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A SUPPLEMENT TO

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A Peer-Reviewed Journal for Managed
Care and Hospital Formulary Management

Implementing Guidelines for Drotrecogin Alfa (activated): Three Perspectives

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**By Gordon Vanscoy, PharmD, CACP, MBA, John Devlin, PharmD, BCPS, John Ponzillo, PharmD,
and David A. Kuhl, PharmD**

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Implementing Guidelines for Drotrecogin Alfa (activated): Three Perspectives

GORDON VANSCOY, PHARM.D, CACP, MBA, JOHN DEVLIN, PHARM.D, BCPS, JOHN PONZILLO, PHARM.D, AND DAVID A. KUHL, PHARM.D

OBJECTIVES

- Describe the clinical outcomes of recombinant human activated protein C (drotrecogin alfa [activated]) in the treatment of severe sepsis.
- Discuss the importance of proper patient selection guidelines for treatment with drotrecogin alfa (activated).
- Identify methods to create and implement patient selection guidelines for drotrecogin alfa (activated).

INTRODUCTION

Sepsis remains a common, frequently fatal, and expensive condition. It is the leading cause of death in noncardiac intensive care units (ICUs) and the 13th leading cause of death among hospitalized patients overall.¹ Severe sepsis—sepsis with associated organ dysfunction—accounts for an estimated 751,000 cases each year in the U.S.² Angus et al. reported that the average cost per case of severe sepsis in the U.S. was \$22,100, with an average length of stay of 19.6 days.²

The clinical challenge in the management of severe sepsis is to define optimal therapeutic strategies for effective and timely intervention and to identify patients who would benefit most from those therapies through the development and implementation of effective guidelines. The use of supportive treatments, such as antimicrobial agents, vasopressors, and fluids, represents a rational approach in sepsis; however, the survival rate remains only 50% to 70%. Some investigational adjunctive agents, such as corticosteroids, monoclonal antibodies to endotoxins, interleukin antagonists, antithrombin III, tumor necrosis factor (TNF) antagonists, and nitric oxide inhibitors, have benefited certain subsets of patients with severe sepsis; until recently, however, no agent has been shown to reduce the overall mortality associated with this condition.

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Drotrecogin alfa (activated) (Xigris™, Eli Lilly and Co.), which was approved by the Food and Drug Administration (FDA) in November 2001, represents a landmark biotechnology innovation in the treatment of severe sepsis. Drug approval was based on the data of the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis) trial, a randomized, double-blind, placebo-controlled, multicenter phase III efficacy and safety study.⁷

Enrolled patients needed to meet three inclusion criteria:

- a known or suspected infection
- three or more criteria for the systemic inflammatory response syndrome (SIRS)
- at least one acute organ dysfunction for a duration of no longer than 24 hours

Several patient groups, however, were excluded from the PROWESS study population, including patients with an increased risk of bleeding, those younger than age 18, and patients whose weight exceeded 135 kg. Patients presenting with an increased bleeding risk included those who had undergone surgery within 12 hours, those with gastrointestinal bleeding within six weeks, those at risk of central nervous system bleeding, and trauma patients at risk of bleeding. The study also excluded patients who were receiving medications associated with altered coagulation or platelet function. Other confounding disease states were also excluded from the trial, such as chronic renal failure and chronic liver failure.³ In the PROWESS trial, patients had to begin treatment within 24 hours of meeting the inclusion criteria.³

In this trial, drotrecogin alfa (activated) significantly reduced mortality in patients with severe sepsis without a morbidity penalty at 28 days.³ Patients given this drug experienced a statistically significant 6.1% reduction in 28-day all-cause mortality (30.8% versus 24.7%, $P = .005$) and a 19.4% reduction in the relative risk (RR) of death (95% CI, 6.6 to 30.5).³ This 6.1% absolute reduction translates into one additional life saved for every 16 patients treated.³ On the basis of the PROWESS trial data, the FDA designated this drug for adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who are at a high risk of death.⁴

Because of the high financial burden associated with severe sepsis, it is essential to ascertain the economic impact of drotrecogin alfa (activated) therapy. The drug is relatively expensive; the acquisition cost of a 5-mg vial is \$210, or \$42 per milligram. Therefore, an average 70-kg patient would require approximately 160 mg for 96 hours, or a course-of-treatment cost of \$6,800. Thus, it is crucial to develop and implement appropriate guidelines to ensure that suitable patients are being targeted.

Guideline Essentials

A goal highlighted in a report by the Institute of Medicine⁵ is to have a system that not only centers on the

needs, preferences, and values of patients but also encourages teamwork among health workers. The ICU team must proactively assess the utility of drotrecogin alfa (activated) in terms of health value and must facilitate the appropriate use of the drug in patients with severe sepsis. Health care systems are encouraged to create effective guidelines to enable appropriate patient selection and proper utilization.

Usage guidelines help in reducing errors and in improving communication between team members. Guidelines ensure that each member of the health care team is following the same plan toward a mutually agreed-on endpoint. The use of selection guidelines for patients with severe sepsis represents a valuable tool for the ICU team. It is imperative to identify patients who would benefit most from drotrecogin alfa (activated) therapy.

Although the PROWESS trial evaluated a specific patient population, it will be important to re-evaluate institutional guidelines as additional data in other patient populations become available. In addition to the guidelines, development of both prospective and retrospective medication use evaluations (MUEs) is encouraged to ensure that the guidelines are being followed appropriately.

THREE INSTITUTIONAL PERSPECTIVES

Three critical care pharmacy specialists next describe how drotrecogin alfa (activated) guidelines were implemented within their particular institutions. Dr. John Devlin at the Detroit Receiving Hospital and University Health Center, Dr. John Ponzillo at St. John's Mercy Medical Center in St. Louis, and Dr. David Kuhl at the Regional Medical Center at Memphis present their perspectives.

Detroit Receiving Hospital and University Health Center

John Devlin, PharmD, BCPS

The Detroit Medical Center (DMC) is an 1800-bed academic health system comprising six acute-care adult hospitals, a tertiary care pediatric hospital, and a rehabilitation institute. The hospitals are the major teaching center for Wayne State University. The health system includes three medical ICUs, seven surgical ICUs, two mixed medical-surgical ICUs, a burn ICU, a pediatric ICU, and two neonatal ICUs, with a total of more than 200 beds. The system's four emergency departments treat more than 150,000 patients each year. Each hospital in the Center has a medication-use committee that meets monthly and reports directly to a systemwide P & T committee.

Soon after the publication of the PROWESS trial in March 2001, a systemwide, multidisciplinary task force on drotrecogin alfa (activated) was convened under the auspices of the system's P & T committee and charged

with the development of prescribing guidelines and a comprehensive MUE process.³ This task force was led by an experienced critical care pharmacist and comprised more than 30 members, including medical, surgical, neurological and pediatric intensivists, a hematologist, an infectious disease specialist, an ethics specialist, a pharmacist administrator, and other critical care pharmacists and nurse clinical specialists. The group met six times over six months before a final version of the prescribing guidelines and MUE criteria were developed and subsequently approved by each site's MUE committee and the Center's P & T committee in early December 2001.

The task force's major concern was that drotrecogin alfa (activated) might be administered to patients for whom further therapeutic intervention was likely to be futile. A subpopulation of patients with severe sepsis eventually deteriorated to the point where the prognosis was so poor that no therapy, including drotrecogin alfa (activated), was likely to improve the outcome.⁶ Committee members, however, were faced with the challenge of developing criteria to identify this population of patients.

Initially, the task force strove to limit administration of the drug to patients who were expected to survive hospitalization and to return to a level of functionality similar to that previously enjoyed. These definitions, however, were met with resistance because no objective method exists to determine exactly which patients will survive severe sepsis.⁷ Furthermore, the task force thought that the assessment of level of functionality was very subjective and would be difficult to apply on a consistent basis in clinical practice.

On the basis of these limitations, the group instead decided to simply state that drotrecogin alfa (activated) should not be administered to patients when further aggressive therapeutic interventions would be futile. Rather than establish specific criteria for defining futility, the task force would leave the determination of futility up to the attending intensivist on a patient-by-patient basis. In addition, the committee members recognized a role for the ethics service in this decision-making process.⁸

Although the inclusion and exclusion criteria from the PROWESS trial were used as the basis for most of the guidelines (e.g., the objective definition of severe sepsis), the task force considered several areas in the PROWESS trial criteria to be too restrictive.³ The members were concerned that the definitions of organ dysfunction in the PROWESS study were not explicit enough to guide the appropriate use of drotrecogin alfa (activated) in clinical practice.

For example, the criteria used to define both cardiovascular (e.g., hypotension) and renal (e.g., oliguria) failure rely on the adequacy of fluid resuscitation. The clinical subjectivity of evaluating adequate fluid requirements in critically ill patients can result in disparate practices among clinicians when they are deter-

mining whether an adequate fluid challenge has been administered.⁹

To address this concern, the task force recommended the following guidelines:

- All fluid resuscitative efforts should include at least 20 ml/kg in the first hour, and a physician at the attending level should assess the adequacy of fluid resuscitation.
- All patients with cardiovascular failure should be dependent on a vasopressor such as dopamine (more than 5 mcg/kg per minute), norepinephrine, or phenylephrine.
- Diuretic resistance and oliguria related to concomitant drug therapy should be ruled out in all patients with renal failure.
- Hematological failure (i.e., thrombocytopenia) should not be attributable to other medical conditions or drugs (e.g., recent chemotherapy).

The group debated whether or not to restrict drotrecogin alfa (activated) therapy to patients with more than one failed organ. This discussion was based on the subgroup analysis of the 28-day mortality data in the PROWESS trial that found no benefit from drotrecogin alfa (activated) in patients with only one failed organ.³ The group concluded that the PROWESS trial did not have adequate power to make this decision and that although this was certainly an issue that warranted further research, the trial results should not be used to guide current drotrecogin alfa (activated) prescribing decisions.¹⁰

The task force members also debated whether or not drotrecogin alfa (activated) should be restricted to patients with a score above 25 in the Acute Physiology and Chronic Health Evaluation (APACHE II) trial.¹¹ This was based on the fact that subgroup analysis of the PROWESS study had demonstrated that an APACHE II score below 24 in the 24 hours prior to study enrollment did not help patients gain a mortality benefit at 28 days with the administration of drotrecogin alfa (activated) compared to placebo. In general, task force members did not support using an APACHE II score as a criterion to rationalize drotrecogin alfa (activated) use. Their primary concern was that the PROWESS trial did not prospectively stratify patients by APACHE II score and therefore was underpowered to confirm whether an APACHE II score below 24 would, in fact, not lead to a mortality benefit from drotrecogin alfa (activated).³

Another limitation of APACHE II scores to guide therapy was that the APACHE II score has not been validated as a predictor of outcome in any period of ICU stay other than the first 24 hours of admission.¹² In addition, task force members thought that the APACHE II score could be cumbersome to calculate as a part of routine patient care and might be imprecise if an untrained assessor performed the calculations.

Task force members were concerned about the potential risk for serious bleeding events related to drotrecogin alfa (activated). The PROWESS trial defined serious bleeding as:

- any intracranial hemorrhage
- any life-threatening bleeding
- any bleeding requiring the administration of three units of packed red cells on two consecutive days
- any bleeding classified as serious by the investigator

Although the increase in serious bleeding observed in the PROWESS study was not statistically significant, the study criteria, excluding patients with risk factors for bleeding, were extensive.¹³ The group felt that significant variability existed among patients with severe sepsis related to their likelihood of experiencing a drotrecogin alfa (activated)-related bleeding event.

Bleeding risks were subsequently stratified into *absolute* or *relative* contraindications for the administration of drotrecogin alfa (activated). Patients with relative contraindications to the drug could still receive it as long as the expected benefits of treatment outweighed the risks of experiencing adverse bleeding events.

Absolute contraindications were based primarily on those contained in the product insert, although the description of each was often modified to improve clarity (Figure 1).⁴ The task force devoted considerable time to discussing many of the relative contraindications to drotrecogin alfa (activated) therapy; unlike the absolute contraindications, these often necessitated that the prescribing physician make an informed risk-benefit decision on whether to administer this drug. The task force members decided that recent surgery or trauma should be a contraindication only if the patient was still deemed to be at risk for bleeding (i.e., in the event of uncertain hemostasis). They anticipated that physicians would probably still consider drotrecogin alfa (activated) for severely thrombocytopenic patients (e.g., red blood cells below $30,000 \times 10^3$). However, patients with dysfunctional platelets or underlying coagulopathy should be treated with increased caution and carefully monitored for signs and symptoms of bleeding (e.g., oozing around an intravenous catheter site, hematemesis, hypotension, or sudden changes in neurological function).

Previous gastrointestinal bleeding was generally not considered a contraindication for drotrecogin alfa (activated) therapy unless the bleeding had necessitated surgery or extensive transfusion of blood products. Although patients with underlying alcoholic liver disease were excluded from the PROWESS trial, the task force recognized that this population frequently develops severe sepsis and should be considered for drotrecogin alfa (activated) therapy unless a significant underlying coagulopathy is present.

It was felt that only rarely should concomitant anticoagulation or antithrombotic therapy be a reason to avoid the use of drotrecogin alfa (activated) as long as the initiation of therapy was delayed until most of the anticoagulant was cleared from the body (generally requiring three to four drug half-lives). The guidelines contain recommendations for the duration of time to delay drotrecogin alfa (activated) therapy after discontinuation of common antithrombotic agents.

Task force members also recommended including a "catch-all" statement to cover situations in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location. Finally, to ensure that an informed risk-benefit assessment was completed for all patients with a relative contraindication to drotrecogin alfa (activated), prescribers were asked to document on the guideline form that the potential benefits of this drug outweigh any risks.

Although the efficacy and safety of drotrecogin alfa (activated) in pediatric patients have not been prospectively evaluated in a controlled fashion, it was felt that the drug would probably be used in children according to the results of pharmacokinetic studies suggesting that the distribution and clearance of the drug is identical across all ages. Separate prescribing guidelines for children, using the adult guidelines as a template, were drafted. The pediatric guidelines used age-based criteria for SIRS and a definition different from that used for adults to delineate the adequacy of volume resuscitation.

The task force discussed locations in the hospital where drotrecogin alfa (activated) could be administered and which physicians in the health system should have the independent authority to prescribe it. It was decided that this drug should be administered only in a unit where continuous cardiorespiratory monitoring would be available because of the severity of illness of the patients, coupled with the potential risk for bleeding. Interestingly, the infectious disease service at DMC, although it participated in guideline development, was not interested in being involved in the prescribing decisions. The specialists felt that the decision to administer drotrecogin alfa (activated) should rest with the primary attending intensivist. It was decided that although emergency department physicians could identify potential candidates for drotrecogin alfa (activated) therapy, prescribing authority should remain in the hands of attending intensivists. Similarly, the guidelines required that house staff physicians obtain approval from attending intensivists before drug administration.

The incidence of drug-related adverse effects can increase when a drug is used outside the setting of a controlled clinical trial, because patient screening techniques and monitoring practices may become less rigorous. The task force unanimously decided that an MUE should be completed for all patients receiving drotrecogin alfa (activated) in order to document compliance with the institutional prescribing guidelines and



DMC Guidelines for the Accepted Use of Drotrecogin alfa (activated)
[recombinant human activated protein C, Xigris®] in **ADULTS** with Severe Sepsis

Drotrecogin alfa (activated) should only be prescribed when **EACH** of the following criteria are met:

YES <input type="checkbox"/>	A. Further aggressive therapeutic intervention is NOT FUTILE .
YES <input type="checkbox"/>	B. Has a known or suspected INFECTION ?
YES <input type="checkbox"/>	C. Has the Systemic Inflammatory Response Syndrome (SIRS) ? MUST have at least 3 of the following SIRS signs/symptoms: <ul style="list-style-type: none"><input type="checkbox"/> Disordered temperature regulation ($\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$)<input type="checkbox"/> Tachycardia [heart rate ≥ 90 beats/min (unless drug or disease induced alteration)]<input type="checkbox"/> Respiratory distress (rate ≥ 20 breaths/min or PaCO_2 of ≤ 32 mmHg), or need for mechanical ventilation<input type="checkbox"/> Leukocytosis/leukopenia (white cell count $\geq 12,000/\text{mm}^3$ or $\leq 4,000/\text{mm}^3$ or > 10 percent immature neutrophils)
YES <input type="checkbox"/>	D. Clinical evidence of organ dysfunction attributable to sepsis based on at least ONE of the following? <ul style="list-style-type: none"><input type="checkbox"/> Hypotension unresponsive to fluids and dependence on vasopressors: SBP ≤ 90 mmHg or MAP ≤ 70 mmHg for at least 1 hour despite adequate fluid resuscitation*** AND reliance on vasopressor therapy including dopamine ≥ 5 mcg/kg/min or any dose of norepinephrine, phenylephrine, or vasopressin.<input type="checkbox"/> Oliguria unresponsive to fluids: urine output < 0.5 ml/kg/hr for 1 hour, despite adequate fluid resuscitation*** and/or diuretic therapy that is not attributable to drug-related effects. NOTE: patients with chronic renal failure must have at least one other organ dysfunction<input type="checkbox"/> Hypoxemia: $\text{PaO}_2/\text{FiO}_2 \leq 200$ torr (or $\text{PaO}_2/\text{FiO}_2 \leq 250$ torr if other organ dysfunction)<input type="checkbox"/> Thrombocytopenia: platelets $\leq 80,000/\text{mm}^3$ OR a decrease by 50% in the previous 3 days to $< 100,000/\text{mm}^3$ that cannot be explained by other medical conditions or drugs.<input type="checkbox"/> Metabolic acidosis: pH ≤ 7.30, or base deficit ≥ 5 mmol/L and a blood lactate above the upper limit of normal <p>***Adequacy of resuscitative effort must be assessed in consultation with an attending physician and should be at least 20 mL/kg/hour for the first hour of resuscitation.</p>
Contraindications to drotrecogin alfa (activated) administration	
YES <input type="checkbox"/>	E. The following ABSOLUTE contraindications to drotrecogin alfa administration have been excluded? <ul style="list-style-type: none"><input type="checkbox"/> Active major bleeding at any site<input type="checkbox"/> Uncontrollable bleeding diathesis except coagulopathy related to sepsis<input type="checkbox"/> Current or recent (< 24 hrs) epidural or spinal catheterization<input type="checkbox"/> Recent intracranial or intraspinal trauma, instrumentation, or surgery (< 2 months)<input type="checkbox"/> Intracranial neoplasm, or mass lesion, or evidence of cerebral herniation<input type="checkbox"/> Recent hemorrhagic stroke (< 3 months)<input type="checkbox"/> Known hypersensitivity to drotrecogin alfa (activated)
YES <input type="checkbox"/>	F. All RELATIVE contraindications have been identified or excluded? (check all that apply) <ul style="list-style-type: none"><input type="checkbox"/> Recent surgery or trauma with uncertain hemostasis<input type="checkbox"/> Platelet count $< 30,000/\text{mm}^3$, dysfunctional platelets (e.g., uremia, ASA therapy), INR ≥ 3, or other coagulopathy<input type="checkbox"/> Recent gastrointestinal bleeding (< 6 weeks) requiring surgical or medical intervention (≥ 3 units PRBC)<input type="checkbox"/> Recent ischemic stroke (< 3 months)<input type="checkbox"/> Intracranial arteriovenous malformation or aneurysm<input type="checkbox"/> Cirrhosis with portal hypertension<input type="checkbox"/> Concomitant medications:<ol style="list-style-type: none">1. need for therapeutic anticoagulation:<ul style="list-style-type: none">- unfractionated heparin $> 15,000$ U/day (wait 6 hours after discontinuation to start) [prophylaxis doses permitted]- low molecular weight heparin $>$ enoxaparin 30 mg twice daily (wait 12 hours after discontinuation to start)- INR ≥ 3 related to warfarin therapy (consider reversal with vitamin K)- lepirudin (wait 6 hrs after discontinuation to start)2. recent thrombolytic therapy (catheter clearance doses permitted)3. recent glycoprotein IIb/IIIa antagonist therapy (< 7 days since abciximab; < 48 hr for tirofiban and eptifibatide)<input type="checkbox"/> Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location
YES <input type="checkbox"/>	G. The RELATIVE contraindications have been excluded, or, if any are present, the potential benefit of drotrecogin alfa therapy outweighs the risks?

For patients meeting **ALL** of the above criteria, drotrecogin alfa (activated) may be only authorized by a **DMC Attending Medical or Surgical Intensivist** and may only be administered in an intensive care unit

Authorizing Intensivist: Name _____ Beeper _____ Date _____
Prescribing Physician: Name _____ Beeper _____ Approved DMC P&T 12/14/01

FIGURE 1 Guidelines for drotrecogin alfa (activated) in patients with severe sepsis. (Reprinted with permission from Detroit Medical Center.)

DMC MUE Criteria for Drotrecogin Alfa (activated)

1. Were DMC prescribing criteria fully met?	<input type="radio"/> YES	<input type="radio"/> NO
a. Known or suspected infection	<input type="radio"/> YES	<input type="radio"/> NO
Type/location of infection _____		
Organism isolated _____		
b. SIRS (≥ 3)	<input type="radio"/> YES	<input type="radio"/> NO
<input type="checkbox"/> Temp ($\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$)		
<input type="checkbox"/> WBC ($\geq 12\text{K}$ or $\leq 4\text{K}$ or $> 10\%$ neutrophils)		
<input type="checkbox"/> HR (≥ 90 beats/min)		
<input type="checkbox"/> RR (≥ 20 or $\text{PaCO}_2 \leq 32$ mm Hg or mechanically ventilated)		
c. Organ Dysfunction (at least one)	<input type="radio"/> YES	<input type="radio"/> NO
<input type="checkbox"/> Hypotension <input type="checkbox"/> Metabolic acidosis		
<input type="checkbox"/> Hypoxemia <input type="checkbox"/> Thrombocytopenia		
<input type="checkbox"/> Oliguria _____		
d. Contraindications	<input type="radio"/> YES	<input type="radio"/> NO
If yes, what?		
<input type="checkbox"/> Absolute Specify: _____		
<input type="checkbox"/> Relative Specify: _____		
2. Did an approved DMC attending authorize use of the drug?	<input type="radio"/> YES	<input type="radio"/> NO
3. APACHE II score: (Please complete attached worksheet)		
a. admission _____		
b. 24 hrs prior to drotrecogin alfa _____		
4. Did the patient experience adverse events associated with the drug?	<input type="radio"/> YES	<input type="radio"/> NO
If yes, what? Major bleeding		
Site of bleed: _____		
Magnitude of decrease in Hgb _____		
Did patient receive a transfusion? _____	<input type="radio"/> YES	<input type="radio"/> NO
If yes, please quantify blood products given (on reverse)		
Was drug infusion stopped?	<input type="radio"/> YES	<input type="radio"/> NO
Was infusion restarted?	<input type="radio"/> YES	<input type="radio"/> NO
<input type="checkbox"/> Other, explain: _____		
<input type="checkbox"/> Doctor Quality™ entry initiated	<input type="radio"/> YES	<input type="radio"/> NO
Other comments: _____		
5. Did patient survive hospitalization?	<input type="radio"/> YES	<input type="radio"/> NO
Length of ICU stay (days): _____		
Total length of hospital stay (days): _____		
If survived, patient was discharged to:		
<input type="checkbox"/> Rehabilitation <input type="checkbox"/> Skilled-nursing facility		
<input type="checkbox"/> Home with care nurse <input type="checkbox"/> Home		
6. Were there any drug-related medication errors?	<input type="radio"/> YES	<input type="radio"/> NO
If yes, please explain: _____		
7. Was any drug wasted?	<input type="radio"/> YES	<input type="radio"/> NO
If yes, please explain: _____		
8. Was patient assessed for indigent reimbursement?	<input type="radio"/> YES	<input type="radio"/> NO

FIGURE 2 Medication Use Evaluation (MUE) Criteria for drotrecogin alfa (activated). (Reprinted with permission from Detroit Medical Center.)

to identify any adverse drug events (e.g., bleeding). Standardized drotrecogin alfa (activated) data collection forms are presented in Figure 2. These data are to be collected by a designated critical care pharmacist at each DMC hospital and presented on a quarterly basis to the systemwide P & T committee.

St. John's Mercy Medical Center

John Ponzillo, PharmD

In March 2001, the PROWESS trial was published in the *New England Journal of Medicine*. St. John's Mercy Medical Center began discussing the formulary status and guideline development of this drug immediately following an article in *The Wall Street Journal* on January 4, 2001, about a dramatic reduction in sepsis deaths with an Eli Lilly drug.¹⁴ This article, which speculated on the cost of drotrecogin alfa (activated), caught the attention of the hospital's medical staff and administration.

St. John's Mercy Medical Center is a 979-bed community teaching hospital in St. Louis County. It is a level I trauma center, and critical care is provided by intensivists and fellows. The critical care medicine fellowship is affiliated with St. Louis University School of Medicine. The Medical Center currently operates 40 medical and surgical critical care beds, 16 coronary care/cardiovascular surgery beds, and a nine-bed burn unit.

St. John's was concerned about the potential financial impact of drotrecogin alfa (activated) on its operating budget. Thus, discussion began with the critical-care staff, which has been intimately involved with clinical trials of newer sepsis drugs for more than 10 years. Based on participation in previous sepsis trials, hospital staff estimated that they could treat 50 patients per year with drotrecogin alfa (activated).

The next step was to assemble a multidisciplinary group of individuals from intensive care, trauma, infectious diseases, pharmacy, nursing, oncology, and family practice disciplines to develop guidelines for the appropriate use of this novel therapeutic agent. Guidelines were based on the inclusion and exclusion criteria from the PROWESS trial. Since the publication of this trial, several well-developed guidelines have been published.^{15,16} Numerous and extensive revisions of St. John's guidelines were presented to the Critical Care Quality Improvement Group, and the final draft was sent to the P&T committee for approval. The next step was to implement these guidelines.

Dr. Tom Peters, in his book *Thriving on Chaos*, writes: "Work-force training must become a corporate (and indeed national) obsession."¹⁷

With the continual introduction of new and complex therapies, this statement is especially true in health care.

St. John's began with frequent presentations to its physician staff, including noon conferences, grand rounds, and morning discussions. Next, similar discussions were held with the pharmacy staff, critical care nurses, respiratory therapy, and hospital administration. These meetings and lectures are still ongoing, so that all staff members are aware of any new developments and so that personnel are aware of the guidelines. Since the development of these guidelines, new information has led to new questions.

Most drug use evaluation (DUE) criteria for drotrecogin alfa (activated) use the inclusion and exclusion criteria from the PROWESS trial (Figure 3). Although the measurement of proinflammatory cytokine levels (e.g., TNF) seems to be a logical way to assess the severity of sepsis, such a measurement is not readily available. To examine outcomes, some have shown interest in measuring D-dimer levels in critically ill patients. Elevation of D-dimer levels is seen with the activation of the coagulation system and is used to assess patients with suspected disseminated intravascular coagulation (DIC). Because coagulation abnormalities are seen in patients with severe sepsis, it seems logical to assess D-dimer levels in patients with clinical signs of severe sepsis.

The results of two trials, with 321 and 79 patients, respectively, suggest that elevated D-dimer levels correlate with poor outcomes in critically ill patients.^{18,19} The cost of a D-dimer evaluation is approximately \$5.00. Additional data are required to understand the role of D-dimer levels identifying appropriate candidates for drotrecogin alfa (activated) therapy.

Since the FDA's approval of drotrecogin alfa (activated), St. John's Mercy Medical Center has been addressing the development of a standard order form for the patient's permanent medical record. This measure would serve two purposes:

- It would be documented that the patient has met the appropriate inclusion criteria for the drug.
- Having the dosage guidelines preprinted on the form would reduce the potential for medication errors.

Next, the hospital is contemplating what to do with unique patient groups, such as burn and oncology patients. It has been decided that patients will be reviewed on an individual basis to evaluate their outcomes according to whether they fall within the hospital's guidelines.

According to famed football coach Vince Lombardi, a failure to succeed depends not on a lack of strength or knowledge but on a lack of will. Collaboration will produce the strength, knowledge, and will to effectively introduce new pharmacotherapy in the critical care setting.

XIGRIS® USAGE CRITERIA {DROTRECOGIN ALFA (ACTIVATED), APC} ST. JOHN'S MERCY MEDICAL CENTER

Xigris (Activated Protein C) is indicated as adjunctive therapy for severe sepsis associated with organ dysfunction of recent (<72 hours) onset. This product will be administered in the Intensive Care Units.

Criteria for Appropriate Usage

Yes No Patient must have known or suspected infection.

AND EITHER

Yes No Three or more signs of systemic inflammatory response syndrome (SIRS) plus sepsis-induced dysfunction of at least one organ or system that has lasted no longer than 72 hours. {see next section}

OR

Yes No Patients with purpura fulminans.

Systemic Inflammatory Response Syndrome (SIRS) Criteria (3 required)

Yes No Core temperature $\geq 38^{\circ}\text{C}$ (100.4°F) or $\leq 36^{\circ}\text{C}$ (96.8°F)

Yes No Heart rate of ≥ 90 beats/min, except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia.

Yes No Respiratory rate of ≥ 20 breaths/min or a PaCO_2 of ≤ 32 mm Hg or use of mechanical ventilation for an acute respiratory process.

Yes No White blood cell (WBC) count of $\geq 12,000/\text{mm}^3$ or $\leq 4,000/\text{mm}^3$ or a differential count showing >10 percent immature neutrophils.

Organ or System Dysfunction Criteria (one required)

Yes No Cardiovascular system dysfunction:

a. Arterial systolic blood pressure had to be ≤ 90 mm Hg, or mean arterial pressure (MAP) ≤ 70 mm Hg for at least 1 hour despite adequate fluid resuscitation.*

OR

b. need for vasopressors to maintain systolic blood pressure (SBP) ≥ 90 mm Hg or MAP ≥ 70 mm Hg in the presence of adequate intravascular volume status and/or adequate fluid resuscitation.

*Adequate fluid resuscitation or adequate intravascular volume is defined as one or more of the following:

1. The administration of an IV fluid bolus (≥ 500 ml of crystalloid solution, ≥ 20 grams of albumin, or ≥ 200 ml of other colloids administered over 30 minutes or less)
2. Pulmonary arterial wedge pressure (PAWP) ≥ 12 mm Hg
3. Central venous pressure (CVP) ≥ 8 mm Hg

Vasopressors are defined as:

- a. Dopamine ≥ 5 mcg/kg/min **or**
- b. Norepinephrine, epinephrine, phenylephrine, or vasopressin at any dose
- c. Dobutamine and Dopexamine are **not** considered vasopressors.

Yes No Kidney dysfunction: urine output < 0.5 ml/kg of body weight/hr for 1 hour, despite adequate fluid resuscitation.

Yes No Respiratory-system dysfunction: ratio of PaO_2 to $\text{FiO}_2 \leq 200$.

Yes No Hematologic dysfunction: the platelet count $< 80,000/\text{mm}^3$ or to have decreased by 50 percent in the 3 days preceding enrollment.

Yes No In the case of unexplained metabolic acidosis, the pH had to be ≤ 7.30 or the base deficit had to be ≥ 5.0 mmol/liter in association with a plasma lactate level that was > 1.5 times the upper limit of the normal value for the reporting laboratory.

Contraindications:

Yes No

- | | | |
|--------------------------|--------------------------|--|
| <input type="checkbox"/> | <input type="checkbox"/> | Major surgery (general anesthesia or spinal anesthesia) within 12 hours prior to infusion |
| <input type="checkbox"/> | <input type="checkbox"/> | Active internal bleeding |
| <input type="checkbox"/> | <input type="checkbox"/> | Recent (within 3 months) hemorrhagic stroke |
| <input type="checkbox"/> | <input type="checkbox"/> | Recent (within 3 months) intracranial, intraspinal, or ocular surgery, or severe head trauma |
| <input type="checkbox"/> | <input type="checkbox"/> | Trauma patients with increased risk of life-threatening bleeding |

(continued)

FIGURE 3 Xigris® usage criteria. (Reprinted with permission of St. John's Mercy Medical Center, St. Louis.)

FIGURE 3 Xigris® usage criteria. (continued)

Contraindications (continued):

Yes No

- Patients with an epidural catheter
- Patients with intracranial neoplasm or mass lesion or evidence of cerebral herniation
- Patients with known hypersensitivity to Drotrecogin alfa (activated)
- Presence of an advanced directive to withhold life-sustaining treatment, with the exception of CPR
- Patients not expected to survive 28 days due to uncorrectable medical conditions, such as poorly controlled neoplasm or other end-stage disease
- Patients with chronic renal failure on either hemodialysis or peritoneal dialysis
- An HIV-positive patient whose most recent CD₄ count $\leq 50/\text{mm}^3$
- Patients with acute clinical pancreatitis without a proven source of infection

WARNINGS

In the following conditions, the risks of administration should be weighed against the anticipated benefits:

1. Therapeutic heparin ($\geq 15,000$ units/day)
2. Platelet count $< 30,000 \times 10^6/\text{L}$
3. Recent (within 6 weeks) gastrointestinal bleeding
4. Recent administration (within 3 days) of thrombolytic therapy
5. Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
6. Recent administration (within 3 days) of aspirin > 650 mg/day or other platelet inhibitors
7. Recent (within 3 months) ischemic stroke
8. Patients with intracranial arteriovenous malformation or aneurysm
9. Known bleeding diathesis except for acute coagulopathy related to sepsis
10. Chronic severe hepatic disease
11. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location
12. Patients who are pregnant or breastfeeding (use only if clearly needed)

Dosing and Duration of Therapy

If patient meets criteria for usage, therapy should be initiated at 24 mcg/kg/hour and continued for a total of 96 hours.

1. Yes No **Patient has met inclusion and exclusion criteria.**
2. Mix Xigris _____ mg in _____ cc 0.9% NaCl and infuse at _____ ml/hour. Xigris is available in 5- and 20-mg vials. Please prepare each infusion bag to run over 12 hours and round all dosages to the closest 5-mg or 20-mg dose.
3. Discontinue Xigris after 96 hours of infusion.
4. **Discontinue Xigris infusion and contact the physician if the patient develops any bleeding.**
5. Xigris should be discontinued 2 hours prior to undergoing an invasive surgical procedure or procedures with an inherent risk of bleeding. *Once adequate hemostasis has been achieved*, initiation of Xigris may be reconsidered 12 hours after major invasive procedures or surgery, or restarted immediately after uncomplicated less invasive procedures.
6. Monitoring: CBC, PT, PTT, daily during infusion

Signature _____ Date _____ Time _____
4/15/2002

Regional Medical Center at Memphis

David A. Kuhl, PharmD

The Regional Medical Center at Memphis is a 350-bed, university-affiliated, public institution. The Center has a level-1 trauma center and a regional burn unit and services the medically underserved population in the region. Several months before the introduction of drotrecogin alfa (activated), pharmacy representatives from four institutions in the Memphis area met to review

the available literature and develop guidelines for patient selection. These institutions represented both private not-for-profit and public health care organizations.

The goal of the working group was to develop a template that each institution could use in developing hospital-specific criteria. References used in guideline development included the one published study evaluating drotrecogin alfa (activated) therapy in severe sepsis, sepsis treatment guidelines developed by The International Sepsis Forum (www.sepsisforum.org),²⁰⁻²⁵ sample guidelines available from other institutions, and guidelines

developed by critical care and administrative pharmacists through University Pharmacotherapy Associates.²⁶

The group recommended that each hospital develop a process for identifying and educating approved prescribers, making the drug available only to ICU patients. In addition, general sepsis management would be addressed with the physicians in each hospital. Prescribing guidelines were divided into four sections: (1) inclusion requirements, (2) absolute exclusion criteria, (3) relative exclusion criteria, and (4) patient populations in which the drug's safety and efficacy were unknown.

The final draft of these guidelines was used as a working document for meeting with physicians at Regional Medical Center. The timeline for guideline approval is outlined in Table 1. The physician group included representatives from surgery, pulmonary/critical care, infectious diseases, and general medicine. Patient selection guidelines for drug administration are described in Figure 4.

Patients were required to be in the ICU and to have a reasonable life expectancy beyond 28 days, and there was to be no plan to withhold supportive or resuscitative measures. Management of sepsis in the form of appropriate antibiotic therapy and aggressive fluid resuscitation was also necessary. Furthermore, patients were required have at least three criteria consistent with SIRS.^{3,27,28}

Although the original trial included patients with one or more organ failures,³ the group evaluated the definitions of organ failure and the data provided by the company on patient outcomes based upon APACHE II scoring.⁴ It was decided to include patients with two or more failing organs until more data became available in the less severely ill patients. All of these criteria were required for the patient to receive drotrecogin alfa (activated). In addition, the patient could not have any contraindications (see Figure 4), to maintain consistency with the labeling in the package insert for this drug.⁴

Finally, although these factors might not be an absolute contraindication to use, the physician was required to review conditions that might increase the patient's risk of adverse events and to review patient populations for which available data regarding safety and efficacy were limited.

Upon the P&T committee's approval to add drotrecogin alfa (activated) to the formulary, it was necessary to put pharmacy procedures in place to ensure compliance with criteria, timely drug delivery, and selection of drug doses that would optimize the 12-hour stability of the drug once it was compounded. Table 2 identifies the elements necessary prior to drug administration.

The guidelines were converted to a checklist, which was to be completed by the prescribing physician. Copies of this checklist were placed in the ICUs and in the central pharmacy. If an order for drotrecogin alfa (activated) arrived with an incomplete checklist, the phar-

Table 1 Timeline for Guideline Approval for Drotrecogin Alfa (activated)

P & T committee forms workgroup	November 2001
Workgroup develops institution-specific guidelines	December 2001
Guidelines reviewed by other physician groups	January 2002
Formal approval by P&T committee	February 2002

Table 2 Required Elements Prior to Administration of Drotrecogin Alfa (activated)

Complete criteria checklist (see Figure 4)
All inclusion criteria present
Absence of contraindications
Attending physician approval
Review by clinical pharmacist
Accurate patient weight obtained for dosing

macist would contact the prescribing physician and provide the form for completion. Approval by attending physicians was obtained either through co-signature of the orders or by verbal communication between the attending physician and the pharmacist.

Once a completed checklist was received in the pharmacy, the pharmacist paged a clinical pharmacist to review the patient chart and to verify the information. An accurate patient weight was obtained, and the medication order was entered and the dose prepared. To maximize the drug hang time and to avoid waste, the amount of drug dispensed with each dose was calculated using a weight-based dosing chart (Table 3).

Each dose was hand-delivered by a technician and required sign-off by the nurse caring for the patient. The nurse called for each subsequent dose, and the clinical pharmacist reviewed the medication record daily to verify the proper infusion rate and the remaining drug count. In addition, the infusion time was rounded to the nearest bag to avoid waste.

Difficulties encountered with implementing guidelines have revolved primarily around identifying the eligible patients. Few data are available on drug safety in post-trauma patients, neurological and neurosurgery patients, and patients with co-morbidities such as liver disease. These groups comprise a significant portion of the ICU patients at the Regional Medical Center.

IMPROVING PATIENT CARE AND HEALTH VALUE

Sepsis is frequently fatal and is costly to treat. Drotrecogin alfa (activated) represents the first biotechnology innovation in severe sepsis that significantly reduces mortality by 6.1%. The key is to identify patients who would benefit most from this therapy.

The institutional perspectives provided in this article demonstrate that successful implementation of guide-

DROTRECOGIN ALFA (ACTIVATED) (XIGRIS™) MEDICATION USE GUIDELINES REGIONAL MEDICAL CENTER AT MEMPHIS

This document is a guideline, which should not supersede good medical judgment in individual patients. All questions should be answered "yes" for administration of the drug. Attending approval is required prior to dispensing from pharmacy.

- Yes No Is the patient in an ICU?
- Yes No Do you plan to use all necessary life support measures?
* Drug is not to be administered if "no resuscitation" or similar status.)
- Yes No Exclusive of severe sepsis, is there a reasonable expectation of survival >28 days?
- Yes No Is infection suspected and being appropriately and aggressively treated?
- Yes No Has the patient received adequate fluid resuscitation?
* Defined as CVP \geq 10, PCWP \geq 12 or EDVI 110–140)
- Yes No Are at least three of the following S.I.R.S. criteria present?
 $36^{\circ}\text{C} \leq \text{temperature} \leq 38^{\circ}\text{C}$
 Heart rate \geq 90
 RR \geq 20 or PaCO₂ \leq 32 or need for mechanical ventilation
 $4,000 \leq \text{WBC} \leq 12,000$ or \geq 10% immature neutrophils
- Yes No Have two or more of the sepsis-induced organ failures below occurred within 24 hours, and persisted after adequate fluid resuscitation?
 MAP < 70 or SBP < 90 or need for vasopressor support after adequate fluids
 UOP < 0.5 ml / kg / hr for \geq 3 hours
 PaO₂ / FiO₂ ratio < 250
 Unexplained decrease in platelets to < 80,000 or 50% decline in previous 3 days
 Unexplained metabolic acidosis pH \leq 7.3 or BE \geq -5 with lactate > 1.5 times normal
- If all the above are yes, are any of the following contraindications present, which would exclude drotrecogin administration?
 Active (significant) bleeding from any source
 GI bleed requiring transfusion within past 72 hours
 < 3 months post hemorrhagic CVA, intracranial/spinal surgery, or head trauma with intracranial hemorrhage
 Any history of intracerebral A-V malformation, cerebral aneurysm, or mass lesion of the CNS
 < 12 hours post surgery requiring general or spinal anesthesia
 Presence of epidural catheter
 Pregnancy
 None (OK to administer drotrecogin)

The following conditions may increase the risk of Drotrecogin use. You have carefully considered these conditions and concluded that the benefits of treatment outweigh the potential risks in this patient.

- Yes No An INR > 3
- Yes No Platelet count of < 30,000 (platelet transfusions recommended prior to infusion)
- Yes No Recent use of IIb/IIIa inhibitors or thrombolytics (>72 hours) OR full anticoagulation with heparin or warfarin (Standard DVT prophylaxis is not a contraindication to use) OR use of > 650 mg aspirin daily
- Yes No Cirrhosis with portal hypertension
- Yes No Known bleeding disorders or hypercoagulable state (eg. hemophilia, protein C deficiency)

The following are NOT contraindications to treatment although safety and efficacy are unproven:

- Yes No Age < 18
- Yes No Weight > 135 kg (patients > 135 kg will receive dose based upon adjusted weight)
- Yes No Bone marrow or solid organ transplantation with an acceptable bleeding risk
- Yes No Chronic renal insufficiency requiring dialysis
- Yes No < 3 months following ischemic stroke
- Yes No Acute pancreatitis

FIGURE 4. Medication use guidelines for drotrecogin alfa (activated). (Reprinted with permission of Regional Medical Center at Memphis.)

Table 3 Drug Preparation and Administration of Drotrecogin Alfa (activated)

Weight (kg)	Dose (mg/dl)	Rate (ml/hr)	Bags (No.)
40	10	9.6	9
45	10	10.8	10
50	10	12.0	11
55	10	13.2	13
60	15	9.6	9
65	15	10.4	10
70	15	11.2	11
75	15	12.0	12
80	20	9.6	9
85	20	10.2	10
90	20	10.8	10+1–10 mg bag
95	20	11.4	11
100	20	12.0	11+1–10 mg bag
105	20	12.6	12
110	20	13.2	12+1–10 mg bag
115	20	13.8	13
120	25/150 ml	17.3	11
125	25/150 ml	18.0	11+1–10 mg bag
130	25/150 ml	18.7	12
135	25/150 ml	19.4	12+1–10 mg bag

lines can be accomplished with diligence in obtaining background information, through guideline development by a multidisciplinary team, and by instituting appropriate processes for guideline initiation. Drotrecogin alfa (activated) guidelines require attention to criteria not only for patients for whom the drug is indicated but also for patients at risk for adverse events who should not receive the drug.

In addition to guideline implementation, a thorough retrospective MUE must be conducted. The MUE process is a mechanism that ensures that the guidelines are being followed appropriately and identifies patients who are candidates for drotrecogin alfa (activated) but who have not received therapy. In turn, this information can be used to strengthen the patient-selection guidelines. Future challenges will revolve around modifying existing guidelines as additional data become available.

Through education, adoption of credible patient-selection guidelines, rigorous MUEs, and economic assessment, pharmacists can play a vital role in the contemporary management of severe sepsis. The health care team must systematically assess the role of drotrecogin alfa (activated) in terms of health value and must pursue this opportunity to improve care in appropriately selected patients.

Note

This supplement is based on information presented at a Critical Care Advisory Board Meeting held in April 2002 in San Francisco, California. Participants at that meeting included Bradley Boucher, John Devlin, Brian Erstad, Jim Eskew, Pamela Koerner, Harold Kornfuhrer,

David Kuhl, Henry Mann, Marilyn Keenan-Milligan, James McAllister III, Jennifer Nazworthy, John Ponzillo, Thomas Rihn, Andrew Wilson, and Gordon Vanscoy.

REFERENCES

- Sands K, Bates D, Lanken P, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA* 1997;278:234–240.
- Angus D, Linde-Zwirble W, Lidicker J, et al. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs. *Crit Care Med* 2001;29:1303–1310.
- Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699–709.
- Xigris® package insert. Indianapolis, Eli Lilly and Company, November 2001.
- Crossing the quality chasm: A new health system for the 21st century. Institute of Medicine, 2001.
- Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002;28:108–121.
- Singer PA, Barker G, Bowman KW, et al. Hospital policy on appropriate use of life-sustaining treatment. University of Toronto Joint Centre of Bioethics/Critical Care Medicine Program Task Force. *Crit Care Med* 2001;29:215–217.
- Schneiderman LJ, Gilmer T, Teetzel HD. Impact of ethics consultations in the intensive care setting: A randomized, controlled trial. *Crit Care Med* 2000;28:3920–3924.
- Rudis MI, Zarowitz BJ. Low-dose dopamine in acute oliguric renal failure. *Am J Med* 1997;102:320–322.
- Oxman AD, Guyatt GH. A consumer's guide to subgroup analysis. *Ann Intern Med* 1992;116:78–84.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system for acutely ill patients. *Crit Care Med* 1985;13:818–829.
- Rogers J, Fuller HD. Use of daily Acute Physiology and Chronic Health Evaluation (APACHE II) scores to predict individual patient survival rate. *Crit Care Med* 1994;22:1402–1405.
- Kanji S, Devlin JW, Piekos KA, Racine E. Recombinant human activated protein C, drotrecogin alfa (activated): A novel therapy for severe sepsis. *Pharmacotherapy* 2001;11:1389–1402.
- Burton, TM. "Eli Lilly Drug Reduced Sepsis Deaths by Nearly 20%." *The Wall Street Journal*, January 4, 2001.
- Vanscoy GJ, Rihn TL, Koerner PH. Patient selection guidelines and DUE for drotrecogin alfa (activated). *Formulary* 2002;37(S1).
- Larosa SP. Sepsis: Menu of new approaches replaces one therapy for all. *Cleve Clin J Med* 2002;69:65–73.
- Peters T. *Thriving on Chaos*. New York: Alfred A. Knopf, 1987:323.
- Kollef MH, Eisenberg PR, Shannon W. A rapid assay for detection of circulating D-dimer is associated with clinical outcomes among critically ill patients. *Crit Care Med* 1998;26:1054–1060.
- Shorr AF, Thomas SJ, Alkins SA, et al. D-dimer correlates with pro-inflammatory cytokine levels and outcomes in critically ill patients. *Chest* 2002;121:1262–1268.
- Bochud PY, Glauser MP, Calandra T. Antibiotics in sepsis. *Intensive Care Med* 2001;27:S33–S48.
- Vincent JL. Hemodynamic support in septic shock. *Intensive Care Med* 2001;27:S80–S92.
- Carlet J. Immunologic therapy in sepsis: Currently available. *Intensive Care Med* 2001;27:S93–S103.
- Arndt P, Abraham P. Immunological therapy in sepsis: Experimental therapies. *Intensive Care Med* 2001;27:S104–S115.
- Perez J, Dellinger RP. Other supportive therapies in sepsis. *Intensive Care Med* 2001;27:S116–S127.
- Summary of recommendations. *Intensive Care Med* 2001;27:S128–S134.
- Available at: www.UPA-LLC.com
- Balk RA. Severe sepsis and septic shock: Definitions, epidemiology, and clinical manifestations. *Crit Care Clin* 2000;16:179–192.
- Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definition for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864–874.

CE Test

Implementing Guidelines for Drotrecogin Alfa (activated): Three Perspectives

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Please circle the correct answer

1. For inclusion in the PROWESS trial, patients were required to meet which criterion or criteria?

- a. at least one acute organ dysfunction for a duration of no longer than 24 hours
- b. three or more SIRS criteria
- c. known or suspected infection
- d. all of the above

2. The PROWESS trial showed an absolute reduction in 28-day all-cause mortality of ____%.

- a. 5.5%.
- b. 6.1%.
- c. 13.6%.
- d. 19.4%.

3. The average cost per case of severe sepsis in the U.S. is approximately

- a. \$5,000.
- b. \$22,000.
- c. \$110,000.
- d. \$57,000.

4. Adherence to patient selection guidelines for drotrecogin alfa (activated) facilitates

- a. appropriate drug utilization.
- b. elimination of adverse events.
- c. uniform drug preparation and delivery.
- d. all of the above.

5. A retrospective medication use evaluation of ICU patients with severe sepsis should be conducted for drotrecogin alfa (activated) to

- a. ensure that guidelines are being followed appropriately.
- b. identify potential drotrecogin alfa (activated) candidates who had not received therapy.
- c. utilize information collected to assist in strengthening current patient selection guidelines.
- d. all of the above.

Please return the completed CE Test to the following address, along with the Evaluation Form on page 15:

University Pharmacotherapy Associates, LLC

4105 Monroeville Blvd.

Monroeville, PA 15146

or fax to: (412) 380-8597

For credit, the CE test and Evaluation Form on page 15 must reach University Pharmacotherapy Associates, LLC, by October 1, 2003. CE statements will be mailed to your address on page 15 as soon as possible after receipt of these forms. This program is sponsored by an unrestricted educational grant from Eli Lilly and Company.

Notes

Notes



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