BMJ 2016;353:i2735 doi: 10.1136/bmj.i2735 (Published 17 May 2016)

EDITORIALS

Late mortality after sepsis

Downstream effects of sepsis include unexplained late deaths

Stephen J Brett *consultant in intensive care medicine*

Centre for Perioperative Medicine and Critical Care Research, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London W12 0HS, UK

A new series of definitions of sepsis[1] along with simple guidance for early diagnosis has recently been published, and a NICE guideline is due shortly.[2] Sepsis is an extreme manifestation of the body responding to a severe infection—in part adaptive and protective, but potentially maladaptive and life threatening. Naturally, perhaps, the focus has been on early diagnosis and management. This is not always performed well, as highlighted by a 2015 report from the UK National Confidential Enquiry into Patient Outcome and Death.[3] In a linked paper, Prescott and colleagues (doi:10.1136/bmj.i2375) report that patients who survive an episode of sepsis have a significant excess risk of mortality for a prolonged period of time.[4] In the past, staff working in intensive care units discharged patients to the rest of the hospital with a feeling of a job well done; somehow that part of the patient's journey had come to an end and recovery was about to begin. Since then numerous publications have challenged this optimistic assumption. For substantial numbers of patients, leaving the intensive care unit does not represent the end of something, rather it represents the start of something else, often not anticipated by them or understood by others. Many studies have described the difficulties sustained by patients and of course their families. Such difficulties include loss of muscle mass and strength,[5] cognitive dysfunction, anxiety and depression,[6] and post-traumatic stress.[7] Along with this come challenges, both medical and financial, for those who become informal caregivers.[8 9] In the UK this has been addressed, at least in ambition, with the publication of NICE guidelines for rehabilitation after critical illness.[10]

Prescott and colleagues conducted a detailed study exploring whether there is an extra burden of risk of mortality for survivors of sepsis from a large well established cohort of retirees in North America. The authors used a series of comparisons between different populations, using a propensity score to adjust for obvious confounding factors. For many of us, propensity based analyses seem to be something of a leap of faith. Superficially, they aim to recreate the conditions (well matched groups) and unbiased outputs of a trial, under circumstances in which a trial would not be possible. These investigators used propensity adjusted comparisons derived from the background characteristics of plausible comparator groups: patients not in hospital; patients in hospital with inflammatory but non-infective disease; and patients in hospital with infection but non-septic disease. They identified an additional burden of mortality associated with sepsis that persists into longer term recovery for up to at least two years.

Though it is always possible that some unidentified confounder has contributed to an inaccurate result, it is difficult to see how this particular research question could have been approached in an alternative or more rigorous way. There are of course several important unanswered questions. Does this apparent late risk of mortality extend to patients aged under 65? What are the mechanisms? From what do people actually die? Finally, what could be done to ameliorate this excess risk? The paper contains some intriguing data on "terminal admissions," which seemed dominated by diagnoses related to infection; sepsis can reappear in people whose constitution has been eroded by previous critical illness.[11]

Those of us who see many patients in follow-up after a period in intensive care are often impressed by how resilient many individuals seem. However, we also see many people whose general robustness seems seriously diminished and who apparently lack the necessary strength to withstand any further major challenges to their health. Such individuals commonly require substantial amounts of assistance with activities of daily living, have a reduced quality of life, and do not seem to have the necessary capacity to recover their pre-illness functional status. The authors speculate that accelerated cardiovascular pathology could be a contributing factor. This is certainly plausible, as is the potential contribution of a persistent inflammatory (and possibly immunosuppressed) phenotype.[12]

What should we do with this new information? Perhaps we need to educate healthcare professionals in both primary and secondary care, along with patients and the wider public, about these downstream effects of sepsis, in a similar way to the educational efforts currently being expended on presentation and early treatment[2] (www.sepsistrust.org). Prescott and colleagues have done well to identify this issue from a system

Correspondence to: stephen.brett@imperial.ac.uk

not prospectively designed for this purpose. With several "big data" initiatives developing, and the potential to link data on acute illness with future community healthcare information, we might soon be in a position to set up prospective registries of critical illnesses such as sepsis and hence understand the long term risks in more detail.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Shankar-Hari M, Phillips GS, Levy ML, et al. Sepsis Definitions Task Force. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:775-87. doi:10.1001/jama.2016.0289 pmid:26903336.
2 National Institute for Health and Care Excellence. Sepsis: the recognition, diagnosis and management of sepsis. 2016. https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0686/documents.
3 National Confidential Enquiry into Patient Outcome and Death. Just say sepsis! A review of the process of care received by patients with sepsis. 2015. http://www.ncepod.org.uk/2015report2/downloads/JustSaySepsis_FullReport.pdf.
4 Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. *BMJ* 2016;353:i2375.
5 Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA* 2013;310:1591-600. doi:10.1001/jama.2013.278481 pmid:24108501.
6 Sukantarat KT, Burgess PW, Williamson RC, Brett SJ. Prolonged cognitive dysfunction in survivors of critical illness. *Anaesthesia* 2005;60:847-53. doi:10.1111/j.1365-2044.2005.04148.x pmid:16115244.
7 Wade DM, Howell DC, Weinman JA, et al. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. *Crit Care* 2012;16:R192. doi:10.1186/cc11677 pmid:23068129.
8 Griffiths J, Hatch RA, Bishop J, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. *Crit Care* 2013;17:R100. doi:10.1186/cc12745 pmid:23714692.
9 Cameron JI, Chu LM, Matte A, et al. RECOVER Program Investigators (Phase 1: towards RECOVER) and the Canadian Critical Care Trials Group. One-Year Outcomes in Caregivers of Critically Ill Patients. *N Engl J Med* 2016;374:1831-41. doi:10.1056/NEJMoa1511160 pmid:27168433.
10 National Institute for Health and Care Excellence. Rehabilitation after critical illness in adults. 2009. https://www.nice.org.uk/guidance/cg83.
11 Shen HN, Lu CL, Yang HH. Risk of recurrence after surviving severe sepsis: a matched cohort study. *Crit Care Med* 2016; [Epub ahead of print]. doi:10.1097/CCM.0000000000001824 pmid:27120256.
12 Griffith DM, Lewis S, Rossi AG, et al. RECOVER Investigators. Systemic inflammation after critical illness: relationship with physical recovery and exploration of potential mechanisms. *Thorax* 2016;thoraxjnl-2015-208114.pmid:27118812.