, such as cardiomyopathy, atherosclerotic heart disease, and acute myocardial infarction.^{62, 71, 107} Dobutamine has been used following surgery for myocardial revascularization, cardiac transplantation, and other procedures associated with postoperative myocardial dysfunction, although undesirable chronotropic effects have been recorded when used after cardiac surgery.^{73, 98, 108} Several studies in infants and children^{9, 52, 75, 91, 109} demonstrate that dobutamine improves myocardial function in various settings. Stroke volume and cardiac index improve without a substantial increase in cardiac rate. Systemic vascular resistance and pulmonary vascular resistance may decrease toward normal.

Dobutamine is not a first-line agent to treat patients with low-output states that are caused by intracardiac shunt or abnormal cardiac chamber structure. Dobutamine is used following corrective or palliative cardiovascular surgery in children; however, in this context, its use also should be limited to occasions in which demonstrated or suspected myocardial dysfunction exists. Dobutamine may be of adjunctive value in treating patients with myocardial dysfunction that complicates a primary condition, such as adult respiratory distress syndrome or septic shock. It is rarely, however, appropriate to use dobutamine as the sole agent to treat patients with hemodynamic compromise associated with sepsis, adult respiratory distress syndrome, or shock following an episode of severe hypoxia-ischemia.

Adverse Effects

Dobutamine usually increases myocardial oxygen demand. In subjects with myocardial dysfunction, coronary blood flow and oxygen supply improve with the increase in demand⁷²; however, if dobutamine is used when myocardial contractility is normal, oxygen balance is adversely affected. Significant tachycardia greatly increases oxygen use by the heart and should prompt a reduction in the dosage of dobutamine (or an alternate agent).

Although dobutamine is less likely than other catecholamines to induce severe atrial and ventricular dysrhythmias, these complications occur, particularly in the context of myocarditis, electrolyte imbalance, or high infusion rates. Dobutamine and other inotropes should be administered cautiously to patients

with dynamic left ventricular outflow obstruction (i.e., hypertrophic aortic stenosis).

Preparation and Administration

Therapy is initiated at a rate of 2.5 to 5 µg/kg/min. One should consider changing to epinephrine if no substantial improvement occurs with infusion rates of 20 µg/kg/min, although rates of 40 to 50 µg/kg/min have been effective.

Summary

The resuscitation of children from cardiac arrest and shock remains a challenging goal. The pharmacologic principles underlying current recommendations for intervention in pediatric cardiac arrest have been reviewed. Current research efforts, points of controversy, and accepted practices that may not be most efficacious have been described. Epinephrine remains the most effective resuscitation adjunct. High-dose epinephrine is tolerated better in children than in adults, but its efficacy has not received full analysis. The preponderance of data continues to point toward the ineffectiveness and possible deleterious effects of overzealous sodium bicarbonate use. Calcium chloride is useful in the treatment of ionized hypocalcemia but may harm cells that have experienced asphyxial damage. Atropine is an effective agent for alleviating bradycardia induced by increased vagal tone, but because most bradycardia in children is caused by hypoxia, improved oxygenation is the intervention of choice. Adenosine is an effective and generally well-tolerated agent for the treatment of supraventricular tachycardia. Lidocaine is the drug of choice for ventricular dysrhythmias, and bretylium, still relatively unexplored, is in reserve. Many pediatricians use dopamine for shock in the postresuscitative period, but epinephrine is superior. Most animal research on cardiac arrest is based on models with ventricular fibrillation that probably are not reflective of cardiac arrest situations most often seen in pediatrics.

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Pediatric Advanced Life Support (PALS): The Pharmacist's Role

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The provision of pharmaceutical care to the patient undergoing cardiopulmonary resuscitation (CPR) is an important evolving concept. Pediatric resuscitation and advanced cardiac life support (ACLS) presents a particularly challenging situation for the practicing pharmacist. Etiologies of pediatric arrests include pulmonary conditions such as bronchopulmonary dysplasia, respiratory distress syndrome, respiratory syncytial virus (RSV) infection, and a myriad of accidental factors. Important initial determinations on arriving at a pediatric arrest are described, such as determining the correct weight of the patient, assessing the need for vascular access and/or intubation, and establishing the "code" leader. Recent American Heart Association guidelines for the pharmacotherapy of pediatric ACLS are discussed in detail. Included are recommendations on oxygen delivery, routes of fluid and medication administration, recent changes in epinephrine dosing, and guidelines for the proper use of adjunct

medications. A detailed description of a method of using adult emergency drug syringes in the pediatric arrest is provided. Proper use of this method can expedite drug dispensing in an arrest, minimize the potential for needle-stick injury, and optimize the delivery of a patient-specific dose of medication. A "mock code" program is described that includes involvement with pharmacists, nurses, medical residents, and respiratory therapists. This program provides a hands-on role-playing model of a simulated pediatric arrest and serves as a valuable teaching tool for those charged with the responsibility of patient care during an actual arrest. While the ultimate role of the pharmacist in the pediatric arrest continues to be defined, developing the competency to provide pharmaceutical care in this clinical setting can be extremely rewarding.

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PERHAPS THE MOST startling and anxious moment a pharmacist encounters is the instant a cardiopulmonary arrest is announced over the public address system of a health care facility. As someone's life literally hangs in the balance, the pharmacist must at once discontinue all present activities, promptly and efficiently gather whatever materials and supplies may be necessary, and quickly respond to the emergency while maintaining composure. By any moniker, a "no. 1 Emergency," "Code 4444," "Doctor Stat," or "Code Blue" presents the most immediate and critical of challenges for those charged with the care of patients. When this situation involves a pediatric patient, the anxiety and emotion of the event can become even more charged. Unfortunately, all too often the reason for these uneasy feelings is insufficient training in this area of clinical practice. As no one can accurately predict the exact moment an arrest will occur, staffing a department with pharmacists experienced in advanced life-support is optimal. Because emergencies

can occur at any time, however, experienced personnel may or may not always be available. Similarly, off-hours such as the midnight shift and weekends are typically staffed with minimal coverage, which often precludes pharmacist involvement with the cardiac arrest team. This article will review the etiologies and unique complications of the pediatric arrest. Current guidelines from the American Heart Association on emergency medication use during pediatric advanced life support (P.A.L.S.) will be provided along with suggestions for the pediatric pharmacist practitioner to become a more active (or *pro-active*) member of the arrest team. Finally, a description will be provided of the author's experience with a mock code program designed to provide a multidisciplinary, hands-on, role-playing model for review of cardiopulmonary arrests in the pediatric patient.

An exhaustive summary of all aspects of the pediatric arrest situation, including fundamental basic life-support techniques, is beyond the scope of this review. The reader is reminded that before any pharmacological intervention in an arrest situation, the basic "ABC's" of life support (airway, breathing, circulation) need to be established before initiating "drug," or pharmacological, therapy.

Basic life support includes, but is not limited to, determining the responsiveness of the pa-

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tient: the initiation of respirations and chest compressions in a pulseless, nonbreathing patient; and the use of necessary equipment to aid in the maintenance of the respiratory and circulatory effort.

ETIOLOGIES OF THE PEDIATRIC ARREST

The most common cause of cardiac arrest in a pediatric patient is secondary to pulmonary compromise.¹ The progression of events typically involves respiratory failure with worsening hypoxemia, hypercarbia, and metabolic acidosis that progresses to asystole and cardiopulmonary arrest. Unlike the adult population, acute myocardial infarction in the child is an extremely rare phenomenon. Similarly, the incidence of ventricular fibrillation associated with pediatric pulseless arrest is reported to be less than 10%.² Common underlying pulmonary etiologies that place the pediatric patient at increased risk for arrest include prematurity with resultant bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), cystic fibrosis, and respiratory syncytial virus (RSV). Other accidental factors that contribute to respiratory emergencies including smoke inhalation, near-drowning, foreign body aspiration, suffocation episodes, and unintentional strangulation. Lastly, metabolic or organic etiologies of respiratory arrest can include intractable seizures, central nervous system (CNS) toxicity secondary to drug overdose (intentional or unintentional), severe electrolyte abnormalities, or hypoglycemia.^{3,4}

In pediatric patients with impending respiratory failure, certain compensatory mechanisms usually take place that offer warning signs to the progression of more serious, life-threatening events such as shock and respiratory demise. These warning signs include tachypnea, decreased breath sounds, insufficient chest excursion, changing mental status (from initial restlessness or agitation to lethargy or unresponsiveness), decreased response to painful stimuli, cyanosis and/or poor overall respiratory effort. Signs that herald the onset of shock in the pediatric patient include tachycardia, rapid, thready peripheral pulses, diaphoresis, and/or signs of end-organ perfusion compromise such as decreased urine output or worsening mental status.

A prospective analysis of more than 100 arrests in a pediatric population concluded that the only variable which influenced the ultimate survival of the patient was the type of arrest (respiratory vs cardiac vs cardiorespiratory).⁵ Patients who suffered a respiratory arrest had a 25% mortality rate, compared with 87% mortality for cardiac (only) arrests and an 83% mortality rate for cardiorespiratory arrests. In a retrospective review of 183 patients treated in a pediatric trauma/cardiopulmonary resuscitation room of an emergency department, apneic and *pulseless* patients showed poor survival (10%) compared with the excellent survival rates (97%) of apneic children.⁶ In addition to etiology, duration of arrest is significantly associated with decreased neuropsychological functioning in childhood survivors of cardiac arrest. The child with underlying respiratory disease in the first year of life is at greatest risk for arrest, because 45% to 65% of all pediatric arrests occur in the first 12 months of life.⁷

ARRIVING AT THE CODE SCENE: ASSESSING THE SITUATION

Although still an evolving concept, the notion of the pharmacist as an integral member of the code team was first described nearly 30 years ago.⁸ Whether notification of the arrest comes via overhead page or digital pager, the responding pharmacist needs to act immediately to gather both supplies and thoughts to respond efficiently and professionally to the situation. Invariably, logistical and demographic constraints usually require several seconds, or perhaps minutes between initial announcement of an arrest and arrival at the code scene. Preparation for the provision of pharmaceutical care to the patient should begin during these first critical moments. The pharmacist's thought processes should begin to focus on what information to ascertain on arrival at the arrest. Of paramount importance is to determine the weight of the patient. The pediatric emergency is not unlike most other clinical situations in the field of treating sick and hospitalized children in that drug dosages are usually expressed in terms of weight (ie, "mg/kg"). If the weight of the patient is not known, an accurate estimation can be determined by measuring the length of the patient with a tape that estimates weight from

measured length.⁹ As a last resort, if a parent, nurse, or caregiver is unable to provide a recent documented weight, a "best-guess" estimate should be determined for calculation of drug dosing. Pharmacists have taken a preemptive role in this area by establishing bedside charts for pediatric patients, including the patient's current weight and calculated doses for commonly used emergency drugs.¹⁰ In the event of an arrest, the correct drug dose calculations are then readily available at the bedside (Fig 1), which greatly facilitate prompt medication administration.

If possible, a brief history should be ascertained including the nature and history of the illness or injury, and the medications the patient may be currently taking or has accidentally ingested. Knowledge of underlying disease states

If the weight of the patient is not known, an accurate estimation can be determined by measuring the length of the patient with a tape that estimates weight from measured length.

is also important in determining the etiology of the arrest and in anticipating potential pharmacotherapeutic needs of the patient. For example, knowing that a patient is currently undergoing chemotherapy for acute lymphocytic leukemia may aid in the diagnosis and management of presumed septic shock, including the need for aggressive fluid resuscitation and antibiotic administration. Because examination of the pupils of the eye is routinely performed on any unconscious patient, knowledge of whether or not the patient has recently been administered medications that may alter the pupillary response (eg. belladonna alkaloids such as atropine) can be of vital importance in proper patient assessment. Another factor to determine is whether or not the patient has vascular access. Hospitalized patients often have intrave-

nous access, especially in an intensive care unit (ICU) setting. Conversely, patients brought into the emergency department usually *do not* have intravenous access, thus vascular access needs to be established.

A critical determination to be made by those directly involved is which individual is leading, or "running" the code. The importance of communication in this clinical circumstance is critical. Because a typical arrest situation may have several physicians in attendance, identification of the individual (usually, but not always, a physician) charged with the responsibility of clinical decision-making in the code becomes important for several reasons. First, as the situation is unfolding and patient assessment is taking place, several requests may be generated at once by a multitude of physicians. These requests can include fluids, medications, saline flushes, in addition to a multitude of supplies stocked on the "crash cart." A pharmacist trying to efficiently respond to a flurry of simultaneous requests may increase the chance of committing a dispensing error, or at the very least cause delays in drawing up doses. A proactive approach would be to identify oneself as the pharmacist on the code team, ask who is leading the code, then interact *solely* with that individual in responding to medication and fluid requests. Trying to respond to more than one "code leader" increases the risk of administering incorrect or duplicate doses or otherwise compromising control and continuity of medication use at the arrest. As doses are drawn up and administered, it is incumbent on the pharmacist and/or recording nurse to make the code leader aware of how many doses of each medication has been administered up to that point. All too often, two or more doses of medication may have been requested, whereas, because of unavoidable delays, the initial dose has yet to be given.

Unfortunately, the code scene is frequently populated with far too many people than are necessary for successful resuscitation of the patient. Arrest "over-attendance" can actually impede the progress and successful execution of a resuscitation. Although the motive behind a health care professional's desire to respond to an arrest is usually in the interest of patient care

**Pediatric Intensive Care Unit
Emergency Drug / Drip Worksheet**

Patient Name _____

Date of Admission _____

Admission Weight _____ (kg)

Calculated By _____ Checked By _____

Please update with significant weight changes

<i>Drug</i>	<i>Initial Dose</i>	<i>Calculation</i>	<i>Dose (mg)</i>
Atropine (1 mg/1 mL)	0.02 mg/kg IV/IO/ET (minimum dose 0.1 mg)	0.02 × _____ (wt in kg) = _____ mg	_____ cc
Epinephrine (0.1 mg/mL)	0.01 mg/kg IV/IO (1:10,000)	0.01 × _____ (wt in kg) = _____ mg	_____ cc
	0.1 mg/kg IV/IO/ET (1:1,000)	0.1 × _____ (wt in kg) = _____ mg	_____ cc
Sodium bicarbonate (1 mEq/mL)	1 mEq/kg IV/IO	1 × _____ (wt in kg) = _____ mEq	_____ cc
Calcium chloride 10% (100 mg/mL)	20 mg/kg IV/IO	20 × _____ (wt in kg) = _____ mg	_____ cc
Lidocaine 1% (10 mg/1 mL)	1 mg/kg IV/IO/ET	1 × _____ (wt in kg) = _____ mg	_____ cc
Dextrose 25% (250 mg/1 mL)	2-4 mL/kg IV/IO	2-4 × _____ (wt in kg) = _____ mg	_____ cc

Fig 1. Pediatric intensive care unit emergency drug/drip worksheet.

or educational advancement, the reality of the situation is that the most efficiently run and ultimately successful resuscitations can be managed by a limited number of key individuals. The physical space limitations, noise level, and delays in getting equipment and blood samples mobilized to and from the room are just a few of the reasons that a well defined, dedicated "Code Team" consisting of a limited number of members is ideal. With proper communication and understanding of everyone's role, an effective resuscitation effort is usually best achieved with fewer, rather than more, individuals. A typical code response team includes the following individuals: anesthesiology resident or attending physician; intensive care attending physician;

pediatric senior resident on duty; surgical resident or attending physician; pharmacist; respiratory therapist; intensive care nursing personnel, or floor nurses as required; messenger; and ancillary personnel as necessary (chaplain, administrative coordinator, security).

PHARMACOTHERAPY OF THE PEDIATRIC ARREST

In 1992, the American Heart Association-sponsored National Conference on Cardiopulmonary Resuscitation (CPR) and Emergency Critical Care (ECC) convened with the express purpose of updating standards and guidelines for all aspects of basic and advanced cardiac life support.¹¹ The conference resulted in several

new recommendations in the area of pediatric advanced life support.

Oxygen and Endotracheal Intubation

Oxygen has clearly been proven to be of unquestionable benefit in the management of seriously ill and deteriorating children with respiratory distress. Oxygen delivery to tissues is compromised by respiratory insufficiency, circulatory failure, and hypovolemia. Even with excellent basic life-support technique in the areas of mouth-to-mouth resuscitation and external chest compressions, the percentage of inspired oxygen (16% to 17%) is less than that of normally inhaled room air (21%) and cardiac output is likewise markedly diminished.¹ Concentrations of inspired oxygen of 100% are usually administered in the pediatric arrest situation either by a nonbreathing face mask (conscious patient) or via endotracheal intubation (unconscious or comatose patient). Pharmacists responding to arrests can play an active part in the intubation sequence by bringing with them to all arrests a bag of "intubation meds," such as succinylcholine, atracurium, atropine, thiopental, and lorazepam. Although most anesthesiologists have their own preference of medications to use in rapid sequence intubation, the previously mentioned list of agents should allow for some degree of flexibility in the pharmacological management of this emergency procedure.

Routes of Fluid and Drug Administration

A necessary component to pediatric ACLS is the establishment of vascular access. Pediatric arrest is often accompanied by dehydration and subsequent hypovolemia, thus making the task of establishing a line for fluid and drug administration a difficult one. If central access is already existing in the patient, it should be used. Commonly used sites for gaining access to the central circulation include the femoral, subclavian, internal, and external jugular veins. For most clinicians, the femoral vein provides the fastest and easiest site of cannulation in the pediatric patient. If central access cannot be achieved, peripheral access should be attempted in veins of the hand, foot, arm, leg, or scalp (in the case of an infant). In a well designed code team protocol, time limits are placed on establishing peripheral access. After

1 to 2 minutes of unsuccessful peripheral intravenous attempts, an intraosseous (IO) catheter is placed. IO access is a reliable alternative in children younger than 6 years of age. The rich microvascular bed of vessels (venous plexus) existing within the bone space of small children before closing of the long bones provides direct venous access. A special IO needle, similar to a bone marrow needle, *must be used* when attempting IO placement to minimize the chance of the needle breaking off during the attempt. The most common site used for IO placement is the anterior aspect of the tibia. Intraosseous access can be achieved in as little as 30 seconds to 1 minute by a skilled clinician.^{12,13}

Although IO access has been associated rarely with such complications as compartment syndrome, osteomyelitis, and tibial fractures, it remains an extremely valuable alternative for access to the vascular system. Crystalloid and

For most clinicians, the femoral vein provides the fastest and easiest site of cannulation in the pediatric patient.

colloidal IV solutions, inotropic infusions, and other emergency medications can be safely administered via an IO line. Once the patient is stabilized in the ICU, the IO line should be replaced with a more permanent site of central access. Another alternative route of drug administration, although inferior to IV or IO, is via the endotracheal tube. Lipophilic medications, including lidocaine, atropine, naloxone, and epinephrine (mnemonic: L.A.N.E.) have been successfully administered via the endotracheal tube (see Table 1). Because drug absorption varies widely with this route of administration, definitive dosing guidelines are not well defined.

Table 1. Medications Able to be Given Via the Endotracheal Route of Administration

L	Lidocaine
A	Atropine
N	Naloxone
E	Epinephrine

Based on a study in adult patients showing that 10% or less of an endotracheally administered epinephrine dose ultimately reaches the terminal alveoli for absorption, doses up to 10 times the IV dose are given.¹⁴ All drug doses administered via the endotracheal route should be followed with a normal saline flush (1 or 2 mL) to ensure maximal drug delivery to the site of absorption in the terminal alveoli.

Intravenous Fluid Selection

Prompt fluid resuscitation must be considered early in the treatment options available to the clinician when caring for the seriously ill child. Crystalloid or colloid fluid boluses at doses of 10 to 20 mL/kg are administered to restore circulating blood volume in cases of hemodynamic compromise or severe dehydration. This early, aggressive effort in maintaining an effective circulatory volume can prevent more serious sequelae such as progression to cardiac arrest or shock.¹⁵ Commonly used crystalloid fluids include Ringer's lactate and normal saline, whereas 5% albumin is typically used as a colloid solution. Dextrose-containing solutions are not recommended, because a large glucose load could result in hyperglycemia with resultant osmotic diuresis, which could precipitate adverse neurological sequelae including intracranial hemorrhage and seizures.¹⁶ Hypoglycemia detected via a bedside reagent test (Accucheck, Chemstrip BG) should be managed with administration of 0.5 to 1 g/kg of dextrose (2 to 4 mL/kg of 25% Dextrose). Dextrose concentrations exceeding 25% should be avoided because of complications associated with hyperosmolarity. If 50% Dextrose solutions are provided on the emergency carts, they must be diluted 1:1 with sterile water before administration in a pediatric patient.

Potassium-containing IV solutions and hyperalimentation solutions should be administered with great caution in the arrest situation. Compromises in cardiac output can lead to decreased renal blood flow with subsequent diminished urine output and low potassium excretion. As a result, serum potassium levels can increase, precipitating cardiac arrhythmias or asystole. Potassium-containing IV solutions infusing at the onset of an arrest should be switched to a potassium-free crystalloid or colloid solution for

acute fluid resuscitation. Once the patient is stabilized, close monitoring of urine output, overall fluid status, and serum chemistries will allow modifications in fluid and electrolyte therapy.

Resuscitation Management

Epinephrine. Specific pharmacotherapy of bradycardia or asystole begins with epinephrine as initial therapy. Epinephrine is a naturally occurring catecholamine compound with dose-dependent effects on both the α - and β -adrenergic nervous systems. In a cardiac arrest, epinephrine has been unequivocally proven to be beneficial in restoring cardiac function. This effect is related to epinephrine-induced systemic vasoconstriction via α -adrenergic mediated sympathetic stimulation, which results in decreased venous pooling of available blood throughout the body with subsequent increases in coronary perfusion pressure, thereby increasing oxygen delivery to the heart muscle. The ability to increase aortic diastolic pressure through systemic vasoconstriction has been associated with successful cardiopulmonary resuscitation efforts.¹⁷ Epinephrine also causes increased force of cardiac contractions (positive inotropic action) and increased heart rate (positive chronotropic action) through its β -adrenergic effects, which also play a role in establishing cardiac function in the bradycardiac or asystolic patient. Another unique pharmacologic function of epinephrine is its ability to change a mild but persistent ventricular fibrillation ("fine" ventricular fibrillation) into the more classic "sawtooth" or coarse rhythm of ventricular fibrillation. This action is advantageous, because the coarse ECG rhythm associated with classic ventricular fibrillation is more amenable to cardioversion (electric defibrillation) than is fine ventricular fibrillation.^{18,19}

The initial dose of epinephrine for infants and children in an arrest is 0.01 mg/kg (10 μ g/kg). Epinephrine is commercially available in two concentrations: 1:1,000 (1 mg in 1 mL) and 1:10,000 (1 mg in 10 mL). To deliver a dose of 0.01 mg/kg, the 1:10,000 strength should be used because 0.1 mL/kg of this strength provides a dose of 0.01 mg/kg. Pharmaceutical care for the patient in this situation includes ensuring that both the appropriate dose and concentra-

tion are correctly drawn up and administered. Before the American Heart Association conference in 1992, this dose was recommended for initial and all subsequent doses of epinephrine administered at a pediatric arrest. However, in a pivotal study²⁰ focusing on the neurological outcomes of pediatric patients resuscitated with the aid of high-dose epinephrine, improved outcomes were noted with a high-dose regimen (0.1 mg/kg); thus the American Heart Association has adopted this stance. The second and subsequent doses of epinephrine should be 0.1 mg/kg (100 µg/kg) whether administered by the IV or IO route. Consequently, the 1:1,000 strength epinephrine at a dose of 0.1 mL/kg will deliver 0.1 mg/kg (100 µg/kg). Doses as high as 0.2 mg/kg (0.2 mL/kg of the 1:1,000 solution) have been used. Likewise, multiple doses of epinephrine may be required. Three to 5 minutes should elapse between doses of epineph-

Consequently, the 1:1,000 strength epinephrine at a dose of 0.1 mL/kg will deliver 0.1 mg/kg (100 µg/kg).

rine. This somewhat-confusing dosing scheme is further complicated when IV or IO access is unobtainable and epinephrine must be administered via the endotracheal tube. In this situation, the initial dose of epinephrine is 0.1 mg/kg (100 µg/kg), or 0.1 mL/kg of the 1:1,000 strength epinephrine solution. The expertise of the pharmacist is beneficial in these initial stages of P.A.L.S. perhaps more than at any other time, because dosing errors secondary to calculation mistakes or unfamiliarity with product strengths can easily lead to 10-fold overdoses or underdoses, thus endangering clinical outcomes. The role of the pharmacist is to ensure that not only is the appropriate dose ordered, but the available routes of administration are assessed and the proper concentration for the chosen route of administration (IV/IO vs endotracheal tube) are prepared.

Epinephrine has been administered as a con-

tinuous infusion in cases of sustained asystole. Doses as high as 20 µg/kg/min have been administered to children to restore cardiac function after prolonged asystole.¹ Continuous infusion of epinephrine has been associated with hypertension and cardiac arrhythmias; thus, prompt dose decreases and/or titration should accompany any clinical response. Tissue necrosis with scarring can result from extravasation of epinephrine solutions when administered peripherally, and thus central access should be used when possible. At high doses, perfusion to vital organs may likewise be compromised secondary to decreased renal, mesenteric, cerebral, and splanchnic blood flow. Despite these potential concerns and precautions, epinephrine remains the quintessential pharmacological tool in the treatment of both pediatric and adult cardiopulmonary arrest.

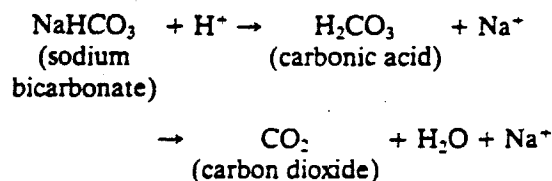
Atropine. Parasympathetic effects on cardiac tissue are mediated through the vagus nerve. The neurotransmitter of the parasympathetic nervous system, acetylcholine, reduces sinoatrial node spontaneous depolarization, thereby decreasing heart rate.²¹ At the atrioventricular node, acetylcholine reduces conduction velocity and increases the effective refractory period, which decreases ventricular response in the setting of atrial tachycardias. The vagus nerve thus acts as the "brake" for the heart; stimulation of the vagus nerve (ie, vagal maneuvers) is a common treatment option for patients experiencing supraventricular tachycardias. Atropine, a belladonna alkaloid and perhaps the classic anticholinergic compound, has proven efficacy in the management of sinus bradycardia, especially when hypotension and inadequate peripheral perfusion are present. Atropine acts by blocking the vagus nerve, resulting in increased sinus and atrial pacemaker activity and increased atrioventricular (AV) node function. Atropine is an especially useful treatment option in the small infant, because children younger than 6 months of age rely almost exclusively on heart rate for cardiac output.²² It should be stressed, however, that despite the usefulness of atropine in increasing heart rate in the small child, epinephrine is still the treatment of choice for managing bradycardia associated with low cardiac output. Atropine is considered the second-line agent in the management

of bradycardia and asystole in the pediatric patient. The usefulness of atropine in resolving ventricular asystole is less clear than with other agents such as epinephrine.

The recommended dose of atropine for bradycardia is 0.02 mg/kg, with a minimum dose of 0.1 mg. Administration of at least the minimum dose of 0.1 mg is important, because atropine can cause a paradoxical *stimulation* of the vagus nerve at lower doses, thus aggravating a preexisting bradyarrhythmia. The maximum single dose of atropine for a child is 0.5 mg, whereas single doses as high as 1 mg can be administered to the adolescent patient. The maximum total dose of atropine is 1 mg and 2 mg for the child and adolescent, respectively. Doses can be repeated approximately every 5 minutes if needed during a prolonged arrest. The expertise of the pharmacist is essential in drawing up doses of atropine because commercially available concentrations include 1 mg/1 mL, 0.4 mg/1 mL, and 1 mg/10 mL. For example, a 0.02 mg/kg dose in a 25-kg patient would be 0.5 mg, with a measured volume of 0.5 mL, 1.25 mL, or 5 mL based on atropine concentrations of 1 mg/1 mL, 0.4 mg/1 mL, and 1 mg/10 mL, respectively.

Sodium Bicarbonate. For many years an axiom in the management of patients who had arrested was, "Witnessed arrest, give one dose of bicarb; unwitnessed arrest, give two doses." Indeed, for many years the injudicious, copious use of sodium bicarbonate in the early stages of an arrest seemed warranted because catecholamines are well known to have decreased efficacy in the setting of acidosis. Correcting the downward pH shifts associated with respiratory and metabolic acidosis by administering an alkalinizing agent was thought to enhance the efficacy of catecholamine compounds (ie, epinephrine) in "jump-starting" the heart. However, clinical studies have not borne out these assumptions.²³ The aggressive use of sodium bicarbonate in the absence of effective ventilation has been shown to paradoxically exacerbate existing respiratory acidosis through generation of carbon dioxide dissolved as a gas in the blood. Once in plasma, the dissolved carbon dioxide diffuses across cellular membranes at a rate more rapid than existing bicarbonate, resulting in a decrease in intracellular pH.²⁴ Because respiratory failure is the most common cause of

cardiac arrest in children, the cavalier use of this agent can actually worsen existing respiratory acidosis. This chemical reaction is described by the following equation:



It is therefore imperative that effective ventilation be established before the administration of bicarbonate in the arrest setting.

Currently no specific recommendations on when to administer bicarbonate exist. The pharmacist together with the code leader and other members of the arrest team must assess such

The aggressive use of sodium bicarbonate in the absence of effective ventilation has been shown to paradoxically exacerbate existing respiratory acidosis through generation of carbon dioxide dissolved as a gas in the blood.

factors as length of arrest, arterial or venous blood gases, patient response, and respiratory and ventilatory function in determining the appropriateness of sodium bicarbonate administration. If the decision is made to administer sodium bicarbonate, the initial dose is 1 mEq/kg (1 mL/kg of 8.4% solution) intravenously or via the intraosseous route. (Note: Sodium bicarbonate *cannot* be administered down the endotracheal tube!) Sodium bicarbonate is commercially available in two strengths, 4.2% (0.5 mEq/mL) and 8.4% (1 mEq/mL). The 4.2% concentration, or "infant" bicarbonate, is used in the setting of a neonatal arrest because the 8.4% concentration can result in intracranial hemorrhage, thrombophlebitis and complications associated with the high osmolarity (2,000 mOsm/L) of the solution. For infants and

children weighing more than 5 kg, the 8.4% concentration can be used at doses of 1 mEq/kg (1 mL/kg). Second and subsequent doses of 1 mEq/kg sodium bicarbonate can be administered approximately every 10 minutes in a prolonged arrest.

In addition to its questionable therapeutic efficacy, sodium bicarbonate is associated with several adverse effects, including shifts in the oxyhemoglobin dissociation curve to the left, resulting in a tighter affinity of oxygen for the hemoglobin molecule and ultimately less readily available oxygen for tissue saturation²⁴; acute intracellular potassium shifts secondary to metabolic alkalosis; relative intracerebral acidosis as plasma pH responds more rapidly to the alkalinizing effects of bicarbonate vis-à-vis cerebrospinal fluid pH²⁵; hypernatremia; and hyperosmolality.

Another concern with the use of sodium bicarbonate in the arrest situation is the associated physical and chemical incompatibilities. Calcium salts (eg. gluconate, chloride) will instantly react with bicarbonate to yield an insoluble precipitate which, in addition to generating a potentially dangerous precipitate circulating through the vascular system, diminishes the amount of calcium and bicarbonate ions available for their desired effects. In addition, sodium bicarbonate will chemically inactivate catecholamines (eg. epinephrine) be admixed together into the same IV line. For these reasons, doses of sodium bicarbonate must be followed with a saline flush to clear the IV line before subsequent medication administration.

Calcium Salts. Like sodium bicarbonate, the routine use of calcium salts in the arrest setting has been brought into question in recent years as a result of outcome studies that have showed little or no effect on patient survival.^{22,27} Calcium has historically been thought of as the agent of choice in electromechanical dissociation (EMD), a clinical situation in which the electrical and mechanical harmony usually enjoyed by cardiac tissues becomes disjointed. Well designed studies to assess the efficacy of calcium administration for EMD have failed to show a beneficial effect of calcium. The American Heart Association currently recommends calcium use to be limited to the following clinical settings: hyperkalemia associated with

cardiac arrhythmias (calcium has been shown to protect the heart against the arrhythmogenic effects of elevated serum potassium levels¹); hypocalcemia; hypermagnesemia; calcium channel blocker overdose.

The *chloride* salt of calcium is the preferred salt for these conditions because calcium chloride dissociates most readily in the blood to deliver elemental calcium, the active component. The recommended calcium chloride dose is 20 mg/kg to be infused slowly and repeated approximately every 10 minutes. Calcium chloride is commercially available in a 10% concentration, thus doses of 0.2 mL/kg will deliver 20 mg/kg of the salt and 5.4 mg/kg of elemental calcium.

Arrhythmia Management

Adenosine. Adenosine, a naturally occurring endogenous nucleoside, has profound effects on AV nodal conduction when administered via rapid intravenous push. Adenosine momentarily blocks AV nodal conduction, which interrupts the reentry circuits responsible for aberrant dysrhythmias such as paroxysmal supraventricular tachycardia (PSVT). PSVT-related symptoms of hemodynamic instability such as hypotension or low cardiac output are optimally treated with electrical cardioversion at a dose of 0.5 J/kg. If IV access is available, adenosine may be administered before cardioversion. Adenosine is *rapidly* metabolized by the red blood cell enzyme adenosine deaminase. The half-life of adenosine is estimated to be less than 10 seconds. Effective use of this medication requires a rapid IV push administration (1 to 3 seconds) to ensure that an adequate dose reaches cardiac tissues. The pharmacist can play a crucial role in ensuring that the dose is rapidly administered and followed promptly by a saline flush to propel the dose into the systemic circulation.

Adenosine has been reported to be effective in terminating a variety of arrhythmias, including AV reciprocating tachycardia, AV node reentry tachycardia, and junctional ectopic tachycardia, in addition to PSVT.²⁸⁻³¹ The pediatric dose of adenosine is 0.1 mg/kg administered *rapidly* via IV push, with subsequent doses doubled (0.2 mg/kg) if necessary to achieve a response. Some investigators have reported suc-

cess with smaller doses of adenosine when administered directly into a central line. Maximum single doses of adenosine should not exceed 12 mg. The adverse effects described by patients receiving adenosine include chest tightness, flushing, and bronchospasm; however, these effects are usually very short-lived owing to the short half-life of the drug in serum.

Verapamil. Verapamil, the prototypical calcium channel antagonist, was at one time considered a key agent in the treatment of PSVT in children. The AV nodal blocking effects of verapamil resulted in early clinical successes in the management of atrial and AV node-generated arrhythmias. Currently, the American Heart Association recommends against using verapamil for arrhythmia suppression in infants because of reports of cardiac arrest after its use.^{32,33} Likewise, verapamil use is presently discouraged in any pediatric patient for arrhythmia management because of the potential for myocardial depression and profound hypotension secondary to the negative inotropic effects of the drug,¹ especially when combined with intravenous beta-adrenergic blocking agents (eg, propranolol, metoprolol).

Lidocaine. Intravenous lidocaine is the pharmacological treatment of choice for arrhythmias of ventricular origin. As with PSVT, however, electrical cardioversion should be used first in any patient exhibiting ventricular tachycardia or fibrillation on ECG when IV access and/or lidocaine are unavailable. Lidocaine acts by suppressing the automaticity of conduction tissue, and increasing the fibrillation threshold of the ventricles and His-Purkinje system through decreases in the permeability of sodium ions in neuronal membranes.

Lidocaine therapy is initiated at a loading dose of 1 mg/kg followed by a continuous infusion at a rate of 20 to 50 $\mu\text{g/kg/min}$. Patients receiving lidocaine should be closely monitored for central nervous system (CNS) toxicity, including nervousness, tremor, obtundation, respiratory depression, seizures, and coma. Lidocaine is commercially available in a wide variety of concentrations, including 1% and 2% (used for bolus doses), 4%, 10%, and 20%. These latter strengths are commercially available in "additive syringes" that are equipped with a plastic housing, or "shield," around the

needle and designed to spike the port of a large-volume parenteral solution for infusion. The intent of this design is to discourage the user from administering these high concentrations directly via IV push. Unfortunately, patients have received inadvertent administration of toxic boluses of lidocaine by direct IV push with fatal outcomes. Most, if not all, of these concentrated additive syringes, have been discontinued. The presence of a pharmacist, with their knowledge and familiarity of dosage forms, is instrumental in decreasing the likelihood of a tragic medication error such as this from occurring.

Using Adult Emergency Drug Syringes in the Pediatric Arrest

A major rate-limiting step the pharmacist encounters during a pediatric arrest is the preparation and delivery of patient-specific doses

Unfortunately, patients have received inadvertent administration of toxic boluses of lidocaine by direct IV push with fatal outcomes.

of emergency medication from available dosage forms. Several pharmaceutical companies market "emergency syringe" dosage forms for epinephrine, sodium bicarbonate, lidocaine, and other medications. These packages typically contain two components: a glass container holding a single adult dose of the medication, and a syringe/needle device designed to accept the medication cartridge for unit-dose delivery. An "emergency syringe" should never be used for drug administration during a pediatric arrest unless the patient-specific dose is equal to the full syringe contents.

Although not approved for use in the product labeling, a quick and easy method to draw up pediatric doses from these medication cartridges is described below:

1. Take the medication cartridge (clear glass with fluid inside) and remove the plastic cap (usually colored yellow) from the end.

2. Do not engage the plastic syringe/needle portion of the device to the medication cartridge.
3. Attach a needle to a standard "leur-lok" syringe of the appropriate volume to draw up the dose. Draw back the plunger to the desired volume.
4. Invert the medication cartridge and, using it as a "vial," insert the needle from the leur-lok syringe into the rubber stopper. Slowly displace air into the glass container, being very careful to stop every 2 to 3 mL to allow solution to flow back into the syringe. Continue in this manner until the desired patient-specific dose has been drawn up. (Note: Displacing the entire volume of air from the syringe into the glass container may cause the rubber stopper to pop out, expelling the fluid from the container and wasting some or all of the contents.)

The use of these emergency syringes in the manner described previously is advantageous for several reasons:

1. Intravenous tubing used in an emergency setting often has *only* leur-lok connection sites for bolus fluid and drug administration. Because the syringe/needle device on the emergency cartridges has the needle fused to the plastic syringe, they are incompatible with a leur-lok system.
2. Even if the IV line is equipped with a port to allow for direct needle access, the pharmacist deciding to use an emergency syringe must first squirt out fluid from the syringe so that only the patient-specific dose is left in the syringe. This practice is wasteful and can lead to needle-stick injuries.
3. Using the medication cartridge as a vial allows for easy preparation of an exact *unit-dose* of emergency medication, because subsequent doses can then be drawn from the same *labeled* "vial."

Drug Infusions Used in P.A.L.S.

If asystole is resolved and sinus rhythm is reestablished, inotropic support may be necessary to maintain cardiac output. This is especially true in the setting of shock, in which poor peripheral perfusion may not optimally respond

to aggressive attempts at fluid resuscitation. Catecholamine compounds including epinephrine, dopamine, and the synthetic catecholamine dobutamine are commonly used to maintain cardiac output and blood pressure in pediatric resuscitation. Care must be taken to avoid extravasation of these agents because severe tissue sloughing, ulcer formation, and necrosis of subcutaneous tissue can result. These infusions should only be administered into a patent, well running IV line, with central line infusion preferred.

Epinephrine Infusion. Epinephrine infusion is usually started at a dose of 0.1 $\mu\text{g}/\text{kg}/\text{min}$ and titrated to the desired clinical effect or a maximal dose of 1 $\mu\text{g}/\text{kg}/\text{min}$ and more if necessary to maintain cardiac output. The "Rule of Sixes" is an easily remembered calculation for the preparation of the solution (Table 2). A disadvantage to this method is the quick development of fluid overload when high doses or multiple infusions are required. An alternative calculation is to divide the total microgram dose per hour by a convenient infusion rate to determine the needed concentration in order to correctly prepare the solution. For example, an epinephrine infusion of 0.1 $\mu\text{g}/\text{kg}/\text{min}$ for a 12-kg patient to run at 6 mL/h would be calculated as follows:

$$0.1 \mu\text{g}/\text{kg}/\text{min} \times 12 \text{ kg} \times 60 \text{ min}/\text{h} = 72 \mu\text{g}/\text{h}$$

$$72 \mu\text{g}/\text{h} \text{ divided by } 6 \text{ mL}/\text{h} = 12 \mu\text{g}/\text{mL}$$

$$12 \mu\text{g}/\text{mL} \times 100 \text{ mL of solution}$$

$$= 1,200 \mu\text{g}, \text{ or } 1.2 \text{ mg}$$

$$(1.2 \text{ mL of } 1:1,000 \text{ epinephrine})$$

added to a 100-mL minibag

Table 2. The "Rule of Sixes" in Preparing Emergency Drug Infusions

Drug	Dose Delivered	Preparation
Dobutamine, dopamine	1 mL/h = 1 $\mu\text{g}/\text{kg}/\text{min}$	$6 \times \text{weight (kg)} = \text{mg}$ to be added to 100 mL of solution
Epinephrine	1 mL/h = 0.1 $\mu\text{g}/\text{kg}/\text{min}$	$0.6 \times \text{weight (kg)} = \text{mg}$ to be added to 100 mL of solution

Adapted from JAMA 1992;268:2270. Copyright 1992, American Medical Association.

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Dopamine. It has been said that dopamine is actually "three drugs for the price of one" because of the wide and dramatically different pharmacological response to various doses of the drug. At low doses (1 to 3 $\mu\text{g/kg/min}$), dopamine stimulates primarily the dopaminergic receptors, which results in increased blood flow to renal, splanchnic, mesenteric, and cerebral vascular beds. Clinicians often take advantage of low-dose dopamine infusions to help augment renal blood flow in normotensive, acutely ill patients at risk for renal impairment. At infusion doses of 5 to 10 $\mu\text{g/kg/min}$ (moderate-dose dopamine), effects include stimulation of β -adrenergic receptors in cardiac tissue, resulting in increased heart rate and cardiac output. High-dose dopamine ($> 15 \mu\text{g/kg/min}$) causes systemic vasoconstriction via stimulation of α -adrenergic receptors and subsequent loss

It has been said that dopamine is actually "three drugs for the price of one" because of the wide and dramatically different pharmacological response to various doses of the drug.

of renal and splanchnic vasodilatory effects. This dose is used in the setting of life-threatening hypotension unresponsive to fluid resuscitation. An alternative method³⁴ of preparing dopamine infusions in emergency situations is as follows: (1) prepare a 600-mg/L concentration of dopamine by adding 60 mg dopamine (1.5 mL of a 40 mg/mL concentration) to a 100-mL minibag of IV solution; (2) infuse this solution at a rate of (patient weight) mL/h to deliver a dose of 10 $\mu\text{g/kg/min}$ (eg, a 15-kg patient receiving 600 mg/L of dopamine at 15 mL/h would be receiving 10 $\mu\text{g/kg/min}$, a 28-kg patient receiving 600 mg/L of dopamine at 28 mL/h would be receiving 10 $\mu\text{g/kg/min}$).

Dobutamine. Dobutamine is a synthetic catecholamine analog of dopamine with relatively selective action on the β -adrenergic receptors in cardiac tissue, resulting in increased heart rate,

myocardial contractility, and cardiac output. Dobutamine is clinically used in cases in which inotropic support is needed for a patient with stable or slightly low systemic blood pressure. Dobutamine has little, if any, action on α -adrenergic receptors and thus does not possess the vasoconstrictive effects of epinephrine and high-dose dopamine. Dobutamine infusions can likewise be calculated to deliver 10 $\mu\text{g/kg/min}$ as described previously for dopamine by preparing a 600-mg/L concentration and infusing the admixture at an hourly rate equal to the patient's weight in kilograms. (Note: Dobutamine is commercially available at a concentration of 12.5 mg/mL, thus 4.8 mL of dobutamine is added to a 100-mL minibag to deliver a 600-mg/L concentration.)

PRACTICING FOR AN ARREST: THE 'MOCK CODE' PROGRAM

Even the most experienced and dedicated pediatric health care professionals assist in cardiac resuscitation on a sporadic basis at best. Consequently, the development of a multidisciplinary, hands-on, role-playing model ("mock" code) is important in maintaining the skill level necessary to provide optimal delivery of care in the actual pediatric arrest situation. The program at The Children's Memorial Hospital in Chicago has been in place for more than 10 years and includes members of the pediatric house staff, nursing, pharmacy, anesthesia and respiratory care.

Mock codes are scheduled to coincide with each nursing unit's annual mandatory yearly review process, providing all shifts of each nursing unit the opportunity to review skills necessary for resuscitation annually. Preparation, including delineation of specific responsibilities, begins about 4 weeks before the mock code. The program is designed as a training tool primarily for resident physicians and nursing staff, although pharmacy students and newly hired pharmacists are also involved routinely as a means of gaining experience in this area of clinical practice. The role of the pharmacist in this model is to act as an evaluator of both the nurses and the resident staff. Approximately 1 week before the scheduled mock code, a code situation, or "scenario" is developed and distributed to the nursing staff of the unit being

evaluated. The pediatric medical residents scheduled to attend are not given the opportunity to review the scenario before the event. The mock code site is set up using a plastic resuscitation training doll (Resusci-Annie[®], Laerdal Medical Corp., Armonk, NY) placed on a bed or hospital gurney in an examination room on the nursing unit. A "mock code" emergency crash cart is available for use at the exercise that is stocked with expired emergency medications, IV fluids, and other supplies typically found in the actual emergency carts. The room includes a medical resident, pharmacist, ICU nurse, and respiratory therapist who act as evaluators of those involved in the "arrest." A nurse then arrives on the scene and begins to role-play the situation based on the scenario. The rest of the team gradually arrives over the next few minutes, with various residents taking the role of code leader, anesthesiologist, or supporting phy-

tain off-hours (ie, midnight shift) sometimes preclude their involvement in the initial stages of a cardiac arrest.

The role of the pharmacist as an evaluator includes the following activities: monitoring the appropriateness of the pharmacotherapy of the mock arrest (correct doses, concentrations of medications asked for at the correct intervals, proper routes of administration being utilized, adequate flushing of IV lines between medication administration, identification of drug incompatibilities and interactions commonly associated with emergency medications, etc); assessing the degree of communication at the arrest; and providing follow-up by way of discussion with the attendees of the mock code following conclusion.

After the mock code, a multidisciplinary discussion takes place, focusing on both positive and negative aspects of the code. The medical resident and nurse evaluators comment on aspects of basic life-support, correctness in using monitoring equipment, and pharmacotherapy. The pharmacist evaluator further elucidates on drug therapy, including the resident's ability to order the correct doses in proper sequence, the ability of the nurses to correctly prepare the medications and fluids, and relative level of communication during the role-play. Although participants are not "graded" in their overall performance during the mock code, deficiencies and commendations are noted on an evaluation sheet that is then used to reinforce proper techniques after the exercise. This program has met with a positive response because both the nurses and residents think it helps them to be prepared for actual emergency situations as they arise.

Although this model uses the pharmacist primarily as mentor, other programs provide opportunities for pharmacists to review their skill level in a mock arrest format. Where no such formalized program exists, pharmacy departments should at the very least offer some type of yearly mandatory review of this topic as a means to review and refresh these necessary skills among their staffs. The development of a program similar to that described in this section would serve as a sterling example of a multidisciplinary project designed to improve quality of

The role of the pharmacist in this model is to act as an evaluator of both the nurses and the resident staff.

sicians. Nursing staff in this model is responsible for drawing up and administering all medication orders including boluses, intravenous fluids, and inotropic drips. Although pharmacists are responsible for medication delivery in actual arrest situations at The Children's Memorial Hospital, nursing staff assumes this role in the mock code program. The reason is twofold: First, a nurse is invariably the person most likely to find an unresponsive patient in a hospitalized setting. As several minutes may elapse between calling the code and the arrival of the entire code team, situations may arise in which ACLS is initiated before the arrival of the pharmacist. For this reason, the mock code committee thought that nurses needed to have a basic appreciation for and understanding of proper techniques in calculating and preparing pediatric emergency drug doses from the crash cart. Second, reduced pharmacist staffing during cer-

patient care, a major focus of present Joint Commission on Accreditation of Healthcare Organization (JCAHO) standards.

CONCLUSION

The ultimate role of the pharmacist in the pediatric arrest continues to be defined. Traditionally, the pharmacist's role as member of the code team has included responsibilities such as calculating drug doses, double-checking the accuracy of ordered doses, drawing up medications, providing information related to drug interactions and incompatibilities, preparing emergency drips, and ensuring that the proper route of administration and administration techniques are used. In addition to the universally accepted role as dispenser of medication, the pharmacist as provider of pharmaceutical care

in a cardiopulmonary arrest must position him or herself to be the pharmacotherapeutic specialist. This responsibility can range from the aforementioned functions all the way to being the code leader. Developing the knowledge base to efficiently and expertly respond when a young life hangs in the balance is no small commitment. The satisfaction one experiences in being partially responsible for saving that life is perhaps like no other. For this reason, the commitment is more than worth the effort.

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Clinical and laboratory observations

A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children

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Disturbances of ionized calcium levels have been reported in sick neonates,¹ and we have found a high rate of occurrence of ionized hypocalcemia,² which was associated with a significantly increased mortality rate in critically ill non-neonatal pediatric patients. Calcium chloride and calcium gluconate are two of the standard salt preparations that are used to correct hypocalcemia; the former is usually preferred because it is in the ionized form and therefore provides more readily available ionized calcium for use.

In this study, critically ill pediatric patients with ionized hypocalcemia received either calcium chloride or calcium gluconate in a randomized manner. The purposes of this study were (1) to determine whether calcium chloride and calcium gluconate provide equal bioavailability of ionized calcium and (2) to assess whether there were any differences in physiologic effects after administration of the two salts.

METHODS

Patient selection. All patients admitted to the Le Bonheur Children's Medical Center intensive care unit were eligible for participation in this study if they were found to have hypocalcemia. Patients were enrolled in the study after informed consent was obtained in compliance with the investigational review boards of the University of Tennessee and LBCMC. Exclusion criteria were (1) calcium administration before arrival in the ICU and (2) no documentation of

ionized calcium level after calcium therapy. Therapeutic decisions were determined by the attending physicians, independent of patient involvement in this study.

Protocol. Patients were randomly assigned to receive either calcium chloride or calcium gluconate through central venous catheters. Randomization was performed by our medical center's Pharmacotherapeutic Center of Excellence. Dosages were calculated as milliequivalents of elemental calcium and were given in milliequivalents per kilogram per dose; all patients received 0.136 mEq/kg per dose. All physician and nurse caretakers were unaware of the

HR	Heart rate
ICU	Intensive care unit
LBCMC	Le Bonheur Children's Medical Center
MAP	Mean arterial blood pressure

agent being administered. Administration of calcium salts was repeated as clinically indicated but was not included as a new data set. Ionized calcium levels were obtained before and 30 minutes after administration of the calcium salt. Arterial pH values were obtained simultaneously. Heart rate and mean arterial blood pressure were monitored before, during, and after calcium therapy.

In addition to ionized calcium and arterial pH levels, measurements of renal function, hepatic function, and serum electrolyte values were also obtained on admission or within 12 hours after initial ionized calcium measurements. Clinical data, including but not limited to medical history and medications, were recorded on admission, and clinical course was evaluated. Outcome and any significant morbidity were also noted.

Blood sampling and analysis. Venous or arterial blood

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Table I. Diagnosed disease processes of patients assigned randomly to received either calcium chloride or calcium gluconate therapy

Diagnosis*	Chloride	Gluconate
Neurologic	4	5
Pulmonary	3	4
Cardiovascular	7	4
Gastrointestinal	3	3
Infectious	6	6
Genetic/metabolic	1	1
Renal	1	3

*Patients may have had one or more disease processes. There were no differences in the types of disease processes present in the two study groups ($p > 0.05$).

samples were obtained by puncture or from indwelling lines for determination of ionized calcium levels³ and arterial pH⁴ with the use of ion-specific electrodes. Blood for ionized calcium levels was obtained, placed in heparinized containers (Radiometer A/S, Copenhagen, Denmark) on ice water, and evaluated immediately. All samples were analyzed on the Radiometer ICA 1E Ionized Calcium Analyzer within 5 minutes of time of collection.

All laboratory tests were performed at the LBCMC diagnostic laboratory, where two levels of control samples were assayed at 8-hour intervals each day. Normal reference ranges for all chemistry tests as described by Meites⁵ are $\pm 2SD$ and are adjusted for age. Hypocalcemia was defined as any value less than the normal range. Data are listed by the present reference system used in our laboratory with SI units in parentheses.

Severity of illness. A nursing intervention-based scoring system that yields an acuity rating has been developed in our institution and is used to measure severity of illness. This acuity rating has been shown to correlate with outcome (unpublished data). An acuity rating is assigned to all patients on admission to the LBCMC ICU and repeated during each subsequent 8-hour period by the responsible nursing caretaker. The acuity rating at the time of the initial blood sampling was used for this study.

Statistical analysis. The two treatment groups were compared for all pretreatment variables and for the magnitude of ionized calcium change with the use of an unpaired, two-tailed student *t* test. The age and the acuity ratings for both treatment groups were compared with the use of an unpaired, two-tailed student *t* test. A paired, two-tailed student *t* test was used to compare pretreatment and post-treatment values for HR, pH, MAP, and ionized calcium. All data are reported as means $\pm$ SD.

RESULTS

Clinical correlation. Forty-nine critically ill pediatric patients were eligible for participation and entered into this

protocol on admission to the ICU. Subsequently 12 patients were excluded from final analysis on the basis of one of the exclusion criteria. Thirty-seven patients were thus enrolled in the study and were randomly assigned to one of two treatment groups, calcium chloride or calcium gluconate. Twenty patients received calcium gluconate therapy; 17 received calcium chloride.

The ages of the children studied ranged from 1 day to 17 years. The mean age of patients was 3.7 ± 5.0 years in the chloride treatment group and 3.0 ± 4.7 years in the gluconate treatment group ($p > 0.05$). This study group comprised 20 boys and 17 girls, with no difference in the gender proportion in the two groups. Similar numbers of patients with neurologic, pulmonary, cardiovascular, infectious, and gastrointestinal diseases were seen in both groups (Table I). The acuity rating denoting severity of illness was 15.5 ± 3.7 in the chloride treatment group and 13.2 ± 3.4 in the gluconate treatment group ($p = 0.06$).

Pretreatment values. There were no differences in the two groups before treatment in HR, MAP, arterial pH, and ionized calcium level ($p > 0.05$) (Table II).

Posttreatment values. There was no significant change in the mean pH or in HR after treatment with either salt ($p > 0.05$) (Table II).

Ionized calcium (Table II). Treatment with one dose of either salt produced a significant increase in the mean serum ionized calcium level compared with the pretreatment level ($p < 0.05$). The mean increase in ionized calcium levels was 0.19 mmol/L for the chloride group and 0.09 mmol/L for the gluconate group ($p < 0.05$). After one dose, ionized calcium levels increased in all patients who received calcium chloride; however, of the patients who received calcium gluconate, two patients had no change in ionized calcium levels and five had posttreatment levels that were less than pretreatment levels.

Blood pressure. The group receiving calcium chloride had an increase in MAP of nearly 6 mm Hg ($p < 0.05$) (Table II). No change in blood pressure was seen in the group receiving calcium gluconate.

Mortality. Of the 17 patients (82%) receiving calcium chloride, 14 ultimately survived, and 15 (75%) of 20 receiving calcium gluconate survived. This difference was not statistically significant.

Patients were also monitored after repeated doses of calcium salts, and the effects of calcium administration on the final ionized calcium levels were determined. All patients eventually achieved normal serum ionized calcium levels with either therapeutic agent.

DISCUSSION

Our results demonstrated that both calcium salts produce a significant increase in ionized calcium levels but that calcium chloride appears to have greater bioavailability. Patients receiving calcium chloride had a greater increase

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Table II. Effects of administration of calcium salts

Measurement	Calcium chloride		Calcium gluconate	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment
HR (beats/min)	140 ± 34	135 ± 28	132 ± 32	130 ± 31
MAP (mm Hg)	66 ± 22	71.5 ± 20*	63 ± 17	64 ± 18
Arterial pH (U)	7.43 ± 0.11	7.41 ± 0.08	7.42 ± 0.09	7.40 ± 0.09
Ca ⁺⁺ (mmol/L)	1.03 ± 0.14	1.22 ± 0.12*	1.07 ± 0.12	1.16 ± 0.09*
ΔCa ⁺⁺ (mmol/L)		0.19		0.09*

Ca⁺⁺, ionized calcium.*Statistical significance at $p < 0.05$.

in the serum ionized calcium levels, and the effects of calcium gluconate on ionized calcium were much less predictable in these patients.

These data are in contrast to those of a previous report by Côté et al.,⁶ which demonstrated equal bioavailability of calcium gluconate and calcium chloride in children who were recovering from thermal burns. Our study differs from theirs in two respects. First, all our patients were critically ill and had ionized hypocalcemia; in contrast, the patients studied by Côté et al. were in the recovery phase of burns and in a stable clinical condition, and all had normal ionized calcium levels before going to the operating suite for burn débridement. Second, in our study, calcium chloride produced a greater rise in the ionized calcium concentration than calcium gluconate did when both groups of patients were given an equal amount of calcium (measured in milliequivalents per kilogram), in contrast to the Côté study, in which both calcium salts produced an equal rise in ionized calcium levels.

Previous studies have assessed the efficacy of calcium chloride, gluconate, and gluceptate in adults⁷ or have compared calcium chloride and gluceptate⁸ and have noted equal bioavailability. Calcium gluconate therapy has been shown to elevate calcium levels adequately in symptom-free newborn infants^{9,10} with ionized hypocalcemia and to be adequate for maintenance therapy in pediatric patients with mild hypocalcemia. No previous studies have compared the efficacy of calcium chloride and calcium gluconate in the treatment of critically ill children.

Some authors have postulated that calcium gluconate must be metabolized by the liver to become ionized and to be utilized by the body, and have recommended that calcium gluconate not be given to patients with hepatic impairment. Heining et al.¹¹ reported that equimolar quantities of calcium chloride and calcium gluconate produced similar elevations in plasma ionized calcium levels in anesthetized ferrets and when added to human blood in vitro. In our study, only one of the seven patients with no improvement in the ionized calcium level had liver disease. The re-

maining patients who had a decrease or no change in their ionized calcium levels with calcium gluconate therapy had diseases with low flow states. The disease processes in the patients treated with calcium gluconate were similar to those in the patients in the calcium chloride group who had a significant elevation of their ionized calcium levels in response to therapy. These data are in contrast to the results of Drop and Laver,¹² who demonstrated that ionized hypocalcemia in critically ill adult patients with low flow states was not corrected with the administration of calcium chloride.

Perhaps of even greater clinical relevance than the actual increases in ionized calcium levels is the difference between the two treatments in their effects on MAP. Our results are consistent with reports by other authors^{10,13} of increases in MAP concomitant with the correction of ionized hypocalcemia. Others have reported no changes in blood pressure with the administration of calcium⁶ or no differences in the changes in blood pressure based on which calcium salt was used.⁸ Our study demonstrated changes in blood pressure with calcium chloride administration but not with calcium gluconate.

Several recent studies^{2,14,15} have demonstrated a frequent occurrence of ionized hypocalcemia in critically ill pediatric patients. In our previous study,² children with ionized hypocalcemia had a higher mortality rate than others. Perhaps both the mortality rate and the presence of hypocalcemia reflect the "sicker child" and the seriousness of the patient's condition rather than cause and effect. Although no direct effect of calcium administration on the mortality rate has been demonstrated in this study, we were able to demonstrate an improvement in MAP after administration of the chloride salt. Others^{1,10} have demonstrated improved myocardial contractility in critically ill patients. These previous reports and our recent data demonstrating an increase in MAP with calcium chloride therapy suggest that there may be a decrease in morbidity in those patients who receive calcium chloride therapy.

We conclude that calcium chloride produces a greater

increase in serum ionized calcium concentration than does calcium gluconate when administered to critically ill children. Furthermore, calcium chloride administration produced significant improvement in MAP in these patients, whereas calcium gluconate did not. These data support the supposition that calcium chloride may be the preferred agent in the treatment of hypocalcemia in critically ill children.

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Omeprazole treatment of severe peptic disease associated with antral G cell hyperfunction and hyperpepsinogenemia I in an infant

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Peptic ulcer disease is no longer a rare diagnosis in infants and children. Ethnic, genetic, and environmental factors contribute to its pathophysiologic and clinical heterogeneity.¹ Increased levels of serum gastrin or pepsinogen I or both, coupled with acid hypersecretion, have occasionally been reported in children with peptic ulcer.¹ Hypergas-

trinemia in patients with peptic ulcer disease may arise from a gastrinoma (Zollinger-Ellison syndrome) or from antral gastrin cell hyperfunction with or without hyperplasia (also called pseudo-Zollinger-Ellison syndrome).² The response

ECL cell	Enterochromaffin-like cell
G-cell	Gastrin cell

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of serum gastrin to a meal and the histologic quantification of G cells are helpful in differentiating these hypergastrinemic syndromes.² Antral G cell hyperplasia has been described in a 7-year-old child in association with mild peptic

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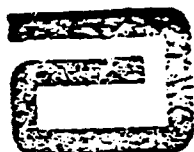
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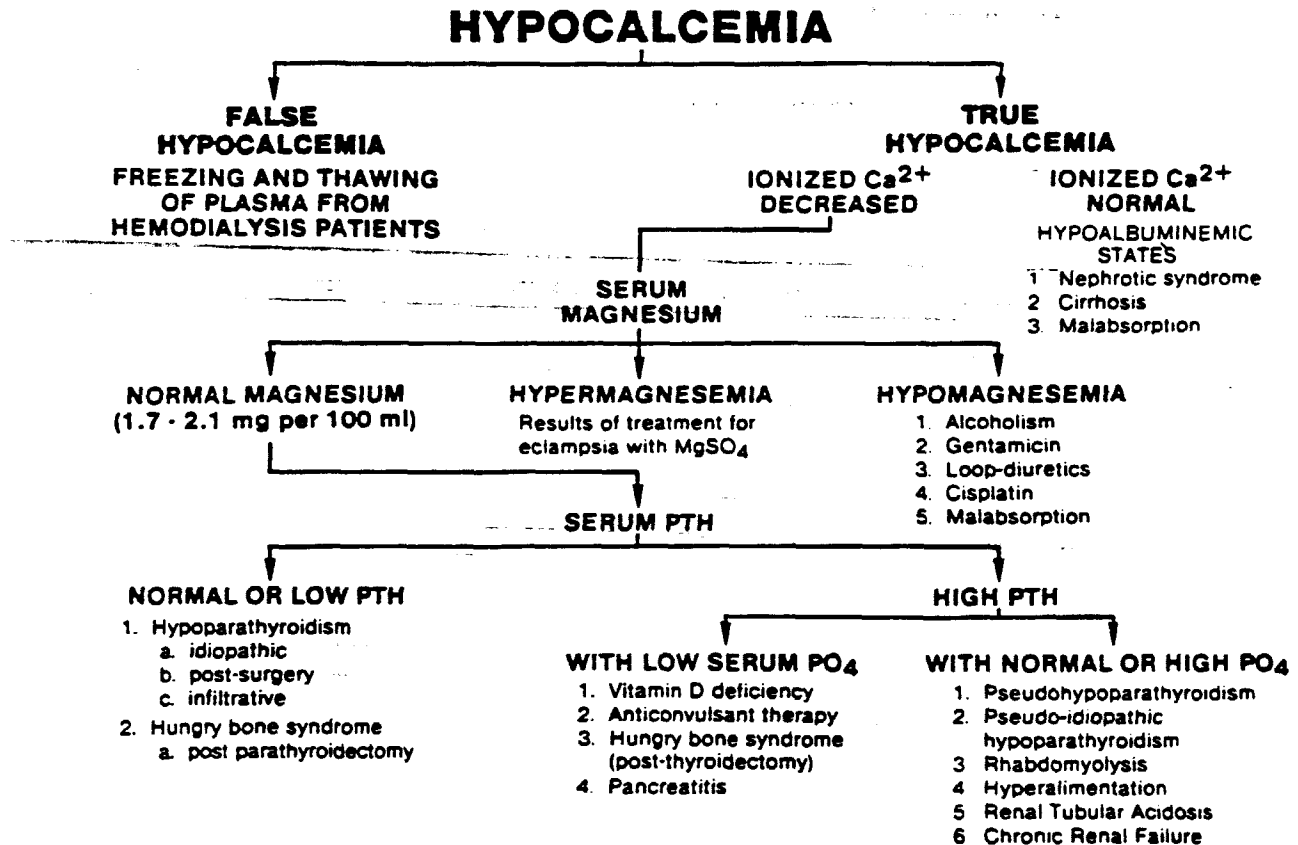


FIGURE 32-4 • Diagnostic steps in the evaluation of hypocalcemia.

calcemia is transient; it has occurred in approximately 17 percent of patients in one series who underwent thyroid surgery.³⁰⁹ It has been proposed that the hypocalcemia may result when Ca^{2+} is deposited in bone to compensate for preexisting thyrotoxic osteopenia. Intraoperative release of calcitonin has been proposed as another possible mechanism for hypocalcemia that complicates thyroid surgery.⁴⁹¹ In a recent report Watson et al. found a close correlation between the decrements in serum $[\text{Ca}^{2+}]$ and the increase in plasma calcitonin;⁴⁸⁵ no significant changes in the levels of PTH were observed, suggesting that calcitonin released during surgery accounts for the initial fall in serum $[\text{Ca}^{2+}]$. In addition, it was suggested that interference with normal parathyroid function as a result of trauma to the glands does not allow PTH to increase and that this also contributes to low serum $[\text{Ca}^{2+}]$.⁴⁸⁵ Once calcitonin levels fall serum $[\text{Ca}^{2+}]$ values return to normal.⁴⁸⁵ Permanent postsurgical hypoparathyroidism occurs in only a small percentage of cases: the incidence in recent series approximated 3 percent.^{179,188} The frequency of this complication depends on variables such as the experience and technical prowess of the surgeon. Extensive neck surgery is also likely to be associated with a high incidence of permanent hypoparathyroidism.³²⁹

A less frequent cause of hypoparathyroidism is *metastasis* to the parathyroids. While the incidence of para-

thyroid involvement in widespread metastatic disease can be as high as 5 to 12 percent, hypocalcemia is uncommon.²¹⁰ Iron deposition in the parathyroid glands due to *hemochromatosis* can also lead to hypoparathyroidism. It has been speculated that *Wilson's disease* may be associated with hypoparathyroidism in a similar way, by leading to deposition of copper in the parathyroid glands.⁶⁹

Hypomagnesemia

Magnesium depletion and hypomagnesemia (<1 mg/dl) may produce hypocalcemia by several mechanisms. In normal subjects, an acute change in serum magnesium concentration will alter PTH secretion: hypomagnesemia stimulates while hypermagnesemia inhibits secretion of the hormone. During chronic and severe magnesium deficiency, however, PTH secretion is impaired.^{11,12,126} In a study by Rude et al., patients with hypomagnesemia and hypocalcemia were found to have low, normal, or even high serum PTH levels.³⁸⁷ Nevertheless, magnesium replacement provoked increases in serum PTH regardless of the baseline values of the hormone. In hypomagnesemic patients with chronic renal disease, and high PTH, magnesium administration has also been shown to stimulate PTH secretion.³⁰² These findings indicate that normal or even high PTH values may be inadequate to maintain a normal serum Ca^{2+} in magnesium-depleted subjects.

Skeletal resistance to PTH can also contribute to the development of hypocalcemia in hypomagnesemic states. In a study by Frietag and coworkers using isolated bone perfusion, the uptake of PTH and the formation of cAMP were found to be significantly diminished in perfused bones from hypomagnesemic animals.¹⁵⁵ Correction of hypocalcemia without affecting serum PTH has been described in some patients with renal failure, hypocalcemia, hypomagnesemia, and high PTH who were given magnesium.²⁶⁴ In some patients with renal insufficiency, therefore, resistance to PTH action may be the result of hypomagnesemia.

Impaired release of PTH and skeletal resistance to the hormone can be assumed to contribute to hypocalcemia in hypomagnesemic conditions. Since Mg^{2+} is an important cofactor for the activation of adenylate cyclase it is possible that severe deficiency may lead to impaired function of the adenylate cyclase-related receptor²¹⁹ and account, in part, for the observed derangement in PTH release and for the skeletal resistance during hypomagnesemia. Bellorín-Font and coworkers have provided support for this inference: substitution of Mg^{2+} by Mn^{2+} leads to a progressive decline in the ability of PTH to stimulate adenylate cyclase activity in isolated kidney cortical membranes.³⁰

Another mechanism proposed to explain the hypocalcemia of magnesium depletion is that skeletal exchange of Ca^{2+} and Mg^{2+} is reduced, thereby leading to decreased Ca^{2+} resorption from bone. This hypothesis is based on the finding that induction of hypomagnesemia in parathyroidectomized animals leads to a further decrease in serum Ca^{2+} .¹⁸⁰ Direct experimental evidence for this mechanism is not available.

Patients with hypocalcemia due to magnesium deficiency are resistant not only to PTH but also to parenteral calcium and vitamin D therapy. The resistance to vitamin D is probably the result of impaired metabolism since plasma levels of $1,25(OH)_2D_3$ are low.³⁸⁸

Excess plasma magnesium may also influence parathyroid function. Experimental²⁹³ and clinical¹¹⁴ evidence suggests that hypermagnesemia can decrease PTH release and cause hypocalcemia.

Gentamicin

Hypocalcemia produced by gentamicin results from the hypermagnesuria which leads to hypomagnesemia and subsequently to hypocalcemia.¹⁹ Replacement of serum magnesium corrects the hypocalcemia.

Pancreatitis

Hypocalcemia is a common complication of acute pancreatitis; it occurs in 40 to 75 percent of patients with acute pancreatitis.^{86,183} Several factors have been identified that can contribute to the decrease in serum $[Ca^{2+}]$ levels. The findings of Ca^{2+} deposition in areas of fat necrosis in the pancreas initially led to the proposal that

the formation of calcium-soaps was the main cause of the hypocalcemia in pancreatitis.^{343,374} It is now clear that diminished secretion of PTH also contributes to the hypocalcemia. Studies of patients with hypocalcemia and pancreatitis have reported inappropriately low levels of PTH^{63,216,294,299,374} for the degree of hypocalcemia. Moreover, hypocalcemia can be corrected by the administration of exogenous PTH. Others have reported undetectable plasma PTH levels due to either parathyroid gland exhaustion or destruction of PTH by proteolytic enzymes.⁸⁶ Results of some studies suggest that increased glucagon secretion³⁴³ and hypercalcitoninemia⁶³ may be contributors to the development of hypocalcemia in some patients with pancreatitis. However, elevated levels of these hormones have not consistently been found.⁴⁸⁷ Other factors that have been proposed to contribute to the hypocalcemia in pancreatitis include hypomagnesemia,¹⁸³ hypoalbuminemia,²¹⁶ acute renal failure,^{183,294,418} and an as yet unidentified defect of bone metabolism.⁴⁸⁷

Neonatal hypocalcemia

Neonatal hypocalcemia occurs during the first 72 h of life. It is most commonly seen in premature newborns, those born to insulin-dependent diabetic mothers, and infants with asphyxia at birth.^{462,464-466} Functional immaturity of the parathyroid glands has often been considered among the pathogenetic mechanisms for the hypocalcemia.^{425,462,463} Occasionally, hypercalcemia (from any cause) during pregnancy can suppress fetal parathyroid gland secretion and produce transient hypocalcemia in the newborn.⁹⁹

Hypocalcemia occurring later than the first three days of life can be caused by feeding milk containing a low calcium:phosphorus ratio. A low GFR per body surface area in the newborn combined with high tubular phosphate reabsorption causes hyperphosphatemia; that in turn leads to hypocalcemia. Low serum calcium level can persist until the parathyroid glands function well enough to respond.

Other factors that have been identified as contributing to the hypocalcemia of the newborn are hypomagnesemia,^{97,467,469} high calcitonin level,⁶⁴ and vitamin D deficiency.²⁰²

Decreased vitamin D activity

Pseudohypoparathyroidism

Albright et al. reported in 1942 the first three cases of pseudohypoparathyroidism (PHP).⁷ Many of the patients with the syndrome exhibited characteristic features including round face, short stature, and obesity. Bone abnormalities are common; they include exostosis and shortening of the metacarpals, metatarsals, and phalanges, particularly of the fourth digit. These somatic features, sometimes called Albright's hereditary osteo-

dystrophy (AHO), are present in most patients with PHP but are not essential to its diagnosis.⁴⁸ Hypocalcemia, hyperphosphatemia, and high circulating levels of PTH are present in patients with PHP. Administration of exogenous PTH does not correct the calcium and phosphate abnormalities; the disorder has been postulated to result from resistance to the actions of PTH.⁷

Since Albright's original description, it has become clear that there are several varieties of PHP.¹⁰⁹ Patients with PHP type I have markedly blunted nephrogenous cAMP responses to exogenous PTH, suggesting that the plasma-bound adenylyl cyclase complex of renal tubule cells is abnormal. The defect, however, does not seem to be specific for PTH. Some patients with PHP type I display resistance to multiple hormones that activate adenylyl cyclase, and express other abnormalities such as hypothyroidism, hypogonadism, mental retardation, impaired olfaction,^{131,270} and Albright's hereditary osteodystrophy (see above).

Studies by different investigators have given support to this hypothesis.¹³⁰ Drezner and Burch¹¹² demonstrated that plasma membranes obtained from cells from the renal cortex of a patient with PHP had an abnormal guanine-nucleotide-binding regulatory protein (G protein) in the adenylyl cyclase receptor that rendered the receptor refractory to hormone stimulation. These findings have been corroborated by other investigators^{42,107,129,269} using different sources of adenylyl cyclase. This disorder is now known as PHP type 1a. Patients in this group demonstrate an approximately 50 percent reduction in G_s activity in plasma membranes from multiple cell types, whereas their membrane levels of G_s are normal.¹⁰⁸ Recent studies have suggested that in some patients a mutation in the gene encoding the stimulatory G protein of adenylyl cyclase is responsible for AHO.³⁴⁸

Some patients, however, have been found to have normal G_s protein activity (PHP type 1b). The cause for the metabolic resistance to the effects of PTH in this group has not been defined. Only a few patients with PHP type 1b manifest the bone abnormalities that are common with PHP type 1a.

A third group of PHP patients has been reported. These individuals respond to exogenous PTH with an increase in urinary cAMP but without phosphaturia.¹⁰⁹ In this group with PHP type 2, a defect distal to the site of formation of cAMP has been postulated. The adenylyl cyclase receptor has the normal capability to increase urinary cAMP. Thus, the nature of this defect is unknown.

The information on PHP that has accrued so far is consistent with a disorder of heterogenous pathogenesis and clinical manifestations that exhibits hypocalcemia and hyperphosphatemia with high circulating PTH levels.

Serum 25-OH- D_3 has been found to be normal in patients with PHP. Nevertheless, the combined effects of resistance to PTH and hyperphosphatemia in PHP

can lead to suppression of 1 α -hydroxylase activity producing 1 α ,25-(OH) $_2D_3$ deficiency and hypocalcemia.^{110,246,252,305}

A rare disorder that resembles PHP has been described in several patients.³³⁵ Subjects affected with this condition have normal to high levels of immunoreactive PTH but respond to exogenous PTH by increasing urinary phosphate and cAMP excretion. The condition is known as pseudo-idiopathic hypoparathyroidism. It is believed to represent formation of defective PTH molecules by the parathyroid glands.

Hyperphosphatemia

Exogenous administration of phosphate can cause hyperphosphatemia and hypocalcemia. This situation commonly develops during hyperalimentation or the treatment of hypercalcemia with oral or IV phosphate. Hyperphosphatemia can also occur as a result of diminished phosphate excretion (e.g., in acute renal failure from rhabdomyolysis and chronic renal failure) or increased endogenous release (e.g., during treatment of certain lymphomas and leukemias of lymphocytic cells).⁴⁶⁸ Hyperphosphatemia can cause hypocalcemia by inhibiting 1 α -hydroxylase, which results in diminished 1 α ,25-(OH) $_2D_3$ formation.¹⁹⁰ Inhibition of bone resorption^{364,365} and precipitation of calcium phosphate complexes in soft tissues⁶⁵ also occurs.

In patients with or without hyperphosphatemia who are on hemodialysis, refrigeration or freezing of plasma, and refrigeration but not freezing of serums cause a fall in calcium concentration; the calcium loss is abolished if the samples are diluted with a lanthanum solution prior to storage. The mechanism underlying this *false hypocalcemia* is not known. It does not occur in uremic patients who are not on dialysis.⁸¹

Vitamin D_3 deficiency states

The principal sources of cholecalciferol (vitamin D_3) are the conversion in the skin of 7-hydroxycholesterol to cholecalciferol and from exogenous nutrients. Nutritional deficiency of vitamin D has been largely eliminated by supplementation of dairy products with vitamin D; nevertheless, it can occur in breast-fed infants or in malnourished elderly patients. The minimum daily requirements for vitamin D_3 for children and adults is 2.5 μ g (100 IU). The recommended daily dietary allowance is 10 μ g (400 IU).

Factors predisposing to nutritional vitamin D_3 deficiency include rapid growth, premature birth, inadequate light exposure, malabsorption, intestinal surgery, and hepatobiliary disease.

Hypocalcemia can also occur in hereditary deficiency of 1 α -hydroxylase (vitamin D-dependent rickets). This disease is a rare autosomal recessive disorder³⁶⁸ in which levels of 1 α ,25-(OH) $_2D_3$ are very low or undetectable. In contrast to vitamin D-resistant rickets, patients do re-

spond to exogenous vitamin D₃. Brooks and coworkers have described a single patient with vitamin D-dependent rickets and increased serum 1 α ,25-(OH)₂D₃.⁵¹ The patient responded to exogenous vitamin D₃. The authors have suggested therefore that diminished target cell responsiveness to endogenous vitamin D₃ metabolites may have caused the hypocalcemia.⁵¹

A disorder resembling vitamin D-dependent rickets but in which circulating levels of 1 α ,25-(OH)₂D₃ are normal represents resistance to the actions of the vitamin D₃ metabolite. This is vitamin D-resistant rickets;³⁶⁸ it is an inherited X-linked condition. Treatment of this condition requires combined use of phosphate and calcitriol.^{169,368}

Malabsorption syndromes

Most vitamin D is absorbed in the proximal small intestine. Bile salts play an important role in the absorption of fat-soluble vitamins such as vitamin D. Thus, intestinal absorptive disorders are likely to produce hypocalcemia by decreasing the absorption of vitamin D, bile salts, and calcium. Other factors that can contribute to hypocalcemia in malabsorption syndromes include hypoproteinemia, hypomagnesemia, and the use of drugs that can interfere with Ca²⁺ metabolism (e.g., corticosteroids, cimetidine).

Partial gastrectomy with gastrojejunostomy is among the common causes of vitamin D deficiency in gastrointestinal disease.⁴¹⁵ Hypocalcemia has been found in approximately 7 percent of such patients.³⁰³ Malabsorption of vitamin D can occur as a result of rapid gastric emptying because of duodenal bypass, bacterial overgrowth, or avoidance of fatty foods.³⁰³

Malabsorption of vitamin D with hypocalcemia can also occur in Crohn's disease, treatment of obesity with jejunoileal bypass, nontropical sprue, pancreatic insufficiency, and hepatobiliary disease.³⁰³

When chronic diarrhea and hyperchloremic metabolic acidosis accompany the hypocalcemia of a malabsorptive state, rapid correction of the acidosis may precipitate tetany; alkalization increases binding of protein to Ca²⁺. Hypomagnesemia, which is prominent in malabsorption, causes resistance of serum calcium level to augmentation by PTH. Hypomagnesemia should thus be corrected prior to or concurrently with correction of acidosis.

Renal tubular acidosis

Classical distal tubular acidosis can cause hypocalcemia, hypophosphatemia, and metabolic bone disease (see Chap. 27). Proximal renal tubular acidosis (RTA) can result in bone disease if the renal wastage of phosphate is severe enough to lead to hypophosphatemia. In distal RTA resulting hydrogen ion retention, hypobicarbo-

natemia, and acidemia increase bone resorption. As a consequence, serum [Ca²⁺] increases and PTH level decreases, leading to hypercalciuria.²⁶⁶ The hypercalciuria is a consequence, in addition to increased Ca²⁺ mobilization from bone,²⁶⁵ of increased filtered load and decreased renal tubular reabsorption.⁴⁴¹ Metabolic acidosis also decreases the activity of 1 α -hydroxylase in the kidney and decreases the production of 1 α ,25-(OH)₂D₃.⁴⁹³ The combined effects of decreased intestinal Ca²⁺ absorption due to low 1 α ,25-(OH)₂D₃ and increased urinary Ca²⁺ excretion eventually lead to hypocalcemia. Replacement of 1 α ,25-(OH)₂D₃ and correction of the metabolic acidosis can correct the Ca²⁺ disorder.

Acute and chronic alcoholism

Alcohol abuse can cause hypocalcemia by several mechanisms. Peng et al. demonstrated that the oral administration of alcohol to dogs and rats is followed within minutes by hypocalcemia.³⁵¹ The hypocalcemia occurred even after removal of the thyroid and parathyroid glands, suggesting that Ca²⁺ is incorporated into bone or soft tissue; the calcium uptake is independent of changes in PTH or calcitonin.

The acute effects of alcohol on calcium and parathyroid hormone were recently studied in normal men and women.^{251a} Ingestion of 1.2 to 1.5 g of alcohol per kilogram of body weight over a 3-h period (doses sufficient to cause acute alcohol intoxication) led to transient hypoparathyroidism as indicated by a reduction in circulating parathyroid hormone concentration of 58 percent at the end of the 3 h. Eight hours after alcohol exposure, serum ionized calcium had fallen to its nadir and urinary calcium excretion increased. In addition, serum magnesium levels rose and hypermagnesuria supervened. Of interest was the development of rebound hyperparathyroidism during the last 6 h of the study period. These results suggest that significant hypoparathyroidism and hyperparathyroidism may be responsible for some of the long-term effects of alcohol on bone and mineral metabolism.

The hypocalcemia of chronic alcoholism is multifactorial. Chronic alcoholics exhibit low levels of 25-OH-D₃

TABLE 32-3 • Causes of hypocalcemia in alcoholism

Direct effect of ethanol
Low levels of 25-(OH)-D ₃
Hypomagnesemia
Hypoalbuminemia
Pancreatitis
Intestinal malabsorption
Alkalosis
Liver cirrhosis

even when the liver is not cirrhotic.⁴⁷² Hypomagnesemia appears to occur concomitantly with hypocalcemia. Parenteral administration of vitamin D to alcoholic patients with hypocalcemia and hypomagnesemia does not correct the Ca^{2+} disorder.¹²⁶ Responsiveness to PTH and correction of the hypocalcemia are, however, attained with magnesium replacement; magnesium deficiency thus appears to play a central role in this disturbance. Hypocalcemia may also result from hypoalbuminemia, pancreatitis, respiratory or metabolic alkalosis, or intestinal malabsorption (Table 32-3).

Nephrotic syndrome

A decrease in serum albumin concentration is always accompanied by a decrease in total serum calcium. Free $[\text{Ca}^{2+}]$ usually does not change, but it may be low in patients with nephrotic syndrome. The low calcium level may not result from hypoalbuminemia itself. Haddad et al. found low levels of vitamin D binding protein in nephrotic patients.¹⁷⁸ Goldstein and coworkers studied 26 patients with nephrotic syndrome who were found to have low levels of 25-OH- D_3 .¹⁷² These investigators found an inverse correlation between the levels of 25-OH- D_3 and the degree of proteinuria. They proposed that the low levels of vitamin D in nephrotic patients were due to its excretion in urine; this, in turn, was responsible for the hypocalcemia. Long-term replacement of vitamin D in nephrotic syndrome has been shown to correct the low levels of 25-OH- D_3 as well as those of $1,25\text{-(OH)}_2\text{D}_3$; the effect of this therapy on Ca^{2+} metabolism remains to be completely evaluated.¹⁸⁴

"Hungry bone" syndrome

Deposition of Ca^{2+} in bone during the healing of osteodystrophies can lead to hypocalcemia. When bone formation exceeds bone resorption, Ca^{2+} deposition may surpass intake and make it difficult to maintain normocalcemia. The hypocalcemia that ensues may be severe enough to impair cell function.^{128,477} This syndrome has been observed after *parathyroidectomy* in primary hyperparathyroidism³⁶¹ or after *thyroidectomy* for hyperthyroidism.³⁰⁹ Compared with patients with uncomplicated metabolic responses to parathyroid surgery, patients with hungry bone syndrome are usually older by a mean of 10 years. In addition, they have higher preoperative serum levels of calcium, alkaline phosphatase, N-terminal parathyroid hormone, and blood urea nitrogen. The resected parathyroid adenomata in these individuals are larger.⁴⁶

Increased bone formation and hypocalcemia may also occur during *osteoblastic metastasis* from prostate,⁴¹⁹ breast,¹⁸⁵ and lung³¹⁸ malignancies. In rare instances, symptomatic hypocalcemia may occur in calcitonin-producing tumors.^{275,301}

Drugs and miscellaneous causes

The *anticonvulsants* phenobarbital and diphenylhydantoin are recognized causes of hypocalcemia. These drugs have been shown to induce hepatic microsomal P450 oxidase activity, which accelerates the rate of metabolism of vitamin D_3 and 25-OH- D_3 into polar, hydroxylated, and biologically inactive products of cholecalciferol.^{87,181} Anticonvulsant drugs may also cause hypocalcemia by inhibition of intestinal Ca^{2+} absorption and by reduction of PTH-induced bone resorption.¹⁸¹

Cisplatin can also cause hypocalcemia.²⁷⁴ Renal tubular damage caused by cisplatin can lead to renal magnesium wasting and magnesium depletion.³⁹⁴ Hypocalcemia may be a consequence of the hypomagnesemia and its correction can be attained by magnesium replacement.²⁷⁴

Estrogen therapy is another cause of drug-induced hypocalcemia.⁵³ Riggs et al. demonstrated that estrogens inhibited bone resorption without changing bone formation in patients with osteoporosis.³⁷¹ These effects of estrogen on bone metabolism were associated with a significant fall in serum $[\text{Ca}^{2+}]$. Hypocalcemia has been shown to occur in women after menopause;⁴⁹⁷ these women tend also to be hypercalcemic relative to premenopausal women. Inhibition of bone resorption may directly cause hypocalcemia during therapy with mithramycin and calcitonin. Excess endogenous production of calcitonin may be a mediating factor, as it is in the hypocalcemia seen in the toxic shock syndrome.⁷⁴

Up to 40 percent of critically ill patients, including those with sepsis and shock, exhibit hypocalcemia.⁴ Incidence of hypocalcemia is similar whether the patient has gram-positive or gram-negative infections. In a study of 80 patients the nadir of serum calcium concentration was achieved on days 6 to 8, and was significantly lower in males than in females.⁴ Serum calcium concentration did not correlate with serum levels of albumin, transaminase, or creatinine but had an inverse relationship to the degree of fever. The mechanism for the hypocalcemia or bacteremia is not clear, but reduced vitamin D production, increased resistance to PTH, or altered PTH secretion could, individually or in any combination, be responsible.

Hypocalcemia may also arise following the use of *citrate-buffered blood*,^{203,338} presumably due to binding of free Ca^{2+} with citrate. This has also been observed during plasmapheresis and exchange transfusions utilizing citrated blood.⁴⁶⁰ Treating hypercalcemia by *infusing phosphate salts* or sodium *EDTA* to chelate calcium can also lead to hypocalcemia.

Enhanced Ca^{2+} excretion induced by *loop diuretics* may precipitate hypocalcemia, particularly in patients with hypoparathyroidism. Volume reduction and alkalosis resulting from the use of these diuretics increases concentrations of serum proteins and protein-bound calcium and decreases free $[\text{Ca}^{2+}]$.¹⁶¹

TABLE 32-4 • Drugs associated with hypocalcemia

Gentamicin	Propylthiouracil
Cimetidine	Glutethimide
Estrogens	Furosemide
Heparin	Cisplatin
Mithramycin	Dilantin
Phosphate salts	Phenobarbital

Other drugs presumed to cause hypocalcemia include propylthiouracil,⁴⁰² glutethimide (with chronic abuse),³³⁶ and cimetidine¹¹⁸ (Table 32-4). Spurious hypocalcemia due to in vitro formation of calcium soaps in blood samples has been reported in hemodialysis patients after heparinization.¹⁷⁰

CONSEQUENCES OF HYPOCALCEMIA

General, neurological, and neuromuscular effects

The most important clinical manifestations of hypocalcemia are those related to the neuromuscular and central nervous systems. Tetany, the classic manifestation of neuromuscular irritability in hypocalcemia, can be elicited by tapping the facial nerve and producing a contraction of the facial muscles (Chvostek's sign) or by inflation of a blood pressure cuff above systolic pressure for 3 min to observe if carpopedal spasm develops (Trousseau's sign). Chvostek's sign is present in 25 percent of normal adults;²⁰⁶ it is not, therefore, specific for hypocalcemia. Trousseau's sign is equally nonspecific; neither is it sensitive, occurring in 4 percent of the normal population, and may be negative in 30 percent of subjects with latent tetany.²⁸¹

Seizures are another important neurological manifestation of hypocalcemia. The precise mechanism involved is not known, but high $[Ca^{2+}]$ in the CSF has been shown to have an anticonvulsive action.⁵⁰³ Thus, it is intuitively reasonable to expect that low CSF calcium concentration may predispose to seizures in hypocalcemic disorders.

Hypocalcemia may also lead to extrapyramidal manifestations. These include parkinsonian tremors, dystonia, ataxia, hemiballismus, and choreoathetosis.⁴²⁰ There are calcifications of the basal ganglia in long-standing hypocalcemic disorders. These, however, are believed not to cause the extrapyramidal symptoms, since treatment of the hypocalcemia corrects the symptoms without changing the basal ganglia calcifications.

Hypocalcemia may also impair higher cerebral functions. In adults depression, emotional instability, confusion, anxiety, or even frank psychosis may be the primary manifestation of hypocalcemia.^{124,418}

Proximal muscle weakness is another important and potentially disabling manifestation of hypocalcemia, par-

ticularly in vitamin D₃ deficiency states. Absence of vitamin D₃ has been shown to have important effects on skeletal muscle calcium metabolism. Pleasure and co-workers³⁵⁵ have shown that mitochondria isolated from skeletal muscle of vitamin D₃-deficient chicks with muscle weakness contain significantly less calcium than normal mitochondria. Correction of serum calcium in these animals by oral calcium administration does not re-establish the normal mitochondrial calcium level and does not improve the muscle weakness. However, treatment with vitamin D₃ increases mitochondrial calcium content and the muscle weakness improves. These findings suggest that vitamin D₃ deficiency alone, rather than the hypocalcemia, accounts for the muscle weakness.

Cardiovascular, ectodermal, and gastrointestinal effects

Calcium ions play an important role in the contraction of cardiac muscle. Clinical and experimental studies have shown that hypocalcemia induced by transfusions of citrated blood results in cardiac index, stroke volume, and left-ventricular stroke work values that are significantly lower than during normocalcemia.^{338,432} Congestive heart failure that is refractory to treatment with digitalis can occasionally result from hypocalcemia.^{75,88}

Electrocardiographic manifestations of hypocalcemia include prolongation of the Q-T interval and nonspecific T wave changes that revert to normal upon correction of the hypocalcemia.

Long-standing hypocalcemia is known to cause ectodermal defects. Children with hypoparathyroidism may exhibit failure of teething, dental hypoplasia, or carious teeth.¹⁵⁶ Coarse, dry, and scaly skin has also been described in hypocalcemic patients. Their nails are brittle with transverse grooves; thin brittle, sparse hair, and, frequently, scanty eyelashes and eyebrows, and absence of axillary or pubic hair are also observed after prolonged hypocalcemia.

Psoriasis and eczema can be exacerbated by hypocalcemia. Bilateral cataracts may also occur; their progression can be avoided by normalizing serum calcium concentration. The gastrointestinal manifestations of hypocalcemia include severe diarrhea with or without steatorrhea,⁸⁰ gastric achlorhydria,¹⁰³ and malabsorption of vitamin B₁₂.¹⁸⁶

TREATMENT OF HYPOCALCEMIA

Acute

Acute symptomatic hypocalcemia requires immediate correction to avert serious complications. Adults requiring emergency treatment can be given 10 to 20 ml of 10 percent calcium gluconate (one 10-ml ampule contains 90 mg of elemental calcium) intravenously. The infusion rate should not exceed 2 ml/min. Patients receiving digi-