Predicting 30-day mortality in patients with Sepsis; an exploratory analysis of process of care and patient characteristics

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Ethics, consent and permissions

Observational quality improvement project prospectively reviewed by the Nottingham University Hospitals NHS Trust Research and Innovation Committee in 2004. Permission granted for data collection and reporting of results by the Caldicott Guardian. The need for ethical review was waived. The project was registered with the audit office, registration number 2890. All patient identifiable metrics removed from data prior to analysis.

Declarations of interest

MJRS was an unpaid member of the NICE Sepsis (CG51) Guideline Development Group. All other authors, no conflicts to declare.

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Background: Sepsis represents a significant public health burden, costing the NHS £2.5 billion annually, with 35% mortality in 2006. The aim of this exploratory study was to investigate risk factors predictive of 30-day mortality amongst patients with sepsis in Nottingham.

Methods: Data was collected prospectively from adult patients with sepsis in Nottingham University Hospitals NHS Trust as part of an on-going quality improvement project between November 2011 and March 2014. Patients admitted to critical care with the diagnosis of sepsis were included in the study. 97 separate variables were investigated for their association with 30-day mortality. Variables included patient demographics, symptoms of SIRS (systemic inflammatory response syndrome), organ dysfunction or tissue hypoperfusion, locations of early care, source of sepsis and time to interventions.

Results: 455 patients were included in the study. Increased age (adjOR=1.05 95%CI=1.03-1.07 p<0.001), thrombocytopenia (adjOR=3.10 95%CI=1.23-7.82 p=0.016), hospital-acquired sepsis (adjOR=3.34 95%CI=1.78-6.27 p<0.001), increased lactate concentration (adjOR=1.16 95%CI=1.06-1.27 p=0.001), remaining hypotensive after vasopressors (adjOR=3.89 95%CI=1.26-11.95 p=0.02) and mottling (adjOR=3.80 95%CI=1.06-13.55 p=0.04) increased 30-day mortality odds. Conversely, fever (adjOR=0.46 95%CI=0.28-0.75 p=0.002), fluid refractory hypotension (adjOR=0.29 95%CI=0.10-0.87 p=0.027) and being diagnosed on surgical wards (adjOR=0.35 95%CI=0.15-0.81 p=0.015) were protective. Treatment timeliness were not significant factors.

Conclusion: Several important predictors of 30 day mortality were found by this research. Retrospective analysis of our sepsis data has revealed mortality predictors which appear to be more patient related than intervention specific. With this information, care can be improved for those identified most at risk of death.

Introduction

Sepsis is defined as life threatening organ dysfunction resulting from a dysregulated host response to infection [1] and represents a significant burden to UK healthcare. Between 5.1% and 7% of all deaths in the UK are associated with sepsis [2], costing the NHS £2.5 billion annually [3]. Sepsis is the second highest cause of mortality in the UK, with between 36,000 to 64,000 people dying per year [4].

Following "unacceptably high" [5] mortality rates from sepsis (and associated historical terms severe sepsis), the *Surviving Sepsis Campaign* set out to standardise treatment through protocols. Early Goal Directed Therapy (EGDT) detailed interventions for treating patients with sepsis and their time-frame. After multiple permutations of the guidelines, and their latest revision in 2016, the current recommendations include time critical administration of antimicrobial therapy and cardiovascular resuscitation (target within 1 hour and 3 hours respectively) [1]. Initial studies showed improved in hospital mortality for septic patients treated with EGDT [6]. However, subsequent research including three large clinical trials and their associated meta-analysis, have shown no significant improvement in patient outcome when using EGDT [7–10], undermining initial treatment strategies.

Despite the overwhelming burden of the disease, slow progress on treatment strategies has prompted calls for further research into sepsis. In particular, more knowledge is required of the factors that increase the risk of death from sepsis, in order to guide treatment protocols and delivery of care, and ultimately reduce sepsis-associated mortality. This exploratory study aims to investigate patient factors, signs, symptoms and process of care and their association with 30 day mortality.

Methods

Data was prospectively recorded between November 2011 and March 2014 on adult patients with sepsis presenting Nottingham University Hospitals NHS Trust, as part of an ongoing quality improvement project in managing sepsis since 2005. Patients were identified as those admitted to the critical care department including the intensive care unit, and both the medical and surgical high dependency units with the diagnosis of sepsis [11]. Inclusion criteria were based on the penultimate consensus definition for severe sepsis, with presence of two or more signs of the systemic inflammatory response syndrome (SIRS) and one or more sign of organ dysfunction or tissue hypoperfusion with a background of proven or suspicion of infection. Confirmatory blood culture was not an inclusion criterion. Patients were excluded if they were transferred from another hospital with pre-existing sepsis.

A dedicated sepsis team collected the information using a previously validated data collection tool [12]. Variables included patient demographics, symptoms of SIRS, markers of organ dysfunction or tissue hypoperfusion, source of sepsis, locations of early care, and time to interventions. These 97 variables were then assessed for association with 30 day mortality, the primary outcome (online supplement Table E1). Data on 30 day mortality was collected routinely from the hospital administrative system, including both hospital and community deaths. Time zero was the time of the initial symptom, sign or indicator of organ dysfunction or tissue hypoperfusion due to severe sepsis.

Basic characteristics were obtained using summary statistics and univariate analyses. Chi^2 and Fisher's exact test were used to assess categorical variables. Independent samples t-test and Mann-Whitney test were used for continuous data, as appropriate.

A multi-variate model was built including all those variables that were significant predictors of 30 day mortality ($p<0.05$). Those variables that that were no-longer significant were removed, then each non-significant variable was added individually to the model and keeping significant variables. Likelihood-ratio test determined the

significance of categorical variables in terms of 30 day mortality. For all tests, a significance level of $p<0.05$ was used. All data was analysed in Stata (version 13)

The data collection was registered under the Nottingham University Hospitals Audit Office, with the reference number 2890. Initial permission for data collection was granted in 2004, with an institutional waiver for informed consent. For analysis, data was anonymised, with all patient-identifiers removed from the database.

Results

455 patients were identified with severe sepsis, with 26.2% mortality. Age ranged from 17 to 95 and mean age was 64.0 years (standard deviation=16.6). 42% of patients were female.

Following univariate analysis for association with 30 day mortality (Online table E1-E11), fever (>38.3°C) (OR=0.35 95%CI=0.23-0.55), (Table E2, additional file), sepsis from skin infection (OR=0.34 95%CI=0.12-0.99), (Table E5, additional file), and not needing inotropes within 6 hours (OR=0.36 95%CI=0.15-0.89), (Table E10, additional file), were shown to be protective. Increased age (Table E1, additional file), hypothermia (core temperature <36°C) (OR=3.44 95%CI=1.83-6.45), (Table E2, additional file), altered mental status (OR=1.88 95%CI=1.14-3.10), (Table E2, additional file), coagulation abnormalities (OR=2.94 95%CI=1.00-8.61), (Table E3, additional file), thrombocytopenia (platelet count $<100x10^9$/L) (OR=2.85 95%CI=1.32-6.15), (Table E3), mottling of the skin (OR=4.50 95%CI=1.55-13.08), (Table E3, additional file), elevated serum lactate concentration (Table E8, additional file), remaining hypotensive after vasopressors (OR=3.80 95%CI=1.53-9.40), (systolic blood pressure <90mmHg or mean arterial pressure <70mmHg) (Table E9, additional file) and hospital acquired sepsis (symptoms first shown >24hours after hospital admission with different diagnosis) (OR=1.80 95%CI=1.11-2.94), (Table E11, additional file) were shown to increase odds of 30 day mortality.

Multivariate analyses (Table 1) demonstrated increasing age (OR per year increase=1.05 95%CI=1.03-1.07), thrombocytopenia (OR=3.10 95%CI=1.23-7.82), higher lactate value (OR per mmol increase=1.16 95%CI=1.06-1.27), remaining hypotensive after vasopressor treatment (OR=3.89 95%CI=1.26-11.95), hospital-acquired sepsis (OR=3.34 95%CI=1.78-6.27) and mottling (OR=3.80 95%CI=1.06-13.55) to be predictors of increased odds of 30 day mortality. In addition, fever (OR=0.46 95%CI=0.28-0.75), being on a surgical ward at the time of sepsis presentation (OR=0.35 95%CI=0.15-0.81 and fluid refractory hypotension as defined by the 2008 and subsequently 2012 Surviving Sepsis Campaign guidelines, (OR=0.29 95%CI=0.10-0.87) were shown to be protective against 30 day mortality. No process of care factors was significant in either univariate or multivariate analysis.

Table 1: Multivariate logistic regression model indicating variables significantly associated with 30 day mortality

Variable	OR[a]	AdjOR*	95%CI[b]	*p*-value
Age (per year)		1.05	1.03-1.07	<0.001
Temperature >38.3°C	0.35	0.46	0.28-0.75	0.002
Thrombocytopenia (<100x10^9/L)	2.85	3.10	1.23-7.82	0.016
Hospital-acquired sepsis	1.80	3.34	1.78-6.27	<0.001
Lactate Value (per mmol/L)		1.16	1.06-1.27	0.001
Fluid Refractory Hypotension[c]	0.60	0.29	0.10-0.87	0.027
Remain in Hypotensive State[cd]	3.80	3.89	1.26-11.95	0.02
Surgical Ward at Time Zero	0.57	0.35	0.15-0.81	0.015
Mottling of the skin	4.50	3.80	1.06-13.55	0.04

[a] Odds Ratio

*Adjusted Odds Ratio- mutually adjusted for everything in the table

[b]95% Confidence Interval

[c] Persistent systolic blood pressure <90mmHg or mean arterial pressure <70mmHg despite fluid resuscitation

[d]15 patients missing data

Discussion

Although there were a number of factors investigated, only 9 variables were predictors of 30 day mortality, and none of these were process of care variables such as timeliness of care, or seniority of doctor. Important predictors were increased age, thrombocytopenia ($<100x10^9$), hospital-acquired sepsis, increased serum lactate concentration, remaining hypotensive following vasopressors and mottling of the skin, all of which increased odds of 30 day mortality. In our data set, temperature >38.3°C, fluid refractory hypotension and being on a surgical ward were protective against 30 day mortality. With the exception of fluid refractory hypotension proving significantly protective, these variables are largely consistent with other research(13–15).

Age

There are two reasons why older age may be associated with increased mortality in patients with sepsis. First, with increased age is associated with decreased lymphocyte function, causing weakened immune responses [16]. This is compounded by poor nutritional status and altered cytokine response [17]. The second possibility is that older patients have more comorbidities (itself an independent risk factor for death from sepsis [18]).

Temperature >38.3°C

Fever may be associated with improved outcomes for both pathophysiological and care-process reasons. Fever has been associated with better outcomes in other studies including the *FACE Study Group* [13], which found the odds ratio for mortality associated with fever (37.5°C-38.4°C) was 0.45 (p=0.014), almost identical to the odds ratio found in this research. Fever enhances immune cell activity, with increased cytokine production [19], and inhibits pathogen growth, improving survival [13,20,21]. Additionally, as a widely recognised symptom and sign of sepsis even amongst non-healthcare professionals, fever may result in earlier recognition and faster treatment, which may in turn be beneficial for survival.

Thrombocytopenia (<100x10^9/L)

The finding that thrombocytopenia was significantly associated with 30 day mortality in septic patients, with an odds ratio of 3.1, is supported by other research [22–24]. *Lee et al* found that platelet count was significantly higher in survivors of sepsis than those who died (194+/-27x10^9/L versus 97+/-18x10^9/L, p<0.004), concluding also that thrombocytopenia is an independent risk factor for mortality in septic patients. Indeed low platelet count is included as a marker of poor prognosis in the SOFA score (sequential organ failure assessment), used to assess severity of organ failure [25].

Lactate value

Elevated lactate is either a marker of reduced global perfusion and tissue hypoxia with associated anaerobic cellular respiration or reduced hepatic clearance of lactate [26]. Previous studies have shown a linear relation between increased lactate and increased mortality [14], in accordance with our finding that increased serum lactate is a marker poor prognosis.

Mottling of the skin

Mottling (*livedo reticularis*) is caused by peripheral blood vessel constriction [15]. Previous studies have demonstrated an association between skin mottling and mortality [15,27]. One theory suggests that mottling reflects microvascular abnormalities, associated with organ dysfunction from microvascular shunting and hypoperfusion, and therefore increased mortality from multiple organ failure.

Fluid refractory hypotension (septic shock)

In this study, the mortality rate of patients with septic shock at 30 days was 23.9%, which is at the lower end of previous mortality estimates (22%-50%(28,29)). However, these studies above do not distinguish between patients who did not respond to vasopressor therapy, found to increase odds of 30 day mortality (see below), and

patients who did respond. Therefore, the difference in observed mortality rates may be explained by the proportion of patients who remained hypotensive after receiving fluid and subsequent vasopressors. Another plausible arugment of the apparently protective characteristic of septic shock is that it may represent the beneficial effect of expedient transfer of patients into critical care to receive vasopressor therapy, which is otherwise unavailable within the hospital. In this data set, 247 patients remained hypotensive after fluid therapy, with a median average time of admission to critical care of 6 hours (inter quartile rage [IQR] 3.86-10 hours) compared to 97 patients who responded to fluid with a median average admission time of 7 hours (IQR 4.25-14.3 hours). The wide range of times and presence of outliers; fluid refractory 0-80 hours, and fluid responsive 0-244 helps to explain why this demonstrated a trend towards statistical significance with p=0.0527.

Remaining hypotensive after vasopressor treatment

Fluid and vasopressor refractory hypotension was associated with increased mortality. In combination with the previous finding that fluid refractory hypotension was protective, this may indicate that prognosis is only poor in patients with septic shock, who fail to respond to vasopressors.

Hospital-acquired sepsis

The care of septic patients admitted to critical care from wards rather than emergency departments seems to be less well established, leading to higher in-hospital mortality [30]. This supports our findings of an increased 30 day mortality in patients diagnosed with severe sepsis on wards rather than from emergency admission areas such as the Emergency Department or acute admission unit. Additionally, comorbidity and reason for hospital stay may itself cause higher mortality within this population.

Patient on surgical ward at time of diagnosis of sepsis

Diagnosis of sepsis in patients on a surgical was found to be associated with a reduction in 30 day mortality. Surgical patients may have a source of sepsis more amenable to

source control through surgical management, such as debridement or drainage, improving survival prospects compared to medical patients in whom source control is impossible to achieve, for example in severe pneumonia. Additionally, as sepsis is a known complication of surgery [31,32], it is also possible that clinicians are more receptive of the signs and symptoms necessary to facilitate rapid diagnosis.

Process of Care Factors

Process of care factors, such as time delay to be seen, seniority of assessing clinician, and time delay to intervention were not found to significantly affect 30 day mortality. This contradicts much of the early research into sepsis care [6,33,34], which formed the foundations of EGDT and subsequent sepsis care bundles. However, recent research including a systematic review [10] of three large clinical trials [7–9] also found no significance between mortality and EGDT. It also must be considered that the apparent lack of significance between the process of care factors and 30-day mortality may be due to the low variability of care provided at our institution following over a decade of service improvement in the care of patients with sepsis. This has included hospital wide screening systems, multi-specialty and multi-disciplinary education programs, audit and performance related feedback by a dedicated sepsis team. Therefore, whilst these process factors such as time to treatment may still be significant with large variation in practice, this was not detectable in this study. This is reinforced by the recent findings of Seymour and colleagues [35].

Strengths and limitations

Exclusion criteria were minimised, making the study population representative of patients in Nottingham. As the fourth largest acute trust in the UK, the results of this study are highly generalizable to the rest of the UK. Missing data was low and the study took place in a real-world setting. Data collection was carried out by a trained and dedicated sepsis team with over a decade of experience in using the data collection

tools. It is important to note that this sepsis team were not involved in treatment of these patients.

Limitations of this study include the large number of tests carried out, increasing chance of false positive findings. If Bonferroni correction was applied only those results with a *p*-value of <0.0005 would be considered significant. This work was carried out as an exploratory study and therefore further work with larger data sets would be required to confirm the findings of interest. For the duration of this work, the historical penultimate sepsis definitions were used [11]. Although the term severe sepsis is no longer used and the definition of septic shock has changed, it is felt that the results of this study are still applicable as the core disease processes underpinning the definition have not changed.

It is important to realise a significant limitation of this study is the apparent selection bias involved in patient identification of only those admitted to critical care areas with the diagnosis of sepsis. This risks omitting a group of patients who were treated appropriately with good response demonstrating early resolution of organ dysfunction. However, this method of identification yields similar numbers compared to previous work at Nottingham University Hospitals NHS Trust [12], this may be explained by evolving practice in terms of managing patient acuity, disease severity and patient flow through the hospital pathways such that a greater proportion of unwell patients are managed on critical care than a decade ago.

Conclusion

In conclusion, this exploratory analysis presents the factors significantly associated with 30 day mortality in patients diagnosed with sepsis. Results suggest importance of patient factors associated with mortality. Age, thrombocytopenia, remaining hypotensive after vasopressor administration, hospital-acquired sepsis, increased serum-lactate concentration and mottling all increased odds of 30 day mortality. Presentation on a surgical ward, fever and septic shock were found to be protective. This paper highlights some interesting risk factors associated with mortality from sepsis, indicating the

direction of further research, particularly into the seldom researched matter of hospital acquired sepsis.

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