Prospective audit of bacteraemia management in a university hospital ICU using a general strategy of short-course monotherapy

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Objective: As optimal antibiotic therapy for bacteraemia remains unknown, different strategies have evolved. Routine practice in the University College London Hospitals intensive care unit (ICU) is to use short-course (5–6 days) monotherapy, unless specifically indicated (e.g. endocarditis, osteomyelitis). We decided to assess this approach for treating community-, hospital-, and ICU-acquired bacteraemia by monitoring clinical response, relapse rate and patient outcome.

Design: Six-month prospective observational study from February to July 2000.

Setting: Mixed medical-surgical tertiary referral ICU.

Patients: All 713 patients admitted to the ICU over the study period.

Measurements and results: In total, 102 bacteraemic episodes occurred in 84 patients. Eight (57%) of 14 community-acquired bacteraemias, 22 (79%) of 28 hospital-acquired bacteraemias, and 48 (80%) of 60 ICU-acquired bacteraemias (in 49 patients) were treated with short-course monotherapy. Compared with previous reported studies, these patients had a low rate (23.8%) of death directly attributable to the bacteraemia and a satisfactory clinical response in 72%. Of six relapses (all Gram-negative), four had received combination therapy for severe deep-seated infections. ICU-acquired multidrug-resistant Gram-negative bacteraemias (6.5%) and fungaemias (3%) were also uncommon. No patient discharged from ICU subsequently developed a new bacteraemia relapse, or any long-term complication such as osteomyelitis.

Conclusions: Our general strategy of short-course antibiotic monotherapy for treating bacteraemia in the critically ill appears to provide a satisfactory clinical response, low relapse rate and no long-term complications in a well-defined group of patients. Multicentre studies are warranted to compare short versus long course therapy, and monotherapy versus combination therapy.

Keywords: fungaemia, intensive care unit, antibiotic therapy

Introduction

Bacteraemia in the intensive care unit (ICU) patient results in significant mortality and morbidity. Patients may present with a community-acquired, bacteraemia-related illness, but the majority develop bacteraemia as a secondary nosocomial event. This occurs as a consequence of host defence alteration through their underlying disease(s), extensive use of invasive procedures (surgery, tubes, catheters, drains, etc.), and coexisting endogenous or exogenous immunosuppression. The incidence of nosocomial bacteraemia in ICU patients ranges from 2.5% to 26%, varying according to casemix but usually related to prolonged ICU and hospital stay. Associated mortality remains high at 21–56%, albeit decreasing as a consequence of improved support for organ failure.

Appropriate antibiotic therapy is the mainstay of treatment, in conjunction with removal of any source (viscus perforation, abscess, foreign body, etc.), organ support, and amelioration or cure of the underlying disease. Timely selection of appropriate therapy influences patient outcome. Treatment response is primarily based on signs of clinical improvement, yet patients often deteriorate as a result of the ensuing inflammatory response, the underlying illness or a non-infectious complication, despite successful eradication of the responsible microorganism. Direct...
or indirect attribution of death to the bacteraemia can be difficult in the ICU setting. 10–13 As a consequence, optimal antibiotic therapy remains unknown.

As no ICU-specific randomized trials exist, individual ICUs have evolved different strategies, using short (4–7 days) or long (10–14 days plus) courses of either mono- or combination antibiotic therapy. 14 The latter offers broad spectrum and often synergic cover, whereas short-course monotherapy reduces both antibiotic pressure in the environment and drug expenditure. 15,16 Prolonged combination therapy could carry inherent dangers such as drug toxicity and, possibly, a higher incidence of fungaemia. 15,16 However, short-course monotherapy may not eradicate the infecting microorganisms, with an increased likelihood of relapse. Ironically, both policies are considered to be major influences on selection for antimicrobial resistance. 15,16 Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), Gram-negative bacilli—either multidrug-resistant or producing extended-spectrum β-lactamases (ESBL), fluconazole-resistant Candida spp. and, most recently, MRSA strains with reduced susceptibility to vancomycin, are nosocomial pathogens of increasing concern. 17 Different strategies (e.g. periodic rotation of first-line therapies, restricted use of antibiotic classes), in combination with an infection control programme, are mooted to decrease the prevalence of multidrug-resistant pathogens within the ICU. 18–21 However, these have yet to be evaluated by appropriately designed multicentre studies.

Ideally, prospective randomized trials should be conducted to determine optimal antibiotic strategies for bacteraemia-related illnesses. As no data currently exist for the critically ill patient, we decided to conduct a 6-month prospective observational investigation to inform the design of any future study. We assessed:

(i) the incidence, underlying factors, clinical presentation and severity of illness of community-, hospital- & ICU-acquired bacteraemia (C-BACT, H-BACT and ICU-BACT, respectively);
(ii) how patients treated with short-course monotherapy respond in terms of clinical improvement/deterioration, ICU survival, long-term complications and the incidence of relapsing episodes due to the same microorganism;
(iii) the incidence of fungaemia and antibiotic-resistant microorganisms.

Materials and methods

The University College London Hospitals (UCLH) ICU is a 22-bedded, mixed medical-surgical tertiary referral centre that receives daily input from a consultant microbiologist. Routine antibiotic policy is to use short-course monotherapy, unless specifically indicated (e.g. endocarditis, osteomyelitis) and, at 12 monthly intervals, to permute first-line therapy for presumed Gram-negative community (co-amoxiclav or cefuroxime) and nosocomial (piperacillin–tazobactam or ceftazidime) pathogens. Second- and third-line therapy consists of ciprofloxacin or a carbapenem. Fluclaxacillin and teicoplanin are routinely used for community- and hospital-acquired staphylococcal infections, respectively.

Patients

The following data were collected on all patients admitted to the ICU from February 1st 2000 for 6 months: (i) demographics; (ii) admission diagnosis and first 24 h APACHE II score; (iii) risk factors (e.g. MRSA carriage, immunosuppression, recent surgery); and (iv) duration of ICU stay and outcome.

Bacteraemic/fungaemic cases

Clinically significant bacteraemias or fungaemias were identified by daily prospective surveillance of all positive blood cultures. 22–25 Affected patients had the source of infection identified where possible. Collections were drained and intravascular catheters removed as appropriate. ACCP/SCCM sepsis criteria were collected retrospectively: (i) at the time blood cultures were taken; (ii) when culture results were notified; and (iii) when antibiotics were commenced. 24

Patients were prospectively followed with recording of: (i) antibiotic therapy (type, duration, changes) and ACCP/SCCM sepsis criteria at the time of stopping (and changing, if necessary) antibiotic therapy; (ii) ICU support techniques (e.g. mechanical ventilation, intra-vascular catheter changes, abscess drainage or surgery); and (iii) development of further bacteraemic or fungaemic infections or relapses.

Microbiology

When systemic infection was clinically suspected, blood was taken for culture with gloved hands, through a clean stab and/or arterial and central venous lines via a three-way tap, though not through any diaphragm and with prior cleaning with an alcohol impregnated wipe. Five millilitres of blood were injected aseptically into aerobic and anaerobic bottles and incubated for a mean time of 5 days (Bactec 9240; Becton Dickinson Microbiology Systems, Sparks, MD, USA). Isolation and identification of microorganisms were usually made using standard media, methods and techniques. The API 20E system (bioMérieux, Marcy l’Etoile, France) was used to identify Gram-negative organisms, and DNAnse and latex agglutination/coagulase to identify staphylococci. The Stokes disc diffusion method was used for antimicrobial susceptibility testing. 25 The Maki roll plate semi-quantitative technique was used for catheter tip culture. 25 The microbiology laboratory has clinical pathology accreditation and is subject to designated quality controls.

For all positive results, Gram stain, identification and antibiotic susceptibility patterns were noted. To assess the significance of isolates, laboratory results were reviewed in relation to clinical findings. Culture from swabs, catheter tips or fluid taken from other sites (e.g. tracheo-bronchial secretions, surgical wounds, line sites) was carried out as clinically indicated.

Statistical analysis

SPSS software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. For continuous variables, rank values were compared using non-parametric tests (Mann–Whitney U-test, Wilcoxon Rank Sum W, or Kruskal–Wallis one-way analysis of variance). Differences in proportions were compared using either χ² or Fisher’s exact tests for expected cell frequencies less than 5. Multinomial logistic regression was used to estimate the independent effect of each risk factor on ICU-BACT. Binary logistic regression was used to estimate the effect of each risk factor on a death (yes/no) outcome for ICU-BACT patients. P values less than 0.05 were considered significant.

Definitions

See the Appendix. CDC definitions were used for every type of infection. 26
Bacteraemia management with short-course monotherapy

Table 1. ICU and hospital outcome, APACHE II score, probability of death and standardized mortality rate (SMR)

<table>
<thead>
<tr>
<th>Population (n)</th>
<th>ICU deaths (%)</th>
<th>Hospital deaths (%)</th>
<th>APACHE II score median (IQR)</th>
<th>APACHE II probability of death median (95%CI)</th>
<th>SMR median (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population (713)</td>
<td>143 (20)</td>
<td>173 (24)</td>
<td>16 (11–21)</td>
<td>0.16 (0.01–0.77)</td>
<td>0.96 (0.3–25)</td>
</tr>
<tr>
<td>General population without bacteraemia (629)</td>
<td>106 (17)</td>
<td>130 (21)</td>
<td>15 (11–20)</td>
<td>0.14 (0.01–0.78)</td>
<td>0.9 (0.35–20)</td>
</tr>
<tr>
<td>ICU stay &lt; 3 days (354)*</td>
<td>51 (14.4)</td>
<td>58 (16.4)</td>
<td>13 (10–18)</td>
<td>0.09 (0.1–0.76)</td>
<td>0.86 (0.2–16)</td>
</tr>
<tr>
<td>ICU stay &gt; 3 days (359)*</td>
<td>92 (25.6)</td>
<td>115 (32)</td>
<td>19 (14–23)</td>
<td>0.25 (0.02–0.78)</td>
<td>1.1 (0.4–16)</td>
</tr>
<tr>
<td>Source: emergency department (77)*</td>
<td>16 (21)</td>
<td>21 (27.3)</td>
<td>14 (10–24)</td>
<td>0.14 (0.008–0.74)</td>
<td>1.2 (0.4–21)</td>
</tr>
<tr>
<td>Source: hospital wards (184)*</td>
<td>70 (38)</td>
<td>83 (45)</td>
<td>20 (14–26)</td>
<td>0.3 (0.04–0.86)</td>
<td>1.2 (0.5–11)</td>
</tr>
<tr>
<td>Source: operating theatre (338)*</td>
<td>32 (9.5)</td>
<td>40 (11.8)</td>
<td>14 (11–18)</td>
<td>0.1 (0.02–0.6)</td>
<td>0.7 (0.2–5.7)</td>
</tr>
<tr>
<td>Source: other hospitals (114)*</td>
<td>25 (21.9)</td>
<td>29 (25.4)</td>
<td>15 (12–22)</td>
<td>0.2 (0.1–0.72)</td>
<td>1 (0.35–2.5)</td>
</tr>
<tr>
<td>Patients admitted from ER with C-BACT (14)†</td>
<td>4 (28.6)*</td>
<td>6 (43)</td>
<td>23 (18–27)</td>
<td>0.4 (0.2–0.86)</td>
<td>1.2 (0.5–2.1)</td>
</tr>
<tr>
<td>Patients admitted from ER without C-BACT (63)†</td>
<td>12 (20)</td>
<td>15 (23.8)</td>
<td>12 (9–18)</td>
<td>0.1 (0.08–0.7)</td>
<td>1.2 (0.35–3)</td>
</tr>
<tr>
<td>Patients admitted from wards with H-BACT (28)‡</td>
<td>17 (60.7)*</td>
<td>19 (68)</td>
<td>23 (20–31)</td>
<td>0.4 (0.3–0.9)</td>
<td>1.2 (0.8–2.3)</td>
</tr>
<tr>
<td>Patients admitted from wards without H-BACT (170)‡</td>
<td>63 (37)</td>
<td>75 (44)</td>
<td>19 (14–26)</td>
<td>0.29 (0.03–0.9)</td>
<td>1.5 (0.5–15)</td>
</tr>
<tr>
<td>Patients with ICU-BACT (49)†</td>
<td>22 (45)*</td>
<td>24 (49)</td>
<td>22 (15–25)</td>
<td>0.27 (0.02–0.74)</td>
<td>1.4 (0.7–24)</td>
</tr>
<tr>
<td>Patients with ICU-BACT (310)†</td>
<td>70 (22.6)</td>
<td>91 (29.4)</td>
<td>19 (13–23)</td>
<td>0.25 (0.2–0.78)</td>
<td>1 (0.4–1.3)</td>
</tr>
</tbody>
</table>

*One non-surviving patient had both C-BACT and H-BACT.
‡Four non-surviving patients had both H-BACT and ICU-BACT.
§P < 0.001 and §P < 0.05 for ICU and hospital deaths, APACHE II score and probability of death.
†P < 0.05 for ICU and hospital deaths and APACHE II score only.

Results

Study population (Table 1)
In total, 713 patients [455 male; 47% surgical; median age 62 years (inter-quartile range, IQR 45–72)] were admitted in the 6 month period. Median ICU stay was 3 days (IQR 2–5) with 143 (20%) dying in the ICU, 51 within 3 days. Twenty-five were transferred to other hospitals, and 545 were discharged to a general ward, of whom 30 died. Overall APACHE II standardized mortality rate (SMR) was 0.96. Patients admitted from the ward had higher APACHE II scores and hospital mortality (P < 0.001, Kruskal–Wallis test).

Bacteraemia
Fourteen (1.9%) patients were admitted with C-BACT and 28 (3.9%) with H-BACT, 11 of whom had haematological malignancy. Six H-BACT patients subsequently developed ICU-BACT, but with different microorganisms. Forty-nine patients suffered 60 episodes of ICU-BACT, one patient having three episodes over 63 days. Using multimonial logistic regression, predictive factors for development of ICU bacteraemia were duration of ICU stay, coexisting renal failure [OR = 146.5 (95% CI: 6.4–3349)], MRSA carriage [OR = 0.021 (95% CI: 0.001–0.68)], recent surgery [OR = 218.7 (95% CI: 2.24–21 289)], and duration of mechanical ventilation [OR = 0.8 (95% CI: 0.57–0.99)] (P < 0.01, all). The risk of developing ICU-BACT rose progressively with time, being 39% after a stay of 7 days in the ICU, doubling after 14 days, and reaching 100% after 5 weeks.

Culture results and onset (Figure 1)
Gram-positive organisms caused the majority of bacteraemias in each subgroup. There was a median gap of 20 days between the onset of the first and second ICU-acquired bacteraemia episodes. *Escherichia coli* was the only causative pathogen of Gram-negative C-BACT, whereas *Klebsiella* spp. constituted 19.3% of all cases of H-BACT and ICU-BACT. Only two patients had ICU-acquired fungaemia, the monomicrobial case occurring after femoral venous catheter insertion into an infected groin.

Sources of bacteraemia (Table 2)
Main sources for C-BACT were cardiovascular (endocarditis) and urinary tract, and gastrointestinal and respiratory for H-BACT. Intravascular devices were considered the source in 27 (45%) of ICU-BACT. The rate of central venous catheter infections was 7 per 1000 line days. Line-related bacteraemias (40% due to coagulase-negative staphylococci) occurred after a median time post-insertion of 10 days (IQR 6–13).

Susceptibility patterns (Figure 1)
In the C-BACT group, MRSA was isolated from one previously hospitalized patient. *Escherichia coli* strains were susceptible to all antibiotics except amoxicillin. In the H-BACT group, two *Staphylococcus aureus* and all coagulase-negative staphylococci were methicillin-resistant; one *Enterococcus faecium* isolate was both vancomycin- and teicoplanin-resistant. Only two (13%) multidrug-resistant Gram-negatives were identified, one being...
extended-spectrum β-lactamase (ESBL)-producing. Of seven *Candida* spp., five were fluconazole-resistant. In the ICU-BACT group, all 13 *S. aureus* isolates were methicillin-resistant. Five (38%) were MRSA carriers before ICU admission, the others being colonized after a median ICU stay of 14 days (IQR 7–21). The former developed MRSA bacteremia 21 days (IQR 9–22) earlier (*P* < 0.05, Mann–Whitney test). All vancomycin-resistant organisms were isolated in long-stay hospital patients (median 2 months, IQR 15–83 days), but no differences in either illness severity or mortality were recorded. Only two (6.5%) Gram-negative isolates were multidrug-resistant and no ESBL-producing microorganisms were found.

Severity of illness (Table 3)

Septic shock and severe sepsis were more common in C- and H-BACT (*P* < 0.05, χ² test). Gram-negative microorganisms were more often related to septic shock in C-BACT (75%) and ICU-BACT (48%), whereas Gram-positive pathogens resulted in septic shock in 84% of H-BACT. Fungaemia was associated with septic shock in all hospital-acquired episodes, but with a low-grade illness severity in community- and ICU-acquired cases.

Antibiotic therapy

A 5 day median course of monotherapy was used in the majority of C-BACT (57%), H-BACT (79%) and ICU-BACT (80%) patients, despite many having septic shock or severe sepsis. Among 78 episodes (considering together C-BACT, H-BACT and ICU-BACT) treated with short-course monotherapy, 27 were central venous catheter (CVC)-related bacteremia, 15 were respiratory tract infection related (11 pneumonia) and 15 had
Bacteraemia management with short-course monotherapy

Table 2. Source of bacteraemia and severity of infection related to bacteraemia group

<table>
<thead>
<tr>
<th>Source</th>
<th>Community-acquired</th>
<th>Hospital-acquired</th>
<th>ICU-acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular catheters</td>
<td>0</td>
<td>3</td>
<td>27</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>1</td>
<td>10 (6)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>2</td>
<td>6 (2)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Surgical wound</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>3 (1)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primary (source unknown)</td>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>28</td>
<td>60</td>
</tr>
</tbody>
</table>

(n) = presumed source of bacteraemia.

The gastrointestinal tract as a supposed source (two abdominal sepsis and one gall bladder empyema); only six episodes were considered primary bacteraemia. In terms of severity of illness: 34 (43.6%) episodes were complicated by a septic shock and 17 (21.8%) by a severe sepsis; no asymptomatic or low symptomatic bacteraemia were recorded. Combination therapy was reserved for severe deep-seated infections, i.e. endocarditis, necrotizing fasciitis, osteomyelitis, cerebral abscess (n = 6), multidrug-resistant Gram-negative bacteraemia (n = 2), and polymicrobial infections (n = 7). Three ICU-BACT episodes had low-grade pyrexia and received no treatment other than vascular catheter change.

Despite opting for monotherapy, in most cases before culture results were known, antibiotic therapy was not subsequently altered in 12 (86%) episodes of C-BACT, 23 (88%) episodes of H-BACT and 48 (90%) episodes of ICU-BACT. Two patients with C-BACT, three with H-BACT and five with ICU-BACT received additional antibiotics due to lack of clinical response, even though therapy was appropriate in terms of laboratory susceptibility testing.

Eighteen patients died during therapy, and seven more within 3 days of stopping therapy. Excluding those 18 patients not completing their course of antibiotics, the median duration of treatment was not significantly prolonged for either C-BACT [monotherapy 6 days (IQR 5–6), combination 21 days (8–21)], H-BACT [monotherapy 6 days (5–8), combination 7 days (5–14)], or ICU-BACT [monotherapy 5 days (5–7), combination 8 days (5–13)]. Fourteen patients received ≥10 days of therapy and eight ≥14 days of therapy.

The decision to stop antibiotics was based upon clinical response, i.e. resolution of bacteraemia-related clinical findings ± improvement in related organ dysfunction. Using these criteria, a clinical response was recorded in most patients for each episode treated with short-course monotherapy (Table 3). Thirteen patients responded to antibiotic therapy with resolution of the related systemic inflammatory response but subsequently died due to persisting organ failure. Twenty deaths were directly attributable to bacteraemia, where organ function continued to deteriorate despite susceptible antibiotic therapy.

Four H-BACT and three ICU-BACT patients who died while still receiving antibiotics developed breakthrough bacteraemia, three being due to *S. aureus*. An additional antibiotic was added in two cases, and a withdrawal decision taken in three cases. The deaths occurred after a median therapy duration of 4 (IQR 2–7) days for H-BACT and 5 (IQR 1–7) for ICU-BACT.

Relapses

Gram-negative microorganisms were responsible for all six relapse episodes, namely *E. coli* for one C-BACT, and *Klebsiella* spp. (3), *Serratia marcescens* (1) and a *Pseudomonas* spp. (1) for ICU-BACT. Four relapses likely resulted from non-changing of intravascular catheters colonized after the first episode. The other two ICU-BACT relapses occurred in patients with faecal peritonitis 7 days (IQR 5–9) after finishing antibiotic therapy. Four of five relapsing ICU-BACT had received an 8 day median course of combination therapy. Three relapsing episodes were treated with 7 days of monotherapy, and three with 7 days of combination therapy; no further relapses occurred.

Mortality (Tables 1 and 3)

Crude ICU and hospital mortality (unadjusted for illness severity) was higher in bacteraemic patients (P < 0.001, x² test). Thirty-eight of the 84 bacteraemic patients died, providing a crude mortality rate of 45%, however the directly attributable mortality rate was 23.8% (20 patients). ICU-BACT was not a predictive factor for death [OR = 0.7 (95% CI: 0.4–1.7), P = 0.394] using binary logistic regression with death (yes/no) as the response variable and ICU-BACT, APACHE II probability and score, age, sex, diabetes, renal failure, liver failure, neoplasia, immunosuppression, ARDS, neutropenia and the presence of other infection as explanatory variables. As a result of low patient numbers, C-BACT and H-BACT were not examined. Out of all MRSA bacteraemia (considering together C-BACT, H-BACT and ICU-BACT), 56.5% of patients survived, whereas 34.3% died directly related and 8.7% indirectly.

Six of the seven patients with more than one bacteraemia (i.e. H-BACT + ICU-BACT, or C-BACT + H-BACT) died, with five being directly related. Six of the 10 patients developing more than one ICU-BACT episode died, four being directly related. Of the six patients relapsing with the same microorganism, four died though only one was directly related to the bacteraemia. Three of the 46 (55%) bacteraemic patients who survived were transferred to other hospitals and the remaining 43 were discharged to hospital wards. During a 3 week (IQR 7–75) median follow-up, none developed either relapses or further bacteraemic episodes. No long-term complications such as osteomyelitis or endocarditis have since come to our attention. Six (two C-BACT, two H-BACT and two ICU-BACT) patients subsequently died in hospital.

Discussion

Numerous studies have focused on the incidence of nosocomial bacteraemia in the ICU, stressing the high related mortality. Though appropriate and adequate antibiotic therapy is likely to influence patient outcome, remarkably, no clinical trials have been conducted to define optimal therapy for bacteraemia in the critically ill. As no data exist to inform practice, ICUs have evolved their own strategies. From informal discussions, many UK ICUs use short duration therapy (5–7 days), whereas North
Table 3. Therapy, clinical response and outcome of bacteraemic patients

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Episodes (%)</th>
<th>Median course (IQR)</th>
<th>Bone criteria</th>
<th>ICU mortality, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>septic shock</td>
<td>severe sepsis</td>
</tr>
<tr>
<td>C-BACT: 14 patients, 14 episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>8 (57)</td>
<td>5.5 (5–6)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>6 (43)</td>
<td>8 (6–23)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>H-BACT: 28 patients, 28 episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>22 (79)</td>
<td>5 (4–8)</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>4 (14)</td>
<td>5 (4–12)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ICU-BACT: 49 patients, 60 episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>48 (80)</td>
<td>5 (5–7)</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>5 (8)</td>
<td>8 (6–13)</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*One patient had a withdrawal decision instituted; the second had a Candida glabrata fungaemia which improved without treatment; the patient was later discharged from hospital without any major infectious complications.

+All four patients had a withdrawal decision instituted; all had experienced prior H-BACT and are shown in the groups denoted by §.

+Same patient developed both C-BACT and H-BACT; death was attributed to both types of bacteraemia.

+One patient is the same in both groups.
Bacteraemia management with short-course monotherapy

American and mainland European ICUs generally use longer courses (7–14 days).14 Definitive assessment of the efficacy of short-course monotherapy requires large, randomized, prospective multicentre studies. However, we are encouraged by the generally satisfactory clinical response, the low rate of breakthrough bacteraemia, the low numbers requiring addition of antibiotics due to clinical deterioration, and the low relapse rate, even in those suffering from septic shock or severe sepsis. These data are consistent with those reported in the literature.11,12 As further corroboration, no bacteraemic patient discharged to the wards developed either relapse or a new episode of bacteraemia, nor any late related infections such as endocarditis or osteomyelitis.

In our practice, antibiotic therapy is usually stopped promptly on resolution of bacteraemia-related clinical findings ± improvement in related organ dysfunction. However, due to the severity of underlying disease and concurrent multiple organ failure, it is often difficult to establish when clinical response actually occurs, or whether death can be directly or indirectly attributed to the bacteraemia. Clinical response could be corroborated by microbiological response, i.e. negative blood cultures taken after cessation of appropriate therapy. However, our standard practice dictates that blood cultures are not taken unless the patient clinically deteriorates and infection is suspected. Furthermore, concurrent renal and/or hepatic dysfunction may result in an antibiotic presence persisting for days (or even weeks). Thus, for the purpose of this observational study, a positive microbiological response included either non-appearance of the infecting microorganism or the lack of clinical need for subsequent blood cultures, extended into the duration of hospital stay post-ICU discharge to exclude late reoccurrence.

In keeping with accepted practice, longer duration combination therapy was prescribed for deep-seated infections such as endocarditis, necrotizing fasciitis, osteomyelitis, and faecal peritonitis. Relapses were more frequent in these patients, with failure to eradicate microorganisms being more likely with intra-vascular device colonization and persistence of intra-abdominal abscesses. The worse clinical response and higher mortality in these patients reflect their underlying illness severity. Similarly, the poorer outcome in H-BACT patients reflects their higher APACHE II score, their underlying disease severity and the high proportion (46%) of immunosuppression.27 The higher mortality in ward patients has been attributed to delays in antibiotic treatment and inadequate resuscitation.27

Patients that developed ICU-BACT were sicker on ICU admission compared with other long-stay (≥3 days) patients not developing ICU-BACT. This increased susceptibility with related to their underlying disease processes and the greater requirement for invasive procedures (e.g. vascular access, mechanical ventilation).3–9 If admission illness severity was taken into account, logistic regression showed that ICU-BACT was not an independent variable predictive of death, notwithstanding its effect on prolonging stay.10

The low incidence of ICU-acquired multidrug-resistant microorganisms and the zero incidence of ESBL-producing Gram-negative pathogens are uncommon when compared with recent North American and European studies that routinely express concern about the high frequency of such infections.28,29 All ICU-acquired _S. aureus_ bacteraemias were methicillin-resistant. All patients affected were MRSA carriers, a known risk factor for MRSA bacteraemia. An earlier onset was recorded in those carrying MRSA before ICU admission than those colonized during their ICU stay.30 Our short-course treatment approach to MRSA and pseudomonas bacteraemia differs from the orthodoxy that is based on expert consensus rather than prospective randomized trials.31,32 Our 38.5% mortality rate recorded in the 13 ICU-acquired MRSA bacteraemic patients compares favourably with the 63.8% mortality recently reported by Blot et al.33 The apparent success of this strategy over many years, with an absence of long-term complications, does suggest the need for prospective controlled studies to resolve this conflict of opinion.

Our incidence of 1.4 ICU acquired fungaemias per 500 patients (0.5% of long-stay patients) is similar to two multicentre studies from Germany and Spain, but much lower than reported by the EPIC or SENTRY surveillance studies.34 Any link between short-course monotherapy and a low incidence of fungaemia and multidrug-resistant Gram-negative bacteraemia must remain as supposition at present, but offers an important hypothesis that warrants further investigation. In support of this theory, multidrug-resistant Gram-negative bacteraemia and fungaemia occurred more often in those H-BACT patients suffering from malignancy, with prolonged hospital stay and/or receiving prolonged courses of antibiotic therapy.30 Moreover, as reported by others, we recorded a higher prevalence of non-albicans _Candida_ species; this is likely due to over-utilization of fluconazole which has shifted the spectrum of _Candida_ to more resistant species such as _Candida glabrata_ and _Candida krusei_.35–37

The limitations of this study are its observational nature and the relatively small numbers of patients considered. However, this study is the first, to our knowledge, that suggests short-course monotherapy does result in a satisfactory clinical response and a low relapse rate. The concurrent low rate of ICU-acquired fungaemia and multidrug-resistant and ESBL-producing Gram-negative pathogens suggests the intriguing possibility that these findings are related. Presentation of this work has stimulated the development of a large, prospective, international audit that is under way. Verification of the above findings will hopefully lead to randomized controlled studies and important guidance as to optimal antibiotic treatment strategies in the critically ill.

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References


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Appendix: definitions
Bacteremia/fungemia: the growth of a viable single bacteria/yeast, in one or more blood cultures, associated with signs of infection.1,26,38
Coagulase-negative staphylococci and all common skin contaminants (Bacillus spp., Corynebacterium spp.) isolated, from
at least two blood cultures, that met the above definition, were considered as ‘infection-associated’; they were otherwise designated as ‘contaminant’. If associated with a device-culture positive result for the same microorganism, only one positive blood culture from a distant site was necessary to consider this as a related bacteraemia.39

An episode of bacteraemia was defined when one or more microorganisms were isolated from one or more blood cultures, and clinical evidence suggested they had arisen from a common source and were part of the same episode. If the source was unknown, all positive blood cultures occurring within 48 h of each other are considered as a single bacteraemic episode.40

Poly microbial bacteraemia: either growth of two or more different species of microorganisms in the same blood culture, or growth of different species in two or more separate blood cultures within the same episode (< 48 h) and with clinical or microbiological evidence of the same source.40

Break-through bacteraemia: bacteraemia due to the same microorganism and occurring in patients treated with appropriate therapy for more than 24 h.41

Relapse: a recurrent bacteraemia due to the same microorganism occurring within 1 week of cessation of appropriate antibiotic therapy.1,26,38

Bacteraemia was defined as community-acquired if occurring within 72 h of hospital admission; as hospital-acquired if occurring within 72 h of patient admission from the ward to the ICU; and ICU-acquired either when occurring after 72 h following ICU admission, or sooner if the bacteraemia could be directly sourced to an ICU procedure, e.g. catheter insertion.1

Sepsis was defined by having at least two of the four (Bone) criteria for the systemic inflammatory response syndrome (SIRS), i.e. body temperature ≥38°C or <36°C, heart rate ≥90 beats/min, respiratory rate >20 breaths/min, WBC >12000 or ≤4000 cells/mm3 or ≥10% immature bands, which were associated with positive blood cultures. Severe sepsis: sepsis with organ dysfunction (we used a SOFA score ≥3 for one or more organ systems). Septic shock: sepsis or severe sepsis with a persisting fall in blood pressure despite adequate fluid resuscitation, plus perfusion abnormalities and the need for inotrope or vasopressor support.25

Appropriate antibiotic therapy: refers to an antimicrobial agent shown to be effective in vitro against the microorganism(s) responsible for the infection and considered to be an acceptable option by standard guidelines, at sufficient dosage, and by an acceptable route of administration.1,10–12

Clinical response to treatment: this was deemed positive if the bacteraemia-related systemic inflammatory response had resolved at the time of antibiotic cessation, though organ dysfunction may have still persisted.

Microbiological response: strictly speaking, this requires negative blood cultures taken after cessation of appropriate therapy. However, as routine clinical practice on the UCLH ICU is to take blood cultures only when clinically indicated, many responders would not have had repeat cultures taken unless there was clinical deterioration for which infection was suspected. Furthermore, concurrent renal and/or hepatic dysfunction may result in an antibiotic presence persisting for days (or even weeks) following cessation. Thus, for the purpose of this observational study, a positive microbiological response included either non-appearance of the infecting microorganism or the lack of clinical need for subsequent blood culture testing. This was extended into the duration of hospital stay post-ICU discharge to exclude late re-occurrence.

Multiple-drug resistance: resistance to at least three antibiotic classes in addition to any intrinsic resistance of the particular species.1,10–12

Primary bacteraemia: a bacteraemia occurring without any recognized source; secondary bacteraemia when the blood culture was positive for the same microorganism isolated from another site, recognized as its source.1

A gastrointestinal source of bacteraemia was designated when significant intra-abdominal disease (biliary tract disease, bowel ischaemia, infarction or perforation) was present in conjunction with an appropriate organism isolated from blood. The source was defined as recognized if the bacteraemia was related to an infection caused by the same microorganism; suspected if the bacteraemia was related to an infection only clinically defined, or due to the same microorganism colonizing the patient at any site; or unrecognized in the absence of a primary focus.1,9

In the case of likely multiple sources, we considered the primary source of bacteraemia as the first both clinically and microbiologically defined.

Intravascular device related infection was defined when the semi-quantitative culture (yielding ≥15 colonies) of the catheter tip was positive for the same microorganism isolated from blood taken from a distant site.1,26

Onset day of bacteraemia was considered the day when the positive blood culture was taken.

Death was considered attributable to the bacteraemia if it could be readily explained by infection without any other recognized causes of death; indirectly related if the bacteraemia caused organ dysfunction or failure resulting in death after the infection was clinically and microbiologically eradicated; or unrelated if death was related to a cause independent of the bacteraemia.1,10–12