



TITLE: Recognition and Diagnosis of Sepsis in Adults: A Review of Evidence-Based Guidelines

DATE: 13 January 2017

CONTEXT AND POLICY ISSUES

Sepsis is a condition resulting from the body's response to severe infection and is a growing health concern in Canada.¹ In Canada, more than 30,000 are hospitalized due to sepsis and related complications. Moreover, sepsis has a mortality rate of 30% and kills more than 9,000 people each year.² Despite the significant risk of morbidity and mortality, adequate initial therapy is initiated in septic patients in fewer than 58% of cases.² Sepsis represents a significant burden on health system resources; including an average of nine additional days in hospital compared to patients without sepsis.³ Moreover, literature suggests that simple interventions administered early in an emergency department visit can significantly impact sepsis mortality rates.⁴ Early diagnosis and effective treatment of sepsis is an important priority for policy especially in rural and remote settings wherein limitations to access care, lack of resources and low physician to population ratio are significant barriers.¹ A standardized set of guidelines for management and detection of sepsis in adults would be a significant progression in decreasing the burden of sepsis on population health.⁴

This Rapid Response report aims to review the guidelines or evidence-based recommendations for diagnostic technologies or procedures to address the recognition and detection of sepsis in adults with suspected sepsis. These guidelines associated with the use of tests and processes used for sepsis diagnosis and assessment may help inform the development of practice guidelines and practice tools in remote and rural settings.

RESEARCH QUESTION

What are the evidence-based guidelines regarding the use of tests or procedures for the recognition and diagnosis of sepsis in adults with suspected sepsis?

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that the Canadian Agency for Drugs and Technologies in Health (CADTH) could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

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KEY FINDINGS

Six evidence-based guidelines were identified for diagnostic tests or processes for the recognition and detection of sepsis in adult populations. Three of these guidelines explored the recognition and detection of sepsis in broader populations, while three others focused on sepsis in cancer patients, sepsis in pregnancy and sepsis following pregnancy.

Overall, areas of agreement across the guidelines included a variety of tests for the detecting sepsis, such as: temperature, heart rate, respiratory rate, blood pressure, level of consciousness, oxygen saturation, blood cultures; urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection; lactate; urea; electrolytes; C-reactive protein; full blood count; kidney and liver function tests (including albumin). Finally, the guidelines consistently noted that imaging studies be complete to confirm a potential source of infection, with the exception of the NICE guideline for Neutropenic Sepsis in Cancer Patients, which stated “Do not perform a chest X-ray unless clinically indicated”.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systemic reviews, meta-analyses, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and December 8, 2016.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

| Population | Adults with suspected sepsis |
|---------------|---|
| Intervention | Diagnostic tests or processes for the recognition and detection of sepsis (e.g., blood culture, urine culture, CBC, inflammatory markers, imaging technology) |
| Comparator | Not Applicable |
| Outcomes | Evidence-based guidelines (e.g., which tests or processes should be used to detect or diagnose sepsis) |
| Study Designs | Evidence-based guidelines |

Exclusion Criteria

Evidence based-guidelines were selected if a literature review was conducted to inform guideline committee recommendations. Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published prior to 2011.

Critical Appraisal of Individual Studies

The included guidelines were assessed using the AGREE II instrument. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 379 peer-reviewed citations and 59 grey literature citations. Twelve potentially relevant guidelines were selected for full-text review. Of these, six guidelines were included.²⁻⁷ The PRISMA flowchart in Appendix 1 details the process of study selection.

Additional references of potential interest are provided in the Appendix 5.

Summary of Study Characteristics

Six guidelines were included in this review:

- NICE guideline: Sepsis: recognition, diagnosis and early management. (2016)⁴
- Dellinger RP et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock. (2013)⁵
- NICE Guideline: Neutropenic sepsis: Prevention and management of neutropenic sepsis in cancer patients. (2012)³
- Royal College of Obstetricians and Gynaecologists: Bacterial sepsis following pregnancy. (2012)⁶
- Royal College of Obstetricians and Gynaecologists: Bacterial Sepsis in pregnancy. Guideline. (2012)⁷
- BC Sepsis Network: Sepsis guide improving care for sepsis. A 'getting started kit' for sepsis improvement in emergency departments. (2012)²

One of the six guidelines identified was Canadian, from the BC Sepsis Network, which provided guidelines for sepsis care improvement in the emergency department setting.² The other guidelines included two from the National Institute for Health and Clinical Excellence (NICE; UK),^{3,4} two from the Royal College of Obstetricians and Gynaecologists (RCOG; UK),^{6,7} and an international guideline from the Surviving Sepsis Campaign Guidelines Committee.⁵

Three guidelines addressed the diagnosis of sepsis in adult populations in acute care and emergency department settings,^{2,4,5} while three guidelines considered specialized health populations including pregnancy,⁷ post-pregnancy,⁶ and neutropenic cancer.³

A summary of guideline characteristics is provided in Appendix 2.

Summary of Critical Appraisal

Overall, the guidelines included in the review were well conducted. All included guidelines were based on a review of the literature and included external review processes. The National Institute for Health and Care Excellence (NICE),^{3,4} Royal College of Obstetricians and Gynaecologists (RCOG)^{6,7} and the Surviving Sepsis Campaign⁵ clearly state their processes for guideline development and recommendations. The BC Sepsis Network² noted a literature review was conducted separately to the guideline report¹ but lacked clarity in methodological details which limited quality appraisal.

All the included guidelines utilized a collaborative process including guideline committees and key stakeholders. Apart from the NICE guidelines, other guidelines provided minimal advice on implementation of guideline recommendations. All but one guideline² provided information on guideline updating.

A summary of the critical appraisal for the included guidelines is provided in Appendix 3.

Summary of Findings

Overall, the recommendations for the management and treatment of suspected sepsis in acute care settings were consistent across the included guidelines. Many of the guidelines also noted that clinicians and staff should be well-versed in the clinical signs of sepsis, and highlighted the importance of stratifying risk for patients with suspected sepsis. Early identification of sepsis was recommended to be detected through a variety of assessments, including:

- temperature, heart rate, respiratory rate, blood pressure, level of consciousness, oxygen saturation
- blood cultures,
- lactate
- urea,
- electrolytes
- C-reactive protein,
- full blood count,
- kidney and liver function tests (including albumin),
- urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection
- imaging studies be complete to confirm a potential source of infection (the NICE guideline for Neutropenic Sepsis in Cancer Patients states “Do not perform a chest X-ray unless clinically indicated”)

The NICE guideline (2016) provided a comprehensive list of recommendations.⁴ The first set of recommendations focused on identifying people with suspected sepsis, through presentation of

signs or symptoms that indicate possible infection, concerns expressed by the patient or carers, as well as identifying factors that may increase the risk of sepsis and utilizing a structured set of observations to assess the patient in a face-to-face setting to stratify risk. NICE highlighted the following elements for face-to-face assessment of patients with suspected sepsis.

- “Assess temperature, heart rate, respiratory rate, blood pressure, level of consciousness and oxygen saturation in young people and adults with suspected sepsis.” (p.8)
- “Measure oxygen saturation in community settings if equipment is available and taking a measurement does not cause a delay in assessment or treatment.” (p. 9)
- “Examine people with suspected sepsis for mottled or ashen appearance, cyanosis of the skins, lips or tongue, non-blanching rash of the skin, any breach of skin integrity (for example, cuts, burns or skin infections) or other rash indicating potential infection.” (p. 9)
- “Ask the person, parent or carer about frequency of urination in the past 18 hours.” (p. 9)⁴

The international guidelines for management of severe sepsis and septic shock (2012)⁵ “recommend routine screening of potentially infected seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy.” (Recommendation grade 1C; p. 590) For diagnosis, the committee highlighted obtaining cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay (> 45 minutes), which include at least two sets of blood cultures, as well as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection. (Grade 1C). Additionally, the committee recommended imaging studies be complete to confirm a potential source of infection.⁵

The BC Sepsis Network² noted that in patients with 2 of the 4 signs of Systemic Inflammatory Response Syndrome (Heart Rate >90, Respiratory Rate >20, temperature ≥ 38 °C or < 36 °C, altered level of consciousness) and a suspected infection, as well as one of the following risk factors (looks unwell, age > 65, recent surgery, immuno-compromised, or chronic illness):

- “Lactate measurement within 30 minutes of presentation to triage should be taken with initial blood draw and this will require access to a machine with rapid turn-around time (results to clinician within 30 minutes)” (p. 3)
- If initial lactate is elevated, have a repeat venous lactate measurement drawn in next 2-4 hours”(p. 3)²

In the NICE guideline for the *Prevention and Management of Neutropenic Sepsis in Cancer Patients*,³ the following assessments were noted for clinical management and risk stratification once a patient has been referred to secondary/tertiary care: history and examination, as well as “full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate and blood culture”. (p. 9) The guideline recommendations noted that once the initial clinical assessment had been completed further assessments include: “additional peripheral blood culture in patients with a central venous access device if clinically feasible” (p. 9).³

The RCOG guidelines provided recommendations for bacterial sepsis during and following pregnancy. The guidelines highlighted clinical signs which should prompt recognition of sepsis in the puerperium, including one or more of the following: pyrexia, hypothermia, tachycardia, tachypnoea, hypoxia, hypotension, oliguria, impaired consciousness and failure to respond to treatment.^{6,7} In both populations, the guidelines recommended the following investigations when

sepsis is suspected: blood cultures (should be obtained prior to antibiotic administration; however, antibiotic treatment should be started without waiting for microbiology results); serum lactate (measured within six hours of the suspicion of severe sepsis), and in order to identify/confirm the source of the infection, relevant imaging studies should be performed.^{6,7} Following pregnancy, the guideline noted several investigations which should be performed, including:

- “Other samples taken should be guided by the clinical suspicion of focus of infection as appropriate.” (p. 8)
- “Routine blood tests should include full blood count, urea, electrolytes and C-reactive protein (CRP).” (p. 8)
- “Any woman with symptoms of tonsillitis/pharyngitis should have a throat swab sent for culture.” (p. 8)
- “If the MRSA status of the woman is unknown, a premoistened nose swab may be sent for rapid MRSA screening where such testing is available.” (p. 8)⁶

The recommendations and grading from the included guidelines are provided in Appendix 4.

Limitations

The main limitation among the included guidelines is generalizability. The NICE 2016 Sepsis guidelines⁴ were the only guidelines to address all populations; whereas the remaining guidelines looked at specific sub-populations or settings. In addition, only one Canadian guideline from the BC Sepsis Network was identified and these recommendations were specific to emergency department settings.

The Canadian guideline² did not provide grading for the strength of the recommendations. Because recommendations were not graded and minimal methodological details were reported for the guideline development process, it is unclear which guidelines are based on literature and which are based on expert opinion only. For the remaining guidelines, broadly speaking, many of the recommendations were given lower grades based on the quality of evidence, or were based on expert opinion. As noted in the international guideline “further programmatic clinical research in sepsis is essential to optimize these evidence-based medicine recommendations.” (p. 619).

None of the included guidelines were specific to the recognition and diagnosis of sepsis in remote or rural populations. However, the NICE guideline⁴ development group (GDG) considered the role of ambulatory service and emergency departments in the care of rural populations, noting that “The GDG agreed that the majority of people in England are within an hour of a hospital. For this reason they did not recommend that ambulance services should be equipped to give antibiotics to people with sepsis. However in more remote areas where there is delay in getting to emergency departments it may be appropriate for local services to plan interventions by paramedics. Ideally blood cultures should be taken before antibiotics are given” (p. 404). As this guideline was produced in the UK, the applicability to Canadian settings is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Six guidelines addressing the recognition and diagnosis of sepsis were included in this report; three of which considered specialized sub-populations including pregnancy, post-pregnancy and neutropenic cancer. Overall the guidelines were consistent in the recommendations for the detection of sepsis highlighting a variety of tests, such as: temperature, heart rate, respiratory rate, blood pressure, level of consciousness, oxygen saturation, blood cultures; urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection; lactate; urea; electrolytes; C-reactive protein; full blood count; kidney and liver function tests.

Future research addressing sepsis diagnosis in rural and remote settings may help to build health equity across all populations impacted by sepsis. Finally, auditing and monitoring processes for guideline recommendations may help ensure recommendations are implemented.

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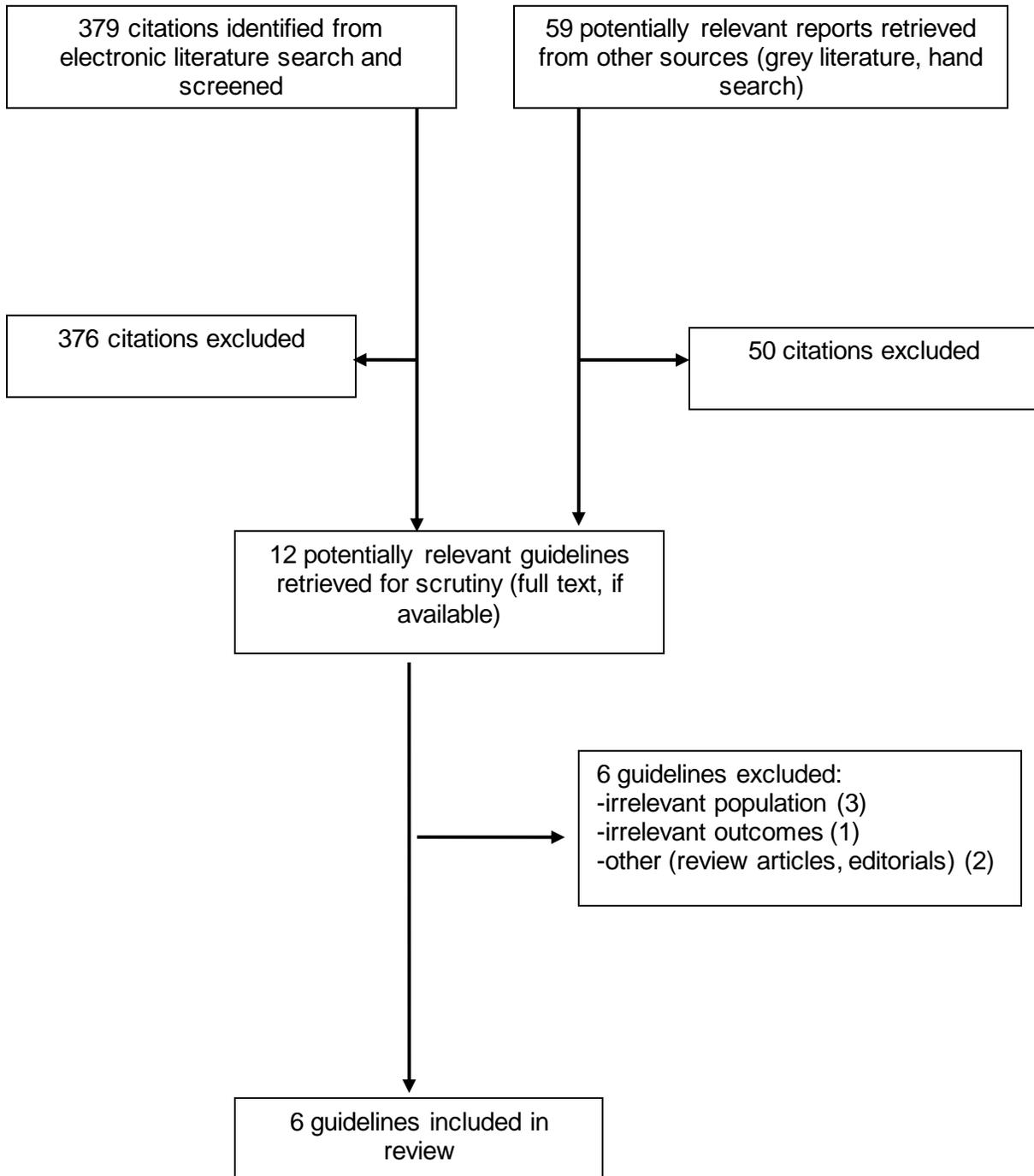
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

| Objectives | | | Methodology | | | |
|--------------------------------------|--|---|--|---|---|----------------------|
| Intended users/ Target population | Intervention and Practice Considered | Major Outcomes Considered | Evidence collection, Selection and Synthesis | Evidence Quality and Strength | Recommendations development and Evaluation | Guideline Validation |
| NICE, 2016⁴ | | | | | | |
| Healthcare professionals, public | This guideline aims to help healthcare professionals and the public recognise when and in whom to suspect sepsis, how to identify the source of infection, parts of clinical risk assessment (e.g. existing scoring tools and blood tests, initial fluid management and the timing of the escalation of care and staff involvement, and early disease monitoring and information/support for patients and their relatives or carers. | Diagnostic parameters considered for this guideline are: - blood gas (arterial, venous or capillary): pH, bicarbonates, base deficit - glucose - lactate - full blood count - biochemical tests - clotting screen - C-reactive protein (CRP) - creatinine - DIC - assessment tools. | Systematic review of literature | Interventional Studies - evaluated and presented using an adaptation of the GRADE toolbox Diagnostic Studies - the QUADAS-2 checklist was used. Prognostic Studies - A modified GRADE methodology was used. Qualitative Studies - the checklist for qualitative studies (Appendix H in the NICE guidelines manual 2014). | Systematic review of literature; quality appraisal, meta-analysis and cost-effectiveness analysis where appropriate, drafted recommendations in collaboration with the Guideline Development Group. | External review |
| Delinger, 2012^o | | | | | | |
| Clinicians | Recommendations were classified into three groups: 1) those directly targeting severe sepsis; 2) those targeting general care of the critically ill patient and considered high priority in severe sepsis; and 3) pediatric considerations. | Not reported. | Systematic review | GRADE Toolbox | Guidelines development groups were responsible for drafting the initial update to the 2008 edition in their assigned area. Procedures for literature review and evidence analysis. A meeting to finalize the draft guideline. | External Review |

Table A1: Characteristics of Included Guidelines

| Objectives | | | Methodology | | | |
|--|---|--|--|--|---|----------------------|
| Intended users/ Target population | Intervention and Practice Considered | Major Outcomes Considered | Evidence collection, Selection and Synthesis | Evidence Quality and Strength | Recommendations development and Evaluation | Guideline Validation |
| | The recommendations in this document are intended to provide guidance for the clinician caring for a patient with severe sepsis or septic shock.. Most of these recommendations are appropriate for the severe sepsis patient in the ICU and non-ICU settings. | | | | | |
| NICE, 2012³ | | | | | | |
| Clinicians; patients and their carers. | <p>To produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients</p> <p>Chapter 2 - The objective of this chapter is to define neutropenic sepsis to identify those patients for whom treatment for bacterial sepsis should be undertaken before any clear diagnosis of infection is established</p> <p>Chapter 4 – Identification and Assessment: The objectives of this chapter are: To identify patients</p> | Sensitivity and Specificity of various tests, including: full blood count, biochemical profile and other blood, urine or imaging investigations; C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and other inflammatory markers; urinalysis, chest x-ray, lactate and blood gases | Systematic review of literature | <p>interventional questions were evaluated and presented using a modification of GRADE Toolbox</p> <p>For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was given</p> | Systematic review of literature; quality appraisal, meta-analysis and cost-effectiveness analysis where appropriate, drafted recommendations in collaboration with the Guideline Development Group. | External review |

Table A1: Characteristics of Included Guidelines

| Objectives | | | Methodology | | | |
|-----------------------------------|--|---------------------------|--|--|---|----------------------|
| Intended users/ Target population | Intervention and Practice Considered | Major Outcomes Considered | Evidence collection, Selection and Synthesis | Evidence Quality and Strength | Recommendations development and Evaluation | Guideline Validation |
| | who require assessment in secondary or tertiary care. To identify best practice in the initial emergency assessment of a patient. To evaluate risk stratification systems. | | | | | |
| RCOG, 2012b⁶ | | | | | | |
| Clinicians | The purpose of this guideline is to provide guidance on the management of sepsis in the puerperium (i.e. sepsis developing after birth until 6 weeks postnatally) | Not Reported. | Systematic review of literature | Classification of evidence levels: 1++ High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias 1+ Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias 1– Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias 2++ High-quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal | Systematic review of literature; quality appraisal, meta-analysis and cost-effectiveness analysis where appropriate, drafted recommendations in collaboration with the Guideline Development Group. Grades of Recommendations: A: At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall | External review |

Table A1: Characteristics of Included Guidelines

| Objectives | | | Methodology | | | |
|--------------------------------------|---|---------------------------|--|--|---|----------------------|
| Intended users/ Target population | Intervention and Practice Considered | Major Outcomes Considered | Evidence collection, Selection and Synthesis | Evidence Quality and Strength | Recommendations development and Evaluation | Guideline Validation |
| | | | | 2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal 2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal 3 Non-analytical studies, e.g. case reports, case series 4 Expert opinion | consistency of results B: A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+ C: A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++ D: Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ | |
| RCOG, 2012a | | | | | | |
| Clinicians | The scope of this guideline covers the recognition and management of serious bacterial illness in the antenatal and intrapartum periods, arising in the genital tract or elsewhere, and its management in secondary care. | Not Reported. | Systematic review of literature | See above. | Systematic review of literature; quality appraisal, meta-analysis and cost-effectiveness analysis where appropriate, drafted recommendations in collaboration with the Guideline Development Group. | External review |

Table A1: Characteristics of Included Guidelines

| Objectives | | | Methodology | | | |
|--|--|---------------------------|--|-------------------------------|--|---|
| Intended users/ Target population | Intervention and Practice Considered | Major Outcomes Considered | Evidence collection, Selection and Synthesis | Evidence Quality and Strength | Recommendations development and Evaluation | Guideline Validation |
| BC Sepsis Network, 2012² | | | | | | |
| Emergency Departments | Managing adult patients presenting to the emergency department with sepsis, severe sepsis and septic shock | Not Reported | Not Reported | Not Reported | The Clinical Care Management initiative included consultations with our local, national and international sepsis partners and BC sepsis expert groups. Provincial guidelines were developed for managing adult patients presenting to the emergency department with sepsis, severe sepsis and septic shock. These recommendations have been recognized by the Canadian Association of Emergency Physicians' Critical Care Committee. | External Review with the Canadian Association of Emergency Physicians |

GRADE, Grading of Recommendations Assessment, Development and Evaluation; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies version 2

APPENDIX 3: Critical Appraisal of Included Publication

| Table A2: Strengths and Limitations of Guidelines using AGREE II^o | |
|---|--|
| Strengths | Limitations |
| NICE, 2016⁴ | |
| <ul style="list-style-type: none"> Detailed scope and purpose Stakeholder involvement Systematic review methodology External review process Guideline update information Clear and actionable recommendations Guideline implementation and auditing Independent Guideline Committee | <ul style="list-style-type: none"> Resource implications not specified |
| Delinger, 2012⁵ | |
| <ul style="list-style-type: none"> Detailed scope and purpose Systematic review methodology External review process Guideline update information Clear and actionable recommendations Independent Guideline Committee | <ul style="list-style-type: none"> Views of target population unclear Process for updating the guidelines unclear Implementation and auditing criteria not specified |
| NICE, 2012³ | |
| <ul style="list-style-type: none"> Detailed scope and purpose Stakeholder involvement Systematic review methodology External review process Guideline update information Clear and actionable recommendations Guideline implementation and auditing Independent Guideline Committee | <ul style="list-style-type: none"> Not applicable to all populations Resource implications not specified |
| RCOG, 2012b⁶ | |
| <ul style="list-style-type: none"> Detailed scope and purpose Stakeholder involvement Systematic review methodology External review process Guideline update information Clear and actionable recommendations Guideline implementation and auditing Independent Guideline Committee | <ul style="list-style-type: none"> Not applicable to all populations Resource implications not specified |
| RCOG, 2012a⁷ | |
| <ul style="list-style-type: none"> Detailed scope and purpose Stakeholder involvement Systematic review methodology External review process Guideline update information Clear and actionable recommendations Guideline implementation and auditing Independent Guideline Committee | <ul style="list-style-type: none"> Not applicable to all populations Resource implications not specified |
| BC Sepsis Network, 2012² | |
| <ul style="list-style-type: none"> Stakeholder involvement External review process Clear and actionable recommendations Guideline implementation and auditing | <ul style="list-style-type: none"> Lack of detailed scope and purpose Views of target population unclear Non-systematic review methodology Process for updating the guidelines unclear |

| Table A2: Strengths and Limitations of Guidelines using AGREE II⁸ | |
|---|---|
| Strengths | Limitations |
| <ul style="list-style-type: none"> Independent Guideline Committee | <ul style="list-style-type: none"> Facilitators and barriers to application not specified Competing interest of guideline committee members are not noted |

APPENDIX 4: Main Study Findings and Author’s Conclusions

Table A3: Summary of Recommendations

| Key Recommendations |
|--|
| NICE, 2016 ⁴ |
| <p>Identifying people with suspected sepsis</p> <p>1.1.1. “Think ‘could this be sepsis?’ if a person presents with signs or symptoms that indicate possible infection.” (page 5)</p> <p>1.1.2. “Take into account that people with sepsis may have non-specific, non-localised presentations, for example feeling very unwell, and may not have a high temperature.” (page 6)</p> <p>1.1.3. “Pay particular attention to concerns expressed by the person and their family or carers, for example changes from usual behaviour.” (page 6)</p> <p>1.1.4. “Assess people who might have sepsis with extra care if they cannot give a good history (for example, people with English as a second language or people with communication problems).” (page 6)</p> <p>1.1.5. “Assess people with any suspected infection to identify:</p> <ul style="list-style-type: none"> • possible source of infection • factors that increase risk of sepsis (see Risk factors for sepsis) • any indications of clinical concern, such as new onset abnormalities of behaviour, circulation or respiration.” (page 6) <p>1.1.6. “Identify factors that increase risk of sepsis (see Risk factors for sepsis) or indications of clinical concern such as new onset abnormalities of behaviour, circulation or respiration when deciding during a remote assessment whether to offer a face-to-face assessment and if so, on the urgency of face-to-face assessment.” (page 6)</p> <p>1.1.7. “Use a structured set of observations (see Face-to-face assessment of people with suspected sepsis) to assess people in a face-to-face setting to stratify risk (see Stratifying risk of severe illness or death from sepsis) if sepsis is suspected.” (page 6)</p> <p>1.1.8. “Consider using an early warning score to assess people with suspected sepsis in acute hospital settings.” (page 6)</p> <p>1.1.9. “Suspect neutropenic sepsis in patients having anticancer treatment who become unwell. [This recommendation is from NICE’s guideline on neutropenic sepsis.]” (page 6)</p> <p>1.1.10. “Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care. [This recommendation is from NICE’s guideline on neutropenic sepsis.]” (page 6)</p> <p>1.1.11. “Treat people with neutropenic sepsis in line with NICE’s guideline on neutropenic sepsis: prevention and management in people with cancer.” (page 7)</p> <p>Risk factors for sepsis</p> <p>1.2.1. “Take into account that people in the groups below are at higher risk of developing sepsis:</p> <ul style="list-style-type: none"> • the very young (under 1 year) and older people (over 75 years) or very frail people • people who have impaired immune systems because of illness or drugs, including: <ul style="list-style-type: none"> – people being treated for cancer with chemotherapy (see recommendation 1) – people who have impaired immune function (for example, people with diabetes, people who have had a splenectomy, or people with sickle cell disease) – people taking long-term steroids – people taking immunosuppressant drugs to treat non-malignant disorders such as rheumatoid arthritis • people who have had surgery, or other invasive procedures, in the past 6 weeks • people with any breach of skin integrity (for example, cuts, burns, blisters or skin infections) • people who misuse drugs intravenously • people with indwelling lines or catheters.” (page 7) <p>1.2.2. “Take into account that women who are pregnant, have given birth or had a termination of pregnancy or miscarriage in the past 6 weeks are in a high risk group for sepsis. In particular, women who:</p> <ul style="list-style-type: none"> • have impaired immune systems because of illness or drugs (see recommendation 5) |

Table A3: Summary of Recommendations

Key Recommendations

- have gestational diabetes or diabetes or other co-morbidities
- needed invasive procedures (for example, caesarean section, forceps delivery, removal of retained products of conception)
- had prolonged rupture of membranes
- have or have been in close contact with people with group A streptococcal infection, for example, scarlet fever
- have continued vaginal bleeding or an offensive vaginal discharge.” (page 7-8)

Face-to-face assessment of people with suspected sepsis

1.3.1. “Assess temperature, heart rate, respiratory rate, blood pressure, level of consciousness and oxygen saturation in young people and adults with suspected sepsis.” (page 8)

1.3.6. “Measure oxygen saturation in community settings if equipment is available and taking a measurement does not cause a delay in assessment or treatment.” (page 9)

1.3.7. “Examine people with suspected sepsis for mottled or ashen appearance, cyanosis of the skins, lips or tongue, non-blanching rash of the skin, any breach of skin integrity (for example, cuts, burns or skin infections) or other rash indicating potential infection.” (page 9)

1.3.8. “Ask the person, parent or carer about frequency of urination in the past 18 hours.” (page 9)

Stratifying risk of severe illness or death from sepsis

1.4.1. “Use the person’s history and physical examination results to grade risk of severe illness or death from sepsis using criteria based on age (see Table 79, Table 80 and Table 81).” (page 9)

Adults and children and young people aged 12 years and over

1.4.2. “Recognise that adults and children and young people aged 12 years and over with suspected sepsis and any of the symptoms or signs below are at high risk of severe illness or death from sepsis:

- objective evidence of new altered mental state
- respiratory rate of 25 breaths per minute or above, or new need for 40% oxygen or more to maintain oxygen saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)
- heart rate of 130 beats per minute or above
- systolic blood pressure of 90 mmHg or less, or systolic blood pressure more than 40 mmHg below normal
- not passed urine in previous 18 hours (for catheterised patients, passed less than 0.5 ml/kg/hour)
- mottled or ashen appearance
- cyanosis of the skin, lips or tongue
- non-blanching rash of the skin.” (page 11)

1.4.3. “Recognise that adults and children and young people aged 12 years and over with suspected sepsis and any of the symptoms or signs below are at moderate to high risk of severe illness or death from sepsis:

- history of new-onset changed behaviour or change in mental state, as reported by the person, a friend or relative
- history of acute deterioration of functional ability
- impaired immune system (illness or drugs, including oral steroids)
- trauma, surgery or invasive procedure in the past 6 weeks
- respiratory rate of 21–24 breaths per minute, heart rate of 91–130 beats per minute or new-onset arrhythmia or if pregnant, heart rate of 100–130 beats per minute
- systolic blood pressure of 91–100 mmHg
- not passed urine in the past 12–18 hours (for catheterised patients, passed 0.5–1 ml/kg/hour)
- tympanic temperature less than 36°C
- signs of potential infection, including increased redness, swelling or discharge at a surgical site, or breakdown of a wound.” (page 11-12)

Table A3: Summary of Recommendations

Key Recommendations

1.4.4. "Consider adults and children and young people aged 12 years and over with suspected sepsis who do not meet any high or moderate to high risk criteria to be at low risk of severe illness or death from sepsis." (page 12)

Children, young people and adults with suspected sepsis**Temperature in suspected sepsis**

1.4.11. "Do not use a person's temperature as the sole predictor of sepsis." (page 20)

1.4.12. "Do not rely on fever or hypothermia to rule sepsis either in or out." (page 20)

1.4.13. "Ask the person with suspected sepsis and their family or carers about any recent fever or rigors." (page 20)

1.4.14. "Take into account that some groups of people with sepsis may not develop a raised temperature. These include:

- people who are older or very frail
- people having treatment for cancer
- people severely ill with sepsis
- young infants or children." (page 20)

1.4.15. "Take into account that a rise in temperature can be a physiological response, for example after surgery or trauma." (page 20)

Heart rate in suspected sepsis

1.4.16. "Interpret the heart rate of a person with suspected sepsis in context, taking into account that:

- baseline heart rate may be lower in young people and adults who are fit
- baseline heart rate in pregnancy is 10-15 beats per minute more than normal
- older people with an infection may not develop an increased heart rate
- older people may develop a new arrhythmia in response to infection rather than an increased heart rate
- heart rate response may be affected by medicines such as beta-blockers." (page 21)

Blood pressure in suspected sepsis

1.4.17. "Interpret blood pressure in the context of a person's previous blood pressure, if known. Be aware that the presence of normal blood pressure does not exclude sepsis in children and young people." (page 21)

Confusion, mental state and cognitive state in suspected sepsis

1.4.18. "Interpret a person's mental state in the context of their normal function and treat changes as being significant." (page 21)

1.4.19. "Be aware that changes in cognitive function may be subtle and assessment should include history from patient and family or carers." (page 21)

1.4.20. "Take into account that changes in cognitive function may present as changes in behaviour or irritability in both children and in adults with dementia." (page 21)

1.4.21. "Take into account that changes in cognitive function in older people may present as acute changes in functional abilities." (page 21)

Oxygen saturation in suspected sepsis

1.4.22. "Take into account that if peripheral oxygen saturation is difficult to measure in a person with suspected sepsis, this may indicate poor peripheral circulation because of shock." (page 21)

Table A3: Summary of Recommendations

| Key Recommendations |
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| Delinger, 2012 ⁵ |
| <p>Screening for Sepsis and Performance Improvement</p> <ol style="list-style-type: none"> 1. "We recommend routine screening of potentially infected seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy (grade 1C)." (page 590) 2. "Performance improvement efforts in severe sepsis should be used to improve patient outcomes (UG)." (page 590) <p>Diagnosis</p> <ol style="list-style-type: none"> 1. "We recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay (> 45 minutes) in the start of antimicrobial(s) administration (grade 1C). To optimize identification of causative organisms, we recommend obtaining at least two sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial therapy, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (< 48 hours) inserted. These blood cultures can be drawn at the same time if they are obtained from different sites. Cultures of other sites (preferably quantitative where appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection, should also be obtained before antimicrobial therapy if doing so does not cause significant delay in antibiotic administration (grade 1C)." (page 590) 2. "We suggest the use of the 1,3 β-d-glucan assay (grade 2B), mannan and anti-mannan antibody assays (grade 2C) when invasive candidiasis is in the differential diagnosis of infection." (page 591) 3. "We recommend that imaging studies be performed promptly in attempts to confirm a potential source of infection. Potential sources of infection should be sampled as they are identified and in consideration of patient risk for transport and invasive procedures (eg, careful coordination and aggressive monitoring if the decision is made to transport for a CT-guided needle aspiration). Bedside studies, such as ultrasound, may avoid patient transport (UG)." (page 591) |
| NICE, 2012 ³ |
| <p>Definition of neutropenia and fever</p> <ul style="list-style-type: none"> • "Diagnose neutropenic sepsis in patients having anticancer treatment whose neutrophil count is 0.5×10^9 per litre or lower and who have either: <ul style="list-style-type: none"> ○ a temperature higher than 38°C or ○ other signs or symptoms consistent with clinically significant sepsis" (page 9) <p>Signs and symptoms that necessitate referral to secondary/tertiary care</p> <ul style="list-style-type: none"> • "Suspect neutropenic sepsis in patients having anticancer treatment who become unwell." (page 9) • "Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care." (page 9) <p>Emergency assessment in secondary/tertiary care</p> <p>Investigation appropriate for clinical management and risk stratification</p> <ul style="list-style-type: none"> • "Include in the initial clinical assessment of patients with suspected neutropenic sepsis: <ul style="list-style-type: none"> ○ history and examination ○ full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate and blood culture (see also recommendations in section 4.2.2)." (page 9) <p>Further assessment</p> <ul style="list-style-type: none"> • "After completing the initial clinical assessment (see recommendations in section 4.2.1), try to identify the underlying cause of the sepsis by carrying out: <ul style="list-style-type: none"> ○ additional peripheral blood culture in patients with a central venous access device if clinically feasible |

Table A3: Summary of Recommendations

| Key Recommendations |
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| <ul style="list-style-type: none"> ○ urinalysis in all children aged under 5 years. • Do not perform a chest X-ray unless clinically indicated” (page 9) <p>Assessing the patient’s risk of septic complications</p> <ul style="list-style-type: none"> • “A healthcare professional with competence in managing complications of anticancer treatment should assess the patient’s risk of septic complications within 24 hours of presentation to secondary or tertiary care, basing the risk assessment on presentation features and using a validated risk scoring system” (page 10) |
| RCOG, 2012b ⁶ |
| <p>What should prompt recognition of sepsis in the puerperium?</p> <ul style="list-style-type: none"> • “All health professionals should be aware of the symptoms and signs of maternal sepsis and critical illness and of the rapid, potentially lethal course of severe sepsis and septic shock. Suspicion of significant sepsis should trigger urgent referral to secondary care.(D)” (page 5) • “Clinical signs suggestive of sepsis include one or more of the following: pyrexia, hypothermia, tachycardia, tachypnoea, hypoxia, hypotension, oliguria, impaired consciousness and failure to respond to treatment. These signs, including pyrexia, may not always be present and are not necessarily related to the severity of sepsis.” (page 5) • “Mastitis must never be overlooked. (✓)” (page 5) • “Abdominal pain, fever (greater than 38°C) and tachycardia (greater than 90 beats/minute in the puerperium) are indications for intravenous antibiotics and senior clinical review. (✓)” (page 5) • “Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided for pain relief in cases of sepsis as they impede the ability of polymorphs to fight GAS infection (✓)” (page 5) <p>What is the optimum way to monitor women with suspected sepsis in the puerperium?</p> <ul style="list-style-type: none"> • “Monitoring of the woman with suspected severe sepsis or established sepsis should be multidisciplinary but preferably under the leadership of a single consultant. A senior obstetrician should be involved, in consultation with an intensivist, microbiologist or infectious disease clinician. (✓)” (Page 6) • “Regular observations of all vital signs (including temperature, pulse rate, blood pressure and respiratory rate) should be recorded on a modified early obstetric warning score (MEOWS) chart. (✓)” (Page 6) <p>What are the appropriate triggers or features of sepsis in the puerperium that should prompt hospital admission?</p> <ul style="list-style-type: none"> • “Community carers should be aware of the importance of early referral to hospital of recently delivered women who feel unwell and have pyrexia, and should be aware of the possibility of sepsis in the puerperium (see Table 2). (✓)” (page 7) • “If sepsis is suspected in the community, urgent referral to hospital is indicated. (✓)” (page 7) <p>What are the appropriate triggers for involvement of other specialties?</p> <ul style="list-style-type: none"> • “All cases of sepsis in the puerperium should be discussed with a clinical microbiologist or infectious diseases physician. Appropriate specimens should be sent for urgent examination. Antimicrobials should be started within 1 hour of recognition of severe sepsis. (✓)” (page 8) • “Women with previously documented carriage of or infection with multiresistant organisms (e.g. ESBL-producing organisms, MRSA, GAS or PVL-producing staphylococci) should prompt notification of the infection control team. (✓)” (page 8) • “Suspicion of necrotising fasciitis should prompt involvement of intensive care physicians and referral for surgical opinion, ideally from plastic and reconstructive surgeons if available. (✓)” (page 8) |

Table A3: Summary of Recommendations

| Key Recommendations |
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| <p>What investigations should be performed?</p> <ul style="list-style-type: none"> • “Blood cultures are the key investigation and should be obtained prior to antibiotic administration; however, antibiotic treatment should be started without waiting for microbiology results. (D)” (page 8) • “Serum lactate should be measured within 6 hours of the suspicion of severe sepsis to guide management. Serum lactate ≥ 4 mmol/l is indicative of tissue hypoperfusion. (D)” (page 8) • “Any relevant imaging studies should be performed promptly in an attempt to confirm the source of infection. This could include a chest X-ray, pelvic ultrasound scan or computed tomography scan if pelvic abscess is suspected. (D)” (page 8) • “Other samples taken should be guided by the clinical suspicion of focus of infection as appropriate. (✓)” (page 8) • “Routine blood tests should include full blood count, urea, electrolytes and C-reactive protein (CRP). (✓)” (page 8) • “Any woman with symptoms of tonsillitis/pharyngitis should have a throat swab sent for culture. (✓)” (page 8) • “If the MRSA status of the woman is unknown, a premoistened nose swab may be sent for rapid MRSA screening where such testing is available. (✓)” (page 8) |
| RCOG, 2012a ⁷ |
| <p>What should prompt recognition of sepsis in the pregnant woman?</p> <ul style="list-style-type: none"> • “All healthcare professionals should be aware of the symptoms and signs of maternal sepsis and critical illness and of the rapid, potentially lethal course of severe sepsis and septic shock. Suspicion of significant sepsis should trigger an urgent referral to secondary care. (D)” (page 3) • “Clinical signs suggestive of sepsis include one or more of the following: pyrexia, hypothermia, tachycardia, tachypnoea, hypoxia, hypotension, oliguria, impaired consciousness and failure to respond to treatment. These signs, including pyrexia, may not always be present and are not necessarily related to the severity of sepsis. (D)” (page 3) • “Regular observations of all vital signs (including temperature, pulse rate, blood pressure and respiratory rate) should be recorded on a Modified Early Obstetric Warning Score (MEOWS) chart. (✓)” (page 3) • “All staff taking observations should have annual training in the use of the MEOWS chart. (✓)” (page 3) <p>What are the appropriate investigations when sepsis is suspected?</p> <ul style="list-style-type: none"> • “Blood cultures are the key investigation and should be obtained prior to antibiotic administration; however, antibiotic treatment should be started without waiting for microbiology results. (D)” (page 4) • “Serum lactate should be measured within six hours of the suspicion of severe sepsis in order to guide management. Serum lactate ≥ 4 mmol/l is indicative of tissue hypoperfusion. (D)” (page 4) • “Any relevant imaging studies should be performed promptly in an attempt to confirm the source of infection (D)” (page 4) <p>Who should be involved in the collaborative care of women with sepsis?</p> <ul style="list-style-type: none"> • “If sepsis is suspected, regular frequent observations should be made. The use of a MEOWS chart is recommended. There should be an urgent referral to the critical care team in severe or rapidly deteriorating cases, and the involvement of a consultant obstetrician. (D)” (page 5) • “The expert advice of a consultant microbiologist or infectious disease physician should be sought urgently when serious sepsis is suspected.(D)” (page 5) |

Table A3: Summary of Recommendations

| Key Recommendations | |
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| BC Sepsis Network, 2012 ² | |
| 1. | <p>“All patients with 2 of the 4 signs of Systemic Inflammatory Response Syndrome (Heart Rate >90, Respiratory Rate >20, temperature $\geq 38^{\circ}$ C or $< 36^{\circ}$ C, altered level of consciousness) and suspected or confirmed infection and one of the following risk factors will be triaged as a CTAS =2.</p> <ul style="list-style-type: none"> • Looks unwell • Age > 65 • Recent surgery • Immuno-compromised (AIDS, Chemotherapy, neutropenia, asplenia, transplant, chronic steroids) • Chronic illness (diabetes, renal failure, hepatic failure, cancer, alcoholism, IV drug use)” (page 3) |
| 2. | <p>“If a patient has 2 of the 4 signs of Systemic Inflammatory Response Syndrome and suspected infection (with one of the risk factors above):</p> <ul style="list-style-type: none"> • Lactate measurement within 30 minutes of presentation to triage should be taken with initial blood draw and this will require access to a machine with rapid turn-around time (results to clinician within 30 minutes) • If initial lactate is elevated, have a repeat venous lactate measurement drawn in next 2-4 hours” (page 3) |
| 3. | <p>“If systolic blood pressure is < 90 mmHg at presentation, triage as CTAS =1, and:</p> <ul style="list-style-type: none"> • Administer antibiotics within 1 hour • Draw a blood culture before administering antibiotics • Start a second liter of crystalloid within 1 hour” (Page 3) |
| 4. | <p>“If initial lactate result is > 4 mmol/L:</p> <ul style="list-style-type: none"> • Start antibiotics within 1 hour of measurement of elevated lactate • Draw a blood culture before administering antibiotics • Start a second liter of crystalloid started within 1 hour of measurement of elevated lactate” (page 4) |
| 5. | <p>“If systolic blood pressure is > 90 mmHg at presentation and initial lactate is < 4 mmol/L, but the patient has been admitted to the hospital and received IV antibiotics:</p> <ul style="list-style-type: none"> • Ensure the antibiotics have been administered within 3 hours • Draw a blood culture before administering antibiotics” (page 4) |
| Additional recommendations | |
| | <ul style="list-style-type: none"> • “Early investigations to determine infectious source (radiologic, surgical, other cultures (e.g. cerebrospinal fluid, joint aspiration).” • “Early source control with appropriate consultation.” • “Early critical care (ICU) contact or BC Bedline (www.BCbedline.ca) contact if early knowledge exists that the patient will need a higher level of care.” • “Encourage a ‘culture of lactate’ where any nurse, respiratory therapist, or physician is empowered to check a lactate if concerned. Check early and check often (if lactate elevated or patient unwell).” • “If hypotensive despite fluid bolus (30 ml/kg) or lactate fails to improve by 10% after second measurement (at least 2 hours after initial measurement), consider: <ul style="list-style-type: none"> ○ Placing central venous catheter and arterial catheter, continue fluid resuscitation and initiate norepinephrine or epinephrine to maintain mean arterial pressure of > 65 mmHg. Use inotropes as needed and begin invasive monitoring and quantitative resuscitation. ○ Consultation with critical care (ICU) in your facility or BC Bedline for critical care consultation/transfer to ICU.” (Page 4) |

APPENDIX 5: Additional References of Potential Interest

Outside date range

Green RS, Djogovic D, Gray S, Howes D, Brindley PG, Stenstrom R, et al. Canadian Association of Emergency Physicians Sepsis Guidelines: the optimal management of severe sepsis in Canadian emergency departments. CJEM. 2008 Sep; 10(5):443-59.