JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)

Sepsis Management in Prolonged Field Care (CPG ID:83)

This CPG focuses on the most common etiologies of sepsis, and the treatments of those forms of sepsis that the austere provider can reasonably manage.

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Publication Date: 28 Oct 2020

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INTRODUCTION

This Role 1 prolonged field care (PFC) guideline is intended for use in the austere environment when evacuation to higher level of care is not immediately possible. A provider must first be an expert in Tactical Combat Casualty Care (TCCC). The intent of this guideline is to provide a functional, evidence-based and experience-based solution to those individuals who must manage patients suspected of having or diagnosed with sepsis in an austere environment. Emphasis is placed on the basics of diagnosis and treatment using the tools most familiar to a Role 1 provider. Ideal hospital techniques are adapted to meet the limitations of austere environments while still maintaining the highest standards of care possible.

Sepsis and septic shock are medical emergencies. Patients suspected of having either of these conditions should be immediately evacuated out of the austere environment to higher echelons of care. These patients are often complex, requiring 24-hour monitoring, critical care skills, and a great deal of resources to treat. Obtaining evacuation is the highest treatment priority for these patients. This Clinical Practice Guideline (CPG) utilizes the minimum, better, best paradigm familiar to PFC, and gives medics of varying capabilities and resources options for treatment.

SEPSIS DEFINITIONS

Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection (Sepsis-3 definition, adopted by Surviving Sepsis Campaign in 2017).[1]

Septic Shock: Persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) > 65 mmHg and having a serum lactate > 2 mmol/L despite adequate volume resuscitation.

Shock is one of the most common complications of severe injury or illness. Shock is separated into four different classes: 1) hypovolemic (including hemorrhagic), 2) cardiogenic, 3) obstructive, and 4) distributive. Septic shock is a form of distributive shock. The hallmark of managing shock is:

1. early recognition (including an awareness that the magnitude of injury or illness has the potential to lead to shock);
2. identification of the cause of shock; and
3. early, decisive treatment of the cause and initiation of cause-specific resuscitation.

Severe infection is often a greater risk than trauma in the PFC environment. Trauma-associated sepsis is an important subset of sepsis in the military population, with a potential for casualties to develop severe wound, respiratory, urinary, and bloodstream infections related to their initial injury and initial treatment procedures (IV/IO catheters, foley catheters, etc.). Up to 38% of trauma-related sepsis is bloodstream-related.[2] In the trauma patient, the manifestation of sepsis is often several days after initial presentation which makes sepsis particularly relevant in the PFC environment over a Role 1 with greater medevac capability.[3] Early antibiotic therapy and hemodynamic resuscitation with fluids and vasopressors are the key initial therapies for the septic patient. Source control is similarly critical and may require surgery. When this is not possible in the PFC environment, the patient must be supported and transported to a location with surgical capability as rapidly as possible.

SEPSIS MANAGEMENT GOALS

Sepsis management goals should include the following:[1]

- Early suspicion and recognition.
- Source identification.
- Early antimicrobial therapy.
- Resuscitation.
- Source control.
- Patient monitoring through trending patient information.
- Early telemedicine consultation.
- Evacuate to definitive care.

EARLY SUSPICION AND RECOGNITION

***GOALS**: Recognize sepsis and review the differential diagnosis; identify systemic infection before it progresses to decompensated shock; and identify patients who require evacuation.*

Infection may take many forms in initial presentation. Common examples include viral upper respiratory infections, gastroenteritis, urinary tract infections, cellulitis, and pneumonia. In addition, infections associated with travel, to include diarrhea, vector-borne diseases (malaria, dengue fever, etc.) and some respiratory pathogens will be particularly common in certain areas of the world. A comprehensive history of illness, to include travel history, should be obtained initially. Many infections may be managed adequately without evacuation or need for higher levels of medical care.

Differential diagnoses of presentations attributed to infections must be considered as well. Sepsis "mimics" anaphylaxis, gastrointestinal emergency, pulmonary disease including pulmonary embolism, metabolic abnormality including hyperthyroidism and adrenal insufficiency, toxin ingestion, toxin withdrawal, vasculitis, and spinal injury.[4] If the condition progresses to septic shock, "mimics" may include other causes of shock such as myocardial infarction, gastrointestinal bleeding, dehydration, heat injury, and hypovolemia secondary to gastrointestinal losses. If infection and sepsis are still prominent in the differential diagnosis after considering these other causes of shock, a focused assessment should be pursued, as detailed below. Any patient showing evidence of sepsis or septic shock should immediately be classified as an urgent evacuation priority.

HISTORY AND PHYSICAL EXAM

Minimum: "**SAMPLER**" history (**S**ymptoms/subjective complaints: **A**llergies to medications; **M**edications taken or prescribed; **P**ast medical and surgical history; **L**ast meal/oral intake; **E**vents leading up to presentation; and **R**ecent travel). Initial vital signs on presentation. Trending of vital signs (e.g., on PFC flow sheet found on the JTS Forms website) when looking for signs of severe infection are: fever or hypothermia; increase in heart rate; increase in respiratory rate; and, generally later rather than earlier, a decrease in blood pressure. Additionally, monitor mental status, SpO2, and capillary refill. Complete secondary survey physical exam. Look for Systemic Inflammatory Response Syndrome (SIRS), quick

Sepsis-related Organ Failure Assessment (qSOFA) criteria[5] and/or a high NEWS2 score[6], listed below. Look for potential sources of infection. Establish blood type of patient using an Eldon card.

- **Better**: Above, plus: Addition of simple labs: urine dipstick, BinaxNOW (malaria), i-STAT (or other point-of-care laboratory) values with vitals monitoring mentioned above. See i-STAT values in Appendix B. If available, monitor lactate.
- **Best**: Above, plus: Thick and thin smear (malaria), laboratory values (including lactate), culture data from likely source(s).

The more indicators of systemic infection, the higher the suspicion for the treating clinician. This is the "whole-patient" approach. A comprehensive problem list will be important to organize patient care. If sepsis is suspected, telemedicine should immediately be initiated (if possible) to help guide both diagnosis and therapy. Monitor vital signs constantly to guide treatments.

The Systemic Inflammatory Response Syndrome (SIRS) is a sign of an inflammatory reaction to a severe physiologic insult. Although no longer part of the definition of sepsis, SIRS is a useful tool in identifying patients at risk of acute decompensation. The SIRS criteria consist of four indicators:

1. tachycardia (heart rate >90 beats/minute)
2. tachypnea (respiratory rate >20 breaths/minute or PaCO2 < 32 mmHg)
3. fever or hypothermia (temperature >38°C/100.4°F or <36°C/96.8°F)
4. leukocytosis or leukopenia (white blood cell count >12,000/mm³, <4,000/mm³, or > 10% bands).[7]

A practitioner in an austere environment may not be able to measure all these indicators (especially WBC), but an understanding of these features of early sepsis may prompt earlier identification of disease and direct more-timely therapeutic interventions.

qSOFA is the more recent sepsis screening tool; it seeks to identify patients at an increased risk of death.[5] The presence of two or more of the following three qSOFA indicators should increase the clinician's index of suspicion for sepsis: 1) altered mental status, 2) tachypnea (>22 breaths per minute), and 3) hypotension (SBP <100mmHg).

WARNING

Hypotension is a late sign in sepsis. ***Do not wait for blood pressure to fall before initiating treatment and resuscitation*** *in a patient who is showing multiple signs of systemic infection (fever, tachycardia, tachypnea, altered mental status, decreased urine output). Delaying intervention until blood pressure falls can make it harder to get the systemic inflammatory reaction under control and increase risk of death.*

A more in-depth tool used in the prediction of ICU admission shown to be more effective than qSOFA is the NEWS2 score which is based on only clinical measurements and assessment. NEWS2 incorporates more variables, making it less "quick" than the qSOFA. Although not applied in clinical practice to sepsis evaluation exclusively, it may be a very useful tool in predicting clinical deterioration. The clinical variables required to compute a NEWS2 score include respiratory rate, hypercapnic respiratory failure (yes/no), oxygen saturation (and need for supplemental oxygen), temperature, heart rate, systolic blood pressure, and general level of consciousness. These parameters are recorded using a scale system, assigning points between 0-3 for each parameter. This tool has been shown to be superior to qSOFA for detecting sepsis with organ dysfunction in the emergency department.[8]

The following clinical assessment – history and physical exam findings – should raise the suspicion for early sepsis:

SUBJECTIVE ASSESSMENT

- Patients with sepsis may report the below complaints, with no other obvious non-infectious source (i.e. bleeding, traumatic brain injury, heat injury).
- Chills and rigors
- Confusion
- Malaise: feeling weak, with little or no energy

OBJECTIVE ASSESSMENT

Physical exam findings of patients with sepsis may include:

- Concerning (or obvious) sources of infection:
  - Wound(s) displaying signs of infection (i.e. pain, redness warmth, purulent drainage, swelling).
  - Indwelling catheters (IV/IO/urinary) or devices in less-than-sterile/field environment.
- Temperature of >38°C/100.4°F or < 36°C/96.8°F.
- Cool skin, cyanosis, delayed capillary refill time (>3 seconds).
- Abnormal vital signs, particularly tachycardia (> 90 bpm), sustained hypotension (systolic blood pressure <90 mmHg), tachypnea (>20/min).
- Low urine output (oliguria).
- Altered or worsening mental status (confusion, lethargy).
- Rash, purpura (meningococcemia, Rocky Mountain spotted fever, other rare etiologies).
- Meets the SIRS Criteria; qSOFA criteria and/or high NEWS2 score (see above).
- Lab specific values. (See Appendix B.)

***NOTE**: Typical symptoms may not be present in some patient populations. Signs of sepsis may be attenuated and/or muted in the elderly, delayed manifestation in the very young, or masked in pregnancy due to the normal physiologic changes and absence of a febrile response in up to 50% of pregnant patients.*

SOURCE IDENTIFICATION

***GOAL**: Locate probable cause of infection to most appropriately address the source.*

Approach to Source Identification:

- Gather a complete patient history of recent and/or ongoing illnesses.
- Conduct a thorough head-to-toe exam to look for evidence of infection – wounds, bites, etc. Be sure to examine the genitourinary and perirectal areas, as these are common sites of missed infections.
- Perform rapid malaria, dengue, and point of care source tests if in an endemic area, as well as urine dipstick and i-STAT labs.[9]

Sepsis may be of bacterial, fungal, viral, or parasitic origin. Bacterial infections are the most common causes of sepsis followed by parasitic (mainly malaria), viral (e.g., dengue, influenza, COVID-19), and finally, fungal diseases.[10] The prevalence of each is directly related to a given region.[11] Identifying the cause of sepsis is challenging in the PFC environment where advanced diagnostic tests are unavailable, and antiviral and antifungal therapies are rarely available. This CPG focuses on the most common etiologies of sepsis, and the treatments of those forms of sepsis that the austere provider can reasonably manage. Advanced preparation is important, and a medical area study and/or medical threat-model analysis should be done prior to traveling to gather data on microbes specific to that given region.

For a given region, bacterial sepsis is most often due to a limited number of common pathogens to include streptococci (including *S. pneumoniae*, which causes pneumonia and meningitis), Staphylococci, *Neisseria meningitidis* (also a cause of meningitis, particularly common in regions of sub-Saharan Africa), and gram-negative bacteria arising in the gut. Treatment of many of these infections is complicated by rising rates of antibiotic resistance worldwide.[12]

Malaria must be considered high on a differential diagnosis list as a leading cause of any febrile illness in an endemic region. In the typical patient from an industrialized country without prior exposure to the infection, malaria can be rapidly fatal in the absence of early and specific therapy.[13]

A significant minority of sepsis cases (up to 15%) are due to fungal infections. *Candida* species are normal flora in the human gut and vaginal canal and are the most common causes of fungal sepsis, followed by invasive mold infections such as *Aspergillus* and by endemic fungi causing community-acquired disease, including *Histoplasma*, *Coccidioides*, and *Talaromyces*. In the PFC environment, *Candida* infections may follow penetrating abdominal trauma with perforation of the gut, while invasive molds may arise after blast injuries with devitalized tissue (such as after a high lower extremity amputation). Therapeutic options for both of these scenarios are very limited in a PFC setting.

Because war wounds are considered grossly contaminated wounds, they must be attended to meticulously. Unattended wounds can lead to acute infection and sepsis within days (or possibly within hours for very large and contaminated wounds).[14] Quality wound care is essential to infection and sepsis prevention as detailed in the *JTS Acute Traumatic Wound Management in the Prolonged Field Care Setting CPG*.[15]

TREATMENT

ANTIMICROBIAL THERAPY

***GOAL**: Use targeted and most appropriate antibiotic therapy when possible.*

Antibiotic regimens: See the *JTS Acute Traumatic Wound Management in the Prolonged Field Care Setting CPG*.

- **Minimum**: Moxifloxacin 400 mg PO daily (or levofloxacin 750 mg PO daily to provide better coverage of bacteria found in wet terrain/jungle environment).
- **Better**: Ertapenem (Invanz) 1 gram IV/IO once per day (q24 hrs) given over 5 to 10 minutes or IM (not preferred), OR ceftriaxone (Rocephin) 2 grams IV/IO given over 10 minutes q24hrs.
- **Best**: Ceftriaxone (Rocephin) 2 gm IV/IO q24 hrs given over 30 minutes, PLUS vancomycin (Vancocin) 15 mg/kg IV/IO q12 hrs. (given after ceftriaxone, given over 2 hours) PLUS metronidazole (Flagyl) 500 mg IV/PO/IO q8hrs, given over one hour.

ANTIPARASITIC REGIMENS

If sepsis is suspected in a malaria-endemic area and there is no other clearly identified source, conduct a malaria point-of-care test BINAX Now® and thick and thin smears, if available. If positive, administer both antibiotics and antimalarials. If unable to test for malaria, empiric antimalarial therapy can also be considered. Additionally, in a malaria-endemic area, when a patient is initially unresponsive to antibiotic therapy, add antimalarials.

- **Minimum:** Atovaquone/progauanil (Malarone) 4x3 regimen – 4 tablets PO once a day for 3 days.
- **Best:** Artemether/lumafantrine (Coartem) 4 tablets PO initially, then 4 tablets after 8 hours, then 4 tablets PO twice daily for 2 more days (24 tablets total).
- **Severe Malaria:** The optimal treatment for severe malaria (defined as malaria with associated findings such as altered mental status, acidosis with lactate >5 mmol/L, prostration, hypoglycemia, parasitemia >10%, hemoglobin <7 g/dL, creatinine >3 mg/dL, pulmonary edema, shock, or pathologic bleeding), the drug of choice is IV artesunate 2.4 mg/kg IV/IO at 0, 12, 24, and 48 hours (4 doses), followed by 3 days of either Malarone (4 tablets PO, for 3 days) or Coartem (4 tablets initial dose, followed by 4 tablets given 8 hours later, followed by 4 tablets twice daily for the next 2 days; 24 total tablets).

- ***NOTE 1:** Although artesunate may be available in tropical countries, the quality of formulation may not be at FDA standards and telemedicine assistance and initiation of medevac should be initiated for severe malaria.*
- ***NOTE 2:** If unable to obtain artesunate, we recommend Coartem or Malarone with teleconsultation assistance and initiation of medevac.*

ANTIFUNGAL REGIMENS

Do NOT administer without telemedicine. When advised, antifungal drugs are administered in conjunction with the antibiotic regimen mentioned above.

- **Minimum**: Fluconazole 400 mg PO or IV daily (note that PO is equipotent to IV).
- **Better/Best**: Due to the complexity and toxicity of many anti-fungal medications, this CPG will not extend beyond the minimum recommendation.

RESUSCITATION

***GOAL**: Meet perfusion goals by replenishing intravascular volume and using adjunctive medications (i.e. vasopressors) as indicated.*

***CAVEAT: If you are treating sepsis in the setting of trauma, resuscitate with whole blood or blood component therapy as you would for trauma. (See *JTS Damage Control Resuscitation – PFC CPG*.[16])

FLUID RESUSCITATION CONSIDERATIONS

- **Minimum**: In the absence of IV/IO capability, have the patient drink water and monitor urine output with a goal of averaging 0.3-0.5 mL/kg/hr. Include an oral rehydration solution for those patients who cannot consume food but can drink water (use either proprietary mixtures or fabricated – 6 teaspoons of granulated sugar with ½ teaspoon of table salt in 1 liter of water. See the *JTS Nursing Intervention – PFC CPG*.).[17] Rectal fluids (begin at 100mL/hour and increase rate to a maximum of 500mL/hour) may be used for patients who cannot tolerate oral fluids. Use oral rehydration solution mentioned above for rectal administration.
- **Better**: IV/IO crystalloid bolus (up to 30mL/kg of IV crystalloid within the first 3 hours) until a urine output of 0.3-0.5 mL/kg/hr is reached. This output can be measured using any external measuring device – water bottles, graduated collecting bottle, etc.
- **Best**: The same fluid resuscitation strategy as above with the addition of a urinary catheter in place for more precise measuring of urine output (ensure the first catch from a recently placed catheter is discarded and not documented in total output calculations).

The first step in resuscitation of the sepsis/septic shock patient is the replenishing of intravascular volume ("fill the tank"), ideally with IV/IO administration of crystalloids. The preferred fluids for IV/IO resuscitation in order of preference are: Lactated Ringers (LR) (or Plasmalyte A), then normal saline. Chloride-restricted IVF (LR/Plasmalyte A) are ideal for larger boluses (>3-4L) or ongoing resuscitation.[18] When administering large amounts of IV/IO fluids, monitor for over-resuscitation and pulmonary edema, indicated by lung auscultation (rales or "wet lungs"), increased work of breathing/decreased oxygen saturations, and evidence of edema on a plain chest film or ultrasound (if available). Urine output, with a goal of 0.3-0.5mL/kg/hr, should indicate adequate fluid resuscitation in a patient with normal kidney function, however, some patients in septic shock may have acute kidney injury (AKI). As such, initial bolus of crystalloids should not exceed 2-3 liters maximum, and further fluid administration should be based on blood pressure and measures of perfusion (capillary refill), as well as measured losses (gastrointestinal, etc.). Higher urine output (> 0.5mL/kg/hr) indicates over-resuscitation. Additionally, if labs are available, resuscitation to a normalized lactate level would be further indication

of positive improvement. It is also important to monitor serum electrolytes as abnormalities of sodium and potassium levels are particularly common during fluid resuscitation.

Negative trends of sepsis-induced hypoperfusion may include low and/or steadily decreasing SBP and/or delayed capillary refill (>3 seconds), an important indicator for measuring perfusion. In response to negative shifts in the patient's hemodynamic status – a SBP that drops below 90 mmHg, and/or a Mean Arterial Pressure (MAP) that drops below 65 mmHg – initially increase the fluid resuscitation by 20 percent (watching for signs of over-resuscitation above).

***Key point**: Over-resuscitation carries considerable risk including acidosis, dilution of clotting factors, pulmonary edema, ascites, hypernatremia and peripheral edema. If the patient's blood pressure and organ dysfunction (e.g., urine output and mentation) is not responding to recommended maximum resuscitation of 30 mL/kg over the first 2-4 hours of initiating treatment, seek telemedicine guidance on whether to cautiously give more fluids or start vasopressors.*[19]

DRUG CONSIDERATIONS

Vasopressors: Consider, if, after initial fluid resuscitation (reaching initial urine output goals or maximum of 30mL/kg IVF bolus in the first 2-4 hours), there is no observed positive change in SBP, MAP, urine output and/or mentation (fluid-refractory shock). If vasopressors are used after initial fluid resuscitation, do not administer more fluids as this can likely cause dangerous fluid shifts; implement telemedicine. ***Consider starting low dose vasopressors ONLY under guidance of telemedicine consultation**, with norepinephrine (first choice) or epinephrine (alternate)*[20] See Appendix F.

SOURCE CONTROL

***GOAL**: Eliminate the source of infection.*

Some infection sources are treated only with antibiotics, while others may require surgery to remove or drain the infection source. A full patient exam should be performed to look for sources of infection that may not have been identified on the initial patient survey and serial exams should be performed as part of ongoing patient assessment to track physical signs of infection spread or response to therapy. With wound sepsis, quality wound care is critical to infection and sepsis treatment and prevention as previously detailed in the *JTS Acute Wound Management - PFC CPG.*

Any identified potential infection sources such as foreign bodies, old indwelling catheters (to include IV/IO, urinary, etc.) and dead or dying tissue must be evaluated and attended to immediately. All previously inserted urinary or other indwelling catheters and IV/IO catheters should be removed and replaced if possible. Those that are not needed to immediately care for the patient should be considered for removal. All wound dressings should be removed, and any sign of infection requires surgical wound exploration. All dead infected tissue must be removed, up to and including amputation when needed. Any abscesses or infected spaces must be completely drained. Any suspected intrathoracic or intraperitoneal infection sources must be attended to by a surgeon urgently. Always initiate antibiotics and fluid resuscitation prior to attempting surgical interventions.

Aggressive and adequate surgical source control is essential to the patient's survival. Obtain telemedicine consultation from a surgeon.

MONITOR THE PATIENT

Monitor the patient for trend available vital signs, urine output, capillary refill, and adjuncts (ultrasound and/or labs if available).

***GOAL**: Establish a baseline and measure response to interventions.*

- **Minimum**: Serial vital signs measurement, mental status assessment, and urine output. Vital signs trends and interventions recorded on flowsheet.
- **Better**: Add point-of-care lactate every 6 hours until normal.
- **Best**: Add ultrasound monitoring to assess and trend inferior vena cava (IVC) and left ventricular (LV) filling, decrease in "hyperdynamic" cardiac physiology.

Employing focused, goal-oriented interventions as early as possible has shown to decrease mortality. The following goals will direct treatment initiatives. Medical providers should develop and prioritize a problem list with an accompanying treatment-solutions plan to meet the below therapy goals.

- **Systolic blood pressure (SBP) > 90 mmHg and/or palpable radial pulse** (if blood pressure monitoring is not available). SBP is the most appropriate and feasible modality for monitoring a patient's perfusion status.
- **Mean Arterial Pressure (MAP) > 65**. MAP is manually calculated using the formula (Systolic BP + (2 x Diastolic BP))/3. Most electronic monitors will automatically calculate the MAP. At times, the MAP may be adequate even when the SBP is low, however, SBP may be used when it is easier to monitor.
- **Capillary refill** is an easy physical exam skill and important indicator of adequate perfusion as a high-fidelity marker for effective resuscitation. It should be performed and recorded as a trend at least every 30 minutes for the unstable septic patient. The proper way to measure capillary refill is to apply pressure down on the fingernail until it blanches (turns white), and after the removal of the pressure, time the nail's return to normal color as compared to the other nails. Normal values are a return to baseline color in three seconds or less. Longer times indicate normal perfusion has not been restored.
- **If a soft tissue infection is suspected,** inspect and monitor the identified site (e.g., cellulitis) for improvement. Use a marker to outline any redness; time and date it. Monitor for any progression beyond the marked lines. If redness worsens after 24 hours or failure to improve within 48 hours, consider changing antibiotics or the need for surgical debridement after consulting telemedicine.
- **Urine output (UOP)** should be maintained at an average of 0.3-0.5mL/kg/hr.
- **Perform and repeat available labs** as indicated. Diagnostics: urine dipstick, malaria tests. Trend: i-STAT, lactate.
- **Initiate telemedicine early** and often and report trends.
- **Monitor overall respiratory status**. Many patients who are critically ill with sepsis will need ventilatory support at some point in their management – see the *Airway Management - PFC CPG*,[21] as well as the PFC reference paper: *"MSMAID" Applying an Anesthesia Checklist to SOF Medicine*.[22] Always be prepared to manage a complex airway with septic patients. Also, see the *CCAT Mechanical Ventilation CPG.* [23]

EARLY TELEMEDICINE

***GOAL**: Gather appropriate and complete information and enlist the help of a critical care and/or surgical expert early in your management.*[24]

The following information, if obtainable, should be prioritized to enable the most effective telemedicine support: subjective comments; objective – vital signs (HR, RR, Systolic BP, MAP, urine output); mental status; skin exam, lactate (if available); treatments administered or available – antibiotics; any other drugs, and the amount and type of fluids given so far.

- Ensure the complete medical history and documentation of any preceding events.
- Communicate capabilities available where you are managing the patient (e.g., by completing the "capabilities checklist" on the *PFC WG Telemedicine Template* on prolongedfieldcare.org and emailing/texting if possible before calling the consultant).
- Document any infected wounds, bites, or other potential sources of infection, etc. Send photographs or real-time video if possible.

EVACUATE TO DEFINITIVE CARE

***GOAL**: Patients identified as being septic should be assigned the highest priority of evacuation to higher levels of medical care.*

Patients with sepsis or with conditions concerning for the deterioration to sepsis will be best managed in a clinical setting conducive to monitoring and addressing multi-organ failure and associated complications. Also, see the *JTS Nursing Intervention - PFC CPG* and *JTS Analgesia and Sedation Management - PFC CPG*.[25]

NUTRITION CONSIDERATIONS

Septic patients are most often in a hypermetabolic state due to the body's efforts to fight off the infection. Nutrition is not the most important consideration in the early treatment. However, given that some patients may require continued treatment in an austere environment, may have pre-existing malnutrition, or may present for treatment after being septic for a period of time, attention must be paid to the patient's nutrition as a part of a treatment plan. This can be difficult if the patient is nauseated and/or vomiting, has an intraabdominal source of infection, resources are severely limited, or the patient's mental status is not conducive to eating and drinking.

Most patients do not require nutritional support when evacuation is anticipated within 72 hours. When evacuation is delayed beyond 72 hours or not possible, adequate nutrition should be sustained as outlined below.

***GOAL**: Goal 25-30kcal/kg/day + 1-1.2gm/kg protein. Most patients with a normal mental status can feed him or herself without the placement of a feeding tube.*

1. Enteral nutrition (oral or administered by orogastric or nasogastric tube) should be withheld in hemodynamically unstable patients (i.e. those on high or increasing doses of vasopressors) due to the risk of causing ischemic GI injury to include perforation.
2. Nasogastric Tube (NGT) should be placed in patients deemed in critical for gastric decompression. If medical evacuation is significantly delayed (greater than 48 – 72 hours) or the patient has been without significant caloric intake for over 3 days (due to delayed presentation), consider starting enteral nutrition (orally if they can take PO safely, via tube if not). If the patient requires continuous vasopressors, avoid the bolus nutrition sources, and opt for a lower volume hourly rate of infusion (10 – 20cc/hr.).
3. At a minimum, confirm presence of gastric placement with auscultation over both lung fields and the abdomen, along with aspiration of gastric contents. Best recommendation is obtaining plain film radiography to confirm proper placement PRIOR to instilling any substances through the tube.
4. Ensure presence of normal bowel sounds prior to initiating any enteral feeding.
5. Enteral feeding is contraindicated in the presence of severe abdominal distension, abdominal pain and/or gastro-intestinal bleeding.

Oral Feed vs Tube Feed

If a patient has a normal mental status they likely can take oral nutrition - do not put a tube down their nose. If they cannot cooperate or tolerate oral feeds, and evacuation is not likely or not possible within 72 hours, consider tube feeds. If tube feeds are initiated without an ability to obtain x-ray verification of placement, monitor for signs of misplacement or GI obstruction very closely (e.g., nausea, increasing abdominal distension or pain) and stop feeding if they occur. Patients require continuous hydration, but those who receive adequate hydration will not experience clinically significant adverse effects from starvation for several days to over a week.

Severe Malnutrition

If someone has signs of severe malnutrition (e.g., local nationals in setting of famine, hostages), obtain telemedicine consultation before starting enteral nutrition. Refeeding syndrome is a life-threatening metabolic and electrolyte derangement that can develop from feeding severely malnourished patients too much, too quickly. It is very difficult to detect in the PFC environment. The first sign may be cardiac collapse from electrolyte derangements which is nearly impossible to resuscitate.

6. Meal supplement drinks are sufficient. 1x Muscle Milk Light bottle contains 150kcal and 28gm protein in 500mL.
7. A more concentrated alternative is to use commercially available protein powder (with similar caloric/protein content per scoop) at 1/4 the recommended concentration and mix until no clumps are visible.
8. Administer tube feeds in small volume boluses (e.g., 60mL via Toomey syringe) 2-4 hours for a goal of 1gm/kg/day protein content.
9. If vomiting or increased abdominal distension occur, hold tube feeds for 6 hours and then try again.
10. For more information, see *JTS Nutrition Support Using Enteral and Parenteral Methods CPG*.[26]

PERFORMANCE IMPROVEMENT (PI) MONITORING

POPULATION OF INTEREST

Casualties receiving PFC or Prolonged Casualty Care (PCC).

INTENT (EXPECTED OUTCOMES)

Prehospital documentation is received by JTS on all PFC and PCC patients.

PERFORMANCE/ADHERENCE MEASURES

- Sepsis patient with >2hr prehospital care that arrives intubated to Role 2 or 3.
- Sepsis patient with >2hr prehospital care requiring dialysis at Role 3 or 4.
- Sepsis patient with >2hr prehospital care that dies in first 30 days.

DATA SOURCES

- Patient Record
- Department of Defense Trauma Registry (DoDTR)
- PFC Flowsheet

SYSTEM REPORTING & FREQUENCY

The above constitutes the minimum criteria for PI monitoring of this CPG. System reporting will be performed annually; additional PI monitoring and system reporting may be performed as needed.

The system review and data analysis will be performed by the JTS Chief and the JTS PI Branch.

RESPONSIBILITIES

It is the trauma team leader's responsibility to ensure familiarity, appropriate compliance and PI monitoring at the local level with this CPG.

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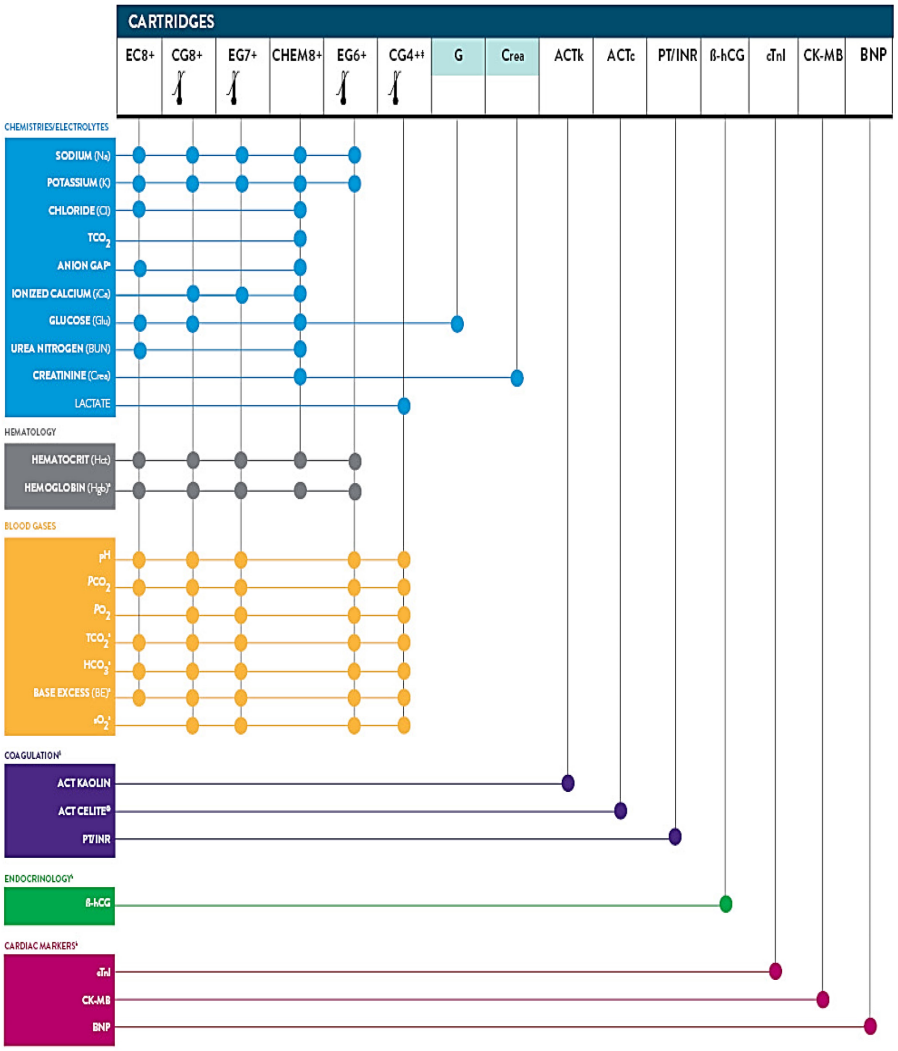
APPENDIX A: SEPSIS PATIENT MANAGEMENT CHECKLIST

If sepsis is suspected, the following checklist should be employed to begin treatment and set up a safety net for ongoing patient care:

- ☐ Placement of 2 IV access points (Large bore IV/IO).
- ☐ Collect blood cultures x2 (if available).
- ☐ Start IVF with goal resuscitation of adequate urine output, up to maximum bolus of 30ml/kg (usually about 2-3 Liters). See Resuscitation recommendations.
- ☐ Consider placement of advanced monitoring equipment (if available).
- ☐ Place a Foley catheter.
- ☐ Monitor all vital signs and continuously trend heart rate, blood pressure, respiratory rate, and mental status every 15 minutes on a flowsheet. (See *JTS Documentation PFC CPG*). Temperature and urine output should be documented hourly.
- ☐ Place on oxygen if indicated and available (for SpO2 < 92%).
- ☐ Ensure a secure airway is in place, or the equipment for a definitive airway is on hand along with the elements of M.S.M.A.I.D. (See *JTS Airway Management for Prolonged Field Care CPG*.)
- ☐ Search for the source of infection. Address this as appropriate (wound care, removal of infected catheters, surgical consultation, etc.)
- ☐ Give the most appropriate antibiotics.
- ☐ Call telemedicine consultant early and often.
- ☐ Take/Give Approach: Take – Vital signs, neurologic assessment, wound/ skin infection exams, serum lactate level, urine output (Foley catheter), rapid tests. Give – Antibiotics, Fluids, Oxygen (if available), Vasopressors (with telemedicine).
- ☐ If providing nutrition, monitor for signs of GI upset or obstruction: nausea, abdominal pain, and abdominal distension.

APPENDIX B: I-STAT LAB VALUES

The laboratory values shown in the table are a composite of the laboratory values, by cartridge, that i-STAT has available. Lab values that may indicate sepsis are elevated lactic acid (lactate), procalcitonin (PCT), and white blood cell (WBC) count. See the *i-STAT Portable Blood Analyzer in Austere Locations CPG*. The values represent a peripheral venous collection. Lab results should be compared to the i-STAT normal range shown in the reference table. *(Preprinted with permission from Abbott Labs, July 2020)*



*Calculated-note that TCO_2 is measured on CHEM8+ cartridge and calculated on all others.
§See individual cartridge web pages for intended use information.
Celite is a registered trademark of Celite Corporation, Santa Barbara, CA for its diatomaceous earth products.

= CLIA waived: granted waived status for lithium heparin whole-blood venous samples only collected in a lithium heparin evacuated tube.

ANALYTE	REPORTABLE RANGE	REFERENCE RANGE, ARTERIAL	REFERENCE RANGE, VENOUS
Sodium (Na)	100-180 mmol/L	138-146 mmol/L	138-146 mmol/L
Potassium (K)	2.0-9.0 mmol/L	3.5-4.9 mmol/L	3.5-4.9 mmol/L
Chloride (Cl)	65-140 mmol/L	98-109 mmol/L	98-109 mmol/L
TCO_2	5-50 mmol/L	23-27 mmol/L	24-29 mmol/L
Anion Gap*	(-10)-(+99) mmol/L	10-20 mmol/L	10-20 mmol/L
Ionized Calcium (iCa)	0.25-2.50 mmol/L	1.12-1.32 mmol/L	1.12-1.32 mmol/L
Glucose (Glu)	20-700 mg/dL	70-105 mg/dL	70-105 mg/dL
Urea Nitrogen (BUN)	3-140 mg/dL	8-26 mg/dL	8-26 mg/dL
Creatinine (Crea)	0.2-20.0 mg/dL	0.6-1.3 mg/dL	0.6-1.3 mg/dL
Lactate§	0.30-20.0 mmol/L	0.36-1.25 mmol/L	0.90-1.70 mmol/L
Hematocrit (Hct)	15-75 %PCV	38-51 %PCV	38-51 %PCV
Hemoglobin (Hgb)*	5.1-25.5 g/dL	12-17 g/dL	12-17 g/dL
pH‡	6.50-8.20‡	7.35-7.45	7.31-7.41
PCO_2‡	5-130 mmHg‡	35-45 mmHg	41-51 mmHg
PO_2‡	5-800 mmHg‡	80-105 mmHg	
TCO_2*	5-50 mmol/L	23-27 mmol/L	24-29 mmol/L
HCO_3*	1.0-85.0 mmol/L	22-26 mmol/L	23-28 mmol/L
Base Excess (BE)*	(-30)-(+30) mmol/L	(-2)-(+3) mmol/L	(-2)-(+3) mmol/L
sO_2*	0-100 %	95-98 %	
ACT Kaolin	50-1000 Seconds	74-137 Seconds (Prewrm)	74-137 Sec. (Prewrm)
ACT Celite®	50-1000 Seconds	74-125 Seconds (Prewrm)	74-125 Sec. (Prewrm)
PT/INR	0.9-8.0 INR^		
ß-hCG	5.0-2000.0 IU/L		<5 IU/L
cTnI	0.00-50.00 ng/mL		0.00-0.08 ng/mL#
CK-MB	0.0-150.0 ng/mL		0.0-3.5 ng/mL#
BNP	15-5000 pg/mL		<15-50 pg/mL#

EXPECTED VALUES

‡ Reportable ranges for the (blue) CG4+ cartridge are: pH = 7.00-7.70; PO_2 = 15-530; PCO_2 = 15-130

^ Performance characteristics have not been established for INR values over 6.0.
# Represents the 0-99% range of results.
* Represents the 0-95% range of results.

APPENDIX C: ABNORMALITIES DETECTION

Urine Dipstick: A dipstick — a thin, plastic stick with strips of chemicals on it — is placed in the urine to detect abnormalities. The chemical strips change color if certain substances are present or if their levels are not normal. The color variation often is indicative of how severe the abnormality is. Urine dipsticks are another tool and indicator to measure a patient's well-being. Its values should be included in the "whole patient" approach to the medical evaluation. A dipstick test checks for:

- **Acidity (pH).** The pH level indicates the amount of acid in urine. Abnormal pH levels may indicate a kidney or urinary tract disorder or a potential systemic infection – sepsis.

- **Concentration**. A measure of concentration, or specific gravity, shows how concentrated particles are in your urine. A higher than normal concentration often is a result of not drinking enough fluids. In the setting of sepsis, it is a sign of clinically significant volume depletion.

- **Protein**. Low levels of protein in urine are normal. Small increases in protein in urine usually are not a cause for concern, but larger amounts may indicate a kidney problem.

- **Sugar**. Normally the amount of sugar (glucose) in urine is too low to be detected. Very high levels of glucose, especially when ketones are also elevated and pH decreased, can indicate diabetic ketoacidosis which may mimic sepsis. This can occur in individuals who were not previously aware they are diabetic and is a life-threatening condition, obtain telemedicine consult.

- **Ketones**. As with sugar, high levels of ketones detected in your urine could be a sign of diabetic ketoacidosis. Ketones in urine may also be a sign of malnutrition and protein-calorie deficit in the septic patient that should prompt consideration of starting caloric intake or enteral nutrition.

- **Bilirubin**. Bilirubin is a product of red blood cell breakdown or bile synthesized in the liver. Normally, bilirubin is carried in the blood and passed into the liver, where it is conjugated and becomes part of bile. Bilirubin in your urine may indicate liver damage, bile duct obstruction, or hemolysis (e.g., distributed intravascular coagulopathy).

- **Evidence of infection**. If either nitrites or leukocyte esterase — a product of white blood cells — is detected in your urine, it may be a sign of a urinary tract infection or systemic infection – sepsis.

- **Blood**. Blood in your urine requires additional testing — it may be a sign of kidney damage, infection, kidney or bladder stones, kidney or bladder cancer, or blood disorders.

APPENDIX D: MALARIA RAPID TEST & MICROSCOPY

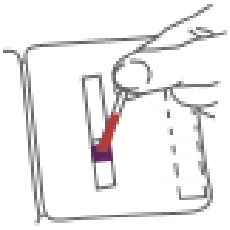
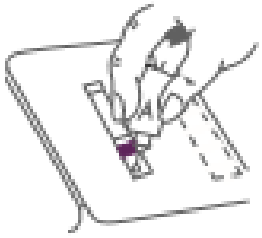
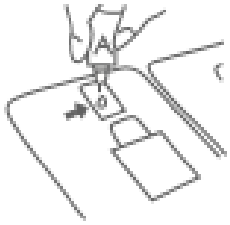
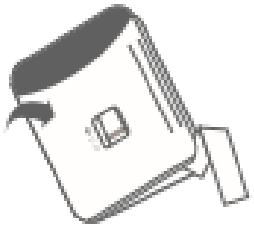
Reprinted with permission from Abbott Labs, July 2020.

BINAXNOW®

The BinaxNOW® Malaria test is a rapid and simple diagnostic test that can differentiate a deadly P. falciparum infection from a pan-malarial infection caused by P. vivax, P. ovale or P. malariae in 3 simple steps using 1 reagent. Typically, the limiting factor for mass-testing is the amount of reagent on-hand.

- Results appear in 15 minutes
- Sensitivity: 99.7% (P.f.); 93.5% (P.v.)
- Specificity: 94.2% (P.f.); 99.8% (P.v.)

Directions for BinaxNOW Use

Step 1	Step 2	Step 3	Step 4
Apply 15uL of blood to the bottom half of the purple pad.	Apply 2 drops of Reagent to the white pad immediately below where the blood was applied.	Apply 4 drops of Reagent to the pad located at the top of the left-hand side of the test card.	When the blood sample reaches the base of the white absorbent pad at the top of the test strip, close device and read after 15 minutes.
			

Binaxnow Results Table

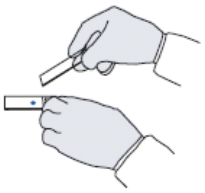
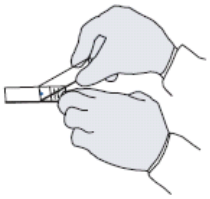
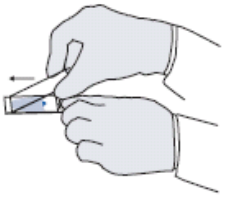
Positive P. Falciparum Mixed	Positive P. Falciparum	Positive P. Vivax P. Ovale P. Malariae	Negative
			

MICROSCOPY

When done correctly, microscopic examination of thick and thin blood smears is the most reliable test for malaria. Blood smears are taken most often from a finger prick and a few drops of blood. Thick and thin blood smears allow direct visualization of parasites and their reproductive derivatives – schizonts in malaria. See *U.S. Department of Defense. Special Operations Forces Medical Handbook. 2011.*

- A thick blood smear is a drop of blood on a glass slide. Thick blood smears are most useful for detecting the presence of parasites, because they examine a larger sample of blood. (Often there are few parasites in the blood at the time the test is done).
- A thin blood smear is a drop of blood that is spread across a large area of the slide. Thin blood smears help providers discover what species of malaria is causing the infection.
- The two smears can work in tandem if a thick and thin smear is made. This method allows the provider to observe both thick and thin smears and find the blood density that is most likely to yield visualization of the parasite to the given observer.
- If a high index of suspicion exists for malaria in a given patient, but microscopy does not reveal an obvious malarial infection, serial thick and thin smears can be repeated every 8 or 24 hours depending on the severity of the case.

Making a thick and thin smear

Step 1	Step 2	Step 3	Step 4	Step 5
Bring a clean spreader slide, held at a 45-deg. angle, toward the drop of blood on the specimen slide.	Wait until the blood spreads along the entire width of the spreader slide.	While holding the spreader slide at the same angle, push it forward rapidly and smoothly.	Wait until the smear is completely dry. Fix the thin film with 100% (absolute) methanol.	When the film is completely dry, stain with 7.5% Giemsa stain for 15 minutes.
				

The thick and thin film should be air-dried, fixed with 100% (absolute) methanol, and allowed to dry before staining with 7.5% Giemsa stain for 15 minutes. Plasmodium parasites are always intracellular, and they demonstrate, if stained correctly, blue cytoplasm with a red chromatin dot (see images 1-4 below). Common errors in reading malaria films can be caused by platelets overlying a red blood cell, concern regarding missing a positive slide, and misreading of artifacts as parasites. The slide is best read by starting at the thin end of the slide and moving it towards the thick side until the RBCs are side by side, but NOT overlapping. This will give the observer the highest concentration of RBCs in view, giving him or her the highest probability of identifying the parasite. Move the slide along this plane of side-by-side RBCs to accurately rule out or in a malarial parasitic infection (Image 1). If the malaria parasite is identified, begin appropriate anti-malaria/anti-parasite treatment immediately in conjunction with the antibiotic therapies (minimum, better, best) mentioned above.

Malaria parasites

Images 2-4 demonstrate plasmodium within cells with the characteristic "signet ring" sign.

Image 1. *Malaria parasites are identifiable by their blue stain inside the cells. This picture shows an excellent example of a properly prepared thick/thin smear – the cells are side by side without overlapping.*

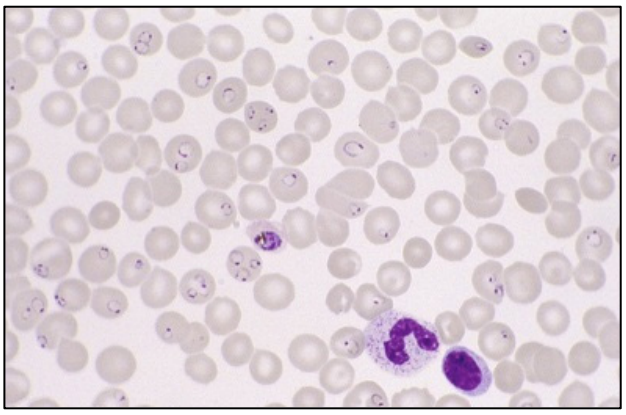


Image 2

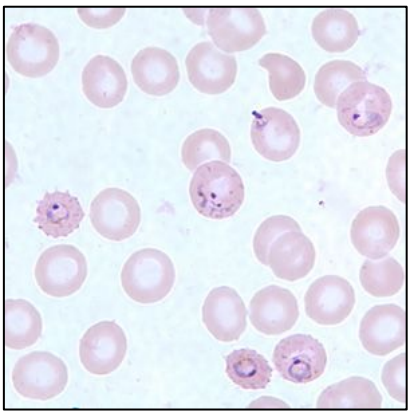


Image 3

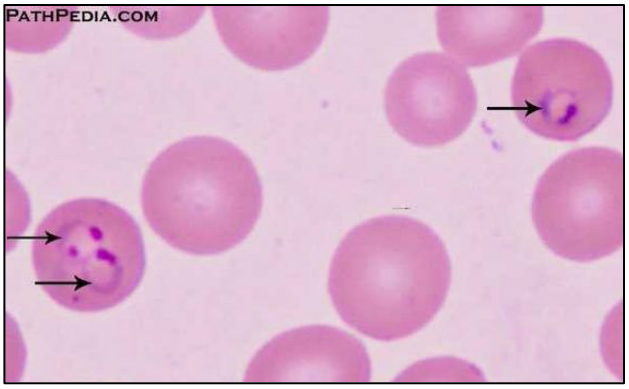
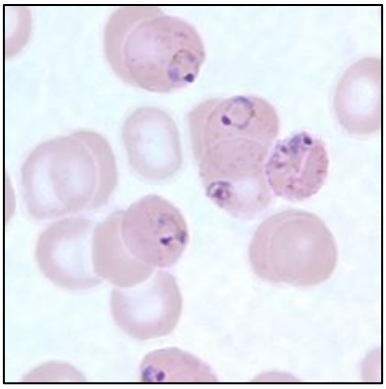


Image 4



Images 2-4 from cdc.gov; image 3 from pathpedia.com.

APPENDIX E: LACTATE

Lactate can be measured with the CG4 i-STAT cartridge. This specific cartridge must be stored in a temperature-controlled environment. Lactate can also be measured using a lactate-specific device but many are not approved for medical management of critical patients.[1]

Adding lactate to other resuscitation endpoints is beneficial, however patients should be monitored using a "whole patient" approach. He or she could be doing well clinically with an adequate blood pressure and capillary refill, good urine output, and down-titrating vasopressors, but continues to have a persistently elevated lactate level. There are many reasons for this, some of which do not require a clinical response, only further monitoring. Lactate levels have a direct impact on a patient's pH (acidosis), however the main adverse effects of acidosis are a) decreased cardiac output and vascular "tone," which will be seen as persistent hypotension and b) impaired coagulation, which will be seen as bleeding despite adequate blood product resuscitation and source control. In general, these effects do not occur at a pH above 7.2 (which does not correlate directly to a specific lactate level).

If lactic acid levels are available, they should be integrated into patient monitoring as follows:

- Trend lactic acid levels at a frequency of every 4 – 6 hours. Lactate improvement will lag behind improvement in vital signs, mental status, and urine output.
- If patient is under-resuscitated, or resistant to resuscitation, vital signs and organ dysfunction assessments will continue to be abnormal, with no appreciable response, and lactate will remain elevated.
- If other markers of resuscitation are improving and the patient is clinically improving, but lactate is not decreasing or is increasing, it could be an indication of tissue reperfusion (flushing out vascular beds that have not been perfused due to shock). Keep trending lactate, and if it remains elevated or is increasing, this could be an indication of a source of infection that has not been adequately addressed and may require a change in antibiotic regimen, and/or surgical intervention. Obtain telemedicine consult.

1. *Bonaventura JM, Sharpe K, Knight E, et al. Reliability and accuracy of six hand-held blood lactate analysers. J Sports Sci Med. 2015 Mar 1;14(1):203-14.*

APPENDIX F: EPINEPHRINE (NOREPINEPHRINE) - VASOPRESSOR GUIDE

Consider starting low dose vasopressors – either epinephrine, or norepinephrine if available -after 30mL/kg of IVF and no changes in MAP, urine output or mentation.[1] Epinephrine can improve blood pressure by a) vasoconstriction and b) increasing cardiac contractility, thus improving cardiac output.[2] Vasopressors are rarely used outside of a critical care setting and use in an austere environment indicates a dire situation and must be monitored extremely closely. The dose of either epinephrine or norepinephrine are the same for drip calculations. Epinephrine is presented as it is far more available in austere practice settings. These are presented as low-dose starting points and any adjustments should be directly under telemedicine guidance. Of note: if monitoring, levels of lactate may rise with use of epinephrine as a vasopressor.

Epinephrine, as an IV or IO push-dose: A 10mL syringe consisting of 9mL of Normal Saline (0.9% NaCl) with 1mL of cardiac epinephrine (1:10,000 or 100mcg/mL). Administer to acutely correct a blood pressure indicative of shock (systolic <90). Administer a lower-end dose (0.5 – 1mL) while preparing a longer-term IVF drip (below).

- Concentration: 10mcg epinephrine/mL
- Onset: 1 minute
- Duration: 5 – 10 minutes
- Dose: 0.5 – 2mL every 2 – 5 minutes (5 – 20mcg)
- Administration: very slow IV push. 1 cc/min for 10 minutes. Rapid administration can cause rebound tachycardia, hypertensive emergency, and cardiac arrest.

Epinephrine as a vasopressor drip: Epinephrine; 4mcg/min bag reference chart. This dose is a starting/maintenance point in the application of an epinephrine (vasopressor) IV drip bag – Epinephrine Challenge. Gold-standard hospital practice utilizes a central line for this intervention; however, in an austere setting, peripheral antecubital access is acceptable (humeral, tibial, and sternal IO are also acceptable if flow rate can be precisely managed). The drip rate should be adjusted up, down or discontinued depending on the perfusion or vitals status of the patient. Once a vasopressor is started, the patient must be constantly monitored. Whenever possible, telemedicine consultation is required when vasopressor support is initiated.

Epinephrine 1:10,000 (Adrenaline) or Norepinephrine (Levophed) Drip Table

0.9% NaCl IVF Bag Size	Add to bag: EPI (or NOREPI): 1:10,000 (0.1 mg or 100mcg)/mL	Starting Dose (mcg/min)	DRIP SET:10gtts (Drops/mL) DRIP RATE: (Drops/min or gtts/min)	DRIP SET: 15gtts (Drops/mL) DRIP RATE: (Drops/min or gtts/min)
50mL	1mL (100mcg)	4 mcg/min	20 drops/min	30 drops/min
100mL	2mL (200mcg)	4 mcg/min	20 drops/min	30 drops/min
250mL	5mL (500mcg)	4 mcg/min	20 drops/min	30 drops/min
500mL	10mL (1mg)	4 mcg/min	20 drops/min	30 drops/min
1000mL (1L)	20mL (2mg)**	4 mcg/min	20 drops/min	30 drops/min

***This is the least recommended approach as it commits a high volume of epinephrine to a large bag. If the patient's vital signs (BP/MAP/HR) stabilize, the bag must be discontinued and the medic risks wasting some of his or her resources – "you can mix a drug in an IV bag, but you can't take it out."*

Key point: If administering epinephrine infusion via a peripheral IV, monitor the IV site with every vital signs check for signs of redness, swelling or induration (firm, chord-like feeling of vessel above IV site). If any of these are present, epinephrine may be leaking out of the IV ("extravasating") which can cause permanent scarring and damage to the vessel. Stop the infusion immediately and seek telemedicine consultation.

WARNING

Vasopressors are extremely potent medications. Besides the risk associated with peripheral infusions, dosing must be strictly monitored, and care must be taken to ensure proper dose is being consistently delivered. Providers should expect to see increases in both heart rate and blood pressure, but extreme tachycardia (as a sign of malignant cardiac rhythms) should prompt stopping the infusion and consulting telemedicine advice. Careful medical history should be obtained and patients with hypertension and/or coronary artery disease should only be administered these medications under strict guidance.

Use IV hydrocortisone, 100 mg every 8 hours, for at least 3 days in a military-aged male to treat septic shock in patients if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability. Due to the low volume and quality of evidence with this intervention, telemedicine is required before IV hydrocortisone is initiated as a treatment.[3]

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APPENDIX G: ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGS

PURPOSE

The purpose of this Appendix is to ensure an understanding of DoD policy and practice regarding inclusion in CPGs of "off-label" uses of U.S. Food and Drug Administration (FDA)–approved products. This applies to off-label uses with patients who are armed forces members.

BACKGROUND

Unapproved (i.e. "off-label") uses of FDA-approved products are extremely common in American medicine and are usually not subject to any special regulations. However, under Federal law, in some circumstances, unapproved uses of approved drugs are subject to FDA regulations governing "investigational new drugs." These circumstances include such uses as part of clinical trials, and in the military context, command required, unapproved uses. Some command requested unapproved uses may also be subject to special regulations.

ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGS

The inclusion in CPGs of off-label uses is not a clinical trial, nor is it a command request or requirement. Further, it does not imply that the Military Health System requires that use by DoD health care practitioners or considers it to be the "standard of care." Rather, the inclusion in CPGs of off-label uses is to inform the clinical judgment of the responsible health care practitioner by providing information regarding potential risks and benefits of treatment alternatives. The decision is for the clinical judgment of the responsible health care practitioner within the practitioner-patient relationship.

ADDITIONAL PROCEDURES

Balanced Discussion

Consistent with this purpose, CPG discussions of off-label uses specifically state that they are uses not approved by the FDA. Further, such discussions are balanced in the presentation of appropriate clinical study data, including any such data that suggest caution in the use of the product and specifically including any FDA-issued warnings.

Quality Assurance Monitoring

With respect to such off-label uses, DoD procedure is to maintain a regular system of quality assurance monitoring of outcomes and known potential adverse events. For this reason, the importance of accurate clinical records is underscored.

Information to Patients

Good clinical practice includes the provision of appropriate information to patients. Each CPG discussing an unusual off-label use will address the issue of information to patients. When practicable, consideration will be given to including in an appendix an appropriate information sheet for distribution to patients, whether before or after use of the product. Information to patients should address in plain language: a) that the use is not approved by the FDA; b) the reasons why a DoD health care practitioner would decide to use the product for this purpose; and c) the potential risks associated with such use.