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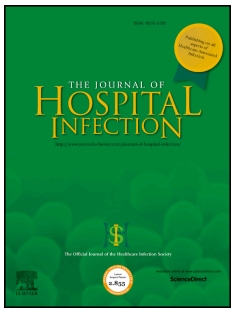

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Sepsis caused by bloodstream infection in patients in the intensive care unit: the impact of inactive empiric antimicrobial therapy on outcome

Daniel Brooks[1]*, Padmaja Polubothu[2]*, D. Young[2], MG. Booth[3] and A. Smith[1]

1. School of Medicine, Glasgow University, G12 8QQ
2. Clinical Microbiology, Glasgow Royal Infirmary,Glasgow, G4 0SF
3. Intensive Care Unit, Glasgow Royal Infirmary, Glasgow, G4 0SF

Corresponding author: Daniel Brooks Telephone Number: 07890624041 email: brooks.daniel42@yahoo.com

*D Brooks and P Polubothu contributed equally to this work.

Structured Summary

Background: Sepsis is one of the leading causes of death in the UK.

Aims: The aims of this study were to identify the rate of inactive antimicrobial therapy (AMT) in the ICU and whether inactive AMT had an effect on in hospital mortality, ICU mortality, 90-day mortality and length of hospital stay. Additionally, we wanted to identify risk factors for receiving inactive AMT.

Methods: This was a retrospective observational study conducted at Glasgow Royal Infirmary ICU between January 2010 and December 2013, with 12,000 blood cultures taken over this time period, of which n=127 were deemed clinically significant. Multivariate logistic regression was used to identify risk factors independently associated with mortality. To identify risk factors for receiving inactive AMT a univariable and a subsequent multivariate analysis was constructed.

Results: The rate of inactive AMT was 47% (n =60). Our multivariate analysis showed that receiving antibiotics within the first 24 hours of ICU admission led to a reduced mortality (RR 1.70; 95% CI 1.19-2.44.) Furthermore, it showed that severity of illness (as defined by SIRS criteria sepsis vs septic shock) increased mortality (OR 9.87; 95% CI 1.73-55.5). However, inactive AMT did not increase mortality (OR 1.07; 95% CI 0.47-2.41) or length of hospital stay (53.2 vs 69.1 days p=0.348.) We identified fungal bloodstream infection as a risk factor for receiving inactive AMT (OR 5.10;95% CI 1.29-20.14)

Conclusion: Mortality from sepsis is influenced by multiple factors. We were unable to demonstrates that inactive AMT had an effect on mortality in sepsis.

Keywords : Sepsis, Intensive care, Bacteraemia, Antibiotics, Organism, Fungal

Introduction

Blood-stream infection (BSI) can have a mortality in the intensive care unit (ICU) of up to 70%[1]. Antimicrobial therapy (AMT) is a cornerstone for treating patients with suspected infection – the Surviving Sepsis Campaign recommends initiating AMT within the first hour of recognition of sepsis[2]. However, empiric AMT started for the suspicion of infection in the ICU may be inactive in over 1 in 5 cases[3]. A positive impact of empiric AMT that is active against the infecting organism in ICU patients has not been consistently demonstrated, with some authors finding that it improves survival in severe sepsis/septic shock [4–6] whilst others have concluded that it makes no difference[7–9]. Few studies have assessed the impact of adequate antimicrobial therapy on length of stay in the ICU [10,11]. Finally, the factors that increase the risk of ICU patients receiving inactive AMT are not well known; identifying these could reduce exposure to inappropriate antimicrobials and healthcare costs.

The aims of this study were to determine the effect of inactive antimicrobial therapy on the mortality of patients in intensive care with BSI and to identify risk factors for receiving inactive AMT in such patients.

Methods

Study setting
This study was a retrospective observational study of prospectively gathered data undertaken in the intensive care unit of Glasgow Royal Infirmary (GRI), a 20 bed mixed surgical-medical ICU admitting 1000 patients annually.

Patients
All patients who had at least one blood culture drawn between 1st Jan 2010-31st Dec 2013 were identified from microbiological records. No patients admitted for specific conditions or with comorbidities were excluded. Only the index positive culture episode, consisting of all cultures taken at the initial drawing of blood, was evaluated.

Definitions
Definitions of sepsis were in line with the criteria established by Bone et al. [12]
Bacteraemia was defined as the growth of a viable organism in a blood culture taken from a patient during their ICU stay. Organisms commonly considered to be contaminants – coagulase-negative staphylococci, *Propionibacterium acnes* and *Corynebacterium spp* – were considered true infections only if isolated from a patient in two or more consecutive cultures taken on different days. Coagulase-negative staphylococci were not identified to the species level. In all cases of coagulase negative staphylococcal bacteraemia this was due to line infection.
Bacteraemia identified within <48 hours of a patient being admitted to hospital was considered community acquired. Patients admitted from wards, operating theatre or another hospital were considered to have nosocomial bacteraemia.
Empiric therapy was defined as agents that were started before a positive blood culture, and the antimicrobial susceptibility of the isolated organism, was identified. If it had *in vitro* activity against the isolated pathogen(s), the AMT was considered active. Other authors have used this approach. [8,13]

Patients who were on no antimicrobial therapy were included in the inactive cohort. Antimicrobial sensitivity testing was carried out using the automated broth microdilution Vitek ® 2 system from BioMérieux.

Study design

Demographic, clinical and microbiological data were gathered from eligible patients, including isolated organism(s), time and number of cultures and antimicrobial therapy at time culture, from WardWatcher (Critical Care Audit Limited, West Yorkshire, UK) and CareVue (Philips Medical Systems, Surrey, UK). The empiric AMT of all patients was reviewed by a clinical microbiologist prior to their records being included in this study.

Statistical analysis

Continuous variables were compared using Student's *t*-test or the Mann-Whitney U test for continuous variables and categorical variables Pearson chi-square test. Univariate factors with a p-value of <0.2 were entered into a multivariate logistic regression model along with the outcome variable to determine factors independently associated with increased mortality.

To identify risk factors for receiving inactive AMT a multivariate analysis was constructed as above, with 'inappropriate AMT' as the outcome variable. A p-value of <0.05 was considered significant. Data were analysed using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS, Chicago, IL).

Results

Study population

Over the study period, 1083/3759 patients admitted to the ICU had blood cultures taken. Positive blood culture episodes were identified in 207 (19.1%) patients, of which 127 were considered clinically significant and could have empiric antimicrobials assessed.

Patient characteristics and presentation

The mean age was 55.8 years (SD 15.5) and the mean APACHE II score was 22.7 (SD 8). Seventy-two patients (57%) were male and 14 (11%) had a previous ICU admission. Fifty-eight patients (46%) were classified as a medical admission, 77 patients (61%) had received antimicrobials prior to ICU admission whilst 91 patients (72%) received antimicrobial therapy within two days of ICU admission. At the index positive culture episode, 20 patients (16%) met criteria for sepsis, 55 (43%) for severe sepsis and 52 (41%) for septic shock. Of all admissions, 42 (33%) patients were admitted from the emergency department or from operating theatres having not resided previously in hospital. Twenty-one of these had a time between admission and positive culture episode of ≤2 days and were thus classified as community acquired bacteraemia, with 106 cases (84%) classified as nosocomial bacteraemia. The median time to a positive culture from ICU admission was 2.0 days (IQR 0-7).

Antimicrobial therapy

Sixty patients (47%) had inactive empiric AMT; in 43 cases (72%) this was due to the patient either being on no therapy when the positive culture was taken or because the therapy they were on had no intrinsic activity against the organism isolated

('wrong' antibiotics). The remaining 17 cases received an antibiotic to which the organism was resistant.

Microbiology

A breakdown of the organisms isolated from all cultures making up the index positive episodes is available in Table I. Table II shows the breakdown of these organisms by AMT exposure status. The total number of isolates exceeding the number of patients/blood culture episodes assessed is due to patients having multiple sets of cultures drawn simultaneously (for example from an indwelling line and peripherally, or two peripheral cultures) and polymicrobial isolates. Fifty-nine patients (46%) had two or more cultures from different sites positive with the same organism(s). Nine patients (7%) had cultures positive for two or more clinically significant organisms (polymicrobial). Of the remaining unimicrobial episodes, 66 (52%) were gram negative, 44 (35%) were gram positive and ten (8%) were fungal. The most commonly isolated organisms were *Staphylococcus aureus* (16%, n=33) and *Escherichia coli* (19%, n=39).

Mortality

Sixty-eight patients (54%) did not survive to hospital discharge. Within the active AMT group, 37 (55%) patients did not survive, compared to 31 (52%) in the inactive AMT group. Table II provides a breakdown of active vs inactive AMT by organisms isolated. Risk factors for in-hospital mortality are shown in Table III. In the univariate analysis patients who died had significantly higher APACHE II scores and were more severely ill. Community acquired bacteraemia was also associated with a higher risk of death. Receiving antibiotics within 24 hours of ICU admission and having a surgical reason for admission were both protective factors. No specific microorganisms were associated with greater mortality (data not shown). Inactive empiric therapy was not associated with an increased in-hospital mortality. This held true when stratifying by severity of infection or analyzing only cases due to resistance (RR 0.88, 95% CI 0.71-1.09) or no intrinsic activity (RR 1.19 95% CI 0.88-1.61). Subgroup analyses did not demonstrate greater mortality with inactive AMT in any specific group.

The results of multivariate logistic regression for ICU, in-hospital and 90-day mortality are listed in Table IV. The only factor independently associated with increased in-hospital mortality was severity of illness (septic shock vs sepsis OR 9.87 (95% CI 1.73-55.5)). Inactive AMT did not independently increase in-hospital mortality, (OR 1.07 (0.47-2.41)).

Length of stay

In patients who survived to hospital discharge, there was no significant difference in length of stay between those who received active or inactive empiric AMT (53.2 vs 69.1 days, p=0.348).

Risk factors for inactive empiric antimicrobial therapy

We also analysed the 60 patients who received initially inactive therapy and compared to them to the patients who received active therapy. In a multivariate analysis, only the presence of a fungal infection (OR 5.10; 95% CI 1.29-20.14) was independently associated with receiving inactive AMT.

Discussion

A number of factors have been shown to increase mortality in sepsis including immunosuppression, age, illness severity, high APACHE II score, delay in receiving AMT, and hospital acquired sepsis. [9,14] Our study showed that septic shock was associated with increased mortality (OR 5.24 (1.35-20.36)) whereas receiving antibiotics within 24 hours of ICU admission led to a reduced mortality (RR 0.79; 95% CI 0.65-0.98). This emphasises the importance of recognising sepsis early and instituting treatment as per the Surviving Sepsis Campaign. [2,15]

In the univariate analysis, we found that mortality was greatest with a higher APACHE II score (24.4 in non-survivors vs 20.8 in survivors, p=0.011) and in community acquired bacteraemia (RR 5.21; 95% CI 1.61-16.80). The higher mortality with community acquired bacteraemia contrasts with others who have found that patients with hospital acquired bacteraemia have a higher mortality. [14,16] We found that the community acquired patients had a higher APACHE II score (26 vs 21 p=0.04); met more SIRS criteria at time of culture (3.1 vs 2.5 p=0.01) and a higher proportion of these patients were in septic shock at time of culture (62% vs 37% p=0.06). Therefore, our community acquired bacteraemia group had a greater severity of illness than the hospital acquired group.

We defined therapy as active if the antimicrobial(s) the patient was on when a culture was flagged as positive were effective against the isolated organism. This included fungal organisms and patients receiving no therapy which may explain why our rate of inactive therapy is higher than reported elsewhere although comparing rates of inactive AMT is problematic due to varying definitions. Some studies defined AMT as active if empiric therapy was active prior to organism identification and sensitivity results; here rates of inactive AMT of 8.5% [17] and 23.5% [8] were found . Marshcall et al and Kang et al defined AMT as active if given within 24 hours of sampling with rates of inactive AMT of 31.6% [18] and 52.8% [9] respectively. The rate of inactive AMT by Garnacho-Montero et al was 17% and they defined it as adequate based on the patients' admission antibiotics to ICU. [11] Varying definitions of 'inactive' therapy likely contribute to different studies of the impact of inactive AMT reaching opposing results.

Our results demonstrated that septic shock increases mortality, however we did not find that inactive AMT affects mortality or length of stay. This was a surprising finding given our own observation that receiving antibiotics within 24 hours of admission reduced mortality. A high proportion of our population (84%) met criteria for severe sepsis or septic shock at time of positive culture, implying that they were experiencing some form of organ dysfunction. Whilst antimicrobials are essential for treating the initiating/underlying infection, it is likely they have less of an effect on the immune dysregulation and subsequent organ dysfunction that characterise sepsis. In these cases, factors such as intensive organ support available in ICU, comorbidities, age and underlying genetics probably have a far greater prognostic influence. When we analysed mortality with inactive AMT by severity of infection, we found no difference. We believe this supports our theory that by the time patients have developed sepsis or shock, immunological and genetic factors primarily determine outcome. Additionally, organisms such as enterococci or coagulase negative staphylococci comprised a high proportion of isolates; it is possible that this 'diluted'

excess mortality caused by more pathogenic isolates such as *Pseudomonas* species, and thus reduced the observable mortality benefits of antimicrobial therapy. We analysed the impact of inactive AMT stratified by organism, however no differences between subgroups was found, likely because the numbers available were simply too small for an effect to be detected. Organisms such as *S. aureus* can produce toxins that may increase mortality that other low virulence organisms such as coagulase negative staphylococci do not. Whilst with *S. aureus* no effect on mortality has been found for Panton-Valentine leucocidin toxin producing strains or superantigen producing strains, there has been a potential link with increased mortality and cytotoxic exotoxin producing strains[19].

Our laboratory uses the Vitek ® 2 system for antimicrobial sensitivity testing. Broth microdilution systems have reported higher MIC's for piperacillin/tazobactam than agar dilution methods for *Escherichia coli* and therefore potentially overcall resistance. [20] Users of the Vitek ® 2 during our study period have reported higher piperacillin/tazobactam MIC's from the system than with manual Etests for gram negative organisms. Our study period overlaps with the period when resistance testing was potentially inaccurate, however; none of the patients who received inactive AMT were on piperacillin/tazobactam monotherapy.

Previous antibiotic exposure [11,17], antibiotic resistant bacteria [5], Pseudomonas [7], hospital acquired infection [5,7] and fungal infection [5,11] have all been identified as risk factors for inactive AMT. Our study only identified fungal infection as a risk factor for inactive AMT (OR 5.10; 95% CI 1.29-20.14.) ICU patients will often have risk factors for fungal infection such as invasive catheters, immune-compromise or GI surgery[21]. Clinicians may not assess for these risk factors and therefore do not think of antifungal cover as part of their antimicrobial escalation regimes when patients deteriorate. Because of this study we will now assess patients for risk factors for candidaemia.

This study had several weaknesses that need to be considered. Firstly, the efficacy of dosing of antibiotics was not assessed and this is particularly relevant for antibiotics such as aminoglycosides. AMT was assessed to be active or inactive at the time blood culture sensitivities were known; we did not assess the impact on mortality of changes to AMT therapy made once a positive culture was flagged up, which is a potential confounder. Finally, our study was conducted with a relatively small sample size in a single centre.

Conclusions

Sepsis/shock caused by bacteraemia in the intensive care population will comprise a small, but significant and resource intensive proportion of sepsis cases in hospitals. Such patients will have multiple factors influencing prognosis. We have demonstrated that in our patient cohort, inactive empiric therapy compared with active empiric antimicrobial therapy did not affect outcome measures. Further insight in future studies by use of greater stratification of patient cohorts, particularly by causative infective agent would be helpful. Our findings underline the complexities when assessing active empiric antimicrobial efficacy and outcome in all cases of

sepsis. Finally, we identified candidaemia as a risk factor for receiving inactive antimicrobial therapy.

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Table IV - Multivariate logistic regression for risk factors associated with ICU, in-hospital and 90 day mortality in intensive care patients with sepsis caused by blood stream infection

Risk factor	ICU mortality	In-hospital mortality	90 day mortality
	OR (95% CI)		
APACHE II	1.03 (0.97-1.09)	1.04 (0.98-1.10)	1.04 (0.98-1.11)
Age	0.99 (0.96-1.02)	1.00 (0.98-1.03)	1.01 (0.98-1.04)
Admission type			
PS* vs Medical	0.55 (0.17-1.79)	0.50 (0.16-1.57)	0.53 (0.17-1.67)
US[+] vs Medical	0.92 (0.36-2.32)	0.77 (0.30-1.96)	1.22 (0.47-3.18)
US vs PS	1.67 (0.48-5.81)	1.53 (0.47-4.99)	2.28 (0.70-7.40)
Nosocomial BSI[#]	0.63 (0.25-1.61)	0.53 (0.21-1.35)	0.56 (0.21-1.44)
Antibiotics within 24 hours of ICU admission	0.35 (0.25-0.89)	0.51 (0.20-1.37)	0.41 (0.15-1.13)
Severity of illness			
Severe sepsis	1.92 (0.47-8.00)	2.88 (0.76-10.89)	2.79 (0.79-9.85)
Septic shock	1.93 (1.31-23.2)	5.24 (1.35-20.36)	3.89 (1.06-14.30)
Inactive AMT[$]	1.35 (0.61-3.11)	1.07 (0.47-2.41)	0.99 (0.44-2.24)

* PS: planned surgical
[+]US: unplanned surgical
[#]BSI: blood-stream infection
[$]AMT: antimicrobial therapy

Table I- Organisms isolated from index positive blood cultures

Gram positive	
Staphylococcus aureus	33
Coagulase-negative *Staphylococci*	20
Enterococcus spp.	31
Clostridium spp.	2
Streptococcus pneumonia	1
Other *Streptococcus* spp.	2
Gram negative	
Escherichia coli	39
Klebsiella spp.	23
Pseudomonas spp.	10
Enterobacter spp.	7
Proteus mirabilis	2
Acinetobacter baumannii	2
Citrobacter braakii	2
Stenotrophomonas maltophilia	1
Aeromonas hydrophilia	2
Morganella morganii	2
Serratia marcescens	4
Burkholderia cepacia	2
Fungi	
Candida albicans	16
Other *Candida* spp.	4
Saccharomyces cervisiae	2
Total	207

Table II- List of organisms that were exposed to active antimicrobial therapy and inactive antimicrobial therapy

Inactive AMT		Active AMT	
Gram positive			
Clostridium spp.	2	*Clostridium spp.*	2
Enterococcus spp.	19	*Enterococcus spp.*	12
S. aureus	13	*S. aureus*	20
CNS	12	*CNS*	8
Streptococcus pneumoniae	1	*Streptococcus pneumoniae*	1
Other strep spp.	0	*Other strep spp.*	2
Gram negative			
Enterobacter spp.	3	*Enterobacter spp.*	4
Pseudomonas spp.	3	*Pseudomonas spp.*	7
Acinetobacter spp.	2	*Acinetobacter spp.*	0
E coli	6	*E coli*	33
Klebsiella spp.	5	*Klebsiella spp*	18
Stenotrophomonas	1	*Stenotrophomonas*	0
Proteus spp.	2	*Proteus spp.*	0
Morganella spp.	2	*Morganella spp.*	0
Serratia spp.	4	*Serratia spp.*	0
Burkholderia spp.	2	*Burkholderia spp.*	0
Citrobacter spp.	0	*Citrobacter spp.*	1
Aeromonas spp.	0	*Aeromonas spp.*	1
Fungi			
Candida albicans	11	*Candida albicans*	5
Other candida spp	4	*Other candida spp*	0
Saccharomyces	0	*Saccharomyces*	2

Table III- Univariate analysis of risk factors for in hospital mortality in intensive care patients with sepsis caused by blood stream infection

Factor	Survivors	Nonsurvivors	RR (95% CI)	P-value
Age	53.4	58.6	-	0.086
APACHE II	20.8	24.4	-	0.011
Gender (female)	24	31	1.12 (0.75-1.68)	
Antibiotics within 48 hours of ICU	47	44	0.79 (0.65-0.98)	
Admission type				
Medical	21	37	1	
Planned surgical	18	9	0.42 (0.22-0.83)	
Unplanned surgical	19	22	0.78 (0.49-1.25)	
CCI score*				
0	17	16	1	
1-2	22	25	1.08 (0.75-1.56)	
≥3	19	27	1.18 (0.81-1.75)	
Severity of infection				
Sepsis	15	5	1	
Severe sepsis	28	27	1.30 (0.99-1.69)	
Septic shock	16	36	1.70 (1.19-2.44)	
Community acquired bacteraemia	3	18	5.21 (1.61-16.80)	
Inactive AMT (all)	29	31	1.07 (0.7-1.49)	
Inactive AMT (sepsis)	7	3	0.75 (0.23-2.42)	
Inactive AMT (severe sepsis)	15	10	1.35 (0.83-2.22)	
Inactive AMT (septic shock)	7	18	0.88 (0.52-1.53)	
Gram negative organisms				
Sepsis (inactive; n=6/12)	4	2	5.00 (0.29-86.4)	
Severe sepsis (inactive; n=10/31)	8	2	0.32 (0.09-1.17)	
Septic shock (inactive; n=7/21)	2	5	0.93 (0.55-1.59)	
Individual organisms				
Enterococcus spp. (inactive; n=10/13)	3	7	2.10 (0.40-10.94)	
E coli (inactive; n=4/27)	1	3	0.41 (0.07-2.31)	
Klebsiella spp. (inactive; n=5/16)	3	2	0.73 (0.22-2.45)	
Pseudomonas spp.(inactive; n=3/9)	2	1	0.25 (0.05-1.36)	
Staphylococcus aureus (inactive; n=11/21)	6	5	1.13 (0.42-3.10)	
*Charlson Comorbidity Index score				