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An Algorithmic Computerised Order Entry Approach to Assist in the Prescribing of New Therapeutic Agents

Case Study of Activated Protein C at an Academic Medical Centre

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Abstract

Background: Academic medical centres face the need to care for patients with complex medical conditions, educate physicians-in-training and conduct research, all with increasingly constrained budgets. The adoption of new therapeutic technology presents challenges and opportunities in each of these areas. Severe sepsis remains a major cause of morbidity and mortality, especially in tertiary-care facilities. Recombinant human activated protein C reduces mortality in patients with severe sepsis, but trial data indicate that the benefit of the drug is confined to the more seriously ill patients, while the risk of bleeding complications can be considerable. The cost of the drug is approximately $US6000–8000 per treated patient. Integration of this product into routine care has produced unique challenges concerning clinical decision making, safety and cost.

Objectives: To describe one hospital's multidisciplinary approach to the adoption of this new medication.

Methods: Before activated protein C was approved for use, Brigham and Women's Hospital (BWH) convened a working group to formulate clinical guidelines proactively. This new agent did not fit into an obvious therapeutic category but cut across multiple clinical disciplines requiring the involvement of several hospital departments in developing policy. As new data on efficacy emerged during the US FDA review of the drug, the working group had to devise a method for using the available information to assist clinical decision making

while placing appropriate restrictions on the use of activated protein C. The goal was to make accurate information available to guide ordering physicians' decision making interactively, 24 hours a day.

Results: The committee developed a utilisation policy for activated protein C that provided guidance on patient selection, contraindications and risk stratification. Interactive computer-based order entry screens were developed to guide physicians through a complex set of clinical criteria to ensure appropriate evidence-based use. A careful review of contraindications is required as a second step. To risk stratify patients in accordance with the trial subset analyses and the FDA labelling guidelines, ordering physicians are guided in calculating an APACHE II (Acute Physiology and Chronic Health Evaluation) score for the patient. Physicians from several specialties are available for advice and consultation on patients with difficult or controversial conditions. Approximately two-thirds of completed orders passed the clinical algorithm; an additional 35% of patients did not meet the medication criteria but received the drug after the attending physician requested an override of the guidelines.

Conclusion: The BWH approach to activated protein C used an innovative multidisciplinary approach and computer-assisted order entry to guide clinical use of a new agent with substantial clinical efficacy, risks and costs. This approach provides a model for strategies to deal with other new and complex medical technologies.

Background

Academic medical centres must balance diverse obligations, educating the next generation of clinicians and conducting research while also providing care for large numbers of seriously ill patients. At the same time, teaching hospitals face increasing financial pressures.[1] When new technologies are introduced, the clinical indications, possible risks and cost all need to be considered in making decisions about guideline formation and appropriate utilisation.

Severe sepsis remains a major cause of morbidity and mortality worldwide. Over 700 000 cases occur annually in the US, resulting in over 200 000 deaths.[2] In septic shock, infection initiates a combination of haemodynamic, coagulopathic and inflammatory processes[3] that can progress to hypoperfusion and organ failure.[4] The incidence and mortality of sepsis both rise exponentially with age and comorbidity, with mortality ranging from 20% to 60%.[4-7]

Numerous trials over the last several decades have studied agents directed at components of the bacterial wall or secondary mediators of inflammation, but until recently no treatments based on these strategies have been shown to be effective. A review of 131 studies of septic shock published over a 40-year period showed persistently high mortality rates, with only a slight decrease over time.[8]

More recent hypotheses regarding the pathobiology of sepsis have implicated endothelial damage and a hypercoagulable state. A new product, recombinant human activated protein C (drotrecogin alfa; Xigris®),[1] inhibits the activated forms of factors V and VIII, which serve as cofactors in the clotting cascade. This appears to inhibit formation of microthrombi and in turn reduces the organ damage seen in septic shock. The efficacy of activated protein C in patients with severe sepsis was evaluated in the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial.[7] This randomised, placebo-controlled trial in-

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cluded 1690 patients with severe sepsis. Patients were randomised to receive either activated protein C or placebo as a 96-hour continuous infusion. The primary outcome was 28-day mortality.

The study was halted early by its data safety monitoring board because of the significant mortality advantage seen in the treatment group.[7] Patients receiving activated protein C had a death rate of 24.7% compared with 30.8% for patients receiving placebo, corresponding to an absolute mortality reduction of 6.1%. The major adverse event noted during the trial was bleeding, with an excess risk of serious bleeding of 1.5% in the treated group compared with controls.

Several risk-stratification groups had been defined *a priori*, and the original published report of the PROWESS trial noted that a "consistent effect of treatment with drotrecogin alfa activated was observed among the subgroups".[7] However, as the US FDA considered approval of activated protein C, data from the trial emerged[9,10] indicating that the benefit of the drug was limited to the more seriously ill patients, as defined by the APACHE II (Acute Physiology and Chronic Health Evaluation) score[11] (figure 1). Patients with APACHE II scores of ≤24 had nearly identical mortality rates whether treated with activated protein C (18.8%) or placebo (19.0%). Among patients with APACHE II scores of ≥25, however, the mortality was 43.7% for patients receiving placebo but only 30.9% for patients treated with activated protein C.

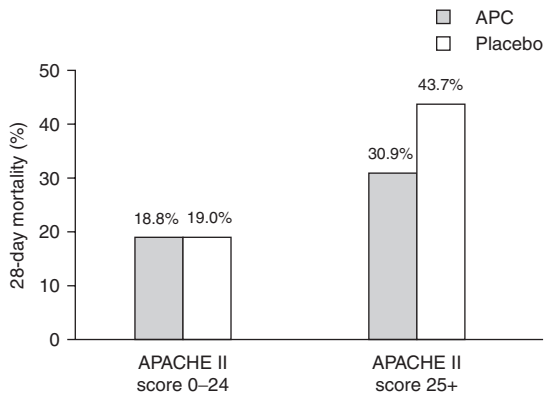

Fig. 1. Treatment effect and APACHE II (Acute Physiology and Chronic Health Evaluation) score. **APC** = activated protein C.

The risk of a serious bleeding complication had to be balanced against the mortality benefit. Intracranial haemorrhage was initially reported at a rate of only 0.2% in the PROWESS trial,[7] but subsequent data presented by the manufacturer to the FDA from open-label use indicated that the rate could be as high as 2.5% in other settings.[9] Although more recently published data have demonstrated that bleeding complications were indeed as rare as indicated in the PROWESS results,[12] at the time of the FDA debate these reports generated considerable anxiety about toxicity. Facing increasingly constrained budgets, many hospitals also grew concerned over the anticipated high cost of activated protein C,[13,14] projected at $US6000–8000 per treated patient.

After a divergence of opinions during the FDA hearings, the advisory committee vote was evenly split, with ten members voting to approve activated protein C and ten members voting against. The FDA approved activated protein C in November 2001,[15] requiring the following statement in the product labelling:[16] "Xigris is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g. as determined by APACHE II)".[17]

The wording of the FDA approval posed new challenges for hospitals, since the APACHE II score has generally been used as a research instrument rather than as a routine clinical tool. In contrast to the FDA approach, the European Commission approved activated protein C for the treatment of sepsis in patients with multiple organ failure[18] and did not make APACHE II scores an explicit part of the approval.

Debate over the results of the PROWESS trial and additional analyses of the original data continue and have largely corroborated the findings of efficacy and rates of adverse events reported in the initial trial.[10,12,15,19-23]

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Objective

We describe one hospital's development of guidelines to promote appropriate use of this new agent so as to maximise its clinical benefit, contain its risk and avoid unnecessary expenditures.

Methods

Brigham and Women's Hospital (BWH) is a 732-bed academic tertiary care centre and a main teaching hospital of Harvard Medical School; 90 of the beds are in adult intensive care units. Nearly all medication ordering at BWH is done by house officers using a computerised order entry system.[24] After the PROWESS trial results were published, BWH assembled a multidisciplinary team to develop hospital policy for activated protein C. This team included representatives from the Divisions of Pharmacoepidemiology and Pharmacoeconomics, Infectious Diseases, Pulmonary Critical Care and Anesthesia Critical Care and the Departments of Pharmacy and Information Systems. Representatives from the nursing staff and the hospital administration were also consulted during the process of guideline development.

The team began work soon after the advance publication of the PROWESS trial on the *New England Journal of Medicine* website. At that time, the only data describing large numbers of patients treated with activated protein C were from this trial. Given the lack of experience with use of this medication and the fact that it was the first member of a new therapeutic class, the team focused on creating a process to help physicians identify patients who were as similar as possible to those who benefited from it in the PROWESS trial. In light of the recommendations of the FDA regarding the use of activated protein C, the team adopted ordering guidelines that included APACHE II score criteria.

To evaluate the use of activated protein C at our institution after the program was put in place, we obtained permission from the BWH Institutional Review Board to review the medical charts of all patients who received it. Data were obtained from the computerised order entry system, which recorded physician responses as they proceeded through the interactive ordering screens. These data included patients' clinical characteristics at the time of initial activated protein C use. Electronic medical records were reviewed for demographic characteristics, laboratory values, length of stay and in-hospital mortality. Individual patient identifiers were removed prior to analysis.

Results

Computerised Order Entry Intervention

The team developed an interactive intervention in the computerised order entry system, designed to accomplish three goals: (i) include patients as similar as possible to those in the PROWESS trial; (ii) exclude patients who would have been excluded from the trial based on an increased risk of bleeding, who were more likely to experience harm; and (iii) incorporate the newer data and FDA labelling guidelines regarding the risk stratification of patients.

The decision-support process begins after a physician initiates an order for activated protein C in the computerised order entry system. The computer screen displays a general message (figure 2) describing the process required to order activated protein C and explaining the reasons for this requirement. The intervention then guides the physician through the three steps outlined previously, beginning with the inclusion criteria.

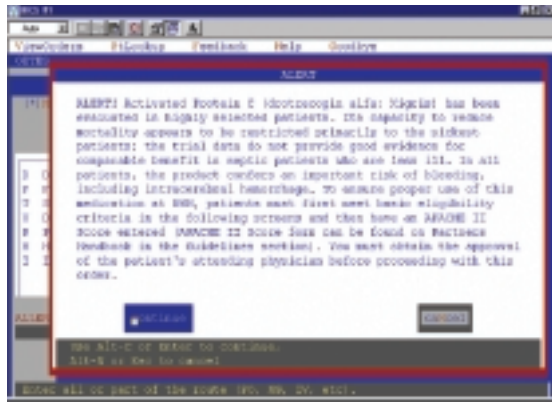

Fig. 2. Initial screen in order entry system, notifying physician of ordering process and data review.

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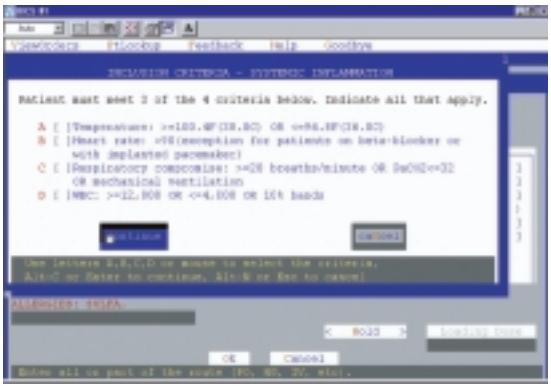

Fig. 3. Order entry screen for second element of inclusion criteria: systemic inflammatory response syndrome.

The inclusion criteria consist of three components. The first is documentation of infection, either known or suspected. The algorithm emphasises the importance of ruling out other causes of shock and asks the physician to confirm that infection has been proven or is strongly suspected on clinical grounds.

The second component of the inclusion criteria is establishing the presence of the systemic inflammatory response syndrome, as defined by abnormalities in three of four physiological parameters (temperature, heart rate, respiratory status and white blood cell count). The ordering program lists those physiological elements and the threshold levels for abnormal results and requires the physician to indicate which parameters are abnormal (figure 3).

The final inclusion criterion is documented acute dysfunction in one (or more) of five organ systems: cardiovascular, renal, respiratory, haematological or metabolic. Patients enrolled in the PROWESS trial had developed organ dysfunction within the 24 hours prior to drug initiation, a window in which reversal of the organ damage might still be achieved.[7] The ordering physician is presented with the clinical criteria used in the PROWESS study and is asked to indicate which systems meet these criteria for acute dysfunction (figure 4).

The relative contraindications included patient groups excluded from the PROWESS trial based upon the perceived risk of adverse event. These included recent trauma or surgery, thrombocytopenia, anticoagulant therapy and intracranial mass. The physician is presented with a list of these relative contraindications and must indicate whether any are present (figure 5).

The computer system then performs an initial check of the data entered. If a patient meets the inclusion criteria and has no relative contraindications, then the order entry process continues. If the patient data do not meet the initial criteria, the physician is informed of this and has the option of either discontinuing the order or initiating an override procedure. For orders that meet the initial criteria, the physician is presented with a screen explaining the need for risk stratification with the APACHE II scores. The physician is asked to calculate the patient's APACHE II score using a scoring sheet provided in the hospital computer system and then enter that score.

If the APACHE II score is ≥25, then the ordering process proceeds to completion. The dose and duration of treatment are automatically set to the regimen used in the PROWESS trial. After the order is received a clinical pharmacist goes to the hospital unit and reviews the chart to confirm the accuracy of the clinical data entry before authorising preparation of the medication. If the APACHE II score is <25, the physician is informed that the guideline conditions have not been met and is offered the option of initiating an override procedure. During a subsequent review of the policy, concerns were raised that in patients who are rapidly deteriorating into septic

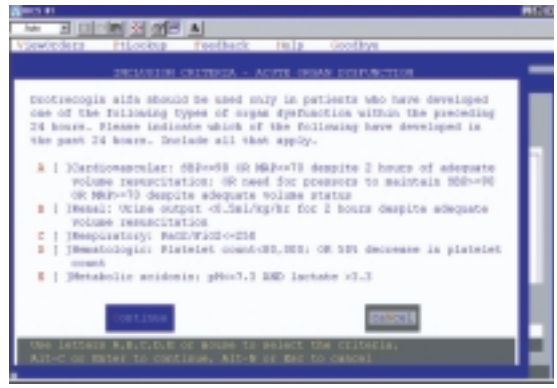

Fig. 4. Order entry screen for third element of inclusion criteria: acute organ dysfunction. **MAP** = mean arterial blood pressure; **SBP** = systolic blood pressure.

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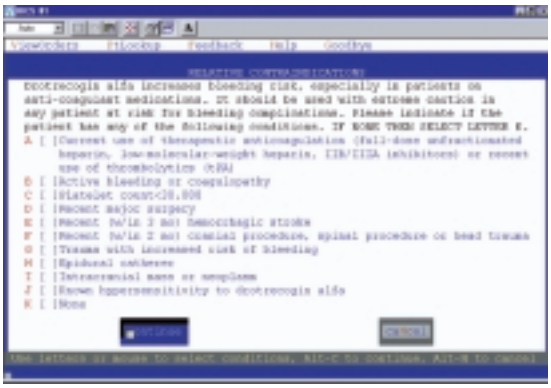

Fig. 5. Order entry screen for relative contraindications.

shock but also being aggressively resuscitated, the APACHE II score may not capture the severity of their illness. A modification was therefore made to this portion of the algorithm, adding the statement: "In selected clinical situations, patients with an APACHE II score of 20–24 and refractory hypotension or progressive organ dysfunction in the face of aggressive therapy may also benefit from activated protein C". APACHE II scores <20 continued to require an override procedure.

To override the guidelines, the ordering physician must consult with a designated specialist from the divisions of medical critical care, surgical critical care or infectious diseases. If the specialist agrees that the use of activated protein C is clinically indicated, the guidelines can be overridden. The ordering physician enters the name of the specialist consulted and the clinical reason for the override into the system. The override approval is then confirmed by a clinical pharmacist prior to preparation of the medication.

Clinical Experience

Orders were reviewed from the first 2 years of activated protein C use. The drug was ordered on 63 occasions during that time period. Review at the time of ordering by clinical pharmacists did not reveal any instances of physicians entering inaccurate data. Of the 63 patients treated, 36 (57%) were male. The average patient age was 62 years, with a range of 20–90 years. Forty-six (73%) of the patients were White, three (5%) were Black and four (6%) were Hispanic, reflecting the hospital's demographic mix. The average length of stay was 28.7 days, with a range of 1 day (a patient who died soon after treatment began) to 164 days. All of the treated patients were in intensive care units: 37 (59%) in medical intensive care units and the remaining 26 (41%) in surgical intensive care units. The activated protein C infusion was completed in 41 patients (65%); 13 patients (21%) died before the infusion was completed and in nine patients (14%) the medication was stopped. Of the 63 patients treated, 28 (44%) died before hospital discharge.

Forty-one patients (65%) received the drug according to the computer-based algorithm, and overrides were used for an additional 22 patients (35%). In-hospital mortality was 50% among the patients with guideline overrides and 41% in the remaining patients; this difference was not statistically significant. Some physicians indicated the steps that they were taking to deal with relative contraindications, such as discontinuing other anticoagulation medication to minimise bleeding risk. If the override process was triggered based on the initial inclusion and exclusion criteria, the APACHE II score calculation was generally skipped.

APACHE II scores were calculated for 45 patients, including four with overrides. The mean APACHE II score was 29.7. There were five scores of <25 (3 of 20 and 2 of 22), during the period after the ordering protocol was modified to allow scores between 20 and 24. The largest number of scores (18) were between 25 and 29. There were eight scores of >35; the highest APACHE II score was 48. Based on manual chart review, the estimated mean APACHE II score for the remaining 18 patients was 27, although these scores were approximate since the Glascow Coma Scale portion of the APACHE II score was difficult to approximate retrospectively and was likely underestimated.

Failure of multiple organ systems, as indicated by the ordering physician, was common. Only five patients had failure of a single organ system, 26 patients had failure of two organ systems and 32 patients had failure of three of more organ systems.

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Failure of the cardiovascular system was ubiquitous, occurring in 60 of the 63 patients. Respiratory and renal failure were the next most common, both occurring in 38 patients. Major bleeding complications during treatment were not observed in any of the treated patients.

Discussion

Novel biological agents are being developed and approved for clinical use at an increasing rate. When the use of these agents also carries the potential for significant adverse events, their optimal use presents challenges for physicians, hospitals and regulatory bodies. Extremely high cost can provide an additional reason for containing overuse of some of these newer products. One approach for agents such as activated protein C that have nontrivial risks of adverse events is to prescribe these agents based on risk-stratification algorithms. In particular, if an identifiable subpopulation of patients experiences less benefit but is at the same risk for having an adverse event, the prescribing physician must take this into account. Physicians need tools with which to target these new therapies to the patients most likely to benefit without unduly increasing the risk of harm.

Hospitals have tried to give physicians these tools, developing and implementing guidelines to aid patient selection for activated protein C therapy.[25,26] Common themes include the use of multidisciplinary teams to develop policy, structured forms to determine patient appropriateness and involvement of intensivist physicians for difficult cases.[26] We have described a patient selection tool embedded in a pre-existing computerised order entry system that provides immediate feedback to the ordering physician if a patient does not appear to meet hospital guidelines and allows for prompt initiation of an override procedure when needed.

Over the first 2 years, the majority of orders for activated protein C (41 of 63, 65%) were completed via the automated system. A few of the 22 instances requiring overrides appear to have occurred as a result of difficulty in navigating the interactive screens, but the majority of override prompts were a result of complicated clinical situations or relative rather than absolute contraindications. In these situations, ordering physicians entered data indicating that risks and benefits were weighed carefully and that physicians with appropriate advanced training were involved in the decision. The pharmacist review of the non-override orders agreed with the physician data entry and evaluation in all cases, suggesting that physicians were using the ordering protocol and the override option appropriately. However, one important limitation of our evaluation was that we were unable to track instances in which the computerised algorithm resulted in denial of the medication and the physician chose to abandon the order rather than initiate an override procedure.

The mortality rate in this population was higher than the mortality rate reported in the PROWESS trial. It appears that these patients treated in actual practice had a higher burden of illness than those enrolled in the clinical trial, with an average APACHE II score of 29.7, as opposed to 24.6 in the PROWESS trial.[7] Likewise, while 25% of patients in the trial had failure of a single organ system and 4% had failure of five organ systems,[7] among the patients treated in our institution, only 8% had failure of a single organ system and >14% had failure of five organ systems.

Implementing this system required a considerable investment of computer programming time, as well as the time of working group members. This sort of extensive order entry guide is not practical for most routinely used medications, but for costly medications with the potential to cause harm, the requirement of several minutes of physician time to order the medication is a reasonable expectation and can allow care of critically ill patients to proceed without significant delay. The process can also have considerable educational value by reminding the physician at the time of ordering about proper means of establishing a diagnosis, as well as about the indications and contraindications of a drug. In addition, this protocol provides a template that can be adapted for future novel therapies, which are likely to carry different sets of challenges and controversies.

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As physicians, pharmacists and hospitals try to deal with risk stratification for new medications, the FDA remains a critical factor. The decision taken by the FDA in the case of activated protein C suggests new developments in the drug approval process. The assessment of outcomes in patient subpopulations, in a study that was not powered to analyse subgroups, was a particularly controversial element of the evaluation of activated protein C. In addition, the incorporation of the APACHE II score as an explicit part of the FDA labelling guidelines represents a new departure, taking a tool that is often an element of research protocols and redefining it as a tool to be used in clinical decision making. There is controversy over when to calculate the APACHE II score and whether to adjust it as a patient's clinical condition changes during initial stabilisation treatment for severe sepsis.[23] How well different hospitals incorporate the APACHE II score into patient selection for activated protein C remains to be seen.[26] Of note, 58 (92%) of the 63 patients treated at our institution had failure of multiple organ systems and would have met the European standards for administration of activated protein C.[18] Whether the European approval language is better suited to creating interventions that are easy for clinicians to use at the bedside is not clear from our data but would be an important area for additional research.

Economic concerns regarding activated protein C and other new biological agents cannot be overlooked.[13,14,27] In a time of limited resources, hospitals are struggling to make medications such as activated protein C available when they can help patients while not squandering dollars on products that may make no difference or, worse, may cause adverse outcomes for patients. The cost effectiveness of activated protein C has been investigated, and although it remains controversial it is clear that it represents a small fraction of the cost of caring for those receiving it.[27-30] The federal government has recognised the economic burden that medications like this may impose on hospitals and has approved supplemental Medicare payments for patients treated with activated protein C provided that a clinical diagnosis of severe sepsis has been adequately documented.[31,32]

Four lessons emerge from our hospital's experience with this novel therapeutic agent:

1. Anticipatory development of guidelines is critical. The initial available data on activated protein C were confusing, and building consensus on hospital policy took time. If the working group had not convened at the time of publication of the initial randomised trial, there would not have been time to properly develop guidelines prior to FDA approval.
2. Broad-based consensus must be reached. Patients develop severe sepsis in a variety of clinical settings. To be well accepted by clinicians, guidelines must incorporate input from the range of physicians who may care for patients requiring the medication. A multidisciplinary team approach allowed for acceptance of the activated protein C guidelines.
3. Flexibility is critical. Guidelines were almost complete when the additional data about APACHE II scores were publicised, and a rapid response was needed to make the final guidelines correspond to the actual labelled indication.
4. Monitoring ensures that guidelines work in practice and can be modified as needed. Monitoring of medication use can help uncover problems and oversights that may occur with even the best processes.

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