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The role of the innate immune response in hospital- versus community-acquired infection in febrile medical patients

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Summary
Objectives: To study the role of the innate immune response in the higher mortality of hospital- than of community-acquired infections, in febrile medical patients.
Methods: We studied presumably immunocompetent patients with new-onset fever and a clinically presumed focus of infection ($N = 212$) at a university department of internal medicine. Clinical and microbiological data were collected for 2 days from inclusion, and circulating complement activation product C3a, secretory phospholipase A_2, interleukin (IL)-6, procalcitonin, and elastase-α_1-antitrypsin were measured. Patients were followed for septic shock and outcome, up to a maximum of 7 and 28 days after inclusion, respectively. Infection was considered hospital-acquired if it developed at least 72 h after admission.
Results: Fifty-four patients had hospital-acquired infections and 158 had community-acquired infections, with septic shock and mortality rates of 15% and 24%, and 4% and 6% ($p = 0.001$), respectively. Bloodstream infection predisposed to septic shock and the latter predisposed to death. Bloodstream infection was relatively more common in septic shock originating from community-acquired infection and was associated with an innate immune response in both hospital- and community-acquired infection, as judged from circulating immune variables. In contrast, circulating C3a, IL-6, and procalcitonin were more elevated when septic shock developed following hospital- than community-acquired infection, independent of infectious focus. The levels of C3a, secretory phospholipase A_2, IL-6, and elastase-α_1-antitrypsin were more elevated in ultimate non-survivors than in survivors in both infection groups.
Conclusions: The data suggest that rates of septic shock and mortality from hospital- vs. community-acquired infections in febrile medical patients are not increased by impaired innate immunity. In contrast, proinflammatory factors may be particularly useful to predict a downhill course in hospital-acquired infections.

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Introduction

A better understanding of the mechanisms leading to mortality during hospital-acquired infections may have important preventive and therapeutic implications. Indeed, hospital-acquired infections are increasingly common and may affect medical patients almost as often as surgical ones, even though the latter have been studied more often.[1–6] According to the literature, in studies mainly using non-infected controls for comparison, risk factors include (intravascular) devices, interventions, and other external and patient-related factors.[2,6–9] Hospital-acquired infections carry a higher mortality rate than community-acquired infections, and contributing factors include underlying disease, bloodstream infection, and associated septic shock.[2,3,6,7,9–11]

Even though hemato-oncologic disease and the use of cytostatic drugs are well known to lead to immunocompromise in the host, with an increased susceptibility to fatal infections in the hospital, the role of innate immunity in hospital- vs. community-acquired infections and the effect on outcome are unclear in presumably immunocompetent patients.[2,8] The innate immune response to infection involves various cellular and humoral effector mechanisms, which are reflected by changes in circulating levels of a variety of mediators, including complement activation products, cytokines, lipid mediators, procalcitonin, and neutrophil degranulation products.[1,3,12–32] Indeed, plasma levels of these factors may aid in predicting bloodstream infection, septic shock, and mortality from microbial infections even though their value varies among studies.[1,3,4,7,12–27,29–32] Some of the studies have been performed on predominantly hospital- or intensive care unit-acquired infections,[1–3,13–15,19,21,22,24,27] on community-acquired infections treated in the hospital,[16,18,23,25,26,29,31,32] or both,[17] and this difference might also explain some of the variation in results.[14]

We hypothesized that the development of septic shock and mortality are associated with innate immune suppression for a given clinical and microbiological focus, during hospital- vs. community-acquired infections, even in the prior immunocompetent host. Therefore, we prospectively studied the demographic, clinical, microbiological, and innate immunological characteristics of febrile medical patients with hospital- or community-acquired infections, in the absence of hemato-oncologic disease and cytostatic treatment.

Patients and methods

Patients

Three hundred consecutive patients with new-onset fever (body temperature $>38\,^{\circ}C$ axillary or $38.3\,^{\circ}C$ rectally), admitted to the department of internal medicine at a university hospital over a 1-year period, have been described elsewhere.[20,24] Here we report on the 212 patients for whom a clinical focus of infection was presumed. A previous paper on this cohort dealt with clinical risk factors for hospital-acquired infection and death.[9] The study was approved by the local ethics committee. All patients or their closest relatives gave informed consent. Exclusion criteria were pregnancy, shock, and a life expectancy of less than 24 h. Moreover, patients who had received recent cytokine or cytostatic drug treatment for solid tumors and malignant hematological diseases, and those potentially having an overtly abnormal host response, for instance in the course of AIDS (related to HIV), were excluded. Patients were cared for by physicians not involved in the study. Diagnostic and therapeutic decisions were made by these physicians independently of the study protocol. The assessment of the clinically presumed focus of infection by the treating physician was supplemented, if necessary, by imaging techniques.

At inclusion, demographic data and clinical characteristics were recorded. These included age, gender, use of immunocompromising drugs (such as corticosteroids given in the absence of hemato-oncologic disease), prior cardiovascular, endocrine (and diabetes), genitourinary, neurological, or respiratory disease, active malignancies, and surgery within two months prior to inclusion. The International Classification of Disease (ICD-9) definitions were used to describe the disease states. We recorded the use of devices and interventions. Clinical variables (temperature, respiratory rate, heart rate, mean arterial blood pressure (MAP), score on the Glasgow Coma Scale (GCS), and leukocyte count) were measured at inclusion and in the morning on the first and second days thereafter (days 0, 1, and 2).

Infection was considered hospital-acquired if it developed at least 72 h after admission into the hospital. All other patients were considered to have community-acquired infection. An estimate of the time interval between development of fever and inclusion in the study was made. The clinically presumed focus of infection and all local and blood culture results during a follow-up period of 7 days after inclusion were noted. Patients were followed for 7 days for the development of septic shock and for 28 days for outcome. Septic shock was defined as a fall in arterial blood pressure below 90 mmHg (or a systolic decrease >40 mmHg in previous hypertension) in the presence of systemic inflammatory response syndrome (SIRS) criteria, with fever (or hypothermia), tachycardia, tachypnea, and leukocytosis (or leukopenia).[5] Patients discharged from the hospital within the follow-up period were classified as survivors.

Microbiology

Local specimens for microbiological evaluation were collected at admission. Two blood cultures were obtained by venipuncture at inclusion and thereafter as judged necessary by the treating physician. Blood cultures were processed for aerobic and anaerobic cultures (Bactec 9120/9240, Becton Dickinson, Erembodegem, Belgium). Bottles were incubated for a maximum of 7 days. If the analyzers showed growth, Gram stains were prepared and identification and sensitivity cultures were processed. Blood cultures containing *Staphylococcus epidermidis* were considered contaminated if only one bottle revealed growth and there were no indwelling vascular catheters. Local specimens were processed using standard procedures. An infection was considered proven if microbiological results were positive and if the treating physician decided to prescribe or continue antimicrobial therapy based on these results.

Immune markers

Blood samples for determination of plasma levels of inflammatory mediators were obtained at inclusion and daily