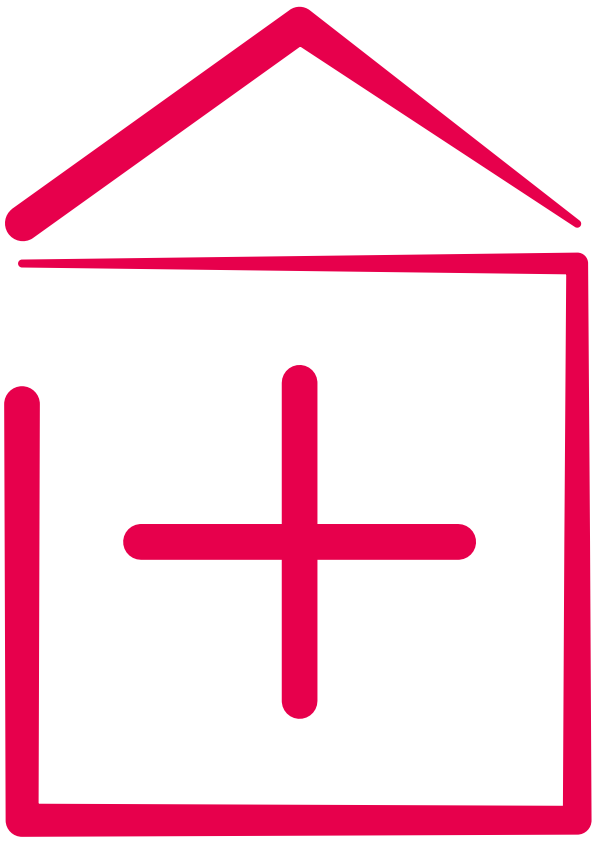
October 2022 v2.0

(Replaces May 2022 version)

Academy of Medical Royal Colleges

Statement on the initial antimicrobial treatment of sepsis



Contents

Figures and tables

Introduction

Sepsis still kills far too many people – tens of thousands in the UK each year, and we know that if infection is identified and treated early, some cases of sepsis and some sepsis-related deaths may be preventable.

Prior to the pandemic, the Council of the Academy of Medical Royal College, which comprises the president and heads of all the Medical Royal Colleges, Colleges and major Faculties, agreed to a proposal that the Faculty of Intensive Care Medicine (FICM) should lead a project, on behalf of the Academy, to establish the most appropriate clinical approach to the management of sepsis. They would then produce a joint guideline, setting out this agreed approach across all specialties.

FICM established a cross-colleges group, led by Professor Julian Bion, Professor of Intensive Care Medicine, University of Birmingham. The work was inevitably delayed by the emergence of the Covid19 pandemic. However, the project is now complete, and the Academy Council endorsed and adopted the report at its meeting in April 2022.

This is a very significant piece of work that has already been very well received by a range of organisations; the list of those endorsing the guidance is set out at the end of the report. The report has also been welcomed by all four of the UK Health Departments.

We believe it will be hugely helpful to clinicians and NHS organisations across the UK, in enabling them to manage and treat sepsis in a more standardised evidence-based way.

The Academy wishes to place on record its huge appreciation to Professor Bion and all members of his working group for their dedication and focus in producing the guidance and to the Faculty of Intensive Care Medicine for conceiving the concept and leading the project through to completion.

Professor Dame Helen Stokes-Lampard DBE PhD FRCGP
Chair, Academy of Medical Royal Colleges

1. Plain English summary

This document proposes a change in the way people with suspected severe infection (sepsis) are treated with antibiotics. We will continue to prioritise those who are the most severely ill, while giving healthcare staff more time to investigate those who are less severely ill, so they receive the right treatment. This will help to reduce excessive and often unnecessary use of antibiotics and the growing risk of antibiotic resistance. Our proposals are based on a review of best evidence and the expert opinions of a wide range of healthcare staff.

'Sepsis' means a serious infection which affects one or more of the body's organs such as the lungs, heart and kidneys. Sepsis has a big impact on individuals, their families and healthcare resources. Many of those who die in the UK have significant co-existing health conditions, for example connected with old age, but other people could potentially survive sepsis if they had the right treatment in a timely manner.

Having the right treatment in time requires that:

- The person must be seen by a healthcare professional, such as a doctor, nurse or paramedic. In the early stages of sepsis people often think they are not ill enough to seek medical help.
- The healthcare professional must recognise that the person has a potentially serious illness and that it could be sepsis. This can be challenging as early signs of sepsis can be mild and mimic other illnesses.
- The patient must be transferred promptly to an appropriate location (acute hospital).
- The clinical team must provide basic support for the person when their body is not working properly, for example giving extra fluid to increase blood pressure or oxygen to assist breathing. The team must also perform tests to see why the person is ill.
- If an infection is thought to be the cause of the illness, or tests show that that this is the case, antibiotics must be given promptly and then changed or stopped later on when more test results are available.

It is very important to choose the right antibiotic to treat sepsis, but test results may not be ready quickly enough to help the medical team choose or may not even identify the responsible microbe. Rapid diagnostic tests are being developed which will assist in speedier identification. However, at present, because of this diagnostic uncertainty,

people with possible sepsis are often given one or more antibiotics to cover a broad-spectrum of possible microbes. Current national guidance recommends these should be given intravenously (by a tube into a person's arm) within one hour of diagnosis. These antibiotics can then be changed or stopped depending upon the subsequent test results. Although giving antibiotics within the hour is appropriate for the very sickest people with sepsis, it has meant that people who are not as ill with sepsis, or even those who do not have sepsis, can be given the wrong antibiotics or antibiotics they do not need. Controlled use is important as all antibiotics can in themselves cause important and sometimes life-threatening side-effects to an individual patient. On a population level, antibiotic overuse increases the risk that the microbes become resistant, so antibiotics no longer work. Antimicrobial resistance is recognised by the World Health Organisation as a major global threat.

The strong weight of evidence shows there does not have to be such a rush in less sick patients. Many national and international emergency and intensive care and infectious diseases organisations now consider that the guidance should be changed to give staff more time to assess, investigate and treat people – for example, in three hours rather than only one hour. We consider the more measured approach we are now recommending will result in more accurate treatment, with better patient outcomes and less antimicrobial resistance.

This document has been led by the Academy of Medical Royal Colleges (AoMRC) which invited the Faculty of Intensive Care Medicine to convene a UK-wide working group, made up of different healthcare professionals and a patient representative. The group began work in January 2020. The group examined multiple guidelines, systematic reviews (where evidence is combined to give more information) and more recent research publications about sepsis. Using this information, the group put together a framework for helping healthcare professionals work out who may have sepsis and who might need treatment quickly. In December 2021 the draft document was sent for review by stakeholder professional and patient organisations and healthcare organisations agencies. The feedback was then incorporated in the final document, which was approved by the AoMRC.

What does this document say? It proposes that the updated National Early Warning Score (version 2, NEWS2) should be used to supplement clinical judgement to identify adult patients with suspected sepsis who are critically ill and need treatment quickly. This rapid bedside score is already recommended by NHS England as the national system to monitor acutely ill adult patients in the community, primary care and in hospital. For children there is an equivalent paediatric version called PEWS (Paediatric Early Warning Score). There are other illness severity scores for special groups, for example, pregnant women. All these scores look at a person's vital signs such as their level of consciousness, heart rate, blood pressure and blood oxygen levels measured with a finger probe. Each vital sign is given a value according to how abnormal it is.

These values are then added up to give an overall score of severity of illness. This composite score determines the speed and seniority of clinical response.

Using research evidence and clinical experience, the AoMRC working group determined how quickly the person needed to be assessed, and the circumstances under which there was time to perform more tests to decide what treatment they needed. People with higher scores need to be assessed and given antibiotics more quickly. These suggested times are not to allow hospitals to delay assessment and treatment, but to give healthcare professionals some more time to find out what the best treatment is for that person. The document makes clear that there is some flexibility; healthcare professionals need to use their own judgement and consider other factors. For example, treatment could be given more quickly for certain high-risk groups even if their NEWS scores do not put them into that category. There are also reminders that treatments must be adapted to patient or parental preferences, any advance care planning wishes and whether certain treatments, for example, admission to intensive care, is in the person's best interests.

The recommendations in this document must be prospectively checked to confirm they do improve care for people with sepsis. This can be done through local audits in individual hospitals and research carried out between different hospitals. It does not remove the need for professional judgement from doctors and nurses about the best way to care for people with sepsis and the duty of care from the wider healthcare system. The working group believes that this guidance allows healthcare professionals the time to wait for test results before giving antibiotics where it is safe to do so, thereby giving the right treatment to that person and reducing the risk of making bacteria more resistant to antibiotics.

2. Executive summary

2.1 Overview

2.1.1 This report proposes that urgency of treatment of adult and paediatric patients with suspected sepsis is based on National Early Warning Scores in secondary care (NEWS2 for adults, PEWS for children) combined with clinical and laboratory assessments of severity, urgency and probability of infection. A structured approach is presented in the form of clinical decision support frameworks linking time frames for initial assessment and treatment to severity bands. These frameworks should be subject to local audit and multicentre research evaluation for subsequent refinement.

2.2 Background

2.2.1 Sepsis is a complication of infection in which a dysregulated host response is associated with organ dysfunction and increased risk of death. For twenty years, the care of patients with sepsis has been the subject of national and international quality improvement initiatives. These have included the recommendation that broad spectrum antimicrobials be administered within one hour of presentation. While this degree of urgency may be appropriate for the most severely ill patients with septic shock or where sepsis is the result of a surgical emergency, the mandate was extended to all patients with presumed sepsis, even though supporting evidence is weak and contested, and a significant proportion of patients do not benefit. The evolution of clinical guidelines into performance metrics with penalties for non-compliance inhibit the exercise of clinical judgement and distract from making a non-infective diagnosis. They also hamper antimicrobial stewardship, and likely contribute to increasing antimicrobial resistance. Recent International and American guidelines are cognizant of these issues and have adopted a more measured view.

2.3 Aims

2.3.1 The Academy of Medical Royal Colleges requested the UK Faculty of Intensive Care Medicine to lead a working group to review and make recommendations on the initial antimicrobial management of adult and paediatric patients with sepsis.

2.4 Methods

2.4.1 A national multidisciplinary working group was convened in January 2020 to include patient representatives, adult and paediatric clinical specialities involved in the care of acutely ill patients in hospital, primary care and the community, microbiology and pharmacy. A series of plenary scoping meetings held in person and by videoconference were supplemented by email discussion. The working group evaluated national and international guidance and current literature, enriched by the experience of frontline clinicians. Iterative development of a clinical decision support tool was accompanied by local evaluation by frontline staff. The outputs were reviewed by a stakeholder group including representatives of all national organisations involved in the care of acutely ill patients throughout the patient pathway, by patient groups, and by representatives of NHS England and the devolved nations, and the Department of Health and Social Care.

2.5 The Current Position: Narrative Review

2.5.1 Determining the true incidence and burden of sepsis is complicated by variability in clinical diagnosis, coding definitions, reimbursement policies and case mix. It is estimated that there are in the region of 918,000 adult sepsis admissions per year, and 66,096 deaths in the UK. In high- and middle-income countries, deaths from sepsis afflict primarily the elderly, frail, those with comorbid diseases, and the immunocompromised, many of whom are at or near the end of life. In children, sepsis occurs in fewer than a quarter of those presenting to hospital with infection, and mortality rates are low.

2.5.2 Antimicrobial resistance is now regarded as a worldwide threat to public health. Efforts to counter antimicrobial resistance have been hampered by a near-doubling in antimicrobial consumption internationally since 2000. In the UK, prescription of antimicrobials has diminished in the community since 2015, but has increased in hospital settings. This particularly applies to broad-spectrum agents which could, in part, be a consequence of exhortations to administer such drugs within one hour of identifying presumed sepsis.

2.5.3 In both adults and children, the propensity of physicians to prescribe antimicrobials is increased by diagnostic uncertainty, by assuming equivalence between uncomplicated infection and sepsis, and by performance targets which prioritise potentially unnecessary prescribing over antimicrobial stewardship.

2.5.4 Evidence that survival from sepsis is improved by administering antimicrobials within one hour of presentation, compared with three, four or six hours, is largely derived from observational studies with methodological weaknesses and risks of confounding. Outcomes are worse for patients receiving inappropriate antimicrobials, indicating the importance of matching treatment to pathogen, a diagnostic process which takes time. Of note, interventions that support clinical decision-making can also enhance effective

stewardship. If there is an hour-by-hour effect of antimicrobial delay on outcomes, it appears to be confined to the most severely ill patients, such as those with septic shock or those requiring an emergency procedure to control the source of sepsis, where deterioration can be rapid and is often compounded by additional perioperative physiological stressors.

2.5.5 Directing antimicrobials to those patients who can benefit involves matching treatment priorities to severity of illness while allowing clinicians sufficient time to make an informed judgement based on the patient's needs and preferences. Sepsis is a pleiomorphic and dynamic condition which, in its early phases, may not be recognised by healthcare professionals. Delayed diagnosis is commonplace in patients presenting with atypical features. Point-of-care diagnostics may be a useful adjunct but are, at present, costly and not yet sufficiently specific. Generic vital sign-based measures of severity of illness require minimal technology, are largely context-independent, and offer a common language for assessing and monitoring all acutely ill patients. While sensitive in detecting patient deterioration they lack specificity for an infection-based aetiology. The UK's National Early Warning Score (NEWS2) (Appendix Fig 1) and the Paediatric Early Warning Score (PEWS) (revisions currently in development [RCPCH]) are widely accepted. NEWS2 is well-validated and while PEWS is still undergoing piloting, both provide a suitable framework for a structured approach to the initial management of acutely ill patients with suspected sepsis.

2.6 Synthesis and Recommendations

2.6.1 The working group unanimously agreed with the principle that treatment urgency for adults and children in secondary care should initially be determined by severity of illness using NEWS2 or PEWS, respectively as part of clinical assessment. A clinical decision support framework was developed based on NEWS2 bands of 0, 1-4, 5-6, and ≥7 (Fig 1), and PEWS bands of 0, 1-4, 5-8, and ≥9 (Fig 2), as these indicate clear step changes in risk of adverse outcomes irrespective of diagnosis. The severity score should then be interpreted in the light of clinical assessment, to include rapidity of deterioration and trajectory, likely diagnosis (such as infection and sepsis), immune status, and evidence of organ dysfunction and likelihood of requiring emergency surgery and/or interventional radiological control of a source of sepsis. If additional concerns are identified at this stage, the clinician can 'upgrade' the actions required at least to the next highest severity band. Assessment of comorbid disease, frailty and patient preferences must also be considered to inform judgements about treatment intensity. As with all scoring systems, the NEWS2 should be used as an aid to clinical assessment, and not a substitute for competent clinical judgement. Any concern about a patient's clinical condition should prompt an urgent clinical review, irrespective of the NEWS2/PEWS score.

2.6.2 This assessment phase is followed by generic actions in terms of monitoring, escalation plan, senior clinical involvement, and investigation and treatment. In parallel

with these activities, the clinician will consider the clinical likelihood of infection. For patients with possible, probable or definite infection, infection-specific diagnostic tests and administration of antimicrobials should be completed within 6, 3, or 1 hour of recording a NEWS2 of 1-4, 5-6, or ≥7, respectively, and for children within 4, 3 and 1 hour of recording a PEWS of 0-4, 5-8 and ≥9, respectively. These are maximum periods, not targets. The aim is not to delay treatment, but to allow sufficient time to make an informed clinical judgement.

2.6.3 Antimicrobial treatment must be accompanied by source identification and control and antimicrobial stewardship through iterative review. When adult patients with a NEWS2 of ≥5 are likely to require an emergency procedure to control a presumed surgically-remediable source of sepsis, their urgency band should be increased to that for a NEWS2 of 7 or more: they should receive appropriate antimicrobials within 1 hour, preferably after collection of blood cultures, be reviewed urgently by senior surgical and intensive care clinicians and undergo emergency control of the source of sepsis within 3-6 hours (according to clinical urgency) consistent with current national [RCSEng 2018] and international [Peden 2021] guidelines.

2.6.4 The frameworks aim to provide a balance between patient safety and antimicrobial stewardship, while allowing clinicians to exercise accountable judgement in the care of individual patients. As with all service delivery interventions, the framework should be subject to local audit and prospective research evaluation leading to future modifications and improvements.

2.7 Action Points

We invite the following organisations and individuals to consider:

- Reviewing and revising current sepsis triage guidance:
  - NHS in England and the devolved nations, NHS Improvement and the Department of Health and Social Care
  - The National Institute for Health and Care Excellence
- Introducing and auditing the sepsis clinical decision frameworks:
  - Lead clinicians for sepsis and Deteriorating Patient Committees in Acute Hospital Trusts, Ambulance Trusts and Primary Care Trusts
- Funding health services research evaluating the safety and efficacy of using severity of illness-guided triage of patients with sepsis:
  - National Institute for Health Research
- Improving the coding of infection and sepsis:
  - NHS Digital

Figure 1: Clinical Decision Support framework for initial evaluation of sepsis in adults ≥16 years

Vital signs	**Vital signs: NEWS-2 'Physiology first'**	0	1-4	5-6	≥7
Initial assessment	**History, examination, lab results**	***If clinical or carer concern, continuing deterioration, surgically remediable sepsis, neutropaenia, or blood gas / lab evidence of organ dysfunction, including elevated serum lactate, upgrade actions at least to next NEWS-2 level →***			
	Comorbid disease, frailty, patient preferences?	*Consider influence of comorbid disease, frailty and ethnicity on NEWS-2, and patient preferences for treatment intensity, limits, end-of-life care*			
Initial (generic) actions	**Monitoring and escalation plan**	Standard observations	• Registered nurse review <1 h • Obs 4-6 hrly if stable. • Escalate if no improvement	• Obs hourly. • Review <1 hr by clinician competent in acute illness assessment • Escalate if no improvement	• Obs every 30 mins. • Review <30 min by clinician competent in acute illness assessment. • Senior doctor review <1 hr if no improvement: refer to Outreach or ICU
	Initial treatment of precipitating condition	Standard care	<6 hr	<3 hr	<1 hr
Likelihood of infection & specific actions	Unlikely	Standard care	Review daily and reconsider infection if diagnosis remains uncertain		
	Possible	Review at least daily	**< 6 h** • Source identification & control plan documented.	**< 3 h:** • Microbiology tests • Antimicrobials: administer or revise • Source identification & control plan documented. **< 6h** • Source control initiated **48 – 72 h** • Review antimicrobials with ID/micro/senior clinician	**< 1 h:** • Microbiology tests • Antimicrobials: administer or revise (broad-spectrum if causative organism uncertain). **< 3 h** • Source identification **3-6 h** • Source control initiated according to clinical urgency **48 – 72 h:** • Review antimicrobials with ID/micro/senior clinician
	Probable or definite	**< 6 h** • Diagnostic tests & R plan	**< 6 h** • Microbiology tests • Antimicrobials: administer or revise • Source identification & control plan. • D/w ID/micro if uncertain, & review		

Notes on clinical decision support framework for sepsis in adults in Figure 1.

- NEWS2 should be used in conjunction with clinical assessment, and not to replace clinical judgement.
- Time zero = first NEWS2 on presentation to ED, or ward deterioration. Clinicians should take into account lag-time bias (NEWS2 recorded in the community or in the ambulance, potential delays in monitoring) and changes in the patient's condition which might indicate the need to upgrade actions and timelines.
- NEWS2 should be used in secondary care to assess and monitor acutely ill patients.
- NEWS2 may be used in community settings (e.g. primary care, care homes) and particularly at the interfaces of care (e.g. referral and communication from one setting to another) to enable adequate and appropriate prioritisation, planning and placement.
- Additional concerns about a serious infective diagnosis may include the presence of septic shock or conditions in which rapid deterioration to septic shock is especially likely, such as necrotising fasciitis, intestinal perforation or ischaemia and meningitis, or conditions which increase susceptibility to sepsis such as immunocompromise. For these conditions, the severity status and accompanying actions should be upgraded according to patient need, and at least to the next NEWS band. The timelines given above indicate outer time limits; if a decision is made to give antimicrobials or to undertake a source control procedure there should not be avoidable delay.
- Other urgent management to provide organ-system support or analgesia may be necessary.
- Whenever possible promptly obtain appropriate microbiological samples before giving antimicrobials.
- Document rationale for prescription (or not) of antimicrobials and provide rationale for choice
- Reserve broad-spectrum antimicrobials for high illness severity or higher-risk e.g. immunocompromised) patients when the infective agent has yet to be characterised.
- The term 'antimicrobial' includes antibacterial, antifungal and antiviral agents. The time intervals specified refer to antibacterial agents as it may take longer to identify non-bacterial pathogens.
- Review appropriateness of initial broad-spectrum antimicrobials within 48 – 72 hours. Seek senior clinical input, including from microbiology or infectious disease physicians, if the patient is not improving.
- Discontinue antimicrobials at the earliest appropriate opportunity.

Figure 2: Clinical Decision Support Framework for the initial evaluation of sepsis in children <16 years

Child appears unwell to health professional YES / NO

Vital signs	**National PEWS**	**0**	**1-4**	**5-8**	**≥9**
Initial assessment	**Assessment**	Assess Airway, Breathing, Circulation, Disability - correct urgent problems as identified • Other Rx as indicated (e.g. analgesia, correct hypoglycaemia)			
		Inform senior clinical decision maker^ if concerned		Arrange Senior clinical review (ST4+)^	Appears unwell to health professional /High PEWS: • If septic shock suspected, resuscitate and administer antimicrobials following microbial tests • Arrange Senior clinical review (ST4+)^ , ± ICU/HDU referral
Initial (generic) actions	**Initial monitoring, escalation plan**	Standard observations Laboratory / imaging tests as indicated	• Registered nurse review <1 h • Obs 4-6 hrly if stable. • Escalate if no improvement • Laboratory / imaging tests as indicated	• Obs hourly. • Review <30 min by clinician competent in acute illness assessment • Escalate if no improvement • Laboratory / imaging tests as indicated	• Obs every 30 mins. • Review <15 min by clinician competent in acute illness assessment. • Senior doctor review <1 hr if no improvement: refer to ICU • Laboratory / imaging tests as indicated
	Timeframe for definitive decision regarding further treatment	< 4 hrs		<3 hrs	<1 hr
Likelihood of infection & specific actions	**Unlikely**	Treat other underlying causes. Consider whether antibiotics should be used empirically or not from clinical perspective.			
	Possible/Definite	**Within 4 h** **Re-assess patient and test results OR earlier if PEWS worsens ≥2 points OR clinical concern** • Source identification/control • Microbiology tests • Antimicrobials: prescribe or revise • D/w ID/micro if uncertain • If parent still concerned, discuss with senior clinical decision maker^		**Within 3 h** **Re-assess patient and test results OR earlier if PEWS worsens ≥2 points OR clinical concern** • Source identification/control • Microbiology tests • Antimicrobials: prescribe or revise • D/w ID/micro if uncertain **Within 48 h** • Review antimicrobials with ID/micro	**Within 1 h:** **Re-assess patient and test results OR earlier if PEWS worsens ≥2 points OR clinical concern** • Microbiology tests • Antimicrobials: prescribe or revise (broad-spectrum if causative organism uncertain). • Source identification/control **Within 24 h:** • Review antimicrobials with ID/micro

Notes on clinical decision support framework for sepsis in paediatrics in Figure 2.

- These guidelines are intended to support, not to replace, clinical judgement.
- Parental concern should always be taken seriously, and clinical decisions made in partnership.
- If National PEWS is not in routine use in an ED/Assessment unit, then other risk stratification tools such as local PEWS, local sepsis screening algorithms should be used, with locally appropriate risk threshold bands.
- The initial No/Yes question for the child's appearance is the first risk stratification tool and is ***independent*** of the PEWS score, which is the second risk stratification tool.
- Initial assessment starts with whether the child appears unwell to a health professional. If so, the health professional must proceed immediately to assess Airway, Breathing, Circulation, Disability, and correct any immediate physiological abnormalities.
- Other urgent management, such as correcting hypoglycaemia or administering analgesia, may be necessary.
- If the child appears unwell, this should override the PEWS system and the clinician should proceed to resuscitation (if indicated) and senior review. After initial resuscitation/stabilisation, the PEWS should still be calculated; if ≥5, proceed to senior review ± HDU/PICU referral. Laboratory / imaging tests should be performed as indicated.
- If the child does not appear unwell, then the National PEWS score should be calculated alongside the Airway, Breathing, Circulation, Disability assessment (Fig 2). This will guide ongoing assessment and management according to green/yellow/orange/red categories. This schema helps identify children who may initially appear well to the assessing health professional (either due to inexperience or because of some occult quality to the child's illness) but have a high (red) PEWS score which would help to identify their subsequent risk of deterioration more rapidly. In this scenario, the schema should lead to the same actions as "appearing unwell to a health professional".
- Microbiology tests: blood and body fluid sampling, before antimicrobials.
- Laboratory / imaging tests as indicated.
- Document clearly the rationale for the management plan.
- Avoid unnecessary delay once decision is made to give antimicrobials.
- Consider antecedent risk factors as per NICE NG51 in assessing risk (age, immunosuppression surgery/trauma in the last 6 weeks, or indwelling lines/catheters or other breach of skin integrity).

Notes on clinical decision support framework for sepsis in paediatrics in Figure 2. (continued)

Symbols:

^Arrange immediate review by senior clinical decision maker (paediatric or emergency care doctor ST4 or above) to assess patient and consider diagnosis and management.

‡ Sepsis = infection + new organ dysfunction.

Septic shock = suspected sepsis plus acute haemodynamic instability.

* Source control examples ... removal of infected cannula, radiological drainage of collections, surgical drainage/repair.

Reference: RCPCH 2021: Paediatric Early Warning System (PEWSystem) – developing a standardised tool for England. RCPCH National PEWS https://www.rcpch.ac.uk/resources/paediatric-early-warning-system-pewsystem-developing-standardised-tool-england

3. Background

3.1 Sepsis is a dysregulated host response to an infection associated with life-threatening organ dysfunction [Singer 2016]. The term 'antiseptic' was first used in 1750 by Sir John Pringle who performed experiments testing acids and alkalis 'resisting putrefaction' [Pringle 1750]. The development of intensive care units in the 1950s and of techniques for extended organ system support provided the opportunity to study the pathophysiology of sepsis, and to test novel therapies targeting the inflammatory response. However, despite a better mechanistic understanding, most interventions demonstrating benefits in animal models have not been replicated in critically ill patients. This scientific challenge was accompanied by the perception that, despite the magnitude of the problem [Rudd 2020], sepsis was inadequately recognised by health systems as a discrete nosological entity. Consequently, in 2002, the Surviving Sepsis Campaign was launched [Surviving Sepsis Campaign] [Bosch 2002] by the European Society of Intensive Care Medicine, the Society of Critical Care Medicine and the International Sepsis Forum to raise global awareness of sepsis as a public health emergency, to advocate for increased resources for sepsis research and education, to agree common definitions for the diagnosis of sepsis, and to develop and promote adoption of best practice guidelines for clinical staff in the front line. Many other organisations joined the campaign, and the focus on sepsis has been endorsed by the World Health Organisation [WHO Aug 26 2020].

3.2 The Surviving Sepsis initiative coincided with growing concerns about patient safety in healthcare [IOM 2000] [WHO 2004]. This convergence allowed sepsis to be framed as a patient safety problem, the solution for which was to ensure more reliable delivery of existing knowledge using sepsis 'bundles' – aggregates of interventions which should be delivered within a specific period of time in a specific location. The original sepsis resuscitation bundle included five components to be completed within the first 6 hours from time of presentation, including the administration of broad-spectrum antimicrobials within three hours. The guidance evolved into a one-hour bundle for all components including antimicrobials [Surviving Sepsis Campaign 2019] with the caveat that these should be narrowed or discontinued in the light of blood culture results and other diagnostic investigations [Levy 2018]. This guidance has been modified in the most recent iteration of the Surviving Sepsis Campaign's recommendations [Evans 2021] so that a three-hour window for administering antimicrobials for possible sepsis without shock is now permitted, recognising the low quality evidence available. There is some retrospective evidence that this welcome focus on sepsis has contributed to an improvement in patient outcomes in adults [Damiani 2015] [Seymour 2017a] [Khan 2019] [Townsend 2021] and children [Gigli 2020] without increasing costs [Bourne 2020], though

separating the direct effects of multicomponent bundles from non-specific changes over time is difficult [Husabo 2020] [Bion 2013]. Some of the perceived improvement is likely attributable to ascertainment bias [Rhee 2020], financial incentivization including re-coding [Sjoding 2015], or improvements in general patient care [Kaukonen 2014]. What may appear to be a series of simple discrete steps is in fact a complex intervention when aggregated in the clinical frontline [Tarrant 2016].

3.3 The bundling of interventions to include the requirement to administer broad-spectrum antimicrobials rapidly within a short time-limited window was contentious from the start. Proponents base their arguments on retrospective observational studies and interrogation of databases and registries [Kumar 2006] [Ferrer 2014] [Gaieski 2010] [Peltan 2019] and a pragmatic view that unhindered bacterial replication could only be harmful: sepsis should be treated with the same urgency as a myocardial infarction or stroke [Funk 2011]. Others however argue for a more nuanced approach with speed dictated by illness severity [Nauclér 2021] [Klompas 2018]. They point to the lack of high quality and often conflicting evidence [Sterling 2015] [Asner 2021] [Nauclér 2021], overuse of antimicrobials with risks of side-effects and encouragement of antimicrobial resistance, and overdiagnosis of sepsis leading to delayed recognition and potential undertreatment of non-septic conditions [Heffner 2010], [Klein Klouwenberg]. Concerns are also voiced that guidelines may become mandated targets susceptible to gaming [Kanwar 2007] [Wachter 2008] [Sjoding 2015].

3.4 Despite these concerns, in the USA, time-to-antimicrobials within three hours is currently a performance metric [Joint Commission 2019]. Yet in 2007, the same body had lengthened time to first antimicrobial dose for community-acquired pneumonia as a quality performance measure from 4 hours to 6 hours in the face of significant criticism regarding diagnostic certainty, lack of benefit, and antimicrobial misuse [Wachter 2008]. In England, administration of broad-spectrum antimicrobials is part of a sepsis quality indicator linked to reimbursement [NHS England 2017] which mandates escalation to a senior doctor in the event of failure of patients with presumed sepsis to respond to treatment within one hour [NHS England 2019]. This is based on NICE guidance NG51 [NICE 2017] on antimicrobial treatment for patients with suspected sepsis who meet high risk criteria in the acute hospital setting, recommending that a broad spectrum IV antimicrobial at maximum recommended dose should be given within one hour of meeting any one of the high-risk criteria. 'High-risk' is defined as (any one of) the physiological variables in the National Early Warning Score (NEWS2) [RCP 2017] (Appendix Fig 1) being recorded in the 'red' zone of the NEWS chart (a score of 3), thus acting as a 'red flag' for sepsis. However, this single extreme parameter score system for defining sepsis has not been shown to be predictive of outcomes with suspected sepsis, potentially increasing clinical workload by 40% yet failing to identify up to 45% of patients at high risk of death [Kopczynska 2018] [Smith 2008] [Smith 2016] [Unwin 2021].

3.5 While the requirement for prompt competent clinical review is uncontentious, the mandate to administer broad spectrum antimicrobials to all patients with sepsis within a

specified time period, and particularly within one hour, is potentially problematic. Concerns are based on the following factors:

- 3.5.1 The benefit of early antimicrobials in sepsis (as distinct from septic shock) is not supported by higher quality evidence including a randomised controlled trial [Alam 2017], large prospective multicentre educational intervention studies [Bloos 2017] [Ferrer 2018], and prospective observational studies [de Groot 2015], [Abe 2019] [Ascuntar 2020].
- 3.5.2 Even in the setting of blood culture-positive septic shock, the period of delay which impacts adversely on outcomes is reported to vary from two hours [Corl 2020], more than three hours [Rhee 2018] [Ko 2021], six hours [Bodilsen 2016] to 24 hours [Lodise 2018]. This is well reviewed by Asner et al [Asner 2021].
- 3.5.3 A conservative strategy allowing clinicians time to select focused antimicrobials was not associated with worse outcomes [Hranjec 2012].
- 3.5.4 The introduction of the Centers for Medicare and Medicaid Services Sepsis Core Measure on Antimicrobial Use in 2015 has resulted in a sustained increase in the use of broad spectrum antimicrobials [Pakyz 2020]. Adherence to the 3-hour time window in the SEP-1 bundle is associated with an increase in unnecessary use of antimicrobials [Miller 2020]. In a retrospective cohort study, bundle adherence increased survival only for patients with hospital-acquired sepsis, but not community-acquired sepsis [Baghdadi 2020].
- 3.5.5 The 1 hour mandate potentially conflicts with the principle of antimicrobial stewardship [Strich 2020] [Seok 2020a], requiring parallel interventions to prompt de-escalation [Burston 2017] which are context-sensitive [Tarrant 2021].
- 3.5.6 Attending medical staff may be penalised for not meeting the time target irrespective of actual patient need [Schinkel 2020]. In England, to meet a financially incentivised target, some hospitals authorised antimicrobial administration before patients were reviewed by a physician, potentially undermining professional and public confidence in care quality.
- 3.5.7 The first-hour mandate presupposes that a reliable diagnosis of microbial sepsis can be made rapidly by frontline staff [Latten 2020]. This may not be the case [Lopansri 2019] [Smyth 2016]. As severity of illness is a more important outcome predictor than specificity of antimicrobial therapy [Aryee 2020], and as physiology-based severity scoring systems perform well in the early detection of sepsis [Lane 2020] [Valik 2020], therapeutic urgency should be determined by physiologic measures of severity, not just a generic label like ‘sepsis’, or a conveniently accessible ‘time zero’ such as emergency department admission [Venkatesh 2013]. Evidence that the use of severity measures alone may drive prescription of inappropriate antimicrobials [Denny 2018] emphasises the importance of linking severity assessment to bedside clinical review.
- 3.5.8 The NICE criterion for high risk can be attained with only one non-specific clinical parameter in the ‘red zone’ of the NEWS2 chart such as new onset

confusion. This is equivalent to a NEWS score of only 3. The Royal College of Physicians recommends [RCP 2017] that patients with a NEWS score of 3 in a single parameter (or aggregate NEWS of 5-6) require hourly monitoring. Whether this level of severity in suspected sepsis is sufficient also to justify mandated administration of broad-spectrum antimicrobials within one hour is debatable. A recent systematic review of antimicrobial timing and mortality in 35 sepsis studies involving 154,330 patients concluded that although '*two thirds…reported an association between early administration of antimicrobial therapy and patient outcome, the time-to-antimicrobials metrics varied significantly across studies and no robust time thresholds emerged*' [Asner 2021].

— 3.5.9 A large retrospective study of febrile children presenting to the ED from a single centre reported that while 55% (6787/12241) of febrile children met ≥1 NICE high-risk criteria, only 1.8% (0.8% with 1 high-risk, and 6% with 2 high-risk) required admission to critical care within 48 hours [Romaine 2020].

3.6 These factors have generated calls for a more nuanced approach to the diagnosis and initial treatment of sepsis, in which accountable clinical judgement should still play a part in decision-making [Klompas 2018] [Klompas 2020] [Ascuntar 2020] [Schinkel 2020] [Singer 2019] [Pepper 2019] [Fitzpatrick 2019] [IDSA Sepsis Task Force 2018]. Recent policy statements from US infectious diseases and emergency medicine societies [Rhee 2021] [IDSA Sepsis Task Force 2018] [Yealy 2021] have supported this stance and argued against time-critical windows as advocated within the Surviving Sepsis Campaign's one-hour mandate and the SEP-1 three-hour bundle. The most recent iteration of the Surviving Sepsis Campaign's recommendations have now been modified to permit a three-hour window for administering antimicrobials for possible sepsis without shock, while retaining the requirement for broad spectrum antimicrobials to be administered 'ideally' within one hour of recognition for patients with possible septic shock or high likelihood of sepsis without shock; the guidance recognises the low quality evidence for making firm recommendations [Evans 2021]. Getting the balance right between prompt treatment and accurate treatment requires a clinical decision-making framework in which a dynamic measure of illness severity, combined with a judgement on the likelihood of infection, guides timely administration of appropriate treatments, including antimicrobial agents if required.

4. Aims

4.1 To resolve these differences, in 2020 the Academy of Medical Royal Colleges (AoMRC) invited the UK Faculty of Intensive Care Medicine (FICM) to lead a multi-professional working group to examine the issues, produce a consensus position on the initial management of paediatric and adult patients with sepsis, and develop practical guidance for healthcare professionals which would ensure timely care while permitting the exercise of professional judgement on the judicious use of antimicrobials.

4.2 The remit of the working group did not extend to a wider consideration of all aspects of the treatment of sepsis, nor to neonatal sepsis which has been the subject of recent NICE guidance [NICE Guideline 195 2021].

5. Methods

5.1 A working group was convened under the aegis of the Academy of Medical Royal Colleges and included patient representatives. The membership is provided at the back of this position statement. The group first met in February 2020 in person, with a further eight meetings by videoconference supplemented by numerous additional subgroup meetings and extensive email exchanges. The group examined current guidance, systematic reviews and newer publications, and through a process of moderated discussion gradually refined a framework for helping clinical staff to identify and prioritise patients with sepsis. Complete agreement was achieved after seven meetings and in December 2021 the draft proposals were sent for review by stakeholder professional and patient organisations and healthcare agencies. The feedback was then incorporated in the final document, which was approved by the AoMRC.

5.2 Meetings took the form of a moderated multidisciplinary expert panel with iterative discussion and agreed action points which were then developed by the core group for subsequent review by all panel members and modification through email exchanges. The work was supported by narrative reviews of the relevant literature in subgroups. The first meeting was used to identify key issues and establish common objectives. A total of five plenary videoconferences were required to achieve consensus outputs. Template guidance was piloted by frontline staff at each iteration. The guidance was then circulated to a wider stakeholder group of professional organisations and special interest groups for review. Responses were reviewed by the working group to create a final version of the guidance. The term ‘antimicrobial’ is used throughout to cover antibacterial, antifungal and antiviral agents. ‘Broad-spectrum’ refers specifically to antibacterial agents.

6. Narrative review of the literature

6.1 The current position

6.1.1 As with most acute diseases, the early phases of infection and sepsis are accompanied by uncertainty about diagnosis, cause, timing of onset, degree of urgency, and likely outcome. Guidance on management tends to be based on data from studies later in the patient pathway (for example, critical care) rather than in the community or the Emergency Department (ED) [Sakr 2018][Abe 2020]. Clinicians must therefore act under uncertainty, but are judged with hindsight. Consequently, in the pressured environment of emergency care, it may be easier to give antimicrobials to patients who might be septic than to justify delay while refining the diagnosis. This hampers efforts at antimicrobial stewardship and may mask potential causative pathogens resulting in inappropriate therapy. However, this trend is not inevitable: educational and clinical support interventions can empower clinicians to make more nuanced judgements [May 2021] [Ouldali 2017].

6.1.2 We review here the current position on infection and sepsis in adults, children and obstetrics, trends in the use of antimicrobials, antimicrobial stewardship, and newer diagnostics. We then evaluate current methods for measuring severity of illness and consider the evidence for timing of antimicrobials before proposing a sepsis clinical decision support tool.

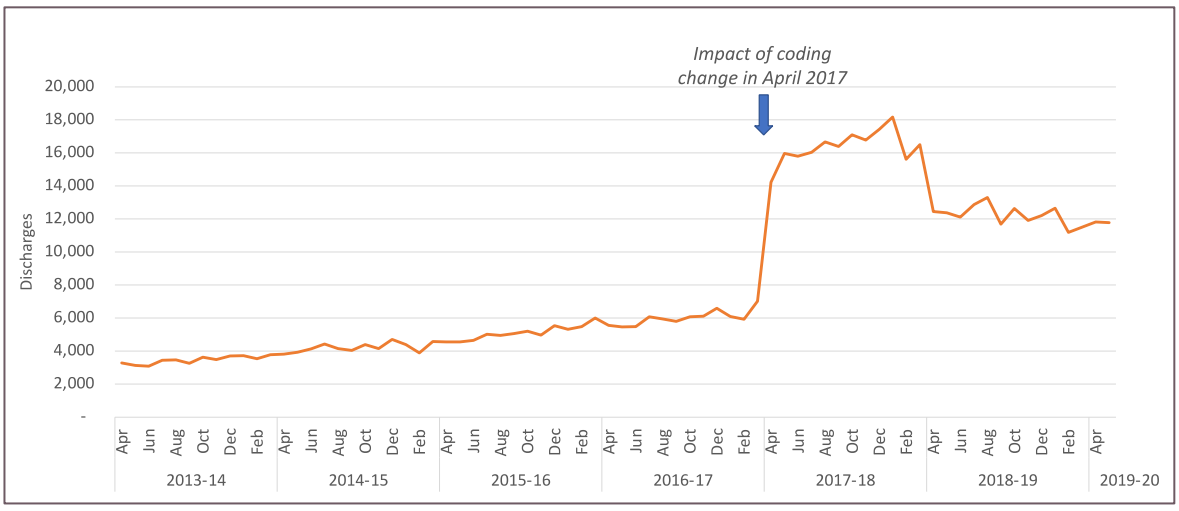
6.2 Infection and sepsis in adults

6.2.1 Determining the scale of the sepsis burden is challenging. Using data from the Global Burden of Disease project [Rudd 2020], the worldwide incidence of sepsis in 2017 has been estimated at 48·9 million cases per annum (95% uncertainty interval (UI) 38·9–62·9) with 11 million (10·1–12·0) sepsis-related deaths annually [Rudd 2020]. However, variability in clinical diagnosis, coding definitions, reimbursement policies, type of infections and case mix [Rudd 2018] means that these data are contested, even by those offering estimates of magnitude [Fleischmann-Struzek 2020]. An analysis of 2.5M sepsis cases In the USA estimated per-patient costs of treatment to range from $18,023 for patients with sepsis present at admission, to $68,671 for patients who developed septic shock following hospital admission [Paoli 2018]. In the UK, a report commissioned by the UK Sepsis Trust estimated from HES data an incidence of sepsis of 147,000 per year, at an estimated cost of £7.76 billion [Whitewater Charitable Trust 2017]. Inada-Kim et al used 'suspicion of sepsis' (coding of all bacterial infective diagnoses for admitted patients) in

the Oxford Region in 2013-14 to estimate 17 admissions per 1000 adults per year, with a mortality of 7.2%; for the UK as a whole this would be 918,000 adult sepsis admissions per year, and 66,096 deaths [Inada-Kim 2017]. The true number of confirmed bacterial sepsis admissions will be lower than this. During 2011-2015, on average each year there were 39,544 sepsis admissions to intensive care units in England and Wales, these representing the most severely ill hospitalised patients; 7,852 per year were classed as having septic shock based on Sepsis-3 criteria with a hospital mortality rate of 55.5% [Shankar-Hari 2017].

6.2.2 Deriving accurate estimates is difficult as there is no standardisation of operational criteria. Second, there is no gold-standard diagnostic test. Third, in the initial phase of acute illness clinicians usually treat *suspected* sepsis, but there is wide inter-observer disagreement between physicians when applying diagnostic criteria to standardised case histories [Rhee 2016]. Fourth, a rise in awareness, changes in national sepsis coding guidance and an increase in sepsis reimbursement has led to an artificial 300% increase in reported sepsis numbers [AHSN Network] [Singer 2019] (Fig 3). Finally, case mix heterogeneity accounts for variations in secular trends for mortality [Shankar-Hari 2016] and likely explains some of the variation in outcomes between countries [Ranzani 2018].

Figure 3. Number of sepsis admissions to hospital England 2013-14 to 2019-20 showing the impact of coding change. [https://www.sos-insights.co.uk/]



6.2.3 It may therefore be preferable to measure the infection burden using administrative data collected from emergency hospitalisations in whom antimicrobials were commenced [Inada-Kim 2017]. These patients with a *suspicion of sepsis* will likely include the majority of true community sepsis cases. Numbers have remained more constant over time and are less subject to the vagaries of gaming or coding trends.

Coding is best undertaken using the final hospital discharge diagnosis when results of investigations are available, the response to treatment noted, and other diagnostic possibilities excluded.

6.2.4 The majority of admissions and deaths with presumed bacterial infections occur in the elderly and those with comorbid disease [Rhee 2019] [Kopczynska 2018b]; death is rare in adults under the age of 40 years (Fig 4). This is supported by Office of National Statistics data from death certificates and from studies examining attributability and preventability among those dying ***from*** sepsis as the cause of death ('septicaemia') as opposed to ***with*** sepsis as an accompanying factor ('any mention of sepsis' [ONS 2019] (Table 1). In a study of 521 septic patients in general wards and EDs across all Welsh acute hospitals in 2016 and 2017, 166 (7.2%) died, but death was probably or possibly attributable to sepsis in only 40. Of these 40 (32.4%) sepsis deaths, 31 patients (77.5%) had a Clinical Frailty Score ≥ 6, 28 (70%) had a pre-existing DNA-CPR order, and 17 had other limitations of care orders (42.5%) [Kopczynska 2018b]. In an analysis of 117,510 patients admitted to 114 USA hospitals between 2013-2017, the reduction in mortality rates over time was attributable to an increasing proportion of patients being discharged from hospital to hospice care [Rhee 2021b]. These factors suggest that in a Western context, describing each sepsis death as 'an avoidable tragedy' [Hancock 2019] is substantially overstated.

Figure 4: 'Suspicion of Sepsis' (SOS) admissions and number (%) deaths, England 2011-17

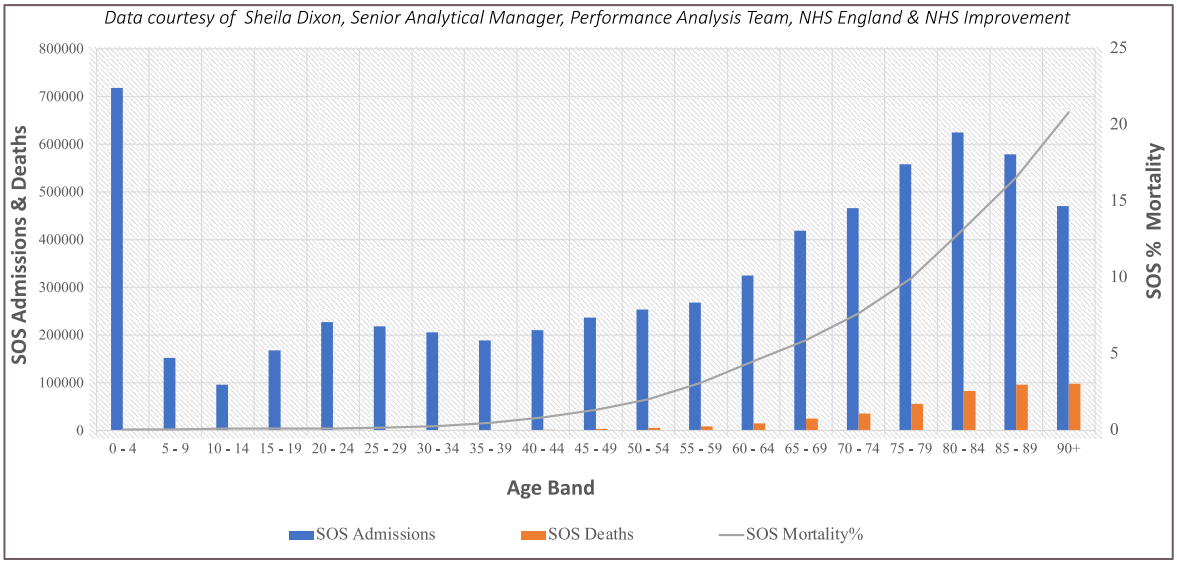


Table 1. Number of deaths where septicaemia was the underlying cause, or was mentioned anywhere on the death certificate – England and Wales, 2016-2018 registrations [ONS 2019]

Year	Septicaemia given as underlying cause of death			Any mention of septicaemia		
	England	Wales	England & Wales	England	Wales	England & Wales
2016	2,665	223	2,900	23,273	1,614	24,973
2017	2,432	191	2,630	22,263	1,400	23,709
2018	2,557	194	2,757	21,726	1,363	23,185

6.2.5 There is a pressing need for a standardised taxonomy for sepsis to emphasize the requirement for both infection and new-onset organ dysfunction, as defined by Sepsis-3 [Singer 2016], now incorporated in ICD-11. Misleading descriptions of uncomplicated urinary tract infection as 'urosepsis' and meaningless terms such as 'septicaemia' need to be jettisoned. Standardisation will permit more accurate estimates of the incidence and burden of illness and provide more reliable evaluations of interventions and services targeting patients with life-threatening infection. A national registry using standard definitions based on current HES data would make it easier to determine current and historical performance, record more accurately patient demographics and the true numbers of admissions and deaths, and provide benchmarks for assessing and comparing improvement initiatives, antimicrobial stewardship and costs. We provide a preliminary taxonomy in Table 2.

Table 2: Taxonomy of sepsis

Infection	Invasion of body tissues by disease-causing microorganisms
Uncomplicated infection	Infection not resulting in new or worsening organ dysfunction i.e. change in SOFA score <2 points
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection. Clinically characterised by a change in SOFA score ≥2 points
Septic shock	A subset of sepsis in which particularly circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Clinically identified by a vasopressor requirement to maintain a mean arterial pressure ≥65 mmHg plus a serum lactate >2 mmol/L that persist despite adequate fluid resuscitation

NEWS2	National Early Warning Score-2. An aggregate severity of illness score (0-20) for adults with points ascribed to increasing physiological abnormalities (respiratory rate, pulse oximetry-measured oxygen saturation, requirement for supplemental oxygen, systolic blood pressure, heart rate, level of consciousness, temperature).
SOFA score	Sequential Organ Failure Assessment score. An aggregate point score (1-4) with points ascribed to increasing physiological and biochemical abnormalities representing dysfunction of six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, neurological).
SIRS	Systemic Inflammatory Response Syndrome. Characterised by ≥2 criteria exceeding thresholds for temperature, heart rate, respiratory rate and white blood count. Formerly used in combination with infection to identify 'sepsis' but now discarded as often represents an appropriate (i.e. non-pathological) host response to any inflammatory (i.e. non-specific for infection) insult.
Severe sepsis	Outdated terminology combining SIRS + organ dysfunction; now replaced by 'sepsis'
Bacteraemia / Fungaemia / Viraemia	Presence of these micro-organism in the blood stream
Septicaemia	Redundant (and meaningless) term formerly used to describe sepsis
Blood poisoning	Redundant (and meaningless) term formerly used to describe sepsis
Urosepsis	Should only be used to describe a urinary tract infection (UTI) with new organ dysfunction, not any type of UTI
Neutropenic sepsis	Should only be used in patients with neutropenia related to an underlying disease or treatment who develop new infection-related organ dysfunction. Neutropenic infection should preferentially be used for neutropenic patients with an uncomplicated infection. n.b. sepsis itself may induce a transient leucopenia but this should not be classified as neutropenic sepsis alongside the above populations.
Febrile neutropenia	Patient with neutropenia and a pyrexia ≥38°C which may or may not be due to infection
Pneumonia	Infection of one or both lungs caused by a pathogen. This term should be reserved for more serious lung infection rather than an uncomplicated lower respiratory tract infection.

6.3 Paediatric sepsis

6.3.1 Fever accounts for around 20% of all visits to Paediatric Emergency Departments [Leigh 2019]. In this context, the probability of serious bacterial infections is between 7% [Craig 2010] and 22% [Hagedoorn 2020]. Approximately 60% of febrile children have a self-limiting viral infection. The incidence of central nervous system infection or sepsis is <1% [Hagedoorn 2020]. The challenge for clinicians is to identify accurately those children at risk of serious bacterial infections with life-threatening and potentially life-changing complications – the "needle in the haystack" [Ladhani 2010]. Because of the catastrophic consequences of missing such cases, a cautious approach to the management of the child with fever is often taken, involving extended observation, investigations, and precautionary use of antimicrobials, often without definitive evidence of bacterial infection [Leigh 2019].

6.3.2 In Europe, mortality in children admitted to hospital with sepsis is low. The causative organism remains unidentified in approximately half of cases. A fatal outcome in children with community-acquired infections was associated with identification of the causative organism, presence of sepsis, increased paediatric ICU (PICU) admission, the need for oxygen or respiratory support (or both), inotrope administration, and a prolonged hospital stay [Martinon-Torres 2018]. In children with community-acquired sepsis admitted to European PICUs, mortality was 6%, increasing to 10% in the presence of septic shock. However, mortality is not the only significant outcome in children with sepsis, as a third of survivors admitted to PICU were discharged with disability [Boeddha 2018]. Co-morbidity is an important risk factor. A single centre study indicated that 29% of children with bacteraemia had underlying co-morbidities [Irwin 2015]. The international, multicentre Sepsis Prevalence, Outcomes and Therapies Study (SPROUT) of PICU admissions with severe sepsis reported that 77% had co-morbid conditions, with the most common being respiratory illness (30.3%); approximately half of children admitted had ≥2 co-morbidities [Weiss 2015]. Antecedent risk factors should also be considered, as listed in the NICE guidance NG51 Section 5 [NICE 2017] in assessing risk (age <1 year, immunosuppression, surgery/trauma in the last 6 weeks, indwelling lines/catheters or other breach of skin integrity).

6.3.3 The Surviving Sepsis Campaign guidance on the management of paediatric septic shock and sepsis-associated organ dysfunction [Weiss 2020] acknowledges the low quality of evidence, resulting in many weak recommendations. Antimicrobial administration within one hour of presentation of septic shock received a strong recommendation despite very low quality evidence. For sepsis-related organ dysfunction, a weak recommendation was made for antimicrobials within 3 hours. The guidelines therefore provide a pragmatic approach for consistent care until additional evidence is available.

6.3.4 As with adult practice, a key concern in sepsis management has been to develop reliable methods for the dynamic assessment of severity of illness. Mortality as the primary outcome in paediatric ED settings has too low an event rate (<1%) for calibration. Critical care admission is a more suitable outcome as this allows assessment of whether the score can identify those patients requiring additional support, regardless of survival. The use of the age-adjusted qSOFA for paediatric sepsis has demonstrated poor or insufficient sensitivity in predicting in-hospital mortality and PICU admission [Schlapbach 2018] [van Nassau 2018] [Romaine 2020] [Eun 2021]. A paediatric SOFA (pSOFA) has been developed for sepsis but cannot be used in the first hour or so following presentation because of the inclusion of bilirubin and creatinine [Matics 2020]. Attention has therefore focused on developing a paediatric version of the adult Early Warning Score (see below) [Roland D 2021], [Romaine 2021]. PEWS, like NEWS, presents an opportunity to have a "common language" across pre-hospital, ED and critical care. The system-wide introduction of NEWS has led to improved outcomes in adults with suspicion of sepsis [Pullyblank 2020]. PEWS could be a useful tool for identifying and tracking physiological changes, and the introduction of a standardised score would potentially allow improvement or deterioration to be tracked from ED to ward to critical care.

6.4 Maternal sepsis

6.4.1 Maternal sepsis is defined as a life-threatening condition due to organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion and the postpartum period [Bonet 2017]. While adverse outcomes from maternal sepsis have improved over the last twenty years, it remains one of the most common causes of maternal death [Chen 2021]. In 2020 the WHO estimated that sepsis contributes to severe maternal outcomes in 10·9 (9·8-12·0) women per 1000 live births admitted to hospital with an infection, with the highest rates in low and middle income countries) [WHO Global Maternal Sepsis Study 2020]. The UK national confidential enquiry system MBRRACE estimates sepsis-related mortality to account for 11% of all maternal deaths and an increased stillbirth rate [MBBRACE 2020]. Factors which may enhance susceptibility to certain infections include altered physiology such as urinary stasis or a reduction in lung volumes, development of gestational diabetes or pre-term pre-labour rupture of membranes, increased exposure to surgical procedures such as caesarean section, and changes in cell-based immunity [Kourtis 2014]. The genital tract, urinary tract and wound infections are the most likely infection source. Streptococcal infection is an obstetric emergency: a study of severe genital tract sepsis found group A streptococcal infection was the single factor associated with an increased odds of septic shock [Acosta 2014]. Herpes simplex virus infection can complicate pregnancy [Straface 2012] and cause post-partum endometritis [Anyebuno 2014] which may be fatal to mother or child.

6.4.2 Assessment of illness severity is facilitated by vital signs scoring systems. Physiological changes in pregnancy in the cardiovascular, respiratory, haematological and coagulation systems may mask or mimic sepsis, making diagnosis more difficult [Greer 2019]. Gestation-specific vital sign reference ranges have recently been published [Green 2020]. A UK national maternal early warning system (MEWS), incorporating six physiological parameters and based on these data, is due for imminent release by the NHS England maternal and neonatal safety improvement program 'MatNeosip' [NHS England 2019].

6.4.3 In 2006-8 an increase in obstetric sepsis deaths stimulated an extensive initiative to raise awareness and improve sepsis management [Cantwell 2011]. Death rates declined in subsequent years, but a UK national cohort study in 2016 suggested ongoing clinical failures in the timely recognition of genitourinary and respiratory infection [Acosta 2016]. The most recent enquiry highlights the importance of timely surgical source control [MBBRACE 2020]. The Royal College of Obstetricians and Gynaecologists' (RCOG) 'Green Top Guidelines' published in 2012 [RCOG 2012] and reviewed in 2017 [RCOG 2017] and the Sepsis Trust UK Inpatient Maternal Sepsis tool [UK Sepsis Trust 2019] are widely used by UK maternity units, though the underpinning evidence base is weak. Based primarily on general adult practice, these recommend administration of broad spectrum antimicrobials within one hour of recognition of 'severe sepsis' (Green Top Guideline). The UK Sepsis Trust's criteria include 'red flag' sepsis combined with evidence of acute kidney injury (AKI). The RCOG is currently revising its sepsis guidance.

6.5 Current antimicrobial use and trends

6.5.1 Community, Primary Care and Hospital Practice

6.5.1.1 Antimicrobial consumption increased worldwide by 90% between 2000 and 2015, with the greatest increase in low-and middle-income countries [Klein 2021]. Antimicrobial resistance (AMR) is a growing threat. Estimates for 2019 indicate 4.95 million deaths associated with, and 1.27 million deaths attributed to, antimicrobial-resistant bacteria [Antimicrobial Resistance Collaborators 2022]. In 2015, the UK ranked 28th of 71 countries in antimicrobial consumption rate by sales [Klein 2018]. The UK AMR 5 year national action plan aimed to reduce inappropriate antimicrobial prescribing in hospital and ambulatory settings by 50% [DoH 2016] [Smiezek 2018], and halve the number of resistant infections by 2020.

6.5.1.2 A 7.5% reduction in total antimicrobial use (as defined daily doses (DDD) per inhabitant in England) has been recorded over the 5-year period from 2015-19. However, this relates to decreased use in primary care (-12%). During the same period hospital in-patient use increased by 13% and outpatient use by 1.7% [ESPAUR 2019-2020]. The use of intravenous and broad spectrum antimicrobials in the emergency department doubled [ESPAUR 2019-2020]. Data from the most recent report [ESPAUR 2020-2021] show a further

marked reduction in primary care antimicrobial prescribing, likely attributable to the COVID-19 pandemic. However, in-patient prescribing has remained static (Appendix Fig 2).

6.5.1.3 A driver for this increased use in in-patients may have been the Commissioning for Quality and Innovation (CQUIN) scheme. This was introduced in 2015-16 [NHS England 2015] to incentivise screening for sepsis and stimulate initiation of treatment within one hour for adults and children arriving at hospitals via emergency departments, based on clinical identification of either suspected severe sepsis, septic shock, or 'Red Flag' sepsis [UK Sepsis Trust]. This was extended to in-patients in 2016-17. A survey demonstrated considerable diversity of approach to sepsis identification [Inada-Kim 2016]. In 2019 the CQuIN contract was adjusted to require use of the NEWS2 for sepsis screening [NHS England 2019], with broad-spectrum antimicrobials administered within one hour to adult patients with a NEWS2 score ≥5 in whom sepsis was suspected.

6.5.1.4 The 2016 aim to halve the number of drug-resistant infections has not been achieved. While resistance of *E.coli* in bloodstream infections has remained stable to third-generation cephalosporins, quinolones, aminoglycosides and piperacillin/tazobactam, increases in resistance have been noted for *K.pneumoniae* (8% in 2019 compared to 6% in 2015). For *Pseudomonas spp* the highest resistance (5%) is to piperacillin/tazobactam [ESPAUR 2019-2020]. The latest UK AMR action plan (2019 – 2024) has updated targets to halve healthcare-associated Gram-negative bloodstream infections; further attempts to reduce the number of specific drug-resistant infections by 10% by 2025; reduce UK antimicrobial use in humans by 15% by 2024; reduce UK antimicrobial use in food-producing animals by 25% between 2016 and 2020; define new objectives by 2021 for 2025; and to be able to report on the percentage of prescriptions supported by a diagnostic test or decision support tool by 2024. While such targets are measurable, they do not take into account appropriate antimicrobial prescribing which is critical in sepsis.

6.5.2 Initial Antimicrobial Prescribing Practices

6.5.2.1 Hospital Trust antimicrobial prescribing guidelines vary in their recommendations for antimicrobial treatment of sepsis of unknown source (Appendix Fig 3) [Howard P 2021] [Pan 2021]. In the setting of septic shock, most add gentamicin to amoxicillin or amoxicillin-clavulanate, or switch to piperacillin-tazobactam or carbapenems. In paediatric sepsis, ceftriaxone use is almost universal. All guidelines provide information about additional cover for patients colonised with multidrug resistance bacteria (e.g. ESBLs, MRSA). The desire to minimise drivers of AMR, particularly in critically ill patients [Denny 2019] creates potential conflicts with current NICE guidance NG51 [NICE 2017] to give broad-spectrum intravenous antimicrobials at maximum dose within one hour to patients with suspected sepsis who meet one or more of their high-risk criteria. In meningococcal disease, the NICE guidance recommends parenteral benzylpenicillin in the community and ceftriaxone in the hospital setting, and piperacillin-tazobactam for suspected neutropenic sepsis in hospital. More recently, NICE has produced treatment

guidance for common infections that should be tailored to local antimicrobial resistance patterns [NICE March 2021].

Broad or narrow spectrum antimicrobials? Key points

- The definition of broad- versus narrow-spectrum antimicrobials is largely based on the intrinsic resistance profile (Reygaert 2018). Emergence of resistance locally may impact on the spectrum of activity. For empiric treatment of sepsis of unknown aetiology, the antimicrobial should be broad spectrum [NICE guidance].
- Empiric antimicrobial therapy should take into account the likely source of infection (e.g. intra-abdominal, wound, ventilator-associated pneumonia), previous bacteriology (prior infections or colonisation with resistant bacteria), and risk factors such as long term residential care, hospital-acquired infection, immunosuppression or overseas travel.
- As more information is gained about the patient's infection, antimicrobial susceptibility pattern and clinical response, antimicrobial treatment should be narrowed accordingly and unnecessary antimicrobials discontinued (de-escalation).
- Selection of antimicrobials should be guided by local antibiograms, speed of action, tissue penetration and patient response. Beta-lactam antimicrobials are widely used as they have good penetration and little impact on renal function; they may be combined with an aminoglycoside for additional bactericidal activity if this is regarded as advantageous, though the evidence base is weak and its use generally discouraged [Paul 2014]. Some centres have adopted continuous infusions to achieve target plasma concentrations.
- In terms of treating infection in general, the WHO has proposed a classification of antimicrobials as Access, Watch and Reserve as part of their Essential Medicines classification. This has been adapted for the UK [Budd 2019] (Appendix Table 1) to guide the use of preferred first line antimicrobials (Access), those broad-spectrum with higher resistance potential (Watch), or those which should be only be used as last-line agents where there are no other option (Reserve). The UK AMR National Action Plan has set targets to reduce the antibacterial consumption in the Watch and Reserve groups by 10%.

Monotherapy or combination therapy: key points

- Cover can be achieved using monotherapy with a broad-spectrum agent or a combination of antimicrobials with narrower spectra depending on local resistance rates, and patient factors including likely infection site, age and allergy status.
- The current literature [Strich 2020] [Evans 2021] suggests that combination therapy with double coverage should be reserved for patients who are severely ill with septic shock and likely to be at risk of having a multidrug resistant Gram negative infection.
- Immunosuppressed patients are more likely to be colonised with multidrug resistant organisms, but the evidence is not conclusive that combination therapy offers better outcomes without patient harm. A review of local antibiograms at a unit level should guide empiric treatment. [Strich 2020].
- In the UK, Gram-negative bacterial resistance to commonly used broad spectrum antimicrobials is low overall, but growing slowly [ESPAUR 2019-2020], thus combination therapy is currently rarely required for empiric therapy. Combination therapy may be considered for treatment of patients with risk factors or in settings where resistance is high (e.g. ICUs with outbreaks of specific resistance). For example, NICE CG151 guidance on neutropenic sepsis [NICE 2012] only recommends cover with piperacillin-tazobactam monotherapy without aminoglycosides unless there are patient-specific or local microbiological indications. Nonetheless, two-thirds of English hospitals add an aminoglycoside, despite a 2019 stakeholder review of the guidance, but this is not unique to the UK [Verlinden 2020].
- Some hospitals, based on their local antibiogram, may use combination therapy to cover for known gaps in cover e.g. amoxicillin-clavulanate plus gentamicin or amikacin, rather than use piperacillin-tazobactam monotherapy.
- Patients with known or presumed penicillin allergy are a potentially problematic group. A health records study in primary care has reported an association between documented penicillin allergy and adverse events including mortality [West 2019]; the authors recommend a penicillin challenge test to establish the patient's true status. In the setting of treating sepsis in hospital, given the low risk of cross-reactivity, most clinicians will substitute cephalosporins or carbapenems for beta-lactam antimicrobials, or conduct a challenge test.

6.5.3 Antimicrobial stewardship

6.5.3.1 Antimicrobial stewardship is emphasised in guidance from NICE [NG15, 2015] and Public Health England "Start Smart then Focus" [PHE 2015], and needs to be embedded in all aspects of infection management and control across health systems [Infection Management Coalition 2022]. NICE and PHE recommend that antimicrobials should not be continued beyond 7 days unless supported by local guidelines or expert review. Shorter course therapy (5-7-days) are as effective as a 14-day course for treating uncomplicated Gram-negative bacteraemia [Yahav 2019] or for empirical therapy [Evans 2021]. Longer

courses may lead to increasing resistance: [Teshome 2019] showed that for each additional day of piperacillin-tazobactam after day three resulted in an 8% increase in resistance. Rapid 'rule-out' tests to exclude bacterial and fungal pathogens [Yui 2020] or normal host response markers [Christ-Crain 2006] in blood samples have the potential to forego or allow earlier discontinuation of antimicrobials if the patient's clinical condition permits. Interventions that support clinical decision-making enhance effective stewardship [May 2021] [Ouldali 2017]. NIHR-funded trials are currently underway in the UK in adults [ADAPT SEPSIS] and children [BATCH] using biomarkers to guide antimicrobial discontinuation, and in the ED to guide stratification of patients who urgently need IV antimicrobials [PRONTO].

6.5.4 Forty-eight hour patient review

6.5.4.1 As more information is obtained about the infection and possible bacterial aetiology, if the patient's condition is improving, the clinician should consider switching to narrow-spectrum treatment and limiting duration of treatment to five days. This will minimise harm from broad-spectrum drugs and limit the potential for developing collateral resistance in non-targeted organisms. Public Health England [PHE 2015] encourages a review of the clinical diagnosis and continuing need for antimicrobials within 48-72 hours from initiation. At this point, additional information about the patient's presenting complaint is usually available, including microbiological results, radiology reports, biomarkers and clinical progress.

6.5.4.2 A bacterial aetiology may not be confirmed, especially in pneumonia, or if a specimen could not be collected before antimicrobial treatment was started. This should not prevent actions being taken for re-evaluation of treatment. Changes impacting AMR include stopping antimicrobials altogether if there ceases to be an indication, de-escalation to narrower spectrum, or switching depending on laboratory and clinical information. The literature on de-escalation is controversial, covers many different settings and interpretation of outcomes is made difficult by differences in local ecology and patient characteristics [De Waele 2020]. However, de-escalation does not appear to produce worse outcomes [Paul 2016] [Tabah 2020].

6.6 Increasing resistance patterns in the UK

6.6.1 In the absence of reliable, inexpensive and rapid diagnostics to identify AMR at the bedside, the choice of antimicrobial for a patient with suspected sepsis in the ED will be empirical and determined by the likely site of infection and the local resistance patterns of pathogens thought to be responsible. With a national focus on antimicrobial stewardship, change in AMR in the UK has been more limited than in some other European countries. However, antimicrobial resistance in some species has been increasing; incorrect antimicrobial choices have contributed to prolonged hospital admission or reduced survival. General practice accounts for 86% of total antimicrobial

use in England, constituting the major pressure on emergence of resistance [ESPAUR 2019-2020]. Stewardship programs have had some success and driven a 14% reduction in prescriptions between 2015 and 2019.

6.6.2 According to European Antimicrobial Resistance Surveillance Network (EARS-Net) data collected for the UK from 2014-2019 [ECDC], resistance of *Klebsiella pneumoniae* to third generation cephalosporins rose from 9.3% to 13.2%, and to quinolones from 7.7% to 12.8%; carbapenem resistance however remained uncommon (0.8% to 0.7%). *Pseudomonas aeruginosa* has become increasingly resistant to piperacillin-tazobactam (4.0% to 5.6%) and quinolones (5.4% to 8.7%) but little change was seen with ceftazidime (4.6% to 5.0%) or carbapenems (6.3% to 5.9%). *Escherichia coli* resistance to third generation cephalosporins and quinolones changed little (10.5% to 11.5%, 16.8% to 17.8%) while carbapenem resistance remained rare (0.1% to 0.0%). By contrast, resistance of *Staphylococcus aureus* to methicillin fell from 11.3% to 6.0% following a national MRSA reduction scheme. Similarly, the PHE ESPAUR report has noted a rise of 2.4% in resistant key pathogen bloodstream infections since 2015.

6.7 Relationship between timing of antimicrobial administration and outcomes

6.7.1 Early studies that retrospectively analysed hospital databases and registries suggested a near-linear relationship between increasing risk of death and delay in administering antimicrobials for suspected sepsis and septic shock, commencing as early as the first hour after diagnosis, triage or even admission to hospital (e.g. Kumar 2006, Ferrer 2014). These data influenced guideline bodies and funders to promote antimicrobial administration within an hour of diagnosis [Rhodes 2017] [US Centers 2021] [NHS Sepsis CQUIN 2015]. However, most other studies failed to confirm such a relationship unless delays to initiation of treatment were considerably longer [Taylor 2021] [Asner 2021]. Such studies include a randomised, controlled trial of pre-hospital treatment [Alam 2018], and prospective observational studies specifically addressing this question (e.g. Seok 2020b, Abe 2019, de Groot 2015). Two prospective multicentre quality improvement programs that aimed to institute antimicrobials within an hour of diagnosis of sepsis/septic shock also failed to show outcome improvements [Bloos 2017, Ferrer 2018], although in both programs the improvement achieved in absolute time to administration of antimicrobials was modest and the aim of instituting antimicrobials within an hour was missed. Rüddel et al have undertaken a pre-planned secondary analysis of 6576 septic patients requiring intensive care admission with time zero defined as first documented organ dysfunction; they found no significant increase in mortality unless delay in antimicrobials exceeded six hours [Rüddel 2022].

6.7.2 There are multiple reasons for this disparity, well discussed in Weinberger [2020] and Asner [2021]. Most of the time-to-antimicrobial studies provide a linear, amalgamated estimate with ranges varying from 6 hours to 24-48 hours, or even longer.

This misleadingly suggests that each hour interval has an equivalent effect on mortality. Ideally, independent estimates should be generated for each hourly interval.

As described below, selecting an effective antimicrobial from the outset and achieving adequate and timely source control may have a greater impact on outcomes.

6.7.3 Infection is not confirmed in as many as 40% of patients admitted with a preliminary diagnosis of an infectious process [Klein Klouwenberg 2015, Heffner 2010, Contou 2016, Shappell 2021]. 'Time Zero' is also contentious [Weinberger 2020] – different studies variably adopt time of arrival in hospital, triage, discovery of hypotension or diagnosis of sepsis. As one example, a large retrospective study reported an hour-by-hour delay to antimicrobial administration was associated with a higher risk-adjusted in-hospital mortality [Seymour 2017b]; however there was a 6 hour window for triggering the treatment protocol after arrival at the Emergency Department and up to 12 hours' delay in commencing treatment despite a mandated 3-hour sepsis treatment bundle. Many studies have failed to address the impact of delay in terms of illness severity, acuity or trajectory, and to analyse these subsets independently. An important unmeasured confounder is presentation with vague symptoms of sepsis; this is particularly seen in elderly, co-morbid populations whose underlying risk of death is much greater and in whom treatment can be markedly delayed as a consequence [Filbin 2018a, Filbin 2018b]. In this study, vague symptoms were independently associated with mortality whereas time-to-antimicrobials was not. Conversely, critically ill patients tend to be identified and treated earlier but their underlying risk of death is often higher. Careful adjustment for illness severity and other risk factors is therefore necessary but often incomplete or poorly described.

6.7.4 Data on the preceding length of signs/symptoms and the trajectory of deterioration are rarely captured. Whiles et al [2017] did identify 984 of 3929 Emergency Department patients who later progressed to septic shock after commencement of antimicrobials. They reported an 8% increased risk of progression to septic shock for every hour's delay in treatment and a 5% increase in mortality risk. However, as described above, description of a linear progression is misleading; the proportion of patients progressing to shock was fixed at approximately 20% for the first five hours of delay, at approximately 35% for delay between 6-18 hours, and 55% in the 2-3% of patients not treated until beyond 18 hours.

6.7.5 Illness severity at presentation likely plays an important role: the need for therapeutic urgency will be more pressing in the critically ill patient than in the patient with an uncomplicated infection and the impact of delay may be greater. The above-mentioned study from Seymour et al [2017b] found risk of death was significantly higher with hour-by-hour delay but only in those septic patients requiring vasopressors. Other studies have found no hour-by-hour relationship, even in patients with septic shock (e.g. Seok 2020b, Abe 2019], though most of the patients in these studies were commenced on antimicrobials within 6 hours of diagnosis. Meta-analyses and primary care studies of

low-risk populations with respiratory tract [Stuart 2021] or urinary tract infection [Shallcross 2020] indicated that, compared to immediate antimicrobial prescription, delayed or withholding antimicrobials was safe and effective for most patients, even in the elderly. Prospective trials randomising patients to early or delayed treatment have not been performed in sicker populations. Intriguingly, a single before-after study conducted in a university hospital surgical ICU did suggest that waiting for objective confirmation of infection before initiating antimicrobial treatment did not worsen mortality and could even be associated with better outcomes [Hranjec 2012]. A prospective study of 3035 septic patients in the ED has shown increased mortality with delay in antimicrobials at 3 hours for patients in septic shock, but not for those with sepsis without shock [Im 2022]. The Surviving Sepsis Campaign's most recent guidance now suggests a three-hour window for administering antimicrobials for possible sepsis without shock [Evans 2021].

6.7.6 Distillation of the published literature in a recent systematic review and meta-analysis highlighted the wide variability in time-to-antimicrobials metrics, subsequent outcomes, and the lack of a robust time threshold [Asner 2021]. A recent narrative review conducted by infectious disease and intensive care specialists assessing the impact of time to antimicrobial therapy on clinical outcomes in emergency department patients with suspected bacterial infections concluded that withholding antimicrobials until diagnostic results are available (e.g. by 4-8 h) appears acceptable in most cases unless the patient is critically ill, e.g. with suspected septic shock or bacterial meningitis [Nauclér 2021]. However, even in bacterial meningitis, an adverse effect on mortality was detectable only if time to antimicrobials exceeded 6 hours [Bodilsen 2016]. Such data have prompted recent policy statements from US infectious diseases and emergency medicine societies to adopt a more nuanced approach to antimicrobial therapy with immediate treatment reserved for the patient in shock, for those with an acute life-threatening infection such as meningitis or necrotising soft tissue infection, or those showing a rapidly deteriorating trajectory [IDSA Task Force 2018, Rhee 2021, Yealy 2021].

6.7.7 The same principle of allowing sufficient time to undertake focused investigations might apply to patients with febrile neutropenia. NICE 2021 guidance [NICE CG151 2012] on neutropenic sepsis recommends immediate empiric intravenous piptazobactam. However, this has become the norm for all patients with febrile neutropenia, not all of whom have sepsis and many of whom can be managed on an out-patient basis avoiding intravenous broad-spectrum antimicrobials [Pettit 2021]. A meta-analysis of three studies in febrile neutropenia which reported mortality (two paediatric, one adult) suggested a possible trend for better outcomes associated with time to antimicrobials of <60 mins compared with >60 mins (OR 0.78, 95%CI 0.16–3.69) [Koenig 2019], though triage bias was a likely confounding factor. This might work in either direction: if more severely ill patients get antibiotics earlier, this might explain one study in which outcomes were worse in neutropenic children who received antimicrobials within 60 mins [De laMaza 2015]. In a prospective study of 249 cancer patients with febrile neutropenia, inappropriate initial antimicrobials were associated with higher mortality (OR 3.5, CI 1.49-

8.28) but time to treatment was not [Peyrony 2020]. This suggests that in less severely ill patients, therapeutic specificity may be more important than urgency. There are three recent paediatric studies which suggest that permitting a longer time for patient-focused decision making is feasible, though caution is required in interpretation as event rates were low. The first study compared specialist with non-specialist paediatric centres in the USA, and reported a greater likelihood of delay in receiving antimicrobials (>60 mins) in non-specialist centres, but no association with subsequent deterioration [Wadhwa 2022]. The second single-centre ED study of 179 episodes of febrile neutropenia in 86 children also found no impact of delay in antimicrobials beyond 60 mins [Dessie 2022]. The third showed that improvements in processes of care reduced time to initial antimicrobials without associated improvements in outcomes [Seltzer 2021].

6.7.8 Assessment of severity of sepsis in this group of patients is conventionally undertaken using either the Multinational Association for Supportive Care in Cancer (MASCC) score or the Clinical Index of Stable Febrile Neutropenia (CISNE) score, the later providing better specificity [Coyne 2017] [Zheng 2020]. A preliminary report suggests that NEWS may also perform well in this group [Nicolino 2017]. Large scale studies are required in these susceptible patients which link severity assessment with point of care diagnostics, and which take into account lead time bias to determine treatment urgency for individual patients.

6.8 Appropriate vs inappropriate empiric antimicrobial therapy and relationship to outcomes

6.8.1 Two recent systematic reviews have focussed on studies examining appropriateness of antimicrobial therapy [Zasowski 2020] [Bassetti 2020]. The first [Zasowski 2020] studied the impact of delay on outcomes in 35 identified studies of which none was randomised and only three were prospective cohort studies. All studies were criticized for the lack of a robust design to assess causality and suboptimal description and/or adjustment of confounding factors. Eighteen studies included only patients with bacteraemia while eight specifically focussed on pneumonia. Illness severity varied considerably across studies. Of the 19 studies comparing mortality in patients receiving appropriate therapy with and without delay, the no-delay group had a significantly lower mortality (OR, 0.57; 95% CI: 0.45-0.72). Non-significant trends were however reported for subsets of patients in septic shock, with pneumonia and infected with Gram positive pathogens. Seven studies reported mortality as a function of time to administering appropriate antimicrobials; mean time to appropriate therapy ranged from 3.8-166 hours in non-survivors and 1.8-67.2 hours in survivors. Overall, no significant difference was noted in time to appropriate therapy between survivors and non-survivors (mean difference, 2.7 hours; 95% CI: -0.45 to 5.86) although between-study heterogeneity was high. A further eight studies reported mortality by multiple periods of time to appropriate therapy, of which half found a significant effect. However, these were mainly reported in terms of days of delay rather than hours.

6.8.2 The second systematic review [Bassetti 2020] compared appropriate versus inappropriate initial antimicrobial therapy on outcomes of patients with severe bacterial infections. They identified 114 studies, 19 conducted specifically in ICU patients. Overall, in 94 studies in which raw data were available, mortality rates were significantly lower in patients receiving appropriate antimicrobials (OR 0.44; 95% CI:0.38-0.50). Treatment failures, reported in six studies, were significantly reduced in the appropriate antimicrobial group (OR 0.33; 95% CI:0.16-0.66). Hospital length of stay was non-significantly shorter, but ICU stay was unaffected.

6.8.3 A retrospective cohort analysis of 21,608 patients with bloodstream infections treated in 131 hospitals in the USA reported that one in five patients received discordant empirical antimicrobial therapy. This was associated with increased risk of mortality (adjusted odds ratio 1.46 [95% CI 1.28–1.66]) which was independent of sepsis but strongly related to the presence of antimicrobial resistant species (OR 9.09) [Kadri 2020].

6.9 Source control

6.9.1 Source control (defined as undertaking physical intervention to treat the origin of sepsis) is of relevance only to bacterial and (less commonly) fungal infection. It can range from straightforward removal of infected intravascular catheters, through radiological drainage procedures, to major intra-abdominal surgery and extensive soft tissue debridement. Patients with sepsis who require source control interventions are unlikely to be treated adequately with only antimicrobial therapy and there is therefore a specific need to consider source control as soon as a clinical diagnosis has been made. The evidence base for optimal timing of source control is limited and analysis problematic, with the few published studies providing only limited data, derived mainly from retrospective analysis of the relationship between timing of source control and mortality in heterogenous patient groups. Additionally, separating the effects of source control from antimicrobial therapy on outcome can be challenging because, for those patients with sepsis for whom source control is also required, it is inevitably provided as part of a package of care which also involves antimicrobial therapy. Finally, surgical interventions undertaken to provide source control are frequently associated with acute pathophysiological changes resulting from the source control intervention itself, such as those related to bleeding, anaesthesia, pain and analgesia.

6.9.2 A target of no more than 6-12 hours after diagnosis has been recommended for implementation of source control [Rhodes 2017]. However, evidence underpinning this guideline is reliant solely on observational data and is also conflicting, even from the same group [Buck 2013][Vester-Andersen 2016]. Some studies suggest better outcomes with intervention before 6 hours [Buck 2013] [Azuhata 2014],[Bloos 2014], and the last of these studies noted that inadequate surgical source control was associated with an increase in mortality at 28 day. However, other studies have failed to identify an association between delay in source control of greater than 6 hours and risk of death, even if delay exceeded 12 hours [Vester-Andersen 2016] [Kim 2019]. In the Vester-

Andersen study of 2,803 patients undergoing emergency abdominal surgery, the crude odds ratio for 90-day mortality was significantly increased when surgical delay up to 48 hours was assessed as a continuous variable; however, significance was lost after adjustment for known adverse prognostic variables and this lack of effect was maintained in sensitivity analyses. For necrotising soft tissue infections, in a retrospective study of 106 patients Boyer et al [Boyer 2009] reported that a delay >14 hours from time of diagnosis to surgical treatment in shocked patients was independently associated with mortality. These differences may be partly explained by the heterogeneity of diagnoses for which source control is required and the nature of the source control intervention. Some studies of source control have combined patients with septic shock with less unstable patients and have also combined patients suffering from gastrointestinal perforation from various sources (for example, upper vs lower gastrointestinal tract), as well as other pathologies, including intestinal obstruction and ischaemia. It is likely that the rate of deterioration and the impact of source control on outcome (and therefore the urgency of source control required to treat sepsis) will vary considerably in these circumstances.

6.9.3 Boyd-Carson et al (2020) noted in 3,809 patients with upper gastrointestinal perforation that even a delay between 1 hour ("immediate") and 3 hours in provision of source control was associated with a statistically significant 18% increase in 90 day mortality and that there was an overall 6% increase in mortality with each hour that passed following admission. Azuhata et al (2014) found that no patient survived 60 days when source control took longer than 6 hours in 154 patients with gastrointestinal perforation and septic shock, whereas 98% survived when surgery was undertaken within 2 hours. Rüddel et al (2022) studied 1,595 patients in 40 German ICUs and found that time to surgical source control was significantly associated with increased odds of death only among patients with septic shock. A recent study [Reitz 2022] of 4,962 patients undergoing source control procedures for community-acquired sepsis has shown a higher risk-adjusted in-hospital and 90-day mortality amongst patients whose source control procedure started six hours or more after sepsis onset ('time zero'), defined as identification in the electronic health record of the first administration of antibiotics and acquisition of a culture specimen. There was a further reduction in risk-adjusted mortality of 0.5% if source control started at three hours, and progressive increases for intervals exceeding six hours. In a post-hoc analysis of 1,077 adult patients with peritonitis in 306 ICUs from 42 countries [De Pascale 2022], the investigators found a lower odds of mortality amongst those patients who underwent source control within 2-6 hours (OR 0.5 [0.34-0.73] compared with a shorter or longer interval.

6.9.4 Current surgical guidance from the Royal College of Surgeons of England [2018] recommends that in surgical patients with septic shock, source control procedures should be initiated within a maximum of 3 hours of diagnosis. In surgical patients with sepsis without shock, source control procedures should be initiated within a maximum of 6 hours. The Enhanced Recovery After Surgery (ERAS) Society guidelines for patients undergoing emergency laparotomy include the same recommendations for timeliness of source control [Peden 2021].

6.9.5 In general, source control should be conducted, when possible, in a setting of adequate 'medical' stabilisation of the patient, including correction of respiratory, haemodynamic and coagulation disturbances, recognizing that prolonged efforts may not necessarily achieve stabilisation in the most unstable patients [Solomkin 2010]. In the sickest patients, simultaneous measures to achieve source control and to stabilize the patient will frequently be required and it may be appropriate to undertake source control in some cases without waiting for confirmatory radiology [Royal College of Surgeons of England 2018].

6.9.6 The method of source control should be chosen on the basis of benefit:risk ratio for each possible intervention, expertise available, risks of transfer for the procedure, potential delays, and likelihood of success.

6.10 Preventability and attributability of deaths in sepsis

6.10.1 The aim of antimicrobials and source control procedures is to reduce mortality and morbidity, hospital stay, costs and long-term sequelae. However, in high and middle-income countries most patients dying of sepsis are elderly [Singer 2019], and their outcomes are strongly influenced by frailty and co-morbidity. A retrospective review of 568 hospital deaths [Rhee 2019] identified sepsis in 300 (52.8%). Of these, significant co-morbidity was present in the large majority and only 3.7% were adjudged definitely or moderately preventable. A retrospective case note review of patients treated for suspected sepsis in a Sheffield emergency department showed a median age of 74 years, 57.5% were not living independently, 58.5% could not walk unaided, 22% had a pre-existing DNA-CPR order, and 90% had important life limiting co-morbidities [Sabir 2021]. Comparable data have been reported from point prevalence studies conducted in all acute Welsh hospitals [Kopczynska 2018]. Of 166 sepsis deaths, 12 (7.2%) were considered directly related to sepsis, 28 (16.9%) possibly related and 96 (57.8%) unrelated to sepsis. Of the 40 likely attributable deaths, more than three-quarters had high Clinical Frailty Scores, 28 (70%) had an existing DNA-CPR order and 17 (42.5%) had limitations of care orders. The implications of these observations are that in many cases the scope for modifiable mortality is limited, the burdens of active treatment may be considerable, and patient preferences for treatment intensity need to be determined through informed discussions, ideally before they become acutely ill.

6.10.2 Given these perspectives, the salient issue is not *'how can we make clinicians prescribe broad-spectrum antimicrobials within one hour to all patients with suspected sepsis'* but '*what is the best method for helping clinicians identify those patients with sepsis most likely to benefit from timely appropriate antimicrobials'*. We consider next two approaches: laboratory methods for diagnosing infection, and clinical methods for assessing severity of illness.

6.11 Developments in the early diagnosis of infection – laboratory methods

6.11.1 Without a fast and reliable means of bedside diagnosis of sepsis, treatment decisions for infection and associated organ dysfunction remain empirical and may result in overuse of antimicrobials, delayed treatment and failure to recognise non-infectious causes [Tidswell 2021]. Sepsis can be caused by bacterial, viral, fungal or parasitic infections; non-infectious causes can produce similar symptoms and laboratory/ radiological findings. Timely antimicrobial treatment reduces morbidity and mortality in bacterial infection but avoiding unnecessary use is also important to minimise adverse effects: Tamma et al found that 20% of patients suffered one or more antibiotic-associated adverse events, and 20% of non-clinically indicated antibiotic regimens were associated with adverse events [Tamma 2017]. Failure to diagnose and treat a non-bacterial infection or a non-infectious cause can be equally damaging.

6.11.2 Diagnosis of sepsis made in the ED is frequently not confirmed by subsequent expert review [Sabir 2021]. Of 300 ED patients with suspected bacterial sepsis who received broad spectrum antimicrobials, 104 (35%) were ultimately considered to have a non-infectious (72%) or viral (28%) cause for their illness [Shappell 2021]. Of 2579 patients admitted to two Dutch ICUs with a diagnosis of suspected sepsis, 13% were subsequently adjudicated as having a post-hoc infection likelihood of "none", and 30% as only 'possible' [Klein Klouwenberg 2015]. Clinical signs and symptoms are often non-specific, but stricter definitions of sepsis carry lower sensitivity. Immunosuppressed or elderly patients may not develop fever, leukocytosis or tachycardia, while younger patients may not present with typical features of physiological deterioration until very late [Knight 2014]. Cases of puerperal sepsis, meningococcal sepsis or necrotising fasciitis may have additional pathognomonic clinical features that alert clinicians to a diagnosis of bacterial infection. However, unless such conditions are suspected, over-reliance on traditional physiological markers can be misleading in the early stages. An emphasis on sepsis could also distract from alternative diagnoses resulting in delays in appropriate treatment for other conditions.

6.12 Microbiological diagnosis

6.12.1 As source identification is a priority, samples of relevant body fluids should be taken as early as possible. Blood cultures are the current gold standard for diagnosis of bloodstream infection (BSI). Poor practices around the blood culture pathway (such as avoidable delays measured in days, not hours) have continued despite established clinical standards, resulting in substandard patient care and misunderstandings about effectiveness. In an optimised pathway most significant positive blood cultures will flag positive within 12 hours of collection. Detection rates depend on the prior (pre-test) clinical probability of infection [Coburn 2012], the volume of blood drawn (two sets, total volume 32-40ml of blood in adults), concurrent antimicrobial therapy, and timely

laboratory processing. Attention to aseptic technique is important to minimise false positive rates [Snyder 2012]. A significant positive blood culture frequently identifies the source of infection, which in an optimised pathway allows timely correction of discordant empirical therapy (20-30% of patients may be on ineffective treatment as judged by laboratory testing) but also permits early de-escalation of antimicrobials, thereby preserving antibiotics for the future [PHE 2019] [NHSEI Nov 2021 *in press*]. As rates of antimicrobial resistance rise, deficiencies in empirical therapy are likely to follow. Early identification of bloodstream pathogens and resistance will probably improve population-level outcomes [Kadri 2021]. NHS England and NHS Improvement will be producing updated guidance on the blood culture pathway to aid preservation of antimicrobials and improve patient outcomes. Newer diagnostic techniques permit faster identification of pathogens from positive blood cultures e.g. matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry [Osthoff 2017] [Yuan 2020].

6.12.2 Concurrent primary bacterial infection in patients with COVID-19 has been reported at 5.5% [Baskaran 2021], with a 1% blood culture positivity rate [Thelen 2021]. Antibacterial treatment is not recommended in the absence of positive cultures and clinical suspicion of bacterial infection [Russell 2021] [NICE 2020] [Scottish Antimicrobial Prescribing Group 2020]. Secondary infection with bacteria or fungi are an important cause of sepsis and mortality in these patients [Guo 2021], the prevention and detection of which require continuing vigilance.

6.13 Rapid molecular tests for identification of pathogen and resistance genes

6.13.1 The emphasis on timely antimicrobial treatment has stimulated the development of many point-of-care or laboratory molecular diagnostic tools for pathogen detection and antimicrobial resistance with a rapid turnaround time. Some devices are already commercially available. Rapid pathogen and resistance gene identification can be performed directly on blood within 3-5 hours without the need for culture yet demonstrate good concordance with traditional culture [Nguyen 2019]. Other fluid samples e.g. sputum, urine, cerebrospinal fluid, stool and throat/nose swabs can also be examined with results obtained within 1-2 hours [Timbrook 2021] [Yoo 2021].

6.13.2 Molecular diagnostics, such as polymerase chain reaction (PCR) identification of pathogen DNA or RNA and resistance genes, nucleic acid hybridisation and electrochemical detection, is an exciting area of development. [Vasala 2020]. Patients with bacterial infection are often not bacteraemic. The yield from molecular tests on blood samples is up to three-fold higher and is associated with worse outcomes in culture-negative patients [O'Dwyer 2017]. The predictive value (rule in and/or rule out) of a blood test in detecting a (blood culture negative) compartmentalised infection also needs to be determined [Kalligeros 2020].

6.13.3 However, there are important outstanding questions surrounding these rapid tests. There is a risk of contamination during sampling, identification of commensal or other organisms that may be unrelated to the presence or cause of infection [Blauwkamp 2019], or a positive result being obtained despite the microorganisms being no longer viable. There are over 1600 antibiotic resistance genes [McArthur 2013] and current technologies allow only a handful of the commonest resistance genes to be detected. The accuracy of any new rapid Antimicrobial Susceptibility Test (AST) must be validated against standard recommended growth-based methods.

6.13.4 This learning curve has meant that rapid pathogen detection tests have not yet been generally accompanied by changes in antimicrobial prescriptions (for example, broad to narrow-spectrum), particularly when reported out of hours [MacGowan 2020, Sweeney 2019]. However, once confidence is gained they will likely play an important role in antimicrobial stewardship by determining the need for specific antimicrobials, in reducing time to appropriate treatment, and in earlier narrowing of the spectrum of treatment [Kalligeros 2020]. Tests to exclude the presence of pathogens are less common though potentially useful [Yui 2020].

6.13.5 The COVID-19 pandemic has demonstrated that molecular (PCR)-based testing for viral infections is both feasible and useful in the ED. Tests that identify a viral pathogen can also act as a helpful "rule out" for a primary bacterial infection in settings where a virus such as Influenza A or SARS-CoV2 might reasonably account for a patient's presentation.

6.13.6 Implementing new tests for sepsis could result in an increase in antimicrobial prescribing. However, if this is a consequence of more appropriate or targeted prescribing, then such an outcome should not be dismissed [Honeyford 2020]. More research is needed to identify the impact of diagnostic tests on clinician-prescribing decisions and patient outcomes, as recommended by the National Institute for Health and Care Excellence [NICE DG20 2020] and currently funded by the National Institute for Health Research [NIHR award 17/136/02].

6.14 Host response biomarkers

6.14.1 Biomarkers related to the host response to an inflammatory insult can be potentially used to predict illness severity, prognosticate, distinguish between infectious and non-infectious causes, distinguish between viral, fungal and bacterial aetiologies, or offer a theranostic capability indicating when a specific treatment is indicated, dose-titrated to an optimal effect and/or discontinued [Opal 2020]. Many rapid diagnostics are being developed that utilise a range of methodologies including lateral flow /ELISA/multiplex techniques for immunoassays, flow cytometry, and PCR.

6.14.2 Standard laboratory tests such as C-reactive protein (CRP) and leukocyte count and, more recently, procalcitonin (PCT) have been traditionally used to guide decisions to

start or stop antimicrobial treatment. Although PCT levels increase faster than CRP, both tests lack specificity, increasing in response to non-bacterial or non-infectious causes of systemic inflammation. Variation in guideline recommendations reflect the ongoing uncertainty in their clinical utility [Tujula 2020]. A study of ED patients has suggested that CRP is a reliable biomarker for serious bacterial infection in the pre-COVID-19 era, but performs poorly where COVID-19 is in the differential diagnosis [Li 2021] [Mason 2021]. Procalcitonin may help to quantify severity of illness in febrile neutropenia [Reyes Mondragon 2021]. Trials are currently in progress to assess these biomarkers as tools for de-escalation.

6.14.3 Many novel biomarkers, alone or in combination, have been proposed to identify patients with sepsis [Kim 2020]. Findings are however often inconsistent, with few biomarker tests to date consistently demonstrating high sensitivity and specificity. This may reflect potential confounders such as differences between patient populations (e.g. adult vs paediatric, immunocompetent vs immunocompromised), and timing of the test in relation to the patient's illness. Such tools, once validated, will likely prove very useful in the future to guide clinical decision making, particularly if cheap, reliable and rapid to implement.

6.15 Clinical assessment of severity of illness and prediction of sepsis

6.15.1 Assessing an acutely ill patient requires the clinician to determine severity of illness, treatment priorities and causation. Scoring systems are an established method for supporting this complex set of processes. Attempts have been made to develop severity scoring systems specifically for sepsis as distinct from scoring systems for-all cause deterioration by including laboratory results or demographic data. However, in clinical practice, this approach may have unintended consequences.

6.15.2 First, diagnostic uncertainty is common to all sick patients [Inada-Kim 2018] regardless of cause, and treatment must be equally prioritised and managed as aggressively as for those with suspected sepsis. Second, the scoring system must be readily calculable in settings such as in the community, primary care or in an ambulance without access to pathology or radiology results. Third, the score must be easily communicable and understood, as patients traverse multiple healthcare settings during the course of a single episode of illness. Given the rationale for a generic system of severity assessment that does not require access to laboratory tests, NHS England published its Sepsis Implementation Guidance in 2017 [NHS England 2017], recommending a combined 'all-cause deterioration' pathway based on the National Early Warning Score (NEWS). This provides guidance as to how quickly senior clinical review is required in response to patients deteriorating with moderate or high NEWS scores. A recent systematic review of tools and triggers for early identification of sepsis recommends use

of either the quick Sequential Organ Failure Score (qSOFA) supplemented by lactate measurement, or NEWS [ACSQHC 2021], now updated as NEWS2. We consider these options below.

6.16 Single parameter systems

6.16.1 Sepsis scoring systems that rely on single extreme physiological parameters as 'sepsis triggers' (e.g. heart rate >130 bpm, systolic BP ≤90 mm Hg) have the appeal of simplicity. However, it is unusual for a single extreme physiological abnormality to occur in isolation as a precursor of significant deterioration; rather, a combination of several (sometimes lower level) abnormalities are more common and more predictive [Smith 2016] [Smith 2008]. When tested on the same population methods such as 'Red Flag Sepsis', the Sequential Organ Failure Score (SOFA), the systemic inflammatory response syndrome (SIRS), and NICE's red and amber bands on the NEWS2 score, all had limited predictive utility and poor concordance [Unwin 2021]. Furthermore, the use of single parameter systems can increase clinical workload by 40% yet fail to identify up to 45% of patients at high risk of death [Kopczynska 2018]. Abnormal single parameters should be used to alert clinicians to the need for more detailed observation and investigation, but not as mandates for specific treatment.

6.16.2 Hyperlactataemia is a biomarker of physiological stress, with levels increasing according to the magnitude of the insult. A systematic review recommended that lactate measurement be included in severity scoring systems with a cut-point of 2 mmol/L [ACSQHC 2021]. However, septic patients with normal lactate levels requiring ICU admission have mortality rates in excess of 20% [Casserly 2015]. Even lactate levels at the upper range of normal are associated with worse outcomes compared to values at the low-normal range. A raised lactate in sepsis is not necessarily associated with tissue hypoxia. In established sepsis, it is more often related to impaired tissue oxygen utilisation than impaired delivery [Gattinoni 2019]. Other factors may also contribute to hyperlactataemia including catecholamine administration, increased muscle sodium pump activity and liver dysfunction. Outcomes are generally better if lactate levels normalise promptly ('lactate clearance') with initial resuscitation. Nonetheless, the recent ANDROMEDA-SHOCK study showed as good, if not better, outcomes using a capillary refill-guided resuscitation strategy compared to a lactate clearance-targeted approach [Hernandez 2019]. Lactate measurement should therefore be regarded as a useful 'single parameter' adjunct to vital signs measurement.

6.17 Quick SOFA (qSOFA)

6.17.1 qSOFA is a quick, simple, validated and easily repeatable method of assessing acuity of illness severity in patients with infection. It outperforms the systemic inflammatory response (SIRS) score by measuring just three bedside parameters

[Seymour 2016] [Singer 2016] (respiratory rate, systolic blood pressure and level of consciousness) which are also represented in NEWS2. The recent Surviving Sepsis Campaign guidelines [Evans 2021] recommended against using qSOFA as a single screening tool; although the presence of ≥1 qSOFA parameters should alert the clinician to the possibility of sepsis, sensitivity in multiple studies was overall found to be poor.

6.18 National Early Warning Score (NEWS / NEWS2)

6.18.1 In 2017, the Royal College of Physicians published NEWS2 [RCP 2017], an updated version of the original NEWS score (Appendix Fig 1). This quickly gained national support as 64% of acute trusts in England had already voluntarily implemented NEWS. This reflects a strong desire to create a standardised language to describe severity of illness across the NHS to improve the early recognition, escalation, communication and response to deteriorating patients from all causes and in all settings. NEWS2 goes further than qSOFA by supplementing the three key parameters of respiratory rate, systolic blood pressure and level of consciousness with additional measures of acute illness severity - oxygen saturation, pulse rate and temperature, as well as considering the effects of oxygen therapy. These extra variables enhance the ability of NEWS2 to identify patients at risk compared with qSOFA [Redfern 2018].

6.18.2 To enhance communication between GPs, ambulance and secondary care services by using the same "common language" of concern throughout the patient pathway, NHS England mandated NEWS2 national implementation across all hospital and ambulance trusts in 2018 [NHS England]. Currently, 99.5% of acute trusts and 100% of ambulance trusts use NEWS2. It is also being increasingly adopted in care homes to monitor residents and when to seek help in the event of deterioration. The Royal College of General Practitioners Guidance [RCGP 2020] recommends the use of physiological measurements when assessing patients at risk of deterioration in primary care as an adjunct to (not as a replacement for) clinical judgement, and recommends further research on the use of NEWS2 in this setting.

6.18.3 While the utility of NEWS2 as a clinical decision-support tool not requiring clinical judgement remains to be validated in general practice, where pre-test probabilities for severe illness are lower than in the ED [Burns 2018], studies in patients referred emergently to hospital showed a clear relationship between increasing scores and increasing mortality risk [Inada-Kim 2020]. Clinical staff working in different contexts view NEWS as a useful adjunct to clinical decision making and communication [Brangan 2018]. NEWS performs well at detecting and monitoring sick patients from all causes [Smith 2013] including those with infection [Redfern 2018] [Liu 2020]. Even a single NEWS aggregate score at either pre-hospital or hospital admission predicts those with sepsis or all-cause deterioration who are likely to die or require critical care [Corfield 2014] [Melhammar 2019]. Caution is required when applying any of the Early Warning Scores to specific (and usually single-organ) disease states [Alhmoud 2021]; recalibration may be

required for Covid-19 and longer-term (30-day) mortality [Richardson 2021] [Baker 2021] [Scott 2022]. The predictive utility of NEWS2 may be enhanced by combination with biomarkers such as mid-regional proadrenomedullin (MR-proADM) [Saeed 2019].

6.18.4 A critical question is how best to link specific values of NEWS2 to specific actions to be completed within specific timeframes. The NICE guideline on sepsis recognition, diagnosis and early management [NICE Guideline 51] uses NEWS2 to categorise as high-risk those adult patients who score 3 on any vital sign (red columns on the NEWS2 chart, Appendix Fig 1), and moderate-to-high risk those patients scoring 2 or more (orange-band). On this basis high risk would be triggered by a single change in either mental status, use of supplementary oxygen to maintain saturations over 92%, systolic blood pressure ≤90 mmHg, or not passing urine for 18 hours [Freitag 2017]. The underpinning evidence for these cut-points is not strong. In a systematic review of studies of patients with infection receiving care outside the intensive care unit, a NEWS score ≥5 predicted death with a pooled sensitivity, specificity, and AUC of 0.80 (95%CI 0.71, 0.86), 0.50 (95%CI 0.36, 0.63), and 0.73 (95%CI 0.69, 0.76), respectively [Zhang 2021]. A study of 91,871 undifferentiated attendances to two English emergency departments reported a high predictive accuracy (AUC >0.9) for NEWS2 mortality at 2, 7 and 30 days following presentation, with the highest likelihood ratio (9) for NEWS ≥5 [Masson 2021]. The authors concluded that a NEWS2 score ≥4 was the best inflection point for escalation of therapy. However, referrals would increase by approximately 40% compared with a trigger of ≥5. Pragmatically, a NEWS ≥5 identifies adult hospital patients who are severely ill with likely organ dysfunction, and it is these patients who require urgent assessment by a senior clinical decision-maker who can then determine appropriate treatment.

6.19 Electronic sepsis alert tools and artificial intelligence approaches

6.19.1 Advances in electronic patient records and patient information systems have led to the development of alerting tools, albeit with mixed results. A recent meta-analysis of digital alerting suggested lengths of stay might be reduced although no improvement in time to antimicrobials or mortality was demonstrated [Joshi 2019]. A meta-analysis of wearable monitoring devices in hospitalised patients found no evidence of benefit, recommending minimisation of false alarms and a focus on the effector response [Areia 2021]. Alert tools can result in ordering of unnecessary investigations, overloading of clinicians and alarm fatigue. Research and development are ongoing, but independent, external validation is crucial to both confirm benefit and avoid the potential for unintended harm [Wong 2021].

6.19.2 Similar caveats apply to the use of artificial intelligence applied to clinical data sets. Multiple groups have developed predictive algorithms using various permutations of structured data (e.g. demographics, vital signs, lab results) and topic-aggregated free text that claim to identify the onset of sepsis or shock well in advance of clinical recognition [Goh 2021] [Komorowski 2018]. To date these have all used retrospective

interrogation of electronic healthcare record systems. None, to our knowledge, has been used in real time nor prospectively validated, let alone shown to impact on patient outcomes.

6.20 Paediatric Early Warning Score (PEWS)

6.20.1 In England, there has been no single, nationally validated system for recognising and responding to acutely unwell children, similar to the NEWS score used in patients over 16 years of age. This significant patient safety risk has been addressed by a Delivery Board with representation from NHS England and NHS Improvement, the Royal College of Paediatrics and Child Health and the Royal College of Nursing (RCN). An English national PEWS called 'system-wide paediatric observations tracking' (SPOT) has been developed and is undergoing piloting to recognise deterioration across primary and community care, through ambulance services, emergency departments and into hospitals [RCPCH] [Roland 2021]. Using a common language could improve outcomes in children, as has been achieved in adults with the use of NEWS [Pullyblank 2020]. This will help to address the high false positive rate and consequent over-treatment of children associated with the use of the NICE Guidance 51 sepsis thresholds [Nijman 2020] [Gomes 2021].

6.20.2 A recent retrospective analysis of over 11,000 febrile children attending a tertiary paediatric ED demonstrated excellent and relatively comparable performance across seven different PEWS scores currently used in the UK, including the proposed National PEWS, in predicting critical care admission and sepsis-related mortality [Romaine 2021]. These findings support the use of the National PEWS in the ED to improve standardisation and reduce variability in escalation of care for sepsis. This will need to be validated in prehospital and inpatient settings, and for non-sepsis presentations. Exploration of its performance in inpatient settings, such as the ongoing NIHR-funded DETECT study of electronic PEWS in a single tertiary centre [Sefton 2019], will allow further assessment of benefit in early sepsis identification.

7. Synthesis and recommendations

7.1 Quality improvement initiatives such as the Surviving Sepsis Campaign have raised awareness of sepsis as a universal global health problem and provided a platform for systematically evaluating new research. In the early stages of the Campaign, improving patient outcomes demanded an approach which simplified and standardised best practice, reducing potentially undesirable clinical variation. Now, some twenty years later, with new research findings available, we propose a modest 'course correction' which makes space for clinical judgement in the urgency and timing of administration of antimicrobials, within an accountable clinical decision framework based on severity of illness as proposed by the National Confidential Enquiry into Patient Outcomes and Death [NCEPOD 2015] and NHS England [NHS England 2017]. This approach will allow clinicians more time to perform investigations, make patient-focused decisions, and take into account antimicrobial stewardship while prioritising the most urgent patients.

7.2 The Clinical Decision Support Frameworks for Sepsis

7.2.1 The clinical decision support frameworks (adults Fig 1, children Fig 2, above) are structured to follow usual care processes. Two sections on initial assessment and a section on generic actions are followed by assessment and actions related to the clinical likelihood of infection. These are dynamic instruments designed to permit upgrading or downgrading of priorities and treatments according to the patient's condition. They offer a preliminary logic model which runs thus:

A. Initial assessments and generic actions:

1. Is this patient sick? (judged by NEWS/PEWS scores)
2. Clinical assessment:
    i. What other severity of illness indicators do I need to consider in addition to NEWS?
    ii. Does the patient have septic shock?
    iii. Is the patient likely to require an emergency procedure to control a source of sepsis?
    iv. Are there any non-acute factors that may affect either urgency or goals and limits of treatment?

3. What immediate actions are needed to assure patient safety?
    i. Monitoring & escalation plan
    ii. Generic actions: Initial stabilisation & treatment

B. Likelihood of infection and specific actions

4. Is the underlying cause likely to be infection? What type of pathogen is likely responsible? Infection + evidence of organ dysfunction (generally suggested by a high NEWS score) = sepsis. What are the goals of treatment and timelines for sepsis?

7.2.2 Initial assessments and generic actions

7.2.2.1 The working group members were unanimous in basing urgency of treatment on an assessment of illness severity using vital signs summarised where possible by the NEWS2 or PEWS scores in secondary care. This assessment of severity and urgency must then be 'interpreted' in the light of the patient's history, clinical examination, evidence of deterioration, laboratory tests, assessment of chronic health, comorbidities and frailty, and personal preferences (patient and next-of-kin or legal representative). The Royal College of General Practitioners did not consider the science sufficiently mature to be able to recommend the adoption of NEWS2 in primary care until further research evidence was available.

7.2.2.2 For adult patients (Fig 1) the NEWS severity bands are: 0; 1-4; 5-6; and ≥7. The working group took into account the opportunity costs associated with different trigger points: the aim was to promote early identification without imposing undue burdens on busy staff. These four bands 'anchor' subsequent generic actions and sepsis-specific interventions, adapted to the clinical likelihood of infection. Urgency increases with a higher band as this is strongly associated with mortality risk. The initial NEWS2 score must be interpreted in the light of clinical assessment. If the attending clinician has particular concerns about the patient's condition or if additional information from laboratory tests indicates specific conditions of concern such as additional organ dysfunction or neutropenia, the severity status and accompanying actions should be upgraded according to patient need, and at least to the next NEWS band.

7.2.2.3 Generic actions include determining the frequency of monitoring, and the required expertise and seniority of clinical input, and for adults these range from standard observations (as determined by hospital policy) for patients with a NEWS2 score of 0, to observations and review within 30 mins by a clinician competent in acute illness assessment for a NEWS2 score ≥7, escalating this to senior medical review within one hour if the patient's condition is not improving.

7.2.2.4 Initial investigation and stabilising the patient's physiology as required (oxygen, fluids, electrolyte replacement, glucose control, treatments for likely underlying conditions) should be complete within 6 hours (NEWS 1-4), within 3 hours (NEWS 5-6) or within one hour (NEWS ≥7).

7.2.2.5 In children (Fig 2), as with the adult guidance, the support framework links the timing of generic actions to the child's PEWS band. These actions include guidance on the required level of expertise and seniority of clinical input, and the frequency of monitoring,

ranging from standard observations (as determined by hospital policy) for children with a PEWS of zero, to observations and medical review within 1 hour for a PEWS ≥7, accompanied by senior medical review within one hour if the patient is not improving. Because of the propensity in children for rapid decompensation, clinical concern about the child being unwell preceding the measurement of PEWS requires immediate escalation to a senior decision-maker and actions commensurate with the highest risk band while observations are being made. Initial investigation and treatment of the precipitating condition must be undertaken within 4 hours (PEWS 1-4), within 3 hours (PEWS 5-8), or within one hour (NEWS ≥9).

7.2.3 Likelihood of infection and specific actions

7.2.3.1 Concurrent with or following these generic assessments and actions, the attending clinician should assess the likelihood of infection, pragmatically categorised in adults as unlikely, possible, or probable/definite, and in children as unlikely or possible/definite. The degree of certainty attaching to these likelihoods will depend on the history, examination and investigations, and will be revised as additional information is obtained. These categories also contribute to determining the degree of urgency of sepsis-related interventions, which should also be revised according to the patient's condition. The working group recommends that the most severely ill - including those with (i) septic shock, (ii) sepsis associated with a likely need for an emergency surgical procedure to control a source of sepsis (iii) sepsis associated with rapid deterioration, or (iv) a NEWS2 score ≥7 (PEWS ≥9) - should continue to receive broad-spectrum antimicrobials within one hour of presentation. For patients with possible or probable infection in NEWS2 band 5-6 without septic shock or a likely need for source control, antimicrobials (if indicated) should be administered within 3 hours. For those in NEWS2 band 1-4 with probable infection, antimicrobials (if indicated) should be administered within 6 hours, while those with possible infection should have diagnostic tests and a source control plan within 6 hours which may include prescribing antimicrobials. For children in PEWS band 1-4, the time window is within 4 hours. These severity-adjusted treatment intervals will allow clinical staff more time to make patient-focused and informed decisions and limit unnecessary antimicrobial prescribing. The term 'antimicrobial' is used throughout to cover antibacterial, antifungal and antiviral agents.

7.2.3.2 For the avoidance of doubt, it should be emphasised that these time frames are indicative: if actions can be completed earlier than the proposed time limit, then they should be. The time frames are not intended to permit delay in treatment, but to offer the clinician time to make a safe and informed clinical decision. Clinicians are expected to exercise clinical judgement, and health systems to provide sufficient resources to ensure that investigations and actions are undertaken promptly. Acute illness is a dynamic state for which treatment priorities must be adjusted accordingly.

7.2.3.2 **'Time zero'** – the point at which the clock starts – is a problematic issue for a disease process with time-critical treatments but an insidious onset. The most recent

Surviving Sepsis Campaign guidance [Evans 2021] defines time zero as the point of recognition of sepsis. The potential difficulty with this approach is that it may take time to arrive at that clinical recognition. The use of NEWS2/PEWS provides an unambiguous time point for initiating diagnostic and treatment activities, as well as linking treatment urgency to severity of illness.

7.2.3.2 In principle, the guidance contained in the decision-support frameworks is location-independent: that is, it applies equally to care in the community or in hospital. On this basis, time zero is the time at which the NEWS2/PEWS value is recorded (whether the first such reading, or subsequent recordings). This could be the point of first contact in the community, on arrival in the emergency department, or on a hospital ward. However, in practice in the pre-hospital phase, documentation of vital signs may be incomplete, judgements about probability of infection may not be informed by point-of-care investigations, and access to intravenous antimicrobials will be limited. While the attending physician will need to take into account potential lag time in monitoring and diagnosis when prioritising care for an individual patient, the working party recognises that in these circumstances time zero for patients referred to hospital will be the first NEWS2 following arrival at hospital or in the emergency department.

7.3 Using and evaluating the Clinical Decision Support Frameworks

7.3.1 The frameworks provide a concise overview of the working group's recommendations, based on the scientific literature presented in this report combined with a pragmatic multidisciplinary judgement about 'what works' in the frontline of care. They can be used in the clinical environment for decision support, and for teaching and training. The frameworks can be formatted by professional organisations, NHS Trusts and training organisations to match local styles of documentation.

7.3.2 Endorsement of this guidance by the Academy of Medical Royal Colleges and national stakeholders demonstrates strong professional support. The National Institute for Clinical and Health Excellence (NICE) will be asked to review the guidance as part of its updating process for Nice Guideline 51 [NICE 2016].

7.3.3 Adoption of the frameworks at local level needs the active engagement of patient representatives, emergency care providers, general practitioners, physicians, nurses and allied health professionals in the acute care pathway, microbiology, infectious diseases, and infection control. Other stakeholders include elderly care and palliative medicine.

7.3.4 We recommend that the frameworks are evaluated to determine their clinical utility, using quantitative and qualitative research methods suitable for complex interventions [Skivington 2021]. This can take the form of process audits in primary and secondary care, and health services outcomes research between centres, incorporating data on antimicrobial stewardship and resistance and health economics. The applicability of this guidance in resource-constrained environments will also need

examination. Relevant methodologies include cluster-randomised trials [Grant 2013], step-wedge designs [Hemming 2015], and realist evaluation [Pawson 2005] [Rycroft-Malone 2018].

7.3.5 Limitations: This report has not attempted to replicate existing systematic reviews or cover the totality of therapies for the initial management of the septic patient. We have not included neonates in this review as they represent a distinct population requiring a special focus. We have attempted to mitigate potential biases through careful moderated discussion over two years by a multiprofessional working group, and extensive stakeholder consultation.

8. Action Points

We invite the following organisations and individuals to consider:

- Reviewing and revising current sepsis triage guidance:
  - NHS in England and the devolved nations, NHS Improvement and the Department of Health and Social Care
  - The National Institute for Health and Care Excellence
- Introducing and auditing the sepsis clinical decision frameworks:
  - Lead clinicians for sepsis and Deteriorating Patient Committees in Acute Hospital Trusts, Ambulance Trusts and Primary Care Trusts
- Funding health services research evaluating the safety and efficacy of using severity of illness-guided triage of patients with sepsis
  - National Institute for Health Research
- Improving the coding of infection and sepsis
  - NHS Digital.

References

Abe T, Kushimoto S, Tokuda Y, Phillips GS, Rhodes A, Sugiyama T, Komori A, Iriyama H, Ogura H, Fujishima S, Shiraishi A, Saitoh D, Mayumi T, Naito T, Takuma K, Nakada TA, Shiino Y, Tarui T, Hifumi T, Otomo Y, Okamoto K, Umemura Y, Kotani J, Sakamoto Y, Sasaki J, Shiraishi SI, Tsuruta R, Hagiwara A, Yamakawa K, Masuno T, Takeyama N, Yamashita N, Ikeda H, Ueyama M, Gando S; JAAM FORECAST group. Implementation of earlier antimicrobial administration in patients with severe sepsis and septic shock in Japan: a descriptive analysis of a prospective observational study. Crit Care. 2019; 23:360. doi: 10.1186/s13054-019-2644-x. PMID: 31744549; PMCID: PMC6862854.

Abe T, Yamakawa K, JAAM SPICE Study Group. Epidemiology of sepsis and septic shock in intensive care units between sepsis-2 and sepsis-3 populations: sepsis prognostication in intensive care unit and emergency room (SPICE-ICU). J Intensive Care 2020; 8:44.

Acosta CD, Kurinczuk JJ, Lucas DN, Tuffnell DJ, Sellers S, Knight M; United Kingdom Obstetric Surveillance System. Severe maternal sepsis in the UK, 2011-2012: a national case-control study. PLoS Med. 2014 Jul 8;11(7):e1001672. doi: 10.1371/journal.pmed.1001672.

Acosta CD, Harrison DA, Rowan K, Nuala LD, Kurinczuk JJ, Knight M. Maternal morbidity and mortality from severe sepsis: a national cohort study BMJ Open 2016; 6:e012323.

AHSN Network. Suspicion of Sepsis Dashboard. NHS Improvement. https://www.sos-insights.co.uk/

Alam N, Oskam E, Stassen PM, Exter PV, van de Ven PM, Haak HR, Holleman F, Zanten AV, Leeuwen-Nguyen HV, Bon V, Duineveld BAM, Nannan Panday RS, Kramer MHH, Nanayakkara PWB; PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands. Prehospital antimicrobials in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med. 2018; 6:40-50. doi: 10.1016/S2213-2600(17)30469-1. PMID: 29196046.

Ali A, Lamont RF. Recent advances in the diagnosis and management of sepsis in pregnancy. F1000Res. 2019;8:F1000 Faculty Rev-1546. Published 2019 Aug 30. doi:10.12688/f1000research.18736.1

Alhmoud B, Bonnici T, Patel R, Melley D, Williams B, Banerjee A. Performance of universal early warning scores in different patient subgroups and clinical settings: a systematic review. BMJ Open. 2021;11(4):e045849. Published 2021 Apr 8. doi:10.1136/bmjopen-2020-045849.

Angus DC, Bindman AB. Achieving Diagnostic Excellence for Sepsis. *JAMA.* Published online December 23, 2021. doi:10.1001/jama.2021.23916

Antimicrobial Resistance Investigators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet Jan 19th 2022. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext

Anyebuno, M., Lopez-Medina, E. & Sánchez, P. Prolonged maternal postpartum fever and neonatal herpes infection. J Perinatol 34, 716–717 (2014). https://doi.org/10.1038/jp.2014.82

Areia C, Biggs C, Santos M. et al. The impact of wearable continuous vital sign monitoring on deterioration detection and clinical outcomes in hospitalised patients: a systematic review and meta-analysis. Crit Care 2021; 25:351 https://doi.org/10.1186/s13054-021-03766-4.

Aryee A, Rockenschaub P, Gill MJ, Hayward A, Shallcross L. The relationship between clinical outcomes and empirical antimicrobial therapy in patients with community-onset Gram-negative bloodstream infections: a cohort study from a large teaching hospital. Epidemiol Infect. 2020; 148:e225. doi:10.1017/S0950268820002083.

Ascuntar J, Mendoza D, Jaimes F. Antimicrobials administration time in patients with suspected sepsis: is faster better? An analysis by propensity score. J Intensive Care. 2020; 8:28. doi: 10.1186/s40560-020-00448-1. PMID: 32337048; PMCID: PMC7178597.

Asner SA, Desgranges F, Schrijver IT, Calandra T. Impact of the timeliness of antimicrobial therapy on the outcome of patients with sepsis and septic shock. J Infect. 2021; 82:125-134.

Association of Ambulance Chief Executives. National Framework for Healthcare Professional Ambulance Responses. 2019.

Australian Commission on Safety and Quality in Health Care. Review of trigger tools to support the early identification of sepsis in healthcare settings. Sydney; ACSQHC; 2021.

Azuhata T, Kinoshita K, Kawano D, Komatsu T, Sakurai A, Chiba Y, Tanjho K. Time from admission to initiation of surgery for source control is a critical determinant of survival in patients with gastrointestinal perforation with associated septic shock. Crit Care. 2014; 18:R87.

Baghdadi JD, Brook RH, Uslan DZ, et al. Association of a Care Bundle for Early Sepsis Management With Mortality Among Patients With Hospital-Onset or Community-Onset Sepsis. JAMA Intern Med. 2020; 180:707-716. doi:10.1001/jamainternmed.2020.0183.

Baker KF, Hanrath AT, Schim van der Loeff I, Kay LJ, Back J, Duncan CJ. National Early Warning Score 2 (NEWS2) to identify inpatient COVID-19 deterioration: a retrospective analysis. Clin Med (Lond). 2021;21(2):84-89. doi:10.7861/clinmed.2020-0688.

Barker RO, Stocker R, Russell S, Roberts A, Kingston A, Adamson J, Hanratty B. Distribution of the National Early Warning Score (NEWS) in care home residents. Age Ageing. 2019; 49:141-145. doi: 10.1093/ageing/afz130. PMID: 31813952; PMCID: PMC6911654.

Bassetti M, Vena A, Croxatto A, Righi E, Guery B. How to manage Pseudomonas aeruginosa infections. Drugs Context 2018; 7:212527.

Bassetti M, Rello J, Blasi F, Goossens H, Sotgiu G, Tavoschi L, Zasowski EJ, Arber MR, McCool R, Patterson JV, Longshaw CM, Lopes S, Manissero D, Nguyen ST, Tone K, Aliberti S. Systematic review of the impact of appropriate versus inappropriate initial antimicrobial therapy on outcomes of patients with severe bacterial infections. Int J Antimicrob Agents. 2020; 56:106184. doi: 10.1016/j.ijantimicag.2020.106184. PMID: 33045353.

Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M, Cassidy J, Eddleston J, Gunning K, Bellingan G, Patten M, Harrison D; Matching Michigan Collaboration & Writing Committee. 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf. 2013; 22:110-23. doi: 10.1136/bmjqs-2012-001325. PMID: 22996571; PMCID: PMC3585494.

Blauwkamp TA, Thair S, Rosen MJ, Blair L, Lindner MS, Vilfan ID, Kawli T, Christians FC, Venkatasubrahmanyam S, Wall GD, Cheung A, Rogers ZN, Meshulam-Simon G, Huijse L, Balakrishnan S, Quinn JV, Hollemon D, Hong DK, Vaughn ML, Kertesz M, Bercovici S, Wilber JC, Yang S. Analytical and clinical validation of a microbial cell-free DNA sequencing test for infectious disease. Nat Microbiol. 2019; 4:663-674. doi: 10.1038/s41564-018-0349-6. PMID: 30742071.

Bloos F, Thomas-Rüddel D, Rüddel H, Engel C, Schwarzkopf D, Marshall JC, Harbarth S, Simon P, Riessen R, Keh D, Dey K, Weiß M, Toussaint S, Schädler D, Weyland A, Ragaller M, Schwarzkopf K, Eiche J, Kuhnle G, Hoyer H, Hartog C, Kaisers U, Reinhart K; MEDUSA Study Group. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care. 2014 Mar 3;18(2):R42. doi: 10.1186/cc13755.

Bloos F, Rüddel H, Thomas-Rüddel D, Schwarzkopf D, Pausch C, Harbarth S, Schreiber T, Gründling M, Marshall J, Simon P, Levy MM, Weiss M, Weyland A, Gerlach H, Schürholz T, Engel C, Matthäus-Krämer C, Scheer C, Bach F, Riessen R, Poidinger B, Dey K, Weiler N, Meier-Hellmann A, Häberle HH, Wöbker G, Kaisers UX, Reinhart K; MEDUSA study group. Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. Intensive Care Med. 2017; 43:1602-1612. doi: 10.1007/s00134-017-4782-4. PMID: 28466151.

Bodilsen J, Dalager-Pedersen M, Schønheyder HC, Nielsen H. Time to antimicrobial therapy and outcome in bacterial meningitis: a Danish population-based cohort study. *BMC Infect Dis*. 2016; 16:392. doi:10.1186/s12879-016-1711-z.

Boeddha NP, Schlapbach LJ, Driessen GJ, Herberg JA, Rivero-Calle I, Cebey-López M, Klobassa DS, Philipsen R, de Groot R, Inwald DP, Nadel S, Paulus S, Pinnock E, Secka F, Anderson ST, Agbeko RS, Berger C, Fink CG, Carrol ED, Zenz W, Levin M, van der Flier M, Martinón-Torres F, Hazelzet JA, Emonts M; EUCLIDS consortium. Mortality and morbidity in community-acquired sepsis in European pediatric intensive care units: a prospective cohort study from the European Childhood Life-threatening Infectious Disease Study (EUCLIDS). Crit Care. 2018; 22:143. doi: 10.1186/s13054-018-2052-7. PMID: 29855385; PMCID: PMC5984383.

Bonet, M., Nogueira Pileggi, V., Rijken, M.J. et al. Towards a consensus definition of maternal sepsis: results of a systematic review and expert consultation. Reprod Health 2017; 14:67. https://doi.org/10.1186/s12978-017-0321-6.

Bosch X. Call to tackle sepsis. Lancet Infect Dis 2002; 2:649. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(02)00424-3/fulltext

Bourne DS, Davis BS, Gigli KH, Chang CH, Yabes JG, Martsolf GR, Kahn JM. Economic Analysis of Mandated Protocolized Sepsis Care in New York Hospitals. Crit Care Med. 2020; 48:1411-1418. doi: 10.1097/CCM.0000000000004514. PMID: 32931187; PMCID: PMC7875140.

Boyer A, Vargas F, Coste F, Saubusse E, Castaing Y, Gbikpi-Benissan G, Hilbert G, Gruson D. Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management. Intensive Care Med. 2009; 35:847-53.

Brangan E, Banks J, Brant H, Pullyblank A, Le Roux H, Redwood S. Using the National Early Warning Score (NEWS) outside acute hospital settings: a qualitative study of staff experiences in the West of England. BMJ Open 2018; 8:e022528. 2018/10/29. DOI: 10.1136/bmjopen-2018-022528.

Buck DL, Vester-Andersen M, Møller MH; Danish Clinical Register of Emergency Surgery. Surgical delay is a critical determinant of survival in perforated peptic ulcer. Br J Surg. 2013; 100:1045-9.

Budd E, Cramp E, Sharland M, Hand K, Howard P, Wilson P, Wilcox M, Muller-Pebody B, Hopkins S. Adaptation of the WHO Essential Medicines List for national antimicrobial stewardship policy in England: being AWaRe. J Antimicrob Chemother 2019; 74:3384-3389.

Burns A. NEWS 2 sepsis score is not validated in primary care. BMJ 2018; 361:k1743. 2018/04/25. DOI: 10.1136/bmj.k1743.

Burston J, Adhikari S, Hayen A, Doolan H, Kelly ML, Fu K, Jensen TO, Konecny P. A role for antimicrobial stewardship in clinical sepsis pathways: a prospective interventional study. Infect Control Hosp Epidemiol. 2017; 38:1032-1038. doi: 10.1017/ice.2017.139. PMID: 28693625.

Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, Harper A, Hulbert D, Lucas S, McClure J, Millward-Sadler H, Neilson J, Nelson-Piercy C, Norman J, O'Herlihy C, Oates M, Shakespeare J, de Swiet M, Williamson C, Beale V, Knight M, Lennox C, Miller A, Parmar D, Rogers J, Springett A. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG. 2011;118 Suppl 1:1-203. doi: 10.1111/j.1471-0528.2010.02847.x. PMID: 21356004.

Carlton HC, Savović J, Dawson S, Mitchelmore PJ, Elwenspoek MMC. Novel point-of-care biomarker combination tests to differentiate acute bacterial from viral respiratory tract infections to guide antimicrobial prescribing: a systematic review. Clin Microbiol Infect. 2021; 27:1096-1108. doi: 10.1016/j.cmi.2021.05.018.

Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, Reinhart K, Selvakumar N, Levy MM. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med. 2015; 43:567-73. doi: 10.1097/CCM.0000000000000742. PMID: 25479113.

Chen L, Wang Q, Gao Y, et al. The global burden and trends of maternal sepsis and other maternal infections in 204 countries and territories from 1990 to 2019. BMC Infect Dis. 2021;21(1):1074. Published 2021 Oct 18. doi:10.1186/s12879-021-06779-0.

Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B. Procalcitonin guidance of antimicrobial therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med. 2006; 174:84-93.

Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia require blood cultures? JAMA. 2012; 308:502-11. doi: 10.1001/jama.2012.8262. PMID: 22851117.

Contou D, Roux D, Jochmans S, Coudroy R, Guérot E, Grimaldi D, Ricome S, Maury E, Plantefève G, Mayaux J, Mekontso Dessap A, Brun-Buisson C, de Prost N. Septic shock with no diagnosis at 24 hours: a pragmatic multicenter prospective cohort study. Crit Care. 2016; 20:360. doi: 10.1186/s13054-016-1537-5. PMID: 27816060; PMCID: PMC5097846.

Corfield AR, Lees F, Zealley I, Houston G, Dickie S, Ward K, McGuffie C; Scottish Trauma Audit Group Sepsis Steering Group. Utility of a single early warning score in patients with sepsis in the emergency department. Emerg Med J. 2014; 31:482-7. doi: 10.1136/emermed-2012-202186.PMID: 23475607.

Corl KA, Zeba F, Caffrey AR, Hermenau M, Lopes V, Phillips G, Merchant RC, Levy MM, LaPlante KL. Delay in antimicrobial administration is associated with mortality among septic shock patients with Staphylococcus aureus bacteremia. Crit Care Med. 2020; 48:525-532. doi: 10.1097/CCM.0000000000004212. PMID: 32205599.

Coyne CJ, Le V, Brennan JJ, Castillo EM, Shatsky RA, Ferran K, Brodine S, Vilke GM. Application of the MASCC and CISNE Risk-Stratification Scores to Identify Low-Risk Febrile Neutropenic Patients in the Emergency Department. Ann Emerg Med. 2017 Jun;69(6):755-764. doi: 10.1016/j.annemergmed.2016.11.007.

Craig JC, Williams GJ, Jones M, Codarini M, Macaskill P, Hayen A, Irwig L, Fitzgerald DA, Isaacs D, McCaskill M. The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses. BMJ. 2010; 340:c1594. doi: 10.1136/bmj.c1594. PMID: 20406860; PMCID: PMC2857748.

Damiani E, Donati A, Serafini G, Rinaldi L, Adrario E, Pelaia P, Busani S, Girardis M. 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:e0125827. doi: 10.1371/journal.pone.0125827. PMID: 25946168; PMCID: PMC4422717.

Denny, K J, Jessica G Gartside, Kylie Alcorn, Jack W Cross, Samuel Maloney, Gerben Keijzers, Appropriateness of antimicrobial prescribing in the emergency department, J Antimicrob Chemother. 2019; 74:515–520, https://doi.org/10.1093/jac/dky447

Denny KJ, De Waele J, Laupland KB, Harris PNA, Lipman J. When not to start antimicrobials: avoiding antimicrobial overuse in the intensive care unit. Clin Microbiol Infect. 2020; 26:35-40. doi: 10.1016/j.cmi.2019.07.007.

de Groot B, Ansems A, Gerling DH, Rijpsma D, van Amstel P, Linzel D, Kostense PJ, Jonker M, de Jonge E. The association between time to antimicrobials and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study. Crit Care. 2015; 19:194. doi: 10.1186/s13054-015-0936-3. PMID: 25925412; PMCID: PMC4440486.

De laMaza V, Simian D, CastroM, Torres JP, Lucero Y, Sep lveda F et al (2015) Administration time for the first dose of antimicrobials in episodes of fever and neutropenia in children with cancer. Pediatr Infect Dis J 34:1069–1073.

Department of Health and Social Care Media Centre Blog 27th May 2016. https://healthmedia.blog.gov.uk/2016/05/27/amr/

De Pascale G, Antonelli M, Deschepper M, Arvaniti K, Blot K, Brown BC, de Lange D, De Waele J, Dikmen Y, Dimopoulos G, Eckmann C, Francois G, Girardis M, Koulenti D, Labeau S, Lipman J, Lipovetsky F, Maseda E, Montravers P, Mikstacki A, Paiva JA, Pereyra C, Rello J, Timsit JF, Vogelaers D, Blot S; Abdominal Sepsis Study (AbSeS) group and the Trials Group of the European Society of Intensive Care Medicine. Poor timing and failure of source control are risk factors for mortality in critically ill patients with secondary peritonitis. Intensive Care Med. 2022 Sep 23. doi: 10.1007/s00134-022-06883-y.

Dessie AS, Lanning M, Nichols T, Delgado EM, Hart LS, Agrawal AK. Patient Outcomes With Febrile Neutropenia Based on Time to Antibiotics in the Emergency Department. Pediatr Emerg Care. 2022 Jan 1;38(1):e259-e263. doi: 10.1097/PEC.0000000000002241.

De Waele JJ, Schouten J, Beovic B, Tabah A, Leone M. Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions-a viewpoint of experts. Intensive Care Med. 2020; 46:236-244. doi: 10.1007/s00134-019-05871-z. PMID: 32025778; PMCID: PMC7224113.

ECDC Surveillance Atlas – Antimicrobial resistance. European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc

ESPAUR 2019-20. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2019 to 2020.

ESPAUR 2020-2021. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR). Report 2020 to 2021. UK Health Security Agency.

Eun S, Kim H, Kim HY, Lee M, Bae GE, Kim H, Koo CM, Kim MK, Yoon SH. Age-adjusted quick Sequential Organ Failure Assessment score for predicting mortality and disease severity in children with infection: a systematic review and meta-analysis. Sci Rep. 2021 Nov 4;11(1):21699. doi: 10.1038/s41598-021-01271-w.

Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Møller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021: 47:1181-1247. doi: 10.1007/s00134-021-06506-y.

Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM. Empiric antimicrobial 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; 42:1749-55. doi: 10.1097/CCM.0000000000000330. PMID: 24717459.

Ferrer R, Martínez ML, Gomà G, Suárez D, Álvarez-Rocha L, de la Torre MV, González G, Zaragoza R, Borges M, Blanco J, Herrejón EP, Artigas A; ABISS-Edusepsis Study group. Improved empirical antimicrobial treatment of sepsis after an educational intervention: the ABISS-Edusepsis study. Crit Care. 2018; 22:167. doi: 10.1186/s13054-018-2091-0. PMID: 29933756; PMCID: PMC6013897.

Filbin MR, Lynch J, Gillingham TD, Thorsen JE, Pasakarnis CL, Nepal S, Matsushima M, Rhee C, Heldt T, Reisner AT. Presenting symptoms independently predict mortality in septic shock: importance of a previously unmeasured confounder. Crit Care Med. 2018; 46:1592-1599. doi: 10.1097/CCM.0000000000003260. PMID: 29965833.

Filbin MR, Thorsen JE, Lynch J, Gillingham TD, Pasakarnis CL, Capp R, Shapiro NI, Mooncai T, Hou PC, Heldt T, Reisner AT. Challenges and opportunities for emergency department sepsis screening at triage. Nature Scientific Reports 2018b; 8: 11059.

Fitzpatrick F, Tarrant C, Hamilton V, Kiernan FM, Jenkins D, Krockow EM. Sepsis and antimicrobial stewardship: two sides of the same coin. *BMJ Qual Saf*. 2019;28(9):758-761. doi:10.1136/bmjqs-2019-009445.

Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, Schlattmann P, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med. 2020; 46:1552–62.

Freitag A, Constanti M, O'Flynn N, Faust S N. Suspected sepsis: summary of NICE guidance BMJ 2016; 354 :i4030 doi:10.1136/bmj.i4030.

Funk DJ, Kumar A. Antimicrobial therapy for life-threatening infections: speed is life. Crit Care Clin. 2011 Jan;27(1):53-76. doi: 10.1016/j.ccc.2010.09.008. PMID: 21144986.

Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, Shofer FS, Goyal M. Impact of time to antimicrobials 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 Apr;38(4):1045-53. doi: 10.1097/CCM.0b013e3181cc4824. PMID: 20048677.

Gattinoni L, Vasques F, Camporota L, Meessen J, Romitti F, Pasticci I, Duscio E, Vassalli F, Forni LG, Payen D, Cressoni M, Zanella A, Latini R, Quintel M, Marini JJ. Understanding Lactatemia in Human Sepsis. Potential Impact for Early Management. Am J Respir Crit Care Med. 2019 Sep 1;200(5):582-589. doi: 10.1164/rccm.201812-2342OC. PMID: 30985210.

Gigli KH, Davis BS, Yabes JG, Chang CH, Angus DC, Hershey TB, Marin JR, Martsolf GR, Kahn JM. Pediatric Outcomes After Regulatory Mandates for Sepsis Care. Pediatrics. 2020 Jul;146(1):e20193353. doi: 10.1542/peds.2019-3353. PMID: 32605994; PMCID: PMC7329251.

Goh KH, Wang L, Yeow AYK, Poh H, Li K, Yeow JJL, Tan GYH. Artificial intelligence in sepsis early prediction and diagnosis using unstructured data in healthcare. Nat Commun. 2021 Jan 29;12(1):711. doi: 10.1038/s41467-021-20910-4. PMID: 33514699; PMCID: PMC7846756.

Gomes S, Wood D, Ayis S, Haliasos N, Roland D. Evaluation of a novel approach to recognising community-acquired paediatric sepsis at ED triage by combining an electronic screening algorithm with clinician assessment. Emerg Med J. 2021 Feb;38(2):132-138. doi: 10.1136/emermed-2019-208746.

Grant A, Treweek S, Dreischulte T, Foy R, Guthrie B. Process evaluations for cluster-randomised trials of complex interventions: a proposed framework for design and reporting. Trials. 2013 Jan 12;14:15. doi: 10.1186/1745-6215-14-15.

Green LJ, Mackillop LH, Salvi D, Pullon R, Loerup L, Tarassenko L, Mossop J, Edwards C, Gerry S, Birks J, Gauntlett R, Harding K, Chappell LC, Watkinson PJ. Gestation-Specific Vital Sign Reference Ranges in Pregnancy. Obstet Gynecol. 2020 Mar;135(3):653-664. doi: 10.1097/AOG.0000000000003721.

Greer O, Shah N. Maternal sepsis update: current management and controversies. The Obstetrician and Gynaecologist 2019; 22(1): 45-55.

Guo M, Gao M, Gao J, et al. Identifying Risk Factors for Secondary Infection Post-SARS-CoV-2 Infection in Patients With Severe and Critical COVID-19. Front Immunol. 2021;12:715023. doi:10.3389/fimmu.2021.715023.

Hagedoorn NN, Borensztajn DM, Nijman R, Balode A, von Both U, Carrol ED, Eleftheriou I, Emonts M, van der Flier M, de Groot R, Herberg J, Kohlmaier B, Lim E, Maconochie I, Martinon-Torres F, Nieboer D, Pokorn M, Strle F, Tsolia M, Yeung S, Zavadska D, Zenz W, Vermont C, Levin M, Moll HA; PERFORM consortium. Variation in antimicrobial prescription rates in febrile children presenting to emergency departments across Europe (MOFICHE): A multicentre observational study. PLoS Med. 2020 Aug 19;17(8):e1003208. doi: 10.1371/journal.pmed.1003208. PMID: 32813708; PMCID: PMC7444592.

Hancock M. Twitter. https://twitter.com/MattHancock/status/1105021047265550336?s=20

Heffner AC, Horton JM, Marchick MR, Jones AE. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. Clin Infect Dis. 2010; 50:814–20.

Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ. 2015 Feb 6;350:h391. doi: 10.1136/bmj.h391.

Herberg JA, Kaforou M, Wright VJ, Shailes H, Eleftherohorinou H, Hoggart CJ, Cebey-López M, Carter MJ, Janes VA, Gormley S, Shimizu C, Tremoulet AH, Barendregt AM, Salas A, Kanegaye J, Pollard AJ, Faust SN, Patel S, Kuijpers T, Martinón-Torres F, Burns JC, Coin LJ, Levin M; IRIS Consortium. Diagnostic Test Accuracy of a 2-Transcript Host RNA Signature for Discriminating Bacterial vs Viral Infection in Febrile Children. JAMA. 2016 Aug 23-30;316(8):835-45. doi: 10.1001/jama.2016.11236. Erratum in: JAMA. 2017 Feb 7;317(5):538. PMID: 27552617; PMCID: PMC5997174.

Hernández G, Ospina-Tascón GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019 Feb 19;321(7):654-664. doi: 10.1001/jama.2019.0071. PMID: 30772908; PMCID: PMC6439620.

Honeyford K, Cooke GS, Kinderlerer A, Williamson E, Gilchrist M, Holmes A; Sepsis Big Room, Glampson B, Mulla A, Costelloe C. Evaluating a digital sepsis alert in a London multisite hospital network: a natural experiment using electronic health record data. J Am Med Inform Assoc. 2020 Feb 1;27(2):274-283. doi: 10.1093/jamia/ocz186. Erratum in: J Am Med Inform Assoc. 2020 Mar 1;27(3):501. PMID: 31743934; PMCID: PMC7025344.

Howard P 2021 (personal communication). Unpublished audit of 94 hospital antimicrobial guidelines using Microguide in June 2021. Guidance - Induction Healthcare Group

Hranjec T, Rosenberger LH, Swenson B, Metzger R, Flohr TR, Politano AD, Riccio LM, Popovsky KA, Sawyer RG. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. Lancet

Infect Dis. 2012 Oct;12(10):774-80. doi: 10.1016/S1473-3099(12)70151-2. Epub 2012 Aug 28. PMID: 22951600; PMCID: PMC3462590.

Husabø G, Nilsen RM, Solligård E, Flaatten HK, Walshe K, Frich JC, Bondevik GT, Braut GS, Helgeland J, Harthug S, Hovlid E. Effects of external inspections on sepsis detection and treatment: a stepped-wedge study with cluster-level randomisation. BMJ Open. 2020 Oct 20;10(10):e037715. doi: 10.1136/bmjopen-2020-037715. PMID: 33082187; PMCID: PMC7577024.

IDSA Sepsis Task Force. Infectious Diseases Society of America (IDSA) POSITION STATEMENT: Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines. Clin Infect Dis. 2018;66:1631–5.

Im Y, Kang D, Ko RE, et al. Time-to-antibiotics and clinical outcomes in patients with sepsis and septic shock: a prospective nationwide multicenter cohort study. *Crit Care*. 2022;26(1):19. Published 2022 Jan 13. doi:10.1186/s13054-021-03883-0.

Inada-Kim M, Mackenzie P, Brain P, O'Brien V, Nsutebu E. The National Patient Safety Collaborative Sepsis Cluster Guidance Survey. Patient Safety Collaboratives, AHSN Network. December 2016.

Inada-Kim M, Page B, Maqsood I, Vincent C. Defining and measuring suspicion of sepsis: an analysis of routine data. BMJ Open 2017;7:e014885. doi: 10.1136/bmjopen-2016-014885.

Inada-Kim M, Nsutebu E. NEWS 2: an opportunity to standardise the management of deterioration and sepsis *BMJ* 2018; 360 :k1260 doi:10.1136/bmj.k1260.

Inada-Kim M, Knight Thomas, Sullivan M, Ainsworth-Smith M, Pike N, Richardson M, Hayward G, Lasserson D. The prognostic value of national early warning scores (NEWS) during transfer of care from community settings to hospital: a retrospective service evaluation BJGP Open 2020; 4 (2): bjgpopen20X101071. DOI: 10.3399/bjgpopen20X101071.

Infection Management Coalition. White Paper. British Society for Antimicrobial Chemotherapy 2022. https://theimc.org/

Institute of Medicine (US) Committee on Quality of Health Care in America. To Err is Human: Building a Safer Health System. Kohn LT, Corrigan JM, Donaldson MS, editors. Washington (DC): National Academies Press (US); 2000. PMID: 25077248.

Irwin AD, Drew RJ, Marshall P, Nguyen K, Hoyle E, Macfarlane KA, Wong HF, Mekonnen E, Hicks M, Steele T, Gerrard C, Hardiman F, McNamara PS, Diggle PJ, Carrol ED. Etiology of childhood bacteremia and timely antimicrobials administration in the emergency department. Pediatrics. 2015 Apr;135(4):635-42. doi: 10.1542/peds.2014-2061. Epub 2015 Mar 9. PMID: 25755240.

Joint Commission 2019. Specifications Manual for National Hospital Inpatient Quality Measures.
https://www.jointcommission.org/-/media/tjc/documents/measurement/specification-manuals/hiqr_specsman_july2019_v5_6.pdf

Joshi M, Ashrafian H, Arora S, Khan S, Cooke G, Darzi A. Digital Alerting and Outcomes in Patients With Sepsis: Systematic Review and Meta-Analysis. J Med Internet Res. 2019 Dec 20;21(12):e15166. doi: 10.2196/15166.

Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, Demirkale CY, Dekker JP, Palmore TN, Rhee C, Klompas M, Hooper DC, Powers JH 3rd, Srinivasan A, Danner RL, Adjemian J; forming the National Insititutes of Health Antimicrobial Resistance Outcomes Research Initiative (NIH-ARORI). Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis. 2021 Feb;21(2):241-251. doi: 10.1016/S1473-3099(20)30477-1.

Kahn JM, Davis BS, Yabes JG, Chang CH, Chong DH, Hershey TB, Martsolf GR, Angus DC. Association Between State-Mandated Protocolized Sepsis Care and In-hospital Mortality Among Adults With Sepsis. JAMA. 2019 Jul 16;322(3):240-250. doi: 10.1001/jama.2019.9021. PMID: 31310298; PMCID: PMC6635905.

Kalligeros M, Zacharioudakis IM, Tansari GS, Tori K, Shehadeh F, Mylonakis E. In-depth analysis of T2Bacteria positive results in patients with concurrent negative blood culture: a case series. BMC Infect Dis 2020; 326. https://doi.org/10.1186/s12879-020-05049-9.

Kanwar M, Brar N , Khatib R, Fakih MG. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antimicrobials: side effects of the 4-h antimicrobial administration rule. Chest 2007;131:1865-1869.

Kaukonen K, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311(13):1308–1316. doi:10.1001/jama.2014.2637.

Kim H, Chung SP, Choi SH, Kang GH, Shin TG, Kim K, Park YS, Han KS, Choi HS, Suh GJ, Kim WY, Lim TH, Ko BS; Korean Shock Society (KoSS) Investigators. Impact of timing to source control in patients with septic shock: A prospective multi-center observational study. J Crit Care. 2019 Oct;53:176-182. doi: 10.1016/j.jcrc.2019.06.012. Epub 2019 Jun 17. PMID: 31247517.

Kim M-H, Choi J-H. An update on sepsis biomarkers. Infect Chemother. 2020; 52:1–18].

Klein Klouwenberg PM, Cremer OL, van Vught LA, Ong DS, Frencken JF, Schultz MJ, Bonten MJ, van der Poll T. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care. 2015 Sep 7;19(1):319. doi: 10.1186/s13054-015-1035-1. PMID: 26346055; PMCID: PMC4562354.

Klein E Y, Van Boeckel T P, Martinez E M, Pant S, Gandra S, Levin S A,Goossens H, Laxminarayan R. Global increase and geographic convergence in antimicrobial consumption between 2000 and 2015. Proceedings of the National Academy of Sciences Apr 2018, 115 (15) E3463-E3470; DOI: 10.1073/pnas.1717295115.

Klein EY, Milkowska-Shibata M, Tseng KK, Sharland M, Gandra S, Pulcini C, Laxminarayan R. Assessment of WHO antimicrobial consumption and access targets in 76 countries, 2000-15: an analysis of pharmaceutical sales data. Lancet Infect Dis. 2021 Jan;21(1):107-115. doi: 10.1016/S1473-3099(20)30332-7. Epub 2020 Jul 24. PMID: 32717205.

Klompas M, Calandra T, Singer M. Antimicrobials for Sepsis-Finding the Equilibrium. JAMA. 2018; 320:1433-1434.

Klompas M, Rhee C. Current Sepsis Mandates Are Overly Prescriptive, and Some Aspects May Be Harmful. Crit Care Med. 2020 Jun;48(6):890-893. doi: 10.1097/CCM.0000000000003579. PMID: 30865616.

Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ. Maternal, Newborn and Infant Clinical Outcome Review Programme (MBRACE-UK). Saving Lives, Improving Mothers' Care. 2014. https://www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/Saving%20Lives%20Improving%20Mothers%20Care%20report%202014%20Full.pdf

Ko BS, Choi SH, Shin TG, et al. Impact of 1-Hour Bundle Achievement in Septic Shock. J Clin Med. 2021;10(3):527. Published 2021 Feb 2. doi:10.3390/jcm10030527.

Komorowski, M., Celi, L.A., Badawi, O, Gordon A C, Faisal A A. The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. *Nat Med* 24, 1716–1720 (2018). https://doi.org/10.1038/s41591-018-0213-5

Kopczynska M, Sharif B, Cleaver S, Spencer N, Kurani A, Lee C, Davis J, Durie C, Joseph-Gubral J, Sharma A, Allen L, Atkins B, Gordon A, Jones L, Noble A, Bradley M, Atkinson H, Inns J, Penney H, Gilbert C, Walford R, Pike L, Edwards R, Howcroft R, Preston H, Gee J, Doyle N, Maden C, Smith C, Azis NSN, Vadivale N, Battle C, Lyons R, Morgan P, Pugh R, Szakmany T; Welsh Digital Data Collection Platform Collaborators. Red-flag sepsis and SOFA identifies different patient population at risk of sepsis-related deaths on the general ward. Medicine (Baltimore). 2018a Dec;97(49):e13238. doi: 10.1097/MD.0000000000013238. PMID: 30544383; PMCID: PMC6310498.

Kopczynska M, Sharif B, Cleaver S, Spencer N, Kurani A, Lee C, David J, Durie C, Joseph-Gubral J, Sharma A, Allen L, Atkins B, Gordon A, Jones L, Noble A, Bradley M, Atkinson H, Inns J, Penney H, Gilbert C, Walford R, Pike L, Edwards R, Howcroft R, Preston H, Gee J, Doyle N, Maden C, Smith C, Nik Azis N S, Vadivale N, Szakmany T. Sepsis-related deaths in the at-risk population on the wards: attributable fraction of mortality in a large point-prevalence study. BMC Res Notes. 2018b; 11: 720.

Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370(23):2211-2218. doi:10.1056/NEJMra1213566.

Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589-96. doi: 10.1097/01.CCM.0000217961.75225.E9. PMID: 16625125.

Kumar A, Haery C, Paladugu B, Kumar A, Symeoneides S, Taiberg L, Osman J, Trenholme G, Opal SM, Goldfarb R, Parrillo JE. The duration of hypotension before the initiation of antimicrobial treatment is a critical determinant of survival in a murine model of Escherichia coli septic shock: association with serum lactate and inflammatory cytokine levels. J Infect Dis. 2006 Jan 15;193(2):251-8. doi: 10.1086/498909. Epub 2005 Dec 13. PMID: 16362889.

Ladhani S, Pebody RG, Ramsay ME, Lamagni TL, Johnson AP, Sharland M. Continuing impact of infectious diseases on childhood deaths in England and Wales, 2003-2005. Pediatr Infect Dis J. 2010 Apr;29(4):310-3. doi: 10.1097/INF.0b013e3181d73322. PMID: 20216475.

Lane DJ, Wunsch H, Saskin R, Cheskes S, Lin S, Morrison LJ, Scales DC. Screening strategies to identify sepsis in the prehospital setting: a validation study. CMAJ. 2020 Mar 9;192(10):E230-E239. doi: 10.1503/cmaj.190966.

Latten G, Hensgens K, de Bont EGPM, Muris JWM, Cals JWL, Stassen P. How well are sepsis and a sense of urgency documented throughout the acute care chain in the Netherlands? A prospective, observational study. BMJ Open. 2020 Jul 19;10(7):e036276. doi: 10.1136/bmjopen-2019-036276. PMID: 32690518; PMCID: PMC7371221.

Leigh S, Grant A, Murray N, Faragher B, Desai H, Dolan S, Cabdi N, Murray JB, Rejaei Y, Stewart S, Edwardson K, Dean J, Mehta B, Yeung S, Coenen F, Niessen LW, Carrol ED. The cost of diagnostic uncertainty: a prospective economic analysis of febrile children attending an NHS emergency department. BMC Med. 2019 Mar 6;17(1):48. doi: 10.1186/s12916-019-1275-z. PMID: 30836976; PMCID: PMC6402102.

Levy, M.M., Evans, L.E. & Rhodes, A. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 44, 925–928 (2018). https://doi.org/10.1007/s00134-018-5085-0.

Li, HK, Kaforou, M, Rodriguez-Manzano, J, Channon-Wells, S, Monir, A, Habgood-Coote, D, Gupta, RK, Mills, EA, Lin, J, Chiu, Y-H, Pennisi, I, Miglietta, L, Mehta, R, Obaray, N, Herberg, JA, Wright, VJ, Georgiou, P, Shallcross, LJ, Mentzer, AJ, Levin, M, Cooke, GS, Noursadeghi, M, Sriskandan, S. Discovery and validation of a 3-gene transcriptional signature to distinguish COVID-19 and other viral infections from bacterial sepsis in adults: a case-control then observational cohort study. Lancet Microbe 2021. http://dx.doi.org/10.2139/ssrn.3766286

Liu VX, Lu Y, Carey KA, et al. Comparison of Early Warning Scoring Systems for Hospitalized Patients With and Without Infection at Risk for In-Hospital Mortality and Transfer to the Intensive Care Unit. JAMA Netw Open. 2020;3(5):e205191. doi:10.1001/jamanetworkopen.2020.5191.

Lodise TP, Zhao Q, Fahrbach K, Gillard PJ, Martin A. A systematic review of the association between delayed appropriate therapy and mortality among patients hospitalized with infections due to Klebsiella pneumoniae or Escherichia coli: how long is too long?. *BMC Infect Dis*. 2018;18(1):625. Published 2018 Dec 5. doi:10.1186/s12879-018-3524-8.

Lopansri, B.K., Miller III, R.R., Burke, J.P. Levy M, Opal S, Rothman R E, D'Allesio F R, Sidhaye V K , Balk R, Greenberg J A, Yoder M, Pael G P, Gilbert E, Afshar M, Parada J P, Martin G S, Esper A M, Kempker J A, Narasimhan M, Tsegaye A, Hahn S, Mayo P, McHugh L, Rapisarda A, Sampson D, Brandon R A, Seldon T A, Yager T D, Bradon R B. Physician agreement on the diagnosis of sepsis in the intensive care unit: estimation of concordance and analysis of underlying factors in a multicenter cohort. j intensive care 7, 13 (2019). https://doi.org/10.1186/s40560-019-0368-2.

MacGowan A, Grier S, Stoddart M, Reynolds R, Rogers C, Pike K, Smartt H, Wilcox M, Wilson Kelsey M, Steer J, Gould FK, Perry JD, Howe R, Wootton M. Impact of rapid microbial identification on clinical outcomes in bloodstream infection: the RAPIDO randomized trial. Clin Microbiol Infect 2020; 26: 1347-54.

Martinón-Torres F, Salas A, Rivero-Calle I, Cebey-López M, Pardo-Seco J, Herberg JA, Boeddha NP, Klobassa DS, Secka F, Paulus S, de Groot R, Schlapbach LJ, Driessen GJ, Anderson ST, Emonts M, Zenz W, Carrol ED, Van der Flier M, Levin M; EUCLIDS Consortium. Life-threatening infections in children in Europe (the EUCLIDS Project): a prospective cohort study. Lancet Child Adolesc Health. 2018 Jun;2(6):404-414. doi: 10.1016/S2352-4642(18)30113-5. Epub 2018 Apr 28. PMID: 30169282.

Mason CY, Kanitkar T, Richardson CJ, Lanzman M, Stone Z, Mahungu T, Mack D, Wey EQ, Lamb L, Balakrishnan I, Pollara G. Exclusion of bacterial co-infection in COVID-19 using baseline inflammatory markers and their response to antimicrobials. J Antimicrob Chemother. 2021 Apr 13;76(5):1323-1331. doi: 10.1093/jac/dkaa563. PMID: 33463683; PMCID: PMC7928909.

Masson H, Stephenson J. Investigation into the predictive capability for mortality and the trigger points of the National Early Warning Score 2 (NEWS2) in emergency department patients. Emergency Medicine Journal Published Online First: 09 June 2021. doi: 10.1136/emermed-2020-210190. https://emj.bmj.com/content/early/2021/06/08/emermed-2020-210190.citation-tools

Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. JAMA Pediatr. 2017 Oct 2;171(10):e172352. doi: 10.1001/jamapediatrics.20.

May L, Quiros AM, Oever JT, Hoogerwerf J, Schoffelen T, Schouten J. Antimicrobial stewardship in the emergency department: characteristics and evidence for effectiveness of interventions. Clin Microbiol Infect 2021; 27: 204-9.

MBRACE. https://www.npeu.ox.ac.uk/mbrrace-uk

MBRACE. Saving Lives Improving Mothers' Care (confidential Enquiries into Maternal Deaths and Morbidity 2018-18). MBRRACE-UK, NPEU Oxford Dec 2020.

McArthur AG, Waglechner N, Nizam F, et al. The comprehensive antibiotic resistance database. Antimicrob Agents Chemother. 2013;57:3348-3357.

Mellhammar L, Linder A, Tverring J, Christensson B, Boyd JH, Sendi P, Åkesson P, Kahn F. NEWS2 is Superior to qSOFA in Detecting Sepsis with Organ Dysfunction in the Emergency Department. J Clin Med. 2019 Jul 29;8(8):1128. doi: 10.3390/jcm8081128. PMID: 31362432; PMCID: PMC6723972.

Miller J, Hall B, Wilson K, Cobian J. Impact of SEP-1 on broad-spectrum combination antimicrobial therapy in the emergency department. Am J Emerg Med. 2020 Dec;38(12):2570-2573. doi: 10.1016/j.ajem.2019.12.045. Epub 2020 Jan 7. PMID: 31932126.

Reyes Mondragón AL, Cantú-Rodríguez OG, Garza-Acosta AC, Gutiérrez-Aguirre CH, Colunga Pedraza PR, Del Carmen Tarín-Arzaga L, Jaime-Pérez JC, Hawing Zárate JA, González-Cantú GA, Villalobos-Gutiérrez LE, Jiménez-Castillo RA, Vera-Pineda R, Gómez-Almaguer D. Performance of serum procalcitonin as a biochemical predictor of death in hematology patients with febrile neutropenia. Blood Cells Mol Dis. 2021 Sep;90:102586. doi: 10.1016/j.bcmd.2021.102586.

Nauclér P, Huttner A, van Werkhoven CH, Singer M, Tattevin P, Einav S, Tängdén T. Impact of time to antimicrobial therapy on clinical outcome in patients with bacterial infections in the emergency department: implications for antimicrobial stewardship. Clin Microbiol Infect. 2021 Feb;27(2):175-181. doi: 10.1016/j.cmi.2020.02.032. Epub 2020 Feb 29. PMID: 32120032.

NCEPOD. Just Say Sepsis! A review of the process of care received by patients with sepsis. A report by the National Confidential Enquiry into Patient Outcome and Death. London 2015.

Nguyen MH, Clancy CJ, Pasculle AW, Pappas PG, Alangaden G, Pankey GA, et al. Performance of the T2Bacteria panel for diagnosing bloodstream infections: a diagnostic accuracy study. Ann Intern Med. 2019; 170:845-852.

NHS England Cross Systems Sepsis Prevention Programme Board. Improving outcomes for patients with sepsis: A cross-system action plan. London: NHS England 2017.

NHS England 2015. Commissioning for Quality and Innovation (CQUIN) Guidance for 2015/16. Indicator 2 Sepsis.

NHS England. CQUIN Indicator Specification Information on CQUIN 2017/18 - 2018/19. Indicator 2a. NHS(E) 2019.

NHS England 2017. Sepsis guidance implementation advice for adults. https://www.england.nhs.uk/wp-content/uploads/2017/09/sepsis-guidance-implementation-advice-for-adults.pdf

NHS England 2019. Maternity and Neonatal Safety Improvement Programme. https://www.england.nhs.uk/mat-transformation/maternal-and-neonatal-safety-collaborative/

NHS England 2019. NHS Long Term Plan to reduce toll of 'hidden killer' sepsis. https://www.england.nhs.uk/2019/03/nhs-long-term-plan-to-reduce-toll-of-hidden-killer-sepsis/

NHS England Dec 24th 2020. Standard operating procedure: Lateral flow device testing for emergency department patient pathways. https://www.england.nhs.uk/coronavirus/publication/standard-operating-procedure-lateral-flow-device-testing-for-emergency-department-patient-pathways/

NHS England and NHS Improvement (NHSEI). Improving the blood culture pathway: A national review of blood culture pathway processes to support better antimicrobial stewardship and improved patient safety. Office of the Chief Scientific Officer, NHS England and Improvement. Nov 2021 *(in press).*

NICE guideline 51. Sepsis: recognition, diagnosis and early management. National Institute for Health and Care Excellence. 2016.

NICE Guideline NG151. Neutropenic sepsis: prevention and management in people with cancer. National Institute for Health and Care Excellence. 2012. https://www.nice.org.uk/guidance/cg151/chapter/1-Recommendations#managing-suspected-neutropenic-sepsis-in-secondary-and-tertiary-care-2

NICE Guideline 15. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. National Institute for Health and Care Excellence. 2015.

NICE guideline 173. COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital. National Institute for Health and Care Excellence. May 1st 2020. https://www.nice.org.uk/guidance/ng173/resources/prescribing-tables-to-guide-decision-making-about-antibiotic-choice-pdf-8719038253

NICE guideline DG20. National Institute for Health and Care Excellence. 2020. https://www.nice.org.uk/guidance/dg20/evidence

NICE guideline 195. Neonatal infection: antibiotics for prevention and treatment. National Institute for Health and Care Excellence, 20 April 2021. https://www.nice.org.uk/guidance/ng195

Nicolino B, Vitolo U, Audisio E, D'Ardia S, Frairia C, Iovino G, Evangelista A, Ciccone G, Aydin S. National Early Warning Score (NEWS) and Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Validation in AML Patients during Febrile Neutropenia. Blood (2017) 130 (Supplement 1): 5016. https://ashpublications.org/blood/article/130/Supplement%201/5016/81017/National-Early-Warning-Score-NEWS-and-Quick

Nijman RG, Jorgensen R, Levin M, Herberg J, Maconochie IK. Management of Children With Fever at Risk for Pediatric Sepsis: A Prospective Study in Pediatric Emergency Care. Front Pediatr. 2020;8:548154. Published 2020 Sep 17. doi:10.3389/fped.2020.548154.

O'Dwyer MJ, Starczewska MH, Schrenzel J, Zacharowski K, Ecker DJ, Sampath R, Brealey D, Singer M, Libert N, Wilks M, Vincent JL. The detection of microbial DNA but not cultured bacteria is associated with increased mortality in patients with suspected sepsis-a prospective multi-centre European observational study. Clin Microbiol Infect. 2017; 23:208.e1-208.e6.

Office for National Statistics. Deaths from septicaemia, England and Wales, 2016 to 2018 registrations. ONS 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/10879deathsfromsepticaemiaenglandandwales2016to2018registrations

Opal SM, Wittebole X. Biomarkers of infection and sepsis. Crit Care Clin. 2020; 36:11–22.

Osthoff M, Gürtler N, Bassetti S, Balestra G, Marsch S, Pargger H, Weisser M, Egli A. Impact of MALDI-TOF-MS-based identification directly from positive blood cultures on patient management: a controlled clinical trial. Clin Microbiol Infect. 2017 Feb;23(2):78-85. doi: 10.1016/j.cmi.2016.08.009.

Ouldali N, Bellêttre X, Milcent K, Guedj R, de Pontual L, Cojocaru B, Soussan-Banini V, Craiu I, Skurnik D, Gajdos V, Chéron G, Cohen R, Alberti C, Angoulvant F. Impact of Implementing National Guidelines on Antimicrobial Prescriptions for Acute Respiratory Tract Infections in Pediatric Emergency Departments: An Interrupted Time Series Analysis. Clin Infect Dis. 2017 Oct 16;65(9):1469-1476. doi: 10.1093/cid/cix590. PMID: 29048511.

Pakyz AL, Orndahl CM, Johns A, Harless DW, Morgan DJ, Bearman G, Hohmann SF, Stevens MP. Impact of the Centers for Medicare and Medicaid Services Sepsis Core Measure on Antimicrobial Use. Clin Infect Dis. 2021 Feb 16;72(4):556-565. doi: 10.1093/cid/ciaa456. PMID: 32827032.

Paoli CJ, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. Crit Care Med 2018; 46(12): 1889-1897. doi: 10.1097/CCM.0000000000003342.

Pan D, Hills G, Hamilton AR, Nash T, Hine T, Whitehorn S, Barlow G. Recommended antimicrobial therapy for common inpatient infections: a comparative review of guidelines across 51 hospital trusts in England. Postgraduate Medical Journal 2021;97:782-788.

Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antimicrobial monotherapy versus beta lactam-aminoglycoside antimicrobial combination therapy for sepsis. Cochrane Database Syst Rev 2014; CD003344.

Paul M, Dickstein Y, Raz-Pasteur A. Antimicrobial de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis. Clin Microbiol Infect. 2016 Dec;22(12):960-967. doi: 10.1016/j.cmi.2016.05.023.

Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist review--a new method of systematic review designed for complex policy interventions. J Health Serv Res Policy. 2005 Jul;10 Suppl 1:21-34. doi: 10.1258/1355819054308530.

Peden, C. J., Aggarwal, G., Aitken, R. J., Anderson, I. D., Bang Foss, N., Cooper, Z., Dhesi, J. K., French, W. B., Grant, M. C., Hammarqvist, F., Hare, S. P., Havens, J. M., Holena, D. N., Hübner, M., Kim, J. S., Lees, N. P., Ljungqvist, O., Lobo, D. N., Mohseni, S., Ordoñez, C. A., Scott, M. (2021). Guidelines for Perioperative Care for Emergency Laparotomy Enhanced Recovery After Surgery (ERAS) Society Recommendations: Part 1-Preoperative: Diagnosis, Rapid Assessment and Optimization. World journal of surgery, 45(5), 1272–1290. https://doi.org/10.1007/s00268-021-05994-9

Peltan ID, Brown SM, Bledsoe JR, et al. ED Door-to-Antimicrobial Time and Long-term Mortality in Sepsis. Chest. 2019;155(5):938-946. doi:10.1016/j.chest.2019.02.008.

Pepper DJ, Sun J, Cui X, Welsh J, Natanson C, Eichacker PQ. Antimicrobial- and Fluid-Focused Bundles Potentially Improve Sepsis Management, but High-Quality Evidence Is Lacking for the Specificity Required in the Centers for Medicare and Medicaid Service's Sepsis Bundle (SEP-1). Crit Care Med. 2019 Oct;47(10):1290-1300. doi: 10.1097/CCM.0000000000003892. PMID: 31369426.

Pettit N, Boadu D, Bischof JJ. Emergency department management of chemotherapy related febrile neutropenia: An opportunity to improve care. Am J Emerg Med. 2021 Dec;50:5-9. doi: 10.1016/j.ajem.2021.07.008.

Peyrony O, Gerlier C, Barla I, et al. Antibiotic prescribing and outcomes in cancer patients with febrile neutropenia in the emergency department. PLoS One. 2020;15(2):e0229828. Published 2020 Feb 28. doi:10.1371/journal.pone.0229828.

Pringle J. XV. Some experiments on substances resisting putrefaction. Philosophical Transactions of the Royal Society 1750; January 1st: 480-488. https://doi.org/10.1098/rstl.1749.0092

Public Health England 2015. Start Smart then Focus. Antimicrobial Stewardship Toolkit for English Hospitals. March 2015.

Public Health England. Investigation of blood cultures (for organisms other than Mycobacterium species). Standards Unit, National Infection Service. PHE 2019.

Pullyblank A, Tavaré A, Little H, Redfern E, le Roux H, Inada-Kim M, Cheema K, Cook A; West of England Patient Safety Collaborative. Implementation of the National Early Warning Score in patients with suspicion of sepsis: evaluation of a system-wide quality improvement project. Br J Gen Pract. 2020 May 28;70(695):e381-e388. doi: 10.3399/bjgp20X709349. PMID: 32269043; PMCID: PMC7147668.

Ranzani OT, Shankar-Hari M, Harrison DA, Rabello LS, Salluh JIF, Rowan KM, Soares M. A Comparison of Mortality From Sepsis in Brazil and England: The Impact of Heterogeneity in General and Sepsis-Specific Patient Characteristics. Crit Care Med. 2019 Jan;47(1):76-84. doi: 10.1097/CCM.0000000000003438. PMID: 30247269.

Redfern OC, Smith GB, Prytherch DR, Meredith P, Inada-Kim M, Schmidt PE. A Comparison of the Quick Sequential (Sepsis-Related) Organ Failure Assessment Score and the National Early Warning Score in Non-ICU Patients With/Without Infection. Crit Care Med. 2018 Dec;46(12):1923-1933. doi: 10.1097/CCM.0000000000003359. PMID: 30130262.

Reitz KM, Kennedy J, Li SR, Handzel R, Tonetti DA, Neal MD, Zuckerbraun BS, Hall DE, Sperry JL, Angus DC, Tzeng E, Seymour CW. Association Between Time to Source Control in Sepsis and 90-Day Mortality. JAMA Surg. 2022 Jul 13:e222761. doi: 10.1001/jamasurg.2022.2761.

Reygaert, W. C. (2018). "An overview of the antimicrobial resistance mechanisms of bacteria." AIMS Microbiol 4(3): 482-501.

Rhee C et al. Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes. Crit Care. 2016 Apr 6;20:89. doi: 10.1186/s13054-016-1266-9. PMID: 27048508; PMCID: PMC4822273.

Rhee C, Filbin MR, Massaro AF, Bulger AL, McEachern D, Tobin KA, Kitch BT, Thurlo-Walsh B, Kadar A, Koffman A, Pande A, Hamad Y, Warren DK, Jones TM, O'Brien C, Anderson DJ, Wang R, Klompas M; Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program. Compliance With the National SEP-1 Quality Measure and Association With Sepsis Outcomes: A Multicenter Retrospective Cohort Study. Crit Care Med. 2018 Oct;46(10):1585-1591. doi: 10.1097/CCM.0000000000003261. PMID: 30015667; PMCID: PMC6138564.

Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O'Brien, Anderson D J, Warren D K, Dantes R B, Epstein L, Klompas M; Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program. Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals. JAMA Netw Open. 2019 Feb 1;2(2):e187571. doi: 10.1001/jamanetworkopen.2018.7571. PMID: 30768188; PMCID: PMC6484603. https://pubmed.ncbi.nlm.nih.gov/30768188/

Rhee C, Chiotos K, Cosgrove SE, Heil EL, Kadri SS, Kalil AC, Gilbert DN, Masur H, Septimus EJ, Sweeney A, Strich JR, Winslow DL, Klompas M. Infectious Diseases Society of America Position Paper: Recommended Revisions to the National Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Sepsis Quality Measure. Clin Infect Dis. 2021 Feb 16;72(4):541-552. doi: 10.1093/cid/ciaa059. PMID: 32374861; PMCID: PMC8189682.

Rhee C, Yu T, Wang R, Kadri SS, Fram D, Chen HC, Klompas M. Association Between Implementation of the Severe Sepsis and Septic Shock Early Management Bundle Performance Measure and Outcomes in Patients With Suspected Sepsis in US Hospitals. JAMA Netw Open 2021; 4(12): e2138596. doi:10.1001/jamanetworkopen.2021.38596 [Rhee2021b].

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017 Mar;43(3):304-377. doi: 10.1007/s00134-017-4683-6. Epub 2017 Jan 18. PMID: 28101605.

Richardson D, Faisal M, Fiori M, Beatson K, Mohammed M. Use of the first National Early Warning Score recorded within 24 hours of admission to estimate the risk of in-hospital mortality in unplanned COVID-19 patients: a retrospective cohort study. BMJ Open. 2021 Feb 22;11(2):e043721. doi: 10.1136/bmjopen-2020-043721.

Robbins T, Shennan A, Sandall J. Modified early obstetric warning scores: A promising tool but more evidence and standardization is required. Acta Obstet Gynecol Scand. 2019 Jan;98(1):7-10. doi: 10.1111/aogs.13448. Epub 2018 Oct 16. PMID: 30155879; PMCID: PMC7028086.

Roland D, Stilwell PA, Fortune PM, Alexander J, Clark SJ, Kenny S. Case for change: a standardised inpatient paediatric early warning system in England. Arch Dis Child. 2021 Jul;106(7):648-651. doi: 10.1136/archdischild-2020-320466. Epub 2021 Jan 8. PMID: 33419727.

Romaine ST, Potter J, Khanijau A, McGalliard RJ, Wright JL, Sefton G, Leigh S, Edwardson K, Johnston P, Kerr A, Schlapbach LJ, Pallmann P, Carrol ED. Accuracy of a Modified qSOFA Score for Predicting Critical Care Admission in Febrile Children. Pediatrics. 2020 Oct;146(4):e20200782. doi: 10.1542/peds.2020-0782. PMID: 32978294; PMCID: PMC7786830.

Romaine ST, Sefton G, Lim E, Nijman RG, Bernatoniene J, Clark S, Schlapbach LJ, Pallmann P, Carrol ED. Performance of seven different paediatric early warning scores to predict critical care admission in febrile children presenting to the emergency department: a retrospective cohort study. BMJ Open. 2021 May 4;11(5):e044091. doi: 10.1136/bmjopen-2020-044091. PMID: 33947731; PMCID: PMC8098996. https://pubmed.ncbi.nlm.nih.gov/33947731/

Royal College of General Practitioners. NEWS2 score for assessing the patient at risk of deterioration. Clinical Policy. RCGP 2020

Royal College of Obstetricians and Gynaecologists. Bacterial Sepsis in Pregnancy. Green-top Guideline No.64a. London: RCOG; 2012. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg64a/

Royal College of Paediatrics and Child Health (RCPCH). Paediatric Early Warning System (PEWSystem) - developing a standardised tool for England. https://www.rcpch.ac.uk/resources/paediatric-early-warning-system-pewsystem-developing-standardised-tool-england

Royal College of Physicians. (2017). National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-NEWS2

Royal College of Surgeons of England Working Group on the Perioperative Care of the High-risk General Surgical Patient (2018). The High-Risk General Surgical Patient: Raising the Standard. London 2018

Rudd KE, Kissoon N, Limmathurotsakul D, Bory S, Mutahunga B, Seymour CW, Angus DC, West TE. The global burden of sepsis: barriers and potential solutions. Critical Care 2018; 22: 232.

Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C, Machado FR, Reinhart KK, Rowan K, Seymour CW, Watson RS, West TE, Marinho F, Hay SI, Lozano R, Lopez AD, Angus DC, Murray CJL, Naghavi M. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020 Jan 18;395(10219):200-211. doi: 10.1016/S0140-6736(19)32989-7. PMID: 31954465; PMCID: PMC6970225.

Rüddel, H., Thomas-Rüddel, D.O., Reinhart, K. et al. Adverse effects of delayed antimicrobial treatment and surgical source control in adults with sepsis: results of a planned secondary analysis of a cluster-randomized controlled trial. Crit Care 26, 51 (2022). https://doi.org/10.1186/s13054-022-03901-9.

Russell CD, Fairfield CJ, Drake TM, Turtle L, Seaton RA, Wootton DG, Sigfrid L, Harrison EM, Docherty AB, de Silva TI, Egan C, Pius R, Hardwick HE, Merson L, Girvan M, Dunning J, Nguyen-Van-Tam JS, Openshaw PJM, Baillie JK, Semple MG, Ho A; ISARIC4C investigators. Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. Lancet Microbe. 2021 Aug;2(8):e354-e365. doi: 10.1016/S2666-5247(21)00090-2.

Rycroft-Malone J, Seers K, Eldh AC, Cox K, Crichton N, Harvey G, Hawkes C, Kitson A, McCormack B, McMullan C, Mockford C, Niessen T, Slater P, Titchen A, van der Zijpp T, Wallin L. A realist process evaluation within the Facilitating Implementation of Research Evidence (FIRE) cluster randomised controlled international trial: an exemplar. Implement Sci. 2018 Nov 16;13(1):138. doi: 10.1186/s13012-018-0811-0.

Sabir L, Wharton L, Goodacre S. Retrospective single-centre descriptive study of the characteristics, management and outcomes of adult patients with suspected sepsis in the emergency department. Emerg Med J. 2021 Aug 6:emermed-2020-211111. doi: 10.1136/emermed-2020-211111.

Saeed K, Wilson DC, Bloos F, Schuetz P, van der Does Y, Melander O, Hausfater P, Legramante JM, Claessens YE, Amin D, Rosenqvist M, White G, Mueller B, Limper M, Callejo CC, Brandi A, Macchi MA, Cortes N, Kutz A, Patka P, Yañez MC, Bernardini S, Beau N, Dryden M, van Gorp ECM, Minieri M, Chan L, Rood PPM, Del Castillo JG. The early identification of disease progression in patients with suspected infection presenting to

the emergency department: a multi-centre derivation and validation study. Crit Care. 2019 Feb 8;23(1):40. doi: 10.1186/s13054-019-2329-5. Erratum in: Crit Care. 2019 Jul 15;23(1):255. PMID: 30736862; PMCID: PMC6368690.

Sakr Y, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva SA, Martin-Loeches I, Leone M, Lupu MN, Vincent JL; ICON Investigators. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. Open Forum Infect Dis. 2018 Nov 19;5(12):ofy313. doi: 10.1093/ofid/ofy313. PMID: 30555852; PMCID: PMC6289022.

Surviving Sepsis Campaign. https://www.sccm.org/SurvivingSepsisCampaign/Home

Schinkel M, Nannan Panday RS, Wiersinga WJ, Nanayakkara PWB. Timeliness of antimicrobials for patients with sepsis and septic shock. J Thorac Dis. 2020 Feb;12(Suppl 1):S66-S71. doi: 10.21037/jtd.2019.10.35. PMID: 32148927; PMCID: PMC7024760.

Schlapbach LJ, Straney L, Bellomo R, MacLaren G, Pilcher D. Prognostic accuracy of age-adapted SOFA, SIRS, PELOD-2, and qSOFA for in-hospital mortality among children with suspected infection admitted to the intensive care unit. Intensive Care Med. 2018 Feb;44(2):179-188. doi: 10.1007/s00134-017-5021-8. Epub 2017 Dec 19. PMID: 29256116; PMCID: PMC5816088.

Scott LJ, Tavaré A, Hill EM, Jordan L, Juniper M, Srivastava S, Redfern E, Little H, Pullyblank A. Prognostic value of National Early Warning Scores (NEWS2) and component physiology in hospitalised patients with COVID-19: a multicentre study. Emergency Medicine Journal Published Online First: 15 March 2022. doi: 10.1136/emermed-2020-210624.

Scottish Antimicrobial Prescribing Group. Advice to antimicrobial management teams (AMTs) on antimicrobial prescribing in suspected lower respiratory tract infections in the context of the COVID-19 pandemic. May 12, 2020. https://www.nhstaysideadtc.scot.nhs.uk/Antibiotic%20site/pdf%20docs/SAPG%20COVID%2019%20Update%20for%20AMTs%20Resp%20Infection.pdf

Sefton G, Carter B, Lane S, Peak M, Mateus C, Preston J, Mehta F, Hollingsworth B, Killen R, Carrol ED. Dynamic Electronic Tracking and Escalation to reduce Critical care Transfers (DETECT): the protocol for a stepped wedge mixed method study to explore the clinical effectiveness, clinical utility and cost-effectiveness of an electronic physiological surveillance system for use in children. BMC Pediatr. 2019 Oct 17;19(1):359. doi: 10.1186/s12887-019-1745-7. PMID: 31623583; PMCID: PMC6796473.

Seltzer JA, Frankfurt O, Kyriacou DN. Association of an emergency department febrile neutropenia intervention protocol with time to initial antibiotic treatment. Acad Emerg Med. 2022 Jan;29(1):73-82. doi: 10.1111/acem.14335.

Sepsis Trust 2019. The sepsis Manual. 5th Edition.

Sepsis Trust. Inpatient Maternal Sepsis Tool. [https://sepsistrust.org/wp-content/uploads/2018/06/Inpatient-maternal-NICE-Final-1107-2.pdf].

Sepsis CQUIN [Commissioning for Quality and Innovation] Data Provision Notice. https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/directions-and-data-provision-notices/data-provision-notices-dpns/sepsis-cquin-commissioning-for-quality-and-innovation-data-provision-notice.

Seok H, Jeon JH, Park DW. Antimicrobial Therapy and Antimicrobial Stewardship in Sepsis. Infect Chemother. 2020a Mar;52(1):19-30. doi: 10.3947/ic.2020.52.1.19. PMID: 32239809; PMCID: PMC7113444.

Seok H, Song J, Jeon JH, Choi HK, Choi WS, Moon S, Park DW. Timing of antimicrobials in septic patients: a prospective cohort study. Clin Microbiol Infect. 2020 Nov;26(11):1495-1500. doi: 10.1016/j.cmi.2020.01.037. Epub 2020b Feb 14. PMID: 32062049.

Seymour C W, Liu V X, Iwashyna T J, Brunkhorst F M, Rea T D, Scherag A, Rubenfeld G, Kahn J M, Shankar-Hari M, Singer M, Deutschman C S, Escobar G, Angus D. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:762–74. https://doi.org/10.1001/ jama.2016.0288.

Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017a Jun 8;376(23):2235-2244. doi: 10.1056/NEJMoa1703058. Epub 2017 May 21. PMID: 28528569; PMCID: PMC5538258.

Seymour CW, Kahn JM, Martin-Gill C, Callaway CW, Yealy DM, Scales D, Angus DC. Delays from first medical contact to antimicrobial administration for sepsis. Crit Care Med 2017b 45: 759-765.

Shallcross L, Rockenschaub P, Blackburn R, Nazareth I, Freemantle N, Hayward A. Antimicrobial prescribing for lower UTI in elderly patients in primary care and risk of bloodstream infection: A cohort study using electronic health records in England. PLoS Med. 2020; 17:e1003336.

Shappell CN, Klompas M, Ochoa A, Rhee C; CDC Prevention Epicenters Program. Likelihood of Bacterial Infection in Patients Treated With Broad-Spectrum IV Antimicrobials in the Emergency Department. Crit Care Med. 2021 May 7. doi: 10.1097/CCM.0000000000005090.

Shankar-Hari M, Harrison DA, Rowan KM. Differences in Impact of Definitional Elements on Mortality Precludes International Comparisons of Sepsis Epidemiology-A Cohort Study Illustrating the Need for Standardized Reporting. Crit Care Med. 2016 Dec;44(12):2223-2230. doi: 10.1097/CCM.0000000000001876. PMID: 27352126.

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, BJA: British Journal of Anaesthesia, Volume 119, Issue 4, October 2017, Pages 626–636, https://doi.org/10.1093/bja/aex234.

Singer M, Deutschman C, Seymour C W, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard G R, Chiche J-D, Coopersmith C M, Hotchkiss R S, Levy M M, Marshall J C, Martin G S, Opal S M, Rubenfeld G D, van der Poll T, Vincent J L, Angus D C. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10. https://doi.org/10.1001/jama.2016.0287

Singer M, Inada-Kim M, Shankar-Hari M. Sepsis hysteria: excess hype and unrealistic expectations. Lancet. 2019 Oct 26;394(10208):1513-1514. doi: 10.1016/S0140-6736(19)32483-3. PMID: 31657730.

Singh S, McGlennan A, England A, Simons R. A validation study of the CEMACH recommended modified early obstetric warning system (MEOWS). Anaesthesia. 2012 Jan;67(1):12-8. doi: 10.1111/j.1365-2044.2011.06896.x. Epub 2011 Nov 9. Erratum in: Anaesthesia. 2012 Apr;67(4):453. PMID: 22066604.

Sjoding MW, Iwashyna TJ, Dimick JB, Cooke CR. Gaming hospital-level pneumonia 30-day mortality and readmission measures by legitimate changes to diagnostic coding. Crit Care Med. 2015; 43:989–95.

Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, Boyd KA, Craig N, French DP, McIntosh E, Petticrew M, Rycroft-Malone J, White M, Moore L. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021 Sep 30;374:n2061. doi: 10.1136/bmj.n2061.

Smieszek T, Pouwels KB, Dolk FCK, Smith DRM, Hopkins S, Sharland M, Hay AD, Moore MV, Robotham JV. Potential for reducing inappropriate antimicrobial prescribing in English primary care. J Antimicrob Chemother. 2018 Feb 1;73(suppl_2):ii36-ii43. doi: 10.1093/jac/dkx500. PMID: 29490058; PMCID: PMC5890667.

Smith GB, Prytherch DR, Schmidt PE, Featherstone PI, Higgins B. A review, and performance evaluation, of single-parameter "track and trigger" systems. Resuscitation. 2008 Oct;79(1):11-21. doi: 10.1016/j.resuscitation.2008.05.004.

Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. Resuscitation. 2013 Apr;84(4):465-70. doi: 10.1016/j.resuscitation.2012.12.016.

Smith GB, Prytherch DR, Jarvis S, Kovacs C, Meredith P, Schmidt PE, Briggs J. A Comparison of the Ability of the Physiologic Components of Medical Emergency Team

Criteria and the U.K. National Early Warning Score to Discriminate Patients at Risk of a Range of Adverse Clinical Outcomes. Crit Care Med. 2016 Dec;44(12):2171-2181. doi: 10.1097/CCM.0000000000002000.

Smyth MA, Brace-McDonnell SJ, Perkins GDIdentification of adults with sepsis in the prehospital environment: a systematic reviewBMJ Open 2016;6:e011218. doi: 10.1136/bmjopen-2016-011218.

Snyder SR, Favoretto AM, Baetz RA, Derzon JH, Madison BM, Mass D, et al. Effectiveness of practices to reduce blood culture contamination: a laboratory medicine best practices systematic review and meta-analysis. Clin Biochem. 2012;45:999–1011. doi: 10.1016/j.clinbiochem.2012.06.007.

Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt). 2010 Feb;11(1):79-109. doi: 10.1089/sur.2009.9930. PMID: 20163262.

Sterling SA, Miller WR, Pryor J, Puskarich MA, Jones AE. The impact of timing of antimicrobials on outcomes in severe sepsis and septic shock: a systematic review and meta-analysis. Crit Care Med 2015; 43: 1907-15.

Straface G, Selmin A, Zanardo V, De Santis M, Ercoli A, Scambia G. Herpes simplex virus infection in pregnancy. Infect Dis Obstet Gynecol. 2012;2012:385697. doi:10.1155/2012/385697.

Strich, Jeffrey R, Emily L Heil, Henry Masur, Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance, *The Journal of Infectious Diseases*, Volume 222, Issue Supplement_2, 15 August 2020, Pages S119–S131, https://doi.org/10.1093/infdis/jiaa221

Stuart B, Hounkpatin H, Becque T, Yao G, Zhu S, Alonso-Coello P, Altiner A, Arroll B, Bohning D, Bostock J, Bucher H C, Chao J, de la Poza M, Francis N, Gillespie D, Hay A D, Kenealy T, Loffler C, McCormick D P, Mas-Dalmau G, Munoz L, Samuel K, Moore M, Little P. Delayed antimicrobial prescribing for respiratory tract infections: individual patient data meta-analysis. BMJ. 2021; 373:n808.

Sweeney TE, Wong HR, Khatri P. Robust classification of bacterial and viral infections via integrated host gene expression diagnostics. Sci Transl Med 2016; 8: 346ra91 DOI: 10.1126/scitranslmed.aaf7165.

Sweeney TE, Liesenfeld O, May L. Diagnosis of bacterial sepsis: why are tests for bacteremia not sufficient? Expert rev Molec Diagnostics 2019; 19: 959-962.

Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. JAMA Intern Med. 2017 Sep 1;177(9):1308-1315. doi: 10.1001/jamainternmed.2017.1938.

Tabah A, Bassetti M, Kollef MH, Zahar JR, Paiva JA, Timsit JF, Roberts JA, Schouten J, Giamarellou H, Rello J, De Waele J, Shorr AF, Leone M, Poulakou G, Depuydt P, Garnacho-Montero J. Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP). Intensive Care Med. 2020 Feb;46(2):245-265. doi: 10.1007/s00134-019-05866-w. Epub 2019 Nov 28. PMID: 31781835.

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 Nov 16;11(1):149. doi: 10.1186/s13012-016-0518-z. PMID: 27852320; PMCID: PMC5112724.

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 Nov 16;11(1):149. doi: 10.1186/s13012-016-0518-z. PMID: 27852320; PMCID: PMC5112724.

Taylor SP, Anderson WE, Beam K, Taylor B, Ellerman J, Kowalkowski MA. The association between antimicrobial delay intervals and hospital mortality among patients treated in the emergency department for suspected sepsis. Crit Care Med 2021; 49: 741-747.

Teshome, B. F., S. M. Vouri, N. Hampton, M. H. Kollef and S. T. Micek (2019). Duration of Exposure to Antipseudomonal beta-Lactam Antimicrobials in the Critically Ill and Development of New Resistance. Pharmacotherapy 39(3): 261-270.

Tidswell R, Inada-Kim M, Singer M. Lancet Resp Med 2021; 9: 17-18
https://doi.org/10.1016/S2213-2600(20)30520-8

Timbrook TT, Hueth KD, Ginocchio CC. Identification of bacterial co-detections in COVID-19 critically Ill patients by BioFire® FilmArray® pneumonia panel: a systematic review and meta-analysis. Diagn Microbiol Infect Dis. 2021; 101:115476.

Townsend SR, Phillips GS, Duseja R, Tefera L, Cruikshank D, Dickerson R, Nguyen HB, Schorr CA, Levy MM, Dellinger RP, Conway WA, Browner WS, Rivers EP. Effects of Compliance With the Early Management Bundle (SEP-1) on Mortality Changes Among Medicare Beneficiaries With Sepsis: A Propensity Score Matched Cohort Study. Chest. 2021 Aug 6:S0012-3692(21)03623-0. doi: 10.1016/j.chest.2021.07.2167.

Tujula B, Hämäläinen S, Kokki H, Pulkki K, Kokki M. Review of clinical practice guidelines on the use of procalcitonin in infections. Infect Dis. 2020; 52:227-234.

Umar A, Ameh CA, Muriithi F, Mathai M. Early warning systems in obstetrics: A systematic literature review. PLoS One. 2019 May 31;14(5):e0217864. doi: 10.1371/journal.pone.0217864. PMID: 31150513; PMCID: PMC6544303.

Unwin HJA, Kopczynska M, Pugh R, et al. The Use of Different Sepsis Risk Stratification Tools on the Wards and in Emergency Departments Uncovers Different Mortality Risks: Results of the Three Welsh National Multicenter Point-Prevalence Studies. Crit Care Explor. 2021;3(10):e0558. Published 2021 Oct 21. doi:10.1097/CCE.0000000000000558.

US Centers for Medicare & Medicaid Services (CMS). Severe Sepsis and Septic Shock Early Management Bundle (SEP-1).
https://cmit.cms.gov/CMIT_public/ViewMeasure?MeasureId=1017

Valik JK, Ward L, Tanushi H, et al. Validation of automated sepsis surveillance based on the Sepsis-3 clinical criteria against physician record review in a general hospital population: observational study using electronic health records data. BMJ Qual Saf. 2020;29(9):735-745. doi:10.1136/bmjqs-2019-010123.

van Nassau SC, van Beek RH, Driessen GJ, Hazelzet JA, van Wering HM, Boeddha NP. Translating Sepsis-3 Criteria in Children: Prognostic Accuracy of Age-Adjusted Quick SOFA Score in Children Visiting the Emergency Department With Suspected Bacterial Infection. Front Pediatr. 2018 Oct 1;6:266. doi: 10.3389/fped.2018.00266. PMID: 30327759; PMCID: PMC6174358.

Vasala A, Hytönen VP, Laitinen OH. Modern Tools for Rapid Diagnostics of Antimicrobial Resistance. Front Cell Infect Microbiol. 2020; 10:308.

Venkatesh AK, Avula U, Bartimus H, Reif J, Schmidt MJ, Powell ES. Time to antimicrobials for septic shock: evaluating a proposed performance measure. Am J Emerg Med. 2013 Apr;31(4):680-3. doi: 10.1016/j.ajem.2012.12.008.

Vester-Andersen M, Lundstrøm LH, Buck DL, Møller MH. Association between surgical delay and survival in high-risk emergency abdominal surgery. A population-based Danish cohort study. Scand J Gastroenterol. 2016; 51:121-8.

Wachter RM, Flanders SA, Fee C, Pronovost PJ. Public reporting of antimicrobial timing in patients with pneumonia: lessons from a flawed performance measure. Ann Intern Med. 2008;149:29–32.

Wadhwa A, Oakley J, Richman J, Bhatia S, Kutny MA. Time to Antibiotic for Pediatric Oncology Patients With Febrile Neutropenia at Regional Emergency Departments. Pediatr Emerg Care. 2022 Jan 1;38(1):e94-e99. doi: 10.1097/PEC.0000000000002160.

Wang W, Sung N, Gilman-Sachs A, Kwak-Kim J. T Helper (Th) Cell Profiles in Pregnancy and Recurrent Pregnancy Losses: Th1/Th2/Th9/Th17/Th22/Tfh Cells. Front Immunol. 2020;11:2025. doi:10.3389/fimmu.2020.02025.

Weinberger J, Rhee C, Klompas M. A critical analysis of the literature on time-to-antimicrobials in suspected sepsis. J Infect Dis. 2020; 222(Suppl 2):S110–8.

Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, Singhi SC, Erickson S, Roy JA, Bush JL, Nadkarni VM, Thomas NJ; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med. 2015 May 15;191(10):1147-57. doi: 10.1164/rccm.201412-2323OC.

Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, Nadel S, Schlapbach LJ, Tasker RC, Argent AC, Brierley J, Carcillo J, Carrol ED, Carroll CL, Cheifetz IM, Choong K, Cies JJ, Cruz AT, De Luca D, Deep A, Faust SN, De Oliveira CF, Hall MW, Ishimine P, Javouhey E, Joosten KFM, Joshi P, Karam O, Kneyber MCJ, Lemson J, MacLaren G, Mehta NM, Møller MH, Newth CJL, Nguyen TC, Nishisaki A, Nunnally ME, Parker MM, Paul RM, Randolph AG, Ranjit S, Romer LH, Scott HF, Tume LN, Verger JT, Williams EA, Wolf J, Wong HR, Zimmerman JJ, Kissoon N, Tissieres P. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med. 2020 Feb;46(Suppl 1):10-67. doi: 10.1007/s00134-019-05878-6. PMID: 32030529; PMCID: PMC7095013.

West, R M, C J Smith, S H Pavitt, C C Butler, P Howard, C Bates, S Savic, J M Wright, J Hewison, J A T Sandoe, 'Warning: allergic to penicillin': association between penicillin allergy status in 2.3 million NHS general practice electronic health records, antimicrobial prescribing and health outcomes, *Journal of Antimicrobial Chemotherapy*, Volume 74, Issue 7, July 2019, Pages 2075–2082, https://doi.org/10.1093/jac/dkz127

Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med. 2017; 45:623–9.

Whitewater Charitable Trust 2017. The cost of sepsis care in the UK. YHEC Sepsis Report 2017. http://allcatsrgrey.org.uk/wp/wpfb-file/yhec-sepsis-report-17-02-17-final-pdf/

WHO Global Maternal Sepsis Study (GLOSS) Research Group. Frequency and management of maternal infection in health facilities in 52 countries (GLOSS): a 1-week inception cohort study. Lancet Glob Health. 2020 May;8(5):e661-e671. doi: 10.1016/S2214-109X(20)30109-1. PMID: 32353314; PMCID: PMC7196885.

World Health Organisation. Sepsis. WHO 2020. https://www.who.int/news-room/fact-sheets/detail/sepsis

Wong A, Otles E, Donnelly JP, Krumm A, McCullough J, DeTroyer-Cooley O, et al. External Validation of a Widely Implemented Proprietary Sepsis Prediction Model in Hospitalized Patients. JAMA Intern Med 2021; 181:1065–70.

Yahav D, Franceschini E, Koppel F, Turjeman A, Babich T, Bitterman R, Neuberger A, Ghanem-Zoubi N, Santoro A, Eliakim-Raz N, Pertzov B, Steinmetz T, Stern A, Dickstein Y, Maroun E, Zayyad H, Bishara J, Alon D, Edel Y, Goldberg E, Venturelli C, Mussini C, Leibovici L, Paul M; Bacteremia Duration Study Group. Seven Versus 14 Days of Antimicrobial Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial. Clin Infect Dis. 2019 Sep 13;69(7):1091-1098. doi: 10.1093/cid/ciy1054. PMID: 30535100. https://pubmed.ncbi.nlm.nih.gov/30535100/

Yealy DM, Mohr NM, Shapiro NI, Venkatesh A, Jones AE, Self WH. Early Care of Adults With Suspected Sepsis in the Emergency Department and Out-of-Hospital Environment: A Consensus-Based Task Force Report. Ann Emerg Med. 2021 Jul;78(1):1-19. doi: 10.1016/j.annemergmed.2021.02.006.

Yoo IH, Kang HM, Suh W, Cho H, Yoo IY, Jo SJ, Park YJ, Jeong DC. Quality Improvements in Management of Children with Acute Diarrhea Using a Multiplex-PCR-Based Gastrointestinal Pathogen Panel. Diagnostics (Basel). 2021 Jun 28;11(7):1175. doi: 10.3390/diagnostics11071175.

Yuan Y, Wang J, Zhang J, Ma B, Gao S, Li Y, Wang S, Wang B, Zhang Q, Jing N. Evaluation of an optimized method to directly identify bacteria from positive blood cultures using MALDI-TOF mass spectrometry. J Clin Lab Anal. 2020 Apr;34(4):e23119. doi: 10.1002/jcla.23119.

Yui S, Bercades G, Muzslay M, Blackburn E, Ali S, Smyth D, Macklin A, Ryu JH, Bassett P, MacCallum N, Brealey D, WilsonP. Assessment of a rapid diagnostic test to exclude bacteremia and effect on clinical decision making for antimicrobial therapy. Sci rep 2020; 10: 3122.

Zasowski EJ, Bassetti M, Blasi F, Goossens H, Rello J, Sotgiu G, Tavoschi L, Arber MR, McCool R, Patterson JV, Longshaw CM, Lopes S, Manissero D, Nguyen ST, Tone K, Aliberti S. A Systematic Review of the Effect of Delayed Appropriate Antimicrobial Treatment on the Outcomes of Patients With Severe Bacterial Infections. Chest. 2020 Sep;158(3):929-938. doi: 10.1016/j.chest.2020.03.087. Epub 2020 May 22.
PMID: 32446623.

Zhang K, Zhang X, Ding W, Xuan N, Tian B, Huang T, Zhang Z, Cui W, Huang H, Zhang G. National Early Warning Score Does Not Accurately Predict Mortality for Patients With Infection Outside the Intensive Care Unit: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021 Jul 15;8:704358. doi: 10.3389/fmed.2021.704358. PMID: 34336903; PMCID: PMC8319382.

Zheng B, Toarta C, Cheng W, Taljaard M, Reaume N, Perry JJ. Accuracy of the Multinational Association of Supportive Care in Cancer (MASCC) and Clinical Index of Stable Febrile Neutropenia (CISNE) scores for predicting serious complications in adult patients with febrile neutropenia: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2020 May;149:102922. doi: 10.1016/j.critrevonc.2020.102922.

Appendix

Appendix Table 1. WHO Classification of antimicrobials, adapted for UK by Budd 2019

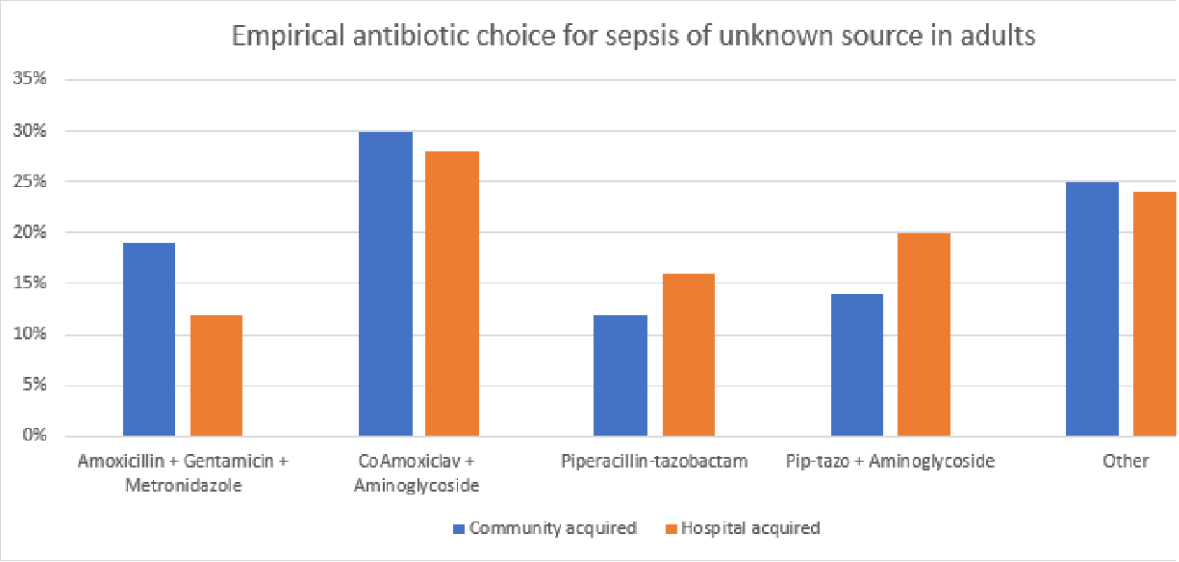
Access	Watch	Reserve
Amoxicillin / ampicillin	Amikacin, tobramycin, etc	Aztreonam
Penicillin – all forms	Macrolides	Ceftobiprole
Co-trimoxazole	Most cefalosporins	Ceftaroline
Doxycycline	Chloramphenicol	Ceftazidime-avibactam
Flucloxacillin	Fluoroquinolones	Ceftolozane-tazobactam
Fosfomycin oral	Clindamycin	Colistin
Fusidate	Amoxicillin-clavulanate	Dalbavancin
Gentamicin	Other tetracyclines	Daptomycin
Metronidazole	Fidaxomicin	Carbapenems
Nitrofurantoin	Piperacillin-tazobactam, etc	Fosfomycin IV
Pivmecillinam	Temocillin	Linezolid / tedizolid
Tetracycline	Vancomycin, teicoplanin	Televancin
Trimethoprim		Tigecycline

Appendix Figure 1: NEWS2

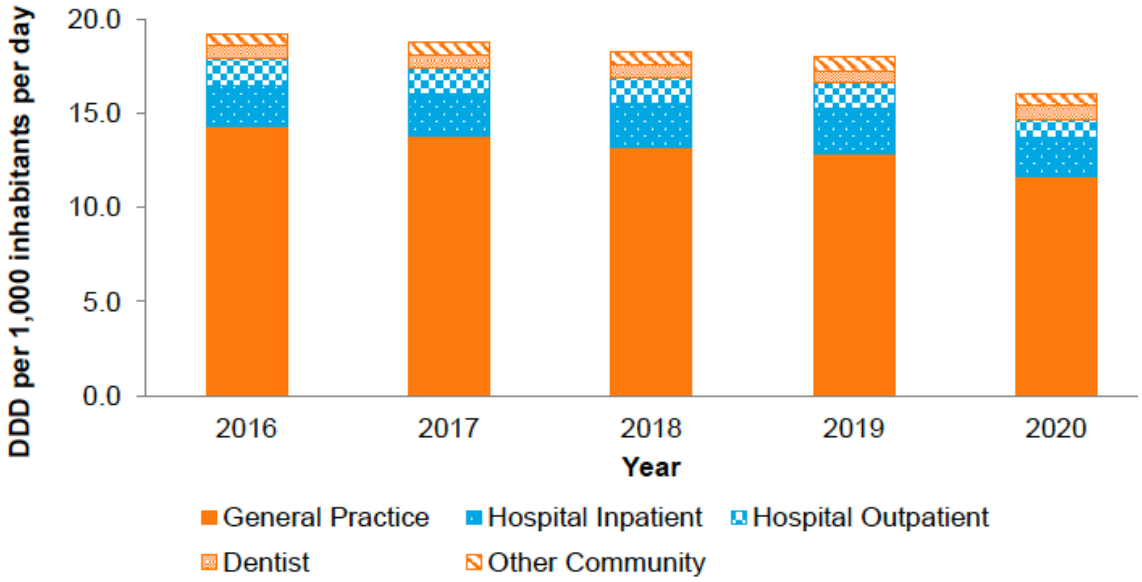
NICE Guideline 51 classifies red-band (score of 3) vital signs as high-risk criteria, and orange-band (score of 2) as moderate-to-high risk criteria for adult patients with suspected sepsis

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)	≤90	91–100	101–110	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	

Appendix Figure 2: Frequency of empirical antimicrobial combinations for sepsis of unknown source in adults recommended by 94 hospital Trust guidelines in England [Howard P 2021



Appendix Figure 3: Total antimicrobial consumption by setting, expressed as DDDs per 1,000 inhabitants per day, England, 2016 to 2020 [from ESPAUR 2020-2021].



Working Group members & declarations of interests

Name and Organisation	Declarations
Prof Julian Bion, Independent Chair	Professor of Intensive Care Medicine, University of Birmingham. Member of Surviving Sepsis Campaign guideline committee 2006-2010. Foundation Dean, UK Faculty of Intensive Care Medicine.
Prof Mervyn Singer, Faculty of Intensive Care Medicine	Co-chair, Third International Consensus Definitions Task Force for Sepsis and Septic Shock (Sepsis-3) 2014-2016. International Sepsis Forum Treasurer 2017-18, Chair 2019-20, Secretary 2021-22. Member of Surviving Sepsis Campaign guideline committee 2014-2016. Current or recent interests with involvement either provided gratis or with fees/donations paid into University/Hospital Research Funds or personal account: Advisory Board positions with Abbott, AM Pharma, Aptarion, Biotest, deepUll, Deltex Medical, Enlivex, Fresenius, Hemotune, Pfizer, Presymptom Health, Roche Diagnostics, Safeguard Biosystems, Santersus, Spiden. Speaker honoraria from AOP, Biomerieux, Mindray, Radiometer. Academic/governmental grant-funded industry collaborative work with Biomerieux, Cornel Medical, DSTL, Mologic, Oxford Optronix. Research fund donations from Deltex Medical. Novel drug developments with UCL Technology Fund and Apollo Therapeutics.
Dr Carl Waldmann, Critical Care Leadership Forum and associated organisations	No conflicts of interest to declare.
Mr Greg Barton, Chair of the Pharmacy Sub Committee, Faculty of Intensive Care Medicine	Chair – Pharmacy Sub-committee – Faculty of Intensive Care Medicine (FICM). Immediate Past Chair - Critical Care Group - United Kingdom Clinical Pharmacy Association (UKCPA). Member - Intensive Care Society Pharmacist Professional Advisory Group (ICS PAG). Advisor to NHSE re critical care medicines and stockpile.

Name and Organisation	Declarations
Dr Adrian Boyle, Royal College of Emergency Medicine	No conflicts of interest to declare.
Professor Gordon Carlson Royal Colleges of Surgeons of England and Edinburgh	Member Royal College of Surgeons of England Working Party, The High-Risk General Surgery Patient-Raising the Standard (2018), Representative of Royal College of Surgeons of England on NHS England Cross Systems Sepsis Board and Acute Deterioration Board.
Professor Enitan Carrol, Royal College of Paediatrics and Child Health	National Institute for Health and Care Excellence (NICE) Diagnostics Advisory Committee – Diagnosis and monitoring of sepsis - The BRAHMS PCT- specialist committee member, June 2014- June 2015. National Institute for Health and Care Excellence (NICE) Sepsis Guideline Development Group member, July 2014- July 2016 BioFire Diagnostics Scientific Advisory Board member for the FilmArray System, February 2015- present. National Institute for Health and Care Excellence (NICE) Quality Standards committee for sepsis, Specialist committee member, November 2016- September 2017. January 2017-present. Surviving Sepsis Campaign Pediatrics Guideline panel member, January 2017-2020. National Institute for Health and Care Excellence (NICE) Diagnostics Advisory Committee member, February 2017- September 2020. Society of Critical Care Medicine Paediatric Sepsis Definition Task Force member, February 2019- present. NIHR-funded research collaboration with Biomerieux NIHR-funded studies: BATCH,PRONTO, PEACH Trials. H2020 funded: PERFORM and DIAMONDS
Dr Will Christian, Royal College of Paediatrics and Child Health	No conflicts of interest to declare.
Dr Sue Crossland, Immediate Past President, Society for Acute Medicine	No conflicts of interest to declare.
Professor Saul Faust, Royal College of Paediatrics and Child Health	SNF was Chair of the NICE sepsis guideline committee (2014-16) and Lyme Disease guideline committee (2016-18). SNF acts on behalf of University Hospital Southampton NHS Foundation Trust as an investigator or providing consultative advice, or both, on clinical trials and studies of COVID-19 and other vaccines and antimicrobial agents funded or sponsored by vaccine and antimicrobial manufacturers including Janssen, Pfizer, AstraZeneca, GlaxoSmithKline, Novavax, Seqirus, Sanofi, Medimmune, Merck, and Valneva. He receives no personal financial payment for this work.

Name and Organisation	Declarations
Prof Matt Inada-Kim, Consultant Acute Physician, Hampshire Hospitals NHS Foundation Trust & University of Southampton	Lecture for Relias learning in 2019 on sepsis.
Marisa Lanzman, UK Clinical Pharmacy Association - Pharmacy Infection Network (UKCPA PIN)	No conflicts of interest to declare.
Mr. Nicholas Lees, Royal College of Surgeons of England	Chair Royal College of Surgeons of England Working Party, The High-Risk General Surgery Patient-Raising the Standard (2018), Royal College of Surgeons of England representative on the Clinical Reference Group of the National Emergency Laparotomy Audit, Advisor to NHS England on the Emergency Laparotomy Best Practice Tariff, 2017-2019.
Professor Mahdad Noursadeghi, Royal College of Physicians of London	No conflicts of interest to declare.
Professor Shiranee Sriskandan, Royal College of Physicians of London	No competing interests other than being RCP lead for sepsis, which is non-remunerated.
Dr Simon Stockley, Royal College of General Practitioners	Financial Interests - Former RCGP Clinical Champion for Sepsis, until 2020, Occasional paid adviser to Masimo Plc, provider of patient monitoring solutions (approx. 500 pounds)
Prof Tim Walsh, Royal College of Physicians of Edinburgh	TSW has received grants from Innovate UK and the NIHR for research in the field of sepsis. He has no conflicts of interest to declare.
Prof Peter Wilson, Infection in Critical Care Quality Improvement Programme (PHE)	Chair of Guidelines Committee, Healthcare infection Society. Grant from Germitec for research into disinfection of ultrasound probes. Grant from NIHR for infrastructure related to whole genome sequencing at University College London. Consultancy for Sky Chemicals, makers of peracetic acid disinfectant.

Name and Organisation	Declarations
Dr Flic Gabbay, Faculty of Pharmaceutical Medicine	President of the Faculty of Pharmaceutical Medicine (receives Innovate grants). Long standing Member of British Society of Antimicrobial Chemotherapy and member of various working parties on developing antibacterials and antivirals. Fellow of the Academy of Medical Sciences and member of their Forum Committee (and their organising committees for recent AMR meetings). Senior Partner and shareholder of tranScrip, a drug development organisation which has been in receipt of funding for consultative and regulatory work on anti-infectives used, or potentially used, in sepsis from Wellcome Foundation and from life sciences companies, AstraZeneca, Pfizer, Basilea and Menarini, and many small companies with anti-infective drugs in research and development. Shareholder in (and previously was Founder Chairman and Chief Medical Officer for) Phico Therapeutics, a company developing novel engineered phage therapeutics: no role in the company now.
Dr Nick Gent, Faculty of Public Health	No conflicts of interest to declare.
Mr Peter Gibbs, ICUsteps	No conflicts of interest to declare.
Dr John Harden, NHS Scotland	No conflicts of interest to declare.
Prof Philip Howard, British Society for Antimicrobial Chemotherapy	Financial – None. Professional – International Federation of Pharmacy (Global Pharmacy Umbrella Organisation) – AMR Collaborative Lead for WHO Europe Region. NICE Common Infections Standing Committee. Academic - Part of NIHR PRONTO (PCT in Sepsis) study.
Prof Alistair Leanord, Advisory Committee on Antimicrobial Prescribing, Resistance & Healthcare Associated Infection, Department of Health	Member of the Department of Health and Social Care advisory committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infections (APRHAI). In the last five years, lectured in the UK sponsored by Eumedica; member and Chair of a data advisory Board for Shionogi; and chaired a webinar for Shionogi.
Mr Pala Rajesh, Royal College of Surgeons Edinburgh	No conflicts of interest to declare.
Mr Suman Shrestha, Professional Lead for Critical Care (Royal College of Nursing)	Attended Gilead online advisory board to explore the awareness and management of invasive fungal disease in Critical Care (Dec 2021-Feb 2022).

Stakeholder organisations

We invited detailed critiques from a wide range of professional organisations involved in acute and emergency care from community, primary care and secondary care, as well as organisations involved in research and advocacy in these areas. We are grateful to all those who responded for their insightful comments which have helped to improve the final report. A transcript of the participating stakeholder organisations, their critiques, and the working group responses, can be downloaded from the Academy of Medical Royal Colleges website.

Endorsing organisations

The Academy of Medical Royal Colleges representing all medical royal colleges and faculties in the UK

Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI)

Association of Chartered Physiotherapists in Respiratory Care (ACPRC)

British Society for Antimicrobial Chemotherapy (BSAC)

Community Nursing

Critical Care Networks of England, Wales and Northern Ireland

Intensive Care Society (ICS)

Getting It Right First Time, Critical Care Medicine section (GIRFT)

National Outreach Forum (NOrF)

Northern Ireland Intensive Care Society (NI-ICS)

NHS England's Adult Critical Care Clinical Reference Group

Paediatric Critical Care Society (PCCS)

Scottish Anti-microbial prescribing Group (SAPG)

Scottish Intensive Care Society (SICS)

Society for Acute Medicine (SAM)

The Association for Cardiothoracic Anaesthesia & Critical Care (ACTACC)

The Neuroanaesthesia and Neurocritical Care Society (NACCS)

The Welsh Intensive Care Society (WICS)

UK Clinical Pharmacy Association (UKCPA)

UK Sepsis Trust

Wales Critical Care and Trauma Network

United Kingdom Critical Care Nursing Alliance (UKCCNA)

United Kingdom Health Security Agency - AMR Programme Team (UKHSA)

Supporting statements

Defence Medical Services: The Defence Medical Services does not endorse guidance or statements produced by civilian organisations, but currently holds broadly similar views to those expressed in this position statement.

The National Institute of Health and Care Research National Specialty Group in Critical Care welcomes the Academy of Medical Royal Colleges' Working Party Position Statement on the Initial Antimicrobial Treatment of Sepsis. Crucially, the Statement helps identify key evidence underpinning clinical uncertainty, associated evidence gaps and the need to progress further primary research at scale across the NHS.

Acknowledgements

We are grateful to the following individuals for their support of the working group, and help in preparing this report for publication,

James Goodwin, Associate Director, Faculty of Intensive Care Medicine

Anna Ripley, Faculty of Intensive Care Medicine Secretariat

Nicola Wood, Faculty of Intensive Care Medicine Secretariat

Claire Price, PA to Professor Bion, University of Birmingham

Alastair Henderson, Chief Executive, Academy of Medical Royal Colleges

Suggested citation

Bion J, Barton G, Boyle A, Carlson G, Carrol E, Christian W, Crossland S, Faust S, Gabbay F, Gent N, Gibbs P, Harden J, Howard P, Inada-Kim M, Lanzman M, Leanord A, Lees N, Noursadeghi M, Rajesh P, Shrestha S, Sriskandan S, Stockley S, Waldmann C, Walsh T, Wilson P, Singer M. Academy of Medical Royal Colleges Statement on the Initial Antimicrobial Treatment of Sepsis. Academy of Medical Royal Colleges 2022.

Academy of Medical Royal Colleges
10 Dallington Street
London
EC1V 0DB
United Kingdom

Website: aomrc.org.uk
Registered Charity Number: 1056565