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Anticoagulation and Thrombolytic Therapy in the Emergency Department: Part II

Authors: **Richard V. Aghababian, MD,** Professor and Chair, Department of Emergency Medicine, University of Massachusetts Medical School, Worcester; **Robert L. Levine, MD**, Associate Professor of Neurosurgery and Emergency Medicine, Chief, Division of Neurointensive Care, The University of Texas School of Medicine at Houston; and **Marcie J. Hursting, PhD, DABCC**, Director, Clinical Science Consulting, Austin, TX.

Peer Reviewers: **Frank LoVecchio, DO, MPH, FACEP**, Medical Director, Banner Good Samaritan Regional Poison Center, Research Director, Maricopa Medical Center, Department of Emergency Medicine, Associate Professor, Arizona College of Osteopathic Medicine, Phoenix, AZ; and **Brian Tiffany, MD**, **PhD**, Chairman, Department of Emergency Medicine, Chandler Regional Hospital, Chandler, AZ; Chairman, Department of Emergency Medicine, Mercy Gilbert Medical Center, Gilbert, AZ.

Part II of this series discusses the use of anticoagulants in the emergency department (ED) and some of the complications seen with their use. As our society ages, more and more patients are on chronic anticoagulants. This leads to a new set of problems for our patients such as increased risk of bleeding and medication interaction. In addition, the emergency physician must be on the lookout for complications such as heparin-induced thrombocytopenia and warfarin-related skin necrosis.

Patients who are on chronic anticoagulation should, in general, have their clotting studies checked when they are seen in the ED if blood is being drawn for other reasons or if they are acutely ill. This is because so many factors change the patient's INR. Changes in medication or diet may lead to changes in the INR. Finding this early can prevent serious issues later on.

One of the difficult situations that an emergency physician faces is the patient on anticoagulation who is bleeding. It can be a delicate decision of whether the bleeding or the need for anticoagulation takes precedence. With more patients than ever on some form of anticoagulation, this decision will be increasingly faced by all physicians.

Finally, the paper discusses the role of pathways in our practice. Many physicians rebel against pathways because they believe they represent "cookbook medicine." However, pathways,

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used intelligently by physicians, have been shown to reduce variation in care, decrease errors, and provide more efficient, effective care. Pathways together with sophisticated medical decision-making will benefit all our patients.

—Sandra M. Schneider, MD, FACEP, Editor

Managing Patients with Acute Vascular Occlusion

Treatment Options. Care of patients with acute vascular occlusion has been significantly improved through the use of treatment pathways. Pathways and guidelines have been developed by many specialty-driven societies and recently have become "evidence-based," limited only by the amount and quality of evidence available. This is true for acute coronary syndrome (ACS) including unstable angina and acute myocardial infarction (AMI), acute venous thromboembolism (VTE), and for acute ischemic stroke. At the institutional levels, local protocols have been developed that have supplemented or replaced published guidelines that have undergone peer review. These local protocols may work well in the institution that created them, but need to be carefully implemented. In addition, they may not extrapolate to other institutions dealing with different patient populations or different formularies. A note of caution is also warranted in that many institutions have implemented "therapeutic-equivalence" policies, allowing substitution of a less expensive agent, usually from the same class of drugs, for the agent in question. For anticoagulants, each drug, even within classes, must stand on its own evidence due to the fact that they have not been shown to be equivalent, and there are no established equivalency dosing schemes to translate treatment of ACS or VTE with the various low molecular weight heparin (LMWH) drugs currently available.

Classes of Pharmacologic Agents. *Anticoagulants.* Anticoagulants inhibit clot formation by reducing the generation or activity of coagulation proteins. These agents vary in their onset of action (slow or rapid) and mechanism of action (indirect or direct). Warfarin and other vitamin K antagonists have a slow onset of action, exerting their anticoagulant effects by inhibiting formation of the vitamin K-dependent coagulation factors II (prothrombin), VII, IX, and X and proteins C and S. Stable, therapeutic levels of warfarin anticoagulation are achieved only after approximately 5 days. Common indications for warfarin include prophylaxis or treatment of venous thromboembolism, prophylaxis or treatment of thromboembolic complications associated with atrial fibrillation, and reduction of thrombotic risk after myocardial infarction. It is also indicated for the prevention of thromboses related to implantation of mechanical heart valves. Although patients may present to the ED who are on warfarin or who ultimately are bridged to warfarin, acute anticoagulation in the ED typically is provided when needed using a rapidly acting drug.

When a patient presents to the ED on chronic anticoagulant therapy, usually warfarin, the PT/INR almost always should be checked. This is especially true for patients presenting with any type of bleeding, no matter how minor (epistaxis, gingival bleeding) or potentially life-threatening complaints (headache on warfarin, or any type of anticoagulant or antiplatelet). The therapeutic range of warfarin is an INR of 2-3 for most conditions. The baseline PT/INR helps establish the next step. The ED physician may be confronted with three situations requiring a change in the patient's warfarin: subtherapeutic INR in a patient with no contraindication to continued anticoagulation; supratherapeutic INR in a patient with no active bleeding; and a therapeutic range or supratherapeutic INR in a patient actively bleeding. The subtherapeutic patient not taking the warfarin should just be restarted on 5 mg/day without a loading dose. If the patient is taking the medication, the dose can be increased by 5-20% based on the patient's cumulative weekly dose, with more frequent monitoring indicated.[1] Daily, follow-up PT/INR should be arranged until the patient's INR stabilizes, at which time the dose can be fine-tuned to achieve the desired INR. Patients with life-threatening bleeding, with an INR in the therapeutic range, or a supratherapeutic INR should be reversed with the administration of 10-25 mg vitamin K daily for 3 days. In addition, these patients should be administered 6 units of fresh frozen plasma (FFP) as soon as possible to reverse warfarin's effects. Factor VII or prothrombin concentrates can be given to immediately reverse warfarin. Finally, the supratherapeutic INR in an asymptomatic patient can be treated with small doses of oral vitamin K (5-10 mg) using established

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Senior Vice President/Group Publisher: Brenda Mooney
Associate Publisher: Lee Landenberger
Specialty Editor: Shelly Morrow Mark
Marketing Manager: Shawn DeMario
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Table 1. Indications for the Rapidly Acting Anticoagulants Available in the United States, Effective November 2006

USE	UFH	LMWHS	FONDAPARINUX	DTIS
Thromboprophylaxis in arterial and cardiac surgery	X			
Thromboprophylaxis after hip replacement surgery		Dalteparin, enoxaparin	X	
Thromboprophylaxis after hip fracture surgery			X	
Thromboprophylaxis after knee replacement surgery		Enoxaparin	X	
Thromboprophylaxis after abdominal surgery, if at-risk	X	Dalteparin, enoxaparin	X	
Thromboprophylaxis in medical patients during acute illness		Dalteparin, enoxaparin		
Prophylaxis ischemic complications in UA/ non-Q-wave MI‡		Dalteparin, enoxaparin		
Prophylaxis and treatment of peripheral arterial embolism	X			
Prophylaxis and treatment of VTE	X			
Inpatient treatment of DVT +/- PE (with warfarin)		Enoxaparin, tinzaparin	X	
Outpatient treatment of PE* (with warfarin)			X	
Outpatient treatment of DVT (with warfarin)		Enoxaparin	X	
Atrial fibrillation and embolization	X			
Thromboprophylaxis/treatment in HIT				Argatroban, lepirudin†
PCI in patients with or at risk of HIT				Argatroban, bivalirudin
PCI with provisional GPIIb/IIIa inhibition				Bivalirudin
PTCA in patients with UA				Bivalirudin
Diagnosis/treatment of consumptive coagulopathies (DIC)	X			
During transfusions, dialysis, extracorporeal circulation; in blood samples for laboratory purposes	X			

* If treatment started in-hospital

† Lepirudin is indicated for patients with HIT and associated TEC to prevent further TEC.

‡ With aspirin; fondaparinux has been extensively evaluated in acute coronary syndrome,[5,6] and the data are under regulatory review.

Key: DIC = disseminated intravascular coagulation; DTI = direct thrombin inhibitor; DVT = deep venous thrombosis; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PTCA = percutaneous transluminal coronary angioplasty; TEC = thromboembolic complication; UA = unstable angina; UFH = unfractionated heparin; VTE = venous thromboembolism

algorithms.[1] The goal is to lower the INR to the therapeutic range without fully reversing warfarin's effects. This can be achieved with small doses of PO or IV vitamin K. In emergent situations, rFVIIa and prothrombin concentrates have been administered for immediate reversal of anticoagulant effect.[2] For example, recombinant factor VIIa is indicated for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage in patients with Glasgow Coma Score > 8 (non-comatose).[3] In addition, recombinant factor VIIa and Prothrombin Complex Concentrates may be used in other life-threatening hemorrhages, although the optimal dose to correct a hemorrhage diathesis in these situations is less well defined.[4] For excellent discussions of this topic, the reader is referred to the articles cited by Ansell and Schulman in *Chest* and *Transfusion Medicine Reviews*, respectively.

The rapidly acting anticoagulants include antithrombin-dependent agents and direct thrombin inhibitors (DTIs). Their indications are summarized in Table 1, and safety concerns in Table 2. The antithrombin-dependent anticoagulants include unfractionated heparin (UFH), which usually is derived from animal sources, e.g., porcine intestine or bovine lung, and low-molecular-weight heparins (LMWHs), which are prepared from UFH by enzymatic or chemical processes. These drugs act indirectly via interaction with the cofactor antithrombin, which in turn predominantly inactivates factors IIa (thrombin) and Xa, but also factors IXa, XIa, and XIIa. (*See Figure 1.*) Compared with UFH, LMWHs have a greater antifactor Xa-to-antifactor IIa activity ratio and superior dose-response relationships. LMWHs available in the United States as of November 2006 are enoxa-

Table 2. Safety Issues with Rapidly Acting Anticoagulants in the United States (Effective November 2006)

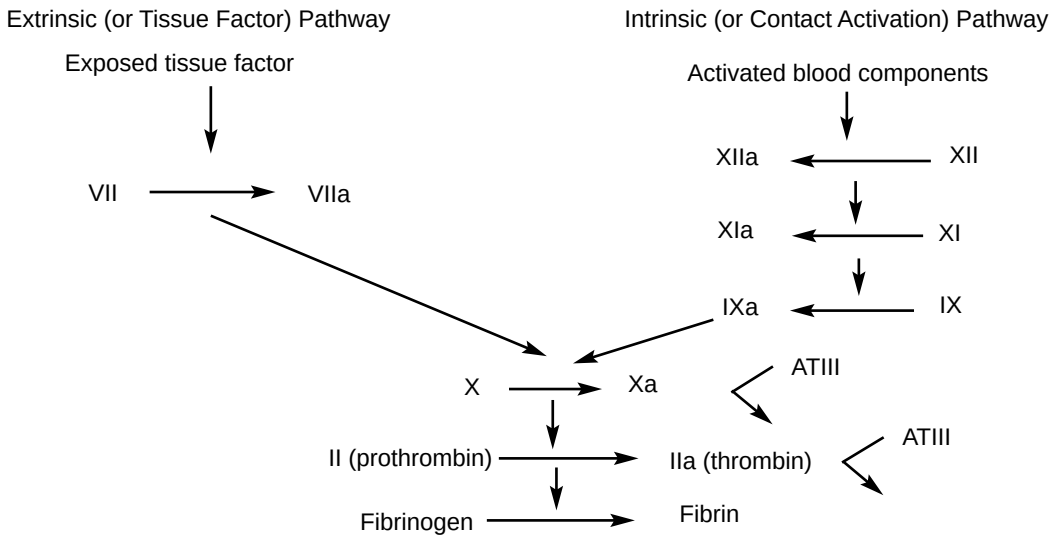
SAFETY CONCERN	UFH	LMWHS	FONDAPARINUX	DTIS
Avoid if hypersensitivity to drug or its components	X	X	X	X
Avoid if active major bleeding	X	X	X (or if bacterial endocarditis)	X
Use with extreme caution if increased risk of bleeding	X	X	X	X
Bleeding, including major hemorrhage, can occur	X	X	X	X
Black box warning: Neuraxial hematoma or spinal puncture	†	X	X	
Avoid in patients with UA or MI undergoing regional anesthesia		Dalteparin		
Avoid if severe thrombocytopenia, cross-reactivity with antiplatelet antibody in presence of drug, or current or previous HIT (or use with extreme caution if history of HIT)	X	X	X*	
Not for intramuscular injection	X	X	X	X
AT-dependent drugs not interchangeably used (unit for unit)	X	X	X	
Presence of renal impairment				
• Avoid if CLcr <30 mL/min and caution if CLcr 30-50 mL/min			X	
• Avoid if CLcr < 15 mL/min and reduce dose if CLcr <60 mL/min				Lepirudin
• Reduce dose if CLcr < 30 mL/min		Enoxaparin		Bivalirudin
Presence of hepatic impairment, reduce dose				Argatroban
Patient body weight				
• Avoid using for prophylaxis if < 50 kg			X	
• Antifactor Xa monitoring if > 150 kg		X‡		
Anaphylaxis risk on re-exposure				Lepirudin
Routine monitoring with coagulation assay	X			X
No antidote			X	X

* In vitro and in vivo cross reactivity with HIT antibody is negligible.
† Event has also been reported in association with UFH
‡ Per ACCP guidelines[7]; not in prescribing information of drugs.
Key: AT, antithrombin; CLcr, creatinine clearance; HIT, heparin-induced thrombocytopenia; MI, myocardial infarction; UA, unstable angina

parin, dalteparin, and tinzaparin. Another antithrombin-dependent anticoagulant is fondaparinux, a synthetic pentasaccharide modeled after the antithrombin-binding region of heparin. Via its interaction with antithrombin, fondaparinux selectively inhibits factor Xa. Unlike heparins or fondaparinux, DTIs bind the thrombin active site and exert their anticoagulant effects without need of a cofactor. There are three DTIs currently available in the United States: lepirudin, a recombinant hirudin protein; argatroban, a small molecule derived from L-arginine; and bivalirudin, a polypeptide with sequence homology to hirudin. Rapid-onset anticoagulants currently in advanced development include the factor Xa inhibitors rivaroxaban (oral) and idraparinux (parenteral), and the oral DTI dabigatran.

Antiplatelet Agents. Antiplatelet drugs decrease platelet aggregation and thereby inhibit thrombus formation. Table 3 summarizes their indications and safety concerns. These agents include aspirin (and other cyclooxygenase inhibitors), dipyridamole, thienopyridines, and glycoprotein (GP) IIb/IIIa receptor antagonists. Aspirin blocks thromboxane A2-mediated platelet aggregation and vasoconstriction. Dipyridamole (Persantine) inhibits phosphodiesterase and adenosine uptake in platelets, leading to increased intraplatelet levels of cyclic adenosine monophosphate, a platelet inhibitor. The thienopyridines, ticlopidine (Ticlid) and clopidogrel (Plavix) inhibit adenosine diphosphate (ADP)-mediated platelet aggregation. (Another ADP receptor antagonist, prasugrel, is currently in advanced development.) Administered intravenously, the GPIIb/IIIa receptor antagonists include abciximab (ReoPro, a monoclonal antibody), eptifibatide (Integrilin, a synthetic peptide), and tirofiban (Aggrastat, a nonpeptide derivative of tyrosine). Each blocks the binding

Figure 1. Coagulation Cascade



Drug	Principle Site of Action
Heparin	Thrombin (via ATIII)
LMWH	Factor Xa (via ATIII)
Warfarin	Factors II, VII, IX, X
DTIs	Thrombin
Fondaparinux	Factor Xa (via ATIII)
Fibrinolytics	Fibrin

of fibrinogen, von Willebrand factor, and other adhesive molecules to GPIIb/IIIa, hence inhibiting platelet-platelet interactions and aggregation.

Thrombolytic Agents. Thrombolytic drugs(also known as fibrinolytic drugs) activate plasminogen to plasmin, which in turn cleaves fibrin (and fibrinogen) and hence dissolves thromboses. Thrombolytics available in the United States include streptokinase (Streptase), urokinase (Abbokinase), anistreplase (Eminase), alteplase (Activase), reteplase (Retavase), and tenecteplase (TNKase). Urokinase and streptokinase, enzymes isolated from human kidney cells and streptococcus respectively, activate plasminogen systemically throughout the entire circulating blood volume. Anistreplase is a complex of streptokinase and plasminogen in which the catalytic region is temporarily blocked by a chemical moiety that is removed hydrolytically in the blood. When unblocked, the complex activates both circulating and clot-bound plasminogen. Alteplase, a recombinant tissue plasminogen activator, primarily activates clot-bound plasminogen with limited systemic proteolysis. Reteplase and tenecteplase are modified, recombinant tissue plasminogen activators. Their indications and complications are summarized in Table 3.

Contraindications and Dosing Issues. Decision-making concerning the choice of an antithrombotic agent should include factors such as its efficacy and safety profile, including contraindications and warnings, in the intended use; availability, if needed, of methods for monitoring; and the patient's status including age, weight, and renal and hepatic function. Pharmacologic agents are contraindicated in patients with hypersensitivity to the drug or components of the drug product. Additional contraindications, safety concerns, and dosing issues are subsequently discussed separately for the anticoagulant (*see Table 2*), antiplatelet, and thrombolytic agents. (*See Table 3.*)

The potential for drug interactions (pharmacodynamic or pharmacokinetic) should be recognized when making pharmacologic decisions. The combination use of any drugs affecting hemostasis, i.e., anticoagulants, antiplatelets, or thrombolytics, potentiates the risk of bleeding, and this risk should be weighed carefully against the benefit of the treatment. Certain combination therapies are routinely used however, such as GPIIb/IIIa receptor inhibition with concurrent aspirin and heparin in patients undergoing PCI, and recombinant TPA agents with concurrent aspirin and heparin in patients with AMI. Warfarin and the DTIs exert a combined effect on the PT/INR. Previously established relationships between INR and bleeding risk are altered during combination therapy with warfarin and argatroban. INRs greater than 5 without bleeding are common during argatroban-warfarin cotherapy and argatroban monotherapy.[8] Pharmacokinetic interactions occur between warfarin and a variety of medications, botanicals, and foods, with effects mainly attributed to liver enzyme induction or inhibition or altered plasma protein binding; careful monitoring is important. The thienopyridines are metabolized extensively in the liver, and the dose of other hepatically metabolized drugs may require adjustments when starting or stopping ticlopidine or clopidogrel. (*See Table 4.*)

Table 3. Indications and Complications of Antiplatelets and Thrombolytics

DRUG	MECHANISM	INDICATIONS	MAJOR COMPLICATIONS
Antiplatelet			
Aspirin*	Thromboxane, cyclooxygenase	ACS, CVA/TIA	Hemorrhage, gastrointestinal
NSAIDs	Thromboxane, cyclooxygenase		Hemorrhage, liver
Dipyridamole*	cAMP	CVA/TIA	Hemorrhage, bronchospasm
Clopidogrel	ADP	ACS, PCI, CVA	Hemorrhage, platelet, TTP
Ticlopidine	ADP	CVA, PCI (post stent)	Hemorrhage, platelet, TTP
Abciximab	GPIIb/IIIa receptor	ACS PCI	Hemorrhage, platelet
Tirofiban	GPIIb/IIIa receptor	ACS PCI	Hemorrhage, platelet
Eptifibatide	GPIIb/IIIa receptor	ACS PCI	Hemorrhage, platelet
Thrombolytic			
Streptokinase	Plasmin	AMI, CVA, VTE	Hemorrhage
Anistreplase	Plasmin	AMI	Hemorrhage
Urokinase	Plasmin	PE	Hemorrhage
Alteplase	Plasmin	AMI, CVA, VTE	Hemorrhage
Reteplase	Plasmin	AMI	Hemorrhage
Tenecteplase	Plasmin	AMI	Hemorrhage

* A combination of aspirin and extended release dipyridamole is commercially available (Aggrenox), platelet = thrombocytopenia

Anticoagulants. The rapidly acting anticoagulants are administered intravenously (UFH, DTIs) or subcutaneously (UFH, LMWHs, fondaparinux) and are not to be given intramuscularly. UFH, LMWHs, and fondaparinux should not be used interchangeably (unit for unit) with one another. The rapidly acting anticoagulants are contraindicated in patients with active major bleeding and should be used with extreme caution in patients at increased risk of hemorrhage, e.g., bacterial endocarditis; congenital or acquired bleeding disorders such as hemophilia; active ulcerative and angiodysplastic gastrointestinal disease; hemorrhagic stroke and intracranial neoplasms; severe uncontrolled hypertension; immediately following lumbar puncture; spinal anesthesia; major surgery, especially involving the brain, spine, or eye; or in patients treated concomitantly with platelet inhibitors. Because of bleeding risk, tinzaparin is contraindicated in patients undergoing regional anesthesia who have unstable angina or myocardial infarction. The antithrombin-dependent anticoagulants have labeled contraindications or warnings against use in patients with current or previous heparin-induced thrombocytopenia (LMWHs), severe thrombocytopenia (UFH), or thrombocytopenia associated with a positive in vitro test for antiplatelet antibodies in the presence of drug (enoxaparin, dalteparin, fondaparinux).

UFH should be monitored routinely using the aPTT (or ACT for higher doses), with doses adjusted as needed to achieve target levels of anticoagulation. Bleeding risk with UFH appears to increase with the heparin dosage and patient age older than 70 years.[9] The American College of Chest Physicians (ACCP) recommends UFH over LMWH for full therapeutic anticoagulation in patients with severe renal failure (creatinine clearance less than 30 mL/min).[9] When enoxaparin is used for thromboprophylaxis (or treatment), a dose reduction is required in severe renal failure. Antifactor Xa monitoring is considered prudent for monitoring weight-based doses of LMWH in patients weighing more than 150 kg[9] and can be used whenever deemed important, such as if severe renal impairment or bleeding develops.

Fondaparinux is contraindicated in severe renal impairment (creatinine clearance less than 30 mL/min) and should be used with caution in moderate renal impairment (creatinine clearance 30-50 mL/min). Renal function should be checked periodically. Fondaparinux also is contraindicated for thromboprophylaxis (but not VTE therapy) in patients weighing less than 50 kg.

DTIs should be monitored, with doses adjusted as needed, using the aPTT or for higher levels of anticoagulation, the ACT. Bivalirudin requires reduced doses in severe renal impairment. Relative overdose can also occur with standard dosing of lepirudin in renal impairment. Depending on the degree of renal dysfunction, lepirudin dosing should be reduced (creatinine clearance 15-60 mL/min) or avoided (creatinine clearance less than 15 mL/min). Argatroban, which is predominantly hepatically metabolized, requires dose reduction in hepatic impairment assessed as a Child-Pugh score greater than 6 or serum total bilirubin greater than 1.5 mg/dL.[10]

Antiplatelets. Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm, and should not be used in children or teenagers for viral infection because of the risk of Reye's syndrome. Aspirin should be avoided during the third trimester of pregnancy and in patients with severe renal failure (glomerular filtration rate < 10 mL/min), severe hepatic dysfunction, or active peptic ulcer disease. Patients with a history of alcohol abuse or with inherited or acquired bleeding disorders have an increased risk of bleeding

while taking aspirin. Aspirin-induced gastrointestinal toxicity appears to be dose-dependent.[11]

Dipyridamole should be used with caution in patients with severe coronary artery disease or hypotension.

The thienopyridines are contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage. Ticlopidine, but not clopidogrel, is also contraindicated in patients with hematopoietic disorders such as neutropenia, thrombocytopenia, or history of thrombotic thrombocytopenia purpura or aplastic anemia; severe liver impairment; or a hemostatic disorder. Reduced doses of ticlopidine may be needed in patients with renal impairment. Clopidogrel should be used with caution in patients at increased risk of bleeding from trauma, surgery, or other conditions and in patients with severe hepatic disease or severe renal impairment.

Because of an increased risk of bleeding, GPIIb/IIIa receptor inhibitors are contraindicated in patients with active internal bleeding or a recent history of bleeding diathesis; recent stroke or history of hemorrhagic stroke; recent major surgery or trauma; and severe, uncontrolled hypertension. Other labeled contraindications include history of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm (tirofiban, abciximab); concomitant use of another parenteral GPIIb/IIIa inhibitor (tirofiban, eptifibatide) or dextran (abciximab); history of thrombocytopenia following prior exposure to the drug (tirofiban); history, symptoms, or findings suggestive of aortic dissection (tirofiban); acute pericarditis (tirofiban); vasculitis (abciximab); recent, clinically significant gastrointestinal or genitourinary bleeding (abciximab); and oral anticoagulant use with 7 days, unless the prothrombin time is less than or equal to 1.2 times control (abciximab). GPIIb/IIIa inhibitors are either contraindicated (abciximab) or should be used with caution (tirofiban, eptifibatide) in patients with a platelet count less than 100-150 x 10^9/L, and each should be used with caution in conjunction with other drugs that affect hemostasis. Patients should be monitored for potential bleeding.

Eptifibatide is contraindicated in patients dependent on renal dialysis, and its dose should be reduced in patients with creatinine clearance less than 50 mL/min. Tirofiban should be used with caution in patients on chronic hemodialysis, and its dose should be reduced in severe renal insufficiency (creatinine clearance less than 30 mL/min). Redosing abciximab should be done with caution due to its long half life.

Thrombolytics. Because the use of thrombolytic drugs increases the risk of bleeding, their contraindications include active internal bleeding; recent cerebrovascular accident; recent intracranial or intraspinal injury or trauma; intracranial neoplasm, arteriovenous malformation, or aneurysm; known bleeding diatheses; and severe, uncontrolled hypertension.

Alteplase is further contraindicated for treating acute ischemic stroke if the patient has evidence of intracranial hemorrhage on pretreatment evaluation; suspicion of subarachnoid hemorrhage on pretreatment evaluation; recent intracranial or intraspinal surgery, serious head trauma, or previous stroke; history of intracranial hemorrhage; uncontrolled hypertension at the time of treatment; or seizure at the onset of stroke. Treatment is not recommended if stroke symptom onset was greater than 3 hours earlier or if the patient has minor neurologic deficit or rapidly improving symptoms.[12]

The increased risk of bleeding associated with thrombolysis should be weighed carefully against the potential benefits in patients with recent major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels; recent trauma; recent serious gastrointestinal or genitourinary bleeding; high likelihood of left heart thrombus; subacute bacterial endocarditis; acute pericarditis; hemostatic defects including those secondary to severe hepatic or renal disease; pregnancy; cerebrovascular disease; diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions; severe hepatic disease; septic thrombophlebitis or occluded arteriovenous cannula at a seriously infected site; advanced age; concurrent use of warfarin; recent GPIIb/IIIa inhibitor administration; and any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location. Care-

Table 4. Warfarin Therapy: Monitoring and Potential Effectors of Activity

- Monitoring the pharmacologic effects of anticoagulants is accomplished by daily measurement of patients: aPTT, PT (INR), CBC, and platelets.
- Prior to initiating therapy with anticoagulants patients should be screened for a history of a bleeding disorder, medication-related anaphylaxis, or HIT.
- Since certain medications and medical conditions may potentiate or attenuate the anticoagulant effects of certain medications, patients should be asked about current medications and medical ailments before starting anticoagulants or when a new medication is introduced to someone on an anticoagulant.

Examples of medications that may potentiate the anticoagulant effect of warfarin:

- Salicylates
- Acetaminophen
- Anabolic steroids
- NSAIDs
- Certain herbal medicines (such as ginkgobiloba)
- Phenytoin
- Sulfonamides
- Clofibrates
- Metronidazole
- Alcohol
- Anesthetics
- Diuretics
- Fluoroquinolones

Examples of medications that may attenuate the anticoagulant effect of warfarin:

- Barbiturates
- Glutethimide
- Rifampin

Medical conditions that may potentiate or attenuate the anticoagulant effects of warfarin:

- Liver disease, fever, hypertension, congestive heart failure, chronic diarrhea, diet low in vitamin K intake, for example.
- Dosing of low molecular weight heparins after required adjustment in the presence of chronic renal failure.

ful monitoring for bleeding is recommended in any treated patient.

Complications Associated with Antithrombotic Therapies in the ED

Bleeding. The primary complication of antithrombotic therapies is bleeding, with major, life-threatening events such as intracranial hemorrhage possible.[9] Bleeding can occur from any site and should be considered if an unexpected fall in hemoglobin or blood pressure or other unexplained symptoms occur. To minimize bleeding during thrombolytic therapy, intramuscular injections should be avoided, and venipunctures should be performed carefully and as infrequently as possible. If arterial puncture is required, compressible vessels of the upper extremity are preferable, with at least 30 minutes of pressure after the puncture and careful monitoring.

When administration of an anticoagulant, antiplatelet, or thrombolytic agent is complicated by severe or life-threatening hemorrhage, the agent should be immediately discontinued, and the patient should be provided symptomatic and supportive therapy. In addition, the agent should be acutely reversed through general and specific means, when possible. Protamine sulfate can be administered to help reverse bleeding associated with UFH and LMWHs, if needed, although protamine does not fully neutralize antifactor Xa activity and carries a risk of anaphylactoid reactions. The DTIs and fondaparinux lack antidotes. Because the DTIs are eliminated relatively rapidly (half-life of 1.7 h for lepirudin, 39-51 minutes for argatroban, and 36 minutes for bivalirudin), their anticoagulant effects usually are reversed completely, returning to baseline within a few hours of discontinuing infusion. However, elimination may take much longer if renal impairment (lepirudin, bivalirudin) or hepatic impairment (argatroban) is present.[13] Recombinant factor VIIa has been used clinically to reverse the effects of warfarin, and may be useful for the immediate reversal of rapid-onset anticoagulant effects. Recombinant factor VIIa has been shown to reverse the effects of fondaparinux in healthy volunteers.[14] In patients receiving abciximab who experience serious bleeding, platelet function may be restored in part with platelet transfusions. If needed, tirofiban can be removed by hemodialysis. If spontaneous bleeding uncontrolled by pressure occurs in a patient receiving thrombolysis, the thrombolytic agent and any concomitant anticoagulant should be stopped immediately, and reversal of the bleeding tendency can be managed by administering whole blood, packed red cells, and cryoprecipitate or fresh frozen plasma.

Evidence-based, comparative information regarding hemorrhagic complications of anticoagulant treatment is available from the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.[9] In treatment of acute VTE, the bleeding risk with intravenous UFH is less than 3%, there is less major bleeding with LMWH than UFH, and the bleeding risk is similar with fondaparinux vs. LMWH or heparin. There is an increased risk of major bleeding and intracranial bleeding with short-term, therapeutic-dose LMWH or UFH in ischemic stroke. In ischemic coronary syndromes, UFH and LMWH are not associated with increased major bleeding, although extended treatment with LMWH is associated with increased bleeding. A more recent study[5] in acute coronary syndromes found that major bleeding is reduced with fondaparinux versus the LMWH enoxaparin. Table 5 summarizes various strategies that have been used for reversing the effects of anticoagulants, antiplatelets, and thrombolytic agents.

Neuraxial Hematoma and Spinal Puncture. Epidural or spinal hematoma is a rare, devastating complication of neuraxial anesthesia that may cause neurologic injury resulting in long-term or permanent paralysis and that often is associated with anticoagulation. The estimated incidence of spinal hematoma is less than 1 in 150,000 epidurals and less than 1 in 220,000 spinal anesthetics.[15] Reports of 43 cases of neuraxial hematoma associated with enoxaparin use between 1993 and 1998 resulted in a class-effect, "black box" warning for LMWHs and danaparoid (a heparinoid no longer available in the United States).[16] In addition, dalteparin is contraindicated due to increased bleeding risk in patients undergoing regional anesthesia who have unstable angina or myocardial infarction. Risk factors for neuraxial hematoma with heparins include the use of indwelling epidural catheters; concomitant use of additional drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs, platelet inhibitors, or other anticoagulants; traumatic or repeated epidural or spinal puncture; immediate preoperative (or intraoperative) or early postoperative LMWH administration; female gender; and increased age.[15,16] In the only published report of neuraxial hematoma associated with fondaparinux, which has a similar black box warning, the event occurred after multiple unsuccessful attempts to place an epidural catheter in a patient receiving a supratherapeutic dose.[17] There have been no reports of neuraxial hematoma in patients administered a DTI.

In patients anticoagulated or scheduled to be anticoagulated for thromboprophylaxis, physicians should consider the benefits vs. risks before neuraxial anesthesia or spinal puncture. Guidelines from the American Society of Regional Anesthesia and Pain Medicine for minimizing risk associated with neuraxial anesthesia are published.[15] Patients should be monitored for neurologic impairment, with prompt intervention critical if neurologic compromise is noted.

Heparin-Induced Thrombocytopenia (HIT). During anticoagulation, thrombocytopenia of any degree should be monitored closely. HIT is an immune-mediated prothrombotic disorder associated with an unexplained 50% drop in the platelet count, often to less than 150 x 10^9/L, that occurs in approximately 1-5% of patients administered UFH and less than 1% administered LMWH for at least 5 days. Approximately 38-76% of affected patients will develop thrombosis, approximately 10% with thrombosis will require a limb amputation, and approximately 20-30% will die within a month.[13] For prompt recognition of HIT, the American College of Chest Physicians[18] recommends routine platelet count monitoring in most heparin-treated patients, including a pretreatment assessment particularly if there is recent (within 100 days) or uncertain history of heparin exposure. HIT also should be considered if a currently or recently

Table 5. Reversal of Anticoagulants and Antiplatelets

DRUG/CLASS	REVERSAL AGENT	T ½	NON-SPECIFIC REVERSAL/SUPPORT
Rapid Onset			
Predominant antifactor II, X			
UFH	Protamine sulfate	90 min	PCC, rFVIIa
LMWH	Protamine sulfate*	3 h	PCC, rFVIIa
Fondaparinux	None	17 h	rFVIIa
Direct thrombin inhibitors			
Argatroban	None	40-50 min	FFP
Bivalirudin	None	25-40 min	FFP
Lepirudin	None	1.3-3 h	FFP
Thrombolytics			
Activate plasminogen to plasmin to lyse fibrin			
Multiple agents	None	25-130 min	Cryoppt, FFP, PCC, rFfVIIa
Antiplatelets*			
Aspirin	None	7 d	dDAVP, Platelet XF
NSAIDs	None	1 d	dDAVP, Platelet XF
Persantine	None	10 h	dDAVP, Platelet XF
Clopidogrel	None	3-8 d	dDAVP, Platelet XF
Ticlopidine			
GPIIb/IIIa Inhibitors		time until < 50% inhibition	
Abciximab**	None	1 d/> 10 d	dDAVP, Platelet XF
Integrelin	None	< 4 h	dDAVP, Platelet XF
Tirofiban	None	2 h	dDAVP, Platelet XF
Slow Onset			
Inhibits factors II, VII, IX, X, Protein C and S synthesis in the liver			
Warfarin	Vitamin K	36-42 h	FFP, Cryoppt, PCC, rFVIIa

* Conjugated estrogens, aprotinin, rFVIIA can be used as well
* Hypersensitivity reactions, increased thrombocytopenia, decreased efficacy with redosing

Note: Readers should go to another source, preferably for guidelines that have been developed by a multidisciplinary panel under their hospital or health system.

heparin-treated patient or a recently hospitalized (and presumably recently heparin-treated) patient presents with thrombosis—an estimated 1 in 8 UFH-treated patients with new or recurrent venous thromboembolism has HIT.[19]

When HIT is strongly suspected, heparins should be stopped and rapid-onset, nonheparin anticoagulation should be initiated.[20,21] Heparins should continue to be avoided, if possible, at least while HIT antibodies persist (a minimum of 90 days), and the British Committee for Standards in Haematology[21] recommends using a heparin alternative for most patients with previous HIT who require anticoagulation. DTIs do not cause thrombocytopenia, do not induce or cross-react with HIT antibodies, and are indicated for use in patients with HIT (argatroban) or HIT with thrombosis (argatroban, lepirudin), and in patients with or at risk of HIT undergoing percutaneous coronary intervention (argatroban, bivalirudin). It has been suggested that fondaparinux, which exhibits negligible crossreactivity with HIT antibodies, may be useful for managing VTE in the context of recent heparin exposure and suspected, but not yet confirmed, HIT.[20]

Other Complications and Safety Concerns. *Anticoagulation.* The use of enoxaparin for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied, and frequent monitoring of antifactor Xa activity, with dose adjustment, may be needed. There is an

increased risk of thrombosis, sometimes fatal, when bivalirudin is used with gamma brachytherapy. Lepirudin frequently induces formation of antihirudin antibodies that may increase plasma lepirudin concentrations, requiring careful monitoring and dose adjustments to avoid bleeding, and approximately 0.2% of patients reexposed to lepirudin experience anaphylactoid reactions, including possible death.[13]

Antiplatelets. Ticlopidine may induce serious, life-threatening hematologic disorders, including thrombotic thrombocytopenia purpura and aplastic anemia, requiring prompt treatment. Severe neutropenia has been reported in 1-3% of ticlopidine-treated patients. Clopidogrel, which has a better safety profile than ticlopidine regarding bone marrow toxicity, has wide patient variability in inhibition of platelet function, with "nonresponders" and "clopidogrel resistance" described.[11] Thrombocytopenia, sometimes severe, may occur during abciximab treatment, usually within the first day. Readministration of abciximab, particularly within a month, is associated with an increased incidence and severity of thrombocytopenia and therefore should be undertaken only with caution. Affected patients should have abciximab stopped immediately.

Thrombolytics. Cholesterol embolization, sometimes fatal, rarely occurs in patients treated with thrombolytics. Coronary thrombolysis may result in arrhythmias associated with reperfusion. Anistreplase should not be used in a patient with a previous severe allergic reaction to streptokinase. Hypotension, sometimes severe and not secondary to bleeding or anaphylaxis, occurs in approximately 1-10% of patients treated with streptokinase. Anaphylaxis and other infusion reactions may occur within an hour of initiation of urokinase. Patients affected by allergic or anaphylactic conditions should be monitored closely and administered appropriate therapy.

Today, emergency physicians must be aware of the use and contraindications for a wide variety of anticoagulation medications. Clearly, the ideal anticoagulant for all patients has not been found. Not all anticoagulants are the same, and physicians must remember that each has a different profile of use, safety, and warnings.

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Physician CME Questions

51. Complications of ED anticoagulation include:

A. gastrointestinal bleeding.
B. chronic bronchitis.
C. heparin-induced thrombocytopenia.
D. A and C.
E. A, B, and C.

52. Argatroban, bivalirudin, and lepirudin are:
A. antithrombin-dependent anticoagulants used in patients with VTE.
B. direct thrombin inhibitors used in patients with HIT.
C. antiplatelet drugs currently in development.
D. recombinant tissue plasminogen activators used in patients with AMI.

53. The combination use of any drugs affecting hemostasis, i.e., anticoagulants, antiplatelets, or thrombolytics, potentiates the risk of bleeding, and this risk should be weighed carefully against the benefit of the treatment.
A. True
B. False

54. Which of the following statements about neuraxial hematoma is *false*?
A. It is a frequent complication of anticoagulation.
B. It may result in long-term paralysis.
C. An indwelling epidural catheter increases the risk of neuraxial hematoma with heparins.
D. There have been no reports of neuraxial hematoma in a patient administered a DTI.

55. A patient presents on day 20 of LMWH therapy for a pulmonary embolism with a new VTE in her other leg. Blood work shows a normal hematocrit and white count, but a platelet count of 50,000. Her INR is 2. Doppler studies confirm the VTE in her leg. At this point you should:
A. increase the dose of her LMWH.
B. switch to another LMWH.
C. stop her LMWH and start argatroban.
D. stop her LMWH and start UFH (unfractionated heparin).

56. A patient presents on chronic warfarin therapy. He has been taking 5 mg alternating with 10 mg for the past 5 years. An aPTT was drawn and shows his INR to be 1. At this time you should:
A. continue his warfarin therapy and suggest follow-up in 2 weeks.
B. increase his warfarin to 7.5 mg alternating with 10 mg.

C. increase his warfarin to 12.5 mg per day.
D. give warfarin 20 mg per day for 5 days then resume the previous dose.

57. Bleeding risk with unfractionated heparin increases with increasing dose and:
A. age > 70 years.
B. female gender.
C. allergy to aspirin.
D. coronary artery disease.

58. Aspirin therapy should be avoided in all of the following *except*:
A. children.
B. third-trimester pregnancy.
C. chronic lung disease.
D. patients with asthma, rhinitis, and nasal polyps.

59. A patient with severe end-stage renal disease (creatinine clearance < 30 mL/min) requires anticoagulation for a pulmonary embolism. Which of the following is true?
A. Fondaparinux is the drug of choice for patients with severe renal disease.
B. Lipirudin can be used without dose reduction.
C. Enoxaparin can be used but requires reduction in dosage.
D. No anticoagulant can be safely used in this patient.

60. A colleague presents a protocol for anticoagulation that was produced at another hospital. He received it from an old classmate who now practices in an inner city hospital. He suggests that your group adopt this protocol for use in your community hospital. What is the best answer for his request?
A. This protocol cannot be extrapolated to a different patient population.
B. Protocols represent cookbook medicine.
C. Protocols are useful when physicians are not well trained.
D. Protocols are meant for nurses and mid-level providers (nurse practitioners and physician assistants).

CME Answer Key

51. D; 52. B; 53. A; 54. A; 55. C; 56. B; 57. A; 58. C; 59. C; 60. A

Emergency Medicine Reports
CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Anticoagulation in the ED, Part II

Indications for the Rapidly Acting Anticoagulants Available in the United States, Effective November 2006

USE	UFH	LMWHS	FONDAPARINUX	DTIS
Thromboprophylaxis in arterial and cardiac surgery	X			
Thromboprophylaxis after hip replacement surgery		Dalteparin, enoxaparin	X	
Thromboprophylaxis after hip fracture surgery			X	
Thromboprophylaxis after knee replacement surgery		Enoxaparin	X	
Thromboprophylaxis after abdominal surgery, if at-risk	X	Dalteparin, enoxaparin	X	
Thromboprophylaxis in medical patients during acute illness		Dalteparin, enoxaparin		
Prophylaxis ischemic complications in UA/ non-Q-wave MI‡		Dalteparin, enoxaparin		
Prophylaxis and treatment of peripheral arterial embolism	X			
Prophylaxis and treatment of VTE	X			
Inpatient treatment of DVT +/- PE (with warfarin)		Enoxaparin, tinzaparin	X	
Outpatient treatment of PE* (with warfarin)			X	
Outpatient treatment of DVT (with warfarin)		Enoxaparin	X	
Atrial fibrillation and embolization	X			
Thromboprophylaxis/treatment in HIT				Argatroban, lepirudin†
PCI in patients with or at risk of HIT				Argatroban, bivalirudin
PCI with provisional GPIIb/IIIa inhibition				Bivalirudin
PTCA in patients with UA				Bivalirudin
Diagnosis/treatment of consumptive coagulopathies (DIC)	X			
During transfusions, dialysis, extracorporeal circulation; in blood samples for laboratory purposes	X			

* If treatment started in-hospital
† Lepirudin is indicated for patients with HIT and associated TEC to prevent further TEC.
‡ With aspirin; fondaparinux has been extensively evaluated in acute coronary syndrome,[5,6] and the data are under regulatory review.

Key: DIC = disseminated intravascular coagulation; DTI = direct thrombin inhibitor; DVT = deep venous thrombosis; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PTCA = percutaneous transluminal coronary angioplasty; TEC = thromboembolic complication; UA = unstable angina; UFH = unfractionated heparin; VTE = venous thromboembolism

Safety Issues with Rapidly Acting Anticoagulants in the United States, Effective November 2006

SAFETY CONCERN	UFH	LMWHS	FONDAPARINUX	DTIS
Avoid if hypersensitivity to drug or its components	X	X	X	X
Avoid if active major bleeding	X	X	X (or if bacterial endocarditis)	X
Use with extreme caution if increased risk of bleeding	X	X	X	X
Bleeding, including major hemorrhage, can occur	X	X	X	X
Black box warning: Neuraxial hematoma or spinal puncture	†	X	X	
Avoid in patients with UA or MI undergoing regional anesthesia		Dalteparin		
Avoid if severe thrombocytopenia, cross-reactivity with antiplatelet antibody in presence of drug, or current or previous HIT (or use with extreme caution if history of HIT)	X	X	X*	
Not for intramuscular injection	X	X	X	X
AT-dependent drugs not interchangeably used (unit for unit)	X	X	X	
Presence of renal impairment				
• Avoid if CLcr <30 mL/min and caution if CLcr 30-50 mL/min			X	
• Avoid if CLcr < 15 mL/min and reduce dose if CLcr <60 mL/min				Lepirudin
• Reduce dose if CLcr < 30 mL/min		Enoxaparin		Bivalirudin
Presence of hepatic impairment, reduce dose				Argatroban
Patient body weight				
• Avoid using for prophylaxis if < 50 kg			X	
• Antifactor Xa monitoring if > 150 kg		X‡		
Anaphylaxis risk on re-exposure				Lepirudin
Routine monitoring with coagulation assay	X			X
No antidote			X	X

* In vitro and in vivo cross reactivity with HIT antibody is negligible.
† Event has also been reported in association with UFH
‡ Per ACCP guidelines[7]; not in prescribing information of drugs.
Key: AT, antithrombin; CLcr, creatinine clearance; HIT, heparin-induced thrombocytopenia; MI, myocardial infarction; UA, unstable angina

Indications and Complications of Antiplatelets and Thrombolytics

DRUG	MECHANISM	INDICATIONS	MAJOR COMPLICATIONS
Antiplatelet			
Aspirin*	Thromboxane, cyclooxygenase	ACS, CVA/TIA	Hemorrhage, gastrointestinal
NSAIDs	Thromboxane, cyclooxygenase		Hemorrhage, liver
Dipyridamole*	cAMP	CVA/TIA	Hemorrhage, bronchospasm
Clopidogrel	ADP	ACS, PCI, CVA	Hemorrhage, platelet, TTP
Ticlopidine	ADP	CVA, PCI (post stent)	Hemorrhage, platelet, TTP
Abciximab	GPIIb/IIIa receptor	ACS PCI	Hemorrhage, platelet
Tirofiban	GPIIb/IIIa receptor	ACS PCI	Hemorrhage, platelet
Eptifibatide	GPIIb/IIIa receptor	ACS PCI	Hemorrhage, platelet
Thrombolytic			
Streptokinase	Plasmin	AMI, CVA, VTE	Hemorrhage
Anistreplase	Plasmin	AMI	Hemorrhage
Urokinase	Plasmin	PE	Hemorrhage
Alteplase	Plasmin	AMI, CVA, VTE	Hemorrhage
Reteplase	Plasmin	AMI	Hemorrhage
Tenecteplase	Plasmin	AMI	Hemorrhage

* A combination of aspirin and extended release dipyridamole is commercially available (Aggrenox), platelet = thrombocytopenia

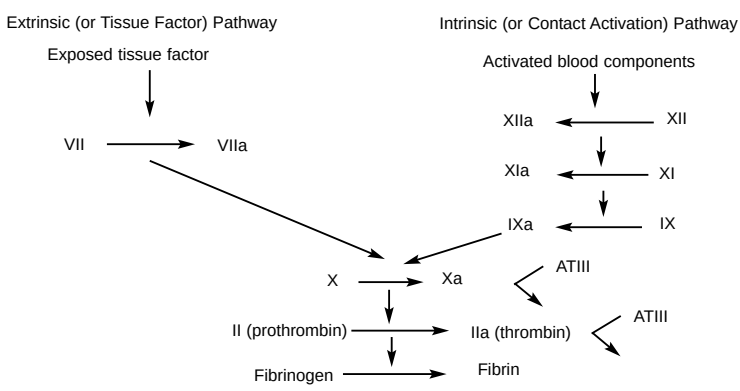
Reversal of Anticoagulants and Antiplatelets

DRUG/CLASS	REVERSAL AGENT	T ½	NON-SPECIFIC REVERSAL/SUPPORT
Rapid Onset			
Predominant antifactor II, X			
UFH	Protamine sulfate	90 min	PCC, rFVIIa
LMWH	Protamine sulfate*	3 h	PCC, rFVIIa
Fondaparinux	None	17 h	rFVIIa
Direct thrombin inhibitors			
Argatroban	None	40-50 min	FFP
Bivalirudin	None	25-40 min	FFP
Lepirudin	None	1.3-3 h	FFP
Thrombolytics			
Activate plasminogen to plasmin to lyse fibrin			
Multiple agents	None	25-130 min	Cryoppt, FFP, PCC, rFfVIIa
Antiplatelets*			
Aspirin	None	7 d	dDAVP, Platelet XF
NSAIDs	None	1 d	dDAVP, Platelet XF
Persantine	None	10 h	dDAVP, Platelet XF
Clopidogrel	None	3-8 d	dDAVP, Platelet XF
Ticlopidine			
GPIIb/IIIa Inhibitors		time until < 50% inhibition	
Abciximab**	None	1 d/> 10 d	dDAVP, Platelet XF
Integrelin	None	< 4 h	dDAVP, Platelet XF
Tirofiban	None	2 h	dDAVP, Platelet XF
Slow Onset			
Inhibits factors II, VII, IX, X, Protein C and S synthesis in the liver			
Warfarin	Vitamin K	36-42 h	FFP, Cryoppt, PCC, rFVIIa

* Conjugated estrogens, aprotinin, rFVIIA can be used as well
* Hypersensitivity reactions, increased thrombocytopenia, decreased efficacy with redosing

Note: Readers should go to another source, preferably for guidelines that have been developed by a multidisciplinary panel under their hospital or health system.

Coagulation Cascade



Drug	Principle Site of Action
Heparin	Thrombin (via ATIII)
LMWH	Factor Xa (via ATIII)
Warfarin	Factors II, VII, IX, X
DTIs	Thrombin
Fondaparinux	Factor Xa (via ATIII)
Fibrinolytics	Fibrin

Warfarin Therapy: Monitoring and Potential Effectors of Activity

- Monitoring the pharmacologic effects of anticoagulants is accomplished by daily measurement of patients: aPTT, PT (INR), CBC, and platelets.
- Prior to initiating therapy with anticoagulants patients should be screened for a history of a bleeding disorder, medication-related anaphylaxis, or HIT.
- Since certain medications and medical conditions may potentiate or attenuate the anticoagulant effects of certain medications, patients should be asked about current medications and medical ailments before starting anticoagulants or when a new medication is introduced to someone on an anticoagulant.

Examples of medications that may potentiate the anticoagulant effect of warfarin:

- Salicylates
- Acetaminophen
- Anabolic steroids
- NSAIDs
- Certain herbal medicines (such as ginkgobiloba)
- Phenytoin
- Sulfonamides
- Clofibrates
- Metronidazole
- Alcohol
- Anesthetics
- Diuretics
- Fluoroquinolones

Examples of medications that may attenuate the anticoagulant effect of warfarin:

- Barbiturates
- Rifampin
- Glutethimide

Medical conditions that may potentiate or attenuate the anticoagulant effects of warfarin:

- Liver disease, fever, hypertension, congestive heart failure, chronic diarrhea, diet low in vitamin K intake, for example.
- Dosing of low molecular weight heparins after required adjustment in the presence of chronic renal failure.

Supplement to *Emergency Medicine Reports*, March 5, 2007: "Anticoagulation and Thrombolytic Therapy in the Emergency Department: Part II." Authors: **Richard V. Aghababian, MD**, Professor and Chair, Department of Emergency Medicine, University of Massachusetts Medical School, Worcester; **Robert L. Levine, MD**, Associate Professor of Neurosurgery and Emergency Medicine, Chief, Division of Neurointensive Care, The University of Texas School of Medicine at Houston; and **Marcie J. Hursting, PhD, DABCC**, Director, Clinical Science Consulting, Austin, TX.

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Evidence-Based ... the ED

Trauma Reports

Enclosed in this issue: CNE/CME Evaluation

Vol. 8, No. 2

Supplement to *Emergency Medicine Reports* and *Pediatric Emergency Medicine Reports*

March/April 2007

Carbon monoxide poisoning is a treatable condition when recognized prior to devastating consequences. Early on, carbon monoxide (CO) poisoning may be subtle and elusive, with vague, nonspecific symptoms that may be inappropriately contributed to other conditions. Particularly, viral syndromes may be confused with CO poisoning and it is important, particularly in the winter months, to screen patients who have isolated vomiting without fever and diarrhea. Also, it is unusual for a whole family to be symptomatic with the "flu" at the same time, and in these situations a careful history and consideration of testing may avert disaster. Early recognition may only occur if the diagnosis is considered in the differential and may be life-saving. The authors comprehensively review the presentation, diagnosis, and treatment of CO poisoning.

— The Editor

Carbon Monoxide Poisoning

Authors: **Colin G. Kaide, MD, FACEP, FAAEM,** Clinical Assistant Professor of Emergency Medicine, Associate Director of Hyperbaric Medicine, The Ohio State University Medical Center, Columbus; **Sorabh Khandelwal, MD,** Clinical Associate Professor of Emergency Medicine, Director of Hyperbaric Medicine, The Ohio State University Medical Center; **Erika Kube, MD;** Emergency Medicine Resident, The Ohio State University Medical Center; **Douglas A. Rund, MD, FACEP**, Professor and Chairman of Emergency Medicine, The Ohio State University Medical Center.

Peer Reviewer: **Ian R. Grover, MD,** Assistant Clinical Professor of Medicine, Department of Emergency Medicine, University of California–San Diego Medical Center.

Introduction

"By turning the outside tap the room could be flooded with gas. With door and shutters closed and the tap full on I would not give two minutes of conscious sensation to anyone shut up in that little chamber."

—From the Sherlock Holmes story "The Adventure of the Retired Colourman" *by Sir Arthur Conan Doyle, in which Josiah Amberley used coal gas to murder his wife. Coal gas is a gaseous mixture—mainly hydrogen, methane, and CO—formed by the destructive distillation (i.e., heating in the absence of air) of bituminous coal and used as a fuel.*

The most devastating situation a physician may encounter is an easily treatable condition that is not recognized and results in a patient's death or permanent disability. Intentional CO poisoning may be obvious (in the case of a sui-

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cidal patient who presents comatose after inhaling car exhaust), but mild, unintentional CO poisoning presents with vague, nonspecific symptoms. Failure to make this diagnosis may result in a potentially treatable patient who is discharged back to the environment that sickened him in the first place, often with dire consequences.

Given that CO poisoning has higher morbidity and mortality rates than all other poisonings and is the most common poisoning overall, the likelihood of encountering a case in any practice is high. This review serves to make the emergency physician aware of the various presentations of CO poisoning as well as pitfalls surrounding diagnosis and management of the CO-poisoned patient.

Cases

Case 1: Daily Headaches. A healthy 30-year-old woman presented to an urgent care facility complaining of daily headaches associated with nausea for two weeks. The headaches were described as diffuse and aching in quality.

She notes that her symptoms began each day as she was driving to work and persisted for four to five hours, with complete resolution by the end of her work day. Her symptoms began again when she went home and lasted most of the evening. Her headache was lessened somewhat with ibuprofen. She denied fever, chills, vomiting, diarrhea, lethargy, stiff neck, confusion, or other systemic complaints.

Upon presentation, she did have a headache. Other than being slightly tachycardic with a heart rate of 110, her physical exam was essentially unremarkable. Her fingerstick glucose level was 90 mg/dL and her urine human chorionic gonadotropin was negative. Her headache improved with 600 mg of ibuprofen and 2 tablets of hydrocodone/acetaminophen (5/500); she was discharged with the diagnosis of tension headache.

She returned three days later with persistent but worsening headaches. Her presentation was similar to the prior visit. She was diagnosed with viral syndrome and a tension headache and discharged home.

She presented a third time after falling asleep at a traffic light on her way to work. She awoke when her car rear-ended another vehicle and went to the emergency department (ED) for further evaluation. The emergency physician, after obtaining a thorough history, established that her headaches always began as she traveled to and from work, a distance of 30 miles each way. Her headaches always improved after several hours and she did not have similar symptoms when taking short car trips. A carboxyhemoglobin (COHb) level was requested in the ED, which showed a level of 16%. (Normal levels are less than 2% for nonsmokers and less than 5% for smokers.) The fire department then tested her car with the engine running and the windows up. After 15 minutes, CO levels in the car reached 400 parts per million (ppm), which greatly exceeded the EPA standards for air quality.

The patient received 15 L oxygen by nonrebreather mask for 180 minutes, at which time her symptoms had resolved completely. She was discharged home with outpatient follow-up. Her car's exhaust system was repaired to prevent further CO poisoning.

Case 2: Flu-like Symptoms. A family of five (mother, father, and three children) presented to the ED on a Sunday morning with "flu-like symptoms." All family members described similar symptoms of fatigue, nausea, headache, and loss of appetite over the previous two days. Two of the three children had vomited several times over the previous day. The eldest child complained of a runny nose and discomfort around her eyes.

Physical examination findings were largely unremarkable for all of the family members. All vital signs were normal, with the eldest daughter having the highest temperature of 99.8°F. The family was diagnosed with flu/viral syndrome and discharged home.

Relatives were contacted the following Monday morning when the adults failed to report to work. Police were dispatched to the residence, where they found four of the family members and their two dogs dead. CO readings, as measured by the fire department, are typically done by averaging 2-3 samples taken in various places in the residence where the victims are found. Readings in this family's home were 890 ppm. The sole surviving family member, the eldest daughter, was found comatose in her bedroom, where the windows were open and CO levels were found to be 465 ppm. She was taken to a local ED, where her COHb level was 44%. She was flown to a tertiary referral center with hyperbaric oxygen therapy

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Table 1. Exogenous Sources of Carbon Monoxide

- Car exhaust fumes
- Paint removers containing methylene chloride
- Pool heaters
- Sterno fuel
- Tobacco smoke
- Wood-burning stoves
- Underground electrical cable fires
- Smoke from fires
- Furnaces
- Gas-powered engines
- Home water heaters
- Burning charcoal

capabilities. Despite aggressive hyperbaric oxygen treatments (HBO_2), she remained in a persistent vegetative state three weeks after the incident.

Case 3: Pregnant Woman. A 28-year-old pregnant mother presents to the ED with her two children, ages 2 and 4. The mother reports that the two children have been increasingly fussy and not eating or drinking well over the previous three days. Her husband is currently overseas serving in the United States Army. The mother states that she feels generally well, other than perhaps being more tired than usual and a little dizzy from time-to-time; both are symptoms that she attributes to being pregnant and caring for two small children.

Both children and the mother were afebrile on presentation, with the only abnormality being a slightly elevated pulse rate in all three. Upon further questioning about recent events, the mother reveals that some sort of "smoke detector" in her house had been going off because the battery in it had died; she was able to remove the old battery but was waiting for her husband to replace the new battery.

The emergency physician, being suspicious about an alarm going off and the presentation of the pregnant mother and children, decided to check a COHb level on all three. The mother's level was 26% and the children were 17% and 18%. Because the fetus is especially vulnerable to the effects of CO poisoning and likely had a level 10-15% higher than the mother, HBO_2 was initiated. She was treated with 3 atmospheres absolute (ATA) of HBO_2 for 60 minutes with a repeat dive at 2.4 ATA for 60 minutes and was discharged in good condition the following day. She delivered a healthy baby at term with no further sequelae. Additionally, she repaired the faulty water heater that caused the CO poisoning and replaced the battery in her CO detector, which she had mistaken for a smoke detector.

Case 4: Complicated CO Poisoning. A 47-year-old male is brought to the ED from a house fire. Paramedics report that the patient was found with agonal respirations in a closed room in the basement where the carpet and wall-paper had fully burned. On presentation to the ED his primary survey showed an intubated male with a blood pressure of 50 systolic and a pulse of 40. The respiratory rate with the assistance of bag-valve-mask was 18.

The patient received 3 mg of atropine with minimal response in heart rate. The patient was started on dopamine and titrated to 20 mcg/kg/min with the blood pressure increasing to 60 systolic. Lab values showed a pH of 7.0, PaO_2 of 400 on FiO_2 of 100%, $PaCO_2$ of 30, and a $HC0_3$ of 3. The patient received a total of 4 amps of bicarb, with the resultant pH rising to 7.1. Serum lactate levels were 18 and the COHb was reported to be 25%.

The emergency medicine resident on the case noticed that the blood return from her central line placement was very bright red, such that she thought she had placed the line inadvertently in the femoral artery. After not finding pulsatile flow, she used the line and made a second stick in the groin to place an arterial line. This produced pulsatile flow that appeared to be the exact same color as the venous blood. At this point she made the connection between the similar colors and possible explanation of a decreased oxygen utilization manifesting in the bright red venous blood. She concluded that cyanide was a likely concomitant agent contributing to the patient's clinical picture. The patient was treated with sodium thiosulfate and sodium nitrite along with hyperbaric oxygen at 3 ATA for 60 minutes. The patient rapidly recovered with normalization of pH and vital signs.

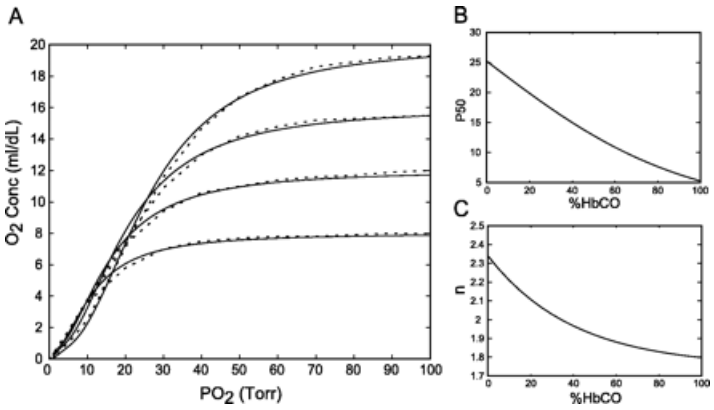
Epidemiology

While CO poisoning is the leading cause of death and injury due to poisoning in the United States,[1,2] the worldwide incidence of CO poisoning is estimated to be largely underdiagnosed, with more than one third of all cases going undetected. A 2001 study had emergency medical technicians use hand-held CO meters to screen for elevated levels of CO during emergency responses. Over a three-month period they obtained readings in 264 residences, of which nine (3.4%) were positive. In these nine homes, 35% of the residents had symptoms that could be attributed to CO exposure.[3]

In the United States, it is estimated that more than 40,000 presentations per year are related to CO poisoning, based on data obtained from three western states.[4] The Centers for Disease Control and Prevention reported that CO poisoning contributed to an average of 1902 unintentional deaths and 2385 intentional suicides per year in the United States from 1968 through 1998.[5,6] In the three-year period from 2001 through 2003, there were more than 15,000 annual ED visits related to CO exposure/poisoning and 500 annual deaths attributed to unintentional, non-fire-related CO exposure.[7] Annual associated mortality rates are estimated to be as high as 31% in large series studies, while other studies have shown mortality rates as low as 1-2%.[2]

CO poisoning epidemics occur commonly during winter months with the misuse of non-electronic heating and cooking devices.[8,9] Use of these devices also has been shown to increase CO poisoning incidence during natural disasters like hurricanes, where prolonged power outages are common.[10]

Figure 1. Oxygen Dissociation Curves



A: Actual (solid line) and predicted (dashed line) oxygen (O_2) dissociation curves of Hb at various levels (0%, 20%, 40%, and 60%) of HbCO. Nonlinear regression relationships for the parameters of Hill's equation [PO_2 necessary to reach 50% Hb saturation (P50; **B**) and n (**C**)] as a function of HbCO level.

Used with permission from: Bruce EN, Bruce MC. A multicompartment model of carboxyhemoglobin and carboxymyoglobin responses to inhalation of carbon monoxide. *J Appl Physiol* 2003;95:1235-1247.

Table 2. Clinical Presentations of CO Poisoning

MILD/MODERATE CO POISONING

- Headache
- Nausea
- Non-specific "dizziness"
- Weakness
- Difficulty concentrating

SEVERE CO POISONING

- Confusion
- Severe lethargy
- Chest pain
- Syncope
- Unconsciousness or coma

CO is the product of incomplete combustion of carbon-based products, such as gas or coal. Because it is colorless, odorless, and tasteless, CO is undetectable by human senses. While there are numerous potential sources (*see Table 1*) for CO, the two most common are motor vehicle exhaust and smoke. Of CO-related deaths between 1979 and 1988, 57% were caused by vehicle exhaust and 83% involved a stationary vehicle.[11] Methylene chloride, a chemical found in some automotive cleaners, spray paints, and other household products, is converted into CO in the liver after the compound is ingested or inhaled.[12]

The effects of CO become apparent after an exposure period of 20 hours to ambient levels as low as 100 ppm. EPA guidelines for CO exposure in the workplace state that levels should not exceed 35 ppm over one hour or 9 ppm over eight hours. While steady state time depends on individual factors (including CO diffusing capacity and alveolar ventilation), in general, in the steady state after equilibrium, CO levels of 100 and 200 ppm produce average COHb levels of 16 and 30%, respectively.[13] Exposure to levels near 1000 ppm for more than two hours can result in COHb levels of 50% or greater. Chimney smoke from a wood-burning stove contains approximately 5000 ppm CO. Warm, undiluted car exhaust contains 7000 to 8000 ppm CO. Undiluted cigarette smoke contains 16,000 to 30,000 ppm CO.[14,15] A CO level of 1200 ppm is considered immediately dangerous to life.[16]

Pathophysiology

CO pathophysiology was accurately described as early as 1846, when Claude Bernard, a French physician and physiologist, referred to CO as a "poison that troubles the blood by displacing oxygen." The effects of CO have been appreciated since ancient times, when Roman and Greek empires used CO in state executions.[17]

CO toxicity is a result of tissue hypoxia and direct CO-mediated damage at the cellular level. CO binds competitively to hemoglobin; in fact, hemoglobin's affinity for CO is 240 times that of oxygen. This is why, even with low ambient levels of CO, significant toxicity can result over time with prolonged exposures. In addition to hemoglobin binding with CO with such great affinity, the binding of CO to hemoglobin causes a leftward shift of the oxyhemoglobin dissociation curve (the Haldane effect). This results in a decrease in oxygen delivery to the peripheral tissues. The net results are impaired oxygen delivery, cellular hypoxia, and increasing minute ventilation (respiratory rate X tidal volume). Increasing minute ventilation results in respiratory alkalosis that further shifts the oxyhemoglobin dissociation curve to the left, facilitating a vicious cycle of worsening tissue hypoxia. *(See Figure 1.)*

In addition to binding hemoglobin, carbon monoxide binds cardiac and skeletal myoglobin, with a three times greater affinity for cardiac myoglobin than hemoglobin.[18] Because carboxymyoglobin dissociation is slower than that of COHb due to its increased affinity, it is possible to see a rebound effect with late release of CO from myoglobin and its subsequent binding to hemoglobin.[19]

During pregnancy, the fetus is particularly vulnerable to CO exposure because fetal hemoglobin binds CO with a greater affinity than hemoglobin A. This, combined with slow transplacental transport and the fact that fetal oxyhemoglobin is naturally shifted to the left, can cause fetal CO levels to be deadly in exposures that would typically be nonfatal.[20,21]

Hypoxia can explain some of the effects of CO in the acute phase, particularly the cardiac and neurological symptoms seen frequently with the presentation of CO poisoning. Hypoxia alone, however, cannot explain all the pathophysiologic consequences of CO poisoning. CO interferes with peripheral oxygen utilization by combining with myoglobin, cytochromes, and triphosphopyridine nucleotide reductase, directly interfering with oxidative phosphorylation.[22] CO also impairs tissue perfusion by inducing hypotension through myocardial depression, ventricular arrhythmias, and peripheral vasodilation.[23] Postischemia reperfusion injury, brain lipid peroxidation, and subsequent demyelination of central nervous system (CNS) lipids are also seen with CO exposure.[24] These CNS effects, which are reversible and occur after CO exposure, are mediated largely by leukocytes.[25] Lastly, CO exposure creates oxidative stress on cells, leading to generation of oxygen free radicals, with implications for further cellular damage.[26,27]

It is not uncommon to see CO poisoning complicated by cyanide poisoning in victims of closed-space fires in which synthetic materials are burned. Cyanide worsens cellular hypoxia by binding of the cyanide to the mitochondrial cytochrome oxidase, thus preventing the ferric iron-dependent reduction of oxygen to water by cytochrome aa_3. This effectively inhibits oxidative phosphorylation, preventing the conversion of adenosine diphosphate to adenosine triphosphate. The net effect is anaerobic metabolism and severe lactic acidosis.[28]

The standard treatment for cyanide toxicity is the cyanide antidote kit, which contains amyl nitrite, sodium nitrite, and sodium thiosulfate. When CO and cyanide poisoning are both suspected, the empiric administration of nitrites is cautioned due to the formation of a significant amount of methemoglobinemia, which further impairs the patient's oxygen carrying capacity. In a patient with severe COHb, HBO_2 confers the benefit of increasing the amount of soluble oxygen many-fold, thus improving tissue oxygenation. However, the increased oxygen saturation would competitively inhibit the formation of methemoglobin, reducing the effectiveness of the cyanide antidote kit. This complicating issue of reducing the effectiveness of the cyanide antidote by treating the CO poisoning may no longer be an issue when hydroxocobalamin or ethylenediaminetetraacetic acid (EDTA) become approved as cyanide antidotes in the United States. Until that time, however, HBO_2 remains the mainstay of therapy for severe CO poisoning, even at the expense of decreasing the amount of methemoglobinemia and the effects of cyanide toxicity.[29]

Presenting Features

The signs and symptoms of CO exposure depend on the amount of CO in inspired air, minute ventilation, and duration of exposure to CO. The diagnosis of CO poisoning can be easily missed because the clinical findings of CO poisoning are highly variable and nonspecific and can mimic a viral syndrome.[30] (*See Table 2.*) The emergency physician must include CO poisoning in the differential diagnosis of every patient who presents with any of the common symptoms. This is especially true in winter months, when both viral syndromes and accidental CO poisonings occur with greater frequency.

Table 3. Carbon Monoxide Neuropsychologic Screening Battery (CONSB)

Purpose of test: To determine if a patient has subtle neurologic symptoms in the acute care setting

Six subtests:
- General orientation
- Digit span
- Trail making
- Digit symbol
- Aphasia screening
- Block design

While there is a correlation between the degree of a patient's symptoms and a rise in measured COHb levels, the actual COHb level does not predict the degree of symptoms that a patient may experience. One can generalize about symptomatology at the extremes of COHb levels. COHb levels between 3% and 10% are common in asymptomatic cigarette smokers.[31] Levels greater than 25% are considered significantly elevated, with levels between 40% and 50% almost always causing overt symptoms.[16]

At lower COHb levels, acute CO poisoning usually presents with symptoms such as headache, dizziness, nausea, and weakness. As COHb levels increase, patients may become confused or have difficulty concentrating, which can proceed to lethargy and coma.[30,32,33] Tachycardia and tachypnea may develop in response to cellular hypoxia. Additionally, the sensation of air hunger and agitation may be seen, which can progress in later stages to hypotension, bradycardia, and decreased respirations.

The extremes of age are at higher risk for morbidity and mortality from CO exposure. Patients with coronary artery disease may have anginal symptoms or actual myocardial infarction after CO exposure, due to the relative hypoxia at the cellular level.[34] Patients with underlying pulmonary and cerebrovascular disease may also experience worsening of their conditions. The classically described cyanotic patient with cherry-red lips is actually rarely seen.[35]

It is not uncommon to have a patient awake and alert on ED presentation, despite having been described by rescuers as unconscious or barely conscious at the scene. Despite their grossly normal cognitive status on presentation, these patients have sustained hypoxia sufficient to cause end-organ injury and syncope and require aggressive treatment. Secondary ischemic injury frequently is seen in severe CO poisoning.

Since patients can be considered "alert and oriented × 3" and still have some degree of cognitive impairment, a neuropsychologic (NP) testing battery has been developed to help assess subtle cognitive changes that may be overlooked during

Table 4. Key Points for the Diagnosis of CO Poisoning

- High index of suspicion
- Diagnosis is confirmed by venous or arterial carboxyhemoglobin level:
  - > 5% for a non-smoker
  - > 10% for a heavy smoker

routine ED examination. The Carbon Monoxide Neuropsychologic Screening Battery (CONSB), which takes up to 30 minutes to administer, consists of six different tests that together assess global cognitive function. *(See Table 3.)* Although some centers use this as criteria for HBO_2 treatment, there is controversy as to whether the testing has the ability to predict which patients will develop delayed neurologic sequelae (DNS). Furthermore, some feel that the testing doesn't allow for differentiation between cognitive impairment from CO and cognitive impairment from other possible coingestants. Finally, it may be difficult to attribute abnormal NP testing to CO poisoning in patients with preexisting psychological and psychiatric illnesses.

Specific Injury Patterns

There are three specific injury patterns that deserve special mention: cardiovascular sequelae, delayed neurological sequelae (DNS), and symptoms associated with long-term exposure.

As moderate to severe CO poisoning is associated with an increased risk of cardiovascular sequelae, an electrocardiogram (ECG) and cardiac biochemical markers should be obtained at presentation and followed throughout the hospitalization.[36] A patient presenting with cardiac injury must be closely followed during hospitalization and at discharge as there does appear to be a correlation between myocardial injury at presentation and long-term mortality.[37]

A significant proportion of patients, up to 40%, with significant CO exposure develop a syndrome of DNS, characterized by variable degrees of cognitive deficits, movement disorders, personality changes, and focal neurological deficits. While onset of DNS is usually within 20 days of recovery from the initial insult, they have been shown to occur as many as 240 days afterward. These deficits may last for a year or longer, necessitating ongoing neurological and neuropsychiatric follow-up.[38-40]

Chronic CO poisoning from long-term exposure at low levels is frequently overlooked due to obscure and vague symptomatology, a wide range of presentations, and a general lack of awareness of the problem. The most commonly reported symptoms are: headache, dizziness, insomnia, anorexia, nausea, weight loss, apathy, and personality disturbance. Palpitations, impaired memory, decreased libido, increased sweating, impairment in sleep, and diminished alcohol tolerance also may be seen. Neurological signs including hyperreflexia, altered pain perception, nystagmus, ataxia, weakness, tremors, myoclonus, hemiplegia, anosmia, aphasia, and facial nerve palsies have been reported.[41,42]

Diagnosis

The diagnosis of acute CO poisoning requires diligence and an algorithmic approach. A history of potential exposure is the most reliable indicator, although this may be difficult to ascertain. Thus a high index of suspicion on the part of the emergency physician is paramount. (*See Table 4.*) In practical terms, this means that the emergency physician must at least consider CO poisoning in any patient who presents with nausea, headache, dizziness, or lethargy. While this consideration is vital, testing COHb levels on all patients with these symptoms is not appropriate.

The emergency physician must consider the diagnosis of CO poisoning and choose whether or not to pursue it based on its apparent likelihood in a given patient. A patient, for example, who presents with a headache who lives with asymptomatic family members and whose home is heated with electricity is unlikely to have CO poisoning. In contrast, a patient with the same symptoms living alone in a home heated by gas would be a reasonable candidate for further testing.

When considering CO poisoning in families or groups of people, it is important to remember that the patients usually have parallel presentations. On the other hand, viral syndromes tend to cause illness in an index member of the family who then passes the disease on to other group members. These other family members present serially and independently to their physicians. When an entire family presents with similar symptoms that fit the demographics and patterns for CO poisoning, this diagnosis must be pursued and excluded.

Emergency physicians must resist the tendency to describe a constellation of symptoms as "flu-like" when they lack the cardinal elements that characterize influenza, such as headache, myalgia, fever, and cough. Additionally, a diagnosis of gastroenteritis is inappropriate when only nausea and vomiting are present. True gastroenteritis is characterized by both vomiting and diarrhea, the latter of which is not a symptom of CO poisoning.

COHb levels may in fact be normal at presentation, particularly if the patient has been removed from the CO source for some time. Once CO poisoning is suspected, the COHb level can be measured in either venous or arterial blood samples, with venous usually being the preferred source.[43] It is important to note that pregnancy and hemolytic anemia can increase COHb levels to 5%, and heavy smoking can elevate levels to as high as 13%.[44]

Pulse oximetry has no role in the screening or diagnosis of CO poisoning, because pulse oximeters misread COHb for oxyhemoglobin and give falsely elevated oxygen saturation values. There is a new noninvasive CO oximeter on the market, which if proven in the acute setting, will greatly facilitate screening for CO toxicity.[45] If a patient's COHb levels are normal at the time of evaluation but the index of suspicion for CO

Table 5. Treatment of CO Poisoning

MILD AND MODERATE CO POISONING

Mild CO: Levels < 30% with no signs or symptoms of impaired CV or neurologic function

Moderate CO: CO Levels between 30-40% with no signs or symptoms of impaired CV or neurologic function

- Normobaric oxygen: Place patient on high-flow (10-15 LPM) oxygen by non-rebreather mask until remaining CO levels are approximately < 5%. There is no need to recheck levels. Assume the half-life of CO is about 90 minutes on high-flow oxygen and treat for 4 half-lives (360 minutes or 6 hours). Very mild symptoms MAY be treated for a shorter duration.
- Consider admitting mild CO poisoning if the patient has a history of cardiovascular disease.
- Discharge asymptomatic patients after normobaric oxygen treatment.
- Patients who are still symptomatic after treatment for 6 hours on normobaric oxygen should be considered for treatment with hyperbaric oxygen.

SEVERE CO POISONING

Severe CO: CO levels > 40% *OR* cardiovascular and/or neurological impairment at any CO level

- Normobaric oxygen: Place patient on high-flow (10-15 LPM) oxygen by non-rebreather mask for 6 hours.
- Immediate transfer to a hyperbaric facility should be undertaken if possible for any of the following:
  - Any neurologic dysfunction such as any history of syncope (even if now awake), current unconsciousness or altered LOC (GCS < 15) or evidence of cognitive impairment.
  - Any cardiovascular dysfunction: Anginal chest pain, ischemic ECG changes or dysrhythmia.
  - Metabolic acidosis with a pH < 7.1.
  - Pregnant patients with CO levels > 15%, regardless of symptoms or if any fetal distress is detected, regardless of the mother's CO level.
- Patients who are still symptomatic after treatment for 6 hours on normobaric oxygen should be considered for treatment with hyperbaric oxygen.
- Admit all patients with severe CO poisoning.

toxicity remains high, it is not unreasonable to send police, emergency medical services, or the local gas company to test ambient CO levels at the site in question.

Treatment

Prompt removal of the patient from the source of CO poisoning and high-flow oxygen by nonrebreather mask at 15 L/min is the mainstay of treatment for acute CO poisoning. (*See Table 5.*) It is important to remember that the highest attainable percentage of oxygen delivery by a nonrebreather mask in conventional treatment settings is 75% fraction of inspired oxygen (FiO_2). This is due to the entrainment of room air into the mask during inspiration. The use of 100% FiO_2 would be ideal to hasten the removal of CO from the hemoglobin molecule; however, this is only attainable in the operating room by way of an anesthesia circuit.[46] Breathing this concentration of oxygen effectively reduces the half-life of COHb from 300 minutes at ambient atmospheric conditions to 90 minutes. Seizures, cardiac ischemia, hypotension, and other complications of acute CO poisoning can be managed supportively.

The use of HBO_2 in the treatment of CO poisoning is widely accepted due to a clear scientific rationale for its use, but controversy does exist in some circles regarding its clinical efficacy. At 3 ATA, which is three times ambient atmospheric pressure, HBO_2 decreases the half-life of COHb to less than 30 minutes.[47] HBO_2 also increases the amount of oxygen dissolved in blood from 0.3 mL/dL with 100% FiO_2 to 6 mL/dL under hyperbaric conditions, which is enough to sustain life even in the absence of hemoglobin. In animal studies, HBO_2 has been shown to promote the dissociation of CO from cytochrome-c oxidase, inhibit leukocyte adhesion, and reduce brain lipid peroxidation.[48-50] These effects appear to play a role in limiting direct cellular toxicity and decreasing the incidence of DNS.

The results of six prospective, randomized trials have been reported to date comparing normobaric O_2 versus hyperbaric O_2 in patients presenting with acute CO poisoning. Of these, four have demonstrated positive results[51-54] while two have shown no effect.[55,56] The two studies that have generated the most discussion in the past several years are the ones headed by Scheinkestel's group from Australia and Weaver's group from the United States. The former study concluded that there was no benefit from HBO_2 in CO poisoning. However, there are numerous criticisms of the study, which affect its validity: poor followup at one month (46%) and poor followup long-term (38%); use of cluster randomization; unconventional treatment regimens that could result in pulmonary oxygen toxicity, including a minimum of three days of normobaric oxygen; delay in initiating hyperbaric treatment for acutely poisoned patients; poor outcomes in both treatment arms when compared to other trials; and the presence of psychoactive substances and depression in a significant percentage of the study population, likely influencing the results of neuropsychiatric testing.[57] Weaver's study demonstrated that HBO_2 therapy reduces cognitive sequelae after acute CO poisoning. Criticisms of this study include the control group hav-

Table 6. UHMS Indications for Hyperbaric Oxygen Therapy

- Air or gas embolism
- Carbon monoxide poisoning
- Carbon monoxide poisoning complicated by cyanide poisoning
- Clostridial myositis and myonecrosis (gas gangrene)
- Crush injury, compartment syndrome, and other acute traumatic ischemias
- Decompression sickness
- Enhancement of healing in selected problem wounds
- Exceptional blood loss (anemia)
- Intracranial abscess
- Necrotizing soft tissue infections
- Osteomyelitis (refractory)
- Delayed radiation injury
- Skin grafts and flaps
- Thermal burns

Table 7. Cyanide Toxicity

SOURCES (PRODUCE CYANIDE WHEN BURNED)

- Wool, silk
- Household plastics, polyurethane foam, other synthetic compounds

PATHOPHYSIOLOGY

- Inactivation of cytochrome oxidase
- Uncoupling of mitochondrial oxidative phosphorylation
- Inhibition of cellular respiration

CLINICAL SYMPTOMS

- General weakness
- Neurologic symptoms
  - Headache
  - Vertigo
  - Dizziness
  - Confusion
  - Seizures
  - Coma
- Gastrointestinal symptoms
  - Vomiting
  - Abdominal pain
- Cardiopulmonary symptoms
  - Apnea
  - Shortness of breath

LABORATORY TESTING

- Pulse oximetry
  May be falsely reassuring
- Arterial and venous blood gases
  Metabolic acidosis combined with reduced arterial-venous oxygen saturation difference (< 10 mmHg) suggests the diagnosis
- Blood lactate level
  > 10 mmol/L in a victim of smoke inhalation suggests significant exposure

TREATMENT

- Sodium bicarbonate should be given if the patient is unconscious, hemodynamically unstable and acidotoc (elevated lactates)
- Cyanide antidote kit
  - Amyl nitrite pearls
  - Sodium nitrite [a]
  - Sodium thiosulfate

[a] The sodium nitrite portion should not be given in patients with smoke inhalation unless the carboxyhemoglobin level is very low (< 10%)

ing a disproportionately higher CO exposure, a higher incidence of pretreatment cerebellar neurologic deficits, and treatment with less normobaric oxygen than in other major published studies. Outcomes also have been called into question after using different criteria to analyze the data.[58] These criticisms are discussed by the respective authors in detail and the reader is encouraged to review these papers.[58-60]

A recent Cochrane Database of Systematic Reviews maintains that data from existing randomized trials do not show that HBO_2 reduces the incidence of adverse neurological outcomes and neurological sequelae in patients with CO poisoning.[61] However, they emphasize that their results should be interpreted cautiously because methodology varied significantly among the trials, and all trials had flaws in design and analysis. The authors of a recent systematic review concluded that HBO_2 should not be used routinely; however, it may benefit patients with moderate to severe CO poisoning.[62] Reviewers from *The New England Journal of Medicine*, and commentaries in *Journal Watch–Emergency Medicine*, *Journal Watch–Internal Medicine*, and the ACP Journal Club all appear to accept Weaver's conclusions.

The Undersea and Hyperbaric Medical Society (UHMS), using an evidenced-based approach, has published its recommendations concerning the use of HBO_2 in the treatment of acute CO poisoning, and they recommend HBO_2 for patients presenting with transient or prolonged unconsciousness, cardiovascular dysfunction, neurologic signs, or severe acidosis.[29] *(See Table 6.)*

While HBO_2 may not be appropriate in every patient, its potential clinical benefit coupled with its minimal side-effect profile (primarily middle ear barotrauma) should result in its administration to patients who demonstrate any of the following: coma; acidosis with a pH below 7.1; history of loss of consciousness (even if awake on presentation); any neurological abnormality; evidence of cardiac dysfunction. Pregnant women would benefit from HBO_2 with COHb levels above 15% or if they exhibit any signs of fetal distress. Patients with persistent neurological symptoms despite normobaric oxygen therapy, patients with neuropsychometric abnormalities, or patients with severely elevated COHb levels may also derive benefit from HBO_2.

Despite the general acceptance of HBO_2 for the treatment of severe CO poisoning, no single, universally accepted protocol for pressure and duration of treatments has been established within the hyperbaric community. Protocols generally range from a single treatment for 60 minutes at a pressure of 2.8-3.0 ATA to multiple treatments at varying pressures. There is evidence to support a multi-treatment regimen based on work by Gorman and Runciman that showed lower mortality and less residual neurological deficits with multiple treatments.[63]

Cyanide Toxicity

Cyanide is by itself a rare cause of poisoning; however cyanide exposure occurs relatively commonly in patients that are victims of smoke inhalation from either residential or industrial fires. Cyanide may be released when many synthesized (e.g., polyacrylonitrile, polyurethane, polyamide) or natural (e.g., wool, silk) compounds are burned. *(See Table 7.)*

Cyanide adversely affects all body tissues and principally inactivates cytochrome oxidase, which uncouples mitochondrial oxidative phosphorylation and inhibits cellular respiration. Rapidity of onset of symptoms is dependent on the type of cyanide involved, route of entry and the dose. Presenting symptoms may include general weakness, neurologic symptoms (headache, vertigo dizziness, confusion, seizures, coma), gastrointestinal symptoms and cardiopulmonary symptoms (apnea, shortness of breath). Although the onset of symptoms may be dramatic, the physical examination findings are typically nonspecific. The patient may have cherry-red skin coloring. The smell of bitter almonds on the breath may be suggestive, but 60% of the population cannot detect the smell. Pulse oximetry may be high and falsely reassuring.

Laboratory testing may include arterial and venous blood gases and blood lactate level. A metabolic acidosis, frequently severe, associated with a reduced arterial-venous oxygen saturation difference (< 10 mmHg) suggests the diagnosis. A plasma lactate level greater than 10 mmol/L, in a victim of smoke inhalation, suggests significant cyanide exposure. Cyanide blood concentrations are typically not available in time to aid in the treatment of acute poisoning.

In addition to supportive care, treatment for cyanide toxicity should be initiated as soon as the diagnosis is suspected. Sodium bicarbonate should be given if the patient is unconscious, hemodynamically unstable and acidotoc (elevated lactates). The cyanide antidote kit should then be administered and contains amyl nitrite pearls, sodium nitrite and sodium thiosulfate. The sodium nitrite portion should not be given in patients with smoke inhalation unless the carboxyhemoglobin level is very low (< 10%).

Conclusion

Every emergency physician should expect to encounter a patient with CO poisoning. It is vital to maintain a high index of suspicion because this complicated and often lethal entity is associated with highly variable clinical presentations. (*See Table 8.*) Intervening in the ED may inhibit or decrease the pathophysiologic consequences that are mediated by multiple mechanisms at the cellular level.

Measuring the COHb level using a venous sample or CO oximeter can help the physician confirm a suspected diagnosis of CO poisoning. Normobaric, high-flow oxygen is the standard treatment, with hyperbaric oxygen reserved for select cases. Additionally, the emergency physician should provide patients information regarding CO toxicity and ways to prevent this common poisoning.

All emergency physicians should be intimately familiar with the varied clinical presentations of CO poisoning to make a life-saving diagnosis and avoid missing it. When a patient presents with headache, lethargy, vomiting, nonspecific dizziness, or an afebrile viral-like illness without signs of upper-respiratory tract infection, the emergency physician should ask the vital question, "Why *isn't* this CO poisoning?"

Table 8. Pitfalls and Perils

- Avoid basing treatment on CO levels and accidentally underestimating the degree of cognitive impairment.
- Syncope, even in a currently awake patient, represents end-organ injury and should be treated as a severe CO poisoning.
- Pregnancy with CO levels > 15% are severe poisonings, owing to increased fetal uptake of CO.
- Do not diagnose patients with "the flu" with absence of fever, cough, headache, myalgia or with gastroenteritis in the absence of diarrhea.
- Pulse-oximetry is of no value in diagnosing CO poisoning
- ***Remember*** to ensure that other family members who may still be in a CO-poisoned environment are warned to leave the affected area.

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CNE/CME Objectives

Upon completing this program, the participants will be able to:

a.) discuss conditions that should increase suspicion for traumatic injuries;
b.) describe the various modalities used to identify different traumatic conditions;
c.) cite methods of quickly stabilizing and managing patients; and
d.) identify possible complications that may occur with traumatic injuries.

Physician CME Questions

1. Which of the following patients should have carbon monoxide poisoning considered in their differential?
   A. A 3-year-old with vomiting for two days who has had no fever
   B. A 17-year-old with headaches that occur in the evening and at night while at home and recede during school hours
   C. A 55-year-old businessman who has had palpitations and shortness of breath and who lives alone
   D. All of the above

2. Which of the following is true regarding CO poisoning?
   A. It is an uncommon cause of death and injury in the United States.
   B. Epidemics of CO poisoning commonly occur during the winter months.
   C. The odor and color of CO is readily apparent, making detection easy.
   D. The two most common potential sources of CO poisoning are gas-powered engines and burning charcoal.

CNE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. **After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided in order to receive a letter of credit.** When your evaluation is received, a letter of credit will be mailed to you.

3. Carbon monoxide toxicity is best described as a result of:
   A. Tissue hypoxia and direct CO-mediated damage at the cellular level
   B. CO binding noncompetitively to hemoglobin resulting in the Haldane effect
   C. Carbon monoxide not binding cardiac and skeletal myoglobin
   D. Decreasing minute ventilation resulting in respiratory alkalosis that further shifts the oxyhemoglobin dissociation curve to the right

4. Which of the following is true regarding CO exposure during pregnancy?
   A. The fetus is particularly vulnerable to CO exposure.
   B. Fetal hemoglobin binds CO with a greater affinity than hemoglobin A.
   C. Slow transplacental transport of CO occurs.
   D. All of the above

5. Which of the following is true regarding cyanide poisoning?
   A. It may complicate CO poisoning in victims of closed-space fires in which synthetic materials are burned.
   B. Cyanide improves cellular hypoxia by releasing the mitochondrial cytochrome oxidase.
   C. Cyanide improves oxidative phosphorylation.
   D. Cyanide toxicity results in aerobic metabolism and reversal of lactic acidosis.

6. Which of the following is *not* true regarding the presentation of patients with CO exposure?
   A. The young and elderly are at higher risk for morbidity and mortality.
   B. At lower COHb levels patients tend to present with symptoms such as headache, dizziness, nausea and weakness.
   C. A cyanotic patient with cherry-red lips is common.
   D. As COHb levels increase patients may become confused or have difficulty concentrating.

7. Which of the following is *not* part of the syndrome of DNS that a significant proportion (up to 40%) of patients with severe CO exposure may develop?
   A. Variable degrees of cognitive deficits
   B. Movement disorders
   C. Personality changes
   D. Tardive dyskinesia

8. A 30-year-old female presents with a worsening headache, no fever, and vomiting. A CO level is obtained and is 20%. Which of the following is the most appropriate initial therapy?
   A. Cyanide kit
   B. Normobaric oxygen therapy
   C. Immediate hyperbaric oxygen therapy
   D. Repeat levels until normalized

9. For which of the following should immediate transfer to a hyperbaric facility, after appropriate stabilization, be considered?
   A. Current unconsciousness or altered level of consciousness
   B. Cardiovascular dysfunction
   C. Metabolic acidosis with a pH < 7.1
   D. All of the above

10. Which of the following is *not* true regarding CO poisoning?
   A. Pregnancy with CO levels > 15% are severe poisonings.
   B. Syncope is not a significant symptom for a patient with CO poisoning.
   C. Clinical information and CO levels should be used together to decide patient treatment.
   D. Pulse oximetry is of no value in diagnosing CO poisoning.

Answers

1. D; 2. B; 3. A; 4. D; 5. A; 6. C; 7. D; 8. B; 9. D; 10. B

In Future Issues:

Hip Fractures

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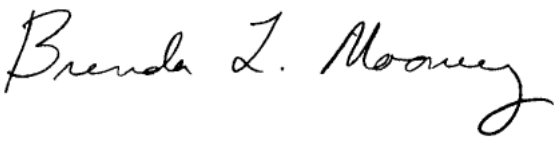

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