Activated protein C and septic shock: A propensity-matched cohort study

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Background

- PROWESS study- phase III rct NEJM -2001 – showed reduced 28 day mortality in severe sepsis by 6.1% (30.8% vs 24.7% p= .005)
- APC was approved by FDA to use in patients with severe sepsis at high risk of death.
- 90 day follow-up data from the original trial failed to demonstrate a sustained benefit
- ADDRESS study(N Engl J Med 2005)- APC in sepsis with low mortality risk showed no significant difference in 28-day mortality.

- RESOLVE study(Lancet2007)- APC in cildren was stopped early after a second interim analysis suggested little benefit
- PROWESS-Shock(NEJM 2012) mortality rates of 26.4% in study group and 24.2% in control group
  - The drug was voluntarily removed from the worldwide market on October 25, 2011

- This study was conducted to determine the effectiveness of rhAPC and to identify possible reasons for the divergent results of previous trials.
- Retrospective, 2:1 propensity-matched, multicenter cohort study.
- Twenty-nine academic and community intensive care units in three countries.

- **Data Source and Study Population**
  - The Cooperative Antimicrobial Therapy of Septic Shock Database
  - Admitted to an intensive care unit (ICU) between 1997 and 2007 with a diagnosis of septic shock

Outcome Measures

- The primary outcome:
  - Mortality over 30 days
  - Mortality stratified by APACHE II quartile
- Secondary outcomes:
  - ICU and hospital mortality
  - lengths of stay
  - ventilator-free days,
  - Mortality stratified by time to appropriate antimicrobials and the type of infection
  - Mortality stratified by the number of organ failures on day 1 of ICU admission.

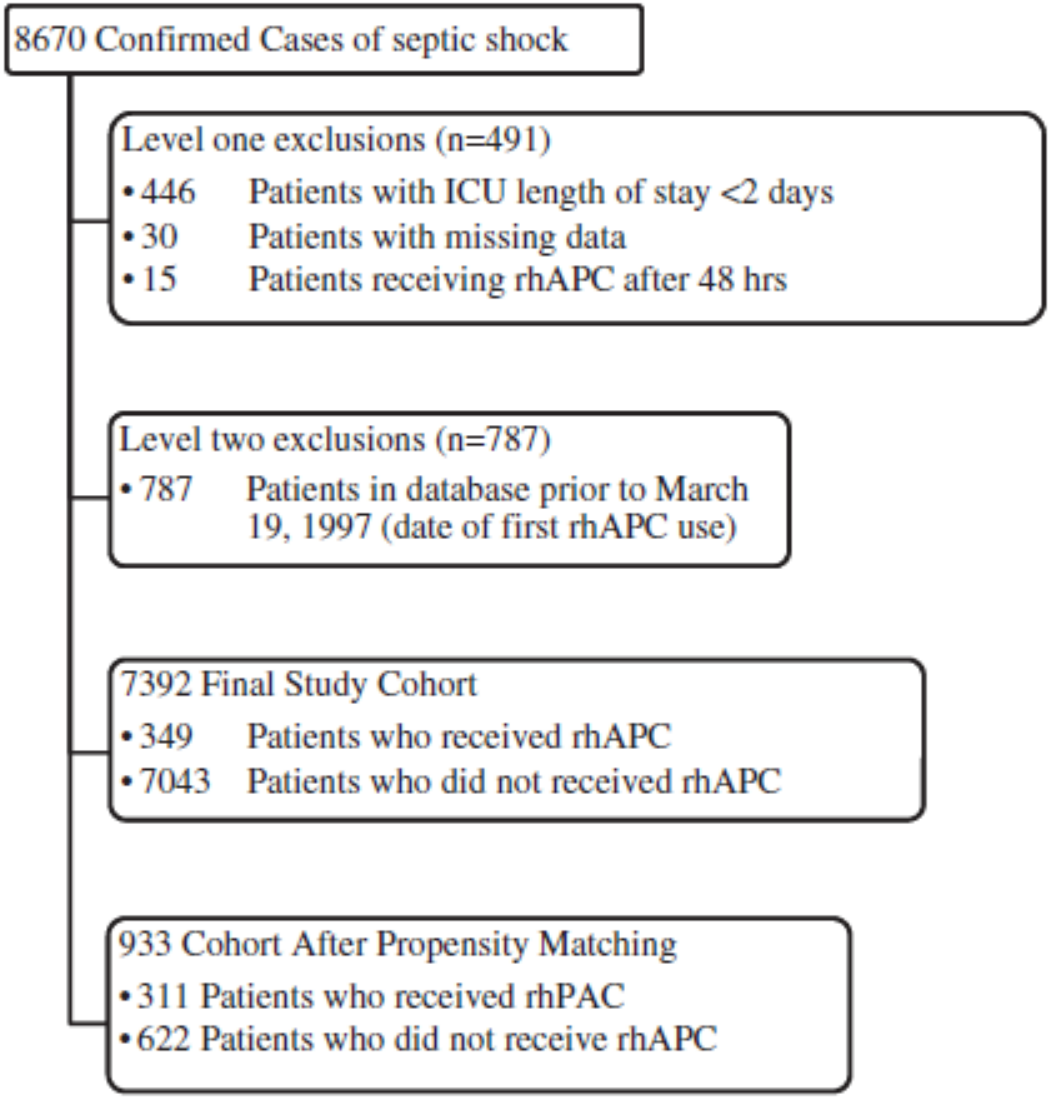


Figure 1. Patient flow through study. *ICU*, intensive care unit; *rhAPC*, recombinant human activated protein C.

- Propensity-matched analysis was undertaken for several reasons:
  - To account for the nonrandom assignment of rhAPC,
  - To mitigate potential confounding factors and selection biases,
  - and to increase statistical efficiency.
- To increase the power of the analysis, propensity matching was done using a 2:1 matching procedure where each patient of rhAPC was matched to two controls
- Mortality over 30 days was evaluated using Cox proportionalhazard model

Results:

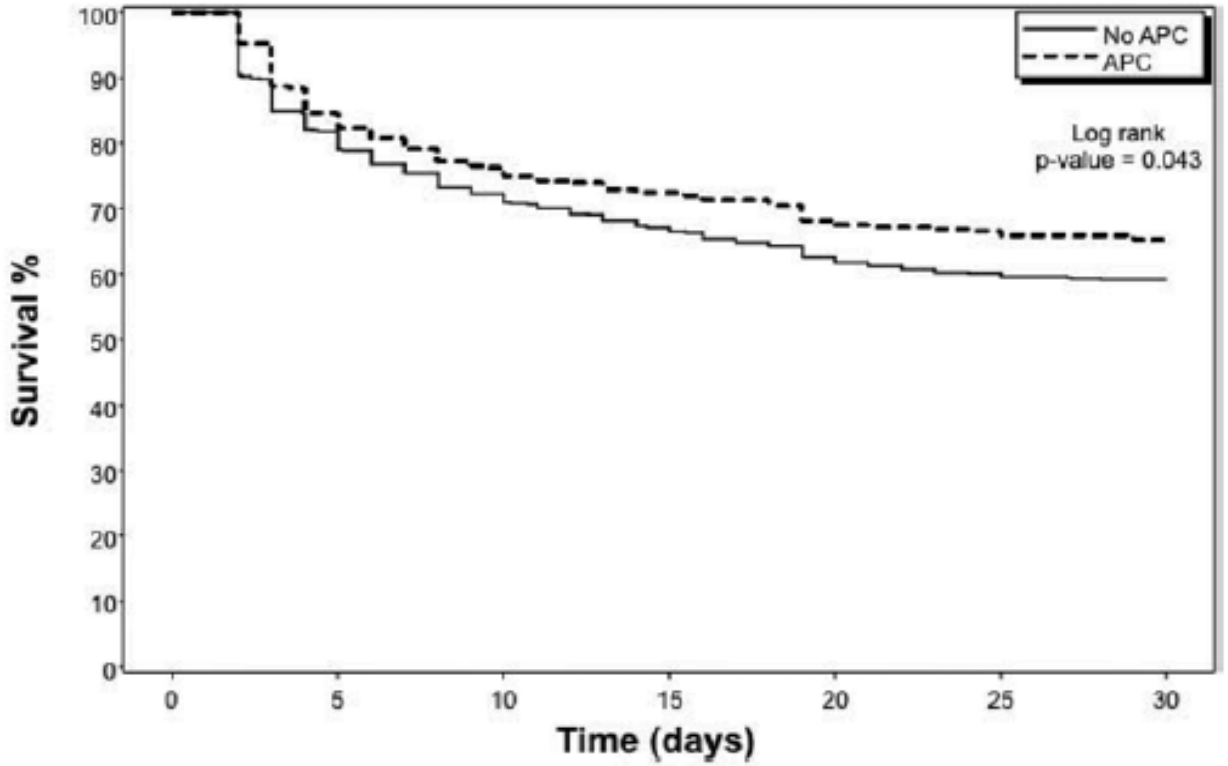
- The mean APACHE II score in both rhAPC and control group was 26.0
- The median time to first appropriate antimicrobial after documented hypotension was 3.8 hrs in the rhAPC group and 4.3 hrs in the control group.
- The mean number of organ failures in day 1 of ICU admission was 4.2 in rhAPC group and 4.3 in the control group

- Significant reduction in mortality over 30 days (108/311 [34.7%] vs. 254/622 [40.8%])
- Subgroup analysis revealed nonsignificant reductions in mortality among all APACHE II quartiles
- Significant reductions in both ICU *hospital* mortality
- A time to event analysis showed that the time to appropriate antimicrobials after documented hypotension decreased for each year of study
- The use of rhAPC was associated with an increase in ICU length of stay (8/7 days) *and a trend toward* increased hospital length of stay (18/16 days)
- No difference in ventilator-free days.

Table 3. Mortality over 30 days

Septic Shock Cohort	Sample Size n	Mortality Rate by Recombinant Human Activated Protein C Status No. of Deaths/Total No. of Patients (%)		Hazard Ratio (95% Confidence Interval)	p
		Recombinant Human Activated Protein C	Control		
Unadjusted[a]	7392	118/349 (33.8%)	3017/7043 (42.8%)	0.75 (0.62, 0.90)	.002
Adjusted for propensity score[b]	933	108/311 (34.7%)	254/622 (40.8%)	0.72 (0.52, 1.00)	.05
Stratified 30-day mortality analysis in matched cohort (Acute Physiology and Chronic Health Evaluation II quartile)					
5–19	204	6/63 (9.5%)	31/141 (22.0%)	0.40 (0.17, 0.95)	.04
20–25	238	17/80 (21.3%)	49/158 (31.0%)	0.64 (0.37, 1.12)	.12
26–30	205	27/72 (37.5%)	53/133 (39.9%)	0.92 (0.58, 1.46)	.72
31–53	239	47/75 (64.0%)	111/164 (66.7%)	0.87 (0.62, 1.22)	.40

[a]Cox proportional hazard model on the unmatched cohort; [b]Cox proportional hazard model using a conditional, matched-pair analysis with a shared γ-frailty model.



# at risk							
No APC	622	509	450	418	390	374	368
APC	311	263	237	225	212	207	203

Figure 3. Adjusted Cox proportional hazard of mortality associated with recombinant human activated protein C (*APC*) in septic shock in the propensity-matched cohort.

Table 4. Secondary mortality outcomes

Propensity-Matched Septic Shock Cohort	Sample Size n	Mortality Rate by Recombinant Human Activated Protein C Status No. of Deaths/Total No. of Patients (%) Recombinant Human Activated Protein C	Control	Hazard Ratio (95% Confidence Interval)	*p*
Hospital mortality					
Adjusted for propensity score[a]	933	129/311 (41.5%)	294/622 (47.3%)	0.76 (0.57, 1.00)	.05
Intensive care unit mortality					
Adjusted for propensity score[a]	933	98/311 (31.5%)	232/622 (37.3%)	0.79 (0.63, 0.98)	.03
30-day mortality stratified by the delay (hours) between documented hypotension and first appropriate antibiotic					
0.00–1.99	217	18/70 (25.7%)	26/147 (17.7%)	1.53 (0.84, 2.78)	.17
2–5.99	211	22/82 (26.8%)	42/129 (32.6%)	0.76 (0.46, 1.28)	.30
6+	283	42/86 (48.8%)	124/197 (62.9%)	0.68 (0.48, 0.96)	.03
30-day mortality stratified by infection type					
Gram positive	305	35/101 (34.7%)	73/204 (35.8%)	0.93 (0.62, 1.39)	.71
Gram negative	303	33/101 (32.7%)	75/202 (37.1%)	0.86 (0.57, 1.30)	.48
Fungal	46	7/14 (50.0%)	22/32 (68.8%)	0.65 (0.28, 1.51)	.31
Culture negative	247	30/85 (35.3%)	73/162 (45.1%)	0.74 (0.48, 1.13)	.16

[a]Cox proportional hazard model using a conditional, matched-pair analysis with a shared γ-frailty model

Discussion

- This study showed mortality benefit with use of APC.
- There have been 2 other proensity matched analysis demonstrating similar benefit.
- But Prowess-shock study – a multinational phase lll RCT failed to show any difference, the possible reasons for this
  - Mortality of patients with septic shock has decreased since the initial PROWESS study (which recruited patients from 1998 to 2000)
  - Availability of of drug outside of a clinical setting: It is therefore possible that patients who were felt to benefit most from rhAPC received the drug off trial.

- Strength of the study:
  - All patients who received rhAPC during the study period were included
  - Use of a large multinational database that allowed for detailed modelling
- Limitations:
  - Retrospective study - unmeasured confounding variables may be present and cannot be accounted for
  - Use of propensity matching
  - Limited size
  - The lack of safety data including bleeding complications and transfusion requirements were not available

Conclusion

- Promising result of this and other propensity matched studies takes us back to 1990`s.
- There is room for further RCT and high chances of reintroduction of APC into clinical practice.