

Activated protein C-protein C inhibitor (APC-PCI) complex as a prognostic marker in sepsis

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Background

The PROWESS study and later trials of APC treatment in sepsis have shown only modest reductions in mortality. The recent Cochrane systematic review (CD004388) records doubtful efficacy and serious adverse effects. To optimize the benefit/risk ratio of APC treatment of each patient, a biomarker of protein C activation is urgently needed and the use of such a marker, APC-PCI, has been investigated in the present study.

Methods

APC-PCI was measured in acid citrate plasma by means of a newly developed sandwich ELISA (median normal value 0.13 ng/mL, range 0.07-0.26, n = 16). The low pH of the plasma prevents *ex vivo* formation of further APC-PCI.

Levels of APC-PCI and protein C were monitored (daily to alternate days) in 135 consecutive critically ill patients, 53 of whom had sepsis during the observation period. Four patients were excluded because of incomplete data. The state of protein C activation to APC was categorized as non-activated, moderately activated or highly activated, based on maximum APC-PCI values in relation to the normal range.

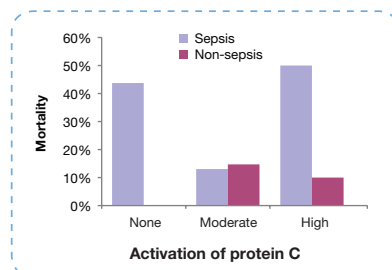
Results

Maximum APC-PCI values ranged from 0.03 to 29 ng/mL (median 0.44 ng/mL).

Overall mortality of the sepsis patients was 32% (17/53).

There was no correlation between maximum APC-PCI and minimum protein C levels in individual patients (Spearman coefficient 0.02, P 0.89).

Activation of protein C and mortality in ICU patients

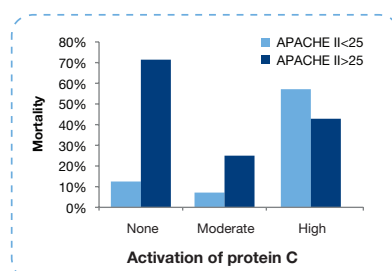


Patients with sepsis showed a bell-shaped mortality relationship with protein C activation, high mortality occurring in both the non-activated and highly activated groups. This relationship was not observed in the patients without sepsis, where no deaths occurred in the non-activated group.

Relative mortality (calculated separately for sepsis and non-sepsis patients) = (activation group mortality)/(overall mortality)

Protein C activation group	Non-activated APC-PCI <0.25 ng/mL		Moderately activated APC-PCI 0.25-0.72 ng/mL		Highly activated APC-PCI >0.72 ng/mL		P (χ^2)
	Mortality	Relative mortality	Mortality	Relative mortality	Mortality	Relative mortality	
Sepsis	43.8% (7/16)	136.4%	13.0% (3/23)	40.7%	50.0% (7/14)	155.9%	0.032
Non-sepsis	0.0% (0/14)	0.0%	14.7% (5/34)	143.4%	10.0% (3/30)	97.5%	0.311

Activation of protein C, APACHE II score and mortality in sepsis patients

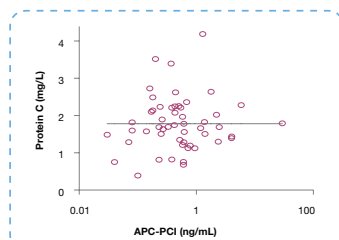


Patients with sepsis were subgrouped according to their APACHE II score (not available for 1 survivor and 1 non-survivor). Both absolute and relative mortalities were highest in the subgroup without protein C activation and APACHE II ≥ 25 .

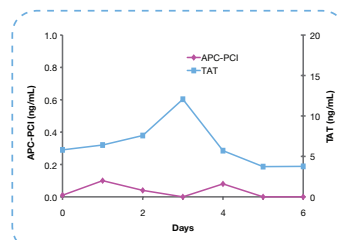
Relative mortality = (subgroup mortality)/(overall mortality for the sepsis patients)

Protein C activation group	Non-activated APC-PCI <0.25 ng/mL		Moderately activated APC-PCI 0.25-0.72 ng/mL		Highly activated APC-PCI >0.72 ng/mL		P (χ^2)
	Mortality	Relative mortality	Mortality	Relative mortality	Mortality	Relative mortality	
APACHE II ≥ 25	71.4% (5/7)	227.7%	25.0% (2/8)	79.7%	42.9% (3/7)	136.6%	0.1946
APACHE II < 25	12.5% (1/8)	39.8%	7.1% (1/14)	22.8%	57.1% (4/7)	208.2%	0.311

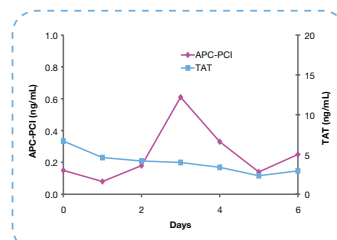
APC-PCI and TAT levels in individual sepsis patients



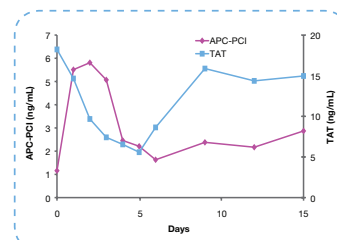
Scatter plot of minimum protein C values against maximum APC-PCI values



Low protein C activation
APACHE II: 29
Non-survivor



Moderate protein C activation
APACHE II: 29
Survivor



High protein C activation
APACHE II: 26
Non-survivor

Conclusion

The relationship between mortality and protein C activation differs in critically ill patients with and without sepsis. In sepsis patients, failure of protein C activation and high protein C activation are both associated with high mortality. Sepsis patients without protein C activation and an APACHE II score ≥ 25 have a particularly high mortality. Patients in this subgroup may be those who are most likely to benefit from APC treatment.