

Has the prognosis of septic patients improved over time?

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Sepsis is one of the leading causes of death in hospitalised patients worldwide. It causes more casualties than prostate cancer, breast cancer and HIV/AIDS combined.¹ Over the last decades multiple clinical trials searching for an effective pharmacological treatment for sepsis have failed to identify 'a magic bullet' that significantly improves the outcome in patients suffering from sepsis. Moreover, several interventions that appeared to exert beneficial effects were not confirmed to be effective in randomised controlled trials.²⁻⁴ It seems that sepsis suffers from more negative clinical trials than any other disease. Yet, despite the absence of a single effective treatment, in March of this year Kaukonen and co-workers published a retrospective, observational study in which they reported an overall decrease in sepsis mortality in Australia and New Zealand.⁵ Over one decade, in 171 participating ICUs, more than 100,000 patients were included. In more detail, absolute mortality in severe sepsis patients decreased from 35.0% in 2000 to 18.4% in 2012. This represents an overall decrease in mortality of 16.7%, with a gradual decline in mortality of 1.3% annually. This is a compelling epidemiological study and on first sight one may conclude that the prognosis for sepsis patients has improved considerably. However, caution is needed in the interpretation of observational studies. Several other possible explanations of the observed effects need to be addressed. Similar to discussions related to population-wide screening for cancer, increased awareness may also lead to an earlier diagnosis for sepsis patients. The subsequent less advanced disease may suggest a better survival time (and thus lower mortality), while this may not be truly the case. Indeed, in Kaukonen's sepsis study, over time fewer patients suffered from concomitant respiratory failure (60 vs 37%) or renal failure (30 vs 25%), important covariates that are mostly present at ICU admission and are known to influence outcome. Also, according to the reported quartiles of APACHE III scores as a measure of their severity of illness, less sick patients were admitted to the ICU over time and the incidence of urosepsis (with a better prognosis than sepsis from other

sites of infection) increased. These differences in case mix may explain the observed improved outcome to an important extent and statistical adjustment for only APACHE score might be insufficient to correct for this. Of interest, the observed decrease in mortality was most pronounced in less severely ill, younger, urosepsis patients without other comorbidities. Moreover, a similar improvement in outcome was observed in non-septic ICU patients, suggesting that it is not a sepsis-specific treatment that accounts for the improvement, but possibly earlier referral to an ICU or an overall improvement of ICU quality of care over time. Nevertheless, while it remains unclear whether changes in case mix, changes in diagnostic procedures or improvements in the treatment of sepsis contribute to the decline in case fatality, similar mortality rates have been found in other recent sepsis studies. For example, Angus et al. recently reported a 60-day mortality of septic shock of approximately 20%.⁶

In the Netherlands, a significant improvement in compliance to the resuscitation bundle of the Surviving Sepsis Campaign between 2005 and 2009 was observed, associated with a decrease in mortality.⁷ Again, with the data available, it was not possible to adjust for other relevant covariates or patient characteristics. Recently, interesting data available from the Netherlands Intensive Care Evaluation database were reported.⁸ In this Dutch multicentre cohort study, a decrease in mortality of 5.8% over 3.5 years was found in sepsis patients in those hospitals that participated in the national surviving sepsis campaign. In hospitals that did not participate, or in patients who were not screened for sepsis, this improvement was not observed. So, in contrast to the Kaukonen study, the beneficial effect appears to be most pronounced in sepsis patients, and adjustments for age, gender, admission type, severity of illness and location of sepsis diagnosis were made. Also, reported severity of illness did not change significantly during the study period, suggesting that the observed change in outcome is not a result of earlier ICU admission. While a similar decrease in

sepsis mortality was observed as in the Kaukonen study, the additional finding of a clear association with adherence to the guideline bundles is of importance. Even more so, adherence to the resuscitation bundle was not associated with the observed decrease in mortality, in accordance with the recent ProCESS trial,⁶ while adherence to the management bundle was. This strongly suggests that predominantly ICU treatments for sepsis patients are beneficial. Taken together, these studies indicate that the prognosis of sepsis is slowly, but steadily, improving.

In summary, the steady decline of mortality rate indicates that a single sepsis-specific therapy does not account for the improved prognosis of sepsis patients over time. It appears that both improved awareness and screening of sepsis, as well as improved general ICU quality of care, account for the observed improvements in outcome. While some may be disappointed that the quest for the 'magic bullet' has not yet been successful, the observation that good clinical care has a major clinical impact is definitely reassuring.

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Op de website van de vereniging (www.nvic.nl) vindt u de instructie voor het inzenden van het onderzoeksvoorstel. Alleen onderzoeksvoorstellen die voldoen aan het genoemde format, zullen in behandeling worden genomen. Uw onderzoeksvoorstel kunt u mailen naar secretariaat@nvic.nl. De deadline voor het indienen is 1 september 2014. De organisatie en jurering is in handen van de NVIC Congrescommissie.

