Long term mortality following sepsis

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The consequences of sepsis extend well beyond the acute illness which required admission to the critical care unit. It is well established that that there is increased late mortality following a hospital admission for sepsis. The cause for this increased late mortality has been disputed, multiple observational studies have aimed to examine whether this risk is associated with pre-existing poor health, or if there is an underlying pathobiological mechanism occurring with sepsis that increases late mortality independent of baseline health.

The observational cohort study published by Garland *et al*. (1) looked to identify which determinants were responsible for short-term and long-term survival in adult patients admitted to intensive care units. They found that with respect to long term mortality i.e., post 90-day mortality the most important determinants were age and co-morbidity, characteristics of the acute illness came a distant third (one major limitation of this study however is that it assessed unselected patients admitted to intensive care units, without specific focus on sepsis).

In the observational study published by Clermont *et al*. (2) over one thousand three hundred patients with community acquired pneumonia were evaluated to determine if acute organ dysfunction (within first 30 days) was associated with 90-day survival, the authors of this study concluded that whilst acute organ dysfunction is associated with late mortality in patients with community acquired pneumonia, their risk is related to poor baseline status rather than the acute dysfunction. Shankar-Hari *et al*. (3) conducted a systematic review to examine evidence of a causal link between sepsis and long-term mortality. This review of included literature concluded that the hypothesis that sepsis exerts an independent and causal effect on post-acute mortality lacks conclusive evidence, the few studies upon which this is based have inadequately adjusted for confounding variables such as age, effect of co-morbidity, and functional status following resolution of the acute episode.

On the opposite side of the debate there have been numerous studies which argue that sepsis in and of itself confer an increased risk of long term mortality independent of baseline health. Leibovici *et al*. (4) looked at long term survival following severe infection whereby adult patients with confirmed bacteremia or fungemia were compared with a control group without any infectious issues, matched for age, sex, and underlying co-morbidities, this study found a significantly higher 1- and 4-year mortality, and shorter median survival in the bacteremia group compared to the control group. With respect to patients with bacteremia this study identified numerous risk factors significantly and independently associated with mortality, including septic shock, inappropriate empirical antibiotic therapy, nosocomial infection, serum creatinine, functional class, serum albumin, age, and malignancy. The authors of this study concluded that patients with bacteremia as well having a higher short term-mortality compared to matched non-infectious patients, also had significantly reduced rates of long term survival with numerous risk factors identified relating to both features of the acute illness as well as baseline functionality.

The cohort study by Quartin *et al*. (5) looked to determine the effect of sepsis on patients long term mortality, like the previous study septic patients were matched to non septic patients with similar baseline health, it found that the septic group had significantly higher mortality from non septic aetiologies, predictably

it also found that the risk of long term mortality rose with increasingly severe sepsis. The authors concluded that an episode of sepsis increase mortality for up to 5 years after the septic episode independently of patient baseline medical morbidities, and that 1-year mortality is correlated with the severity of the acute sepsis. Linder *et al*. (6) looked at long term mortality in young healthy patients with severe sepsis/septic shock compared to those with non septic critical illness. When comparing young (less than 60 years) patients with no co-morbidities. The study concluded that those with severe sepsis/shock had a significantly higher 1- to 10-year mortality compared to both the non septic critical illness group, and the general population from which these cohorts were derived, interestingly the authors from this study suggested that a severe septic illness was equivalent to adding 14 years onto your life in terms of increasing mortality greater than that expected for age. The results of this prospective cohort study suggested that the impact of severe sepsis/septic shock on long term mortality was greatest in patients with no or minimal co-morbidities as well as in those patients aged under 60 years. The authors went on to hypothesize the causes of this increased long term mortality following an acute septic episode and concluded that persistence of organ system dysfunction, with or without chronic immunological dysfunction was most likely.

When trying to explain the more significant effect of sepsis on long term mortality in younger patients; the hyperimmune response and greater procoagulant effect of sepsis seen in younger peoples was thought responsible. Both these factors are believed to persist longer in younger patients and hence associated with greater long term mortality. Another feature of this study was to suggest that the causative organism—gram +ve bacteria in this case may also affect long term mortality following sepsis. Whilst the authors concluded that severe sepsis/septic shock is an independent risk factor for increased long term mortality, and theorised as to why that may be the case, they conceded that further research is required to determine the underlying pathobiological mechanism for this phenomenon.

Wang *et al*. (7) in their longitudinal population-based cohort study evaluated long term mortality following an episode of community acquired sepsis. In this study patients were observed for a period lasting on average just over 6 years, and mortality at 1-, 2-, and 5-year intervals for septic and non-septic patients alike were determined, the results showed that there was significantly increased mortality for septic patients at all intervals compared to the non septic cohort, even when baseline co-morbidities were accounted for. This study like the ones above adjusted for the wide range of potential confounders in each patient cohort and as such could reasonably conclude that the increased mortality with sepsis could not be explained by more severe baseline co-morbidities/impaired functional status.

In a recently published paper Prescott *et al*. (8) explained an observational matched cohort study which looked to determine if late mortality following sepsis is predominantly explained by pre-existing comorbid pathology or if sepsis itself is responsible for the increased mortality via a pathobiolgical process. In this study late mortality was taken to be 31 days to 2 years, patients with sepsis were matched to three control groups; adults not currently in hospital, patients in hospital with an acute sterile inflammatory process, and lastly patients with non-sepsis infection, patients in each group were matched on the basis of baseline characteristics. The results from this study showed a significantly increased risk of late mortality in the sepsis group compared to the three control groups. As in previous studies late mortality was higher in patients with more organ dysfunction during the acute septic episode. This study like previous ones highlighted that the excess late mortality following an acute episode of sepsis cannot be explained baseline health status and levels of functionality. This study like previous ones identifies the potentially modifiable status of late mortality following sepsis, as this study suggests that late mortality from sepsis is not explained by pre-existing co-morbidities and as such, aggressive and targeted treatment during, and after the acute illness could lead to a potentially significant mortality reduction.

All these cohort studies establish a link between sepsis and increased long term patient mortality whilst still not offering a clear explanation for an underlying pathobiological mechanism responsible for the increased mortality. Numerous animal studies have attempted to elucidate a biological mechanism for the increased mortality following sepsis. Kaynar *et al*. (9) looked at the effects of intra-abdominal sepsis on atherosclerosis in mice. Using caecal ligation and perforation as a model of intra-abdominal sepsis was found to accelerate atheroma formation in test subjects, and was proposed to resemble observations seen in the human patient population, Benjamim *et al*. (10) looked at the cellular and molecular mechanisms which dictate longer term sequel of sepsis and related lung injury, again using the caecal ligation perforation model of experimental sepsis this study shows increased susceptibility to a fungal

infection, the authors proposed that the lungs become predisposed to nosocomial infections for extended periods of time after severe sepsis, and this is related to changes in expression of inflammatory mediators which could explain the period of immunosuppression following severe sepsis. It is known that patients have an increased morbidity and mortality (cardiovascular events, repeat infections) following hospitalisation for community acquired pneumonia. In a prospective cohort study by Yende *et al*. (11) the authors sought to establish if persisting inflammation following respiratory sepsis was associated with longer term outcomes, they found that higher circulating levels of IL-6 and IL-10 at hospital discharge were associated with an increased risk of mortality from cardiovascular disease, cancer, infections, and renal failure.

There are significant long term implications following septic illness. What these studies highlight is that there is increased long term mortality associated with sepsis that cannot be explained by pre-existing factors such as medical co-morbidities, age, and functional status. The existence of an independent pathobiological septic process has been proposed by numerous studies (8,12) and has been extensively investigated using animal models of sepsis, which would seem to suggest a pro-inflammatory model of accelerated atherosclerosis and chronic immunosuppression. This suggests that earlier aggressive management of sepsis together with longer term emphasis on rehabilitation following sepsis could lead to a significant reduction in long term mortality.

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Footnote

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