OHSU HEALTH SYSTEM
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

GUIDELINE FOR THE DIAGNOSIS AND INITIAL MANAGEMENT OF SEPSIS IN ADULTS

Background: Sepsis and septic shock are leading causes of mortality and critical illness worldwide, with between one in three and one in six of those affected dying. [1-4] Many aspects of sepsis care – recognition, prompt and adequate antibiotic therapy and circulatory support with fluids and vasopressors for those with septic shock – have been established, yet have been difficult to implement in the health care setting. [5] Sepsis care may be most consequential during the earliest phase of treatment, therefore, the goal of the OHSU Health guideline is to improve the identification, diagnosis, and time to appropriate treatment for hospitalized adult patients with suspected sepsis . [5]

Prevalence:
Over 1.7 million adult sepsis cases are reported annually in the US, which contribute to 270,000 deaths. [6, 7] Despite advances in care, patients with sepsis continue to have a high mortality rate, reaching 20% or more in some settings. [5]

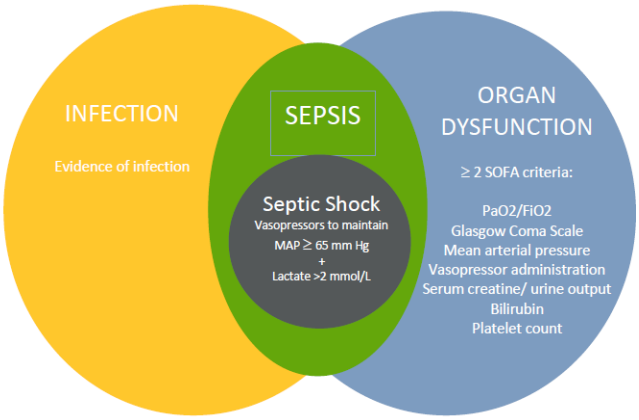
Complications:
For patients who survive sepsis, there is increasing awareness these patients often have long-term physical, psychological and cognitive disabilities with significant health care and social implications. [3, 8]

Definitions:
Sepsis: Life threatening organ dysfunction caused by dysregulated host response to infection.

Septic Shock: a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Clinically this presents as hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities.

Organ Dysfunction:

- Change in SOFA Score > 2
- Change in mental status
- Lactate level >2 mmol/L
- SBP <90 mmHg, MAP <65 mmHg or drop of >40 mmHg
- Platelets <100K microunits/L
- Creatinine >2 mg/dl (excludes end-stage renal disease)
- Total bilirubin >2 mg/dL
- Urine output <0.5 ml/kg/hr for 2 hours
- International Normalized Ratio (INR) >1.5
- New need for invasive or non-invasive mechanical ventilation



Guideline Eligibility Criteria:

- Patients 18 years of age or older
- Patients seen in in-patient care and emergency settings
- Suspected sepsis or diagnosis of sepsis with or without other health conditions

Guideline Exclusion Criteria:

- Patients under age 18
- Outpatient care, primary care, home management

Clinical Practice Recommendations:

Identifying patients with suspected sepsis

Evaluate for suspected sepsis when a patient presents with signs or symptoms that indicate possible infection. In patients with new or worsening organ dysfunction, consider an infection (sepsis) as a cause of the organ dysfunction (**Consensus**). [9]

Examine patient with suspected infection to identify: (**Consensus**) [9, 10]

- Possible source of infection
- Factors that increase risk of sepsis
- Any indications of deterioration or evidence of end-organ dysfunction
- Any new or worsening organ system dysfunction
    - Change in SOFA Score > 2
    - Change in mental status
    - Lactate level >2 mmol/L
    - SBP <90 mmHg, MAP <65 mmHg or drop of >40 mmHg
    - Platelets <100K microunits/L
    - Creatinine >2 mg/dl (excludes end-stage renal disease)
    - Total bilirubin >2 mg/dL
    - Urine output <0.5 ml/kg/hr for 2 hours
    - International Normalized Ratio (INR) >1.5
    - New need for invasive or non-invasive mechanical ventilation

Risk Factors

Patients who are higher risk of developing sepsis include: **(Consensus based on external guideline)** [9]

- Older (over 75 years)
- Very frail
- Impaired immune systems because of illness or drugs, including:
    - Treatment for cancer with chemotherapy
    - Impaired function (for example, patients living with diabetes, patients who have had a splenectomy or asplenia, patients living with end stage liver disease, patients living end-stage renal disease, or patients living with sickle cell disease)
    - Patients taking long-term steroids
    - Patients taking immunosuppressant drugs to treat non-malignant disorders such as rheumatoid arthritis
    - Patients who have had surgery, or other invasive procedures, in the past 6 weeks
    - Patients who any breach of skin integrity (for example, cuts, burns, blisters, decubitus ulcers or skin infections)
    - Patients who use intravenous drugs
    - Patients with indwelling lines or catheters or other indwelling medical devices.

Patients 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 of sepsis. In particular, women in this group are at particularly high risk include those who:

- Patients with impaired immune systems
- Patients with gestational diabetes or diabetes or other comorbidities
- Patients needing invasive procedures (for example, Caesarean section, forceps delivery, removal of retained products of conception)
- Patients with prolonged rupture of membranes
- Patients who have or have been in close contact with people with group A streptococcal infection, for example, scarlet fever
- Patients with continued vaginal bleeding or an abnormal vaginal discharge

Assessment

Sepsis detection can be difficult, and clinical findings of sepsis overlap with many other conditions. Empirical evidence currently supports the use of more than one severity assessment tool, and choosing when to use the different tools requires weighing the benefits and harms of the sensitivity and specificity of each tool (**Strong Recommendation, Moderate Quality Evidence).** [4]

Initial assessment

Because there is no confirmatory diagnostic test, the diagnosis of sepsis requires clinical judgement based on evidence of infection and organ dysfunction. Use of clinical criteria such as systemic inflammatory response syndrome (SIRS) or other early warning markers (NEWS2, Epic Deterioration Index) may help in stratifying patients' risk and help in early assessment of patients with possible sepsis (**Strong Recommendation, Moderate Quality Evidence).** [7, 11-15]

Systemic Inflammatory Response Syndrome (SIRS)
Consider sepsis when two or more SIRS Criteria are present: [11]

1. a body temperature greater than 38.0°C or less than 36°C;
2. a heart rate greater than 90 beats per minute;
3. tachypnea, manifested by a respiratory rate greater than 20 breaths per minute, or hyperventilation, as indicated by a PaCO2 of less than 32 mm Hg;
4. an alteration in the white blood cell count, such as a count greater than 12,000/cu mm, a count less than 4,000/cu mm, or the presence of more than or > 3% immature granulocyte (IG%)

SIRS Criteria in patients >20 weeks gestation and less than 1 week postpartum

1. a body temperature greater than 38.0°C or less than 36°C
2. a heart rate greater than 110 beats per minute pregnant and post-partum patients (sustained over 15 minutes)
3. tachypnea, manifested by a respiratory rate greater than 24 breaths per minute for pregnant and post-partum patients (sustained over 15 minutes)
4. an alteration in the white blood cell count, such as a count greater than 15,000/cu mm, a count less than 4,000/cu mm, or the presence of more than or > 3% immature granulocyte (IG%)

Refer to

- OHSU Delegation Protocol for Sepsis Response – Adult
- Perinatal Sepsis Clinical Consensus Guideline (CCG)

**When evaluating, consider other possible causes for meeting SIRS criteria, such as recent trauma, stress or surgery. Some patients with sepsis may not meet SIRS criteria.*

Stratify risk of severe illness
When two or more SIRS criteria are present, consider using NEWS2 (Appendix A) to determine degree of illness in a patient. Patients with an elevated NEWS2 Score have a higher risk of deterioration and sepsis should be considered in the evaluation (**Conditional Recommendation, Moderate Quality Evidence).** [4, 5, 12-20]

Start initial evaluation for sepsis if the patient: **(Consensus)**

- Has a NEWS2 score of 5 or above
- Has a lactate 2mmol/L or above
- If any of the following clinically significant sign or symptoms are present
  - Deteriorating mental state (including delirium and/or level of consciousness)
  - Systolic BP </= 90 mmHg (or drop of >40 from normal)
  - Heart rate >/= 130 per minute
  - Respiratory rate of >25 per minute
  - Needs O2 to keep SpO2 >/= 92% (88% in COPD)
  - Non-blanching rash / mottled / ashen / cyanotic
  - Not urinated in 18 hours (<0.5 ml/kg/hr if catheterized)
  - Recent chemotherapy

Monitor and consider further evaluation as appropriate if patient has any of the following signs and symptoms:

- Acute deterioration in functional ability
- Immunosuppressed
- Trauma / surgery / procedure in last 8 weeks
- Respiratory rate 21-24
- Heart rate 91-130 or new dysrhythmia

- Temperature <36-degree C
- Clinical signs of wound infection

Laboratory and Imaging Tests

Obtain blood cultures in those with suspected sepsis (**Conditional Recommendation, Low Quality Evidence**) [4, 5]

Practice Implication
Refer to OHSU Health Blood Culture Collection Policy

Measure blood lactate levels (venous or arterial) and repeat lactate measurement after initial resuscitation only if elevated above 2 mmol/L or if there is suspicion of clinical deterioration (**Consensus based on external guidelines)**. [5]

Identify potential source of infection, using chest x-ray, UA reflex to urine culture, and other clinically appropriate laboratory/imaging procedures (**Consensus based on external guidelines)**. [5]

Sample possible infection source based on medical history, symptoms and physical examination findings (eg, sputum, cerebrospinal fluid, peritoneal fluid, wounds). (**Consensus based on external guidelines)**. [5]

Perform CT scanning based on clinical suspicion, not routine whole-body imaging (**Consensus based on external guidelines)**. [5]

Procalcitonin testing can be considered but should be used in limited cases in conjunction with other assessment, and should not be used to decide if a patient is septic or to initiate antibiotics (**Conditional Recommendation, Low Quality Evidence)**. [21-25]

Initial Management

History and physical examination may help to detect infection and organ dysfunction. Clinicians can expedite sepsis care through a focused history and by obtaining corroborating data **(Consensus based on external guidelines).** [5]

Recommended evaluation for most patients includes blood lactate, complete blood count with differential, chemistry panel, liver function tests, mental status assessment, cardiovascular assessment (heart rate, blood pressure), and respiratory assessment (rate, work of breathing, SpO2). Administer supplemental oxygen to maintain >/=92% **(Consensus based on external guidelines).** [5]

Key Principles of Initial Management [5]

- Evaluation for source of infection
- Severity assessment
- Treatment and prevention of hypotension
- Intravenous fluids
- Vasopressors
- Antibiotics
- Infection source control

**Refer to Risk stratification tool for patients with suspected sepsis in Appendix B*

Initial Treatment Bundle (Example in Appendix C)

Initial Treatment Bundle should be implemented as soon as possible and no more than three hours after sepsis is identified.
The Initial Treatment Bundle includes (1) Measuring lactate level (remeasure lactate if initial lactate elevated (> 2 mmol/L); (2) Obtain blood cultures before administering antibiotics with the recommendation to not delay administration of antibiotics if unable to obtain blood cultures in timely fashion; (3) Administer broad-spectrum

antibiotics when sepsis is suspected; (4) Rapid administration of 30 mL/kg crystalloid for hypotension or lactate >/= 4 mmol/L; and (5) Administer vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure >/= 65 mm Hg. (**Conditional Recommendation**, **Low Quality Evidence**). [4, 26]

Type of Antibiotics

For adults with suspected sepsis or septic shock but unconfirmed infection, continuously re-evaluate and search for alternative diagnoses and discontinue empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected (**Consensus based on external guidelines**). [4]

For adults with possible septic shock or a high likelihood for sepsis, administer antimicrobials immediately **(Strong Recommendation; Low Quality Evidence**). [4]

For adults with possible sepsis without shock, we recommend rapid assessment of the likelihood of infectious versus noninfectious causes of acute illness (**Consensus based on external guidelines**). [4]

For adults with sepsis or septic shock, initiate broad-spectrum antibiotics with activity against gram-negative bacteria according to local susceptibility patterns (**Conditional Recommendation, Low Quality Evidence**). [4, 5]

Practice Implication
Stewardship program currently recommends:

- Cefepime is currently the preferred first-line empiric agent for septic shock. For patients with recent cultures (within the previous 12 months) with growth of a cefepime-resistant organism/s, consider alternate therapy
- Add empiric MRSA coverage for patients with suspected/known sepsis due to: skin and soft tissue infection, line infection, injection drug use, HAP/VAP or patients with a hx of infection or colonization due to MRSA within the last 12 months
- For patients without shock and with a clearly suspected source, please refer to OHSU empiric antibiotic guidelines (available for pneumonia, UTI, skin and soft tissue infection and intra-abdominal infection).
- For further questions on antibiotic selection, please page the Infectious Diseases consult team.

Pharmacokinetics/Pharmacodynamics (PK/PD)

For adults with sepsis or septic shock, we recommend optimizing dosing strategies of antimicrobials based on accepted pharmacokinetic/ pharmacodynamic (PK/PD) principles and specific drug properties (**Consensus based on external guidelines**). [4]

Practice Implication

- For gram negative coverage, the usual choices can be given IV push slowly
- For gram positive coverage, an infusion is required, which is administered over a longer time period.
- We recommend administration with the gram-negative coverage first, followed by gram-positive coverage

Delivery

For adults with sepsis or septic shock, we suggest using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion **(Conditional Recommendation; Moderate Quality Evidence**). [4]

Duration

For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we suggest using shorter over longer duration of antimicrobial therapy (**Conditional Recommendation, Low Quality Evidence**). [4, 5]

Biomarkers

For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, procalcitonin can be used in limited cases in conjunction with clinical evaluation to decide when to

discontinue antimicrobials over clinical evaluation alone (**Conditional Recommendation, Low Quality Evidence**). [4]

Antibiotic Stewardship and De-escalation of Antibiotics

For adults with sepsis or septic shock, assess at least once daily for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation (**Conditional Recommendation, Low Quality Evidence**). [4, 5]

A negative MRSA nasal swab may be used to de-escalate MRSA coverage in patients with pneumonia as the source of sepsis **(Consensus)**.

Fluid Management

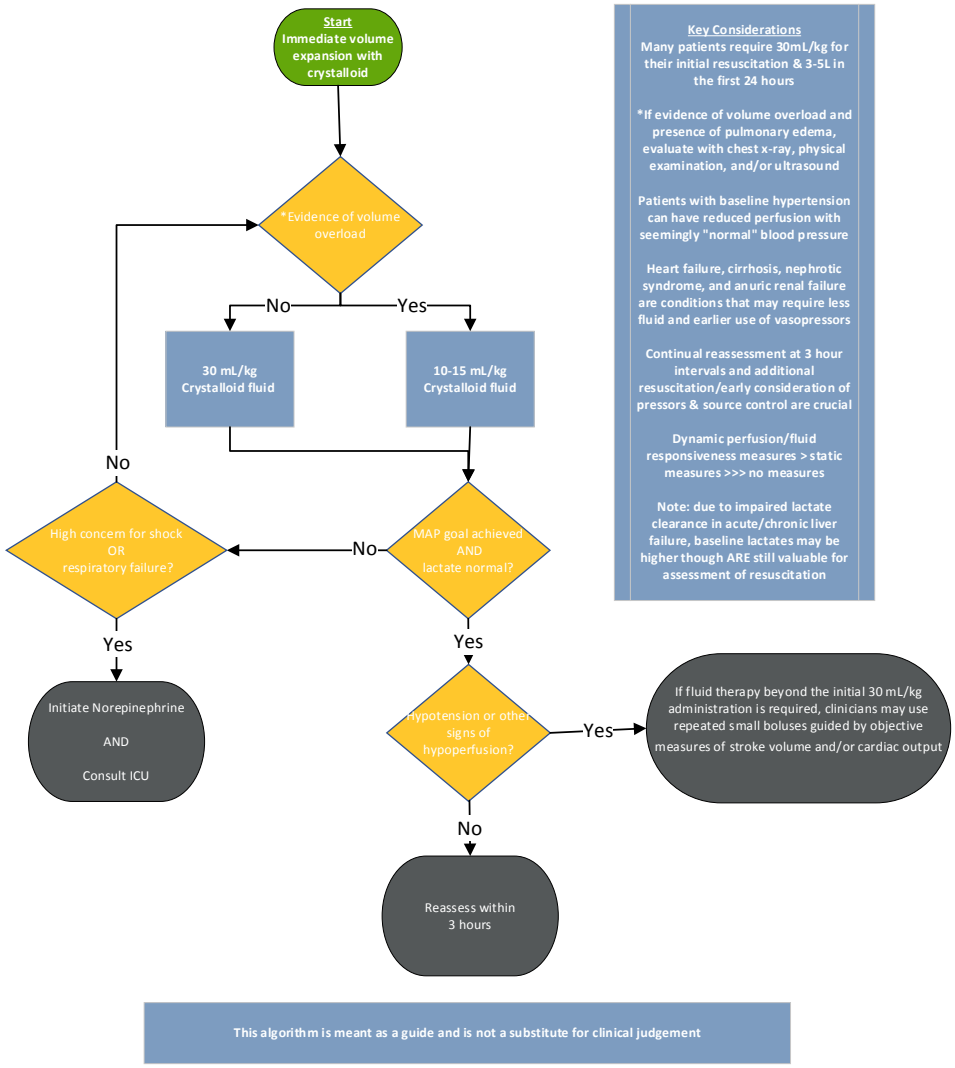
For sepsis induced hypotension or septic shock, many patients will require at least 30 mL/kg of IV crystalloid fluid to be given within the first 3 hr of resuscitation, and 3-5L in the first 24 hours. Patient response serves as the best indicator of the appropriateness of fluid resuscitation volume. (**Conditional Recommendation**, **Low Quality Evidence**). [4, 5, 27, 28]

For adults with sepsis or septic shock, fluid administration after an initial bolus should be based on serial assessments of the patient and response to therapy. Consider using dynamic measures to guide fluid resuscitation, over physical examination, or static parameters alone, but no singular assessment approach is superior so multiple types of assessments should be performed (**Conditional Recommendation**, **Very Low Quality Evidence**). [4, 5]

Patients with comorbidities such as heart failure, cirrhosis, nephrotic syndrome, and anuric renal failure may require less fluid and earlier use of vasopressors (**Conditional Recommendation**, **Very Low Quality Evidence**). [29-35]

For adults with sepsis or septic shock, we suggest guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate (**Conditional Recommendation**, **Low Quality Evidence**). [4]

Figure 1: Fluid Management Algorithm



Vasopressors

For adults with septic shock requiring vasopressors, an initial target mean arterial pressure (MAP) of 65 mm Hg is recommended (**Strong Recommendation, Moderate Quality Evidence**). [4, 5]

Norepinephrine is the first-line vasopressor for patients with septic shock (**Strong Recommendation, Moderate Quality Evidence**). [4, 5]

Practice Implication
Refer to OHSU Health Peripheral Administration of Vasopressors Policy

Source Control
For adults with sepsis or septic shock, rapidly identify or exclude specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical ideally within 6 hours of identification of sepsis. Early consultation and procedural intervention to control infection sources is recommended (**Strong Recommendation, Low Quality Evidence**). [4, 5, 36]

For adults with sepsis or septic shock, promptly remove intravascular access devices when possible and after vascular access has been established (**Consensus based on external guidelines**). [4, 5]

Quality Measures:

Outcome:

- % Sepsis Mortality Rate
- % Present on Admission (POA) Sepsis Mortality Rate
- % Non-Present on Admission (POA) Sepsis Mortality Rate
- % of Overall Sepsis Rate

Additional:

- % with Organ Dysfunction
- % with Septic Shock
- % requiring ICU in 72 hours of Time Zero
- % of Sepsis Readmission Rates

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Guideline Preparation

This guideline was prepared by the Office of Clinical Integration (CI) and Evidence-Based Practice (EBP) in collaboration with content experts across OHSU Healthcare.

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Development Process

This guideline was developed using the process outlined in the CI and EBP Manual (2016). The review summary documents the following steps:

1. Review Preparation - PICO questions established - Evidence search confirmed with content experts
2. Review of Existing Internal and External Guidelines - Literature Review of Relevant Evidence
3. Critically Analyze the Evidence
4. Summarize the Evidence by preparing the guideline, and order sets

Evaluating the Quality of the Evidence

Published clinical guidelines were evaluated for this review using the **University of Pennsylvania's Trustworthy Guideline Rating Scale**. The summary of these guidelines is included in the evidence summary. The rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains. This scale evaluates a guideline's transparency, conflict of interest, development group, systematic review, supporting evidence, recommendations, external review and currency and updates. The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guideline does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated).

The **GRADE (Grading of Recommendations, Assessment, Development and Evaluation)** criteria were utilized to evaluate the body of evidence used to make clinical recommendations. The table below defines how the quality of the evidence is rated and how a strong versus conditional recommendation is established. The evidence summary reflects the critical points of evidence.

Recommendation	
STRONG	Desirable effects clearly outweigh undesirable effects or vice versa
CONDITIONAL	Desirable effects closely balanced with undesirable effects

Quality	Type of Evidence
High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
Moderate	Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies
Low	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence
Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Recommendations

Recommendations for the guidelines were directed by the existing evidence, content experts, and consensus. Patient and family preference were included when possible. When evidence is lacking, options in care are provided in the guideline and the order sets that accompany the guideline.

Approval Process

Guidelines are reviewed and approved by the Content Expert Team, Office of CI and EBP, Knowledge Management and Therapeutics Committee, Professional Board, and other appropriate hospital committees as deemed appropriate for the guideline's intended use. Guidelines are reviewed and updated as necessary every 2 to 3 years within the Office of CI and EBP at OHSU. Content Expert Teams will be involved with every review and update.

Disclaimer

Guideline recommendations are made from the best evidence, clinical expertise and consensus, in addition to thoughtful consideration for the patients and families cared for within the Integrated Delivery System. When evidence was lacking or inconclusive, content experts made recommendations based on consensus. Expert consensus is implied when a reference is not otherwise indicated.

The guideline is not intended to impose standards of care preventing selective variation in practice that is necessary to meet the unique needs of individual patients. The physician must consider each patient and family's circumstance to make the ultimate judgment regarding best care.

Appendix A: NEWS2 Scoring System [37]

Chart 1: The NEWS scoring system

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	

National Early Warning Score (NEWS) 2

Appendix B: Risk stratification tool for patients with suspected sepsis

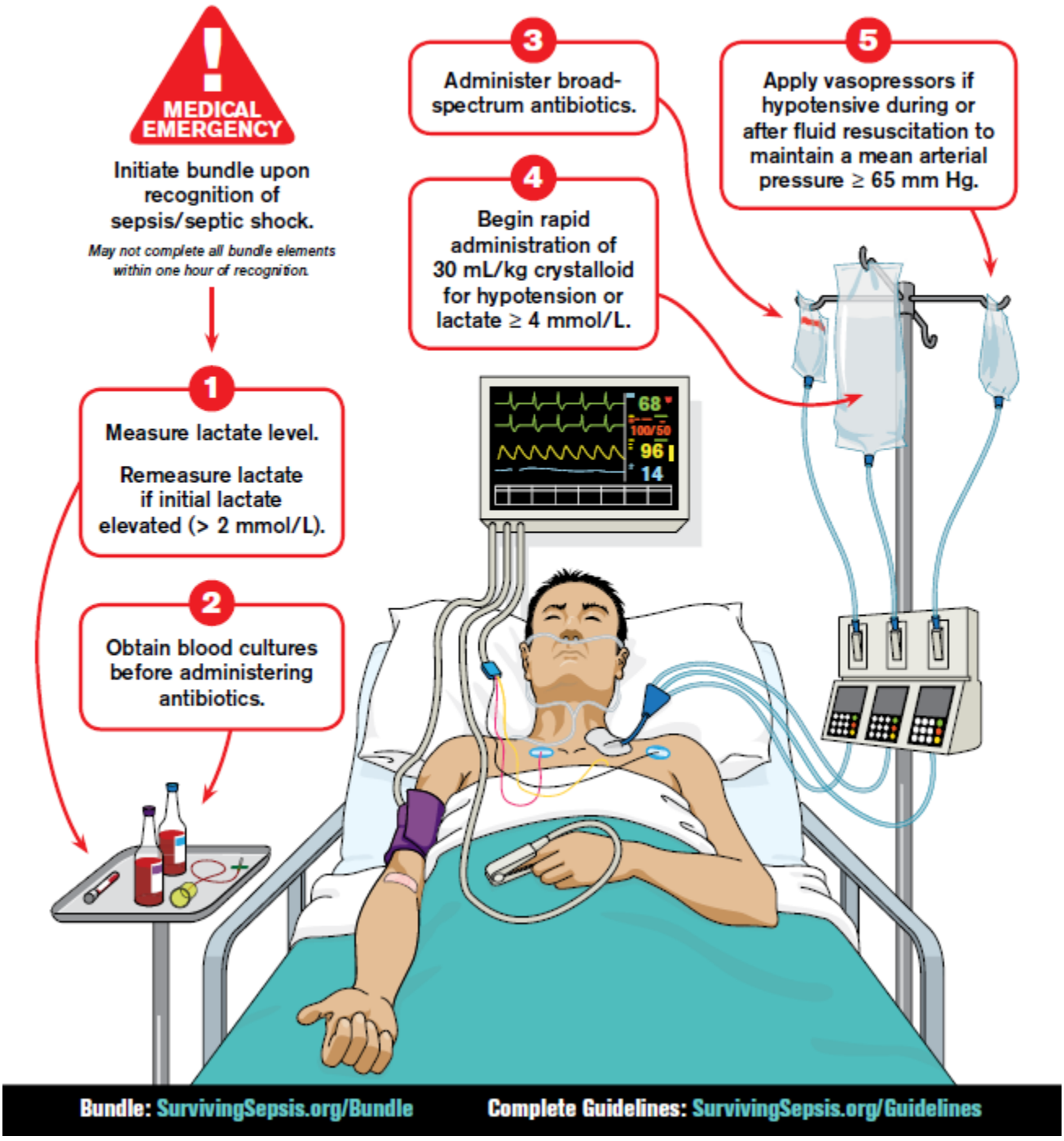
	High	Moderate	Low
History	Objective evidence of new altered mental state	History from patient, friend or relative of new onset of altered behavior or mental state History of acute deterioration of functional ability Impaired immune system (illness or drugs including oral steroids) Trauma, surgery or invasive procedures in the last 6 weeks	Normal behavior
Respiratory	Raised respiratory rate: 25 breaths per minute or more New need for oxygen (40% FiO2 or more) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease); New Productive Cough	Raised respiratory rate: 21 to 24 breaths per minute; New Productive Cough	No high risk or moderate to high risk criteria met
Blood pressure	Systolic blood pressure 90 mmHg or less or systolic blood pressure more than 40 mmHg below normal	Systolic blood pressure >91 mmHg	No high risk or moderate to high risk criteria met
Circulation and hydration	Raised heart rate: more than 130 beats per minute Not passed urine in previous 18 hours. For catheterized patients, passed less than 0.5 ml/kg of urine per hour	Raised heart rate: 91 to 130 beats per minute (for pregnant women 100 to 130 beats per minute) or new onset arrhythmia Not passed urine in the past 12 to 18 hours For catheterized patients, passed 0.5 ml/kg to 1 ml/kg of urine per hour	No high risk or moderate to high risk criteria met
Temperature		Temperature less than 36°C or greater than 38°C	
Skin	Mottled or ashen appearance Cyanosis of skin, lips or tongue Non-blanching rash of skin	Signs of potential infection, including redness, swelling or discharge at surgical site or breakdown of wound	No non-blanching rash

Appendix C: Initial Treatment Bundle – Example from Society of Critical Care Medicine

Initial Treatment Bundle

Initial Resuscitation for Sepsis and Septic Shock

Surviving Sepsis Campaign



Revision History

- Origination Date (Version 01): November 2023