Does the presence of a urinary catheter predict severe sepsis in a bacteraemic cohort?

Dr Mark Melzer (author for correspondence),

Consultant in Infection,

Royal London Hospital,

Barts Health NHS Trust,

3'rd floor Pathology and Pharmacy Building,

80 Newark St.,

London E1 2ES.

mark.melzer1@bartshealth.nhs.uk

Telephone: +44203246 0412

Fax: 020 3246 0325

Dr Catherine Welch, Research Associate and Statistician,

Department of Epidemiology and Public Health,

University College London,

1-19 Torrington Place,

London WC1E 6BT, United Kingdom

catherine.welch@ucl.ac.uk

Telephone: +442076791831

Running tittle: Catheter associated UTIs, severe sepsis

Key Words:

Bacteraemia

Urinary catheter

Severe sepsis

Outcomes

Word count: 2738

Conflicts of Interest: None

Abstract

Background: Sepsis is a major cause of mortality with an estimated 37 000 UK deaths each year. We aimed to determine host factors that can predict severe sepsis in a bacteraemic cohort.

Methods: From December 2012 - November 2013, demographic, clinical and microbiological data were collected on consecutive patients with bacteraemia at a London teaching hospital site. Data were categorised into patients with severe sepsis (Pitt bacteraemia scores less than, or greater than or equal to 2) and multivariate logistic regression used to determine the association between host factors and severe sepsis.

Findings: 594 bacteraemic episodes occurred in 500 patients who were divided according to Pitt scores. The majority of bacteraemic episodes occurred both in patients aged over 50, 382/594 (64.3%), and males, 346/594 (58.2%). Commonest isolates were *Escherichia coli*, 207/594 (34.8%) and Meticillin-sensitive *Staphylococcus aureus*, 57/594 (9.6%). In logistic regression multivariable analysis, site of infection was significantly associated with severe sepsis. For catheter associated UTI, the association was significant after adjustment for age, sex, Charlson co-morbidity index and where infection was acquired, (OR 3.94, 95% CIs 1.70, 9.11).

Conclusions: Urinary catheters increase the risk of severe sepsis. They should only be used if clinically indicated and, if inserted, a care bundle approach should be used and

a removal date anticipated unless a long term catheter is required. In the context of sepsis, the presence of a urinary catheter should prompt immediate implementation of ‘sepsis 6’ and consideration of transfer to a critical care unit.

Introduction

Sepsis is a major cause of mortality with an estimated 37 000 UK deaths each year (1). Death can occur at any age inside and outside of hospital. The presentation of sepsis can be non-specific and, the diagnosis may be delayed or even missed. A recent UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) concluded that there was a lack of urgency in the management of severe sepsis, with only 1 in 3 patients receiving good care (2). The principle recommendations were that hospitals and primary care should have formal sepsis protocols, staff trained in their use and that all septic patients should receive a bundle of interventions, with senior Microbiology advice available within 24 hours. In 2015, NHS England introduced a commissioning for quality and innovation (CQUIN) payment for those NHS trusts screening for sepsis, taking cultures and administrating empirical antibiotics within one hour (3).

Because of delays in diagnosis and initiation of treatment, new sepsis definitions in 2015 were agreed to enable easier 'out of hospital' or bedside diagnosis (4). To optimise outcomes, a care bundle approach implemented within 1 hour is required (sepsis 6) (5) with further actions required within 6 hours if the patient is admitted to critical care. The National Institute of Clinical Excellence (NICE) recommends auditing outcomes in patients with severe sepsis or septic shock (6), not only to provide mortality data comparable to other institutions, but also to offer assurance that processes for managing sepsis are in place and working.

Early recognition and treatment of sepsis is the key to improving outcomes. In the literature, however, there is little data on additional host factors that predict sepsis severity at the time of presentation, other than altered mental state, hypotension and tachypnoea (7). Early identification of factors that predict severe sepsis is important for inpatients that require management in critical care, but also for patients in the community seen before blood is taken and results made available. We, therefore, aimed to determine other patient factors that can predict severe sepsis by analysing data from a bacteraemic cohort at the Royal London Hospital (RLH) in East London.

Methods:

Study setting

The study was undertaken at the RLH, Barts Health NHS Trust. The RLH serves a diverse population of approximately 250 000 patients in Tower Hamlets, East London. It is a regional referral centre for the North East London sector. In addition to Accident and Emergency, general medicine, surgery, paediatric and maternity services, the RLH has 60 high dependency and critical care beds, (including neurosurgical, renal and Obstetric and Gynaecological beds), specialist wards for renal transplant and haemodialysis patients, and a high level neonatal intensive care unit.

Study population

From December 2012 to November 2013, consecutive in-patients with bacteraemia and fungaemia were prospectively collected.

Definitions

Significant bacteraemia or fungaemia was defined as a blood culture isolate, unlikely to be an environmental or skin contaminant, ascertained from a patient with a compatible clinical syndrome. This decision was based on the patient's history, examination findings, response to antimicrobial treatment, blood culture isolate and bacterial cultures from other body sites. Community and hospital-acquired bacteraemia or fungaemia were defined as a positive blood culture obtained at least 48 hours before or after hospital admission respectively. Health-care associated

infection (HCAI) was defined as an infection in a patient who had been hospitalised for more than 48 hours in the last 90 days or, in the 30 days before bacteraemia, resided in a nursing home or attended hospital for haemodialysis or intravenous therapy. Specialities at the time of treatment were categorised as medicine, surgery, critical care, obstetrics and gynaecology and paediatrics.

Sites of infection associated with medical devices and procedures were defined according to the Centers for Disease Control and Prevention surveillance definitions (8). For central venous catheter (CVC)-associated infection, this was defined as evidence of infection (erythema, induration or pus) at a CVC exit site or isolation of the same organism from the blood or line tip. Catheter-associated urinary tract infections (UTIs) were defined as infection in patients with indwelling urethral or suprapubic catheters, or patients who intermittently self-catheterised, in the presence of symptoms or signs compatible with a UTI where no other source was identified. Other sites, not related to medical devices, were defined by clinical assessment, radiological imaging and additional bacterial cultures. Bacteraemia or fungaemia in patients with an unknown source were classified as undefined. Subsequent bacteraemic episodes were defined as an infection with the same organism occurring more than 28 days after the first episode, or a bacteraemic episode with a different organism occurring within 28 days.

Appropriate treatment was defined as any component of an antibiotic regimen, empiric or definitive, used to treat an infection to which the organism was susceptible

'in vitro'. Delay in treatment was measured from the time a significant blood culture was obtained from the patient (9). This was irrespective of the onset of sepsis.

Data collection

Attending physicians were advised to obtain blood cultures from patients presenting with symptoms and signs suggestive of sepsis before administration of empirical antibiotics. Demographical, laboratory and clinical data were collected on all in-patients who developed bacteraemia. A consultant Microbiologist, aided by several specialist registrars, reviewed case notes within 72 h of laboratory confirmation. In addition to demographic data, speciality at the time of bacteraemia, site of infection, organism, susceptibility profile, delay in appropriate treatment, Pitt bacteraemia score, Charlson comorbidity index (CCI) score (10) and outcomes were recorded. The Pitt bacteraemia score is a validated index used in other studies to quantify severity of infection, based on mental status, need for ventilation and vital signs. Patients were followed up until inpatient death, discharge home, transfer to a rehabilitation ward or recovery from infection.

Patients were treated empirically according to local guidelines based on site of infection. Once susceptibility profiles were known, antibiotic treatment regimens were rationalised to narrow spectrum agents. Outcomes were recorded as 7-day, 30-day and inpatient mortality. It was assumed that patients who were discharged prior to 7 or 30 days survived beyond 30 days.

Microbiology data

Blood cultures were analysed using the automated system BacT/ALERT3D (bioMérieux, Mary l'Etoile, France). Isolates were identified using either the VITEK MS system (bioMérieux, Mary l'Etoile, France, database v2.0) or Bruker Biotyper (Bruker Daltonics, Leipzig, Germany, software version 3.0) MALDI-TOF MS systems according to the manufacturer's instructions and the laboratory standard operating procedures. Susceptibility testing was performed on the Microscan walkAway system (Siemans Healthcare Diagnostics, Deerfield, Il, US).

Data analysis

Data were split by bacteraemia episodes with Pitt bacteraemia scores less than 2, or greater than and equal to 2. Even though some patients had more than one episode, we summarised for all episodes because many of these patients' have episodes in both Pitt bacteraemia score categories. The data were presented as numbers with percentages and comparisons using X^2 test were made. Host factors investigated for association with severity (defined as the Pitt bacteraemia score greater than or equal to 2) were age, sex, Charleston co-morbidity index, where infection was acquired and sites of infection. Using the Pitt bacteraemia score as the outcome measure, univariate and multivariate logistic regression analysis was performed and odds ratios, confidence intervals and p-values reported. The regression analysis investigated the association for the patients so we used generalised estimating equations (GEE) to account for any patients with multiple bacteraemia episodes.

Clinical governance

The clinical governance audit committee of Barts Health NHS Trust approved this study. Ethical approval was not required.

Results:

594 bacteraemic episodes occurred in 500 patients who were divided according to Pitt scores (table I). The majority of bacteraemic episodes occurred both in patients aged > 50, 382/594 (64.3%), and males, 346/594 (58.2%). Episodes were roughly distributed between community-acquired, health care associated and hospital-acquired infections. Community-acquired bacteraemia was not associated with severe sepsis (Pitt score greater than or equal to 2). The commonest bacteraemic isolates were *Escherichia coli* 207/594 (34.8%) and methicillin-sensitive *Staphylococcus aureus* 57/594 (9.6%). Patient speciality and site of infection, in particular critical care admission and catheter associated UTIs, were significantly associated with severity. Patient outcomes were significantly associated with severity and, in a subgroup of patients with a Pitt score greater than or equal to 2, mortality at 7-days was 6.0% (95% CI 3.0, 10.5) and inpatient mortality 8.7% (95% CI 5.1, 13.7) respectively.

Gram negative isolates were significantly associated with severe sepsis (table 1). There were significant differences in susceptibility profiles (table II). Co-amoxiclav resistance, meropenem resistance and ESBL production were significantly associated with severe sepsis. There was no association with aminoglycoside resistance.

Logistic regression analysis is summarised in table III. Site of infection was significantly associated with severe infection in multivariate analysis. In particular, this association was strongest for catheter associated UTI, (OR 3.87, 95% CIs 1.82, 8.22)

and this association remained significant after adjustment for age, sex, CCI and where infection was acquired, (OR 3.94, 95% CIs 1.70, 9.11).

Discussion:

In a bacteraemic cohort, after adjustment for age, sex, CCI and where infection was acquired, we demonstrated that site of infection, in particular catheter associated UTIs, was associated with severe sepsis. This is an important finding as device related infections are potentially preventable.

The strength of this study was that the Pitt score (a severity index) was used as the primary outcome rather than mortality, although both are strongly associated. At presentation, confusion, haemodynamic instability and tachypnoea are included in new guidance for recognition of severe sepsis (7). Uniquely, our data suggests that the presence of a urinary catheter is a predictor of severe sepsis and, therefore, at the earliest signs of sepsis, consideration should be given to immediate admission to hospital or, for inpatients, management in a critical care area.

Few studies have examined risk factors for severe sepsis in bacteraemic patients. In a Spanish cohort of community-onset bacteraemic UTIs from eight tertiary hospitals, risk factors associated with severe sepsis were fatal underlying disease, history of urinary obstruction and indwelling urinary catheters (11). In multivariate logistic regression analysis, urinary catheterisation remained a significant risk factor for patients without fatal underlying disease. In patients with E. coli bacteraemia, associations with severe sepsis are variable. In a 12 month prospective cohort study in two French University hospitals, one paper describes no host determinants influencing severity of sepsis at presentation although bacterial and host determinants

both influenced outcomes significantly (12). In another prospective French multicentre cohort study involving 1051 patients from 14 University Hospitals, age, liver cirrhosis, hospitalisation before bacteraemia and portal of entry were significantly associated with mortality, although no mention was made of urinary catheters (13).

Our study is of particular relevance following NHS England's initiative to reduce *E. coli* bacteraemias (14). An important part of this strategy is a reduction in urinary catheter associated bacteraemias, and our study suggests this is an important priority as not only are some of these infections preventable, but they are also associated with severe sepsis. Across the NHS there is a need for a systematic care bundle approach to urinary catheterisation (15), in particular documented reasons for insertion, anticipated date of removal and adherence to aseptic technique at insertion and during after-care. Patients with long term catheters should all receive catheter passports, community nurses should have access to guidance on the use of prophylactic antibiotics when changing catheters and some patients may benefit from suprapubic catheterisation, which is associated with less infection compared to urethral catheterisation (16). Even so, if a 20% reduction in bacteraemic catheter associated UTIs was achieved (17), this may not be sufficient in itself to achieve an overall 10% reduction in *E. coli* bacteraemias (18) for which a CQUIN payment will be available in 2016/17. However, this could have a significant impact on hospital admissions due to severe sepsis, including admission to critical care units.

There was an association between Gram-negative multiple drug resistance and severe sepsis. There is little in the literature to suggest that multiple drug resistant organisms are intrinsically more virulent, and it would appear more plausible that the association with severity was a consequence of delay in appropriate antibiotic administration due to unanticipated resistance (19).

There were limitations to this study. A larger cohort may have identified other host risk factors associated with severe sepsis, although this study was sufficiently powered to demonstrate a strong association with urinary catheterisation. Our findings apply to a bacteraemic cohorts, and it is not clear whether they are applicable to other severe sepsis cohorts without bacteraemia.

We demonstrated that in the context of sepsis, the presence of a urinary catheter should prompt immediate referral to A&E, implementation of 'sepsis 6' and, for inpatients, consideration of transfer to a critical care unit to optimise management. It should also increase awareness that unless there is a good reason, urinary catheters should not be inserted, a care bundle approach should be used, and when they are inserted a removal date anticipated unless long term catheterisation is required. A standardised approach across all UK NHS trusts is likely to contribute to a reduction in the incidence of severe sepsis and *E. coli* bacteraemia, two key elements of NHS England's strategy to improve patient safety and better utilise hospital beds.

Table I: Summary of patient and bacteraemia categorised by high and low Pitt bacteraemia score

Pitt score		**0-1**	**≥2**	
Total bacteraemia episodes		**410**	**184**	
		n (%)	n (%)	p-value
Age at time of bacteraemia infection[a]	≤ 1 month	6 (1.5)	5 (2.7)	0.058
	> 1 month and ≤ 16 years	24 (5.9)	6 (3.3)	
	> 16 years and ≤ 30 years	27 (6.6)	18 (9.8)	
	> 30 years and ≤ 50 years	97 (23.7)	29 (15.8)	
	> 50 years and ≤ 70 years	142 (34.6)	61 (33.2)	
	> 70	114 (27.8)	65 (35.3)	
Gender[a]	Male	247 (60.2)	99 (53.8)	0.141
	Female	163 (39.8)	85 (46.2)	
Where Infection Acquired	Perinatal	3 (0.7)	1 (0.5)	0.776
	Community-acquired	149 (36.3)	65 (35.3)	
	Healthcare-associated	156 (38.1)	65 (35.3)	
	Hospital-acquired	102 (24.8)	53 (0.5)	
Type of infection	Gram +ve	145 (35.4)	50 (27.2)	0.049
	Gram -ve	265 (64.6)	134 (72.8)	
Isolate	E. Coli	134 (32.7)	73 (39.7)	0.054
	K. Pneumoniae	40 (9.8)	15 (8.2)	
	P. Aeruginosa	15 (3.7)	11 (6.0)	
	MSSA	46 (11.2)	11 (6.0)	
	MRSA	3 (0.7)	1 (0.5)	
	S. Pneumoniae	17 (4.2)	10 (5.4)	
	S. Pyogenes	5 (1.2)	2 (1.1)	
	S. Agalactiae	7 (1.7)	0	
	Viridans Streptococcus	6 (1.5)	1 (0.5)	
	Acinetobacter	29 (7.1)	8 (4.4)	
	P. Mirabilis	11 (2.7)	7 (3.8)	
	E. Faecium	7 (1.7)	5 (2.7)	
	E. faecalis	18 (4.4)	2 (1.1)	
	VRE	4 (1.0)	2 (1.1)	
	E. Cloacae	14 (3.4)	8 (4.4)	
	Other	54 (13.0)	28 (15.2)	
Sensitivity patterns	Fully sensitive	97 (23.7)	48 (26.1)	0.052
	Partial resistance	214 (52.2)	74 (40.2)	
	Multiple drug resistance	97 (23.7)	55 (29.9)	
	Missing	*2 (0.5)*	*7 (3.8)*	
Speciality	Medicine (non-renal)	192 (46.8)	92 (50.0)	0.007
	Medicine (renal)	0	0	
	Transplant Recipient >6weeks	22 (5.4)	8 (4.4)	
	Transplant Recipient <6weeks	3 (0.7)	2 (1.1)	
	Non-transplant recipient	60 (14.6)	23 (12.5)	
	Surgery (General)	71 (17.3)	18 (9.8)	
	Surgery (Vascular)	2 (0.5)	1 (0.5)	
	Surgery (Orthopaedic)	4 (1.0)	0	
	ICU	18 (4.4)	23 (12.0)	
	HDU	6 (1.5)	5 (2.7)	
	HDU Surgical	2 (0.5)	2 (1.1)	
	HDU (Neurosurgical)	0	1 (0.5)	
	Paediatrics (non-neonates)	23 (5.6)	4 (2.2)	
	Neonates	7 (1.7)	5 (2.7)	

Pitt score		**0-1**	**≥2**	
Total bacteraemia episodes		**410**	**184**	
		n (%)	n (%)	p-value
Sites of Infection	CVC (uncomplicated)			0.029
	Tunnelled	34 (8.3)	13 (7.1)	
	Non-tunelled	29 (7.1)	7 (3.8)	
	CVC (Complicated/ metastatic spread)	0	0	
	Peripheral cannula	1 (0.2)	0	
	Urinary tract (catheter-associated)	26 (6.3)	33 (17.9)	
	Urinary tract (non-catheter-associated)	109 (26.6)	47 (25.5)	
	HPB			
	Cholangitis/ cholecystitis	39 (9.5)	15 (8.2)	
	Liver abscess	9 (2.2)	0	
	GI Tract	28 (6.8)	8 (4.4)	
	GU Tract	6 (1.5)	3 (1.6)	
	LRT			
	Ventilator-associated	2 (0.5)	3 (1.6)	
	Non-ventilator-associated	22 (5.4)	14 (7.6)	
	Skin and soft tissue infection	24 (5.9)	7 (3.8)	
	Peripheral joints (native)	2 (0.5)	1 (0.5)	
	Peripheral joints (prosthetic)	1 (0.2)	0	
	Vertebral column	4 (1.0)	1 (0.5)	
	Infective endocarditis (native)	8 (2.0)	6 (3.3)	
	Infective endocarditis (non-native)	1 (0.2)	0	
	Pacemaker endocarditis	2 (0.5)	1 (0.5)	
	Meningitis	4 (1.0)	2 (1.0)	
	Not defined	59 (14.4)	23 (12.5)	
Inpatient outcome[a]	Survived	402 (98.1)	168 (91.3)	<0.001
	Died	8 (2.0)	16 (8.7)	
7-day Mortality[a]	Survived	406 (99.0)	173 (94.0)	<0.001
	Died	4 (1.0)	11 (6.0)	
30-day Mortality[a]	Survived	401 (97.8)	164 (89.1)	<0.001
	Died	9 (2.2)	20 (10.9)	

[a]Reported for all bacteraemia episodes rather than patients because for many, patient episodes have both Pitt score 0-1 and Pitt score ≥2

MSSA: methicillin-susceptible staphylococcus aureus; MRSA: methicillin-resistant staphylococcus aureus; VRE: vancomycin-resistant enterococci; ICU: intensive care unit; HDU: high dependency unit, CVC: central venous catheter; HPB: hepato-pancreato-biliary; LRT: lower respiratory tract

Table II: Characteristics of Gram-ve bacteraemia with high and low Pitt bacteraemia score

Pitt score	**0-1**	**≥2**	
Total bacteraemia episodes	**265**	**114**	
	n (%)	n (%)	p-value
ESBL +ve	21 (7.9)	23 (17.2)	0.020
ESBL -ve	199 (75.1)	85 (63.4)	
Amp C +ve	5 (1.9)	2 (1.5)	
Amp C -ve	0	2 (1.5)	
Non-Enterobacteriaceae	3 (1.1)	2 (1.5)	
Missing	*37 (14.0)*	*20 (14.9)*	
Co-amoxiclav sensitive	169 (63.8)	71 (53.0)	0.048
Co-amoxiclav intermediate	12 (4.5)	4 (3.0)	
Co-amoxiclav resistant	51 (19.3)	40 (29.9)	
Missing	*33 (12.5)*	*19 (14.2)*	
Pip-Tazobatam sensitive	208 (78.5)	97 (72.4)	0.068
Pip-Tazobatam resistant	23 (8.7)	20 (14.9)	
Missing	*34 (12.8)*	*17 (12.7)*	
Meropenem sensitive	230 (86.8)	110 (82.1)	0.003
Meropenem resistant	1 (0.4)	6 (4.5)	
Missing	*34 (12.8)*	*18 (13.4)*	
Gentamicin sensitive	211 (79.6)	98 (73.1)	0.105
Gentamicin resistant	19 (7.2)	17 (12.7)	
Missing	*35 (13.2)*	*19 (14.2)*	
Amikacin sensitive	225 (84.9)	109 (81.3)	0.169
Amikacin resistant	3 (1.1)	4 (3.0)	
Missing	*37 (14.0)*	*21 (15.7)*	

Table III: Univariate and multivariate logistic regression analysis to investigate the association between patient characteristics and Pitt bacteraemia score ≥2 compared to Pitt bacteraemia score 0-1

		Univariate analysis			Multivariate analysis		
		OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	≤ 1 month	1.95	0.57,6.69	0.140	2.55	0.65,9.99	0.144
	> 1 month and ≤ 16 years	0.81	0.30,2.15		1.33	0.44,4.00	
	> 16 years and ≤ 30 years	1.69	0.84,3.37		2.39	1.12,5.08	
	> 30 years and ≤ 50 years	0.75	0.44,1.30		0.84	0.48,1.49	
	> 50 years and ≤ 50 years	Reference			Reference		
	> 70	1.38	0.88,2.16		1.08	0.66,1.76	
Sex	Female	Reference		0.426	Reference		0.126
	Male	0.86	0.60,1.24		0.73	0.49,1.09	
Charleston comorbidity index	0	Reference		0.438	Reference		0.292
	1	1.17	0.65,2.11		1.17	0.61,2.25	
	2	1.44	0.88,2.36		1.74	0.97,3.13	
	3	1.65	0.92,2.96		1.96	0.99,3.90	
	4	1.09	0.52,2.31		1.43	0.61,3.33	
	≥ 5	1.64	0.90,2.98		1.93	0.95,3.93	
Where infection acquired	Community acquired	0.85	0.55,1.32	0.504	0.94	0.57,1.56	0.393
	Health care associated	0.77	0.49,1.21		0.71	0.43,1.16	
	Hospital acquired	Reference			Reference		
	Perinatal	0.60	0.06,5.95		0.76	0.07,8.32	
Site of infection	Central vascular access	Reference		0.038	Reference		0.049
	GI tract	0.93	0.35,2.47		0.89	0.32,2.45	
	HPB infections	1.10	0.50,2.41		1.10	0.46,2.62	
	Infective endocarditis	1.50	0.48,4.70		1.82	0.55,6.05	
	LRT (non ventilator associated)	1.92	0.82,4.53		1.90	0.76,4.77	
	Meningitis	1.50	0.25,8.91		1.49	0.23,9.74	
	Orthopaedic infection	0.86	0.16,4.52		0.98	0.18,5.32	
	Soft tissue infection	1.02	0.39,2.69		1.03	0.36,2.89	
	Urinary tract (catheter associated)	3.87	1.82,8.22		3.94	1.70,9.11	
	Urinary tract (non-catheter associated)	1.35	0.72,2.56		1.27	0.63,2.59	
	Other	1.31	0.67,2.54		1.19	0.58,2.45	

Using generalised estimating equations to account for multiple bacteraemia episodes for some patients

OR: odds ratio; CI: confidence interval; GI: gastro intestinal; HPB: hepato-pancreato-biliary; LRT: lower respiratory tract

References:

1. Surviving sepsis campaign. www.survivingsepsis.org/
2. National Confidential Enquiry into Patient Outcome and Death-Sepsis. Just say sepsis! (2015). www.ncepod.org.uk/2015sepsis.html
3. NHS England. Commissioning for Quality and Innovation (CQUIN). Guidance for 2015/16. https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2014/07/CQUIN-Guidance-2015-16-PDF-641KB.pdf
4. Improving outcomes for patients with sepsis-NHS England. https://www.england.nhs.uk/wp-content/uploads/2015/08/Sepsis-Action-Plan-23.12.15-vl.pdf
5. Sepsis in adults-Management-Approach-Best Practice. http://bestpractice.bmj.com/best-practice/monograph/245/treatment/step-by-step.html
6. Sepsis: recognition, diagnosis and early management-NICE. https://www.nice.org.uk/guidance/ng51?unlid=280104107201611917351
7. Seymour CW, Liu VX, Iwashyna TJ et al. Assessment of Clinical criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; **315(8):** 762-74.
8. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1998. *Am J Infect Control* 1988; **16:** 128-40.
9. McGregor JC, Rich SE, Harris AD et al. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteraemic patients. *Clin Infect Dis* 2007; **45:** 329-37.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method for classifying prognostic comorbidity in longnitudial studies: development and validation. *J Chronic Dis* 1987; **40:** 373-83.

11. Shaw E, Benito N, Rodriguez-Bano J et al. Risk factors for severe sepsis in community-onset bacteraemic UTI : impact of antimicrobial resistance in a large hospitalised cohort. *J Infect* 2015; **70(3):** 247-54.
12. Jaureguy F, Carbonnelle E, Bonacorsi S et al. Host and bacterial determinants of initial severity and outcome of Escherichia coli sepsis. *Clin Microbiol Infect* 2007; **13(9):** 854-62.
13. Lefort A, Panhard X, Clement O et al. Host factors and portal of entry outweigh bacterial determinants to predict the severity of E. coli bacteraemia. *J Clin Microbiol* 2011; **49(3):** 777-83.
14. NHS England. Reducing HCAI-What the Commissioner needs to know. https://www.england.nhs.uk/up-content/uploads/2015/04/10-amr_lon_reducing-hcai.pdf
15. High Impact Intervention. Urinary catheter care bundle. http://webarchive.nationalarchives.gov.uk/hcai.dh.gov.uk/files/2011/03/Document-Urinary_Catheter_Care_High_Impact_Intervention_FINAL_100907.pdf
16. Warren JW. Catheter-associated urinary tract infections. *Infect Dis Clin North Am* 1997; **11(3):** 609-22.
17. Knoll BM, Wright D, Ellingson L et al. Reduction in inappropriate urinary catheter at a Veterans Affairs hospital through a multifaceted quality improvement project. *Clin Infect Dis* 2011; **52:**1283-90.
18. Melzer M, Welch C. Is E. coli bacteraemia preventable? *Lancet Infect Dis* 2012; **12(2):** 103-4.
19. MelzerM, Petersen I. Mortality following bacteraemic infection caused by ESBL producing E. coli compared to non-ESBL producing E. coli. *J Infect* 2007; **55:** 254-9.