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In 1980, researchers published a landmark study that demonstrated that transmural myocardial infarction (MI) is caused by occlusive coronary thrombosis.[1] Several years later, the first thrombolytic agent, streptokinase, was found to cause a substantial mortality benefit when administered to patients with ST elevation MI (STEMI),[2,3] and the era of reperfusion therapy was born. Subsequently, reperfusion therapy—accomplished either pharmacologically with fibrinolytics or mechanically with percutaneous coronary intervention (PCI)—has become the cornerstone of treatment for STEMI. Current practice guidelines all center on the concept of prompt restoration of epicardial blood flow. The algorithms by which this is accomplished, however, have undergone continuous evolution.

Any of several reperfusion strategies now is acceptable in the acute MI (AMI) patient—the choice among them is complex and still evolving. Traditional treatment algorithms focused on an "either/or" strategy of primary pharmacologic reperfusion in the community hospital or primary PCI in the tertiary care hospital. This choice was felt to be acceptable when the two were considered equivalent reperfusion strategies. The last decade, however, has seen a multitude of trials comparing fibrinolysis with primary PCI, and one overriding concept has emerged: primary PCI is unquestionably superior to primary thrombolysis in the treatment of AMI. Furthermore, although beneficial in reducing the mortality and morbidity associated with AMI, fibrinolysis is not without its complications.

This discovery prompted a new wave of research, all of it dedicated to the pursuit of more rapid and more complete reperfusion. Some 20 trials have been published in the last few years alone, and sorting through the literature can be dizzying. The following article will highlight the major recent developments in AMI reperfusion therapy. It will accent which of the

Reperfusion Strategies for ST-Segment Elevation Myocardial Infarction: An Overview of Current Therapeutic Options

Part I: Pharmacologic Reperfusion

Author: **Mary C. Meyer, MD**, Emergency Physician, Kaiser Walnut Creek and Richmond, CA.

Peer Reviewers: **Charles L. Emerman, MD**, Chairman, Department of Emergency Medicine, MetroHealth Medical Center, Cleveland Clinic Foundation, Cleveland, OH; and **Steven M. Winograd, MD, FACEP**, Attending Physician, Emergency Department, St. Joseph Medical Center, Reading, PA.

many therapeutic options currently are considered acceptable, and present treatment guidelines for the emergency physician (EP) faced with the patient who presents to the emergency department (ED) with acute STEMI.

—The Editor

Epidemiology and Pathogenesis

Approximately 1.5 million cases of STEMI occur yearly in the United States, resulting in 400,000-500,000 deaths per year.[4] Mortality ranges from 5% to 50%, depending on patient characteristics, and it has been estimated that half of all patients with STEMI die prior to reaching the hospital, as a result of ventricular arrhythmia.[4] This high initial mortality has remained virtually unchanged for 30 years.[5]

In contrast with community mortality, there has been a profound decrease in hospital mortality during the past five decades. In the 1950s, the in-hospital mortality of STEMI appears to have been approximately 25-30%.[6] By the mid-1980s, prior to the thrombolytic era, this number had decreased to 18%—attributed largely to the establishment of coronary care units (CCUs) equipped with defibrillation equipment.[7] With the widespread use of fibrinolytics, aspirin, and coronary interventions, the overall one-month mortality rate is now 6-7% in large-scale trials. A recent European Heart Survey suggested that the mortality of patients admitted to European community hospitals was similar: 8.4% at one month.[8]

The pathogenesis of ST-elevation MI involves a sudden reduction in coronary blood flow, usually caused by atherosclerosis with superimposed thrombosis. It now is understood that coronary occlusion often develops in arteries that have minimal (10-40%) stenosis at baseline.[4,9,10] Rather, it is the sudden rupture of a vulnerable plaque and its resulting cascade of inflammatory and thrombotic mediators that causes arterial occlusion. Plaques most vulnerable to rupture have large lipid cores and are inflamed-infiltrated with macrophages.[11,12] When a plaque becomes disrupted, the highly thrombogenic subendothelial tissues are exposed. This leads to platelet aggregation and, later, stabilization of the platelet plug once it is crosslinked with fibrin. This thrombotic response is dynamic: Thrombosis and thrombolysis occur simultaneously, often associated with vasospasm; the result is distal embolization of microscopic clot fragments as well as arterial obstruction.[13] It is only recently that the importance of distal embolization has been fully appreciated—it causes microvascular obstruction that may prevent successful reperfusion even after the primary infarct-related artery has been opened.[13,14]

MI, or death of cardiac myocytes, begins to occur after 15-30 minutes of severe ischemia.[10] It progresses from the subendocardium to the epicardium due to the greater metabolic demands of the endocardium coupled with lower perfusion and decreased collaterals.[10] The presence of ST-elevation MI (previously referred to as transmural) is recognized on an electrocardiogram (ECG) as new ST-segment elevation of greater than 1 mm in two or more contiguous leads, or the presence of a left bundle-branch block not known to be old. Conversely, resolution of this ST-segment elevation has been demonstrated an excellent marker of tissue perfusion—the degree of resolution has been correlated in several studies with both short- and long-term prognosis.[15,16] STEMI also is recognized by the elevation of serum biomarkers that indicate acute myocardial ischemia. Of the biomarkers, cardiac troponin is preferred due to its high sensitivity and near absolute specificity. However, since current troponin assays require some time, the EP's decision to treat STEMI will be based on ECG changes in conjunction with a history consistent with MI.

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Editorial Group Head: Valerie Loner
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Table 1. Indications and Contraindications to Thrombolysis[12,13]

INDICATIONS

ECG: ST elevation > 0.1 mV in 2 or more contiguous leads or new left BBB

History: Consistent with myocardial infarction and time to symptoms 12 hours or less. Age < 75 years = Class I*, and age > 75 years = Class IIa**

CONTRAINDICATIONS

Absolute:

- Hemorrhagic stroke
- Ischemic stroke in preceding 6 months
- CNS neoplasm
- Recent major trauma/surgery/head injury***
- GI bleed within past month
- Known bleeding disorder
- Aortic dissection

Relative:

- TIA within preceding 6 months
- Oral anticoagulant therapy
- Pregnancy or 1 week post-partum
- Non-compressible puncture sites
- Traumatic resuscitation
- Refractory hypertension****

*Class I = general agreement that treatment is beneficial
**Class IIa = weight of evidence favors the treatment
***Within preceding 3 weeks
****Defined as systolic BP > 180 mmHg

Key:
BBB = bundle-branch block; CNS = central nervous system; GI = gastrointestinal; TIA = transient ischemic attack

Pharmacologic Reperfusion

Fibrinolysis. As noted above, fibrinolytic therapy for the treatment of STEMI began with the discovery that streptokinase offered a clear mortality benefit when compared to placebo.[2,3] More than 150,000 patients now have been randomized in trials comparing fibrinolysis with control, or one fibrinolytic with another.[2,3,17-19] For patients who can be treated within 12 hours of symptom onset, the evidence for benefit of fibrinolysis is overwhelming. According to the Fibrinolytic Therapy Trialists' (FTT) Group, for patients who present within six hours of symptom onset, approximately 30 deaths are prevented per 1000 patients treated with fibrinolysis; among patients treated 7-12 hours after symptom onset, the number is 20 deaths prevented per 1000 patients treated.[17] Initial concerns about thrombolysis in patients older than 75 years have proved largely unfounded. In a re-analysis of the FTT data, mortality rates in patients older than 75 years presenting with STEMI significantly were reduced by thrombolytic therapy (29.4% vs. 26%, p = 0.03).[20]

Five fibrinolytic agents currently are approved for the treatment of STEMI.[21] These generally can be categorized according to the level of fibrin specificity. Streptokinase and anistreplase are non-specific inhibitors of fibrin, and result in systemic thrombolysis.[21] Alteplase (t-PA), tenecteplase (TNK), and reteplase (r-PA) are fibrin-specific and act only on plasminogen already bound to fibrin.[6] Early fibrinolytic comparisons demonstrated the superiority of an accelerated t-PA regimen over streptokinase, (10 lives saved per 100 treated with t-PA instead of streptokinase, or a 14% risk reduction, p = 0.001), establishing t-PA as the preferred drug for fibrinolytic therapy.[22]

Subsequent comparisons between the fibrin-specific agents failed to show significant benefit of one over the other. Accelerated t-PA was compared to r-PA in two trials, and although one study demonstrated a higher rate of TIMI 3 flow with r-PA, no mortality difference was noted in clinical trials.[23,24] Similarly, TNK achieved a similar rate of TIMI 3 flow when compared to t-PA, and 30-day mortality was the same (6.17% and 6.15% respectively, p = 0.006).[25,26] Hence, although some of the newer thrombolytics may achieve more ease of administration with double or single boluses, their efficacy appears to be the same. Current indications and contraindications for thrombolytic therapy are listed in Table 1.[27,28]

One overriding concept to emerge from the fibrinolytic trials was the importance of early drug administration.[2,24,29-32] Although thrombolyics yielded a mortality advantage up to 12 hours after the onset of symptoms, this benefit was noted to be most impressive when fibrinolytics were administered within six hours of symptom onset, particularly if given in the first hour. When 58,600 patients were analyzed in the FTT trial, thrombolytics in the first hour of symptoms resulted in 65 lives saved per 1000 treated patients; this number was reduced by almost half (37 lives saved/1000 treated patients) in those treated after hour one.[17] The finding led to the concept of the "golden hour" in AMI and the American College of Cardiology/American Heart Association (ACC/AHA) recommendation of a "door-to-thrombolytic time" of 30 minutes or less.[27]

As more data on the efficacy and mechanism of the thrombolytic drugs emerged, so did an understanding that there might be an upper limit, or ceiling, to their actions. It appears that, even in the most successful thrombolytic regimens, 90 minute TIMI 3 flow rates do not exceed 50-60%, and in patients with incomplete perfusion mortality remains high.[23,25,33] Thrombolytics are associated with a 5-15% risk of re-occlusion, often resulting in re-infarction.[33] As many as 15-20% of patients with STEMI have a direct contraindication to thrombolytic therapy.[32] And finally, thrombolysis carries an inherent 1-2% risk of intracranial hemorrhage, usually with catastrophic results.[21,33] For these and other reasons, the past five years have seen an increasing focus on adjunctive and alternative therapies to fibrinolysis in the hopes of improved coronary artery recanalization.

Prehospital ECG Transmission and Fibrinolysis

Early in fibrinolytic research it was suggested that the delay between symptom onset and treatment could be improved by moving thrombolytic administration from the CCU to the ED. Although

taken for granted now, this concept at the time represented a paradigm shift in management. There now is growing evidence that a second paradigm shift—moving treatment from the ED to the prehospital arena—similarly may be beneficial to the patient. This shift may be relatively simple: Paramedic units might obtain an ECG in the field and alert a receiving hospital to the patient's imminent arrival. Alternately, paramedics ultimately may be administering thrombolytics in the field.

Technologic advances have made it feasible to obtain 12-lead ECGs in the prehospital setting and transmit them to a base hospital. In two studies, paramedic ECG acquisition had minimal effect on scene-evaluation time (associated with a 1- to 7-minute delay).[34,35] It also is evident that prehospital ECG transmission reduces average time to treatment. Although limited by confounding factors, the NRMI-2 data demonstrated reduced door-to-fibrinolysis and door-to-balloon time with prehospital ECG transmission, with an associated mortality benefit.[36] Even more impressive were the findings of the Myocardial Infarction Triage and Intervention (MITI) Trial. In this study, the control group received an ECG in the field and treatment upon arrival to the ED; when compared to standard hospital patients not enrolled in the study, control patients were fibrinolysed, on average, 40 minutes earlier (20 minutes vs 60 minutes door-to-thrombolyic, $p < 0.001$).[37] It appears that advance notification that an AMI patient will be arriving hastens hospital triage, similar to the concept underlying the trauma activation system. Prehospital ECGs have been studied only in conjunction with prehospital fibrinolysis, but it is an area that warrants more investigation.[38] The small amount of data that exists suggests a real advantage to prehospital ECGs, with improved patient triage.

Before 1993, prehospital fibrinolysis was tested in several small trials outside of North America. The MITI trial was the first large American study to address prehospital thrombolytic administration. The study randomized 360 patients with STEMI to receive either alteplase or placebo and rapid transfer to a receiving ED.[37] Investigators found no difference in mortality or a composite outcome of death, stroke, major bleeding, and infarct size, in spite of the fact that thrombolytic administration in the treatment group was significantly faster than the control group (92 vs 120 minutes, $p < 0.001$).[37] The findings were thought to be due, in part, to the rapid fibrinolysis of the control group. As noted above, even the control group received fibrinolysis 40 minutes earlier than AMI patients not enrolled in the study. The MITI study and its lack of significant findings dampened initial enthusiasm for prehospital thrombolysis. The emphasis once again was placed on rapid ED triage and thrombolytic administration.

However, new data suggest that this conclusion may have been premature. A meta-analysis was performed seven years after the MITI study and included six randomized studies involving 6434 patients.[38,39] Individually, each of the six trials favored prehospital thrombolysis but failed to show a statistically significant benefit. By contrast, the meta-analysis found that time-to-treatment was reduced by 58 minutes with prehospital fibrinolysis, and this time reduction was associated with a 17% relative risk reduction in hospital mortality (1.7% absolute risk reduction, or one life saved for every 62 patients treated by prehospital rather than in-hospital fibrinolysis).[39] Data were insufficient to study 30-day and 60-day mortality. Prehospital fibrinolysis carried no associated risk of inappropriate therapy or compromise of patient safety.

More recently, the Evaluation of the Time Saved by Prehospital Initiation of Reteplase for ST-Elevation Myocardial Infarction (ER-TIMI) 19 trial randomized 945 patients to prehospital or hospital retevase.[40] Both endpoints measured were significantly altered by prehospital fibrinolysis. Time from EMS arrival to fibrinolysis averaged 31 minutes in the treatment group, compared with 63 minutes among controls ($p < 0.0001$).[40] Furthermore, although both groups ultimately obtained the same degree of ST resolution on ECG (49.4% complete and 59.95% > 50% ST resolution), this result was achieved 30 minutes earlier in patients treated with prehospital r-PA.[40] Rates of intracranial hemorrhage did not differ between the two groups.

Finally, in an intriguing hypothesis, the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study was designed to evaluate if prehospital fibrinolysis might be a more effective strategy than primary angioplasty in the treatment of AMI.[41] The study included 840 AMI patients who received either prehospital alteplase or transfer to a hospital for immediate PCI. Among patients who underwent primary PCI, 6.2% experienced the primary endpoint (composite of death, nonfatal reinfarction, and non-fatal disabling stroke within 30 days) compared to 8.2% in the prehospital fibrinolysis group ($p = 0.29$).[41] Rates of hemorrhagic stroke were similar in the two groups. Of note, there was a nonsignificant but concerning trend toward increased mortality in the PCI group (4.8% vs 3.8%). Also important is the fact that 26% of the patients who received fibrinolytics required rescue angioplasty, and a total of 33% required urgent angioplasty compared with just 4% in the primary PCI group ($p < 0.0001$).[41]

The findings of all these studies, and CAPTIM in particular, are intriguing. They suggest that prehospital fibrinolysis certainly is safe, and may even be as effective as primary PCI, with the caveat that fibrinolysis patients frequently will require rescue PCI. Hence, patients who undergo prehospital fibrinolysis often will require transfer to a facility with PCI capabilities. The CAPTIM study does suffer from some limitations; most significantly, the trial enrolled fewer patients than initially planned, resulting in large confidence intervals and reduced statistical power. Nonetheless, it raises an interesting question: Is the combined use of prehospital fibrinolysis with liberal use of rescue PCI a preferential treatment strategy for AMI? An ongoing study—the Prehospital Administration of Thrombolytic Therapy with Urgent Culprit Artery Revascularization (PATCAR)—will help answer this question. The study will examine the effects of prehospital or hospital fibrinolytic administration followed by transfer for acute angiography and stenting.

Current ACC/AHA recommendations endorse prehospital ECG use but are hesitant regarding prehospital fibrinolysis.[27] They express concern about the medical and legal implications of this strategy, but suggest that in certain settings prehospital fibrinolysis may be appropriate, especially if a physician is present in the ambu-

lance or transport times are likely to be prolonged.[27] Taken together, the research in prehospital ECGs and fibrinolysis is encouraging. In the future, ED physicians should expect to see more incorporation of prehospital care into existing AMI treatment protocols.[43]

Combined Fibrinolysis and GP IIB/IIIA Inhibitors

An alternate pharmacological reperfusion strategy is lytic therapy in conjunction with a glycoprotein IIb/IIIa (GPIIb/IIIa) antagonist. Platelet inhibition has been a key component of reperfusion therapy since early trials demonstrated the benefit of aspirin in AMI. However, aspirin is a relatively weak antiplatelet drug. In contrast, the GPIIb/IIIa inhibitors block the platelet aggregation phase of acute thrombus formation—the final common pathway by which a platelet plug is formed over a ruptured plaque.[21] Although thrombolytics increase TIMI 3 flow in the occluded artery, they also paradoxically increase platelet aggregation.[44-46] Hence, the theoretical advantage of combination fibrinolysis-GP IIb/IIIa inhibitor therapy is decreased clot formation and distal embolization. Three GPIIb/IIIa inhibitors currently are available: abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat).[44]

Early studies of reduced-dose fibrinolysis in combination with a GPIIb/IIIa inhibitor were promising. In TIMI-14, the Strategies for Patency Enhancement in the Emergency Department (SPEED), and the Integrilin and Reduced-Dose of Thrombolytics in AMI (INTRO-AMI) studies, higher rates of TIMI 3 flow were reported in patients who received combination therapy over standard-dose thrombolytics.[47-50] In TIMI-14, TIMI 3 flow at 90 minutes significantly was improved in patients who received t-PA and abciximab vs. t-PA alone (77% vs 62%, $p = 0.01$); the combination of r-PA and abciximab similarly was associated with improved flow, although the difference was not significant (73% vs 70%).[47,48] In INTRO-AMI, a combined strategy of t-PA plus eptifibatide achieved significantly higher rates of TIMI flow when compared to t-PA alone.[50]

Unfortunately, the two trials which examined the impact of combination therapy on clinical endpoints were more disappointing. In GUSTO V, 16,588 patients received reteplase or half-dose reteplase and abciximab.[42] At 30 days, the primary endpoint of mortality was no different between the two groups (5.9% vs 5.6%, $p = 0.43$). Nor did a series of prespecified subgroups (women, elderly, diabetics, anterior MI) have a mortality benefit with combination therapy. The study did note modest reductions in a number of secondary endpoints, including recurrent ischemia, re-infarction, and the need for revascularization.[42] These benefits, however, were offset by significantly higher bleeding rates: 1.1% severe bleeding vs. 0.5%, transfusion in 5.7% vs. 4.0%. Most concerning was the increased rate of intracranial hemorrhage that occurred in patients older than 75 years of age (2.1% combination therapy vs 1.1%, $p = 0.069$). Recently, the GUSTO V investigators published their one-year follow-up results: No mortality benefit was seen between the two groups.[51]

In the Assessment of the Safety and Efficacy of a New Thrombolytic-III (ASSENT-III) trial, 6095 patients were randomized to tenecteplase and unfractionated heparin, tenecteplase and low molecular weight heparin, or tenecteplase and abciximab.[52] The primary outcome was a composite of death, reinfarction, and refractory ischemia. Although the primary endpoint was significantly reduced with combination therapy over tenecteplase plus low-molecular-weight heparin, the frequency of major bleeding and intracranial hemorrhage in the elderly was increased. When a combined efficacy and safety endpoint was evaluated, the tenecteplase-enoxaparin arm appeared to be the most attractive option due to lower rates of bleeding.[52]

So where do these studies leave us? Frankly, the role of combination therapy is not clear—there are some benefits but they come at the cost of increased bleeding rates. This has diminished much of the excitement over combination therapy, and most institutions have not implemented the strategy in their STEMI practices.[44-46] In particular, ASSENT-III suggested that fibrinolysis plus low-molecular-weight heparin provides similar clinical outcomes to combination therapy but without the bleeding complications. Combination therapy also is unlikely to be competitive with a primary PCI strategy.[45] Fibrinolysis plus GP IIb/IIIa inhibitors should not be used in patients older than 75 years of age due to increased intracranial hemorrhage rates.

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Physician CME Questions

61. Regarding ST elevation MI, which statement is *not* true?
    A. ST elevation MI is recognized on ECG as a new ST segment elevation of greater than 1 mm in two or more contiguous leads or the presence of a left bundle-branch block not known to be old.
    B. The degree of resolution of ST segment elevation has been correlated in several studies with short- and long-term prognosis.
    C. Cardiac troponin is the preferred biomarker because of sensitivity, specificity, and speed.
    D. The ED decision to treat STEMI is based on ECG changes and a history consistent with myocardial infarction.

62. Coronary occlusion (resulting in ST-elevation MI) only occurs in highly stenotic coronary arteries.
    A. True
    B. False

63. Which fibrinolytic agent has demonstrated superior efficacy in large clinical trials?
    A. t-PA
    B. Reteplase
    C. Tenecteplase
    D. None of the above

64. In the MITI trial, prehospital ECG transmission was associated with

decreased time to fibrinolysis, even among control patients who were fibrinolysed in the emergency department.

A. True
B. False

65. In the CAPTIM study, what percentage of patients who underwent prehospital fibrinolysis ultimately required urgent angioplasty?

A. 1/4
B. 1/3
C. 2/3
D. 3/4

66. Combination therapy with fibrinolysis and a GP IIb/IIIa inhibitor should not be used in which group of patients?

A. 45-55 years old
B. 55-65 years old
C. 65-75 years old
D. Older than 75 years

67. Which of the following factors contraindicates thrombolysis?

A. Hemorrhagic stroke
B. Known bleeding disorder
C. Pregnancy or 1 week post-partum
D. Ischemic stroke in the preceeding 6 months
E. All of the above

68. Current ACC/AHA guidelines endorse prehospital ECG, but suggest that prehospital fibrinolysis may be appropriate in certain situations.

A. True
B. False

69. Which of the following statements is true regarding results of the GUSTO V trial?

A. It showed overwhelmingly positive results on clinical endpoints for combination therapy.
B. Several prespecific subgroups showed a mortality benefit with combination therapy.
C. The study noted modest reductions in secondary endpoints, such as recurrent ischemia, re-infarction, and the need for revascularization.
D. At 30 days, there was a difference in mortality rates with combination therapy.

70. Which of the following statements is true of combination therapy?

A. Most institutions have implemented combination therapy in STEMI practices.
B. The ASSENT-III trial suggested that fibrinolysis plus low molecular weight heparin provides similar clinical outcomes to combination therapy but without the bleeding complications.
C. The role of combination therapy in STEMI is clear.
D. Combination therapy is competitive with the primary PCI strategy.

Correction

In the March 8, 2004, issue, the CME questions should have been numbered 51-60.

CME Answer Key

61. C	66. D
62. B	67. E
63. D	68. A
64. A	69. C
65. B	70. B

In Future Issues:

ST Elevation Myocardial Infarction Part II

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.

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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.

Emergency Medicine Reports®
The Practical Journal for Emergency Physicians

ST Elevation MI Part I

Indications and Contraindications to Thrombolysis

INDICATIONS

ECG: ST elevation > 0.1 mV in 2 or more contiguous leads or new left BBB

History: Consistent with myocardial infarction and time to symptoms 12 hours or less. Age < 75 years = Class I*, and age > 75 years = Class IIa**

CONTRAINDICATIONS

Absolute:

- Hemorrhagic stroke
- Ischemic stroke in preceding 6 months
- CNS neoplasm
- Recent major trauma/surgery/head injury***
- GI bleed within past month
- Known bleeding disorder
- Aortic dissection

Relative:

- TIA within preceding 6 months
- Oral anticoagulant therapy
- Pregnancy or 1 week post-partum
- Non-compressible puncture sites
- Traumatic resuscitation
- Refractory hypertension****

*Class I = general agreement that treatment is beneficial
**Class IIa = weight of evidence favors the treatment
***Within preceding 3 weeks
****Defined as systolic BP > 180 mmHg

Key:
BBB = bundle-branch block; CNS = central nervous system; GI = gastrointestinal; TIA = transient ischemic attack

Supplement to *Emergency Medicine Reports*, March 22, 2004: "Reperfusion Strategies for ST-Segment Elevation Myocardial Infarction: An Overview of Current Therapeutic Options. Part I: Pharmacologic Reperfusion." *Author:* **Mary C. Meyer, MD,** Emergency Physician, Kaiser Walnut Creek and Richmond, CA.

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Emergency Medicine Specialty Reports

Supplement S04178 **March 2004**

Since the early 1980s, HIV and the AIDS epidemic have changed the way medicine is practiced. The disease debuted as a devastating and rapidly progressive syndrome that was uniformly fatal, with few interventions. With the widespread use of effective antiviral agents in the 1990s, HIV infection and AIDS became survivable, long-term illnesses. While much has been learned about the disease and its complications, much work still remains. HIV/AIDS is very much a global epidemic, no longer confined to populations living an alternative lifestyle. In the United States, women comprise the fastest-growing population with HIV, and heterosexual transmission accounts for the fastest-growing risk factor group.

The emergency physician plays a key role in the management of HIV. Emergency physicians encounter all phases of the illness, from counseling patients on safe sex practices to treating the medical complications of chronic immunosuppression. Despite all of the recent advances, HIV infection and AIDS remain challenging and continually evolving diseases. In this issue of Emergency Medicine Specialty Reports*, the authors provide a comprehensive update on the diagnosis and clinical management of HIV infection and its complications.*

— The Editor

Human Immunodeficiency Virus Infection in Emergency Medicine

Authors: **Catherine A. Marco, MD, FACEP**, Associate Professor, Department of Surgery, Medical College of Ohio; Attending Physician, St. Vincent Mercy Medical Center, Toledo, OH; **Richard E. Rothman, MD, PhD, FACEP**, Assistant Professor, Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; and **Samuel Yang, MD**, Instructor, Emergency Medicine, Johns Hopkins School of Medicine, Baltimore, MD.

Peer Reviewer: **Andrew D. Perron, MD**, **FACEP**, Associate Residency Director, Department of Emergency Medicine, Maine Medical Center, Portland.

Epidemiology

According to the Centers for Disease Control and Prevention's (CDC) most recent definition, published in 1993, AIDS is the laboratory evidence of HIV infection plus at least one of the conditions listed in Table 1.[1] While AIDS is a reportable disease in the United States, reporting of HIV infection is optional in most states, making HIV epidemiologic data more difficult to assess.

Worldwide estimates indicate that approximately 37 million adults and 2 million children were living with HIV/AIDS at the end of 2003.[2] The vast majority of HIV-infected persons live in the developing world. In North America, there were an estimated 54,000 new cases of HIV reported in 2003, and an estimated 790,000-1.2 million persons are now living with HIV or AIDS. Within the United States, HIV-positive persons tend to be concentrated primarily in large urban settings.

The majority of cases in the United States have occurred in adult men (80%), as compared to adult women (18%) and children (1%). There is a disproportionate rate of infection among minority groups.[3]

Risk factors associated with acquiring HIV infection include men who have sex with men, injecting drug use (IDU), heterosexual exposure to a partner at risk, blood transfusion prior to 1985, and maternal-neonatal transmission. In recent years, there has been a relative decrease in newly acquired HIV in men who have sex with men, and a relative increase in incidence of HIV among injecting drug users and heterosexual contacts.

Pathophysiology

The HIV virus is a cytopathic human retrovirus. Several modes of transmission of HIV have been proven, including semen, vaginal secretions, blood products, breast milk, and transplacental transmission in utero. HIV selectively attacks cells within the immune system and this accounts for much of the immunodeficiency it produces in affected individuals.

HIV Testing in the ED

HIV infection most commonly is established by HIV serology, or detection of antibodies to the virus. Testing may be performed using enzyme-linked immunoassay (EIA) and a Western blot (WB) assay. Criteria for positive results are a repeatedly positive EIA followed by a positive WB. Overall, sensitivity and specificity of HIV serology is greater than 99.9%. False-negative HIV tests may occur during the window period (usually the first several months) of acute infection, after viral transmission but before the appearance of antibodies.

The single use diagnostic system (SUDS) assay is similar to EIA screening tests, and can be performed in approximately one hour. Another test is the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Inc., Bethlehem, PA). OraQuick is a simple, easy to use, point-of-care that can detect antibodies to HIV-1 in fingerstick or whole blood specimens.

Traditionally, serologic testing of patients for HIV in the ED had been discouraged. However, newer testing modalities have challenged this concept. It is well established that early recognition of HIV and early therapeutic intervention can significantly delay progression of disease, reduce risk of opportunistic infections, and lead to decreased morbidity and mortality. If ED screening is performed, sufficient resources should be in place to ensure appropriate pretest and posttest counseling, and outpatient referral.

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Clinical Presentations Related to HIV Infection

Initial Evaluation and Stabilization. The initial evaluation should be tailored to identify emergent disorders requiring early intervention and stabilization. Airway, breathing, and circulation must be rapidly assessed and stabilized. Following initial stabilization, the remainder of the history and physical may be completed.

Primary HIV Infection. Acute HIV syndrome (acute seroconversion syndrome) commonly occurs 2-6 weeks following initial exposure and may cause nonspecific symptoms such as fever, adenopathy, fatigue, pharyngitis, diarrhea, weight loss, and rash. These relatively nonspecific symptoms may be present for 1-3 weeks, and many patients do not seek medical attention during this phase of illness.

Systemic Symptoms of HIV Infection. Systemic symptoms such as fever, weight loss, fatigue, and malaise are common among ED patients. The differential diagnosis is lengthy and includes a variety of infectious causes, malignancies, and drug reactions.

Fever is a common presenting complaint in patients with AIDS. Evidence of an infectious cause or other reason for fever should be sought by careful history and physical examination. Laboratory investigation of fever may be tailored to the individual patient and severity of symptoms, and may often include chest radiography, complete blood count (CBC), electrolytes, erythrocyte sedimentation rate, liver function tests, serologic test for syphilis, urinalysis and culture, and blood cultures (aerobic, anaerobic, and fungal). If there are neurologic signs or symptoms or if no other source of fever is identified, lumbar puncture should be performed after a cranial computed tomography (CT) scan or MRI. Many patients with fever or other systemic symptoms may be managed as outpatients, if adequate follow-up observation and home assistance are available. Indications for admission include toxic presentation, neutropenia with fever, hypoxia, dehydration, active bleeding, or other need for urgent diagnosis and treatment.

Neurologic Disease. Neurologic diseases are rarely the initial manifestation of AIDS, but the frequency of neurologic complications increases over the course of HIV infection, with 75-90% incidence patients with AIDS experiencing a neurologic disorder. The most common AIDS-defining neurologic complications are HIV encephalopathy, *Cryptococcus neoformans*, toxoplasmosis, and primary central nervous system (CNS) lymphoma. Other CNS infections may include bacterial meningitis, histoplasmosis, cytomegalovirus (CMV), progressive multifocal leukoencephalopathy (PML), herpes simplex virus (HSV), neurosyphilis, and TB. Noninfectious CNS processes include CNS lymphoma, cerebrovascular accidents, and metabolic encephalopathies.

The clinical picture in patients with serious neurologic complications often is nonspecific. The most common symptoms indicative of CNS pathology are headache, altered mental status, seizures, meningismus, and focal neurologic deficits. Most patients who present with neurologic complaints or findings should have a workup to include neuroimaging and possible lumbar puncture (LP). For those with focal deficits, new seizures, or suspicion of focal lesions, immediate neuroimaging is recommended, followed by LP. For most CNS processes that

Table 1. AIDS-Defining Illnesses*

LABORATORY DATA

- CD4 count < 200/mm^3

INFECTIONS

- Candidiasis, esophageal or pulmonary
- Coccidioidomycosis
- Cryptococcosis
- Cryptosporidiosis
- Cytomegalovirus infection
- Herpes esophagitis
- Histoplasmosis
- Isosporiasis
- Mycobacterial disease
- *Pneumocystis carinii* infection
- Progressive multifocal leukoencephalopathy
- Bacterial pneumonia (recurrent)
- Salmonellosis
- Brain toxoplasmosis

MALIGNANCIES

- Cervical cancer
- Kaposi's sarcoma
- Lymphoma

MISCELLANEOUS/OTHER

- HIV encephalopathy
- HIV wasting syndrome

*This represents only a partial list of selected AIDS-defining illnesses. For a complete list, refer to the 1993 CDC Case Definition, available at www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm.

require immediate identification, CT without contrast is considered adequate to identify the majority of mass lesions.

Cryptococcus neoformans is a fungal CNS infection which occurs in 10% of HIV infected patients, and may cause either focal cerebral lesions or diffuse meningoencephalitis. It is found most commonly in those with CD4 counts of less than 100. Presenting symptoms may include fever and headache, often accompanied by nausea and vomiting. Less common symptoms include visual changes, dizziness, seizures, and cranial nerve deficits. Mortality may be up to 30%.

Emergent CT typically is unrevealing. Definitive diagnosis is made by a positive cryptococcal antigen in the cerebrospinal fluid (CSF), which is nearly 100% sensitive and specific. Other diagnostic tests include India ink staining (60-80% sensitive), fungal culture (95% sensitive), and serum cryptococcal antigen (95% sensitive). Treatment of cryptococcal meningitis requires intravenous amphotericin B (0.7 mg/kg/day); 5-flucytosine (100 mg/kg/day) may be added to this regimen. Oral fluconazole (400 mg/day) may be used as initial therapy in patients with normal mental status.

Toxoplasma gondii is the most common organism causing focal intracranial mass lesions in patients with HIV infection. The incidence is approximately 3-4%. Common presenting symptoms include headache, fever, altered mental status, focal deficits, and seizures. Serologic testing is not generally helpful, because antibody to *T. gondii* is widely prevalent in the general population. Diagnosis of toxoplasmosis is most often made by CT findings of multiple subcortical lesions, with ring-enhancement seen on contrast CT. Toxoplasmosis of the brain can be difficult to distinguish from a wide variety of other causes, including lymphoma, cerebral TB, fungi, progressive multifocal leukoencephalopathy, CMV, and Kaposi's sarcoma (KS).

Patients with suspected toxoplasmosis should be treated as inpatients with pyrimethamine (100-200 mg PO loading dose, followed by 50-100 mg/day PO), plus sulfadiazine (4-8 g/day PO) with folinic acid (10 mg/day PO) to reduce the incidence of pancytopenia. Short courses of high-dose steroids are beneficial in cases in which significant edema or mass effect is noted. Seizure prophylaxis with phenytoin also may be used in these cases.

CNS lymphoma occurs in up to 3% of patients with HIV, typically in those with CD4 cell counts of fewer than 100. The most common clinical finding is a change in mental status. Diagnosis is usually made based on CT findings, where hyperdense or isodense round or multiple enhancing lesions, particularly in the periventricular region, are noted. Prognosis for lymphoma is poor and median survival is less than one month.[4]

HIV encephalopathy, or AIDS dementia complex, occurs in up to one-third of patients with HIV. It is a progressive process caused by direct HIV infection and is commonly heralded by impairment of recent memory or subtle cognitive deficits, such as difficulty concentrating. Symptoms typically occur in patients with CD4 counts of less than 200 cells/mm^3. HIV encephalopathy is a diagnosis of exclusion, and ED evaluation should be done to rule out other CNS processes. HIV encephalopathy may be treated with high-dose zidovudine, in coordination with an infectious disease specialist or neurologist.

Ophthalmologic Manifestations. Ocular findings are common in the HIV-infected patient. Cotton-wool spots in the retina are the most common eye finding in AIDS patients and do not require intervention.

CMV retinitis is the most common cause of blindness in AIDS patients, and occurs in 10-30% of patients. CMV retinitis typically produces severe necrotic vasculitis and retinitis. Clinical symptoms may include blurred vision, change in visual acuity, floaters, flashes of light, photophobia, scotoma, redness, or pain.[5] It is diagnosed by its characteristic appearance on ophthalmoscopy of fluffy white retinal lesions, often perivascular. Differential diagnosis includes toxoplasmosis, syphilis, HSV infection, VZV (varicella zoster virus) infection, and tuberculosis. Treatment should be initiated with ganciclovir, 5 mg/kg every 12 hours for two weeks, followed by 6 mg/kg/day maintenance therapy. Other therapies may include foscarnet, intravitreal injections of fomivirsen, and ganciclovir-containing intravitreal implants.

Pulmonary Complications. Pulmonary manifestations of HIV are among the most common reasons for ED visits among AIDS patients. The differential diagnosis of respiratory involvement is broad and includes such etiologies as bacterial infections (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, etc.), protozoal infections (*Pneumocystis jiroveci*, *Toxoplas-*

ma gondii, etc.), viral infections (CMV, adenovirus, etc.), fungal infections (*C. neoformans*, *Histoplasma capsulatum*, *Aspergillus fumigatus*, etc.), malignancies (KS, carcinoma, lymphoma, etc.), and others (lymphocytic interstitial pneumonitis, pulmonary hypertension, etc). Presenting symptoms are often nonspecific and may include cough, dyspnea, fever, or hemoptysis.

Diagnostic evaluation of patients with pulmonary complaints may include chest radiography, CBC, and arterial blood gas (ABG) analysis. Other tests may be indicated in certain situations, such as serum lactic dehydrogenase (LDH), sputum culture, blood culture, Gram's stain, and special stains (Gomori, Giemsa, acid-fast).

Pneumocystis pneumonia (PCP) is one of the most common opportunistic infections in AIDS. More than 80% of AIDS patient's acquire PCP at some time during their illness, and it is the initial opportunistic infection in many cases. PCP is caused by the organism *P. jiroveci*, formerly referred to as *P. carinii*.[6] It is still acceptable to use the acronymn PCP, in reference to Pneumocystis pneumonia. The chest radiograph commonly shows a diffuse interstitial infiltrate, but may also reveal normal findings, asymmetry, nodules, cavitation, or bullae. Other diagnostic tests include gallium scanning of the chest, bronchoscopy (bronchoalveolar lavage, brush biopsy, transbronchial biopsy), and induced sputum with indirect immunofluorescent staining using monoclonal antibodies.

Establishment of a definitive diagnosis is not necessary prior to the initiation of treatment. Treatment should be initiated as early as possible, with 15-20 mg/kg/day of trimethoprim and 75-100 mg/kg/day of sulfamethoxazole (TMP-SMX), given either orally or IV for a total of 21 days. (a typical adult dose may be two TMP-SMX double-strength tablets every eight hours). Other therapeutic options include pentamidine isethionate, dapsone, or other agents. In addition, steroid treatment (prednisone, 40 mg, PO, twice daily with a tapering dose over three weeks) is recommended for patients with a PaO_2 less than 70 mmHg, or an A-a gradient of greater than 35.[7]

The incidence of Mycobacterium tuberculosis (MTB) in HIV-infected patients has increased dramatically, from a low point reached in 1985. The incidence has increased particularly in socioeconomically disadvantaged groups, including prisoners and IV drug users. HIV-infected patients have an estimated 50- to 200-fold increased risk of acquiring TB compared to the general population.[8] Common presenting symptoms include fever, cough, and hemoptysis. Radiographic abnormalities may vary considerably. Extrapulmonary disease is more common among HIV-infected patients, and may occur in up to 75% of cases. Multidrug-resistant tuberculosis is becoming an issue of concern, particularly among the HIV-infected population. Diagnostic testing may include PPD skin testing, sputum stain and culture, or biopsy of affected organs.

AIDS patients with tuberculosis should receive a four-drug regimen for six months with isoniazid, rifampin, pyrazinamide, and either ethambutol hydrochloride or streptomycin.[9] Second-line agents may include ciprofloxacin, ofloxacin, kanamycin, and other agents.

Fungal pulmonary infections may be seen in AIDS patients. Etiologies may include cryptococcosis, aspergillosis, histoplasmosis, coccidioidomycosis, nocardiosis, and blastomycosis.[10] Viral infections also occur in HIV-infected patients. CMV is the most common viral pulmonary pathogen, and typically occurs in advanced immunosuppression. Pulmonary malignancies are also a diagnostic possibility. KS typically is associated with hilar peribronchovascular thickening, lower lobe reticulonodular opacities, adenopathy, pleural effusion, or focal consolidation. Other malignancies, including non-Hodgkin's lymphoma, Hodgkin's disease, and bronchogenic carcinoma may be seen. Lymphoproliferative disorders may include lymphocytic interstitial pneumonia (LIP), nonspecific interstitial pneumonia (NSIP), and bronchiolitis obliterans.

Cardiovascular Manifestations. While autopsy findings suggest cardiac involvement in up to 73% of deceased AIDS patients, clinically significant cardiac disease in the AIDS patient is relatively uncommon.[11] Cardiac findings may include pericardial effusion, cardiomyopathy, increased left ventricular mass, myocarditis, endocarditis, malignancy, and cardiotoxicity of medications.[12] The pericardium is the most common site of cardiac involvement, although most patients have clinically insignificant effusions. Pericardial effusions may be secondary to malignancies, uremia, lymphatic obstruction, or infections. Cardiomyopathies may occur secondary to primary HIV infection, viral, mycobacterial, fungal or protozoal infection, drug-induced, immunologic, or ischemic. Infective endocarditis occurs commonly in HIV-infected patients with a history of injecting drug use. Cardiac neoplasms may also occur, typically either KS or lymphoma.

Gastrointestinal Involvement. The most common GI symptoms are diarrhea, weight loss, malabsorption, abdominal pain, bleeding, esophageal symptoms, and hepatobiliary symptoms. Nonspecific symptoms of nausea, vomiting, and abdominal pain are common adverse effects of antiretroviral therapy. Treatment in the ED focuses on supportive care, fluid and electrolyte repletion, and obtaining of appropriate studies for further investigation.

Oral involvement is common, and may include etiologies such as fungal infections (oral candidiasis, histoplasmosis, cryptococcosis, penicillinosis), viral lesions (herpes simplex, herpes zoster, cytomegalovirus, hairy leukoplakia, papillomavirus), bacterial lesions (periodontal disease, necrotizing stomatitis, tuberculosis, mycobacterium avium complex [MAC], bacillary angiomatosis), neoplasms (KS, lymphoma, Hodgkin's lymphoma), and autoimmune or idiopathic lesions (salivary gland disease, aphthous ulcers, etc.).

Oral candidiasis affects more than 80% of AIDS patients. *Candida albicans*, the most common fungal infection in HIV-infected patients, typically involves the tongue and buccal mucosa, and may be asymptomatic. Symptoms may include soreness, burning, and dysphagia. Candidiasis may be described as whitish lacy plaques, which are easily scraped away from an erythematous base. Microscopic examination of the material on potassium hydroxide smear can confirm the diagnosis. Clotrimazole troches (10 mg, PO, five times daily for 14 days) are the preferred treatment for oral candidiasis. Other treatment options include nystatin vaginal tablets, which may be dissolved slowly in the mouth four times daily, or nystatin pastilles (two pastilles dissolved in the

mouth five times daily). Systemic therapy may be used for resistant lesions, such as ketoconazole, fluconazole, or itraconazole.

Complaints of dysphagia, odynophagia, or chest pain may be indicative of esophageal involvement. Candida, HSV, and CMV infection all may cause painful esophagitis. Other etiologies may include KS, *Mycobacterium avium* complex, reflux esophagitis or idiopathic. The most cost-effective approach to the evaluation of patients with esophageal complaints is to initiate empiric therapy with oral antifungal agents for two weeks, and proceed with endoscopy for patients who fail to improve after two weeks.

Diarrhea is the most common gastrointestinal complaint in AIDS patients and is estimated to occur in 50-90% of patients. Diarrhea can be significant and may lead to massive fluid loss with dehydration, fever, chills, and weight loss. Medication side effects should be considered, as antiretroviral agents have a high incidence of gastrointestinal adverse effects. Potential pathogens causing diarrhea include parasites (*Cryptosporidium parvum*, *Isospora belli*, *Giardia lamblia*, *Entameba histolytica*, and others), bacteria (Salmonella, Shigella, Campylobacter, *Helicobacter pylori*, *Clostridium difficile*, and others), viruses (CMV, herpes simplex, HIV, and others), and fungi (*Histoplasma capsulatum*, *C. neoformans*, and others).

Cryptosporidium and Isospora infections are commonly associated with HIV infection, and both organisms may produce prolonged watery diarrhea.[13] Diagnosis may be sought using acid-fast staining of stool samples, or by monoclonal antibody, or enzyme-linked immunoabsorbent assays. Symptoms may be treated with diet modification and/or loperamide. Cryptosporidium infections may be treated with some success with paromomycin (500-750 mg, PO, four times daily for 2-4 weeks), or azithromycin (2400 mg/day on day 1, followed by 1200 mg/day for four weeks, followed by 600 mg/day). Isospora infections often are successfully treated with TMP-SMX (one DS tablet, PO, three times daily for 10 days, followed by twice weekly therapy for three weeks).

Renal Manifestations of HIV Infection. Renal insufficiency in the AIDS patient may occur due to numeous etiologies. Prerenal azotemia is the most common renal abnormality, especially in conjunction with volume loss related to systemic or gastrointestinal infection. It is diagnosed and treated by evaluation and therapy of fluid status. Acute renal failure may also occur and is often secondary to drug nephrotoxicity (e.g., pentamidine, aminoglycosides, sulfa drugs, foscarnet, rifampin, dapsone, and amphotericin B). HIV-associated nephropathy (HIVAN) is typically a cause of chronic renal insufficiency in the late stages of immunosuppression, but may occur earlier in disease progression.[14] Vasculitis, tuberculosis, or other systemic infections may also contribute to renal insufficiency. Post-renal azotemia may result from tubular, ureteral, or pelvis obstruction, from lymphoma, stones, fungus ball, blood clot, or sloughed papilla.

ED evaluation should include urinalysis, assessment of fluid status, blood urea nitrogen (BUN), and creatinine. If indicated, ultrasound or intravenous pyelogram (IVP) may demonstrate the site and degree of obstruction. Renal biopsy may ultimately be required for patients with proteinuria and undiagnosed renal disease. Treatment depends on the causative agent. Therapies, which have demonstrated limited benefit for HIVAN include corticosteroids, angiotensin-converting enzyme (ACE) inhibitors, and dialysis.

Sexually Transmitted Diseases. Sexually transmitted diseases are commonly seen in HIV infected patients. In addition to testing for the more common entities (e.g., gonorrhea, Chlamydia, and herpes infections), serologic testing for syphilis should be performed for all patients presenting with symptoms suggestive of possible sexually transmitted disease. Syphilis has been associated with increased susceptibility to HIV seroconversion.[15] The prevalence of syphilis in the United States recently has increased.[16]

Dermatologic Disorders. Several common cutaneous manifestations of AIDS likely are to be seen in the ED. Any preexisting dermatologic conditions may be exacerbated by HIV infection. Common infections and conditions may present in an atypical fashion. Generalized cutaneous complaints such as xerosis (dry skin) and pruritus are common and may be manifested before any AIDS-defining illness.

KS is the second most common manifestation of AIDS and has involved approximately 25% of the known cases to date. The disease usually is disseminated widely with mucous membrane involvement, although it rarely is primarily fatal. KS typically presents in HIV-infected patients with any variation of mucocutaneous involvement, lymph node involvement, or involvement of the gastrointestinal (GI) tract or other organs. The typical appearance of cutaneous involvement is pink, red, or purple papules, plaques, nodules, and tumors. Treatments available include cryotherapy, radiotherapy, intralesional or systemic chemotherapy.[17]

Varicella zoster eruptions involving several dermatomes are commonly seen in patients with AIDS. In the HIV-infected patient with simple dermatomal zoster infection, outpatient management should be initiated with oral famciclovir (5 mg, PO, bid or tid, for seven days), acyclovir (800 mg, five times daily), or valaciclovir (1000 mg, bid for seven days). Admission is warranted in any patient with systemic involvement, ophthalmic zoster, or severe dermatomal zoster.

Herpes simplex (HSV) infections are very prevalent among HIV-infected patients. Both HSV-1 and HSV-2 may be seen as local infection and systemic involvement. HSV infections commonly present with fever, adenopathy, malaise, and ulcerative lesions of mucosal and cutaneous sites. Common sites of involvement include oral mucosa, genital areas, and rectum. Oral famciclovir (750 mg, PO, three times daily) or acyclovir, famciclovir, penciclovir, foscarnet, or valaciclovir is recommended.

Scabies should be considered in all HIV-infected patients, particularly those with dermatitis with excoriations, or pruritus. Preferred treatment is with 5% permethrin. Sexual and household contacts also should be treated. Norwegian scabies is a variant seen in HIV-infected patients, and is particularly difficult to eradicate.

Psychiatric Presentations. The diagnosis of AIDS involves complex psychologic and social issues, in addition to physiologic, neurologic, and psychiatric abnormalities. Interactions with family and friends may be changed dramatically, and issues of confronting chronic illness and death may prove devastating.

Depression is common among AIDS patients and often is

responsive to hospitalization and psychosocial intervention. It has been estimated that 60% of HIV-infected patients experience depression during their illness.[18] Patients with a history of depression are at increased risk. Depression may result in suicidal ideation and may bring the patient to the attention of the ED after a suicide attempt, such as a drug overdose. Antidepressant therapy may be considered if symptoms of depression continue longer than two weeks. Other psychiatric disorders may be seen, including personality disorders, addiction disorders, and adjustment disorders.

AIDS psychosis commonly presents with psychiatric symptoms such as hallucinations, delusions, or other abnormal behavioral changes. Treatment should be undertaken with traditional antipsychotic agents.

Hematologic Complications. Common hematologic complications may include anemia (present in up to 80% of patients), neutropenia, and thrombocytopenia. Hematopoieses may be adversely affected by HIV itself, tumor, infection, or medications.[19] Coagulation disorders may be seen, secondary to lupus anticoagulant, viral infections, or idiopathic etiologies.

Drug Reactions. Drug reactions are extremely common among HIV-infected patients for two reasons: First, they are commonly treated with a variety of drugs known to produce adverse effects in some individuals, and second, for unclear reasons, HIV-infected individuals often have more frequent or more severe reactions to commonly used medications. Dermatologic reactions particularly are common. Gastrointestinal effects, such as nausea, vomiting, and diarrhea also are common reactions to many agents. Antimicrobial drugs most commonly are implicated. Potential drug interactions always should be considered when prescribing new medications. Drug reactions should always be considered as a possible cause of new symptoms. Reactions are numerous and current references should be consulted when drug reactions are suspected.

Antiretroviral Therapy. The introduction of highly active antiretroviral therapy (HAART) in 1996 has had dramatic effects on the clinical consequences of HIV infection in the developed world. The incidence of AIDS defining illnesses and death rate have declined significantly.[20] In 2003 the Department of Health and Human Services (DHHS) published updated guidelines for use of antiretroviral agents in HIV-infected adults and adolescents.[21] In general, multiple goals of antiretroviral therapy include virologic, immunologic, clinical, and therapeutic goals. The principal clinical goals of therapy are to prolong and improve quality of life.

There are three basic classes of antiretroviral drugs. These include the nucleoside analog reverse transcriptase inhibitors (NRTIs), the nonnucleoside reverse transcriptase inhibitors (NNRTIs), and the protease inhibitors (PIs) . Each group of drugs independently interrupts the normal life cycle of the HIV.

The NRTIs are a group of drugs which are competitive inhibitors of the viral enzyme reverse transcriptase. Several controlled trials showed zidovudine (Azidothymidine, AZT, Retrovir) decreases the number and severity of opportunistic infections.[22] The most common side effects of these agents include bone marrow suppression and distal sensory peripheral neuropathy.

The NNRTIs are noncompetitive inhibitors of reverse transcriptase and block RNA-dependent and deoxyribonucleic acid (DNA)-dependent DNA polymerase activity. The most commonly used are nevirapine (Viramune) and efavirenz (Sustiva). Target organisms have a high propensity for developing resistance to these agents, which are recommended for use only as part of a three-drug (or more) regimen. Rash is the most common side effect associated with the NNRTIs.[23]

Protease inhibitors block the enzyme HIV protease, which activates the HIV proteins, which are required for infectivity. However, PIs are expensive and they also have been associated with a high frequency of side effects. Short-term effects are principally GI (including nausea, diarrhea, and bloating); long-term effects are metabolic, such as hyperglycemia, hyperlipidemia, and fat redistribution.[24]

Most experts recommend treatment for any patient with either a CD4 count of fewer than 350 cells/mm^3 or an HIV viral load of greater than 55,000 copies/mL. The recommendation to treat asymptomatic patients should be individualized based on the potential benefits and risks of initiating therapy in an asymptomatic person.

Selection of an appropriate combination of drugs is also a complex issue for which no definitive recommendations currently exist. Twenty antiretroviral drugs currently are approved by the FDA. An up-to-date guide for their use can be found on the NIH web site.[25]

Precautions and Post-Exposure Prophylaxis

Precautions/Exposures. Health care workers are often exposed to the blood and body secretions of patients who are at high risk of harboring HIV and other infectious pathogens. The overall risk of having any occupational blood exposure is significant, with more than half of emergency physicians reporting at least one occupational exposure during a two-year period.[26] However, the overall risk of contracting HIV through occupational exposures remains small. The estimated risk of HIV transmission is estimated at 0.3% via percutaneous exposure and 0.09% for mucocutaneous exposure.[27]

HIV transmission by health care workers to patients appears to be extremely rare. There have been only seven cases to date, six of which occurred from a single dentist's practice, and one from a patient who apparently acquired HIV during orthopedic surgery. At this time, routine screening of health care workers is not indicated.[28]

Numerous studies have demonstrated that health care workers can significantly reduce their risk of exposure to blood-borne pathogens by following universal precautions. CDC guidelines for universal precautions include the use of protective equipment (including gloves, gown, mask, and eye protection) for any situation in which the potential for exposure exists.

Postexposure Prophylaxis. *Occupational Exposures.* Postexposure prophylaxis (PEP) has demonstrated reduced risk of HIV transmission and seroconversion.[29] The CDC provides explicit guidelines for PEP for occupational exposure to HIV. (*See Table 2.*)[30] Current guidelines advise case-by-case determination of the risk of the exposure to determine whether PEP should be recommended. Recommendations are based on two primary factors, type of exposure and HIV status of the source. Higher risk percutaneous exposures include deep injuries, visible blood on a device, and injuries sustained when placing a catheter in a vein or artery;

Table 2. Guidelines for Postexposure Prophylaxis*

EXPOSURE TYPE	HIV NEGATIVE SOURCE	UNKNOWN SOURCE	HIV POSITIVE CLASS 1A SOURCE+	HIV POSITIVE CLASS 2B SOURCE+
Less severe (solid needle, superficial injury)	No PEP warranted	Generally, no PEP warranted; consider 2-drug PEP for suspected HIV risk factors	Recommend basic 2-drug PEP	Recommend expanded 3-drug PEP
More severe (large-bore hollow needle, deep puncture, visible blood on device, needle used in artery or vein	No PEP warranted	Generally, no PEP warranted; consider 2-drug PEP for suspected HIV risk factors	Recommend expanded 3-drug PEP	Recommend expanded 3-drug PEP

* Adapted from: Centers for Disease Control, *MMWR* 2001; 50 (No. RR-11):24.

* HIV Positive Class 1A: Asymptomatic HIV infection or known low viral load
HIV Positive Class 2B: Symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load.

lower risk percutaneous exposures include superficial injuries or solid needles (such as suture needles). High-risk sources include patients with AIDS, acute seroconversion or high viral load.[31] When the status of the source is not known (i.e., no recent positive or negative serology), rapid testing should be performed, using a rapid test such as SUDS or OraQuick. Some states allow testing the source without informed consent. State law should be followed regarding testing of source patients.

Current public health guidelines recommend no PEP for HIV-negative sources, and a four-week regimen of two drugs for most HIV exposures via percutaneous or mucus membrane routes.[32] Two-drug therapy options include either zidovudine and lamivudine (first choice), lamivudine and stavudine, or didanosine and stavudine. For highest risk exposures, a three-drug regimen with the addition of either a protease inhibitor (e.g., indinavir or nelfinavir), a NNRTI (e.g. efavirenz), or a NRTI (e.g., abacavir) is advised. PEP should be initiated as soon as possible after the exposure to source person with known HIV infection, and should be continued for four weeks. Current guidelines suggest starting treatment within 1-2 hours and generally restrict therapy to those who seek treatment within 36 hours of exposure. Initial treatment should never be delayed while awaiting information regarding final determination of overall risk of exposure, as therapy can be stopped after the first dose. In addition to evaluation and management of HIV exposure risk, all patients should be tested and treated for other more highly infectious agents such as hepatitis. Institutions should maintain policies regarding occupational exposures and postexposure prophylaxis.

Nonoccupational Exposure. Because the risk of HIV transmission by certain sexual or injection drug exposures is relatively high, PEP for nonoccupational exposures also should be considered. The CDC has not yet issued guidelines for nonoccupational PEP citing the lack of data regarding the efficacy of this therapy in those populations.

Patient populations that may seek nonoccupational PEP include sexual assault victims, police, EMS personnel, sexual partners or needle-sharing partners of sources with known or suspected HIV infection.

As with occupational exposures, PEP should be considered on a case-by-case basis.[33] A thorough history should be taken to assess the risk of the source, risk of the exposure and the risk for ongoing high-risk exposures. Baseline HIV testing of the exposed patient and the source (when possible) should be performed. Patients should be informed regarding the lack of definitive data for nonoccupational PEP.[34] Counseling should be provided regarding medication side effects, which carefully should be considered and balanced with advantages of therapy. All sexual assault victims should be counseled regarding risk/benefits of PEP treatment.

Local infectious disease consultants often should be involved in PEP decisions. Other invaluable resource for information on both occupational and nonoccupational exposures include the CDC/UCSF National Clinicians PEP Hotline, providing a 24-hour assistance (1-888-448-4911) and Univeristy of California—Los Angeles's on-line decision making support at www.needlesick.mednet.ucla.edu.

Disposition

Consultations with an infectious disease specialist, neurologist, psychiatrist, AIDS specialist, and others may be indicated. Disposition decisions for HIV-infected patients are based on clinical condition, availability of outpatient resources, and ability to arrange adequate follow-up observation. Any patient to be discharged must demonstrate ability to care for himself or herself or to be cared for, and to tolerate sufficient oral intake.

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Physician CME Questions

1. Which of the following is true regarding therapy of PCP pneumonia?
   A. Definitive diagnosis should be made prior to initiation of therapy.
   B. Pentamidine is appropriate first-line therapy.
   C. Steroids should be prescribed for patients with PaO_2 less than 70 mmHg.
   D. All patients with suspected PCP pneumonia should be admitted.

2. Which of the following organisms is the most common etiology of focal intracranial mass lesions among AIDS patients?
   A. *Cryptococcus neoformans*
   B. *Mycobacterium tuberculosis*
   C. CNS lymphoma
   D. *Toxoplasma gondii*
   E. Cytomegalovirus

3. Which of the following organisms is the most common etiology of blindness in AIDS patients?
   A. *Cryptococcus neoformans*
   B. *Mycobacterium tuberculosis*
   C. *Pseudomonas aeruginosa*
   D. *Toxoplasma gondii*
   E. Cytomegalovirus

4. Which of the following is the most appropriate postexposure prophylaxis regimen following a deep needlestick injury following an arterial stick in an HIV positive patient with AIDS?
   A. No postexposure prophylaxis indicated
   B. Zidovudine alone
   C. Zidovudine plus ddI
   D. Zidovudine plus lamivudine
   E. Zidovudine plus lamivudine plus indinavir

Answers: 1. C; 2. D; 3. E; 4. E