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Research Article

Look at your patient: appropriate antimicrobial therapy in patients with community- versus hospital-acquired bacteremic sepsis

Abstract

Inadequate antibacterial therapy has been associated with increased mortality in severe sepsis and septic shock. The aim of this study was to evaluate the appropriateness of antibiotics in sepsis patients to determine best empirical regimen.

Prospective surveillance of 239 septic episodes (223 patients; 261 isolates).

Pathogens differed significantly between (1) community- and hospital-acquired sepsis and (2) primary infection sites. In community-acquired infections Gram-negative microorganisms (62/101; 61%) prevailed due to the urinary tract origin of sepsis (33/100; 33%). Carbapenems (95%), piperacillin/tazobactam (89%), ceftazidime (85%), and moxifloxacin (81%) showed in-vitro activities >80%.

In hospital-acquired infections, Gram-positive microorganisms (96/160; 60%) dominated due to catheter-related infections (60/139; 43%). None of the tested antibiotics exceeded a susceptibility rate of 66%, thus a combination therapy might be prudent.

Community vs. hospital onset of sepsis along with the primary infection site seem to be important enabling better prediction of appropriateness of initial empirical antimicrobial regimen.

Keywords: bacteria, antibiotics, multi-drug resistance, sepsis

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Introduction

Sepsis is a frequent and still serious infection with a high mortality [1], [2], [3]. In Germany, a survey conducted by the publicly funded Competence Network Sepsis (SepNet) found an annual incidence of 116 vs. 110 in 100,000 inhabitants for non-severe vs. severe and/or septic shock sepsis, which amounts to 79,000 and 75,000 sepsis cases per year, respectively [2]

Overall, sepsis is responsible for approximately 60,000 deaths per year in Germany and ranks as the third most frequent cause of death in this country [2]. In patients with sepsis or similar serious infections, inadequate initial therapy has been associated in many studies with adverse outcomes, including higher mortality, prolonged hospitalization, and higher healthcare costs [4], [5], [6], [7], [8]. Inadequate antimicrobial therapy is defined in most studies as a treatment with an agent without in vitro activity against the causative pathogen(s) [6], [7]. Since the modification of an inappropriate initial antimicrobial therapy may not improve outcome and that such a delay can further increase the already high mortality rate [8], critically ill patients with a serious infection require an effective initial empirical antibacterial treatment before the results of testing for the causative agents are known [9], [10], [11].

Moreover, since antimicrobial resistance, especially in the setting of a hospitally-acquired sepsis, is a growing health challenge, the ability to better calculate an appropriate initial empirical antimicrobial regimen is of increasing importance [12].

Therefore, the aim of this study was to evaluate the in vitro susceptibility of blood culture isolates from patients with sepsis to antibiotics that are recommended for empirical use in this setting.The rate of in vitro susceptibility of each tested commonly used antibiotic was determined for individual pathogens identified in the blood culture isolates of this cohort of patients. In addition, the severity of sepsis, community vs. hospital acquired, and the primary infection site were documented.

Patients and methods

Patient cohort

This six month prospective study was conducted at the University Hospital Aachen, a 1300-bed tertiary care teaching center. Ten intensive care units (ICUs) offer 107 ICU beds admitting mainly patients from Germany, Belgium, and the Netherlands. From March 1, 2009 to September 30, 2009 all patients with a microbiologically proven bacteremia who fulfilled the clinical criteria for sepsis, severe sepsis or septic shock – according to the guidelines for sepsis as issued by the German Sepsis Society – were consecutively enrolled in the study [1]. Enrollment was stopped for hospital-acquired infections after 100 community-acquired sepsis episodes were documented. Hospital-acquired sepsis was defined as symptoms of sepsis beginning at least 48 hours after admission according to the CDC definition. All patient-related data were recorded pseudonymously. Analyses were performed with regard to the severity, the origin, and the time of onset (community- versus hospital-acquired).

Microbiological testing

For blood culture analyses, the BactAlert system was used (BD Diagnostics; Diagnostic Systems, Heidelberg; Germany). Following culturing blood samples on standardized culture media, all isolates were identified biochemically and tested for resistance patterns with the BD Phoenix™ automated Microbiology System (BD Diagnostics – Diagnostic Systems, Sparks, USA). Results were interpreted according to CLSI. This means that in case of ESBL testing, Piperacillin/Tazobactam was reported as resistant although MIC results indicated susceptibility. Patients revealing positive results indicative for potential contaminants, such as coagulase-negative staphylococci, *Micrococcus ssp.*, or *Corynebacteria ssp.*, were enrolled only when such pathogens were isolated at least in two different sets of bloodcultures in the absence of other microorganisms in addition to a clinically diagnosed sepsis. Etest® (AB BIODISK, Sweden) methodology was used in cases not suitable for automated resistance testing like for streptococci and *Haemophilus ssp.*

Results were interpreted according to CLSI breakpoints. Note that for Gram-positive microorganisms susceptibility testing was not always available for third generation cephalosporines and for fluorochinolones. Finally, concerning the susceptibility rate per patient, a patient with polymicrobial bacteraemia was regarded as having been treated adequately only if all relevant isolates were susceptible to the given antimicrobial agent.

In vitro appropriateness was defined as in vitro sensitivity and in vivo appropriateness was defined as in vitro sensitivity and therapeutic potency for the underlying disease according to the current guidelines of the IDSA.

For comparative analyses, the Fisher's exact test was performed using Sigmastat 3.1, Systat.

Results

A total of 223 patients with 239 episodes of sepsis were enrolled with 100 (42%) and 139 (58%) being community- and hospital-acquired sepsis infections, respectively.

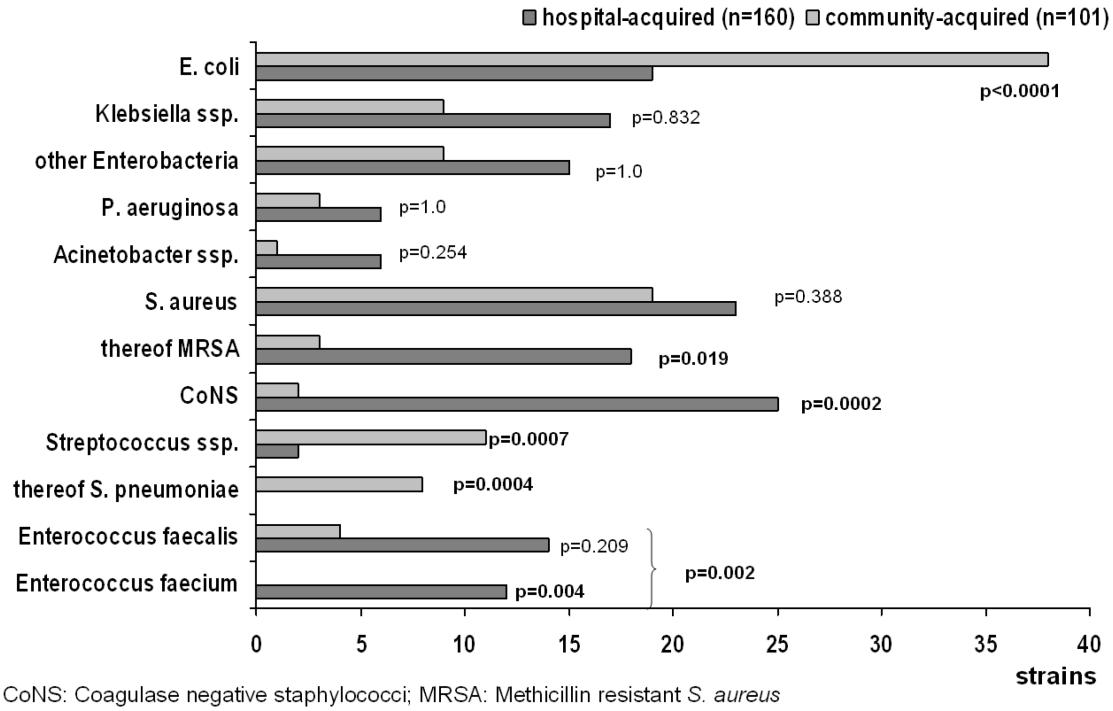
In cases of hospital-acquired sepsis, men dominated significantly (m: 100; f: 39) in comparison to community-acquired sepsis (m: 56; f: 44; p=0.0132) with the mean age being 63.1 versus 67.3 years in patients with hospital-acquired versus community-acquired sepsis. Concerning hospital location, 109 patients (46%) were cared for at an ICU and 130 (54%) at general wards with 83 sepsis episodes (35%) occurring at surgical departments and 156 (65%) at non-surgical departments. Severity pattern of sepsis revealed the following distribution: 71% (N=71) for sepsis, 20% (N=20) for severe sepsis, and 9% (N=9) for septic shock in the community-acquired cases and 59% (N=81) for sepsis, 27% (N=39) for severe sepsis, and 14% (N=19) for septic shock in the hospital-acquired cases, respectively. Urinary tract infections (33% vs. 9%, p<0.001), bone infections (4% vs. 0%, p=0.03), and abdominal sepsis (21% vs. 10%, p=0.023) were significantly more often in community-onset sepsis, whereas venous catheter associated sepsis (43% vs. 6%, p<0.0001) was significantly more often hospital-acquired, respectively. Pulmonary sepsis was not significantly higher in the community- than in the hospital-acquired setting (16% vs. 13%, p<0.57).

A total of 261 relevant isolates were cultured. Polymicrobial episodes were significantly more often when sepsis was hospital-acquired (19/139 versus 1/100; p=0.0002). Moreover, hospital-acquired sepsis was found to be significantly more often caused by Gram-positive bacteria (96/160; 60%) compared to community-acquired sepsis (39/101; 39%; p=0.0015; Figure 1). The appropriateness of empiric antibiotics per sepsis episode in relation to the time of onset of sepsis is analyzed in Figure 2.

Discussion

In this cohort of patients with microbiologically proven sepsis, the microbial spectrum as well as the level of antimicrobial susceptibility was found to be strongly determined by whether the sepsis was community- or hospital-acquired.

For community-acquired sepsis, five of the tested antimicrobials were appropriate in more than 80% of sepsis cases and thus, may be used for initial empirical therapy. Of note is that both carbapenemes showed best appropriateness rates (95%), followed by piperacillin/tazobactam (89%), ceftazidime (85%), and moxifloxacin (81%). Thus, monotherapy seemed to be sufficient. The urinary tract (33%) and the abdomen (21%) dominated the primary infection sides in community-acquired sepsis (p<0.0001; p=0.025). As a result, *E. coli* (38%) was the most frequently isolated pathogen in community-acquired sepsis. Taken the primary infection site into consideration, the four cell-wall active antimicrobials seemed to be suf-



CoNS: Coagulase negative staphylococci; MRSA: Methicillin resistant *S. aureus*

Figure 1: Identified causative agents (N=261) in blood cultures from sepsis patients

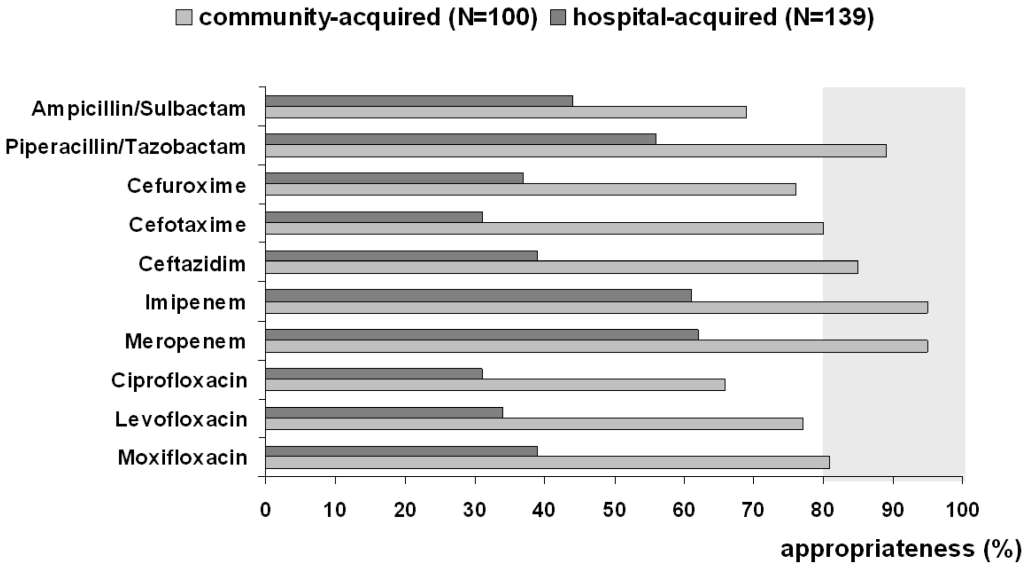


Figure 2: Appropriateness of antibiotics according to the in-vitro susceptibility in community vs. hospital acquired sepsis (%). The light zone grey indicates an appropriateness rate of >80%.

ficient for an initial monotherapy. However, the high rate of urinary tract infections found in the community-acquired sepsis group limits the appropriateness of moxifloxacin due to PD/PK reasons in this group. It is of note that second generation cephalosporines like cefuroxime commonly used for initial empirical therapy of community-acquired sepsis achieved a susceptibility rate per patient of 76% only. On that basis we changed our in-house recommendations accordingly.

Severity of sepsis in the community-onset group did not correlate with susceptibility patterns. Hence, not the severity of illness, but the onset of sepsis, i.e. community vs. hospital and the suspected infection site, should be the major factors influencing the choice of the initial antibiotic therapy. In-line with our results a national surveillanve database revealed susceptibility rates depending on the setting. For example *E. coli* in out-patient with sepsis showed the ESBL phenotype in about 8% in 2012, in in-patients in 11%, respectively. In additional, the ESBL phenotype in Klebsiella pneumonia isolates could be detected in 8% of out-patients with each kind of infection compared to about 13.5% of in-patients in 2012, respectively [13].

Our data showed that for hospital-acquired sepsis, the current widespread practice of an antimicrobial monotherapeutic regimen has several severe limitations [11], [12]. Hospital-acquired sepsis was significantly more often catheter-related compared to community-acquired sepsis (46% versus 10%; p<0.0001) caused by Gram-positive bacteria (60% versus 39%; p=0.0015). Therefore, monotherapy with the tested antimicrobials would have been microbiologically inadequate in at least 38% (if the best fitting monotherapeutic regimen was chosen) of cases. Thus, in hospital-acquired sepsis without a definitive exclusion of a catheter infection, a combination with an agent active against Oxacillin-resistant staphylococci, e.g. a glycopeptide for empiric therapy, seems to be necessary. Alternatively, especially if VRE or MRSA are taken into consideration by previous results daptomycin and linezolid could be used initially depending on the infection site [1], [2].

In patients with severe sepsis or septic shock, initial combination therapy to broaden the spectrum of antimicrobial activity seems to be warranted [14]. For example, among patients with severe community-acquired pneumonia requiring ICU admission, combination therapy significantly improved the survival [14]. However, in sepsis patients, adding aminoglycoside to betalactam did not improve survival [1]. Moreover, the addition of moxifloxacin to meropenem did not influence outcome in community onset sepsis patients as recently demonstrated [15]. A possible explanation is that community-acquired sepsis seems not to be caused by resistant pathogens needing a broader coverage. On the other hand hospital-acquired sepsis is often caused by Gram-positive pathogens needing a glycopeptide or one of the newer agents. As in this study, susceptibility rates for none of the agents tested exceeded 71% per blood culture isolate and 62% per sepsis episode in hospital-acquired sepsis. Therefore, an initial empirical monotherapy would leave at least one out of three patients without adequate treatment.

As a limitation data on a growing number of patients with infections that should be classified as healthcare-associated rather than hospital-associated are lacking [16]. Moreover, we were not able to provide detailed patient data.

Taken together, the onset of sepsis and the primary infection site are two key factors that should influence the choice of the best initial empirical antibacterial therapy in patients with sepsis. Especially in the field of growing resistance, conservative empirical regimens should be used whenever possible. This could be true for community onset and presumed focus. Despite the limitations of a single-center setting with a moderate number of patients, sepsis episodes, and isolates, our study offers the advantage of a randomly selected patient cohort, thereby better representing a typical spectrum of sepsis patient for a large tertiary care hospital.

In conclusion, our study has highlighted that community-onset sepsis patients may not require a broad spectrum antimicrobial regimen, however in hospital-acquired sepsis, especially if catheter-associated patient need an empirical coverage for Oxacillin-resistant Gram-positive microorganisms. Therefore taking into consideration the onset of sepsis may be a simple and efficient approach to enable physicians to better prescribe an initial appropriate antibacterial therapy regimen for sepsis patients.

Notes

Authorship

Simone Scheithauer and Helga Haefner contributed equally.

Competing interests

The authors declare that they have no competing interests.

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