

## Commentary

# Activated protein C: cost-effective or costly?

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See related research by Dhainaut *et al.*, <http://ccforum.com/content/11/5/R99>

### Abstract

The authors offer a commentary on the study by Dhainaut *et al.* on the cost-effectiveness of activated protein C in severe sepsis. Using data from “real world” conditions, the results of this economic evaluation are consistent with previous analyses, and highlight the need for “real world” investigations of new health technologies in critical care.

Dhainaut and colleagues in the French study group PREMISS (Protocole en Réanimation Médico-économique d'une Innovation dans le Sepsis Sévère) report the results of the first economic evaluation of recombinant human activated protein C (APC) in patients with severe sepsis performed using “real world” effectiveness data [1]. Economic evaluations in critical care medicine are relatively new, but given the expense of health care within an intensive care unit (ICU), their use is likely to become more common [2]. The unique nature of this analysis is that it estimated effectiveness using “real world” patients treated before and after the availability of APC, rather than basing effectiveness on the findings of the study Protein C Worldwide Evaluation in Severe Sepsis (PROWESS), a randomized control trial (RCT) which was used for all previous economic evaluations of APC [4-8]. Although using a single RCT as the basis of an economic evaluation is common, this practice has been cautioned against [9,10], and as such, the results of this study are of interest.

The need for assessment of clinical and economic outcomes after the introduction of a novel therapeutic agent is increasingly supported [11]. Effectiveness studies, those which examine clinical outcomes outside the strict guidelines of RCTs, have been advocated by some as the most valid basis for economic evaluations [9] (though arguably only after

RCTs have confirmed medication efficacy). Studies like the present one are therefore important.

Dhainaut and colleagues prospectively collected clinical outcome data in patients with severe sepsis who were managed before and after the introduction of APC, with potential biases minimized through propensity score analysis. The authors found that although survival appeared better in patients managed with APC, the absolute benefit (3.3%) was lower than in the PROWESS study (6.5%) and was not statistically significant [1,3]. Despite matching patients using propensity score analysis, though, patients in this study treated with APC still had slightly higher organ failure scores ( $p = 0.067$ ), and this in part may explain the noted difference. Given that several experts have called into question the results of the PROWESS study and have argued for new clinical trials [12,13], it appears there is a role for generation of new clinical evidence.

Costs in their study were collected using microcosting methods, which are regarded as the most valid means of measuring health care costs [2]. Not surprisingly, given the cost of APC (€7,500 per treatment course), and the cost of managing additional survivors, the cost of caring for patients treated with APC was higher than for patients managed before APC, consistent with another French study which used data from the PROWESS study [8].

While this study is important, there are some methodological issues. First, it should be noted that performing an economic evaluation with effectiveness data taken exclusively from non-randomized studies can be problematic. In fact, readers should be cautious of economic evaluations that are based exclusively on non-RCTs, when RCT data is available, since

APC = activated protein C; ICU = intensive care unit; PREMISS = Protocole en Réanimation Médico-économique d'une Innovation dans le Sepsis Sévère; PROWESS = Protein C Worldwide Evaluation in Severe Sepsis [study]; RCT = randomized control trial.

non-randomized studies typically overestimate the effectiveness of an intervention, thus biasing the analysis in favor of the intervention. Other issues include the fact that the PREMISS study was powered to calculate differences in cost between the pre- and post-launch phases of APC [1], but was underpowered for assessing differences in effectiveness. Despite that, the authors base effectiveness estimates exclusively on their cohort data, without considering sensitivity analyses using PROWESS data. One last issue was that clinical outcomes were not discounted, which would be favorable to APC – these should have been tested with sensitivity analysis.

All in all, the results of this study are consistent with previous economic evaluations, and the methodological biases inherent in this study appear to balance themselves out. The results appear to confirm that the use of APC in the “real world” is associated with a cost effectiveness ratio in the range of other funded interventions [2]. It is reassuring to note that ICU physicians in this study appeared to be using this expensive medication in a cost-conscious manner, restricting its use to those patients with the greatest capacity to benefit (that is, patients with high organ failure scores who have a reasonable life expectancy if they survive their episode of sepsis). Despite that, though, the use of APC is still associated with a large cost that may not be affordable within all health care systems. When determining whether to fund APC, the opportunity cost of this intervention must be considered in relation to other interventions that are not currently funded.

We are entering a new era in health care. While physicians have been used to prescribing medications and offering interventions without consideration of cost, this is unlikely to continue given the rising cost of therapies. Whether an intervention provides “value for money” will become more important, particularly for expensive medications like APC (where its cost is noted to approximate a physicians’ monthly salary). Studies such as the one by Dhainaut and colleagues will help decision-makers determine the best use of APC. This study is also a good example of a “phase 4” economic evaluation, though it is best interpreted in the context of the existing randomized trial and economic evaluations.

### Competing interests

The authors declare that they have no competing interests.

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