



Activated protein C for the treatment of severe sepsis

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Abstract

Background: Recombinant human activated protein C (rhAPC), or Drotrecogin alfa (activated), is approved for use in Australia for adults with severe sepsis associated with acute organ dysfunction. Use of this drug at Southern Health is currently approved on a case by case basis.

The Centre for Clinical Effectiveness was requested to report on the effectiveness of rhAPC for severe sepsis to assist decision making regarding its use.

Clinical Question: In patients with severe sepsis does treatment with rhAPC, as compared to standard care, improve survival?

Methods: We searched The Cochrane Library, including The Cochrane Database of Systematic Reviews, DARE, CENTRAL and HTA in November 2006. We also searched Medline and CINAHL and various guideline websites.

Studies were selected and appraised by two reviewers using inclusion, exclusion and appraisal criteria established a priori. Guidelines were appraised using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument.

Our usual procedure is to identify any existing high quality systematic reviews and search forward from the time of the review. In this case we were also asked specifically to appraise a particular article (Bernard et al, 2001).

Results: Our searching identified one guideline,¹ one Cochrane Systematic Review,² one Health Technology Assessment (HTA)³ and four articles describing RCTs published after the HTA or excluded from the HTA that are relevant to this clinical question.^{4,7} Through general reading an additional unpublished trial was located.

The guideline for the treatment of sepsis¹ was of moderate quality, with many aspects of the development inadequately described. It recommended the use of rhAPC in patients with severe sepsis at high risk of death, sepsis-induced multiple organ failure or sepsis-induced acute respiratory distress syndrome, who have no contraindications.

The Cochrane Review² focused on use of rhAPC in neonates and did not identify any relevant RCTs.

The HTA³ was of high methodological quality and concluded that rhAPC, combined with supportive care appears to be more effective than supportive care alone.

Both the guideline and HTA base their recommendations on the PROWESS RCT.^{1,3,8} There are concerns about the methods used in this trial, including unclear blinding of outcome assessment and changes to the study protocol during the course of the study.

The PROWESS trial found that in a tightly defined group of patients with severe sepsis treatment with rhAPC reduced the relative risk of death at 28 days compared to placebo (RR 0.79, 95%CI 0.68, 0.92). This study excluded patients who had a platelet count $<30,000/\text{mm}^3$; increased risk of bleeding; a known hypercoagulable condition; a bone marrow, lung, liver, pancreas or small-bowel transplant; chronic renal or liver disease; known or suspected portosystemic hypertension; acute pancreatitis with no established source of infection; were moribund or not expected to survive 28 days due to other condition; were HIV positive with CD4 count $\leq 50/\text{mm}^3$; or have used anticoagulants or antithrombotic medications (in specific timeframes). Several subgroups analyses in this trial were

defined post-hoc.

Long term follow up of the PROWESS trial showed no overall survival benefit in patients treated with rhAPC over patients treated with placebo at 3, 6, 12 and 30 months.⁵ We cannot be sure if this is due to no real difference or due to a lack of power to detect such a difference. The original trial was designed to examine mortality at 28 days only.

There was however a significantly better long term survival rate in the group of patients treated with rhAPC when data was analysed for the subgroup of patients with an APACHE II score of ≥ 25 (median survival time 450 days in rhAPC group versus 71 days in placebo group, $p=0.0005$). In patients with an APACHE score of <25 there was a significantly higher survival rate at one year in placebo patients as compared to rhAPC patients (74.3% vs 68.9%, $p=0.04$). At the other time points reported, survival rates were higher in the placebo group, but the differences were not statistically significant. This suggests there is a potential for harm from use of rhAPC in this group of patients.

Analysis of PROWESS data showed a significantly higher rate of bleeding in the group of patients treated with rhAPC (18.8% in rhAPC vs 10.8% in placebo, $p<0.001$) but the difference in rates of serious bleeding was not quite statistically significant (3.5% in rhAPC vs 2% in placebo, $p=0.06$). The PROWESS trial was terminated early as the differences in mortality rate between the groups exceeded the predetermined criteria for stopping the trial. It is unclear whether the trial was still sufficiently powered to detect significant differences in adverse events.

Subsequent to the PROWESS trial, a RCT in adults with severe sepsis and low risk of death, was conducted (ADDRESS⁷) but was terminated early when an interim analysis showed there was $<5\%$ chance of demonstrating a significant reduction in mortality in patients receiving rhAPC and that there was an increased risk of bleeding in the rhAPC group.

A paediatric trial of rhAPC (RESOLVE) in patients aged 0 to 18 years was also terminated early due to the unlikelihood of demonstrating a beneficial effect in the treatment group.^{2,9,10}

Discussion: Evidence for the effectiveness of rhAPC for treatment of adults with severe sepsis comes predominantly from one large, international, multi-centre RCT that examined the use of rhAPC in addition to usual care against placebo and usual care (the PROWESS trial).

The PROWESS trial protocol did not specify what usual care is and thus it is important to consider any differences that may exist between usual care for sepsis in Australia and usual care internationally.

Of concern is the number of subgroup analyses that were performed post-hoc.

It is also pertinent to consider mortality rates from severe sepsis. Two recent studies have reported Australian rates of 31.1% in data from four year period in the Victorian Admitted Episodes Database (1999 to 2003)¹¹ and 37.5% in a study of in-hospital mortality in 23 Australian and New Zealand intensive care units over a three month period in 1999¹². The 28 day mortality rate from severe sepsis in the patients randomised to placebo in the PROWESS trial was 31.3%⁸

Conclusions:

- The recommendations for the use of rhAPC for severe sepsis are largely based on one RCT (PROWESS). This trial has several methodological flaws which are described in detail in the critical appraisal in the appendices.
- In the PROWESS trial rhAPC was shown to reduce mortality at 28 days, however, this was demonstrated in a very tightly defined group of adults with severe sepsis which limits generalisability of this finding to a broader patient group.
- Long term follow up of the PROWESS trial showed that this benefit continued to 3, 6, 12 and 30 months only in the subgroup of patients, defined post-hoc, whose APACHE II score was ≥ 25 .
- For patients with an APACHE II score <25 no long term survival benefit has been demonstrated and a significantly lower survival rate in treatment patients at one year and non-significantly lower survival rates at other timepoints suggests possible harm from use of rhAPC in this subgroup.
- Further trials of rhAPC in adults with severe sepsis and low risk of death (the ADDRESS trial), and in paediatric patients (the RESOLVE trial), have shown no beneficial effect of rhAPC on mortality.
- There is no evidence examining the use of rhAPC for treatment of severe sepsis in neonates.
- Treatment with rhAPC increases the risk of bleeding.

Background

Severe sepsis is defined as sepsis associated with organ dysfunction, tissue hypoperfusion or hypotension. Septic shock is sepsis-induced shock with hypotension, despite adequate fluid resuscitation, along with perfusion abnormalities.³

Standard treatment of sepsis includes treatment of infection with antibiotics and possibly surgical debridement, and supportive care according to patient signs and symptoms. Previous RCTs have focused on anti-inflammatory therapies including tumour necrosis factor alpha and its receptor, interleukin-1 and its receptor, prostaglandins and bradykinins but all have failed to show any improvement in mortality rates.³

rhAPC is a new treatment for severe sepsis. The United States Food and Drug Administration licensed rhAPC for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death as determined by the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system.⁶ The European licence is for the treatment of adult patients with severe sepsis with two or more organ dysfunctions. A UK Health Technology Report (HTA) report adds the recommendation that its use be added to best standard care.³

The Australian licensing indication encompasses both the US and European indications. In Australia the PBAC recommended rhAPC for listing for "Adult patients with severe sepsis who have a high risk of death as determined by acute organ dysfunction in at least two organs or modified Apache II score of at least 25".¹³

The Centre for Clinical Effectiveness was requested to report on the effectiveness of rhAPC for severe sepsis.

Clinical staff at Southern Health are aware of a report by Bernard et al (2001), from the New England Journal of Medicine, which reported a large RCT (the PROWESS trial) comparing rhAPC and placebo for treatment of severe sepsis and septic shock.⁸ We were requested to critically appraise this paper in addition to completing a standard evidence request.

Clinical Question

In patients with severe sepsis does treatment with rhAPC, as compared to standard care, improve survival?

Methods

Study Selection Criteria

Patient	Patients with severe sepsis
Intervention	Treatment with recombinant human activated protein C (drotrecogin alfa(activated))
Comparison	Standard care
Outcomes	Mortality*
Study Type	Any comparative study
Publication Date	2003-2006
Language	English

*Initially only outcomes to 28 days were included. After discussion with clinicians, long terms outcomes were also included.

Search Strategy

Guideline websites	URLs – All searched 10th November 2006
NHMRC Guidelines	www.nhmrc.gov.au
New Zealand Guideline Group	www.nzgg.org.nz
US National Guideline Clearinghouse	www.guidelines.gov
TRIP Database	www.tripdatabase.com
Scottish Intercollegiate Guidelines Network	www.sign.ac.uk
UK National Institute for Clinical Excellence	www.nice.org.uk
Institute for Clinical Systems Improvement	www.icsi.org/index.asp

Our usual procedure is to conduct an initial search for systematic reviews. If a high quality systematic review is found we search forward from the search date of the review for more recent publications. If no systematic review is found a complete search is undertaken.

A search of the above resources identified one guideline, published in 2004, and one Health Technology Assessment (HTA), published in 2005. Having identified the HTA as a high quality systematic review we planned to search forward from the date of the HTA however neither the HTA nor the guideline had identifiable search dates. As the earlier publication stated that their process began in 2003 we chose to search from 2003 to the present time.

It was also requested that we appraise the original article reporting the PROWESS study (Bernard et al 2001), a large, multi-centre RCT examining the use of rhAPC, compared to placebo, in patients with severe sepsis.

Evidence Source	Date of Search or Issue searched
All EBM (Ovid) *	15 November 2006 (Issue 3, 2006)
Medline (Ovid)	15 November 2006
CINAHL (Ovid)	15 November 2006

*(including The Cochrane Database of Systematic Reviews, DARE, CENTRAL and ACP Journal Club)

Search Terms in Medline

Patient	exp Sepsis Syndrome/ OR exp Sepsis/ OR sepsis.mp. OR exp Shock, Septic/ or exp Multiple Organ Failure/ OR septic\$.mp.
Intervention	drotrecogin.mp. OR xigris.mp. OR zovant.mp. OR apc.mp. OR exp Protein C/ OR (protein-c and activate\$.mp.
Comparison	–
Outcomes	–

Data Collection & Analysis

Studies were selected and appraised by two reviewers using study selection and appraisal criteria established a priori. Initially only outcomes to 28 days were included. After discussion with clinicians, long terms outcomes were also included.

Guidelines were appraised using the AGREE instrument. This was developed to provide a framework for assessing the quality of the guideline development process. It does not assess the clinical content of the guideline or the supporting evidence.¹⁴

Systematic reviews and RCTs were appraised using standard criteria outlined in the detailed appraisal tables in the Appendices.

Results

A search of relevant internet websites found one guideline¹⁴ and one Health Technology Assessment (HTA).³

Medline, Cochrane and CINAHL searches identified 481 potentially relevant articles published between 2003 and 2006. After review of titles and abstracts 453 articles were excluded leaving 28 potentially relevant articles for which full text was obtained. After review of full text one Cochrane Systematic Review² and four studies reporting RCTs⁴⁻⁷ met our inclusion and exclusion criteria and are included in this review. These papers were published after the HTA or were excluded from the HTA but are relevant to this question. This search also returned the previously identified guideline and Health Technology Assessment.

An additional unpublished trial was identified through general reading on the topic of rhAPC for sepsis and was also discussed in the Cochrane Systematic Review.

In addition, as requested, we have included an appraisal of the RCT reported by Bernard et al (2001) (Protein C Worldwide Evaluation Study of Sepsis or the PROWESS trial)⁸ on which the guideline and HTA are primarily based, and of which two of the three other included RCTs report subgroup analyses.

A protocol for a Cochrane Systematic Review on the effect of rhAPC on severe sepsis or septic shock in patients of all ages has been written (Marti, 2003).¹⁵ We contacted the lead author to enquire as to an expected completion date but no reply was received.

The findings are summarised below and detailed appraisal tables are included in Appendices.

Appendix A: Assessment of guideline using AGREE criteria

Appendix B: Critical appraisal of systematic reviews

Appendix C: Critical appraisal of studies reporting PROWESS data

Appendix D: Critical appraisal of study reporting ADDRESS data

Dellinger R et al (2004)¹ Evidence based guideline

The Surviving Sepsis Campaign Guideline was written to assist in the management of severe sepsis and septic shock and therefore covers a wide range of treatment options in addition to rhAPC.¹ The guidelines are of moderate quality only with many aspects of the methods of their development inadequately described.

The scope and applicability of the guidelines is unclear. There is no discussion of potential organisational barriers to implementation or cost of implementation and monitoring and audit of the guideline is part of the next phase of the campaign. Its editorial independence is also questionable as it received substantial funding from the company who produce rhAPC (Xigris®). There were substantial conflicts of interest of the guideline development group and though the authors state that the company did not have input into the guidelines they also say that the sponsors approved the final document.

The guideline recommends the use of rhAPC in patients at high risk of death (as defined by APACHE II score of ≥ 25), sepsis-induced multiple organ failure or sepsis-induced acute respiratory distress syndrome (ARDS), who have no absolute contraindication related to bleeding risk or other contraindication that outweighs the potential benefit. This recommendation is based on the results of the PROWESS trial.

Kylat and Ohlsson (2006)² Cochrane Systematic Review

A Cochrane Systematic Review on the use of rhAPC for severe sepsis in neonates was identified. The review found no RCTs addressing this area. The authors concluded that there is currently no high quality evidence to support the use of rhAPC for the treatment of severe sepsis in a neonatal population.²

Green et al (2005)³ Health Technology Assessment

Effectiveness

The HTA by Green et al (2005) is a high quality systematic review (NHMRC level I evidence) of the clinical and cost effectiveness of rhAPC.³ The only RCT identified by the HTA that was powered to address effectiveness was the PROWESS trial. The HTA reports the initial results published in Bernard et al (2001)⁸ as well as many of the subsequently published subgroup analyses.

The authors of the HTA note several concerns with the methods used in the PROWESS trial. These include lack of information about blinding of outcome assessment, copious subgroup analyses, some of which were not planned prior to the study and thus may constitute 'data-dredging', and changes to the study protocol (changes to exclusion criteria, use of an alternate placebo and removal of one of the pre-specified primary outcomes) during the course of the study.

which were not reported in articles describing the study. The PROWESS trial was funded by Eli Lilly and Company who produce rhAPC and the articles were written by employees of the company and others who had received research and other funding from Eli Lilly.

From our critical appraisal of Bernard et al (2001) (see Appendix C) we agree with the issues identified by Green et al and have some additional concerns about the blinding of investigators and outcome assessors to treatment. Further it is important to note that the PROWESS trial was undertaken in a tightly controlled group of patients, excluding those who had a platelet count $<30,000/\text{mm}^3$; a condition that increases the risk of bleeding; a known hypercoagulable condition; a history of bone marrow, lung liver, pancreas or small-bowel transplantation; chronic renal failure requiring haemodialysis or peritoneal dialysis; known or suspected portosystemic hypertension, ; chronic jaundice, cirrhosis or chronic ascites; acute pancreatitis with no established source of infection; are moribund with death perceived as imminent or are not expected to survive 28 days due to other condition; are HIV positive with last known CD4 count $\leq 50/\text{mm}^3$ or have used anticoagulants or antithrombotic medications (in specific timeframes).

On the basis of the PROWESS trial the HTA concludes that rhAPC combined with best supportive care appears to be clinically effective compared with best supportive care alone. In patients with severe sepsis who were treated with rhAPC, intention to treat analysis showed the relative risk of death at 28 days as compared to placebo was 0.79 (95%CI 0.68, 0.92).

Many subgroup analyses were reported from the PROWESS trial and no correction was made for multiple comparisons. Whilst most subgroups were prospectively defined there were some retrospectively defined subgroups. Prospectively defined subgroups in which a statistically significant reduction in 28 day mortality was demonstrated in the rhAPC treated group are shown on in Table 1.

Table 1: Relative risk of 28 day mortality of patients treated with rhAPC in various subgroups

Subgroup	n	RR	95%CI
≥ 2 dysfunctional organs	1272	0.78	0.66, 0.93
APACHE II score 25-29 (third quartile)	366	0.66	0.48, 0.91
APACHE II score ≥ 30 (fourth quartile)	451	0.78	0.63, 0.96
No ARDS	1431	0.78	0.66, 0.92
Shock (PROWESS definition) †	1200	0.77	0.64, 0.91
Shock (FDA definition) ‡	1057	0.81	0.68, 0.98
Mechanical ventilation	1275	0.82	0.70, 0.97
Vasopressor support	1057	0.84	0.71, 0.99
Pneumonia	882	0.77	0.62, 0.95
Community acquired pneumonia	602	0.72	0.55, 0.94
Lung as the primary site of infection	906	0.75	0.61, 0.91
Bacterial infection	1016	0.79	0.64, 0.98

† PROWESS definition of shock: presence or absence of cardiovascular organ failure as defined in the inclusion criteria, with hypotension or vasopressor support within 6 hours prior to study drug administration.

‡ FDA definition of shock: patients with no cardiovascular organ failure by any assessment prior to the study drug administration, i.e. those with a cardiovascular Sequential Organ Failure Assessment score of less than 3 (not requiring high-dose vasopressors), were included in the 'no shock' group.

A statistically significant reduction in 28 day mortality was not identified in a range of other subgroup analyses, however it is not clear whether this is because there was no difference between groups or because the sample sizes were too small to demonstrate a difference between groups.

Long term survival to 90 days was presented in the HTA report as being significantly better in the rhAPC group however examination of the HTA references shows that the information on long term survival came from a conference presentation and not from a peer-reviewed article. This finding is contradicted in a paper by the same authors (Angus et al 2004) published in 2004 (see details below).

Safety

Evidence for the safety of rhAPC comes from two RCTs, PROWESS and an earlier trial EVAA. EVAA was a Phase 2 trial (F1K-MC-EVAA) examining dose and safety and not effectiveness.

There was no statistically significant difference in the incidence of serious adverse events or in serious bleeding events in these two trials. Serious bleeding is defined as a serious adverse event that involves bleeding such as intracranial haemorrhage, a need for transfusion of two or more units of packed red cells on two or more consecutive days or any life-threatening bleeding event.

In the PROWESS trial the incidence of severe bleeding was 3.5% in the rhAPC group and 2.0% in the placebo group ($p=0.06$). This trial was terminated early and it is unclear if it was still powered to detect a difference in serious bleeding events.

In the PROWESS trial there was a significantly higher incidence of all bleeding events in the rhAPC arm (24.9% in rhAPC vs 17.7% in placebo, $p<0.001$).

Ely et al (2003)

The analysis by Ely et al (2003), focused on the subgroup of patients ≥ 75 years of age.⁴ There were several differences in baseline characteristics between the intervention and control groups. The study reported that in patients treated with rhAPC the relative risk of death was 0.68 (95%CI 0.54, 0.87), and the relative risk of in-hospital mortality was 0.70 (95%CI 0.56, 0.88). The number needed to treat to save one life was six. This paper was not included in the HTA as the population was not one of the predefined subgroups of interest.

Long term follow up of patients ≥ 75 years of age reported a significantly higher survival rate over a two year follow up period in patients treated with rhAPC ($p=0.02$) with a median survival time of 31 days in the placebo group versus 119 days in the rhAPC group ($p=0.02$). There were 386 patients aged ≥ 75 years in the PROWESS trial but it is unclear how many of these were followed for the full two years. This subgroup was defined post hoc.⁴

Angus et al (2004)

Angus et al report that long term follow up of PROWESS participants showed that although 28 day survival and in-hospital survival rates were better in patients who were treated with rhAPC, this benefit did not extend beyond 28 days. In patients who survived to 28 days, there was no significant difference between mortality rates for rhAPC or placebo groups at 3, 6, 12 or 30 months.⁵ The PROWESS study was not designed for long term follow up and the numbers followed to latter time points are small. It is unclear if patient numbers are low due to loss to follow up, death or patients not yet reaching the time points. Follow up ranged from 28 days to 3.6 years.

The United States Food and Drug Administration requested a post hoc analysis of results based on subgroups defined by APACHE II scores of <25 or ≥ 25 . A long term survival benefit was seen in patients who had an APACHE II score of ≥ 25 who were treated with rhAPC.⁵

Table 2: Survival rates for patients with APACHE score ≥ 25

Months	% survival rhAPC	% survival placebo	p value
3	58.9	48.4	0.003
6	55.2	45.3	0.005
12	52.1	41.3	0.002
36	45.6	33.8	0.001

These patients also had a higher median survival time (450 vs 71 days, $p=0.0005$).

In patients with an APACHE score of <25 there was a significantly higher survival rate at one year in placebo patients as compared to rhAPC patients (74.3% vs 68.9%, $p=0.04$). At the other time points reported, survival rates remain higher in the placebo group, but the differences are not statistically significant. This suggests that there is a potential for harm from use of rhAPC in this group of patients.

Laterre et al (2005)

The additional analysis by Laterre et al (2005), focused on a subgroup of patients with community acquired pneumonia.⁶ This study reported that after adjusting for baseline differences, the subgroup with community acquired pneumonia treated with rhAPC had an improved 28 day relative risk of death of 0.81 (95%CI 0.67, 0.93) compared to the placebo group, as well as an improved in-hospital mortality relative risk of 0.76 (95%CI 0.60, 0.97). The authors also report 90 day mortality data however as the data collection methods and the number of subjects included in this

analysis are not described, we have not included this data.

Abraham et al (2005)

Abraham et al (2005), in the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis trial (ADDRESS) examined the use of rhAPC in patients with severe sepsis considered at low risk of death determined by single organ failure or APACHE II score <25. This trial planned to enrol 11,444 patients. Inclusion criteria varied between participating centres and it was unclear if allocation was concealed.⁷

At an interim analysis of 2613 patients, the Data-monitoring Committee recommended early termination of the trial as there was less than 5% chance of demonstrating a significant reduction in mortality in patients receiving rhAPC. This was a pre-determined stopping point. In addition, the rate of serious bleeding was significantly higher in the intervention group than in the placebo group both during infusion (2.4% vs 1.2%, p=0.02) and during the 28 day study period (3.9% vs 2.2%, p=0.01). The authors concluded that rhAPC 'should not be used in patients with severe sepsis who are at low risk of death'.⁷ The mortality rate was non-statistically significantly higher in the intervention group than in the placebo group (18% vs 17%, p=0.34). Because the study was stopped early, while it showed that rhAPC did not decrease mortality and does increase risk of bleeding, it also cannot rule out the possibility that rhAPC increases mortality.

RESOLVE trial (unpublished)

The results of Researching Severe Sepsis And Organ Dysfunction In Children: A Global Perspective trial (RESOLVE) have yet to be published in full. This trial was identified through general reading on the topic of rhAPC for sepsis and was also discussed in the Cochrane Systematic Review on the use of rhAPC in neonates.

RESOLVE was designed as a randomised, double-blind, placebo controlled trial of rhAPC in paediatric patients (aged 0 to 18 years) with severe sepsis. This trial began in 2002 and had a target enrolment of 600 paediatric patients with severe sepsis plus sepsis-induced cardiovascular and respiratory dysfunction. This trial was ceased in 2005 after an interim analysis showed that rhAPC was unlikely to result in any improvement in the end-point of 'composite time to complete organ failure resolution' over 14 days. There was also an increase in central nervous system bleeding in the intervention group, though we are unsure if this was a significant increase. The results of this trial are yet to be published.^{2, 9, 10}

Discussion

Evidence for the effectiveness of rhAPC for treatment of adults with severe sepsis comes predominantly from one large, multi-centre, international RCT (PROWESS).

Although there are some limitations of this study the HTA report concluded that rhAPC, combined with best supportive care, appears to be clinically effective compared with best supportive care alone.³ Not included in this HTA report is a later publication which reported no overall long-term survival benefit to the PROWESS patients but a survival benefit in the post hoc subgroup of patients with APACHE II score ≥ 25 . Caution is usually advised when relying on post hoc analysis as it is sometimes considered 'data dredging' to identify statistically significant results. However, in this case, the investigators were asked to conduct this post-hoc analysis by the United States Food and Drug Administration.

These results need to be considered in the Australian setting.

The PROWESS trial did enrol Australian patients but this number is likely to be low. There appear to have been 10 sites in Australia out of 164 internationally⁷ and of the 1690 patients in PROWESS only 259 were from sites other than the US, Canada or Europe.¹⁶

The PROWESS trial protocol compared the addition of rhAPC or placebo to usual care. As the trial protocol does not define 'usual care' it is important to consider any differences that may exist between usual care for sepsis in Australia and usual care internationally.

It is also pertinent to compare mortality rates from severe sepsis in Australia with those in the PROWESS study. A study of 5878 admissions at 23 ICUs in Australia and New Zealand between 1 May 1999 and 31 July 1999 showed that 32.4% of severe sepsis patients died within 28 days and 37.5% died during their hospital admission.¹² This study only examined ICUs and not all patients with sepsis are treated in an ICU. A study of the epidemiology of sepsis in Victoria, using data from the Victorian Admitted Episodes Database between 1 July 1999 and 30 June 2003, calculated the in-hospital mortality rate for patients with severe sepsis as 31.1%.¹¹ Both of these studies defined severe sepsis according to the American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference definition of Systemic Inflammatory Response Syndrome (SIRS) in combination with organ dysfunction. SIRS is defined as two or more of: a) a body temperature of $\geq 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$; b) a heart rate of > 90 beats per minute; c) tachypnea, as defined by a respiratory rate of ≥ 20 breaths per minute, or hyperventilation as defined by a PaCO_2 of < 32 torr; d) a white blood cell count of $\geq 12,000$ cells/ mm^3 or $< 4,000$ cells/ mm^3 or the presence of $> 10\%$ immature

neutrophils.¹⁷ The 28 day mortality rate from severe sepsis in the patients randomised to placebo in the PROWESS trial was 31.3%.⁸

A condition of the US FDA approval was that the manufacturer conducts trials of effectiveness in adults at low risk of death and in a paediatric population. Trials in both of these populations (ADDRESS and RESOLVE) were terminated early after interim analyses found that they were unlikely to find a reduction in mortality in the rhAPC group and a higher risk of bleeding had been identified in the treatment group.

Conclusions

There is some evidence to show that rhAPC is effective for the treatment of sepsis in a very tightly controlled population of adults. This evidence comes from one large RCT, the PROWESS trial which has several methodological flaws and a very tightly defined group of patients that limits generalisability of the findings. This trial reported that patients randomised to treatment with rhAPC had a relative risk of death at 28 days of 0.79 (95% CI 0.68, 0.92) as compared to those randomised to placebo.

A follow up study showed that this benefit continued to 3, 6, 12 and 30 months only in the subgroup of patients whose APACHE II score is ≥ 25 . For patients with an APACHE II score < 25 no long term survival benefit has been demonstrated and a significantly lower survival rate in treatment patients at one year and non-significantly lower survival rates at other time points suggests possible harm from use of rhAPC in this subgroup.

A trial of rhAPC in adults at low risk of death defined by an APACHE score of < 25 or single organ failure, (ADDRESS), and another in a paediatric population (RESOLVE) were both terminated early as interim analyses revealed that they were unlikely to show that rhAPC was beneficial in reducing mortality and there were higher rates of serious bleeding in the treatment groups.

There is no evidence to assess the effectiveness of rhAPC in neonates.

As recommended by the NHS Health Technology Assessment, any use of rhAPC should be in conjunction with best supportive care.

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Appendix A assessment of guidelines using the AGREE criteria

Appraisal

Dellinger R et al. Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock. Critical Care Medicine. 2004;32(3):858-873.

AGREE Domain	Score	Comment
Scope and purpose	8/12	The scope and purpose of these guidelines is quite general and lacks specific definitions of objectives, clinical questions and patients populations.
Stakeholder involvement	8/16	The guideline development group included 44 physicians and 1 nurse. This guideline lacks a consumer/patient input and was not piloted before publishing. Piloting has been planned however, for Phase III of the 'Surviving Sepsis Campaign' (The guideline development was Phase II).
Rigour of development	17/28	Benefits, side effect and risks of recommendations are well discussed and there is an explicit link between recommendations and evidence. More detail is required on searching for and selecting evidence, the results of appraisal of included studies, external review of guidelines and the process for up-dating.
Clarity and presentation	13/16	The recommendations and options for management could be clearer and more concise. The guidelines do not appear to have been published in another format.
Applicability	4/12	The applicability of these guidelines is questionable. There is no discussion of potential organisational barriers to implementation or costs of implementation. There are future plans for monitoring and audit (Phase III).
Editorial independence	5/8	Development of these guidelines was funded by pharmaceutical companies (predominately Eli Lilly and Company which produces rhAPC) and the majority of members of the guideline development group had also received other funding from the pharmaceutical industry. Editorial independence of these guidelines is therefore questionable. Extensive conflicts of interest are declared, though it is stated that committee members were not assigned to subgroups in which they had a potential conflict of interest. The guidelines stated that industry was not allowed any presence at meetings or input into guidelines and that they did not see the document until it had been accepted for peer reviewed publication, however the sponsoring organisations approved the final document.

Recommendations

These guidelines were written to assist in the management of severe sepsis and septic shock and therefore cover a wide range of treatment options in addition to rhAPC. rhAPC is recommended for use in patients at high risk of death (as defined by Acute Physiology and Chronic Health Evaluation II score of ≥ 25), sepsis-induced multiple organ failure, septic shock or sepsis-induced acute respiratory distress syndrome, who have no absolute contraindication related to bleeding risk or other contraindication that outweighs the potential benefit. This recommendation is based on the results of the PROWESS trial.

Readers should bear in mind the substantial conflicts of interest of the guideline development group and the funding of the development by the pharmaceutical industry.

Appendix B Critical appraisal of Systematic Reviews

Kylat and Ohlsson (2006)

Characteristics:

Study Type	Patients	Intervention	Comparison	Outcomes
Cochrane Systematic Review NHMRC Level 1 evidence	Term and preterm infants less than 28 days old with suspected or confirmed severe sepsis treated with antimicrobials.	Treatment with rhAPC	Any	Mortality, morbidity, length of hospital stay

Quality:

Focused research question	Yes	The question was whether treatment with rhAPC reduced mortality and morbidity in neonates with severe sepsis.
Specified inclusion/ exclusion criteria	Yes	Both randomised and quasi-randomised trials were included.
Explicit and comprehensive search strategy	Yes	Detailed search strategy and list of databases and resources searched is provided. Search was performed in July 2005.
Validity of included trials appraised	Yes	It was planned to use the methods developed by the Cochrane Neonatal Review Group to assess methodological quality of any trials.
Homogeneity between studies assessed	n/a	There were no included studies.
Summary of main results presented	n/a	There were no included studies however a description of several excluded studies was given as they may aid in the background and development of any future trials.
Strengths and limitations of included studies discussed	n/a	No included studies.

Results:

No eligible studies were identified in this systematic review on the use of activated protein C to treat severe sepsis in neonates, thus the authors conclude that there are insufficient data to support the use of activated protein C for the treatment of severe sepsis in neonates.

Green et al (2005)				
Characteristics:				
Study Type	Patients	Intervention	Comparison	Outcomes
Systematic review (NHS Health Technology Assessment) NHMRC level 1 evidence	Adult patients hospitalised with severe sepsis or septic shock acquired either in the community or in hospital. Studies in children <18 years were excluded.	Treatment with rhAPC plus conventional care.	Conventional care alone.	Primary outcome was all cause mortality at the end of the study period. Secondary outcome measures included death from septic shock, length of hospital and ICU stay, QOL, APACHE II scores, number of organ failures, organ dysfunction, duration of assisted ventilation and nosocomial infection. Side effect profile and cost-effectiveness were also considered.
Quality:				
Focused research question	Yes	The objective of this review is to assess the clinical and cost-effectiveness of rhAPC for the treatment of severe sepsis in an adult population. This is examined from a United Kingdom perspective.		
Specified inclusion/ exclusion criteria	Yes	To examine the effectiveness of rhAPC only RCTs were considered however to examine the safety both RCTs and other relevant studies were considered, including open-label and compassionate use trials.		
Explicit and comprehensive search strategy	Yes	Search strategy and list of databases and resources searched is provided however the date of the search is not provided.		
Validity of included trials appraised	Yes	This was done according to the guidelines of the Cochrane Infectious Diseases Group with the addition of some items specific to patients with sepsis.		
Homogeneity between studies assessed	N/A	Only one study of effectiveness included		
Summary of main results presented	Yes	Summary data presented in both table and graphical form		
Strengths and limitations of included studies discussed	Yes	<p>The authors note several concerns with the methods used in the PROWESS trial. These include lack of information about blinding of outcome assessment, copious subgroup analyses, some of which were not planned prior to the study and thus may constitute 'data-dredging', and changes to the protocol during the course of the study (changes to exclusion criteria, use of an alternate placebo and removal of one of the pre-specified primary outcomes). The authors do not provide an overall assessment of study quality.</p> <p>These changes to study protocol were not reported in the original report of the PROWESS trial (Bernard). The HTA authors report that the FDA analysed the two participant groups, those enrolled before and after the protocol changes, and concluded that it was likely that the changes would have increased the power of the trial to detect a true treatment effect. The majority of the benefit from rhAPC occurred in the second half of the trial after the protocol change. Eighty-one patients enrolled in the first half of the trial would not have been eligible after the protocol change and after examining these patients the FDA concluded that there had been no systematic attempt to eliminate patients less likely to respond, and that the elimination of these patients did not increase the treatment effect and was not responsible for the difference in treatment effects between the two parts of the trial. The HTA report concludes that although such protocol changes could be cause for concern there is no evidence that they biased the study results in any way.</p>		

Results:

Effectiveness

The main evidence for effectiveness comes from the PROWESS trial (Bernard et al, 2001). An earlier RCT (the EVAA trial) was a smaller trial designed as a dose ranging study and was not powered to demonstrate clinically important differences between groups did not show a significant difference in mortality between placebo and intervention groups.

In patients with severe sepsis who were treated with rhAPC ITT results of the PROWESS trial showed the relative risk of death (as compared to placebo) was 0.79 (95%CI 0.68, 0.92), with an absolute risk reduction of 6.5% (95%CI 2.2, 10.7).

Subgroup analysis

Many subgroup analyses were reported from the PROWESS trial and no correction was made for multiple comparisons. Whilst most subgroups were prospectively defined there were some retrospectively defined subgroups. Prospectively defined subgroups in which a statistically significant reduction in 28 day mortality was demonstrated in the rhAPC treated group, as compared to placebo are shown below.

Subgroup with:	n	RR (28 day mortality)	95%CI
≥2 dysfunctional organs	1272	0.78	0.66, 0.93
APACHE II score 25-29 (third quartile)	366	0.66	0.48, 0.91
APACHE II score ≥30 (fourth quartile)	451	0.78	0.63, 0.96
No ARDS	1431	0.78	0.66, 0.92
Shock (PROWESS definition) †	1200	0.77	0.64, 0.91
Shock (FDA definition) ‡	1057	0.81	0.68, 0.98
Mechanical ventilation	1275	0.82	0.70, 0.97
Vasopressor support	1057	0.84	0.71, 0.99
Pneumonia	882	0.77	0.62, 0.95
Community acquired pneumonia	602	0.72	0.55, 0.94
Lung as the primary site of infection	906	0.75	0.61, 0.91
Bacterial infection	1016	0.79	0.64, 0.98

† PROWESS definition of shock: presence or absence of cardiovascular organ failure as defined in the inclusion criteria, with hypotension or vasopressor support within 6 hours prior to study drug administration.

‡ FDA definition of shock: patients with no cardiovascular organ failure by any assessment prior to the study drug administration, i.e. those with a cardiovascular SOFA of less than 3 (not requiring high-dose vasopressors), were included in the 'no shock' group.

Prospectively defined subgroups in which a statistically significant reduction in 28 day mortality was **NOT** demonstrated in the rhAPC treated group, as compared to placebo are shown below. The lack of statistical significance may be due to small sample size, and it should therefore not be concluded that rhAPC is ineffective in these groups.

Subgroup with	n
APACHE II score 3-19 (first quartile)	433
APACHE II score 20-24 (second quartile)	440
ARDS	259
No shock (PROWESS or FDA definition)	490 or 633
No mechanical ventilation	415
No vasopressor support	633
Nosocomial pneumonia	280
Non-pulmonary infection	808
Abdomen as the primary site of infection	337
Urinary tract as the primary site of infection	171
Fungal infection	62
Unknown infection type	268

A retrospective analysis of patients with two or more dysfunctional organ systems showed that there was also a reduced risk of death in patients from this subgroup who also had overt disseminated intravascular coagulation (DIC) (0.64, 95%CI 0.48, 0.83), those on mechanical ventilation (0.78, 95%CI 0.64, 0.93) and those on vasopressor support (0.81, 95%CI 0.67, 0.98)

Long-term follow up

Long term survival to 90 days was presented in this report as being significantly better in the rhAPC group however despite this HTA being published in 2005 a paper published in 2004 contradicts the information presented in the HTA. Examination of the HTA reference for this information showed it to have been obtained from a conference abstract rather than a peer reviewed publication.

Safety

Evidence for safety came from two RCTs, PROWESS and the earlier trial, EVAA (EVAA was a smaller RCT examining dose and safety and not effectiveness). There was no significant difference in the incidence of serious adverse events or in serious bleeding events in these two trials although in the PROWESS trial there was a significantly higher incidence of all bleeding events in the rhAPC arm (24.9% in rhAPC vs 17.7% in placebo, $p < 0.001$). The original report of the PROWESS trial (Bernard et al, 2001) did not report this higher overall incidence of bleeding.

Treatment of sepsis with rhAPC was associated with a non-statistically significant increased risk of serious bleeding (3.5% vs 2%, $p = 0.06$). It is possible that the early termination of the trial affected the power to detect a significant difference in serious bleeding.

This review also considered the cost-effectiveness of drotrecogin alfa but this is not discussed in this report. The executive summary of this HTA report is available as a separate PDF document.

Appendix C Critical appraisal of studies reporting PROWESS data

Bernard et al (2001)

Characteristics:

Study Type	N (total)	Setting	Patients	Intervention	Comparison	Outcomes
RCT NHMRC level 2 evidence	1690	Multi-centre trial in 164 hospitals in 11 countries. July 1998 to June 2000.	Patients with severe sepsis as defined by known or suspected infection on the basis of clinical data plus three or more signs of systemic inflammation and sepsis-induced dysfunction of at least one organ or system.	rhAPC infusion at 24ug/kg body weight for a total of 96 hours Other than the infusion there was no standard protocol for care.	Placebo infusion for a total of 96 hours Other than the infusion there was no standard protocol for care.	Mortality at 28 days from any outcome, adverse events and various laboratory variables.

Quality:

Specified inclusion/ exclusion criteria	Yes	<p>These criteria are complex but clearly specified. As noted in the appraisal of Green et al above, new exclusion criteria were added partway through the study, however this is not mentioned in the report of the study.</p> <p>Inclusion criteria:</p> <p>Patients meeting all of the following criteria:</p> <ul style="list-style-type: none"> • known or suspected infection as evidenced by specified criteria • meeting at least three of four modified systemic inflammatory response syndrome (SIRS) criteria • sepsis induced dysfunction of at least one organ system, meeting specified criteria. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Pregnancy or breast feeding, aged <18 years, weight >135kg, participation in another investigational study within 30 days of the current study • Platelet count <30,000/mm³ • Conditions that increase the risk of bleeding
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		<ul style="list-style-type: none"> • Known hypercoagulable condition • Physician or family not in favour of aggressive treatment or existence of an advanced directive to withhold treatment • Patient not expected to survive 28 days due to an uncorrectable medical condition, such as poorly controlled neoplasm or other end stage disease • Moribund state in which death perceived to be imminent • HIV infection with last known CD4 count $\leq 50\text{mm}^3$ • History of bone marrow, lung, liver, pancreas or small-bowel transplantation • Chronic renal failure requiring haemodialysis or peritoneal dialysis • Known or suspected portosystemic hypertension, chronic jaundice, cirrhosis or chronic ascites • Acute pancreatitis with no established source of infection • Use of anticoagulant or antithrombotic medications (in specific timeframes)
Adequate method of randomisation	Yes	Block randomisation (1:1) according to site made through a central randomisation centre.
Concealment of allocation	Unclear	Not specified, however likely to be concealed due to central randomisation.
Groups similar at baseline	Yes	Baseline characteristics are presented and groups appear similar, however there is a slightly higher incidence of several pre-existing conditions in the placebo group.
Blinding - patients/ investigators/ assessors	Unclear	<p>The infusion was given from foil wrapped bags and the reason the bags were wrapped is unexplained. This raises the questions of whether the bags were labelled underneath the foil, in which case an individual could unwrap the bag and check, or if there is a difference in the appearance of the solutions, in which case the infusion tubing should also have been wrapped. This is further confused by the fact that the placebo solution was altered during the course of the trial, again suggesting that there may have been differences in the appearance of the solutions. Neither the change of placebo solutions nor the reason for it is mentioned in the report of the study.</p> <p>In a later rhAPC trial, the ADDRESS trial, it is specified that all delivery systems for the infusion were covered to ensure blinding.</p> <p>Otherwise, all patients, investigators and assessors appear to have been blinded. It is unclear if outcome assessors were blinded.</p>
Duration of follow-up	Yes	The initial report followed patients for 28 days from beginning of treatment or until death if death prior to 28 days. Longer term follow-up has since been reported to 1 year.
Proportion lost to follow up	Yes	All patients were accounted for at 28 days. Survival status was known for 94% at 90 days and 93% at 1 year.
Objective & independent assessment of outcomes	Yes	Primary outcome was death. Other outcomes included adverse events, All blood tests were performed by a central laboratory. These are all objective outcome measurements. Assessment of and severity

		of bleeding may be subjective.
Inclusion of all subjects in analysis	Mostly	Thirty-eight patients who were randomised (17 placebo and 21 intervention) did not receive any drug and were not included in the analysis. Reasons included withdrawal of consent, meeting exclusion criteria or becoming moribund before treatment could begin.
Other comments:		This RCT was funded by Eli Lilly and Company who manufactures rhAPC and the articles written by employees of the company and others who had received research and other funding from Eli Lilly and other pharmaceutical companies.
Results:		
<p>This trial was designed to enrol 2280 patients. No power calculation is presented. However, the second of two pre-planned, interim analyses, showed that APC treatment was significantly more effective than placebo and this resulted in a pre-determined suspension of the trial.</p> <p><u>Effectiveness</u></p> <p>The results of the PROWESS trial have been described in detail in the description of the HTA by Green et al above.</p> <p>In the report by Bernard, non-stratified analysis showed that treatment of sepsis with rhAPC activated resulted in a 19.4% relative reduction in mortality (95%CI 6.6, 30.5) and an absolute reduction in the risk of death of 6.1% (95%CI 1.9, 10.4). This effect was consistent when an ITT analysis of all patients, including the 38 patients who were randomised but did not receive treatment was undertaken (absolute reduction in risk of death 6.5%, 95%CI 2.2, 10.7).</p> <p>The number needed to treat to save one life was 16.</p> <p>When the results were stratified by protein C deficiency status of the patient at baseline, the results were only statistically significant in the patient group that were protein C deficient, however the large majority of patients being treated for sepsis were protein C deficient (670 out of 840 in placebo group and 709 out of 850 in intervention group). In protein C deficient patients the absolute reduction in risk of death was 6.4% (95%CI 1.6, 11.2) compared to in non-protein C deficient patients where the absolute reduction in risk of death was 11.1 (95%CI -0.4, 22.6)</p> <p><u>Safety</u></p> <p>Treatment of sepsis with rhAPC was associated with a non-statistically significant increased risk of serious bleeding (3.5% vs 2%, p=0.06). This increase in serious bleeding occurred only during the infusion time. It is possible that the early termination of the trial affected the power of the trial to detect a significant difference in serious bleeding.</p> <p>For every 66 patients treated one additional case of severe bleeding could be expected.</p> <p>A serious bleeding event was defined as any intracranial haemorrhage, any life-threatening bleeding, any bleeding classified as serious by the investigator or any bleeding that required the administration of three units of packed red cells on two consecutive days.</p> <p><u>Conclusion</u></p> <p>The authors conclude that 'Treatment with drotrecogin alfa activated significantly reduces mortality in patients with severe sepsis and may be associated with an increased risk of bleeding'.</p> <p><u>Note:</u> The protocol changes that occurred part way through the study are not presented in the Bernard paper. These are discussed in Green et al (2005).</p>		

Ely et al (2003a)

Characteristics and quality:

This paper reports a subgroup analysis of the PROWESS trial that was not included in the HTA report by Green et al (2005). The characteristics and quality are as for Bernard et al (2001) with the exception of the patients.

The patients reported in this paper are 386 members of the PROWESS trial who were ≥ 75 years of age. Some baseline characteristics vary slightly between the placebo and rhAPC group though authors state that adjustment was made for baseline characteristics in the analysis of mortality data.

Results:

This is a subgroup analysis of the PROWESS trial that was excluded from the HTA as patients ≥ 75 years were not a predefined subgroup of interest for the HTA report.

A total of 386 elderly patients with severe sepsis ≥ 75 year old were included (placebo n=181, rhAPC n=205). This was a retrospectively defined subgroup, and the small sample size results in decreased statistical power to detect differences between groups.

Treatment with rhAPC resulted in an ARR 28 day mortality of 15.5% (p=0.002) and an ARR In hospital mortality was 15.6% (p=0.002), NNT to save one additional life was 6. The RR 28 day mortality was 0.68 (95%CI 0.54, 0.87), RR in-hospital mortality was 0.70 (95%CI 0.56, 0.88).

The rhAPC group showed higher rates of survival over 2 years and an increase in median survival from 31 days in placebo to 119 days in rhAPC group (p=0.02).

In the multivariate analysis, placebo and rhAPC patients appeared to have similar patterns of discharge (ie. to home, nursing home or other hospital) and similar 28 day functional status (however no long term data on functional status). The rhAPC group had significant increases in mean number of vasopressor-free days (3.1 days, p=0.006), ventilator-free days (3.7 days, p=0.001), ICU-free days (3.0 days, p=0.004) and hospital-free days (1.9 days, p=0.008) compared to placebo. The authors conclude that treatment of elderly patients with rhAPC does not appear to result in a 'morbidity penalty' such as increased resource use or decline in functional status.

Incidence of serious bleeding during the 28 day study period was 3.9% rhAPC vs 2.2% placebo (p=0.34). There was a reduction in thrombotic events in the treatment group (2 rhAPC vs 9 placebo, p=0.019). Higher dysrhythmia (5.5% vs 2%, p=0.06) and CNS related events (2.8% vs 0, p=0.02) were demonstrated in the placebo group versus the rhAPC group. These analyses have not been adjusted for baseline differences between the groups.

Angus et al (2004)						
Characteristics:						
Study Type	N (total)	Setting	Patients	Intervention	Comparison	Outcomes
Retrospective cross-sectional blinded follow up of Bernard et al (2001) NHMRC level 2 evidence	1127	As for Bernard et al, (2001)	As for Bernard et al, (2001)	As for Bernard et al, (2001)	As for Bernard et al, (2001)	Long term survival
Quality:						
Specified inclusion/ exclusion criteria	Yes	All patients who were alive at day 28 of the PROWESS trial				
Adequate method of randomisation	Yes	See Bernard et al, 2001				
Concealment of allocation	Yes	See Bernard et al, 2001				
Groups similar at baseline	Yes	See Bernard et al, 2001				
Blinding - patients/ investigators/ assessors	Yes	Investigators, participants and families remained blinded to study assignment during the follow up period.				
Duration of follow-up and proportion lost to follow up	Unclear	<p>Of the initial 1690 patients analysed in the PROWESS trial there were 1220 28 day survivors. Follow up was 94% at three months, and 93% at one year. Figures are not given past one year.</p> <p>The 93 patients for whom follow up was not possible, due either being lost to follow up or having consent refused, were considered lost to follow up at day 28. More patients in the rhAPC group were lost to follow up (n=54) than in the placebo group (n=39) and there are some slight differences in the characteristics of these two groups.</p> <p>The duration of follow up is 28 days to 30 months. Data past 30 months of follow up is not reported as the proportion of the cohort still alive and in follow up was insufficient thereafter.</p> <p>The exact numbers of patients who had reached follow up time points is not reported.</p>				
Objective & independent assessment of outcomes	Yes	The outcome, survival or death and the date of death, was assessed by contact with survivors or families, and where contact was not made, through medical and public records.				
Inclusion of all subjects in analysis	Unclear	It is difficult to establish this as the paper does not report the number of patients followed at all time points and the reasons for loss: ie. death or not reached the time point.				

Results:

This study aimed to determine the effect of rhAPC on hospital survival, on long-term survival. Prior to the PROWESS trial being conducted the analysis of patients by APACHE II quartile was defined. Post the trial, analysis by APACHE score <25 or ≥ 25 was conducted on request of the US FDA and European regulatory agencies. This paper presents the results of this post hoc subgroup. Analysis is also presented for predefined groups of age, functional dependency and number of dysfunctional organs.

Hospital survival was significantly higher in patients who were treated with rhAPC as compared to placebo (70.3% vs 65.1%, $p=0.03$) however this benefit is lost at longer term follow up.

In patients alive at day 28 for whom follow-up data was available, there was no significant difference between survival rates of patients who received rhAPC or placebo at 3, 6, 12 and 30 months (see table below).

Months	% survival rhAPC	% survival placebo	p value
3	66.1	62.4	0.11
6	62.2	60.3	0.44
12	58.9	57.2	0.49
30	52.6	49.3	0.21

When a post hoc analysis was conducted on patients who had an APACHE score of ≥ 25 patients treated with rhAPC had a higher median survival time (450 vs 71 days, $p=0.0005$) and higher rates of survival at months 3, 6, 12, and 30 (see table below).

Months	% survival rhAPC	% survival placebo	p value
3	58.9	48.4	0.003
6	55.2	45.3	0.005
12	52.1	41.3	0.002
30	45.6	33.8	0.001

In patients with an APACHE score of <25 the placebo group have more favourable survival rates. Though this is only significant at the one year time point we cannot rule out that the study was not sufficiently powered to accurately measure this (see table below).

Months	% survival rhAPC	% survival placebo	p value
3	73.0	75.3	0.45
6	68.9	74.3	0.08
12	65.5	72.0	0.04
30	59.2	63.8	0.20

There was no significant difference in survival in patients treated with rhAPC compared to placebo when examining data on the basis of age, functional dependency or number of organ dysfunctions. It is unclear whether the study had sufficient power to detect such differences.

Laterre et al (2005)

Characteristics and quality

This paper reports a subgroup analysis of the PROWESS trial that was not included in the HTA report by Green et al (2005). The characteristics and quality are as for Bernard et al (2001) with the exception of the patients,

The patients reported in this paper are 602 patients admitted to the study with community acquired pneumonia. Some baseline characteristics vary slightly between the placebo and rhAPC group though authors state that adjustment was made for baseline characteristics in the analysis.

The authors report 28-day mortality and morbidity data. They also report 90 day mortality data however as the data collection methods and the number of subjects included in this analysis are not described, we have not included this data.

Results:

This is a subgroup analysis of the PROWESS trial that was published after the HTA. Community acquired pneumonia (CAP) results are presented in the HTA based on a Eli Lilly submission, however the figures presented in the HTA and those in this paper differ slightly.

This analysis included 602 patients from the PROWESS RCT who had CAP and were admitted from home with ≤ 4 days in hospital (placebo n=278, rhAPC n=324). This is a retrospectively defined subgroup.

After adjusting for baseline differences the CAP group treated with rhAPC had an improved 28 day RR of death of 0.81 (95%CI 0.67,0.93) compared to the placebo group, as well as an improved in-hospital mortality RR of 0.76 (95%CI 0.60, 0.97).

Other analyses were performed looking at APACHE scores, vasopressor use, ventilator use and pneumonia severity index (PSI).

Significant improvement in RR of mortality was seen with the use of rhAPC in the CAP group with APACHE score ≥ 25 at 28 days (RR 0.60, 95%CI 0.44, 0.82), hospital discharge (RR 0.64, 95%CI 0.48, 0.85) and 90 day survival (RR 0.74, 95%CI 0.58, 0.95).

The CAP group using mechanical ventilation at baseline and treated with rhAPC had a significant improvement in 28 day mortality (RR 0.71, 95%CI 0.53, 0.96).

The CAP group with a PSI score of ≥ 4 and who were treated with rhAPC had a significant improvement in 28 day mortality (RR 0.72, 95%CI 0.55, 0.93) and at hospital discharge (RR 0.77, 95%CI 0.60, 0.97).

Risk of bleeding was reported to be similar to that of the overall PROWESS trial population but no data were reported.

Appendix D Critical appraisal of study reporting ADDRESS data

Abraham et al (2005)

Characteristics:

Study Type	N (total)	Setting	Patients	Intervention	Comparison	Outcomes
RCT NHMRC level 2 evidence	2613	Multi-centre trial in 516 centres in 34 countries. Sept 2002 to Feb 2004.	Patients with: <ul style="list-style-type: none"> severe sepsis, defined as the presence of suspected or known infection, and a low risk of death 	rhAPC activated infusion at 24ug/kg body weight for a total of 96 hours. Other than the infusion there was no standard protocol for care.	Placebo infusion for a total of 96 hours Other than the infusion there was no standard protocol for care.	Mortality at 28 days from any outcome, adverse events and various laboratory variables. In-hospital mortality within 90 days of start of infusion.

Quality:

Specified inclusion/ exclusion criteria	Mostly	Inclusion and exclusion criteria specified, however there is variation between centres in definition of 'low risk of death'. This is generally defined by an Acute Physiology and Chronic Health Evaluation II score of <25 or single organ failure, however there was substantial variability.
Adequate method of randomisation	Yes	Block randomisation stratified according to site and also within site according to whether it was intended patient would also be receiving low dose heparin for prophylaxis against DVT. They do not state if randomisation was performed centrally.
Concealment of allocation	Unclear	Concealment of allocation is not described.
Groups similar at baseline	Yes	Baseline characteristics were very similar; however patients receiving rhAPC were slightly more likely to have 2 dysfunctional organ systems (26.7% vs 23.1%).
Blinding - patients/ investigators/ assessors	Yes	Patients, investigators and others involved in conducting the study remained blinded to treatment assignment for the duration of the study. All delivery systems for the study drug were covered to ensure blinding. The protocol allowed for un-blinding and administration of rhAPC at the physician's discretion if the patient's disease progressed. This occurred in 47/1297 of placebo group and 39/1316 of intervention group. Un-blinding was necessary so that the correct amount of infused rhAPC was given.
Duration of follow-up	Yes	The primary outcome was mortality at 28 days. Patients still hospitalised at 28 days were followed to hospital discharge or 90 days, whichever came first, and follow-up for survival at one year was continuing.
Proportion lost to follow up	Yes	Small numbers lost to follow up or withdrew consent. 10/1307 in the placebo group and 17/1333 in the intervention group.

Objective & independent assessment of outcomes	Yes	Though death is an objectively determined outcome, bleeding events are not well defined and may be subjective.
Inclusion of all subjects in analysis	Yes	2640 patients randomised, 2613 analysed. Those who did not receive an infusion of placebo or rhAPC and those who were un-blinded to received active drug were analysed in the groups to which they were randomised. Those lost to follow-up or who withdrew consent (10/1307 in placebo and 17/1333 in intervention) were not included in analysis.
Other comments:		This RCT was funded by Eli Lilly and Company who manufacture rhAPC and the article written by employees of the company and others who had received research and other funding from Eli Lilly and other pharmaceutical companies.
Results:		
<p>This study planned to enrol 11,444 patients which allowed a 90% power to detect a significant difference between the two groups with a two-sided p value of 0.05. This assumed mortality rates of 20% in the placebo group and 16% in the intervention group and allowed for 20% of placebo patients to have disease progression and switch to active treatment.</p> <p>Three interim analyses were planned with allowance for other interim analyses as requested by the data-monitoring committee. At the second interim analysis the data-monitoring committee recommended early termination of the trial as there was <5% chance of demonstrating a significant reduction in mortality and there was a concern about the increased risk of bleeding in the rhAPC group. This was a pre-determined stopping point.</p> <p>Data was analysed for 1297 placebo patients and 1316 intervention patients. Although the trial was designed to primarily recruit patients with single organ dysfunction, approximately one third of participants had multiple organ dysfunction.</p> <p><u>Efficacy</u></p> <p>There was no significant difference between groups in 28 day mortality or in-hospital mortality. Note that the mortality rate was non-statistically significantly lower in the placebo group (17% vs 18%, p=0.34) and because the trial was stopped early this data cannot rule out the possibility that rhAPC was associated with increased mortality.</p> <p>Subgroup analysis showed no significant difference in mortality when adjusted for APACHE II score, single or multiple organ dysfunction, recent surgery (within 30 days of enrolment) or use of heparin at baseline. However surgical patients with single organ dysfunction receiving APC had significantly higher 28 day mortality rates than those receiving placebo (20.7% vs 14.1%, p=0.03).</p> <p><u>Safety</u></p> <p>The rate of serious bleeding was significantly higher in the intervention group than in the placebo group both during infusion (2.4% vs 1.2%, p=0.02) and during the 28 day study period (3.9% vs 2.2%, p=0.01).</p> <p>There were also significantly more bleeding events in the subgroup of recent surgical patients with one dysfunctional organ system both during the infusion (10.3% vs 5.1%, p=0.01) and during the 28 day study period (10.9% vs 6.1%, p=0.03).</p> <p><u>Conclusion</u></p> <p>The authors concluded that APC 'should not be used in patients with severe sepsis who are at low risk of death, such as those with single-organ failure or an APACHE II score of less than 25'.</p>		