SEPSIS: DEFINITIONS, PREVALENCE, MANAGEMENT AND OUTCOMES

by

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Abstract

Introduction: Sepsis results in life-threatening organ dysfunction, but if recognised and treated promptly, survival chances increase. Current clinical practice uses the systemic inflammatory response syndrome criteria to identify sepsis, and the sepsis six care bundle for management. Changes to the definitions of sepsis internationally and new national sepsis guidelines call into question the most appropriate way to recognise and manage sepsis.

Method: This was a two-site audit of healthcare provider's compliance to the sepsis six care bundle. All patients admitted to two NHS hospitals over 24 hours were screened for sepsis using the modified systemic inflammatory response syndrome criteria and the quick-sequential (sepsis related) organ failure assessment score. Adherence was assessed for each element of the care bundle for all patients identified with sepsis.

Results: 249 patients were screened for sepsis; 24 fulfilled the modified systemic inflammatory response syndrome criteria for sepsis, and six fulfilled quick-sequential (sepsis related) organ failure assessment criteria. Compliance was poor; only one patient received all elements of the sepsis six care bundle. Three patients (12%) died within 60 days of admission; all three were receiving palliative cancer care.

Conclusion: Current management of sepsis is below recommended standards. The prevalence of sepsis is different depending upon the screening method used. Recommendations for future work include validation of the new sepsis definitions for mortality and morbidity rates.

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List of abbreviations

ACE-inhibitor	Angiotension converting enzyme inhibitor
ARDS	Acute respiratory distress syndrome
AUROC	Area under the receiver operating characteristic curve
BHH	Birmingham Heartlands Hospital
BP	Blood pressure
CI	Confidence interval
CQUIN	Commissioning for quality and innovation
CRAG	Clinical research ambassador group
DAMPs	Danger-associated molecular patterns
DNA	Deoxyribonucleic acid
DNAR	Do not attempt resuscitation
ED	Emergency department
EGDT	Early goal directed therapy
EWS	Early warning score
HEFT	Heart of England NHS foundation trust
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Heart rate
HRA	Health research authority
FiO_2	Fraction of inspired oxygen
GCS	Glasgow coma score
GRADE	Grading of recommendations assessment, development and evaluation
ICU	Intensive care unit
IHI	Institute for health care improvement
IL-1	Interleukin-1

IQR	Interquartile range
IV	Intravenous
kPa	Kilopascals
LODS	Logistic organ dysfunction system
MAU	Medical assessment unit
MDL-1	Myeloid DAP12-associating lectin-1
MEWS	Modified early warning score
mmHg	Millimetres of mercury
NCEPOD	National confidential enquiry into patient outcomes and death
NEWS	National early warning score
NHS	National Health Service
NICE	National institute for health and care excellence
NOD	Nucleotide-oligomerization domain
O_2	Oxygen
OR	Odds ratio
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PAMPs	Pathogen-associated molecular patterns
PaO_2	Partial pressure of oxygen in arterial blood
PMNs	Polymorphonuclear leukocytes
PPI	Patient and public involvement
PRR	Pattern recognition receptors
RIG-1	Retinoic-acid-inducible gene-1
RR	Respiratory rate
qSOFA	Quick sequential (sepsis related) organ failure assessment
SEWS	Standardised early warning score

SIRS	Systemic inflammatory response syndrome
SNP	Single nucleotide polymorphism
SOFA	Sequential (sepsis related) organ failure assessment
SSCG	Surviving sepsis campaign guidelines
TLRs	Toll-like receptors
TNF-α	Tumour necrosis factor alpha
TREM-1	Triggering receptors on myeloid cells
WCC	White cell count
WHA	World Health Assembly
UHB	University Hospital Birmingham
UK	United Kingdom
US	United States
VAP	Ventilator associated pneumonia

1. BACKGROUND

The term sepsis has been in use for thousands of years since the time of Hippocrates and is derived from the Greek word sipsi (to make rotten) (1). In Hippocrates' time it was related to the putrefaction of wounds from infection. Today, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (2). It is a syndrome rather than a disease, caused by infection, with a wide variety of presentations and underlying conditions. This heterogeneity has made sepsis a difficult syndrome to define, leading to controversy over global definitions and inaccuracies in measurements of the prevalence of sepsis. Sepsis recognition by clinicians can be problematic due to the broad range of symptoms and signs related to sepsis, leading to delays in treatment and poor outcomes. Even once sepsis has been identified, management varies widely, with conflicting evidence surrounding the efficacy of current management guidelines.

1.1 The pathophysiology of sepsis

The pathophysiology of sepsis and mechanisms of multiple organ system dysfunction are complex and involve multiple interacting systems and pathways (3). The host response to sepsis will depend on the causative pathogen, microbial load, virulence of the invading micro-organism and the age, genetics and comorbidities of the host (4).

1.1.1 The normal physiological response to infection

The host response to infection begins when innate immune cells recognise and bind to microbial components (3). On the surface of host immune cells there are pattern recognition receptors (PRRs) that can recognise pathogen-associated molecular patterns (PAMPs), such as lipopeptides, peptidoglycan and flagellin (4). PRRs are categorised according to their cellular location and include toll-like receptors (TLRs), nucleotide-oligomerization domain (NOD)-like receptors and retinoic-acid-inducible gene 1 (RIG-1)-like receptors (4). PRRs also recognise endogenous danger signals (alarmins or danger-associated molecular patterns, DAMPs) that are released when there is an inflammatory insult (4).

Triggering receptors expressed by myeloid cells-1 (TREM-1) occur on host immune cells (neutrophils and monocytes) and amplify the inflammatory cascade in response to infection. Co-stimulation of TREM-1 and certain PRRs, especially TLRs, results in a synergistic increase in inflammatory signalling (4). This signalling cascade promotes transcription of genes involved in the host inflammatory response, resulting in an increase in pro-inflammatory cytokines, chemokines and nitric oxide (5). Polymorphonuclear leukocytes (PMNs) are activated and express adhesion molecules, causing them to aggregate to the vascular endothelium (6). The PMNs migrate to the site of injury, and here they release mediators that result in local vasodilatation and increased microvascular permeability (6).

This process is regulated by pro-inflammatory and anti-inflammatory mediators (6):

- Pro-inflammatory mediators include tumour necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), platelet activating factor, interferon and eicosanoids. They lead to the recruitment of more PMNs (4).

- Anti-inflammatory mediators are cytokines that inhibit the production of TNF-α and IL-1 and suppress the immune system by inhibiting cytokine production by mononuclear cells and monocyte-dependent T helper cells (4).

The balance between these mediators regulates adherence, chemotaxis, phagocytosis and bacterial killing. During a successful response to infection the invading microorganism is destroyed and tissue repair and healing takes place (6).

1.1.2 The shift from a normal immune response to sepsis

Sepsis occurs when the immune response to infection becomes dysregulated and the equilibrium between pro-inflammatory and anti-inflammatory responses becomes unbalanced (figure 1) (4). There are multiple factors that may lead to dysregulation of the host response to infection, including the effects of the micro-organism, release of large amounts of pro-inflammatory mediators, complement activation and genetic factors that may make some people more susceptible to sepsis (4):

- Bacterial cell wall components, such as endotoxin, may contribute to the progression of infection to sepsis. Elevated plasma levels of endotoxin are associated with septic shock and when endotoxin is infused into humans it reproduces many of the features of sepsis, such as activation of the complement, coagulation and fibrinolytic systems (7).

- Circulating levels of pro-inflammatory mediators, such as TNF-α and IL-1 are increased in sepsis and cause induction of other pro-inflammatory cytokines and activation of coagulation and fibrinolysis (4).

- The complement system is a protein cascade that helps to clear pathogens from an organism. The complement system appears to play an important role in sepsis; inhibition of the complement cascade decreases inflammation and improves mortality in animal models of sepsis (8).

- The most common form of genetic variation is single nucleotide polymorphism (SNP). These are stable substitutions of a single base that occur more than 1% of the time in at least one population and are scattered through the genome. There are many SNPs that are associated with an increased susceptibility to sepsis and include SNPs of genes that encode cytokines, cell surface receptors and lipopolysaccharide ligands (9).

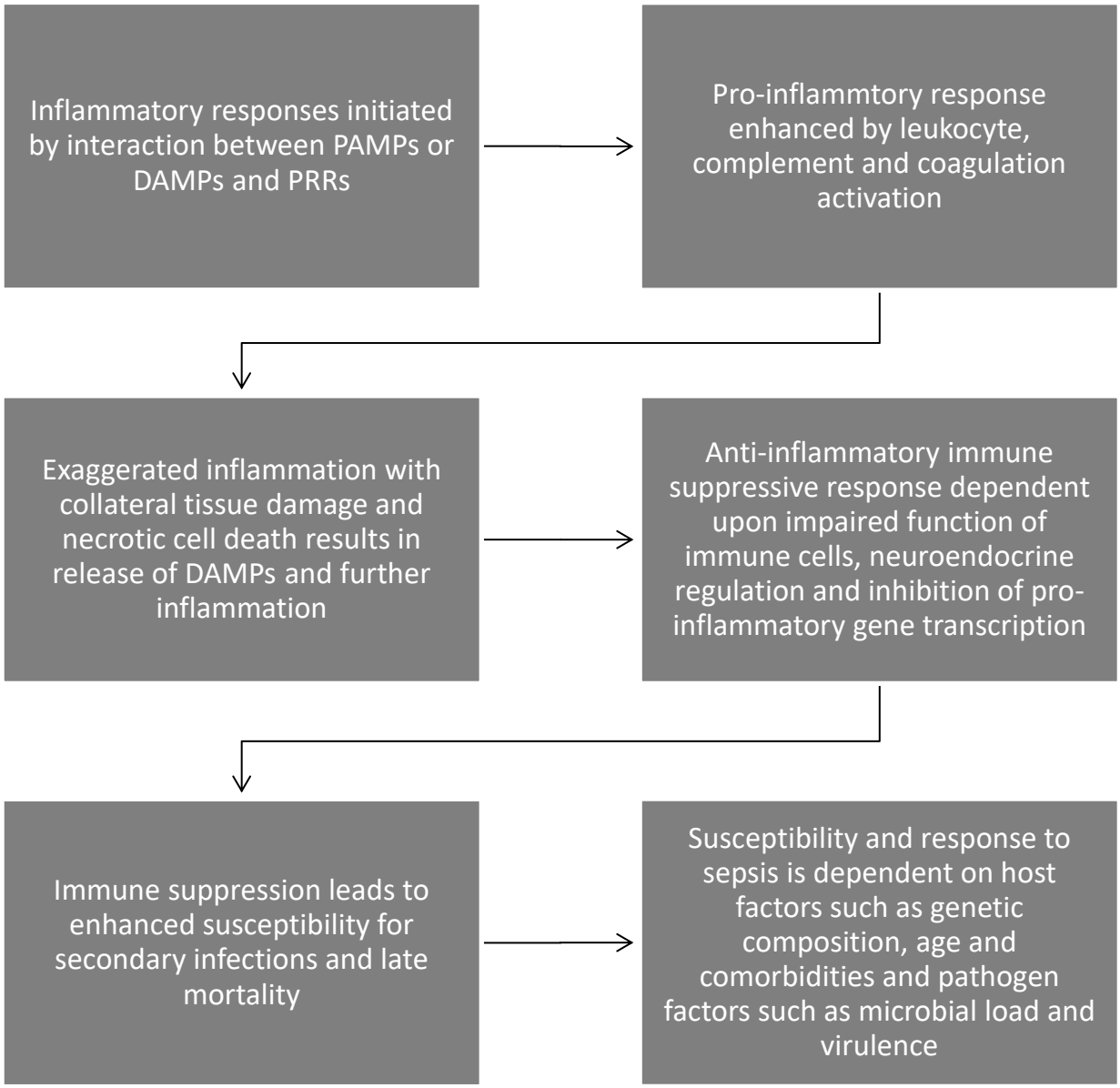

Figure 1 The host response to sepsis.

Sepsis is characterised by both pro-inflammatory and anti-inflammatory responses. Inflammatory responses are initiated by interaction between pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) with pattern recognition receptors (PRRs) on host immune cells.

Adapted from: Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence. 2014;5(1):36-44 (4)

1.1.3 Cellular injury in sepsis

The dysregulated immune response leads to cellular injury, which in turn leads to organ dysfunction. The mechanism for this is not fully understood, but includes tissue ischaemia, cytopathic injury and an altered rate of apoptosis (6).

Microcirculatory lesions occur due to the imbalance between the coagulation and fibrinolytic systems (3). Endothelial lesions occur due to the interaction of PMNs with endothelial cells (3). Erythrocytes lose their ability to deform within the systemic microcirculation, causing changes to blood flow (3). All of these changes disrupt tissue oxygenation, causing ischaemia, cellular injury and organ dysfunction (3).

Pro-inflammatory mediators and other products of inflammation may cause mitochondrial dysfunction in sepsis, due to direct inhibition of respiratory enzyme complexes, oxidative stress damage and mitochondrial DNA breakdown (10). This leads to cytotoxicity and cell injury (10).

During sepsis, pro-inflammatory mediators may delay programmed cell death in activated macrophages and neutrophils (3). This leads to a prolongation of the inflammatory response. Concurrently, epithelial cell apoptosis is increased in sepsis, and is associated with increased mortality (11).

1.1.4 Effects of sepsis on organs

The cellular injury that has been described above, in conjunction with the release of pro-inflammatory and anti-inflammatory mediators, leads to organ dysfunction, commonly

affecting multiple organs and systems.

- Circulation: Vasodilation due to prostacyclin and nitric oxide release results in hypotension. Impaired compensatory secretion of vasopressin contributes to the prolongation of hypotension in sepsis. Redistribution of intravascular fluid due to increased endothelial permeability and reduced arterial vascular tone also results in hypotension. Endothelial dysfunction leads to tissue oedema and micro-particles from circulating and vascular cells results in intravascular inflammation (3).

- Lungs: Endothelial injury in the pulmonary circulation results in disruption of capillary blood flow and an increase in microvascular permeability (3). This leads to interstitial oedema, and due to dysfunction of the alveolar epithelial barrier, this fluid then enters the alveoli. In the microcirculation of the lungs there is neutrophil entrapment, and this contributes to further injury of the alveolo-capillary membrane (6). These changes lead to a ventilation-perfusion mismatch, hypoxaemia and reduced lung compliance. The lungs have a large microvascular surface area, and therefore a large area for cellular injury due to sepsis; lung injury, manifested as acute respiratory distress syndrome (ARDS), often occurs in sepsis (6). Mechanical ventilation of the lungs as a supportive measure in ARDS is in itself associated with lung injury, perpetuating inflammation and further injury in sepsis (3).

- Gastrointestinal tract: The gut normally acts as a barrier, but in sepsis this is compromised due to the circulatory abnormalities that occur, as described previously. This leads to translocation of bacteria and endotoxin into the systemic circulation, causing propagation of systemic inflammation and resultant organ

dysfunction (3). There is an association between increasing intestinal permeability in sepsis and the development of multiple organ dysfunction; a prospective observational cohort study found that a severe derangement of intestinal permeability (measured from the urinary fractional excretion of orally administered lactulose and mannitol) present on admission to the intensive care unit was predictive of subsequent multiple organ dysfunction (natural logarithm of the ratio of the fractional urinary excretion of lactulose and mannitol (lnLMR) = -2.0 +/- 1.10 for patients with multiple organ dysfunction vs. lnLMR = -3.26 +/- 0.83 for patients without multiple organ dysfunction) (12).

- Liver: In health, the reticuloendothelial system of the liver clears bacteria and bacteria-derived products that have entered the portal system from the gut (13). Liver dysfunction prevents elimination of endotoxins and bacteria from the gastro-intestinal tract, which are then able to enter the systemic circulation, leading to bacteraemia (13). In liver dysfunction, the appropriate local cytokine release that should occur in response to an invading pathogen is absent, leading to proliferation of the pathogenic insult (13). Liver dysfunction also leads to a concomitant pro-inflammatory response, with an increase in pro-inflammatory mediators such as nitric oxide and TNFα (13). The liver is integral to metabolic homeostasis and coagulation; liver dysfunction in sepsis contributes to coagulopathy and metabolic abnormalities (13).

- Kidney: Renal injury, as evidenced by a decrease in glomerular filtration rate, is common in sepsis and is likely to be due to multiple factors, including degradation of

the glycocalyx, tubular epithelial damage and capillary endothelial damage (14). Renal failure is associated with an increase in mortality in sepsis (14).

- Central Nervous System: Encephalopathy occurs in sepsis and may be due to changes in metabolism and cell signalling due to inflammatory mediators. Dysfunction of the blood-brain barrier leads to increased leukocyte infiltration, exposure to toxic mediators and transport of cytokines across the barrier (15).

Due to the complexity of the systems involved and the heterogeneity of sepsis, there is ongoing research into the pathophysiology of sepsis. Further understanding of the pathophysiology of sepsis will help to guide subsequent management.

1.2 The global burden of sepsis

Sepsis is now a leading cause of mortality and critical illness across the world (16, 17). It has been estimated that there are 30 million episodes of sepsis and 6 million deaths due to sepsis annually worldwide (18). It's probable that this is an underestimate of the true burden of sepsis, due to a lack of data from low and middle income countries, where 87% of the population lives (18). Hospital coding, where much of the epidemiological data on sepsis originates from, will also underestimate the prevalence of sepsis, as many episodes of sepsis will be coded as the underlying disease, such as pneumonia or urinary tract infection, rather than as sepsis (19). Other studies have been based in the critical care setting, missing patients with sepsis who are treated on the ward (20). In the UK, conservative estimates on the incidence of sepsis are 147,000 per year, but this may be as high as 260,000, costing the NHS between £7.76 billion and £11.25 billion a year (21). Mortality and hospital

readmission rates for sepsis are higher than for patients who have had a myocardial infarction (22, 23). Mortality rates for sepsis are estimated to be 10%, increasing to 40% for patients with septic shock, compared to a mortality rate of 8.1% for ST elevation myocardial infarction (22, 23). Sepsis accounts for 12.2% of hospital readmissions, compared to 1.3% for acute myocardial infarction (23). The incidence of sepsis continues to rise, which is likely to be due to an increasingly ageing population with greater comorbidities, as well as an increase in the recognition of sepsis (24). It is important to establish the prevalence of sepsis on both the wards and critical care to be able to understand the extent of the problem so that resources, training, and further research can be appropriately targeted towards improving outcomes from sepsis.

In recognition of the global impact of sepsis on patient mortality and morbidity, the World Health Assembly (WHA) has adopted a resolution on improving the prevention, diagnosis and management of sepsis (25). In the UK, the National Institute of Health and Care Excellence (NICE) has acknowledged the importance of early recognition and treatment of sepsis and therefore has released guidelines on the recognition, diagnosis and early management of sepsis (26). These guidelines include recommendations for future research on sepsis, and suggest large epidemiological studies to establish the true burden of sepsis on the UK healthcare system, as well as auditing the effect of the new NICE guidelines on sepsis management in NHS hospitals (26).

1.3 Diagnosing sepsis

The survival from sepsis can be improved when sepsis is recognised and treated early (24). However, sepsis can be difficult to diagnose due to non-specific signs and symptoms, the

heterogeneity of infectious diseases that can result in organ dysfunction and the lack of a clinical biomarker to identify sepsis (27). Recent reports from the Parliamentary and Health Service Ombudsman and the National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) highlight cases of unrecognised sepsis leading to patient morbidity and mortality (28, 29), demonstrating the difficulties clinicians face when trying to diagnose sepsis. Overburdened healthcare systems with limited resources and busy staff can also contribute to missed or late recognition of sepsis, highlighting additional system-related barriers to diagnosing sepsis (30).

There is evidence that many healthcare professionals lack sufficient knowledge to be able to recognise and diagnose sepsis. One study surveyed ward nurses and found that many of the signs and symptoms of sepsis were not recognised by the nurses; only 22% of the nurses surveyed recognised that a temperature less than 36°C could be a sign of sepsis (31). Another study of paediatric intensive care nurses also demonstrated difficulties in recognising the early signs and symptoms of sepsis (32). Physicians as well as nurses struggle to understand the definitions of sepsis, as demonstrated by a Brazilian study that found that sepsis was correctly recognised by 27.3% of physicians studied (33). Although these studies focus on small groups of healthcare professionals and were conducted when the definition of sepsis was based upon the inflammatory response, they still demonstrate the differing levels of knowledge among healthcare professionals. Educational campaigns to improve healthcare professionals' knowledge of sepsis have been successful, but require on-going education to sustain knowledge, as a study involving an educational programme to promote sepsis care bundles showed a lapse in improvement after one year (34).

Healthcare professionals are often able to recognise infection and treat this with appropriate antibiotics, but miss the signs and symptoms of organ dysfunction that signify that a patient with an infection has sepsis, requiring more supportive care. Early recognition of physiological deterioration can help clinicians to identify patients with sepsis, and the Early Warning Score (EWS) was developed to help identify deteriorating patients (35). Numerical values are assigned to physiological parameters and a combined score is then assigned to the patient, with triggers for escalation of care depending on the score (35). Although not specifically designed for patients with sepsis, higher EWS has been found to be associated with a greater risk of adverse outcome in patients with sepsis (36). Data collected as part of a national audit from 2003 patients across 20 emergency departments in Scotland found that each rise in the national EWS category was associated with an increased risk of mortality in comparison to the lowest category (category 4-6: odds ratio OR 1.95; 95% confidence interval CI, 1.21 -3.14 vs. category 9-20: OR 5.64; 95% CI, 3.70 -8.60) (36). However, these scoring systems are only useful if healthcare professionals act on the high scores; senior clinical review is mandated and referral to a critical care outreach team may be indicated.

Sepsis diagnosis still proves difficult even when healthcare professional's knowledge of the syndrome is good due to the debate surrounding what actually constitutes sepsis. Ideally, a clinical or biochemical biomarker is needed that can be used as a gold-standard criteria for sepsis diagnosis, but currently there are no tests with the required level of sensitivity and specificity (27, 37). The perfect biomarker for sepsis would have fast kinetics, high sensitivity and specificity, fully automated technology, a short turn-around time, availability as a point-of-care test and low cost (37). There has been extensive research in this area,

aiming to identify early indicators of sepsis or potential predictors of sepsis severity, response to therapy and outcome. A review in 2010 by Pierrakos and Vincent evaluated 3370 studies that assessed 178 biomarkers. Despite the wide range of biomarkers studied, (including lactate, which is routinely used as a surrogate for organ dysfunction in clinical practice) none had sensitivity and specificity greater than 90% for diagnosing sepsis or predicting outcome (37). However, biomarkers could potentially be used to help rule out sepsis; Pierrakos and Vincent identified three biomarkers with high negative predictive value: procalcitonin, activated partial thromboplastin time and fibrin degradation products. However, these studies generally used culture-positive sepsis as the gold standard, yet commonly patients with sepsis have negative culture results (37).

Research in this area is problematic due to the heterogeneity of sepsis; clinical diagnostic trials investigating novel biomarkers are methodologically difficult due to a lack of consensus over the timing and diagnosis of sepsis using clinical parameters (30). It is unlikely that there is one single biomarker that can reliably diagnose sepsis, but it may be possible to have a combination of several biomarkers to accurately diagnose sepsis; further research is needed in this area (37).

1.4 International definitions for sepsis

In order to help with the recognition of sepsis, a consensus was developed in 1991 to agree on international definitions for sepsis (38). Up until 2016 these definitions changed only marginally and focussed on the systemic inflammatory response syndrome (SIRS) criteria to identify those with sepsis, severe sepsis, or septic shock (SEPSIS-2) (39). The emphasis of

the original definitions was based upon the body's inflammatory response to infection. Sepsis was viewed as a continuum in severity from sepsis through to septic shock.

1.4.1 The inflammatory response and sepsis

SIRS results from a systemic activation of the innate immune system, and can be caused by infection, trauma, thermal injury or sterile inflammatory processes such as acute pancreatitis (38). SIRS is considered to be present when a patient has two or more of any of the following clinical findings: a temperature more than 38°C or less than 36°C; a heart rate more than 90 beats per minute; a respiratory rate of more than 20 breaths per minute or a partial pressure of carbon dioxide in arterial blood of less than 32mmHg or 4.2 kPa; a white cell count more than 12000/mm^3 or less than 4000/mm^3 or more than 10% immature bands (table 1) (38).

The SEPSIS-2 definitions use SIRS as part of the criteria for diagnosing sepsis (table 2). However, SIRS lacks specificity and sensitivity to be used as a diagnostic criterion (40, 41). Shortly after the introduction of SIRS, one study found that 68% of patients on three intensive care units and three general wards had SIRS. Among these, only 26% developed sepsis (40). Another study has investigated the ability of SIRS to identify infected patients in the Emergency Department, and results demonstrated a sensitivity of 69%, and a specificity of 35% (41).

Table 1 The systemic inflammatory response syndrome

Two or more of:
• Temperature more than 38˚C or less than 36˚C • Heart rate more than 90 beats per minute • Respiratory rate more than 20 breaths per minute or $PaCO_2$ <32 mmHg (4.3 kPa) • White blood cell count >12 0 0 0 /mm^3 or < 4 0 0 0 /mm^3 or >10% immature bands

A patient is considered to have systemic inflammatory response syndrome (SIRS) if they have two or more of any of the signs or investigations listed in the table (38). ˚C = degrees Celsius. $PaCO_2$ = partial pressure of carbon dioxide in arterial blood. mmHg = millimetres of mercury. kPa = kilopascals.

Table 2 Definitions of sepsis

Consensus	**Term**	**Definition**
SEPSIS-2	Sepsis	SIRS plus documented or suspected infection
	Severe Sepsis	Sepsis complicated by organ dysfunction as defined by Multiple Organ Dysfunction Score or Sequential Organ Failure Assessment Score ≥ 2
	Septic Shock	Severe sepsis with persistent arterial hypotension despite adequate volume resuscitation
SEPSIS-3	Sepsis	A life-threatening organ dysfunction caused by a dysregulated host response to infection
	Septic Shock	A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality

The international consensus definitions of sepsis from 2001 (SEPSIS-2) and 2016 (SEPSIS-3), including the terms sepsis, severe sepsis and septic shock (2). SIRS = systemic inflammatory response syndrome.

1.4.2 Measuring organ dysfunction in sepsis

In 2016 the definitions of sepsis changed (SEPSIS-3), with emphasis moving to organ dysfunction rather than the inflammatory response, with the term severe sepsis being made redundant; what is now described as sepsis would have been defined as severe sepsis using the old definitions (table 2) (2). The SEPSIS-3 definitions were generated by a task force of specialists in critical care, infectious disease, surgery and pulmonary medicine in response to an updated understanding of the pathophysiology of sepsis compared to when the first definition was agreed over two decades ago (2). An expert consensus process then settled upon updated definitions and clinical criteria for assessing sepsis (2). Patients can be clinically identified as having sepsis (as defined by the new definition) by an acute change of two points or more in the sequential (sepsis related) organ failure assessment (SOFA) score (2), shown in table 3. The SOFA score grades abnormality by organ system and takes into account any clinical interventions (2). The higher the SOFA score, the greater the probability of mortality (2).

In addition to the SOFA score, the qSOFA (quick sequential (sepsis related) organ failure assessment) score was established as a simple bedside screening tool requiring minimal investigations to identify those at high risk of death from sepsis on the wards. This score is made up of three parameters and patients are at high risk of mortality from sepsis when two or more of these parameters are present (table 4) (2).

If a ward patient with a suspected infection has a positive qSOFA score then they should be assessed further for evidence of organ dysfunction using the SOFA score. Using the new definitions, septic shock is present when despite adequate fluid resuscitation, vasopressors

are required to keep a mean arterial pressure at or above 65mmHg, or the lactate is above 2mmol/L (2).

Table 3 The sequential (sepsis related) organ failure assessment score (SOFA)

ORGAN SYSTEM	0	1	2	3	4
Respiration: PaO_2 / FIO_2 mmHg (kPa)	$\geq$ 400 (53.3)	< 400 (53.3)	< 300 (40)	< 200 (26.7) (with respiratory support)	< 100 (13.3) (with respiratory support)
Coagulation: Platelets (x $10^3/\mu L$)	$\geq$ 150	< 150	< 100	< 50	< 20
Liver: Bilirubin (mg/dL)	< 1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	> 12.0
(μmol/L)	<20	20 - 32	33 - 101	102 - 204	>204
Cardiovascular: Hypotension	No hypotension	MAP < 70 mmHg	**dopamine < 5.0 or any dose dobutamine	**dopamine 5.1-15 or adrenaline $\leq$ 0.1 or noradrenaline $\leq$ 0.1	**dopamine > 15 or adrenaline >0.1 or noradrenaline >0.1
Renal: Creatinine (mg/dl)	< 1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9	> 5.0
(μmol/L)	< 110	110-170	171-299	300-440	> 440
OR Urine output				or < 500 ml/day	or < 200 ml/day
Neurological: GCS	15	13-14	10-12	6-9	< 6

A scoring system for the measurement of organ dysfunction (2). Score 0 – 24; severity of organ dysfunction rises as the score increases. **adrenergic agents administered for at least one hour (doses are given in μg/kg/minute). PaO_2 = arterial oxygen tension. FiO_2 = fractional inspired oxygen. MAP = mean arterial pressure. GCS = Glasgow coma score, ranges from 3-15; higher score indicates better neurological function.

Table 4 The qSOFA score

Two or more of:
• Respiratory rate of 22 breaths per minute or more • Altered mentation • Systolic blood pressure ≤ 100mmHg

The quick sequential (sepsis related) organ failure assessment score is a simple bedside screening tool to identify those patients at high risk of mortality from sepsis (2). If any two of the three parameters are present, this suggests that the patient has an increased risk of death from sepsis in the ward setting.

1.4.3 Controversy surrounding the new sepsis definitions

There has been significant debate about the validity of these new definitions compared to the older SIRS-based definitions of sepsis (42, 43). There is concern that although helpful to evaluate the epidemiology and economic burden of sepsis, it will not be helpful in the clinical setting when treating individual patients who will vary widely due to the underlying cause of their sepsis, and the heterogeneity of the sepsis syndrome (43).

In addition to concerns over the definitions, there is debate surrounding the use of SOFA and qSOFA to identify patients with sepsis (43). The SOFA score is more complex than using SIRS and requires sequential use to identify a change in the score. This means that in the clinical setting it is only accurate once sepsis has already been present for some time (the baseline SOFA score is presumed to be zero if the patient has not been scored previously), and only critical care patients will have all aspects of the scoring system measured frequently.

The SOFA and qSOFA scores were validated using retrospective data from the United States (US) that compared SIRS, SOFA, qSOFA and the Logistic Organ Dysfunction System (LODS), a weighted organ dysfunction score (42). These data were taken from 1.3 million electronic health record encounters between the 1st January 2010 and 31st December 2012 at 12 hospitals in Pennsylvania in the US. Patients who were identified with suspected infection were included in analysis. Suspected infection was identified as the combination of antibiotics and body fluid cultures (42). This study found that within the intensive care unit (7932 patients with suspected infection), the predictive validity of SOFA (area under the receiver operating characteristic curve (AUROC) = 0.74; 95% CI, 0.73-0.76; $P < 0.001$) for in-

hospital mortality was statistically greater than SIRS (AUROC = 0.64; 95% CI, 0.62-0.66; P < 0.001) or qSOFA (AUROC = 0.66; 95% CI, 0.64-0.68; P < 0.001). SOFA and LODS (AUROC = 0.75; 95% CI, 0.73-0.76; P < 0.001) had similar predictive validity, but LODS is a more complex scoring system than SOFA, leading to SOFA being recommended for use in the intensive care setting when assessing a patient for sepsis (42). On the wards (66522 patients with suspected infection), qSOFA (AUROC = 0.81; 95% CI, 0.80-0.82; P < .001) was found to have statistically greater predictive validity for in-hospital mortality than SIRS (AUROC = 0.76; 95% CI, 0.75-0.77; P < 0.001) and SOFA (AUROC = 0.79; 95% CI, 0.78-0.80; P < 0.001), leading to its adoption for use in the ward setting to identify patients at risk of death from sepsis (42).

Further studies since the publication of the new definitions have attempted to validate the new scoring systems. A study of 152 patients in the US retrospectively compared qSOFA and SIRS in patients admitted to hospital with suspected sepsis who were later admitted to ICU (44). It found that qSOFA was statistically better at predicting in-hospital mortality than SIRS (AUROC = 0.74; 95% CI, 0.66-0.81 vs. AUROC = 0.59; 95% CI, 0.51-0.67; P = 0.03) (44). This cohort only included patients who were admitted to ICU. The results could potentially have been different if patients who were only managed in the ward setting were included.

Another retrospective study in Australia and New Zealand analysed the predictive validity of SOFA, qSOFA and SIRS in the intensive care setting in 184,875 patients, and as found in the original study on validation, SOFA score was found to have significantly better predictive validity (AUROC = 0.753; 95% CI, 0.750-0.757; P<0.001) for in-patient mortality than either

SIRS (AUROC = 0.589; 95% CI, 0.585-0.593; P < 0.001) or qSOFA (AUROC = 0.607; 95% CI, 0.603-0.611; P < 0.001) (45).

However, the SOFA and qSOFA scores have not been validated within the UK healthcare setting, and only one European study of 879 patients has used prospective data to validate the use of qSOFA for the identification of patients at high risk of mortality from sepsis (46). This study found that the qSOFA score performed better than SIRS in predicting in hospital mortality (AUROC = 0.80; 95% CI, 0.74-0.85 vs. AUROC = 0.65; 95% CI, 0.59-0.70; P < 0.001) (46). This study only included patients in the emergency department, limiting the generalisability of the results.

All of the studies described used in-hospital mortality as an end-point, as this was the end-point used by Seymour et al to originally validate the SOFA and qSOFA scores (42). Prediction of longer term mortality cannot be assessed from these studies, yet is relevant as patients who survive an episode of sepsis in hospital have increased risk of mortality and morbidity for a prolonged time period (47, 48). A prospective study in Wales used 30 day mortality as its end point, and was unable to validate the use of qSOFA to predict mortality (49). This study screened patients for sepsis who had a National Early Warning Score (NEWS) of 3 or more. Out of the 5422 patients screened, 431 had a NEWS score of 3 or more and 380 of these were recruited into the study. SOFA was found to be best at predicting mortality risk (AUROC = 0.69; 95% CI, 0.63-0.76; P < 0.001), followed by NEWS (AUROC = 0.58; 95% CI, 0.51-0.66; P < 0.001), but SIRS (AUROC = 0.55; 95% CI, 0.49-0.61) and qSOFA (AUROC = 0.56; 95% CI 0.49-0.64) were unable to predict outcome in this cohort (49). This is quite different from the retrospective results presented by other studies, and

questions whether qSOFA should be used as a tool to predict mortality from sepsis on wards in the UK healthcare setting. It is possible that the results differ due to the use of 30 day mortality rather than in-hospital mortality. It is also possible that the study by Szakmany et al missed patients by only screening patients with a NEWS score of 3 or more, which may have affected their results (49).

A summary of studies assessing the predictive validity of sepsis criteria can be found in table 5. Further research is needed to assess whether clinicians in the UK should adopt the use of the new definitions and their scoring systems when assessing patients with suspected sepsis.

Table 5 Summary of studies assessing predictive validity of sepsis criteria

Study	Study type	Setting	Number of patients	Primary outcome	Criteria validated	Crude AUROC values (95% CI)	P value
Raith and coleagues (45)	Retrospective cohort	Australia and New Zealand	184875	In-hospital mortality	SOFA	0.753 (0.750-0.757)	P<0.001
					qSOFA	0.607 (0.603-0.611)	
					SIRS	0.589 (0.585-0.593)	
Seymour and colleagues (42)	Retrospective cohort	Pennsylvania	148907	In-hospital mortality	SOFA	0.74 (0.73-0.76)	P<0.001
					qSOFA	0.66 (0.64-0.68)	
					SIRS	0.64 (0.62-0.66)	
					LODS	0.75 (0.73-0.76)	
Finkelsztein and colleagues (44)	Retrospective cohort	New York	152	In-hospital mortality	qSOFA	0.74 (0.66-0.81)	P=0.03
					SIRS	0.59 (0.51-0.67)	
Freund and colleagues (46)	Prospective cohort	Europe	879	In-hospital mortality	qSOFA	0.80 (0.74-0.85)	P<0.001
					SIRS	0.65 (0.59-0.70)	
Szakmany and colleagues (49)	Prospective cohort	Wales	380	30-day mortality	SOFA	0.69 (0.63-0.76)	P<0.001
					qSOFA	0.56 (0.49-0.64)	
					SIRS	0.55 (0.49-0.61)	
					NEWS	0.58 (0.51-0.66)	

A table summarising the findings of studies examining the predictive validity of sepsis criteria, including SIRS (systemic inflammatory response syndrome), SOFA (sequential (sepsis related) organ failure assessment score), qSOFA (quick sequential (sepsis related) organ failure assessment score), LODS (logistic organ dysfunction system) and NEWS (national early warning score). Crude AUROC and P values are demonstrated for each main study finding related to the study's primary outcome.

1.5 NICE guidelines on sepsis recognition and diagnosis

Although the NICE guidelines on sepsis recognition, diagnosis and early management have acknowledged the new definitions of sepsis, it has stated that these definitions are not useful in the early identification of people at risk of sepsis (26). NICE endorses actions according to clinical parameters that stratify risk of severe illness or death from sepsis. As a result of this, NICE recommendations do not use either SIRS or SOFA criteria to identify patients with suspected sepsis. Instead there is a comprehensive list of signs, symptoms and risk factors to identify patients at low, moderate or high risk of sepsis. This strategy is likely to identify more patients "at risk" of sepsis than either the SIRS or SOFA criteria, although the aim of this risk stratification is similar to that of the qSOFA score. The NICE risk stratification criteria are far more comprehensive than the three parameters used in the qSOFA score, which may help to ensure that high risk patients are not missed, but may also result in more false positives (table 6) (26). The NICE stratification system is not as user friendly as the qSOFA score, which may result in clinicians being reluctant to use it.

A study conducted at Heartlands Hospital in Birmingham retrospectively reviewed the notes of 415 consecutive patients who presented to the acute medical unit. Twenty per cent of patients were identified with sepsis using the SIRS criteria, 33% had sepsis according to NICE criteria, and 4% were positive for the qSOFA score (51). This demonstrates in this cohort the large number of patients identified with sepsis by NICE guidelines. This study also attempted to assess the sensitivity and specificity for sepsis of the different systems used to identify sepsis by comparing to a consultant's clinical impression of sepsis (51). NICE guidelines were less specific but more sensitive than qSOFA, however a comparison against

one clinician's opinion of what constitutes sepsis is an inaccurate method to use as a gold standard.

Research is needed to assess the validity of NICE guidelines in diagnosing suspected sepsis and identifying those at highest risk of mortality from sepsis, and the impact of the guidelines on patient outcomes.

Table 6 NICE risk stratification tool for adults, children and young people aged 12 years and over with suspected sepsis

Category	High risk criteria	Moderate to high risk criteria	Low risk criteria
History	Objective evidence of new altered mental state	History from patient, friend or relative of new onset of altered behaviour or mental state History of acute deterioration of functional ability Impaired immune system (illness or drugs including oral steroids) Trauma, surgery or invasive procedures in the last 6 weeks	Normal behaviour
Respiratory	Raised respiratory rate: 25 breaths per minute or more New need for oxygen (more than 40% FiO2) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)	Raised respiratory rate: 21-24 breaths per minute	No high risk or moderate to high risk criteria met
Blood pressure	Systolic blood pressure 90mmHg or less or systolic blood pressure more than 40mmHg below normal	Systolic blood pressure 91-100mmHg	No high risk or moderate to high risk criteria met

Category	High risk criteria	Moderate to high risk criteria	Low risk criteria
Circulation and hydration	Raised heart rate: more than 130 beats per minute Not passed urine in previous 18 hours For catheterised patients, passed less than 0.5ml/kg of urine per hour	Raised heart rate: 91-130 beats per minute (for pregnant women 100-130 beats per minute) or new onset arrhythmia Not passed urine in the past 12-18 hours For catheterised patients, passed 0.5-1ml/kg of urine per hour	No high risk or moderate to high risk criteria met
Temperature		Tympanic temperature less than 36˚C	
Skin	Mottled or ashen appearance Cyanosis of skin, lips or tongue Non-blanching rash of skin	Signs of potential infection, including redness, swelling or discharge at surgical site or breakdown of wound	No non-blanching rash

A tool developed by NICE (the national institute for health and care excellence) to help stratify a patient's risk of mortality from sepsis into low, moderate to high, or high-risk criteria (26). Criteria are taken from the patient's history, examination and vital signs. FiO2 = fraction of inspired oxygen. mmHg = millimetres of mercury. ˚C = degrees Celsius

1.6 Management of sepsis

Once sepsis has been recognised, prompt management can help decrease the mortality from sepsis (29). The Surviving Sepsis Campaign has devised international guidelines for the management of sepsis and septic shock (52). These guidelines were most recently updated in 2016 from the 2012 guidelines. A summary of the recommendations for the initial management of sepsis can be found in table 7 (52). A consensus committee of 55 international experts on sepsis convened to develop these guidelines. The committee searched for the best available evidence on sepsis management, and assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (52). This resulted in 93 statements on the early management and resuscitation of patients with sepsis and septic shock. Thirty-two of these were strong recommendations, 39 were weak recommendations, 18 were best-practice statements and there were no recommendations for four of the statements, demonstrating that there is substantial agreement amongst experts on the management of sepsis (52). However, there is controversy over the use of care bundles derived from the Surviving Sepsis Campaign Guidelines (SSCG) for the management of sepsis, due to low compliance rates and conflicting data on patient outcomes (53).

Table 7 Recommendations from the surviving sepsis campaign guidelines on initial sepsis management

Recommendation	Level of evidence/recommendation
In sepsis–induced hypoperfusion, 30ml/kg of IV crystalloid fluid should be given within the first 3 hours	Low quality evidence, strong recommendation
An initial target mean arterial pressure of 65mmHg in patients with septic shock requiring vasopressors	Moderate quality evidence, strong recommendation
Guide resuscitation to normalise lactate in patients with elevated lactate levels	Low quality evidence, weak recommendation
Appropriate routine microbiologic cultures obtained before starting antimicrobial therapy in patients with suspected sepsis as long as there is no delay in starting antimicrobials	Best practice statement
Administration of IV antimicrobials within one hour of recognition of sepsis	Moderate quality evidence, strong recommendation
Identify source of infection as rapidly as possible and implement source control as soon as possible	Best practice statement
Norepinephrine as the first choice vasopressor	Moderate quality evidence, strong recommendation

A summary of recommendations from the Surviving Sepsis Campaign Guidelines related to the initial management of sepsis, with the associated level of evidence and recommendation listed for each recommendation (52). IV = intravenous. mmHg = millimetres of mercury.

1.6.1 Early goal directed therapy in sepsis

Early goal directed therapy (EGDT) is a 6 hour resuscitation algorithm where therapy is guided by optimisation of haemodynamic goals targeting arterial blood pressure, central venous pressure and central venous oxygenation saturation (54). A single centre randomised trial in 2001 of 263 patients presenting to the emergency department with septic shock found that EGDT decreased short-term mortality compared to standard care (in hospital mortality 30.5% in EGDT group vs. 46.5% in the standard therapy group, P = 0.009) (54). This led to the Surviving Sepsis Campaign endorsing EGDT in 2004, but compliance was poor and further trials failed to show any improvement in survival when patients were treated with EGDT.

A multi-centre randomised trial of 1341 patients in the United states on the Protocolized Care for Early Septic Shock (ProCESS study) found that there was no significant difference in mortality when patients were managed either by protocol-based EGDT, protocol-based standard therapy or usual care (relative risk with protocol-based therapy vs. usual care, 1.04; 95% CI 0.82-1.31; P = 0.83; relative risk with protocol based EGDT vs. protocol-based standard therapy 1.15; 95% CI 0.88-1.51; P = 0.31) (55).

An Australasian study (the Australasian Resuscitation in Sepsis Evaluation (ARISE) study) of 1600 patients across 51 centres also found that EGDT did not reduce all-cause mortality at 90 days compared to usual care (absolute risk difference with EGDT vs. usual care, -0.3 percentage points; 95% CI -4.1 to 3.6; P = 0.9) and also demonstrated that patients in the EGDT group received a larger mean volume of intravenous fluids (1964ml vs. 1713ml) in the first 6 hours after randomisation compared to the usual care group and were more likely to

receive vasopressor infusions (66.6% vs. 57.8%), red-cell transfusions (13.6% vs. 7%) and dobutamine (15.4% vs. 2.6%) (P < 0.001 for all comparisons) (56).

A third multi-centre study in the UK (the protocolised management in sepsis (ProMISe) study, which completed the trio of studies on EGDT) of 1260 patients also found no significant difference in 90-day mortality between patients managed using EGDT and patients managed using usual resuscitation (absolute risk reduction −0.3%, 95% CI −5.4 to 4.7; relative risk 1.01, 95% CI 0.85 to 1.20; P = 0.9) (57).

A meta-analysis of 11 randomised controlled trials, including the ProCESS, ARISE and ProMISe multi-centre trials, demonstrated no significant difference in mortality yet an increase in the use of intensive care resources (increased vasopressor use and increased ICU admission) with EGDT compared to standard care. (58). It is possible that the lack of survival benefit is related to an overall increased standard of care in hospitals treating patients with sepsis compared to management in 2001. However, it does highlight the pitfalls of using a bundled approach to sepsis management.

1.6.2 The sepsis six care bundle

Hospitals in England and Wales have adopted the use of the one hour sepsis six care bundle for the management of patients with suspected sepsis. The sepsis six care bundle is a bundle of six interventions designed to improve patient outcomes when completed within one hour of sepsis being identified in a patient (table 8) (22).

Table 8 The sepsis six care bundle

Give high-flow oxygen via non-rebreathe bag	Take blood cultures and consider source control
Give IV antibiotics according to local protocol	Check lactate
Start IV fluid resuscitation e.g. Hartmann's or equivalent	Monitor hourly urine output and consider catheterisation

The six elements of the sepsis six care bundle, which has been adopted by hospitals in England and Wales for the initial management of sepsis (22). All six steps of the bundle should be completed within one hour of recognition of sepsis. IV = intravenous.

Care bundles were developed by the Institute for Health Care Improvement (IHI) and are small collections of evidence-based tasks, that when implemented together should achieve better outcomes than when instigated individually (53). Bundles are designed by selecting interventions with the greatest benefit to be included in the bundle. However, this means that not all potentially beneficial interventions will be included, and there is a lack of peer reviewed data to support the assertion that better outcomes are achieved when bundles are used (53).

Sepsis care bundles have generated controversy for over a decade, with concerns over implementation and absence of supportive evidence (53). Despite its widespread application across England and Wales, evidence on the efficacy of the sepsis six care bundle is lacking. Since the establishment of the one-hour sepsis six care bundle in 2007, there has been limited data on compliance rates with the bundle, and studies related to the impact of the care bundle on mortality rates show conflicting results. A prospective observational cohort study conducted when the bundle was initially established showed that out of 567 patients with severe sepsis, 36.6% received the bundle, with a mortality rate of 20%, compared to 44.1% for patients who did not receive the care bundle (22). In an observational study in Wales of 2716 acute admissions in 2015, of the 51 (1.9%) patients diagnosed with sepsis only three (6%) received the full sepsis six care bundle within one hour (59). No mortality data were collected from this study.

A multicentre, prospective observational study in Wales of 1,111 patients found that completion of the full sepsis six care bundle occurred in 12% of patients with sepsis (60). This study found no significant difference in mortality related to the delivery of the sepsis six

care bundle (60). A quality improvement project in a busy Emergency Department in the UK demonstrated an improvement in mortality rates when compliance to the sepsis six care bundle was improved (61), yet another quality improvement project set in a UK district general hospital showed no significant difference in mortality rates despite an increase in adherence to the sepsis six care bundle (62). Both of these quality improvement projects involved small numbers of patients and included several quality improvement initiatives that had the potential to improve overall patient care even when the sepsis six care bundle was not adhered to, possibly confounding the mortality rate results.

The large reduction in patient mortality observed in the first study when the bundle was originally established has not been replicated in any other studies (22). The original study was observational and involved small numbers and was unable to control adequately for confounding factors. The study was also performed at the same time as an educational campaign at the hospital to highlight sepsis and its management. It could be that the improvement in mortality was related to an overall higher standard of care related to increased clinician awareness of sepsis due to the educational programme, rather than a direct impact of the bundle. Furthermore, a breakdown of compliance to individual elements of the bundle showed a significant reduction in mortality for taking blood cultures, giving fluids and giving antibiotics, and not for the other three bundle interventions (22). This suggests the importance of certain elements of the management of sepsis, such as giving intravenous antibiotics, rather than the importance of a bundle of care as a whole.

1.6.3 NICE guidelines on early sepsis management

The current NICE guidelines on sepsis management have moved away from the one hour sepsis six care bundle, although elements of the care bundle that are evidence based are included, such as obtaining blood cultures prior to the administration of antibiotics (26). However, other elements of the care bundle have been modified, such as only giving oxygen to those who need it to maintain oxygen saturations at an appropriate level, conceding to evidence of the potential detrimental effects of hyperoxia (63). The NICE guidelines on sepsis management are more complicated than the sepsis six care bundle, and involve different management depending on the risk stratification level of the patient. These management guidelines are more tailored to individual patients than the sepsis six care bundle, and respond to changes in the patient's condition, making it more dynamic than the care bundle. The downside of this is an increase in complexity of management that may result in poor compliance to the guidelines. As the guidelines have only recently been implemented, there is currently no published data on adherence to the NICE guidelines, or patient outcomes following instigation of the guidelines.

1.6.4 Timing of sepsis management

As well as concerns over the efficacy of sepsis care bundles, there is a lack of consensus over timing of the management of sepsis. The sepsis six care bundle should be delivered within one hour of identifying a patient as having sepsis (or within one hour of admission to hospital if they are admitted with sepsis). NICE guidelines recommend the treatment and review of patients at high risk of sepsis within one hour (26) and NHS England

Commissioning for Quality and Innovation (CQUIN) national goals include the administration of antibiotics within 60 minutes of a patient being diagnosed with sepsis (64).

A study in New York state of 49,331 patients at 149 hospitals has demonstrated lower mortality for patients who received a bundle of care (intravenous antibiotics, blood cultures and lactate measurement) within three hours of arrival in the emergency department (65). This retrospective study analysed data routinely collected between 2014 and 2016, after New York began requiring hospitals to follow protocols for the early identification and treatment of sepsis in 2013. The study found that each additional hour of time to completion of the 3 hour bundle was associated with higher mortality (odds ratio of death until completion of the 3-hour bundle, 1.04 per hour; 95% CI, 1.02-1.05; $P < 0.001$) (65). Patients who had the bundle completed anytime between 3 and 12 hours had an even higher risk of in-hospital death (OR 1.14; 95% CI, 1.07 to 1.21; $P < 0.001$) (65).

There is also evidence that administering antibiotics within one hour decreases mortality, and that every hour delay shows a stepwise drop in survival (66). A retrospective cohort study of 2,731 patients with septic shock found that administration of antibiotics within the first hour of documented hypotension was associated with a survival rate of 79.9% (66). Each hour of delay over the next 6 hours was associated with an average decrease in survival of 7.6%. This study used retrospective data between 1989 and 2004, before the implementation of sepsis care bundles, and only focussed on patients with septic shock.

A more recent cohort study performed between 2005 and 2006 studied the association between time to antibiotic administration and survival in 261 patients with severe sepsis and septic shock who underwent early goal directed therapy (67). This study found that

mortality was decreased when antibiotics were administered within 1 hour from triage (19.5% vs 33.2%; odds ratio, 0.30; 95% CI 0.11-0.83; P = 0.2). The results from this study are from a smaller cohort at a single-centre in patients managed using early goal directed therapy, making these results less generalisable.

A larger retrospective analysis of 17,990 patients with severe sepsis or septic shock in ICUs in Europe, the United States and South America between 2005 and 2010 found a significant increase in the probability of death associated with delay in antibiotic administration (68). Hospital mortality increased from 32% for patients given antibiotics within 1 hour to 39.6% for patients who didn't receive antibiotics for over 6 hours (P < 0.001). However, a meta-analysis of studies investigating timing of antibiotic administration and mortality in severe sepsis and septic shock found no significant mortality benefit in administering antibiotics within three hours of emergency department triage or within one hour of identifying shock (69). This meta-analysis pooled data from 11 studies conducted between 1989 and 2012. There are several potential reasons why the meta-analysis found no mortality benefit. It could be that the complexity of sepsis means that a single factor such as one dose of antibiotics is unable to have a significant impact on survival (69). It could also be possible that resuscitation of patients prior to the administration of antibiotics improves survival, confounding the results (69). The use of emergency department (ED) triage time as the start point for administration of antibiotics could also confound results, as many patients do not meet the diagnostic criteria for severe sepsis and septic shock until after triage time (69). None of the studies were randomised controlled trials due to the difficulty in conducting such a study, and this may also have confounded the results of the meta-

analysis. Overall, it seems logical to administer antibiotics as early as possible in sepsis, but the exact timing of antibiotics as a measure of the quality of care in sepsis remains unclear.

In addition to this, logistically and practically it can be challenging to deliver the sepsis six care bundle within one hour. An ethnographic study in six hospitals participating in the Scottish Patient Safety Programme Sepsis Collaborative conducted 300 hours of observation in emergency departments, acute medical units and medical and surgical wards, and interviewed 43 members of staff (70). This study identified that although the bundle first appears to be only six simple steps, it is actually a complex process involving multiple interdependent tasks. For example, giving IV antibiotics involves finding a doctor to prescribe the antibiotic, obtaining IV access, finding a nurse with IV certificate to prepare the medication before finally administering the antibiotic (70). The study found that this required significant input from several different members of staff, who also had competing tasks that meant that they could not always prioritise completion of the sepsis six care bundle (70). As this ethnographic study was only conducted in hospitals in Scotland, it could be that these barriers to implementation are specific to the Scottish healthcare system. However, it is likely that hospitals in England and Wales face similar issues, highlighting the complexity of healthcare delivery.

1.7 Summary of the limitations of current research

Currently, our improved knowledge of the pathophysiology of sepsis has led to the development of new definitions and diagnostic criteria for sepsis and updated guidelines on the management of sepsis. However, there is limited evidence to validate the use of the new sepsis diagnostic criteria in the UK healthcare setting, and the recent implementation

of new management guidelines means that it is too early to assess the impact of these guidelines on sepsis outcomes.

Changes to the definitions of sepsis, the lack of research and poor data collection will mean that the prevalence of sepsis is likely to significantly change over the coming years.

Despite its long-term implementation, the sepsis six bundle has been shown to have poor compliance rates and unclear efficacy on sepsis mortality rates (53, 59-62). With the implementation of new criteria to define, diagnose and manage sepsis, it is unclear what impact this may have on compliance to the sepsis six bundle and sepsis mortality outcomes.

This project aims to address some of these knowledge gaps:

- the current compliance rates to the sepsis six bundle following implementation of new sepsis diagnostic criteria and management guidelines (whilst the sepsis six bundle is still in use)
- the prevalence of sepsis in new hospital admissions using a modified SIRS diagnostic criteria and the new qSOFA criteria for sepsis
- the impact of sepsis management on mortality rates of patients identified with sepsis.

2. AUDIT OF COMPLIANCE TO THE SEPSIS SIX BUNDLE

2.1 Aims of the audit

The aims of the audit were to:

1. Assess healthcare providers' compliance to the sepsis six care bundle in two acute NHS Hospitals when managing patients admitted to hospital over a 24-hour period who fulfil the diagnostic criteria for sepsis.
2. Investigate the prevalence of sepsis in new adult hospital admissions over a 24-hour period using a modified SIRS criteria for sepsis and the qSOFA score.
3. Assess in-hospital, 30-, 60- and 90-day mortality rates of patients included in the audit.

2.2 Objectives of the audit

The objectives of the audit were to:

1. Determine standards of practice for the management of sepsis at two NHS hospitals and consider whether healthcare providers' compliance to the sepsis six care bundle when treating patients with sepsis is comparable between the two hospitals.

2. Find out whether the prevalence of sepsis amongst new hospital admissions differs depending upon the criteria used for the diagnosis of sepsis (modified SIRS or qSOFA).
3. Determine whether mortality rates for sepsis are influenced by the level of compliance with the sepsis six care bundle.

3. METHODOLOGY

3.1 Ethical considerations

This was an audit, defined as an assessment of compliance with a recognised standard of care. It did not involve any interventions, patient contact or collection of patient identifiable data, therefore requirement of ethical approval was waived, as demonstrated by the Health Research Authority (HRA) decision tool (71). The audit protocol was reviewed and approved as audit by both the local research and development and audit departments of the participating hospital trusts.

3.2 Patient and public involvement (PPI)

The audit protocol was discussed with the local Patient and Public Involvement (PPI) group who scrutinised and approved the final audit objective, design and outcome measures. The PPI group, called the Clinical Research Ambassador Group (CRAG) were involved from inception of the audit, and offered feedback on the audit design. The PPI group were interested in finding out the impact of patient care on patient deaths and suggested finding out mortality rates of the patients included in the audit. This was felt to be a valid query and was therefore added to the final audit protocol.

3.3 Location and time of audit

Data collection took place on Wednesday 22nd June 2016 at two large university affiliated acute hospitals in the West Midlands: Birmingham Heartlands Hospital (BHH) and

University Hospital Birmingham (UHB). At the time of the audit, BHH was part of the Heart of England NHS Foundation Trust (HEFT), one of the largest NHS trusts in England, serving a population of 1.2 million. BHH is located in Bordesley Green in Birmingham and provides care for a diverse population across Birmingham East and North. It has 692 in-patient beds, including 12 level 3 beds. UHB is located in Edgbaston in Birmingham and is a large tertiary hospital, treating over 1 million patients in 2016. It has 1213 inpatient beds, 32 operating theatres and a 100-bed critical care unit and is the largest single site hospital in England.

The medical teams at each hospital site were informed of the audit when data collection took place. The medical teams were the health care professionals working in each ward during data collection who were responsible for the clinical care of the patients included in the audit. Data were collected by a team independent of clinical delivery.

3.4 Inclusion criteria

All adult acute admissions between 00:00 and 23:59 on 22nd June 2016 were eligible. Based upon average daily hospital admission rates it was expected that around 270 patients would be screened for sepsis.

3.5 Exclusion criteria

Patients under the age of 18 were excluded. Paediatric patients were not included because both SIRS criteria and qSOFA score were designed for use in the adult population.

3.6 Screening for sepsis

Patients were screened for a Modified or Standardised Early Warning Score (MEWS or SEWS) of three or above using either electronic records or medical notes. MEWS is the scoring system used at BHH (table 9), whilst SEWS is used at UHB (table 10).

Both of these scoring systems are modified versions of the National Early Warning Score, which is endorsed by NHS England and produced by the Royal College of Physicians (25).

Both scoring systems use a score of four or more to trigger escalation of care and consideration of sepsis. This score was considered too high for screening purposes and would exclude patients with sepsis. Pragmatically, a score of three or more was used, which is similar to the screening method used in a study by Szakmany et al (60). A lower score than three was felt to be too onerous for data collection and would discourage participation in the audit. Patients with a MEWS or SEWS score of three or above were further assessed for a high clinical suspicion of an infection (based upon clinical history, examination and investigations) by trained members of the audit team. The SEWS score has been reproduced accurately and includes some difficulties in scoring correctly which occur on the real patient SEWS charts. For example, it is unclear what score is given to a patient with a temperature of 35.8 as this falls in between a score of one or zero. For instances where these ambiguities occurred in SEWS charts of the patients screened, the score was taken as that assigned by the patient's medical team. Patients with a high clinical suspicion of infection were further screened for sepsis using a modified SIRS criteria and the qSOFA criteria. The modified SIRS criteria uses altered mental status and hyperglycaemia (plasma

glucose of more than 7.7 mM/l) in the absence of diabetes in addition to the original four parameters developed in 1991 (38). The additional parameters are taken from the updated diagnostic criteria for sepsis developed in 2001 (39). This modified SIRS criteria was used in a previous study on prevalence of sepsis in Wales (59). Patients were deemed to have sepsis and were included for assessment of compliance with the sepsis six care bundle if they met either the modified SIRS criteria, or the qSOFA criteria. Although qSOFA is meant as an identifier of patients at high risk of mortality from sepsis only, and should be followed with an assessment of the patient's SOFA score, for pragmatic reasons patients were considered to have sepsis simply if they were qSOFA positive.

Table 9 Modified early warning score (MEWS), courtesy of Birmingham Heartlands Hospital

Score / Categories	3	2	1	0	1	2	3
Respirations (breaths per minute)		8 or less		9-16	17-20	21-29	30 or more
Oxygen Saturations (%)				94 or more	90-93	85-89	84 or less
Systolic Blood Pressure (mmHg)	70 or less	71-80	81-100	101-199		200 or more	
Pulse (beats per minute)				51-100	101-110	111-129	130 or more
Conscious Level			New confusion/ agitation	**A**lert	Responds to **V**oice	Responds to **P**ain	**U**nresponsive
Temperature (˚C)		35 or less	35.1-36	36.1-37.5	37.6-38.1	38.2 or more	
Urine (ml per hour)				No concerns	21-35	1-20	Nil

The modified early warning score (MEWS) is a simple aggregate scoring system based on seven physiological parameters recorded in routine practice in hospital. A score is allocated to each parameter. The magnitude of the score reflects how widely the parameter varies from normal physiological values. mmHg = millimetres of mercury. %= percentage. °C = degrees Celsius.

Table 10 Standard early warning score (SEWS), courtesy of University Hospital Birmingham

Score	3	2	1	0	1	2	3
Category							
Heart Rate (beats per minute)	<30	30-39	40-49	50-99	100-109	110-129	≥130
Systolic Blood Pressure (mmHg)		70-79	80-99	100-199		≥200	
Oxygen Saturations (%)	<85	85-89	90-92	≥93			
Respiratory Rate (breaths per minute)	<9			9-20	20-30	31-35	≥36
Temperature (˚C)	<34	34	35	36-37	>38	≥39	
Conscious level				Alert	Responds to Voice	Responds to Pain	Unresponsive

The standard early warning score (SEWS) is a simple aggregate scoring system based on six physiological parameters recorded in routine practice in hospital. A score is allocated to each parameter. The magnitude of the score reflects how widely the parameter varies from normal physiological values. mmHg = millimetres of mercury. %= percentage. °C = degrees Celsius.

3.7 Assessing compliance

For the purpose of the audit, time zero for implementing the sepsis six care bundle began when the MEWS or SEWS score was first recorded as three or more. Compliance was defined as implementation of all six steps of the bundle within one hour. Compliance to individual elements was also documented at one hour and at any time point up until time of data collection.

3.8 The data collection team

An independent team of investigators collected the data. All members of the team were qualified doctors, ranging from foundation year to consultant, with training in medicine, emergency medicine or anaesthesia. All the data collectors were recruited by asking for volunteers at educational meetings and via group e-mails to trainee junior doctors. They were selected for the team if they were able to collect data during the time of the audit. As all members of the data collection team had a medical background, it was felt that they all had adequate training to recognise evidence of infection in patients and no extra training was given in this area. The data collectors were asked to input "yes" to high clinical suspicion of infection if there was documentation of infection in the medical or nursing notes, or if in their own opinion there was a high clinical suspicion of infection based upon information in the medical or nursing notes. Examples of this type of situation include a documentation of new onset of productive cough, dysuria with fever or a record of diarrhoea and vomiting.

Training was provided to all team members on aspects of data collection, including where to find the necessary information needed for the audit (e.g. patient charts, paper notes, electronic patient records) and how to use the electronic data collection device and toolkit. At UHB, this training took place one week before the audit took place and took 45 minutes. At BHH, this took place on the day of data collection and also took 45 minutes. Further support for the data collectors occurred in real time via an electronic group messaging application. At BHH, the main investigator (CF) was available to help any data collectors in person, but this was not required.

3.9 Data collection

Data were collected across the two hospitals via a secure open-source web-based toolkit on hand held electronic devices. The devices and toolkit used to collect data were sourced from the Welsh Intensive Care Society. It had originally been developed for use in a study by Szakmany et al (72), and was adapted for use in this audit. The adaptation involved the removal of data entry that could identify individual patients (since this was an audit) and changes to the drop-down box list for name of hospital to UHB and BHH, rather than the list of Welsh hospitals used in the original study. Ward areas were also updated to reflect the wards of UHB and BHH. All other aspects of the toolkit were unchanged. The toolkit involved drop-down boxes for much of the data entry to minimise the chance of error and ensure data quality. The computer operating system used included logic rules to limit progression through the toolkit until all mandatory information is entered by the data collector (72). The algorithm used by the toolkit meant that data collectors did not have to identify patients with sepsis themselves. Instead, the toolkit identified a patient as having

sepsis if two or more modified SIRS or qSOFA criteria were met after each individual criteria was recorded on the toolkit by the data collector. Free text data entry included error messages for values lying outside of possible values to minimise data entry errors. All data entered were reviewed for errors by an investigator (CF). Data were collected from patient observational charts, medical notes and electronic records as appropriate. Data collected are listed in table 11.

The data from the electronic devices was encrypted and encrypted data were entered automatically into an electronic database designed to handle the information. Data security was maintained using industry level encryption during data transmission and by ensuring that data servers were protected by firewalls. The electronic database is stored on a password-protected Heart of England NHS Foundation Trust computer. Only those involved in the audit have access to the database. No patient identifiable data were collected.

Table 11 Data collected for the audit

Data Items	Categories
Age	Free text
Gender	Male Female
Patient's ward area	Medical assessment unit Surgical assessment unit General medical General surgical
Medical Specialty	Free text
Hospital	UHB BHH
Admission Source	Home Other Hospital Nursing home
Time of observations	Free text
Highest MEWS/SEWS score between 00:00 and 23:59 on 22nd June 2016	Free text
Comorbidities	Diabetes Heart failure Hypertension Ischaemic heart disease Liver disease Recent chemotherapy Smoker Ex-smoker
Drug history	ACE-inhibitor Beta blocker Long term antibiotics Diuretics Immunosuppressant Insulin HMG-CoA reductase inhibitors Steroids
Blood culture results (if taken)	Free text

Data Items	Categories
Criteria used to confirm sepsis	Modified SIRS qSOFA Both modified SIRS and qSOFA
Laboratory values for white cell count, platelets, creatinine, bilirubin, lactate and glucose	Free text
Which elements of the sepsis six bundle were fulfilled and whether this was within 1 hour of time zero	Yes No
Whether the patient was seen by critical care outreach at any point	Yes No
Site of suspected infection	Pulmonary Urinary tract Intra-abdominal Indwelling vascular device Other Source Unknown
Antibiotics given	Free text
Whether a DNAR was in place	Yes No
Whether a ceiling of treatment plan was in place	Yes No
Whether a screening tool for sepsis was completed by the medical team	Yes No
Length of hospital stay	Free text
In-hospital, 30-, 60- and 90-day mortality	Free text

Table listing the data collected during the audit. The toolkit involved drop down lists for gender, hospital, medical specialty, admission source, medical conditions, drug history, criteria used to confirm sepsis, elements of the sepsis six bundle fulfilled, critical care outreach involvement, ceiling of treatment and completion of screening tool. Free text boxes displayed error messages for values outside of possible range. MEWS = modified early warning score. SEWS= standard early warning score. DNAR = do not attempt resuscitation order.

3.10 Data analysis

Data were analysed using Excel version 14.0.6112.5000, Microsoft, USA and SPSS Statistics version 23, IBM. Descriptive statistics have been used as this was the most appropriate method for the audit data collected. No sample size calculation was undertaken as the audit was a snapshot of compliance and sepsis prevalence rather than a study attempting to find out a specific comparative difference. Data have been tested for normality using a Shapiro-Wilk test, a common test for normality that is appropriate for small sample sizes. Categorical variables are described using counts and percentage. Measures for continuous variables are described using median and inter-quartile range (IQR) as they were not normally distributed. Differences in categorical variables have been analysed using Fisher's exact test due to the small sample size collected. Statistical significance level has been set at $P < 0.05$ as is standard for scientific medical data.

4. RESULTS

4.1 Implementing the data analysis plan

The planned statistical methods were deemed to be applicable to the dataset collected, making descriptive statistics suitable as intended and the planned statistical tests appropriate. The Shaprio-Wilk test confirmed that data were not normally distributed, and therefore median and inter-quartile range have been used for continuous variables, as intended. The Fisher's exact test was used as planned for the comparison of compliance rates between hospitals as the most appropriate statistical method for a small sample size.

4.2 Patients screened and diagnosed with sepsis

There were 249 acute adult admissions over the 24-hour study period and all of these patients were screened for suspected sepsis (figure 2). Ninety-eight patients were screened at UHB, with ten (10.2%) having a SEWS score of three or more. All ten patients who had a SEWS score of three or more (100%) met the diagnostic criteria for sepsis. At BHH, 151 patients were screened, with 17 (11.2%) having a MEWS score of three or above. Of these, 14 (82.4%) met the diagnostic criteria for sepsis as defined by the study (modified SIRS ≥ 2 or qSOFA ≥ 2 plus infection). Overall, 24 patients (9.6%) met the criteria for sepsis. All 24 patients (100%) met the modified SIRS diagnostic criteria for sepsis but only six (25%) had a qSOFA score of two or above, resulting in a prevalence of sepsis of 9.6% amongst new hospital admissions when the modified SIRS criteria is used, and a prevalence of 2.4% when

qSOFA criteria is used. There were no patients who met the qSOFA criteria alone without also meeting the modified SIRS criteria for sepsis.

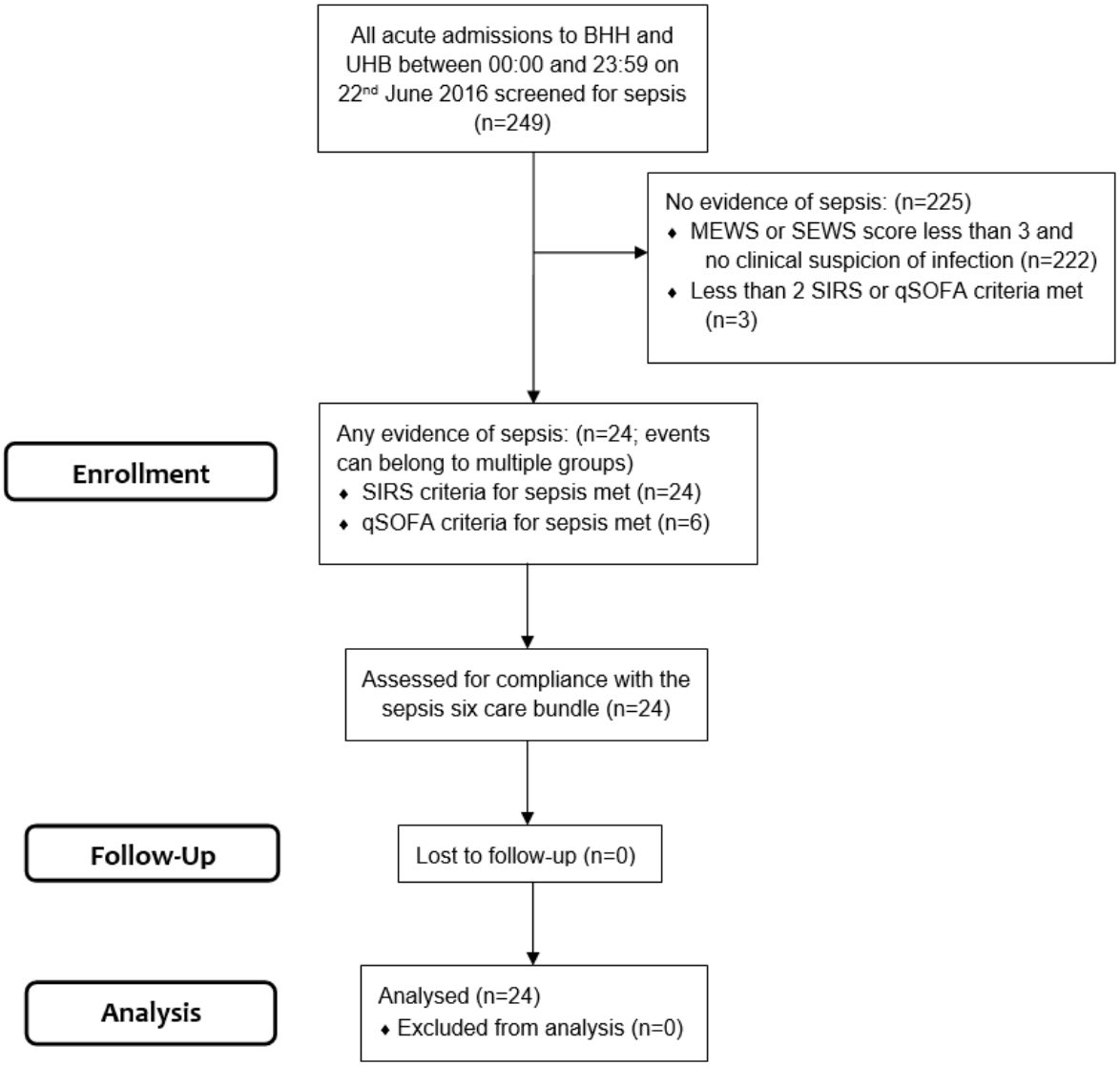

Figure 2 Audit flow diagram

Diagram detailing the screening process of patients and flow of participants in the audit. BHH = Birmingham Heartlands Hospital. UHB = University Hospital Birmingham. MEWS = modified early warning score. SEWS = standard early warning score. SIRS = systemic inflammatory response syndrome (modified version). qSOFA = quick sequential (sepsis related) organ failure assessment.

Adapted from: Consort 2010 Flow Diagram. Available at: http://www.consort-statement.org/ (accessed 10th May 2018)

4.3 Patient demographics

Patient demographics can be viewed in table 12. The majority of patients were admitted from their homes (21 patients, 87.5%) and most patients were admitted under acute medicine (15 patients, 62.5%) with care being delivered on medical assessment units (MAU) (16 patients, 66.7%). Patients had a wide range of comorbidities, most commonly diabetes (six patients, 25.0%), hypertension (seven patients, 29.2%) and hypercholesterolaemia (seven patients, 29.2%). Patients were taking a variety of medications, most commonly diuretics (six patients, 25.0%) and HMG-CoA reductase inhibitors (seven patients, 29.2%). Two patients (8.33%) had a Do Not Attempt Resuscitation (DNAR) order and documented limitations on treatment.

Table 12 Patient demographics

Patient Demographic	**Suspected Sepsis Patients**
Age median (interquartile range)	62 (47.8-77.5)
Gender: male n (%)	14 (58.3)
Admission Source n (%)	
Home	21 (87.5)
Other Hospital	1 (4.17)
Nursing Home	2 (8.33)
Specialty n (%)	
Acute medicine	15 (62.5)
General surgery	2 (8.33)
Respiratory	2 (8.33)
Cardiothoracic	2 (8.33)
Other (oncology, stroke or endocrine)	3 (12.5)
Ward n (%)	
Medical assessment unit	16 (66.7)
Surgical assessment unit	1 (4.17)
General medical	4 (16.7)
General surgical	2 (8.33)
Comorbidities n (%)	
Diabetes	6 (25.0)
Heart failure	2 (8.33)
Hypertension	7 (29.2)
Ischaemic heart disease	4 (16.7)
Liver disease	1 (4.17)
Recent chemotherapy	2 (8.33)
Smoker	4 (16.7)
Ex-smoker	3 (12.5)
Drug History n (%)	
ACE-inhibitor	3 (12.5)
Beta blocker	2 (8.33)
Long-term antibiotics	1 (4.17)
Diuretics	6 (25.0)
Immunosuppressant	2 (8.33)
Insulin	4 (16.7)
HMG-CoA reductase inhibitors	7 (29.2)
Steroids	2 (8.33)
DNAR n (%)	2 (8.70)
Ceiling of treatment (ward) n (%)	2 (8.70)

The demographics of patients assessed in the audit. n = number of patients. ACE = angiotensin-converting enzyme. HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A. DNAR = do not attempt resuscitation order.

4.4 Infection characteristics

The most common modifed SIRS criteria that occurred in patients with suspected sepsis was a raised heart rate of more than 90 beats per minute (18 patients, 75%). The most common qSOFA criteria that occurred was a respiratory rate of more than 22 breaths per minute (10 patients, 41.7%) (table 13).

The commonest suspected source of infection was pulmonary (10 patients, 41.7%), followed by urinary tract (three patients, 12.5%) and intra-abdominal (three patients, 12.5%). Twenty patients (84%) were not diagnosed with sepsis by the admitting team, including three patients (12.5%) who were not identified by the admitting team with any form of infection.

The median MEWS or SEWS scores was four (interquartile range three to five). Fifteen patients had a MEWS or SEWS score of four or more, which mandates a review by critical care outreach as per hospital guidelines. However, only one of these 15 patients (6.67%) was reviewed. This patient had a SEWS score of four. None of the patients were admitted to ICU or had any other critical care involvement.

Eight patients had blood cultures taken and two of these (25%) were positive (Methicillin sensitive Staphylococcus aureus from one patient, Staphylococcus epidermidis and Actinomyces sp from another patient). Both of these positive blood cultures were likely to be due to skin contaminants.

Table 13 Infection characteristics of patients with suspected sepsis

Infection Characteristics	**Total Number of patients (%)**
Source of Sepsis	
Pulmonary	10 (41.7)
Urinary tract	3 (12.5)
Intra-abdominal	3 (12.5)
Indwelling vascular device	2 (8.33)
Other	2 (8.33)
Source unknown	4 (16.7)
Two or more modified SIRS Criteria Present	24 (100)
Individual modified SIRS Criteria Present	
Temperature>38.3°C	8 (33.3)
Temperature<36°C	3 (12.5)
Altered mental state	7 (29.2)
HR>90/minute	18 (75.0)
RR>20/minute	13 (54.2)
WCC>12,000/µL	15 (62.5)
WCC<4000/µL	2 (8.30)
Glucose>7.7mmol/L	7 (29.2)
Two or more qSOFA Criteria Present	6 (25.0)
Individual qSOFA Criteria Present	
RR>22/minute	10 (41.7)
Altered mentation	7 (29.2)
Systolic BP<100mmHg	7 (29.2)
Sepsis screening tool completed	2 (8.33)
Seen by Critical Care Outreach	1 (4.17)
In-hospital Mortality	0 (0)
	Median (interquartile range)
MEWS/SEWS score	4 (3-5)
Length of Stay in days	7.5 (3-12)

The infection characteristics of patients assessed in the audit. SIRS = systemic inflammatory response syndrome. HR = heart rate. RR= respiratory rate. WCC = white cell count. Glucose = blood glucose level. BP= blood pressure. qSOFA = quick sequential (sepsis related) organ failure assessment. MEWS = modified early warning score. SEWS = standard early warning score.

4.4.1 MEWS and SEWS scores

The MEWS and SEWS scores differ slightly in their parameter settings. Therefore the potential SEWS scores of patients from BHH and the potential MEWS scores of patients from UHB were calculated to see if there would be a change in score depending upon the early warning score used. Table 14 shows the MEWS and SEWS score for each patient. There were four patients from BHH who would only have scored two on the SEWS scoring system, meaning that if these patients had presented to UHB, they would not have been included in the audit. All patients from UHB would have scored at least three on the MEWS chart used at BHH and would therefore have all been included in the audit if they had presented to BHH. The MEWS scoring system tended to result in a higher score for most patients compared to the SEWS scoring system for most patients.

Table 14 Comparison of MEWS and SEWS scores for each patient audited

Patient Number (BHH)	MEWS score	SEWS score	Change in score (SEWS compared to MEWS)	Would patient's categorisation have changed if they had presented to UHB?
1	5	4	-1	No
2	5	3	-2	No
3	5	4	-1	No
4	3	2	-1	Yes: would not have been included in audit
5	4	3	-1	No
6	5	4	-1	No
7	5	4	-1	No
8	3	2	-1	Yes: would not have been included in audit
9	4	4	0	No
10	5	3	-2	No
11	5	2	-3	Yes: would not have been included in audit
12	3	2	-1	Yes: would not have been included in audit
13	3	4	+1	No
14	3	3	0	No
Patient Number (UHB)	**MEWS score**	**SEWS score**	**Change in score (SEWS compared to MEWS)**	**Would patient's categorisation have changed if they had presented to BHH?**
15	3	4	+1	No
16	3	3	0	No
17	7	6	-1	No
18	5	4	-1	No
19	3	3	0	No
20	4	3	-1	No
21	5	4	-1	No
22	4	3	-1	No
23	6	4	-2	No
24	5	4	-1	No

The MEWS and SEWS scores of each patient included in the audit. The change in score between SEWS compared to MEWS is listed for each patient and the impact this would have on categorisation is recorded. BHH = Birmingham Heartlands Hospital. UHB = University Hospital Birmingham. MEWS = modified early warning score. SEWS = standard early warning score.

4.5 Observation characteristics

The majority of patients had an abnormal respiratory rate (median 21 breaths per minute; interquartile range (IQR) 18-26) and tachycardia (median 106 beats per minute; IQR 92-119). Blood pressure was less likely to be abnormal (median systolic blood pressure 122mmHg; IQR 111-143) and most patients had a Glasgow coma score (GCS) of 15. Most patients had a low grade temperature (median 37.5°C; IQR 36.4-38.2). The median and interquartile range of patient's observations can be seen in table 15.

Table 15 Observation characteristics of patients with suspected sepsis

Observation Characteristics	**Suspected Sepsis Patients (n=24)**
Observation	**Median (interquartile range)**
Respiratory rate (breaths per minute)	21 (18-26)
Oxygen saturations (%)	96 (92-98)
Heart rate (beats per minute)	106 (92-119)
Systolic blood pressure (mmHg)	122 (111-143)
Diastolic blood pressure (mmHg)	65 (56-82)
Temperature (°C)	37.5 (36.4-38.2)
GCS	15 (15-15)

The observation characeteristics of patients assessed in the audit. n = number of patients. GCS = Glasgow coma score, ranges from 3-15; higher score indicates better neurological function.

4.6 Compliance with the sepsis six care bundle

Overall, compliance with the sepsis six care bundle was low (table 16) with only one patient (4.17%) having all aspects completed. For individual bundle elements, compliance was highest for intravenous fluids (14 patients, 58.3%) and intravenous antibiotics (14 patients, 58.3%). Compliance was lowest for measuring urine output (four patients, 16.7%). For the four patients with sepsis diagnosed by the team responsible for medical management, none received all elements of the care bundle, although all four patients received intravenous antibiotics. Three of the four patients diagnosed with sepsis by the admitting team were given intravenous fluids, two had blood cultures taken and one had a lactate measured. None were given oxygen and none had their urine output measured.

Individual compliance rates at BHH and UHB is shown in table 17. More patients at BHH received intravenous antibiotics and oxygen within one hour than at UHB; however this difference was not statistically significant. Fewer patients at BHH had a lactate measured, blood cultures taken and urine output measured than patients at UHB, but only compliance to the measurement of lactate was statistically significantly higher at UHB. The one patient who received all elements of the sepsis six care bundle was at UHB. The overall rate of compliance with the bundle was not statistically significantly different between the two hospitals.

Table 16 Compliance with each element of the sepsis six care bundle

Therapy	Achieved within 1 hour n (%)	Achieved at any point n (%)
IV fluids	14 (58.3)	18 (75)
IV antibiotics	14 (58.3)	19 (79.2)
Oxygen	5 (20.8)	9 (37.5)
Lactate measured	12 (50.0)	17 (70.8)
Blood cultures taken	5 (20.8)	8 (33.3)
Urine output measured	4 (16.7)	6 (25.0)
All six	1 (4.17)	1 (4.17)

Table of compliance with each element of the bundle as number of patients (n) who received each therapy and percentage of all patients who received each therapy. IV = intravenous.

Table 17 Compliance with each element of the sepsis six care bundle at each hospital

Therapy	Achieved within 1 hour			Achieved at any point		
	BHH n (%)	UHB n (%)	p value	BHH n (%)	UHB n (%)	p value
IV fluids	8 (57.1)	6 (60)	1.0000	10 (71.4)	7 (70)	1.0000
IV antibiotics	9 (64.2)	5 (50)	0.6785	10 (71.4)	8 (80)	1.0000
Oxygen	4 (28.6)	1 (10)	0.3577	5 (35.7)	4 (40)	1.0000
Lactate measured	4 (28.6)	8 (80)	0.0361	7 (50.0)	10 (100)	0.0188
Blood cultures taken	2 (14.2)	3 (30)	0.6146	3 (21.4)	5 (50)	0.2038
Urine output measured	1 (7.14)	3 (30)	0.2721	2 (14.2)	4 (40)	0.1921
All six	0	1 (10)	0.4167	0	1 (10)	0.4167

Table demonstrating the compliance to each element of the sepsis six care bundle at each hospital. n= number of patients who received the therapy. BHH = Birmingham Heartlands Hospital. UHB = University Hospital Birmingham.

4.7 Mortality and length of stay data

No patients died during their hospital admission. One (4.17%) died within 30 days of admission and a further two patients (8.33%) died within 60 days. There were no further deaths up to 90 days. All three patients who died were receiving palliative care for cancer. The median length of stay in hospital was 7.5 days (interquartile range 3-12 days).

5. DISCUSSION AND CONCLUSIONS

5.1 Key findings

5.1.1 Sepsis is common amongst new hospital admissions

The results demonstrate that sepsis is a common problem, affecting nearly 10% of acute hospital admissions. It is one of only a few audits or studies to measure sepsis prevalence in the general ward setting (49, 59, 60). Previous studies on the prevalence of sepsis identified that 4.2%- 5.5% of in-patients had sepsis, depending on the clinical criteria used (59, 60). The higher prevalence found in this audit compared to previous findings may be due to the audit methodology; this audit only identified prevalence of sepsis in new acute hospital admissions, whereas the previous studies investigated the prevalence of sepsis amongst all hospital inpatients (59, 60). Other studies on epidemiological data for sepsis estimate the incidence rather than prevalence of sepsis, making comparison difficult; a study of data from seven high-income countries demonstrated an incidence of hospital-treated sepsis of 437 (95% CI 334-571) per 100,000 person-years and an incidence of severe sepsis of 270 (95% CI 176-412) per 100,000 person-years (18).

However, due to the methodology used for this audit, it is possible that the prevalence of sepsis has been underestimated. Only screening patients with a MEWS or SEWS score of three or more for sepsis may have missed patients who had a lower MEWS or SEWS score, but still had sepsis. This flaw in the audit methodology and the potential impact on the results is discussed further in section 5.3.

The most common source of sepsis in this audit was pulmonary, which correlates with studies that have identified this as the commonest source of infection in patients with sepsis presenting to hospital (20, 22, 60).

5.1.2 The prevalence of sepsis differs depending on the criteria used

In this audit, fewer patients had a positive qSOFA score than patients who met the modified SIRS criteria for sepsis, resulting in a prevalence of sepsis amongst new hospital admissions of 9.6% when the modified SIRS criteria is used, and 2.4% when the qSOFA score is used. This has also been demonstrated in a retrospective analysis of data from the USA: out of 2593 patients admitted to ED or hospital with infection, 1526 met the SIRS criteria and 378 met the qSOFA criteria, with overlap between the two (i.e. some patients met both criteria) (73). The intention of qSOFA is to screen patients with infection and identify those who are at high risk of mortality (42). This may explain why qSOFA identified fewer patients than the modified SIRS criteria; out of the three patients who died, two had a positive qSOFA score.

5.1.3 The MEWS and SEWS scoring systems are not comparable

An analysis of the MEWS and SEWS scoring systems demonstrated marked differences in scores for the same patient, with MEWS tending towards a higher score compared to SEWS. There were four patients at BHH who would have scored two on a SEWS chart at UHB; if they had presented to UHB they would not have been screened for sepsis and would not have been included in the audit. Therefore it is likely that there were patients at UHB who scored 2 or less on the SEWS scoring system and therefore not included in the audit, who

would have had a MEWS score of three or more if they had been admitted to BHH, and subsequently included in the audit. Unfortunately, due to the methodology used, it is not possible to find out how many patients with sepsis were potentially missed. It is likely that the prevalence of sepsis has been underestimated as a result. It also explains why there were less patients identified at UHB with sepsis than at BHH, despite UHB being the larger of the two hospitals.

This has highlighted the discrepancies between different early warning systems in use across the UK. Since December 2018, both UHB and BHH (who are now under one trust) use the NEWS 2 early warning score (table 18) (74). NEWS 2 is the latest version of the National Early Warning Score, first produced in 2012 and updated December 2017. It has been endorsed by NHS England and NHS improvement to be used as the early warning score for all acutely ill patients in hospitals in England. This will allow standardisation across all NHS hospitals, avoiding situations like those highlighted by the audit where one scoring system would miss potentially sick patients compared to another. Following implementation of NEWS 2 nationwide, further auditing and research in this area will be standardised throughout all NHS hospitals. In addition to the implementation of NEWS 2, the national CQUIN indicator on reducing the impact of serious infections (antimicrobial resistance and sepsis) implemented in 2017 is likely to result in increased screening of sepsis and earlier administration of IV antibiotics to patients with sepsis due to the monetary incentive for trusts to complete these tasks (64). Together, NEWS 2 and the sepsis CQUIN is likely to have a positive impact on sepsis recognition and management.

Table 18 The National Early Warning Score (NEWS) 2

Physiological Parameter	**Score**						
	3	**2**	**1**	**0**	**1**	**2**	**3**
Respiration Rate (per minute)	≤ 8		9-11	12-20		21-24	≥ 25
SpO_2 Scale 1 (%)	≤ 91	92-93	94-95	≥ 96			
SpO_2 Scale 2 (%)	≤ 83	84-85	86-87	88-92 ≥ 93 on air	93-94 on oxygen	95-96 on oxygen	≥ 97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	\leg 90	91-100	101-100	111-219			≥ 220
Pulse (per minute)	≤ 40		41-50	51-90	91-110	111-130	≥ 131
Consciousness				Alert			CVPU
Temperature (°C)	≤ 35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥ 39.1	

The national early warning score (NEWS) 2 is a simple standardised aggregate scoring system based on six physiological parameters recorded in routine practice in hospital. A score is allocated to each parameter. The magnitude of the score reflects how widely the parameter varies from physiological values. SpO_2 = oxygen saturations. % = percentage. mmHg = millimetres of mercury. °C = degrees Celsius. CVPU = Confusion, voice, pain, unresponsive. Score for NEW onset of confusion (no score if chronic). Use SpO_2 scale 2 if target range is 88-92%, e.g. in hypercapnic respiratory failure.

5.1.4 Compliance with the sepsis six care bundle is low

Despite the sepsis six care bundle being recommended for nearly a decade, compliance remains low. This was demonstrated in both hospitals, suggesting that the problem is unlikely to be due to local factors affecting just one individual hospital. Compliance for all elements of the bundle was lower in this audit (4.17%) compared to a previous study, which demonstrated an overall compliance level to the sepsis six care bundle of 12% (60). The previous study was conducted in Wales, where there is a national public health campaign (1000 Lives Improvement) to reduce deaths and episodes of harm within NHS Wales through quality improvement programmes (60).

The 1000 Lives Improvement service in Wales aims to achieve sustainable and measurable improvements in healthcare and includes initiatives to "support organisations in the early detection and prevention of acute deterioration" (75). This has included enterprises to improve the management of sepsis across Wales and could explain the higher compliance rates in the study by Szakmany et al. (60). All health boards and trusts within NHS Wales have actively participated in RRAILS (rapid response to acute illness learning set) (76). The RRAILS steering group led to the introduction of NEWS in 2013 (four years before NHS England endorsed NEWS 2 for use in hospitals across England), sepsis screening and the sepsis six care bundle to all NHS hospitals across Wales. This level of national standardisation and implementation of quality improvement standards is likely to have led to the higher compliance rates seen in the study by Szakmany et al (60). Clinicians would be aware of the sepsis screening tool and sepsis six bundle even if they were new starters to the hospital as the implementation of this practice is across the whole of Wales. It is

possible that following the introduction of NEWS 2 and the sepsis CQUIN in England that compliance rates will increase to be comparable with the rates reported by Szakmany et al (60).

Compliance is much lower than when the sepsis six care bundle was initially implemented; compliance rates of 38.6% were demonstrated by Daniels et al. in an observational cohort study completed after the introduction of the sepsis six care bundle (22). Other recent studies have also been unable to establish high compliance rates; two quality improvement projects in the UK and New Zealand had baseline compliance levels of 7% and 4% respectively (61, 62).

Only four (16.7%) patients in this audit were diagnosed with sepsis by the admitting team, suggesting that lack of recognition of sepsis is one reason for poor compliance. The discrepancy between the number of patients identified by the admitting team compared to the data collection team is likely to be a result of the data collection toolkit. The toolkit involved an algorithm that would work out which patients had sepsis based upon whether they fulfilled two or more of the modified SIRS or qSOFA criteria. The data collection team did not have to work out whether a patient had sepsis themselves, they simply inputted each patient parameter for the diagnostic criteria for modified SIRS or sepsis into the toolkit. In contrast, the admitting team did not have access to the toolkit and computerised algorithm, so would have had to diagnose sepsis themselves. It is likely that without the toolkit aiding them, the data collectors would have missed patients with sepsis as well. This highlights the potential advantages of computer-based early warning systems that may pick up acutely ill patients, including those with sepsis, that clinicians may miss.

However, even the patients specifically labelled by the medical team as having sepsis were not managed as per the sepsis six care bundle. It is reassuring to see that compliance is highest for giving intravenous antibiotics and fluids, arguably the more important elements of the sepsis six care bundle, as demonstrated by recent studies that have shown survival benefit with early antibiotics and intravenous fluid bolus (65-68). Compliance for these parts of the bundle were higher than those achieved in a previous study (IV antibiotics compliance: 58.3% in this audit vs. 40% (sepsis) and 54% (severe sepsis) in study by Szakmany et al. IV fluids compliance: 58.3% in this audit vs. 22% (sepsis) and 34% (severe sepsis) in study by Szakmany et al.), but lower than the compliance levels in the study by Daniels et al. (IV antibiotic compliance 61.6% and IV fluids compliance 67.7%) (22, 60). The higher rates of compliance for IV antibiotics and fluids suggests awareness amongst clinicians of the importance of these aspects of the care bundle. In contrast, oxygen was only administered to five patients within one hour of sepsis diagnosis, which could be due to clinician awareness of the potential detrimental effects of hyperoxia (63). There is limited evidence to suggest that measurement of urine output and lactate and taking blood cultures leads to improvements in patient survival from sepsis. The Surviving Sepsis Campaign's international guidelines for the management of sepsis and septic shock advises routine microbiological cultures should be obtained prior to the commencement of antimicrobial therapy as a best practice statement only (52). The measurement of lactate is only recommended by the Surviving Sepsis Campaign in the context of guiding resuscitation to normalise lactate in patients with elevated lactate levels. This was graded as a weak recommendation with low quality of evidence (52). Urine output is used as a marker of illness severity and tissue hypoperfusion and can be used in conjunction with other

physiological variables, such as heart rate, blood pressure and respiratory rate to evaluate a patient's response to treatment (52). However, the Surviving Sepsis Campaign advocates the use of dynamic variables to predict fluid responsiveness, such as passive leg raises or fluid challenges against stroke volume measurements, rather than static variables such as urine output (52). Clinicians who are aware of these guidelines and the lack of evidence relating to these components of the sepsis six bundle may have made a conscious decision to omit these parts of the bundle when managing their patients.

It is also possible that in addition to the questionable efficacy of some elements of the care bundle, the clinical team may have felt that the interventions were inappropriate due to the lack of illness severity in many of the patients. The average MEWS or SEWS score was four, and median observation characteristics were all within normal ranges other than respiratory rate (21 breaths per minute) and heart rate (106 beats per minute). Therefore, given the mildness of illness in the patients in this audit, the omission of elements of the sepsis six bundle may have been deliberate.

Other reasons for poor compliance with the sepsis six care bundle include issues such as quick turnover of medical staff who are not familiar with the care bundle. Junior doctors in NHS hospitals can rotate up to every three months, and therefore may have come from trusts that put less emphasis on the sepsis six bundle for the management of patients with sepsis. Other doctors may have recently relocated from hospitals abroad where the sepsis six bundle is not used. As discussed earlier, this could explain the higher compliance rates in the study by Szakmany et al, where the sepsis six bundle has been implemented and promoted in every NHS hospital in Wales (60).

Another common problem with compliance to any care bundle is the lack of senior doctor involvement. A quality improvement project in an emergency department in the UK found that lack of prompt senior involvement led to uncertainty in management decisions and a delay in implementation of the sepsis six bundle (77). It is junior staff who perform the majority of initial medical assessments and therefore inexperience, lack of knowledge and slow decision making is likely to impact on compliance levels with the sepsis six bundle (77). Poor communication and practical barriers are further reasons for poor compliance, as demonstrated by an ethnographic study of the implementation of the sepsis six bundle (70). Delays in implementation resulted from doctors failing to communicate with nurses (resulting in delays in IV antibiotic administration), difficulty in coordinating multiple tasks (such as finding someone IV trained to administer antibiotics whilst also managing the care of other patients) and operational failures such as a lack of equipment for lactate measurement (70). It is likely that many of these same factors influenced compliance in this audit, particularly lack of communication with nurses who would be administering antibiotics and fluids, and managing the care of multiple patients at once, leading to delays.

Improving compliance to care bundles can be difficult because of the multiple factors involved. Studies on compliance to care bundles which have used a single intervention to improve compliance have had limited success. A study aiming to improve compliance to a ventilator associated pneumonia (VAP) care bundle found that education alone was not enough to improve compliance (78). A further study examining audit and feedback to improve compliance to a VAP bundle demonstrated a non-significant improvement in

overall compliance, and individual aspects of compliance to the bundle had in some instances worsened (79).

Quality improvement projects focussing on increasing compliance to the sepsis six bundle have been moderately successful when using a multifactorial approach. Several projects have used a combination of education, checklists and stickers, sepsis "champions" and sepsis "packs" (61, 62, 80). These combinations of interventions have improved compliance, but are labour intensive and require sustained implementation to work.

A systematic analysis of the effect of performance improvement programmes on compliance with sepsis bundles found that education and process change can successfully improve compliance and showed a concomitant reduction in mortality (81). Quality improvement initiatives in Brazil have reduced hospital mortality from sepsis; however this reduction in mortality resulted from earlier recognition of sepsis, rather than increased compliance to a six-hour sepsis bundle (82).

Lack of compliance to the sepsis six care bundle, difficulties in improving compliance and the absence of evidence of a survival benefit all call into question the suitability of the sepsis six bundle for use in the modern healthcare setting. As discussed in chapter one, there is much controversy surrounding the use of the sepsis six care bundle and it's supposed efficacy (53). The sepsis six care bundle was developed to improve compliance to the Surviving Sepsis Campaign's 6-hour resuscitation bundle (22). The six elements of the sepsis six bundle were identified from those that were found to be poorly performed in an initial gap analysis (22). Therefore, the sepsis six care bundle did not originate from evidence-based medicine but was developed to improve compliance to another bundle (22). The 6-hour resuscitation

bundle involved EGDT, which has since been found to have no survival benefit compared to standard care (54-58). The sepsis six care bundle has not been validated for use; it's widespread implementation was based upon the findings from one observational cohort study by the designers of the bundle (22). The limitations of the observational cohort study and the lack of reproducibility of the results have been discussed in chapter one, and the findings of poor compliance and low mortality rates in this audit further question the use of the sepsis six care bundle.

5.1.5 Mortality rates are lower than reported

Despite the poor compliance to the sepsis six care bundle, mortality within 90 days of admission was low at 12.5% and all three deaths were cancer related. This is lower than the mortality rates found in previous studies: one study demonstrated a 90-day mortality rate of 29% for sepsis and 35% for severe sepsis, whereas another study in Brazil found that mortality rates varied between 33.3% and 58.3% for different institutions. (60, 82). A retrospective study of data from seven high-income countries measured hospital mortality rates at 17% for sepsis and 26% for severe sepsis; the study included data from 1979 to 2015 so it is likely that the higher mortality rates reflect the inclusion of mortality reports from earlier decades (18). The lower mortality rate demonstrated by this audit may reflect the severity of sepsis for this cohort of patients; the average MEWS score was 4, suggesting that these patients may have had less severe illness than patient cohorts in other studies (60).

5.2 Strengths of the audit

The audit met its primary aim and objective, which was to assess compliance with the sepsis six care bundle in two acute NHS trusts in the West Midlands and compare compliance between the two trusts. The novel use of hand-held electronic devices to collect data for the audit allowed quick data collection and instant upload. This saved time replicating data collected on paper data collection forms and allowed for standardisation of data collection. The toolkit can be easily adapted for use in other audits or studies (72). Another strong point of this audit was the rigorous training of the data collectors in the use of the data collection tool, along with an online group messaging service for real-time data collection support, ensuring data collection quality. Data were prospectively collected, allowing real-life utilisation and comparison of the new qSOFA score with the modified SIRS criteria for sepsis in the clinical setting. Using the modified SIRS criteria rather than the original four-parameter SIRS criteria will have reduced the likelihood of missing patients with sepsis and involved the most up to date version of the SIRS criteria. None of the patients were lost to follow up, providing a complete dataset for analysis.

5.3 Limitations of the audit

There are limitations to this audit. Due to the small number of patients involved, it was not possible to assess the effect of compliance to the sepsis six bundle on mortality rates, meaning that this aim and objective of the audit was not met. Furthermore, due to the pragmatic screening method used (only those with a MEWS or SEWS score of three or above were screened for sepsis) it is likely that there were patients with sepsis that were missed,

introducing bias into the audit results. Using either the SEWS or MEWS scoring system, it is possible to meet the modified SIRS criteria of sepsis with a score of zero. This could happen if a patient had a heart rate of 95 beats per minute and a white cell count of 14000/mm^3. It is also possible to meet the qSOFA criteria for sepsis with a MEWS score of 2 (e.g. altered mental state and systolic blood pressure of 100mmHg) or a SEWS score of 1 (e.g. respiratory rate of 25 breaths per minute and systolic blood pressure of 100mmHg). This may mean that the prevalence of sepsis found in this study is an underestimate of the true prevalence of sepsis amongst new hospital admissions. As a result of this introduced bias, the second aim and objective of the study may not have been met accurately. However, the prevalence found in this audit was higher than that found in other studies, suggesting a higher rate of recognition of sepsis in this audit compared to previous studies, despite the methodology used. The distribution of source of infection closely correlates with those found in previous studies, suggesting that the screening method did not bias for or against any subgroup of patients based upon source of infection (20,22,60).

This screening method was used to avoid a labour intensive data collection process and to encourage site participation. It was a pragmatic approach based upon the methodology used in a previous study (59), and it was felt that the small proportion of patients that may be missed as a result would be acceptable in light of increased site participation. However, due to the resulting small number of patients included in the audit, it would be beneficial to change the methodology to screen all patients for sepsis regardless of MEWS or SEWS score in any future audits.

The audit was designed to provide a snapshot of the management of patients with suspected sepsis and involved a small number of patients over a short time period. Only

new hospital admissions were included in the audit, missing patients who had been inpatients for more than 24 hours who had developed sepsis whilst in hospital. The management of these patients is likely to be different from those acutely admitted with sepsis; Daniels et al. found that compliance to the sepsis six care bundle was much higher in the emergency department compared to the wards (22). This could be due to increased awareness amongst acute clinicians of sepsis and its management, as well as the masking of signs and symptoms of developing sepsis on the ward due to concurrent illnesses. The small number of patients makes it difficult to generalise the results, and the short time period means that it is likely to be the same group of clinicians caring for all the patients included in the audit and therefore only the management skills of a small cohort of clinicians will have been scrutinised. It is possible that performing the audit on another day, at an alternative time of the year, with a different set of clinicians could have yielded different results.

5.6 Recommendations

Sepsis prevalence appears to be higher than previously estimated, and it is likely that the findings from this audit have still underestimated the rates of sepsis. Establishing an accurate rate of sepsis prevalence is needed to understand the full impact of sepsis on the UK population.

Focussing on improving compliance to the sepsis six care bundle may not improve patient outcomes. Instead, management of sepsis should focus on recognising those at highest risk of death from sepsis and targeting individualised care to these patients. The new NICE guidelines on sepsis management and the NEWS 2 early warning score have been designed

to enable earlier recognition of sick patients with sepsis and future research will establish the impact of NICE and NEWS 2 on sepsis management.

Although research has established the validity of the SEPSIS-3 definitions in patients admitted to ICU, debate remains over the best way to recognise those at highest risk of sepsis on the wards and further research is needed to validate scoring systems used to identify high risk of mortality from sepsis in ward patients, including the use of NEWS 2 to identify those patients at high risk of death from sepsis (83).

Research is now recommended in the following key areas, in light of the project findings:

1. What is the true prevalence of sepsis in all hospital patients, including acute admissions and inpatients?
2. Has the implementation of NEWS 2 increased clinician recognition of sepsis?
3. Has the implementation of NICE guidelines in the UK improved patient mortality from sepsis?
4. Should SIRS or the SOFA and qSOFA score or NEWS 2 be used in the UK to identify patients at risk of mortality from sepsis in the ward setting?

The true prevalence of sepsis should be established through a national database that records all patients who meet the diagnostic criteria for sepsis as defined by SEPSIS-3. Although a significant undertaking, the success of other large national audit databases, such as the National Emergency Laparotomy Audit (NELA), the Intensive Care National Audit and Research Centre (ICNARC), the National Confidential Enquiry into Patient Outcome and

Death (NCEPOD) and Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK), suggest that it is feasible.

The second and third questions may be answered by studying the compliance of healthcare providers to NICE guidelines on recognition, diagnosis and early management of sepsis to evaluate uptake of the guidance by clinicians and to establish the rate of recognition of sepsis amongst clinicians following the implementation of NEWS 2. A review of mortality and outcomes following this evaluation would then assess the efficacy of the new NICE guidelines.

The fourth question may be answered by conducting a prospective observational study in the UK to compare the mortality rates of general ward patients identified with sepsis using SIRS, SOFA, qSOFA and NEWS-2.

Answering these research questions will establish the true prevalence of sepsis, result in validated criteria for identifying patients at high risk of death from sepsis in the UK ward setting and establish the best practice for sepsis management, leading to improved outcomes for patients.

5.7 Conclusion

Sepsis continues to be a common condition with significantly high mortality rates, despite advances in our understanding of the pathophysiology and management of sepsis. This is due to its heterogeneous nature, making the diagnosis and management of sepsis challenging. This audit has highlighted both of these issues, demonstrating that the prevalence of sepsis will change dependent upon the criteria used to classify sepsis, and

that compliance to the sepsis six care bundle remains low. However, the impact of these issues on patient mortality cannot be demonstrated by this audit. Future research should focus on the ability of sepsis classifications to identify those at high risk of death and the impact of new sepsis management guidelines on patient outcomes.

References

1. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. *N Engl J Med*. 2017;377(5):414-7.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-10.
3. Gotts JE, Matthay ME. Sepsis: pathophysiology and clinical management. *BMJ*. 2016;353:i1585.
4. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. *Virulence*. 2014;5(1):36-44.
5. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol.* 2010;11(5):373-84.
6. Remick DG. Pathophysiology of sepsis. *Am J Pathol.* 2007;170(5):1435-44.
7. Martich GD, Boujoukos AJ, Suffredini AF. Response of man to endotoxin. *Immunobiology.* 1993;187(3-5):403-16.
8. Liu D, Lu F, Qin G, Fernandes SM, Li J, Davis AE, 3rd. C1 inhibitor-mediated protection from sepsis. *J Immunol*. 2007;179(6):3966-72.
9. Retsas T, Huse K, Lazaridis LD, Karampela N, Bauer M, Platzer M, et al. Haplotypes composed of minor frequency single nucleotide polymorphisms of the TNF gene protect from progression into sepsis: A study using the new sepsis classification. *Int J Infect Dis* 2018;67:102-6.
10. Harrois A, Huet O, Duranteau J. Alterations of mitochondrial function in sepsis and critical illness. *Curr Opin Anesthesio*. 2009;22(2):143-9.
11. Coopersmith CM, Stromberg PE, Dunne WM, Davis CG, Amiot DM, Buchman TG, et al. Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis. *JAMA*. 2002;287(13):1716-21.
12. Doig CJ, Sutherland LR, Sandham JD, Fick GH, Verhoef M, Meddings JB. Increased intestinal permeability is associated with the development of multiple organ dysfunction syndrome in critically ill ICU patients. *Am J Respir Crit Care Med*. 1998;158(2):444-51.
13. Yan J, Li S, Li S. The role of the liver in sepsis. *Int Rev Immunol*. 2014;33(6):498-510.
14. Shum HP, Yan WW, Chan TM. Recent knowledge on the pathophysiology of septic acute kidney injury: A narrative review. *J Crit Care*. 2016;31(1):82-9.
15. Iacobone E, Bailly-Salin J, Polito A, Friedman D, Stevens RD, Sharshar T. Sepsis-associated encephalopathy and its differential diagnosis. *Crit Care Med*. 2009;37(10 Suppl):S331-6.
16. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. *J Am Geriatr Soc*. 2012;60(6):1070-7.
17. Vincent JL, Marshall JC, Namendys-Silva SA, Francois B, Martin-Loeches I, Lipman J, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. *Lancet Respir Med*. 2014;2(5):380-6.
18. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. *Am J Respir Crit Care Med*. 2016;193(3):259-72.
19. Jolley RJ, Quan H, Jette N, Sawka KJ, Diep L, Goliath J, et al. Validation and optimisation of an ICD-10-coded case definition for sepsis using administrative health data. *BMJ Open*. 2015;5(12):e009487.

20. Rhodes A, Phillips G, Beale R, Cecconi M, Chiche JD, De Backer D, et al. The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study). *Intensive Care Med*. 2015;41(9):1620-8.
21. Shahin J HD, Rowan KM. Relation between volume and outcome for patients with severe sepsis in United Kingdom: Retrospective cohort study. *BMJ (Online)*. 2012;344(7861):e3394.
22. Daniels R, Nutbeam T, McNamara G, Galvin C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. *Emerg Med J*. 2011;28(6):507-12.
23. Mayr FB, Talisa VB, Balakumar V, Chang CH, Fine M, Yende S. Proportion and Cost of Unplanned 30-Day Readmissions After Sepsis Compared With Other Medical Conditions. *JAMA.* 2017;317(5):530-1.
24. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637.
25. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. *New Engl J Med* 2017; 377: 414-7.
26. National Institute for Health and Care Excellence. Sepsis: recognition, diagnosis and early management. NICE guideline [NG51]. 2016. Available from https://www.nice.org.uk/guidance/ng51. (accessed 20th July 2016).
27. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. *Lancet Infect Dis*. 2015;15(5):581-614.
28. National Confidential Enquiry into Patient Outcome and Death. Just Say Sepsis! A review of the process of care received by patients with sepsis. 2015. Available from https://www.ncepod.org.uk/2015sepsis.html. (accessed 20th May 2016).
29. Parliamentary and Health Service Ombudsman. Time to Act Severe Sepsis: rapid diagnosis and treatment saves lives. 2013. Available from https://www.ombudsman.org.uk/sites/default/files/Time_to_act_report.pdf. (accessed 20th May 2016).
30. Frankling CC, Yeung J, Dark P, Gao F. I spy with my little eye something beginning with S: spotting sepsis. *Br J Anaesth.* 2016;117(3):279-81.
31. Robson W, Beavis S, Spittle N. An audit of ward nurses' knowledge of sepsis. *Nurs Crit Care*. 2007;12(2):86-92.
32. Jeffery AD, Mutsch KS, Knapp L. Knowledge and recognition of SIRS and sepsis among pediatric nurses. *Pediatr Nurs*. 2014;40(6):271-8.
33. Assuncao M, Akamine N, Cardoso GS, Mello PV, Teles JM, Nunes AL, et al. Survey on physicians' knowledge of sepsis: do they recognize it promptly? *J Crit Care.* 2010;25(4):545-52.
34. Ferrer R, Artigas A, Levy MM, Blanco J, Gonzalez-Diaz G, Garnacho-Montero J, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA*. 2008;299(19):2294-303.
35. Royal College of Physicians. Identifying higher standards. National Early Warning Score (NEWS). Standardising the assessment of acute-illness severity in the NHS. Report of a Working party July 2012. Available from: https://www.rcplondon.ac.uk/guidelines-policy/acute-care-toolkit-6-medical-patient-risk. (accessed 9th February 2018).
36. Corfield AR, Lees F, Zealley I, Houston G, Dickie S, Ward K, et al. Utility of a single early warning score in patients with sepsis in the emergency department. *Emerg Med J*. 2014;31(6):482-7.
37. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Critical Care*. 2010;14(1).
38. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644-55.

39. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-6.
40. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA*. 1995;273(2):117-23.
41. Jaimes F, Garces J, Cuervo J, Ramirez F, Ramirez J, Vargas A, et al. The systemic inflammatory response syndrome (SIRS) to identify infected patients in the emergency room. *Intensive Care Med*. 2003;29(8):1368-71.
42. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, 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.
43. Abraham E. New Definitions for Sepsis and Septic Shock: Continuing Evolution but With Much Still to Be Done. *JAMA*. 2016;315(8):757-9.
44. Finkelsztein EJ, Jones DS, Ma KC, Pabon MA, Delgado T, Nakahira K, et al. Comparison of qSOFA and SIRS for predicting adverse outcomes of patients with suspicion of sepsis outside the intensive care unit. *Crit Care*. 2017;21(1):73.
45. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. *JAMA*. 2017;317(3):290-300.
46. Freund Y, Lemachatti N, Krastinova E, Van Laer M, Claessens YE, Avondo A, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. *JAMA*. 2017;317(3):301-8.
47. Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. *BMJ*. 2016;353:i2375.
48. Brett SJ. Late mortality after sepsis. *BMJ*. 2016;353:i2735.
49. Szakmany T, Pugh R, Kopczynska M, Lundin RM, Sharif B, Morgan P, et al. Defining sepsis on the wards: results of a multi-centre point-prevalence study comparing two sepsis definitions. *Anaesthesia*. 2018;73(2):195-204.
51. Moran E, Munang M, Chan C, Chaudhri S, Himayakanthan M, Laird S, et al. Sepsis quality standards are laudable but have low specificity. *BMJ*. 2017;357:j1974.
52. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med*. 2017;45(3):486-552.
53. Fletcher SJ, Quinn AC. The surviving sepsis campaign and sepsis care bundles: substance or sophistry? *Anaesthesia*. 2006;61(4):313-5.
54. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-77.
55. Pro CI, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-93.
56. Peake SL, Bailey M, Bellomo R, Cameron PA, Cross A, Delaney A, et al. Australasian resuscitation of sepsis evaluation (ARISE): A multi-centre, prospective, inception cohort study. *Resuscitation*. 2009;80(7):811-8.
57. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Protocolised Management In Sepsis (ProMISe): a multicentre randomised controlled trial of the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock. *Health Technol Assess*. 2015;19(97):i-xxv, 1-150.

58. Angus DC, Barnato AE, Bell D, Bellomo R, Chong CR, Coats TJ, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. *Intensive Care Med*. 2015;41(9):1549-60.
59. Szakmany T, Ellis G, Lundin RM, Pignatelli I, Sharif B, Joshi S, et al. Sepsis in Wales on the general wards: results of a feasibility pilot. *Br J Anaesth*. 2015;114(6):1000-1.
60. Szakmany T, Lundin RM, Sharif B, Ellis G, Morgan P, Kopczynska M, et al. Sepsis Prevalence and Outcome on the General Wards and Emergency Departments in Wales: Results of a Multi-Centre, Observational, Point Prevalence Study. *PLoS One*. 2016;11(12):e0167230.
61. Pinnington S, Atterton B, Ingleby S. Making the journey safe: recognising and responding to severe sepsis in accident and emergency. *BMJ Qual Improv Rep*. 2016;5(1).
62. Kumar P, Jordan M, Caesar J, Miller S. Improving the management of sepsis in a district general hospital by implementing the 'Sepsis Six' recommendations. *BMJ Qual Improv Rep*. 2015;4(1).
63. Vincent J-L, Taccone FS, He X. Harmful Effects of Hyperoxia in Postcardiac Arrest, Sepsis, Traumatic Brain Injury, or Stroke: The Importance of Individualized Oxygen Therapy in Critically Ill Patients. *Can Respir J*. 2017;2017:1-7.
64. NHS England. CQUIN Indicator Specification Information on CQUIN 2017/18 - 2018/19. 2017. Available from: https://www.england.nhs.uk/publication/cquin-indicator-specification/. (Accessed 12th March 2018).
65. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. *N Engl J Med*. 2017;376(23):2235-44.
66. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-96.
67. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med*. 2010;38(4):1045-53.
68. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42(8):1749-55.
69. Sterling SA, Miller WR, Pryor J, Puskarich MA, Jones AE. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Med*. 2015;43(9):1907-15.
70. Tarrant C, O'Donnell B, Martin G, Bion J, Hunter A, Rooney KD. A complex endeavour: an ethnographic study of the implementation of the Sepsis Six clinical care bundle. *Implement Sci*. 2016;11(1):149.
71. Health Research Authority. Is my study research? Available from: http://www.hra-decisiontools.org.uk/research/. (accessed 11th June 2016).
72. Sharif B, Lundin RM, Morgan P, Hall JE, Dhadda A, Mann C, et al. Developing a digital data collection platform to measure the prevalence of sepsis in Wales. *J Am Med Inform Assoc*. 2016;23(6):1185-9.
73. Donnelly JP, Safford MM, Shapiro NI, Baddley JW, Wang HE. Application of the Third International Consensus Definitions for Sepsis (Sepsis-3) Classification: a retrospective population-based cohort study. *Lancet Infect Dis* 2017;17: 661-70.
74. Royal College of Physicians. National Early Warning Score (NEWS) 2. Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party. 2017. Available from: https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2. (accessed 10th February 2019).

75. Public Health Wales. 1000 lives improvement. 2018. Available at: http://www.1000livesplus.wales.nhs.uk/sitesplus/documents/1011/1000%20Lives%20Improvement%20Brochure%202018%20%28web%20version%29.pdf (accessed 10th February 2019).
76. Public Health Wales. The Framework for Peer Review of Acute Deterioration Services in NHS Wales. 2017. Available at: http://www.1000livesplus.wales.nhs.uk/sitesplus/documents/1011/RRAILS%20-%20The%20Framework%20for%20Peer%20Review%20of%20Acute%20Deterioration%20Services.pdf (accessed 10th February 2019).
77. Bentley J, Henderson S, Thakore S, Donald M, Wang W. Seeking Sepsis in the Emergency Department- Identifying Barriers to Delivery of the Sepsis 6. *BMJ Qual Improv Rep*. 2016;5(1).
78. Hamishehkar H, Vahidinezhad M, Mashayekhi SO, Asgharian P, Hassankhani H, Mahmoodpoor A. Education alone is not enough in ventilator associated pneumonia care bundle compliance. *J Res Pharm Pract*. 2014;3(2):51-5.
79. Lawrence P, Fulbrook P. Effect of feedback on ventilator care bundle compliance: before and after study. *Nurs Crit Care*. 2012;17(6):293-301.
80. McGregor C. Improving time to antibiotics and implementing the "Sepsis 6". *BMJ Qual Improv Rep*. 2014;2(2).
81. Damiani E, Donati A, Serafini G, Rinaldi L, Adrario E, Pelaia P, et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. *PLoS One*. 2015;10(5):e0125827.
82. Machado FR, Ferreira EM, Schippers P, de Paula IC, Saes LSV, de Oliveira FI, Jr., et al. Implementation of sepsis bundles in public hospitals in Brazil: a prospective study with heterogeneous results. *Crit Care*. 2017;21(1):268.
83. Shankar-Hari M, Harrison DA, Rubenfeld GD, Rowan K. Epidemiology of sepsis and septic shock in critical care units: comparison between sepsis-2 and sepsis-3 populations using a national critical care database. *Br JAnaesth*. 2017;119(4):626-36.