Could we treat Bacteraemia In The Critically Ill with a Short-Course Monotherapy Strategy: Results of a 6 Month Prospective Audit

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Abstract

Introduction: Routine practice in the UCL Hospitals mixed medical-surgical ICU is to use short course (5-6 days) monotherapy, otherwise contraindicated (e.g. endocarditis, osteomyelitis). Methods Over a 6 month period, on all bacteraemic patients we recorded demographics, antibiotic therapy and support techniques. For all positive results, Gram stain, identification and antibiotic sensitivity patterns were noted.

Results: Out of 713 admitted to the ICU over the study period, 84 (8.2%) patients experienced 102 bacteraemic episodes: 14 community-, 28 hospital- and 60 ICU-acquired (in 49 patients). A total of 78 (76.4%) episodes [8 (57%) community-, 22 (79%) hospital- and 48 (80%) ICU-acquired] were treated with short course monotherapy. A low rate (23.8%) of death directly related to bacteraemia and a satisfactory (72%) clinical response were recorded. No patient subsequently developed relapse or any long-term related complication.

Conclusions: Short course antibiotic monotherapy strategy appears to provide a satisfactory clinical response without any long-term infectious complications.

INTRODUCTION

Bacteraemia, both community-acquired and nosocomial, can present within a clinical spectrum ranging from asymptomatic through to septic shock (1). The reported incidence of nosocomial bacteraemia in ICU patients ranges from 2.5-26% (2-5) and is usually related to prolonged ICU and hospital stay. Despite advances in antibiotic therapy and general management of the critically ill patient, bacteraemia carries a high mortality (21-56%), ICU patients are at very high risk of developing bacteraemia as their host defence mechanisms are altered through their underlying illnesses, the extensive use of invasive procedures (catheters, tubes, drains etc), and coexisting endogenous/exogenous immunosuppression (6-11).

Timely selection of appropriate therapy influences patient outcome and is the mainstay of treatment of infection, in conjunction with the removal of foreign bodies, any obvious source of infection, drainage of abscesses and amelioration/cure of the underlying disease (12). The traditional approach to suspected infection in most critically ill patients is commencement of empirical broad-spectrum therapy before the results of cultures are obtained, with subsequent modification, depending on the results and/or the patient's condition (13). However, this approach does carry inherent dangers such as selection for antimicrobial resistance and the risks of drug toxicity.

As no data exist for the optimal therapy of ICU bacteraemia, ICUs apply different philosophies using permutations of short (4-7 days) or long (10-14 days or longer) courses of single or multiple antibiotics. Short courses of monotherapy may potentially not eradicate the organism, resulting in relapse, while prolonged ones may be related to drug toxicity as well as fungal overgrowth. Ironically, both policies are considered to be major influences on selection for antimicrobial resistance (14,15). Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), Gram-negative bacilli - either multi-drug resistant or producing extended-spectrum ß-lactamas (ESBL), fluconazole-resistant Candida spp. and, most recently, MRSA strains with reduced susceptibility to vancomycin, are nosocomial pathogens of increasing
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concern (16). Different strategies (e.g. periodic rotation of first line therapies, restricted use of antibiotic classes), in combination with an infection control program, are mooted to decrease the prevalence of multi-drug resistant pathogens within the ICU (17,18,19,20). However, these have yet to be evaluated by appropriately designed multi-centre studies.

Ideally, prospective randomised 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 six month prospective observational investigation to inform the design of any future study. We assessed:

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

MATERIALS AND METHODS

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

Patients: On all patients admitted to the ICU from February to July 2000 the following was recorded: (i) demographics and first 24 hour APACHE II score (ii) risk factors (e.g MRSA carriage, immunosuppression, recent surgery), (iii) duration of ICU stay and outcome.

Bacteraemic/fungaemic cases: Clinically significant bacteraemias were identified by daily prospective surveillance of all positive blood cultures (21,22). Affected patients had the source of infection identified where possible. Collections were drained and intravascular catheters removed as appropriate. Patients were prospectively followed with recording of (i) antibiotic therapy (type, duration, changes) and ACCP/SCCM sepsis criteria, (ii) ICU support techniques (e.g. mechanical ventilation, intra-vascular catheter changes), (iii) development of relapses or further bacteraemia related infections.

Microbiology: When systemic infection was clinically suspected, 5 ml of blood were taken for culture and injected aseptically into aerobic and anaerobic bottles and incubated for a mean time of five days (Bactec 9240, Becton Dickinson Microbiology Systems, Sparks, MD, USA). Isolation and identification of micro-organisms were usually made using standard media, methods and techniques. The API 20E system (Biomerieux, Marcy l'Etoile, France) was used to identify Gram-negative organisms, and DNAse and latex agglutination/coagulase to identify staphylococci. The Stokes disc diffusion method was used for anti-microbial susceptibility testing (22). The Maki roll plate semi-quantitative technique was used for catheter tip culture (22). For all positive results, Gram stain, identification and antibiotic sensitivity 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) was performed as clinically indicated.

Statistical analysis: SPSS software (SPSS Inc., Chicago, IL) was used for statistical analyses. For continuous variables, rank values were compared using non-parametric tests (Mann-Whitney U, Wilcoxon Rank Sum W, or Kruskal-Wallis One-Way Analysis of Variance). Differences in proportions were compared using either Chi-squared or Fisher's exact tests for expected cell frequencies less than 5.

Cumulative Kaplan-Meier plots were constructed from the day of ICU admission and from the onset of ICU-BACT to estimate the probability of developing 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.
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Definitions: CDC definitions were used for every type of infection (13).

RESULTS

Study population 713 patients (455 males; 47% surgical; median age 62 y. [Inter-Quartile Range (IQR) 45-72]) were admitted to ICU in the six-month period. Median ICU stay was 3 days (IQR 2-5) with 143 (20%) dying in the ICU, 51 within three days. Twenty-five were transferred to other hospitals, and 545 were discharged to a general ward, of whom 30 died. Overall APACHE II standardised mortality rate (SMR) was 0.96. Patients admitted from the ward had higher APACHE II scores than the general population [20 (14-26) vs 16 (11-21) p<0.001]. Similarly both patients admitted from Accident & Emergency Department with a C-BACT and those admitted from hospital wards with a H-BACT together with patients experiencing an ICU-BACT during their ICU stay, had higher APACHE II scores than general population [C-BACT: 23 (18-27), H-BACT: 23 (20-31) ICU-BACT: 22 (15-25) vs general population: 15 (11-20); p<0.001].

Bacteraemic patients Fourteen (1.9%) patients were admitted with C-BACT and 28 (3.9%) with H-BACT. Six H-BACT patients subsequently developed ICU-BACT, but with different microorganisms. Forty-nine (6.9%) patients experienced 60 episodes of ICU-BACT, one patient having three episodes over 63 days. The risk of developing ICU-BACT rose progressively with time, being 39% after 7 days' ICU stay, doubling after 14 days, and reaching 100% after 5 weeks. Considering only bacteraemic patients treated with mono-therapy (Table 1), Gram-positive organisms caused the majority of bacteraemia in each subgroup. Escherichia coli was the only causative pathogen of Gram-negative C-BACT, whereas Klebsiella spp. constituted 47.6% of all cases of ICU-BACT. Only two patients had ICU-acquired fungaemia, one case occurring after femoral venous catheter insertion into an infected groin. Main sources (Table 2) for C-BACT were cardiovascular (endocarditis) and urinary tract, whereas gastro-intestinal and respiratory for H-BACT. Intra-vascular devices were considered the source in 23 (42.5%) of ICU-BACT.

Sensitivity patterns (Table 3) (considering only patients treated with monotherapy) In the C-BACT group, MRSA was isolated from one previously hospitalised patient. Escherichia coli strains were sensitive 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%) multi-drug resistant Gram-negatives were identified, one being expanded-spectrum β-lactamase (ESBL) producing. Of seven Candida spp. five were fluconazole-resistant.
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In the ICU-BACT group, all 11 Staphylococcus aureus isolates were methicillin-resistant. Five (45.4%) were MRSA carriers prior to ICU admission, the others being colonised after a median ICU stay of 14 days (IQR 7-21). All vancomycin-resistant organisms were isolated in long-stay hospital patients (median 2 months, IQR 15-83 days). Only two (6.5%) Gram-negative isolates were multi-drug resistant and no ESBL-producing microorganisms were found.

Severity of illness (Table 4) 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%), while 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 Monotherapy policy was applied in most (76%) of patients as shown is Figure 1. Combination therapy was reserved for a total of 24 bacteraemic episodes associated with severe deep-seated infections, (i.e. endocarditis, necrotizing fasciitis, osteomyelitis, cerebral abscess, or multi-drug resistant Gram-negative bacteraemia, or polymicrobial infections. In one patient, experiencing a fungaemia due to Candida glabrata the choice was not to treat him, as in severe renal failure likely to be impaired by using amphotericin B. Despite our odd choice patient survived and no long term sequelae were recorded over a 6 month period follow-up. Three ICU-BACT episodes had low-grade pyrexia and received no treatment other than vascular catheter change. Four patients died within 24 hours from ICU-admission, therefore we had no time to start an adequate antibiotic therapy course.

Table 4 shows that a five-day median course of monotherapy was used in the majority of C-BACT (8 cases, 57%), H-BACT (22 cases, 79%) and ICU-BACT (48 episodes, 80%) patients, despite a lot of them complicated by septic shock (50% for C-BACT, 68% for H-BACT and 31% for ICU-BACT) and/or deep seated infections (50% for C-BACT, 41% for H-BACT and 69% for ICU-BACT. Despite opting for monotherapy, in most cases before culture results were known, antibiotic therapy was not subsequently altered in 73 (93.5%) out of 78 episodes. Two patients with C-BACT, 3 with H-BACT and 5 with ICU-BACT received additional antibiotics due to lack of clinical response, even though therapy was appropriate in terms of laboratory sensitivity testing.
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The decision to stop antibiotics was based upon clinical response, i.e. resolution of bacteraemia-related clinical findings & improvement in related organ dysfunction (eg. dose of norepinephrine). Using these criteria, a clinical response was recorded in most patients for each episode treated with short course monotherapy (Table 4). Six patients responded to antibiotic therapy with resolution of the related systemic inflammatory response but subsequently died due to persisting organ failure. Fourteen deaths were directly attributable to bacteraemia, where organ function continued to deteriorate despite sensitive antibiotic therapy.

Three H-BACT and two ICU-BACT patients who died while still receiving antibiotics developed breakthrough bacteraemia, three being due to Staphylococcus 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 Only 2 out of 6 relapsing bacteraemic episodes occurred in patients underwent a short course of monotherapy, both likely resulted from non-changing of intra-vascular catheters colonised after the first episode. Gram-negative microorganisms were responsible for all six relapse episodes, namely Escherichia coli for one C-BACT, and Klebsiella spp. (3), Serratia marcescens, (1) and a Pseudomonas spp.(1) for ICU-BACT. The other two ICU-BACT relapses occurred in patients with faecal peritonitis seven days (IQR 5-9) after finishing antibiotic therapy. Four of five relapsing ICU-BACT had received an eight-day median course of combination therapy. Three relapsing episodes were treated with 7 days' monotherapy, and three with 7 days' combination therapy; no further relapses occurred.

Mortality (Table 4) Crude ICU and hospital mortality (unadjusted for illness severity) was higher in bacteraemic patients (p<0.001, \textit{t} 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). On the other hand, considering patients treated with mono-therapy, we recorded a crude mortality of 42% and a directly related one of 20.2%. 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. Due to low patient numbers, C-BACT and H-BACT were not examined.

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 ten 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%) (38 treated with mono-therapy) bacteraemic patients who survived were transferred to other hospitals and the remaining 43 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 (2 C-BACT, 2 H-BACT, 2 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 \((2,3,4,5,6,7,8,9,10)\). As further corroboration, no 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), while North American and mainland European ICUs generally use longer courses (7-14 days). Definitive assessment of the efficacy of short course monotherapy requires large, randomised, 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 \((9,10)\). 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 re-occurrence.

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 colonisation and persistence of intra-abdominal abscesses. The worse clinical response and higher mortality in these patients reflects their underlying illness severity. Similarly, the worse outcome in H-BACT patients reflects their higher APACHE II score, their underlying disease severity and the high proportion (46%) of immunosuppression. The higher mortality in ward patients has been attributed to delays in antibiotic treatment and inadequate resuscitation (\textsuperscript{21}).

Patients that developed ICU-BACT were sicker on ICU admission compared to other long stay (≥3 days) patients not developing ICU-BACT. This increased susceptibility is related to their underlying disease processes and the greater requirement for invasive procedures (e.g. vascular access, mechanical ventilation) (\textsuperscript{15,16,71,130}). 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 (\textsuperscript{18}).

The low incidence of ICU-acquired multi-drug resistant microorganisms and the zero incidence of ESBL-producing Gram-negative pathogens is uncommon when compared to recent North American and European studies that routinely express concern about the high frequency of such infections (\textsuperscript{25,26,27}). 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 prior to ICU admission than those colonised during their ICU stay. 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 (\textsuperscript{28,29,30}). 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 (\textsuperscript{11}). 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 (\textsuperscript{31,32,33}). Any link between short course monotherapy and a low incidence of fungaemia and multi-drug resistant Gram-negative bacteraemia must remain as supposition at present, but offers an important hypothesis that warrants further investigation. In support of this theory, multi-drug 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. Moreover, as reported by others (\textsuperscript{11,34}), we recorded a higher prevalence of non-albicans Candida species; this is likely due to over-utilisation of fluconazole which has shifted the spectrum of Candida to more resistant species such as Candida glabrata and Candida krusei.

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 multi-drug 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 underway. Verification of the above findings will hopefully lead to randomised controlled studies and
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important guidance as to optimal antibiotic treatment strategies in the critically ill.

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APPENDIX 1: DEFINITIONS (TAKEN FROM REFERENCES 1, 10-12, 23, 34-37)
Bacteraemia/Fungaemia the growth of a viable single bacteria/yeast, in one or more blood cultures, associated with signs of infection.

Coagulase-negative staphylococcus 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.

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 48h of each other are considered as a single bacteraemic episode.

Polymicrobial 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 hours) and with clinical or microbiological evidence of the same source.

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

Relapse: a recurrent bacteraemia due to the same microorganism occurring within one week of cessation of appropriate antibiotic therapy.

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

Appropriate antibiotic therapy: refers to an anti-microbial 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.

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.

Death was considered attributable to the bacteraemia if it could be readily explained by infection without any other recognised 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.

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