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Predictors of bacteraemia and mortality in patients with acute liver failure

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Abstract *Purpose:* To determine what physiological and biochemical factors predict development of bacteraemia and mortality in patients with acute liver failure (ALF). *Methods:* Retrospective analysis of 206 ALF patients admitted to a specialist liver intensive therapy unit (LITU) from January 2003 to July 2005 (data collected prospectively). *Results:* A total of 206 patients were defined with ALF: 72 (35%) suffered bacteraemia (BAClf) and 134 (65%) did not (NBAClf). Gram positive organisms were observed in 44% of isolates, gram negatives in 52% and fungaemia in 4%. Median time to first bacteraemia was 10 (7–16) days. On admission, BAClf patients had higher SIRS scores and degrees of hepatic encephalopathy (HE). During their LITU course, BAClf patients had significantly increased requirements for renal replacement therapy (RRT), mechanical ventilation, and longer median LITU stay. Multivariate analysis (logistical regression) demonstrated significant predictors of bacteraemia on admission were HE grade >2 (Odds Ratio 1.6) and SIRS score >1 (OR 2.7). In all patients, independent predictors of mortality (logistical) were age (OR 1.41), maximum HE grade pre-intubation (1.76), Lactate (1.14) and Acute Physiology and Chronic Health Evaluation II score (APACHEII) (1.09), but not bacteraemia. Transplantation was protective (OR 0.20). *Conclusion:* In this study, severity of hepatic encephalopathy and SIRS score >1 were predictive of bacteraemia. APACHEII was independently predictive of mortality in all ALF patients but not bacteraemia.

Keywords Sepsis · SIRS · APACHE · Transplantation · Critical illness

Abbreviations

ALF	Acute liver failure
BAClf	Bacteraemic acute liver failure patients
95% CI	95% confidence interval
HE	Hepatic encephalopathy
HR	Heart rate
ICU	Intensive care unit
LITU	Liver Intensive therapy (care) unit
LT	Liver transplantation
MAP	Mean arterial pressure
MV	Mechanical ventilation
NBAClf	Non-bacteraemic acute liver failure
NINSS	Nosocomial infection national surveillance scheme
OR	Odds ratio
RRT	Renal replacement therapy
SIRS	Systemic inflammatory response syndrome
TA	Tracheal aspirates
VAP	Ventilator-associated pneumonia

Introduction

Patients with acute liver failure (ALF) are abnormally susceptible to infection as a result of acquired immunological deficits [1, 2]. In previous studies, the main localisation of bacterial infection in ALF was in the respiratory tract with a median of 5 days to the diagnosis of pneumonia and 3 days to bacteraemia [3]. The rate of clinically significant positive cultures has been reported at between 10 and 80% with attributable mortality ranging from 10 to 37% [4–6].

In common with other immunocompromised patients, those with ALF may respond abnormally when infected. Previous studies have shown a third fail to develop a neutrophil response or a temperature greater than 38°C or less than 36°C [3]. Furthermore, ALF may frequently present almost indistinguishably from septic shock [7], related to the inflammatory focus of the necrotic liver.

Classically, sepsis and septic shock have been defined by the components of the systemic inflammatory response syndrome (SIRS) [8, 9]. Varied clinical and laboratory manifestations of SIRS in ALF are likely to be the result of variable response to increased cytokine production of monocytes and macrophages in response to infectious stimuli, including bacterial lipopolysaccharide [10–12]. Inflammatory responses have been associated with exacerbation of encephalopathy and increased risk of intracranial hypertension and infection may or may not be a contributor to the clinical picture seen at any time.

In this study, we reviewed 72 ALF patients admitted to a specialised liver intensive therapy unit (LITU) between January 2003 and July 2005 who developed bacteraemia, and compared their physiological and biochemical profile along with clinical outcomes with 134 patients with ALF admitted during the same time period who did not [13]. We were particularly interested in answering the following questions; (1) what physiological and biochemical factors predict development of bacteraemia in patients with ALF, and (2) what factors impact upon mortality?

Methods

Our study protocol was approved by an ethics committee (National Health Service, UK). We performed a retrospective analysis of 206 patients admitted with a diagnosis of ALF to LITU at King's College Hospital between January 2003 and July 2005. Physiological and microbiological data had been previously collected and entered into a dedicated database. ALF was defined as the presence of hepatic encephalopathy (HE) in a patient who has developed synthetic dysfunction (jaundice, coagulopathy) in the absence of prior liver disease [14].

Standard aerobic and anaerobic (2 × 10 ml of blood) paired samples were taken on admission from new central lines inserted as well as one peripheral site. Blood cultures were also taken upon clinical suspicion of sepsis (temperature, SIRS, hypotension, abnormalities of central line site). Bacteraemia was defined as one culture yielding a recognised pathogen (e.g., *Staphylococcus aureus*, *Enterococcus*, member of Enterobacteriaciae, *Pseudomonas* spp., *Candida* spp.) from a single sample or an organism that forms part of the normal skin flora isolated from more than one culture occurring within a 48-h period. This is consistent with Nosocomial Infection National Surveillance Scheme, UK (NINSS) criterion one for the definition of bacteraemia [15]. Isolation of different species from different samples or isolates of the same species from samples taken more than 14 days apart were defined as separate episodes. Positive blood culture dates and organisms were collected from microbiology databases. Patients were excluded from this analysis if positive blood culture samples were taken prior to admission to LITU; either from the ward or a referring hospital.

Three SIRS components, white blood count, temperature and heart rate, were documented on admission. As the majority of patients were mechanically ventilated having reached grade III HE, respiratory rate and carbon dioxide levels values were not used in calculating a SIRS score [16]. The definitions of SIRS used were those of the Consensus Conference on Sepsis and multiorgan failure [8].

For both ALF patients with bacteraemia (BAClf) and without (NBAClf), lengths of stay (in hospital and LITU), requirement of renal replacement therapy (RRT) and ventilation (MV) along with other physiological, biochemical and outcome data were obtained from the Riyadh Intensive Care Physiology database (RIP), LITU patient charts and patient discharge summaries. Frequency of patients' meeting King's College Criteria listing criteria (acetaminophen and non-acetaminophen), maximum grade of HE prior to intubation, listing status on the super-urgent list and the number of patients transplanted was recorded [17]. Pathogen prediction in bacteraemia associated with pneumonia by tracheal surveillance cultures is associated with a higher rate of adequate empiric antibiotic therapy [18, 19]. Qualitative tracheal aspirates (TA) collected during the same time period were correlated with bloodstream isolates. Chest radiographic data were not captured in this study.

Patients with ALF (HE, coagulopathy ± acute renal failure) were started prophylactically on piperacillin-tazobactam upon admission to LITU. Amikacin and/or vancomycin were added if indicated by cutaneous swabs. If the patient was penicillin-allergic, meropenem was used as a second-line agent. Patients would receive a course of intravenous fluconazole if they fulfilled King's College Listing criteria or had 2 of 3 criteria. Antibiotics

were adjusted based on positive cultures. Normal antimicrobial courses lasted 5 days unless clinically indicated (e.g. *Pseudomonas*). Transplanted patients who became bacteraemic after LT were included in the BAClf group. The vast majority (97%) of these patients became bacteraemic after LT.

Statistics

Statistical analysis was performed using SPSS version 14 (Chicago, USA) and STATA 10 (College Station, Texas). Differences in categorical variables between groups were analysed using the χ^2-test. Measure of central tendency for continuous variables were compared using the Mann–Whitney *U* test (non-parametric variables) and the paired *t* test (parametric) following normality testing. Continuous non-parametric variables were reported with medians and inter-quartile ranges (IQR). Parametric variables were reported as means with standard deviations (SD). Statistical significance was required at the 95% level ($P < 0.05$).

The study endpoints were bacteraemia (all patients) and in-hospital mortality (total and non-transplanted). Following univariate logistic regression analysis variables found to be significant were used in multivariate modelling using "enter" and "backwards" mode (inclusion $P < 0.10$) for prediction of bacteraemia and mortality. Transplantation was not used with death as a composite outcome measure. Multivariate modelling is reported as odds ratios (OR) with 95% confidence intervals for significant predictors of endpoints.

Results

Etiology and microbiology information

Seventy-two ALF patients (acetaminophen = 36 (50%), drug = 4, hepatitis B = 3, budd-chiari = 3, ischemia = 2, fatty liver of pregnancy = 2, seronegative/undefined = 18) met NINSS criteria for bacteraemia (BAClf), while 134 patients [acetaminophen 69 (52%), fatty liver/HELLP 13, drug 8, hepatitis B7, budd-chiari 6, ischemia 2, seronegative/undefined = 29] did not (NBAClf), giving a total of 206 (Fig. 1).

The 72 BAClf patients suffered 133 episodes of bacteraemia while in LITU. The distribution and frequency of isolates are shown in Fig. 2. Of 163 total isolates, 71 (44%) were gram positive and 84 (52%) were gram negative. Candidemia was observed in 8 isolates (4%). The three most frequent pathogens causing bacteraemia were: *Enterococcus faecium* ($n = 21$, 13%), *Klebsiella* spp. (21, 13%) and vancomycin-resistant *Enterococcus* spp. (18, 11%). The median time to first bacteraemia was 10 (7–16) days.

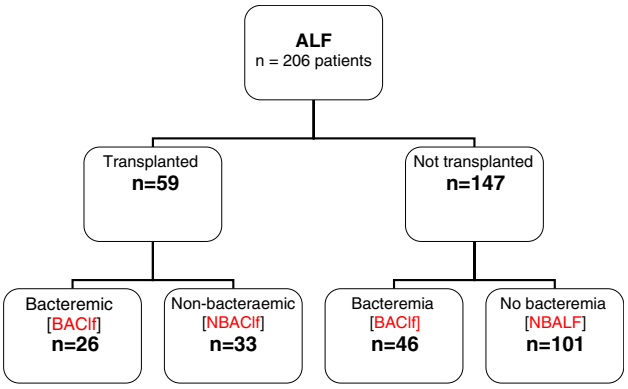

Fig. 1 Study of 206 patients with acute liver failure

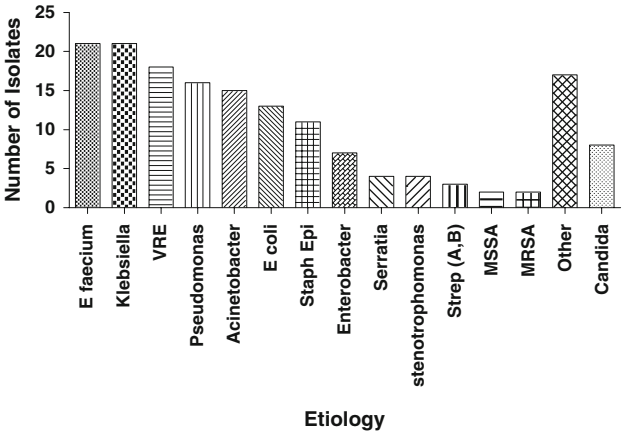

Fig. 2 Frequency of bacteraemia/fungaemia isolates in 72 ALF patients admitted to the Liver intensive therapy unit at King's College (January 2003–July 2005)

Analysis of all 206 ALF patients: admission data, requirement for organ support and transplantation

Univariate analysis

Results of univariate analysis of all 206 patients are presented in Table 1. Several factors showed significant differences. On the day of admission, BAClf patients had a significantly higher SIRS scores with 44 patients having a SIRS score ≥2. During LITU stay, more BAClf patients had a maximum HE grade >2, required RRT and were on it for a longer period. All 72 BAClf patients required MV for >24 h. Length of LITU stay was significantly longer in the BAClf group. Both groups had similar numbers who met King's College criteria and who were subsequently listed for LT. There was no difference in survival to hospital discharge between the groups.

Table 1 Univariate analysis of physiological and outcome data for all ALF patients ($n = 206$)

Variable	NBAClf (%)	BAClf (%)	*P* value
	$n = 134$ (65)	$n = 72$ (35)	
Median age	38 (28–48)	39 (27–47)	0.78
Sex (males)	56/134 (42)	31/72 (43)	0.98
On admission			
Respiratory rate	20 (16–26)	18 (15–24)	0.13
Temperature (°C)	36.2 (1.4)	35.8 (1.1)	0.44
MAP (mmHg)	67 (58–80)	67 (59–79)	0.85
Heart rate	108 (80–122)	107 (95–126)	0.49
On vasopressors	46/134 (34)	22/72 (31)	
White blood count	10.0 (6.1–13.9)	9.9 (5.1–14.1)	0.80
SIRS score	1.0 (1.0–2.0)	2.0 (1–2)	**<0.001**
SIRS score ≥2	54/134 (40)	44/72 (61)	**0.004**
PO_2/FiO_2 ratio	287 (162–404)	242 (157–345)	**0.09**
INR	3.2 (2.0–4.7)	3.0 (1.9–4.9)	0.94
Creatinine (mmol/l)	150 (96–236)	128 (99–199)	0.81
Bilirubin (mmol/l)	87 (49–198)	93 (57–152)	0.90
Lactate (mmol/l)	3.6 (2.3–6.7)	3.4 (2.0–5.1)	0.26
Ammonia (μmol/l)	103 (63–140)	101 (71–162)	0.78
pH	7.4 (7.27–7.40)	7.37 (7.28–7.4)	0.71
APACHEII	17.6 (9.5)	18.1 (8.0)	0.74
Glasgow coma score	8 (6–14)	8 (7–10)	0.50
During total LITU stay			
RRT in LITU	87/134 (65)	66/72 (92)	**<0.001**
Days on RRT	3 (0–9)	16 (8–27)	**<0.001**
MV in LITU	103/134 (77)	72/72 (100)	**<0.001**
Days on MV	5 (2–11)	20 (13–27)	**<0.001**
Maximum HE grade >2	84/134 (63)	58/72 (81)	**0.008**
Length of LITU stay	7 (3–13)	26 (18–36)	**<0.001**
KCH criteria[a]	69/134 (51)	39/72 (54)	0.83
Listed for transplant	41/134 (31)	27/72 (36)	0.40
Transplanted	33/134 (26)	26/72 (36)	**0.08**
Survival[b]	86/134 (64)	45/72 (62.5)	0.93

All parametric continuous data (temperature, APACHEII) are presented as mean values with standard deviation. All non-parametric continuous data are presented as median values with interquartile ranges. All categorical data are presented as absolute numbers and percentages

Significant values shown in bold; $P = NS$ if not otherwise specified

ALF Acute liver failure, *BAClf* bacteraemic acute liver failure patients, *HE* hepatic encephalopathy, *LITU* liver intensive therapy unit, *MAP* mean arterial pressure, *MV* mechanical ventilation, *NBAClf* Non-bacteraemic acute liver failure patients, *RRT* renal replacement therapy

[a] KCH Criteria, King's College Criteria (see [14])

[b] Survival to hospital discharge

Table 2 Logistic regression model predicting mortality in all ALF patients (using APACHEII to adjust for illness severity)

Predictor	Odds ratio	Standard error	95% CI	*P* value
Liver transplant	0.20	0.09	0.08–0.49	<0.0001
APACHEII	1.09	0.03	1.04–1.14	<0.0001
Age	1.41	0.20	1.06–1.86	0.02
Lactate	1.14	0.06	1.03–1.26	0.006
Maximum HE grade	1.76	0.37	1.16–2.67	0.007

Odds ratios are expressed for APACHEII (incremental units), lactate (per 1 mmol/L). Odds ratio per 10-year deviation from the mean age 37.8 years. Maximum hepatic encephalopathy (HE) grade pre-intubation

Multivariate analysis of all patients: bacteraemia and mortality

A multivariate logistical regression of all patients was performed to determine which factors predicted the development of bacteraemia. Significant predictors of bacteraemia on multivariate analysis were admission HE grade ≥3 (OR 1.6; 95% CI, 1.1–2.3; $P = 0.01$) and admission SIRS score ≥2 (OR 2.7; 95% CI, 1.4–5.4; $P = 0.004$). Two regression models were developed to predict mortality; SIRS (not using APACHEII) and APACHEII (not using SIRS). Using multivariate logistic regression analysis, SIRS was not predictive of mortality; however, illness severity as measured by APACHEII was. We subsequently performed a logistical regression for all ALF patients using APACHEII to adjust for illness severity (see Table 2). Transplantation was protective. Age, lactate, APACHEII and maximum grade of HE pre-intubation were independently predictive of mortality while bacteraemia was not.

Multivariate analysis of non-transplanted ALF patients

Two logistical regression models were developed to predict mortality on non-transplanted ALF patients ($n = 147$). Models were developed using SIRS and APACHEII. Using multivariate logistic regression analysis, SIRS was not predictive of mortality however illness severity as measured by APACHEII was. On multivariate logistical regression analysis (data not tabulated), APACHEII (OR 1.08; 95% CI, 1.02–1.15; $P = 0.007$), age (OR 1.04; 95% CI, 1.01–1.08; $P = 0.01$), maximum HE grade (OR 1.66; 95% CI, 1.01–2.74; $P = 0.05$) and lactate (OR 1.41; 95% CI, 1.18–1.69; $P < 0.001$) were significant.

Tracheal aspirate data: bacteraemic ALF patients and controls

Fifty-four patients (BAClf = 41, NBAClf = 13) had 81 positive qualitative TA samples (BAClf 58, NBAClf 23) during their LITU stay (111 isolates; BAClf = 78, NBAClf = 33). In the BAClf group, 33 (80%) patients grew the same bacterial species in both blood and chest samples and of those 17 (51%) had a positive TA sample prior to diagnosis of bacteraemia. Of all isolates ($n = 111$), 70 (63%) were gram negative species, 10 (9%) were gram positive species and 30 (27%) were fungal

(*Candida* = 29, *Aspergillus* = 1). In the 17 patients who developed bacteraemia post positive TA, the median time to positive TA was 8 (6–13) days.

Discussion

In the intervening period since previous studies at King's College Hospital by Rolando (1986–1987) [3] and Wade (1986–1996) [20], the epidemiology and timing of bacteraemia has changed. While Rolando found bacteraemia to occur at day 3 (median), the median time in this cohort was longer (day 10). In Wade's study, 73% of bloodstream infections were gram positive with coagulase negative staphylococcus being the most common (34%). In our review, gram negatives are now more prevalent (52%) globally. Similarly, the aetiology of chest infections has also become predominantly gram negative (63%). Of note, Vaquero et al. showed that gram negative bacteria represented a higher fraction of causative organisms in 227 ALF patients who went on to develop Grade III/IV HE [16]. A possible explanation for this could be changes in empirical treatment for sepsis in LITU, particularly increased use of empirical piperacillin-tazobactam in patients who met King's College Listing criteria. Between 1986 and 1996, the antimicrobial regimens most frequently commenced on admission to LITU were flucloxicillin and gentamicin, flucloxicillin and ceftazidime and piperacillin with gentamicin [20]. The relationship of aetiology with increased length of stay may also reflect the cumulative exposure to environmental reservoirs (e.g. *Pseudomonas aeruginosa* [21]). More importantly, studies have shown that critically ill patients are at increased risk of bloodstream infections with increasing APACHEII score, reflecting worse multiorgan failure [22, 23].

Previous studies have shown that critically ill patients are at an increased risk of antibiotic-resistant pathogens such as *Pseudomonas*, *Acinetobacter* and methicillin-resistant strains of *S. aureus* after prior antibiotic treatment, prolonged hospitalisation or MV, RRT or increasing multiorgan failure [23, 24]. Although our study was not geared to diagnose ventilator-associated pneumonia (VAP) (no radiographic information), given that most positive TA isolates were found at a median of 8 days and were largely gram negative etiologies (27% *Acinetobacter*, 18% *Pseudomonas*), it appears that a significant number of patients may have developed VAP. Risk factors for gram negative VAP in critically ill patients include >48 h on a ward prior to ICU admission, and >8 days in an ICU [25–27].

In this cohort, ALF patients with increased severity of liver disease were more predisposed to bacteraemia and required more organ support. This is supported by the fact that, on multivariate analyses, admission SIRS score ≥2 and maximum HE grade were independently associated with the development of bacteraemia. Of the 155 patients who required RRT following admission to LITU, 60% (94) were initiated within the first 48 h (median time to bacteraemia was 10 days). Leithead et al. showed similarly in 308 patients (multivariate analysis) with ALF, that while admission SIRS and paracetamol induced ALF were independent predictors of renal dysfunction ($P < 0.05$), infection was not [28].

Admission SIRS scores (out of three) were found to be higher in BAClf patients irrespective of whether or not they went on to be transplanted. Given the fact that patients developed bacteraemia 10 days later, this finding on admission may be a surrogate for increased hepatic necrosis contributing to severity of illness and predisposition to multiorgan failure and bacteraemia. Previous studies have shown that patients with higher SIRS scores early on after ICU admission exhibit increasingly severe acute hepatic failure later during their ICU stay, and that higher SIRS scores may reduce the probability of transplantation in patients with non-acetaminophen ALF [29]. Furthermore, an increased SIRS score has also been shown to be an independent predictor of outcome in patients with acetaminophen-induced ALF [30]. In contrast, Vaquero et al. showed that, while SIRS markers on admission in non-infected ALF patients were predictive of future progression of HE, neither SIRS nor infection were predictive of mortality [16]. Our results indicate that while SIRS score (≥2) was an independent predictor of future bacteraemia, APACHEII score (not SIRS) on admission was an independent predictor of mortality. APACHEII has been shown previously to be of similar predictive value as the King's College Criteria in predicting mortality in patients suffering from acute liver failure [31, 32].

The lack of survival difference between the BAClf and NBAClf groups may be explained by the role of early SIRS-related mortality versus late mortality due to the compensatory anti-inflammatory response [33]. Bacteraemic patients who survived the acute systemic inflammatory response of ALF lived long enough to develop bacteraemia, possibly due to immunosuppression from monocyte exhaustion [34]. Potentially, the severity of ALF and not bacteraemia ultimately may have a greater impact on survival. This is supported by multivariate logistical regression analysis, which demonstrated that the maximum grade of HE, APACHEII score and lactate were independently predictive of mortality.

The main limitation of this study is the nature of the retrospective analysis, and hence it is difficult to attribute cause and effect between certain clinical outcomes (e.g. requirement for RRT and bacteraemia) that may emerge at differing points in time in the clinical course. We specifically focused on admission data to determine predictors of endpoints. Nevertheless, a prospective study specifically designed to ascertain the timing of need for

RRT and emergence of bacteraemia would be of interest. Bacteraemia was used as a surrogate of sepsis given that sepsis and ALF are often indistinguishable [35]. We acknowledge that, while standard blood cultures may reflect current standards of care in LITU, we may have missed some bacteraemias that could have been detected by PCR methods and, furthermore, that some patients in the NBAClf group may have had sepsis without bacteraemia [36]. Although the length of accruement was short, we identified over 200 patients with ALF, which is of sufficient power to perform multivariate analysis. In terms of consistency in the provision of supportive medical therapy and anti-infective prescribing policies, a shorter recruitment time in a single centre is as potentially beneficial as many cohort studies in ALF recruited over many years where practice would be expected to change.

Collectively, these findings suggest that, once patients develop ALF, mortality is potentially more reflective of the underlying severity of the hepatic illness contributing to the development of multiorgan failure rather than the subsequent development of bacteraemia. Hence, while previous studies have shown attributable mortality to bacteraemia in ALF patients [4–6], we cannot draw the same conclusions from the present study.

Conclusion

In this study, severity of hepatic encephalopathy prior to intubation and admission SIRS score were independently predictive of bacteraemia in ALF. APACHEII was independently predictive of mortality but not bacteraemia in all ALF patients.

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Conflict of interest statement None.

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