Toolkit: General Practice management of Sepsis

This clinical toolkit has been developed in partnership with the Royal College of General Practitioners. It is designed to provide operational solutions to the complexities challenging the reliable identification and management of sepsis in the primary care setting, and complements clinical toolkits designed for other clinical areas*.

*We acknowledge use of some content from the Acute Medicine Toolkit developed by the UK Sepsis Trust & Royal College of Physicians

Sepsis is a medical emergency. It is responsible for 37,000 deaths annually in the United Kingdom and severe sepsis has a five fold higher mortality than STEMI or stroke. The reliable recognition of sepsis is the responsibility of all health professionals. The campaign in secondary care has increased awareness and helped to structure the management of sepsis once the patient reaches hospital. However, it is essential that sepsis is recognized early for the patient to reach hospital soon enough to avoid serious complication or death. This document provides primary care clinicians with a toolkit for managing at risk of sepsis. It is part of a wider campaign to increase patient awareness of the signs of sepsis and to assist other pre-hospital services in the task of early recognition.

There are significant challenges and barriers to reliable sepsis identification in a Primary Care setting. Sepsis is a complex condition and its presentation variable. General Practitioners will be experienced in assessing need for hospital assessment in patients with probable self-limiting infection: it is not practicable to expect differentiation between uncomplicated viral and bacterial illness in all cases. Patients who are obviously critically ill are likely to be identified without the need for new efforts. However, there are some patients with severe sepsis with less immediately obvious signs of critical illness. Some of this group might be identified earlier with greater awareness and targeted clinical assessment.

This toolkit aims to make GPs and other primary care clinicians familiar with the significant morbidity and mortality associated with severe sepsis and to structure their knowledge and skills so that they can recognize the condition earlier. It advises on specific safety netting in patients presenting with signs and symptoms of infection and addresses the need to work collaboratively with health professionals in other clinical areas to ensure that appropriate further assessment is undertaken and time-critical care is delivered rapidly when necessary.

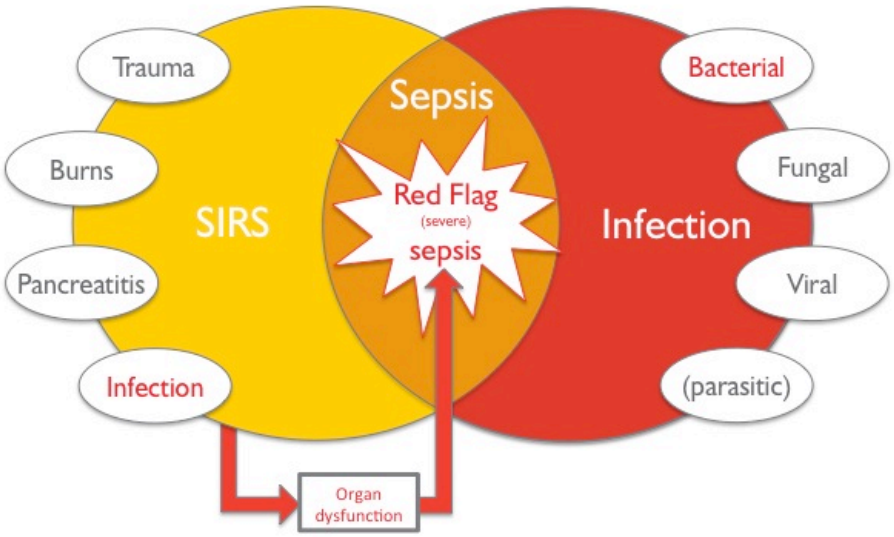
This toolkit is compatible with international guidelines on sepsis management, with the Department of Health's document 'Start Smart- then Focus', and with guidance on infection management in primary care issued by the Health Protection Agency.

Background:

Sepsis is defined as the body's response to an infection. Consensus definitions[1] describe the response as the Systemic Inflammatory Response Syndrome ('SIRS', Box 1). SIRS is not specific to sepsis: it can be caused by non-infective conditions such as pancreatitits, trauma and burns. When SIRS is felt to arise in response to a new infection, this is sepsis. Due to the lack of specificity of SIRS, few data are available on the prevalence of sepsis prior to its progression to severe sepsis.

Severe sepsis occurs when sepsis gives rise to organ dysfunction. Criteria for the identification of severe sepsis are given below in Box 2, however these are focused on a hospital setting and demand full laboratory services with rapid delivery of results. These criteria are less appropriate to those charged with identifying acute illness in the community. In order to address this gap, the UK Sepsis Trust has developed the novel concept of 'Red Flag Sepsis'. Using abnormal physiology rather than waiting for lab results, Red Flag Sepsis is described in detail below. From an operational perspective in Primary Care, this should be considered synonymous with severe sepsis.

Figure 1: Relationship between SIRS, Infection, Sepsis and Red Flag Sepsis



SIRS can be caused by multiple triggers
SIRS due to infection = Sepsis
Sepsis + organ dysfunction = Red Flag Sepsis (severe sepsis once tests confirm in hospital)
Septic shock is a subset of severe sepsis

The overall mortality rate for patients admitted with severe sepsis is 35%- approximately 5 times higher than for ST elevation myocardial infarction and stroke- and is responsible for approximately 37,000 deaths and 100,000 hospital admissions in the United Kingdom (UK) per year[2]. The majority of episodes arise from community-acquired, rather than healthcare-associated, infection. Though evidence is

focused on the hospital setting, data from patients presenting to Emergency Departments (EDs) indicates that severe sepsis is prevalent in the community.

In the United States, the number of patients transported to hospital by Emergency Medical Services with severe sepsis now outnumbers those with heart attack or stroke[3]. In 2007 in the UK, severe sepsis was found to account for 12% of early inpatient deaths after ED admission: this is likely to have been an underestimate due to a further 26% of deaths coded as of respiratory cause[4]. Hospitalizations for the condition have more than doubled over the last 10 years[5,6].

Severe sepsis is a time-critical condition. In the most severe cases, septic shock, for every hour that appropriate antibiotic administration is delayed, there is an 8% increase in mortality[7]. The Sepsis Six is an initial resuscitation bundle designed to offer basic intervention within the first hour. In a prospective observational study across a district general hospital, it was independently associated with survival suggesting that, if it alone were responsible for outcome differences, the number needed to treat (NNT) to prevent one death is 4.6[8]. This compares to an NNT of 42 for Aspirin in major heart attack and 45-90 for PCI in ST elevation myocardial infarction.

Sepsis is poorly recognized and treated. A 24-month, large scale prospective improvement programme across 30 countries measuring the delivery of the Severe Sepsis Resuscitation Bundle showed compliance rising from 10 to just 21% in self-selected centres[9]. More recently in 2013 in the UK, the College of Emergency Medicine (CEM) audited performance against self-imposed standards for the management of severe sepsis and septic shock and identified similarly concerning results, with antibiotics administered in only 33% of patients within the first hour from time of arrival in the ED[10]. Developing a whole-system solution akin to that for chest pain and stroke is likely to raise the profile of the patient with sepsis, encourage hospitals to respond robustly, and significantly reduce variation and time to therapy.

Fixing our healthcare system's response to sepsis will not be easy. To do so will demand that all health professionals involved in the patient's journey are working to the same end. This clinical toolkit will complement those for other community-based healthcare settings, including for residential care facilities, NHS Pathways and 111, and ambulance services.

Professional responsibility & accountability

NHS England has established sepsis as a future indicator in both Domains 1 and 5 of the National Outcomes Framework, and issued a 'stage 2 alert' on sepsis in September 2014. This communication to all NHS Chief Executives and Regional Medical Directors established sepsis as a clinical priority for the NHS. It signposted to clinical toolkits such as this one, to education programmes, examples of good practice, and other available resources. NHS England is working with the UK Sepsis Trust and professional body stakeholders to identify and accredit exemplar acute centres, ambulance services and primary care facilities from which others can learn.

In her report of September 2013 entitled 'A Time to Act', the Parliamentary and Health Service Ombudsman called upon the NHS and the Department of Health to act rapidly to reduce unnecessary deaths from sepsis. As a direct result of this work, NICE will produce a clinical guideline and Quality Standard against sepsis.

We will learn valuable lessons from the report arising from the recent survey on sepsis conducted by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD). Though retrospective and narrative, this report will analyse how many patients arriving in hospital with sepsis had previously consulted their General Practitioner, and the outcome of consultation. Until that time, it is the responsibility of those commissioning services from, designing clinical systems for, and working within primary care that their efforts focus on early recognition including through the use of safety netting, and urgent intervention using existing consensus guidelines from the UK Sepsis Trust and Surviving Sepsis Campaign in areas where transit times may be prolonged.

Delivering Excellent Sepsis Care:

International consensus definitions require adaptation for use outside acute hospitals

The following section describes international consensus definitions in the recognition of sepsis. They are included for completeness' sake, but are in the main not relevant in the Primary Care setting: the definitions have a hospital focus.

Sepsis arises when the body's response to infection causes systemic effects that manifest as two or more of the Systemic Inflammatory Response Syndrome (SIRS) criteria (Box 1) triggered by a new infection[1]. Some patients will develop end-organ dysfunction, denoting severe sepsis. Criteria for the identification of severe sepsis (other than septic shock) are not relevant in the absence of full laboratory services, so are omitted here but can be reviewed in the consensus definitions paper[1] or in hospital-focused toolkits. For Primary Care, the novel concept of Red Flag Sepsis (see below) will be used as an operational solution- it should be considered synonymous with severe sepsis.

Septic shock is a subset of severe sepsis, which strictly speaking (according to international consensus definition) is identified by sepsis with hypoperfusion resistant to fluid therapy (Box 2). The General Practitioner should assume septic shock is present in any patient with a clinical suspicion of infection, the presence of SIRS, and either hypotension or (if available) an elevated serum lactate above 4 mmol/l.

Items in black font are available in all, or most, Primary Care settings. Criteria in orange font (white blood cell count, lactate) are worthy of evaluation for point-of-care testing to increase reliability of recognition of sepsis.

Box 1: Systemic Inflammatory Response Syndrome (SIRS):

SIRS is present if there are at least 2 of:

Temperature >38.3 or $<36.0^0$C	New confusion/drowsiness
Pulse >90/min	WBC >12 or $<4.0 \times 10^9$/L
RR >20/min	Blood glucose >7.7 mmol/L (not if diabetic)

Box 2 : Defining the severity of sepsis

Severity	Definition	Group mortality
Uncomplicated sepsis	SIRS + presumed or confirmed infection	10%
Severe sepsis	Sepsis + one or more organ dysfunction criteria (other than shock)	35%
Septic shock	Sepsis + shock*	50%

*Shock criteria:

- Lactate >4mmol/l at any time point
- Hypotension persisting after 30ml/kg intravenous fluid, defined as Systolic Blood Pressure <90mmHg, Mean Blood Pressure <65mmHg, or a fall of >40mmHg from the patient's usual Systolic Blood Pressure

Describing the solutions – how can we be good at managing sepsis?

1) Early Recognition:

In Primary Care, the lack of laboratory services or point of care tests limit our ability to distinguish between sepsis, severe sepsis and septic shock (according to international definitions) in many cases. Conscious of the challenges this presents in operationalizing care pathways outside hospitals, the UK Sepsis Trust has developed the concept of 'Red Flag Sepsis', based upon criteria within the National Early Warning Score (NEWS).

Sepsis is identified through the presence of SIRS (Box 1) in the context of a clinical suspicion of infection. Pathogens triggering sepsis are almost exclusively bacteria, and the list of causative infections- in decreasing order of frequency, respiratory, abdominal urinary and skin and soft tissues- reflects this.

In high-risk patients, fungi may trigger sepsis, and there are features of certain viral infections (e.g. H1N1, Ebola) that can mimic sepsis. A full description is outside the scope of this document, but General Practitioners and others working in Primary Care should be wary of these potential confounders particularly during a pandemic.

A high degree of vigilance is required for early identification of the septic patient. In the primary care setting, where perceived infection is one of the most common reasons for presentation, the clinical acumen of the General Practitioner is essential in determining which patients to evaluate for sepsis.

Box 3: Suggested clinical indications for undertaking evaluation for sepsis

Undertake clinical evaluation for sepsis in patients:

- with clinical evidence of systemic infection (such as recent history of fever)
- in whom you are considering antibiotic prescription or stewardship discussion
- you suspect to have "flu"
- you suspect to have gastroenteritis
- who are obviously unwell without clear cause
- who are elderly or immunosuppressed and present with signs of infection
- who have deteriorated on antibiotic therapy

As well as the general impression at the time of initial assessment, the presence of abnormal observations should be enough to initiate evaluation for sepsis. Some GPs are now evaluating the use of Early Warning Scores (such as NEWS, see UKST appendix 3- NEWS) and must decide the lowest score that will trigger evaluation for sepsis. As yet unpublished data suggests that 94% of patients who were later found

to have severe sepsis or septic shock presented to Emergency Departments with a NEWS score of 3 or higher.

The use of a two-part screening process to determine severity

Sepsis screening should be done as a two-part process; screening for SIRS followed by, where sepsis is identified, screening for Red Flag Sepsis (Box 4). NHS England and the UK Sepsis Trust recommend that patients with Red Flag Sepsis be transferred immediately for hospital assessment.

Box 4. SIRS screening and evaluation for Red Flag Sepsis

a. *Screening for SIRS*

SIRS is confirmed if ANY TWO of the following are present:

Immediate

- New onset of Confusion or Altered Mental State
- Temperature >38.3 or <36 degrees Celsius
- Heart Rate >90 beats per minute*
- Respiratory Rate (counted over 60 seconds) >20 breaths per minute§

POCT (commonly available)

- Blood Glucose >7.7mmol/L in the absence of known diabetes

POCT (not yet widely available)

- WCC >12 or <4 x10^9/L

b. Evaluation for Red Flag Sepsis

Act immediately if ANY ONE of the following are present:

- Systolic BP <90mmHg (or >40mmHg fall from baseline)*
- Heart rate >130 per minute
- Oxygen saturations <91% §
- Respiratory rate >25 per minute §
- Responds only to voice or pain/ unresponsive

POCT (not yet widely available)

- Lactate >2.0mmol/

* Values are guides. Interpret observations in the context of the normal physiology for the patient. For example, in a young man who runs 3 times a week and has a baseline pulse of 56 a heart rate of 90 is very significantly raised, whereas it might be relatively normal for an older patient with mitral regurgitation. Similarly for an older person, a BP of 106/60 is likely to be lot lower than their baseline BP, whereas for an athlete a systolic of <90 may be perfectly normal.

§ Some patients with chronic pulmonary disease may display low oxygen saturations and elevated respiratory rates 'normally'. Consider whether values are abnormal for the individual patient

Sepsis screening should therefore commence with basic observations to include measurement of heart rate, respiratory rate, blood pressure, temperature and conscious level.

Where resources permit, the measurement of oxygen saturations using a pulse oximeter should be performed in addition to basic physiological assessment. General Practitioners should evaluate whether there is utility in providing point of care testing for lactate and white blood cell count. These systems are now robust, and may assist in recognition of sepsis and Red Flag Sepsis and in transfer decision planning. Normal results are likely to reassure and reinforce decisions to manage in the community, and abnormal results may identify deterioration before the clinical picture becomes evident. This approach will be of particular relevance in remote locations where transit times to hospital can be prolonged.

The use of Point of Care Testing (POCT)

White blood cell count forms part of consensus definitions for SIRS, and differential white cell count can help distinguish between infection of viral or bacterial origin, and non-infective causes of inflammation. POCT devices using optical technology, which require minimal or no maintenance, are now available. Studies are needed to help evaluate the clinical utility of these devices in primary care in decision-making regarding hospital assessment and antimicrobial prescription.

The lactate level in sepsis is highly predictive of death[11] (see Box 5) and poor outcomes and, when initially elevated, the degree of reduction following resuscitation ('lactate clearance') predicts survival[12]. A significant proportion of patients with sepsis who have normal blood pressure have elevated serum lactate and outcomes for these patients with 'cryptic shock' are as poor as for those with overt septic shock[13]. Commercial POCT devices, as used by athletes in performance training, are readily available and have been validated against benchtop assays.

Box 5: The relationship of lactate level in sepsis to mortality

Lactate	Mortality
<2	15%
2-4	25%
>4	38%

From: Trzeciak S, Dellinger RP, Chansky ME, Arnold RC, Schorr C, Milcarek B, *et al. Intensive Care Med* 2007, 33(6):9

2. Urgent Action

The key immediate interventions that increase survival are described in a bundle termed the **Sepsis Six** (Box 6). This bundle has been shown to be associated with significant mortality reductions when applied within the first hour[8].

Box 6: The Sepsis Six (Source: http://sepsistrust.org)

1. Administer high-flow oxygen
2. Take blood cultures and consider infective source
3. Administer intravenous antibiotics
4. Give intravenous fluid resuscitation
5. Check haemoglobin and serial lactates
6. Commence hourly urine output measurement

While few General Practitioners will have the resources to provide much of this bundle of care, it is included to illustrate the time-critical nature of Red Flag Sepsis and the need for collaborative care pathways.

Action for patients with Red Flag Sepsis

For patients identified with Red Flag Sepsis, immediate arrangement should be made for urgent transfer for hospital assessment. This should be by 'blue light' ambulance with a Paramedic crew. A brief, clear handover should accompany the patient to include observations, any relevant medical history and antibiotic history including allergies.

Where resources permit, General Practitioners should initiate high flow oxygen therapy. Patients with sepsis are exempt from British Thoracic Society guidelines for the administration of oxygen to acutely ill adults as the pathophysiology of sepsis is such that organs become critically hypoxic. Hypoxia will kill before hypercapnia. Current theory suggests that hypercapnia occurring in response to oxygen therapy in patients with pulmonary disease is due not to the unproven theory of a loss of 'hypoxic drive' but to changes in ventilation-perfusion matching. Oxygen will not cause sudden apnoea in such patients. Therefore where patients are known to have moderate to severe pulmonary disease (and where available), we recommend that oxygen be administered to maintain target oxygen saturations above 92%.

Particularly in remote areas, consideration should be given to the delivery of other elements of the Sepsis Six.

Once a patient arrives in hospital, the All Party Parliamentary Group (APPG) on sepsis has made a recommendation that organizations should give 'consideration to the development of Sepsis Teams'[14]. Comparisons with heart attack and stroke,

where teams are available to be mobilized when prehospital services or Primary Care pre-alert a suspected case, would make this seem obvious.

It is vital that patients with severe sepsis should be reviewed at the earliest opportunity by the most senior available doctor. This should include in Primary Care- if a doctor in training identifies Red Flag Sepsis, a senior doctor should review the findings immediately or as soon as practicable.

Many patients with sepsis will have multiple co-morbidities, and may be elderly or frail. For such patients, decisions should be taken at senior level (in consultation with the patient and their family as appropriate) regarding the appropriateness of escalation of care to hospital.

Action for patients with sepsis without signs of Red Flag Sepsis

Where no 'Red Flag' signs are identified, clinical judgment will determine appropriate action.

Patients with as yet uncomplicated sepsis can deteriorate rapidly. Fit adults and young people can compensate physiologically in the early stages of sepsis with minimal changes in their observations, right up to the point where shock ensues, and careful consideration should be taken as to the need for a request for hospital assessment. Those over 80, patients on chemotherapy or immunotherapy or those unwell despite antibiotic treatment are all high risk groups. If the patient is not to be referred for hospital assessment, there must be adequate safety netting. One example of a safety-netting tool is in the UK Sepsis Trust's 'Symptom Checker Cards' produced in collaboration with a survivor group. Any safety netting advice given should be clearly documented in the patient's notes, together with observations and antimicrobial therapy offered. It is good practice to agree a planned next day review assessment in any patient with sepsis (SIRS, no Red Flag) managed in the community, together with an invitation for open self-referral should the patient deteriorate or be concerned.

Suggested clinical guidelines for the management of patients attending with sepsis in Primary Care

Sepsis (no Red Flag signs):

- A documented decision whether to manage patient in the community or refer to hospital
- Discussion with a senior doctor (where initial assessment has been by trainee) within 30 minutes of diagnosis
- A full set of observations including heart rate, respiratory rate, blood pressure, temperature, conscious level recorded and documented
- If to be treated in the community, safety netting advice offered and documented
- If to be treated in the community, arrangements to be made for review within 24 hours
- If to be referred for hospital assessment, handover including relevant clinical history and antibiotic history including allergies to be provided

'Red Flag' sepsis pending confirmatory tests:

- Immediate discussion with a senior doctor (where initial assessment has been by trainee)
- Immediate request for 999 Ambulance with Paramedic crew
- Handover including relevant clinical history and antibiotic history including allergies to be provided
- Where resources available, administer oxygen therapy
- Where transfer times may be prolonged, consider need for intravenous antibiotics and fluid therapy if available

Exemplar Standards for Primary Care management of Sepsis

The standards below are those which have been identified by the UK Sepsis Trust and the APPG for sepsis as important in the management of sepsis with specific relevance to Primary Care. They are the 'Exemplar Standards' which organizations should aspire to deliver. Achieving these standards will place a Primary Care organization well on the road to the provision of excellent sepsis care.

1. Clear written guidance, policies and clinical pathways to be in place for the recognition and management of sepsis and Red Flag Sepsis.
2. Clear written criteria for which patients should be screened for sepsis.
3. According to local criteria for screening, 100% of patients satisfying criteria to have, as a minimum, heart rate, respiratory rate, blood pressure, conscious level, oxygen saturations and blood glucose measured and recorded (unless precluded by equipment failure)
4. Risk assessment to be undertaken and maintained regarding the need for Point of Care Testing for lactate and white blood cell count
5. 100% of patients identified with Red Flag Sepsis to be transported for hospital assessment unless limitations of treatment agreed
6. Clear written and verbal handovers to accompany all patients referred for hospital assessment
7. Oxygen therapy to be available and considered for all patients with Red Flag Sepsis
8. Where transit times to hospital are routinely in excess of 60 minutes, risk assessment to be undertaken and maintained regarding the need for administration of antibiotics and intravenous fluids
9. Documented decision to treat in the community or transfer to hospital in 100% of patients with sepsis without Red Flag signs
10. Where patients with sepsis without Red Flag signs are to be managed in the community, documented safety netting advice and review plans to be in place for all patients.

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