Proinflammatory cytokines levels in sepsis and healthy volunteers, and tumor necrosis factor-alpha associated sepsis mortality: A systematic review and meta-analysis

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Abstract

Background

Sepsis is a global health challenge associated with significant morbidity and mortality. Detrimental sepsis effects are attributed to excessive inflammation or a "cytokine storm." However, anti-inflammation therapies have failed to lower sepsis mortality. We aim to characterize levels of key inflammatory cytokines in patients with sepsis and compare levels with those in healthy individuals and relate tumor necrosis factor (TNF) α levels to patient characteristics and outcomes.

Methods

We performed a systematic review and meta-analysis. Medline, Embase, Cochrane Library, and Web of Science Core Collection databases were searched between 1985 and May 2020. Analysis was restricted to studies in English. We included randomized controlled trials (RCTs), controlled trials, cohort studies, case series, and cross-sectional studies that reported mean levels of cytokines in the circulation thought to be relevant for sepsis pathogenesis. We also evaluated concentrations of these cytokines in healthy individuals. The Quality in Prognosis Studies tool was used to assess the methodological quality of included studies. We extracted summary data from published reports. Data analyses were performed using a random-effects model to estimate pooled odds ratios (OR) with 95% confidence intervals for cytokine levels and mortality. This systematic review is registered in PROSPERO (CRD42020179800).

Findings

We identified 3654 records, and 104 studies were included with a total of 3250 participants. The pooled estimated mean TNFα concentration in sepsis patients was 58.4 pg/ml (95% Confidence Interval or CI 39.8–85.8 pg/ml), and in healthy individuals was 5.5 pg/ml (95% CI 3.8–8.0 pg/ml). Pooled estimate means for IL-1β and IFN-γ in sepsis patients were 21.8 pg/ml and 63.3 pg/ml, respectively. Elevated TNFα concentrations associated with increased 28-day sepsis mortality ($p = 0.001$). In subgroup analyses, we did not detect an association between TNFα levels and sepsis source, sepsis severity, or sequential organ failure assessment (SOFA) score. A TNF-α cutoff level ≥14.7 pg/ml separated sepsis patients from healthy individuals with a sensitivity of 82.6%, a specificity of 91.7%, and a likelihood ratio of 9.9.

Interpretation

Sepsis mean TNFα concentration is increased approximately 10-fold compared to mean concentration in healthy individuals, and TNFα associated with sepsis mortality but not sepsis severity. The concept that elevated cytokines cause sepsis should be revisited in the context of these data.