Chapter 37

MANAGEMENT OF INFECTION AND SEPSIS IN THE INTENSIVE CARE UNIT

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INTRODUCTION

From an infection perspective, the intensive care unit (ICU) in a deployed military facility is in many ways no different from that in a civilian hospital. Patients are admitted who are acutely ill, as a result of either a primary community-acquired infection or an infection secondary to another event such as trauma. Management decisions are based on the clinical features of the disease process, specialized investigations including laboratory testing, and a knowledge of local disease epidemiology. However, some differences exist between the two settings, and this chapter explores how careful consideration of all the factors involved may lead to improved decision making.

Areas that will be covered include:

- sources of infection, including trauma and community-acquired infections;
- the "sepsis syndrome" and its clinical management;
- determination of likely pathogens involved, including knowledge of the local epidemiology of infectious diseases and microbial resistance patterns, and laboratory investigations; and
- control of the spread of microorganisms, including infection control and antibiotic policies.

SOURCES OF INFECTION

Although it is easy to become focused on current conflicts and the clinical spectrum of patients managed in ICU, predominantly trauma related, it is important to remember that these conditions may not be typical for all military conflicts. For example, in the early stages of the 2003 campaign in Iraq, the majority of ICU admissions were patients with severe illness caused by acute infective pneumonia, and relatively few battle casualties occurred.[1] During operations in Afghanistan some patients have been managed in the ICU as a direct result of a number of different community-acquired infections. These infections have included cases of *Streptococcus pneumoniae* bacteremia secondary to pneumonia, *Neisseria meningitidis* meningitis, Crimean-Congo hemorrhagic fever, rabies, tetanus, and *Escherichia coli* bacteremia secondary to urinary tract infection (AD Green, written communication, August 2013). Although the saying "common things occur commonly" remains true, it is important to reflect that by implication "rare things occur rarely" and still plan accordingly.

For other patients in intensive care, there can be significant challenges in trying to determine whether clinical infection is present (ie, a disease process) and if so, determine the likely etiological cause. For many patients the normal indicators of disease are heavily modified or obscured by the underlying medical condition and are unreliable means for assessment. Examples include temperature, pulse and respiratory rates, and peripheral white blood cell count. Laboratory markers of an acute phase response such as C-reactive protein may be helpful, but they can be modified by nonspecific responses to inflammatory conditions including trauma, and must be judged over time and in context. Microbiological investigations may also be misleading, since a patient's flora changes rapidly when normal physical barriers are compromised and antimicrobial agents are used.

Colonization and Infection

During recent conflicts there has been understandable concern over the isolation of multidrug-resistant (MDR) bacteria from injured personnel in deployed hospitals and the limited antibiotic options available to combat these organisms. Clinicians have a very low threshold for starting broad, aggressive therapy following isolation of these organisms from patients' samples. However, the bacteria isolated often colonize only, without causing disease, and the broad-spectrum antimicrobials prescribed will only further alter the patient's flora, selecting for the most resistant organisms.

Healthy people have a variety of microorganisms that inhabit their skin and mucous membranes. This flora can be split into (1) resident flora, a fixed variety of microorganisms that is normally age- and patient-dependent and will reestablish itself following a disturbance, and (2) transient flora, a mix of nonpathogenic and potentially pathogenic microorganisms that inhabit the skin or mucous membranes for hours to weeks and may cause illness.[2] A variety of factors may change this normal flora, with the use of broad-spectrum antimicrobials and the nosocomial introduction of new microorganisms in the healthcare setting being of particular importance. These two factors may be responsible for the MDR Gram-negative organisms isolated from patients along the evacuation chain in Iraq and Afghanistan.[3]

Once patients are colonized with these MDR bacteria, the big challenge is differentiating between simple colonization by the bacteria and infection causing disease. Contamination can be defined as the presence of

nonreplicating organisms in a wound, and colonization as the presence of replicating organisms.[4] Infection is a clinical diagnosis and indicates the presence of replicating organisms with host injury, often with invasion of the bacteria into tissue.

The presence of host injury and infection, rather than colonization, can often be difficult to determine by clinical examination. Traditional clinical signs of wound infection include inflammation, discharge of pus, and abscess formation. Many wound-scoring systems, especially those focusing on chronic wounds, now include other more subtle signs of wound infection such as delayed wound healing, pocketing at the base of the wound, abnormal smell, and discoloration.[5] The United Kingdom surgical site infection surveillance schemes are based on the US Centers for Disease Control and Prevention definitions from 1992, with superficial or deep incisional wounds having to fulfill specific criteria to be classified as infected.[6]

Wounds

In a deployed setting, infected wounds are a major source of sepsis. Following the loss of the protective layer of skin, open wounds will be colonized with microbes. This wound colonization is not necessarily a bad thing, with the presence of low levels of microbes able to accelerate the wound healing process by increasing the inflammatory response and local blood flow.[7] There then exists a spectrum from colonization, through local infection or critical colonization, to invasive infection.[8] The progression to critical colonization is often characterized by a wound that has no signs of tissue invasion but is not healing as expected.[9–11]

Ventilators

Other major causes of sepsis in the deployed ICU are nosocomial infections from catheter lines and pneumonia following intubation and ventilation. In both cases the normal anatomical barriers to infection—an important part of the innate immune system—have been disrupted.

In a study of ventilator-associated pneumonia (VAP) in Operation Iraqi Freedom, Landrum and Murray found the most common isolated organism was *Acinetobacter* species, followed by *Klebsiella pneumoniae*, and then *Pseudomonas aeruginosa*.[12] Although many factors can lead to ventilator-associated pneumonia, and it is a common complication seen in civilian practice, of particular note in this study was that the rates of VAP and the number of resistant isolates were reduced following the introduction of targeted infection control measures.

Intravascular Lines

Intravenous catheter lines can become contaminated at various points, in particular the catheter hub/infusion tubing junction and at the point of insertion into the skin. Many risk factors for line-associated bacteraemia exist, in particular alteration of the patient's cutaneous microflora (most commonly by antibiotics or colonization with an epidemic strain carried by hospital personnel), active infection at another site, and failure of the healthcare provider to wash his or her hands.[13] The excessive use of broad-spectrum antibiotics combined with poor infection control practices—both of which are very difficult to avoid in a deployed setting—can lead to increased catheter line infection rates and patient morbidity.

Biofilms

The bacteria that cause such concern are able to thrive in the hospital environment due to a number of virulence mechanisms that increase the disease-causing potential of the organism. Certain virulence factors are not found in all bacteria of a species, but only in disease-causing subtypes; for example, strains of *Streptococcus pyogenes* that contain the gene for the M1 protein are associated with more invasive disease and necrotizing fasciitis.[14] In catheter line infection, ventilator-associated infection, and wound infections, the development of a biofilm is a key virulence mechanism. Bacteria produce a biofilm to protect themselves. Biofilm is an extracellular polysaccharide matrix that forms once the colonies reach a particular size. The bacteria are able to detect the size of their colony, develop a mature biofilm, and respond to factors such as nutrient availability by a process called quorum sensing—communication between bacteria using signalling molecules.[15] The biofilm provides mechanical protection to the bacteria, preventing antibiotic penetration and the patient's phagocytic cells from attacking the colony.[16] Bacteria in a biofilm are substantially more resistant to antibiotic treatment than planktonic bacteria (floating outside a biofilm); therefore, although an organism may appear sensitive to a drug in the laboratory, bacteria with biofilm will not be affected and the patient will not improve despite antimicrobial therapy.[17,18] The ability of *Acinetobacter baumannii* to survive so well in hospital environments is due to many virulence factors, especially its ability to form a biofilm on a variety of biological and abiotic surfaces.[19] This ability to survive in the hospital environment was demonstrated in a cluster of VAP cases in Canadian soldiers injured in Afghanistan. The source of the isolate was thought to be environmental, from

the Kandahar military hospital, and the *Acinetobacter baumannii* isolate in four soldiers was indistinguishable from an isolate found growing on a ventilator air intake filter.[20]

SEPSIS

"Sepsis" has been defined by a consensus agreement between the American College of Chest Physicians and the Society of Critical Care Medicine.[21] The definition has been accepted internationally and is used by the global Surviving Sepsis Campaign initiated in 2004. The definition states that sepsis is the presence of a systemic inflammatory response syndrome resulting from infection (Exhibit 37-1). Severe sepsis exists when organ dysfunction develops. When a patient becomes hypotensive despite adequate fluid resuscitation, he or she is in septic shock.[22] Septic shock represents a state of vasopariesis and maldistribution of fluid rather than fluid deficit. Early fluid resuscitation is a temporizing measure that may mitigate poor organ perfusion while vasopressor therapy, appropriate antibiotic therapy, and source control are instigated.

Managing the Patient: The Surviving Sepsis Campaign

The Surviving Sepsis Campaign promotes a set of guidelines agreed upon by an international editorial board following a comprehensive literature review, most of which are directly transferable to the military setting.[23] The guidelines divide management of the septic patient into three parts: (1) the initial resuscitation bundle (Exhibit 37-2), occurring over the first 6 hours; followed by (2) a sepsis management bundle (Exhibit 37-3) extending up to 24 hours; and (3) other supportive therapy (Exhibit 37-4). Although described in sequence, the interventions recommended by the guidelines are implemented concurrently and as soon as possible.

The Resuscitation Bundle

Achieving the initial resuscitation bundle reduces mortality in sepsis by 50%, and treatment should begin as soon as severe sepsis is recognized and before the patient arrives at the ICU. Obtaining cultures before antibiotic administration provides the best chance of

EXHIBIT 37-1

CRITERIA FOR THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Two of the four following parameters in the presence of inflammation:

- temperature (> 38°C or < 36°C)
- white blood cell count (< 4 or > 12 x 109 [or > 10% immature forms])
- tachycardia (HR > 90 bpm)
- tachypnea (RR > 20 min^{-1} [or a $PaCO_2$ < 32 mmHg/4.3 KPa])

bpm: beats per minute
HR: heart rate
$PaCO_2$: partial pressure of arterial carbon dioxide
RR: respiratory rate

EXHIBIT 37-2

THE RESUSCITATION BUNDLE

Bundle Element	Notes
1. Measure serum lactate.	
2. Obtain cultures prior to administering antibiotics.	Obtain all relevant cultures: blood, sputum, urine, tissue, pus, CSF.
3. Administer broad-spectrum antibiotics.	As soon as possible and preferably within the hour.
4. Treat hypotension and/or a lactate > 4 mmol/L.	Administer fluid boluses while patient is fluid responsive and subsequently begin vasopressors to maintain MAP > 65 mm Hg.
5. Obtain source control.	Surgical debridement, percutaneous drainage, or removal of invasive lines.
6. Determine targets for ongoing use of fluid and vasopressors.	Achieve a CVP of > 8 mm Hg, an $ScvO_2$ of > 70%, or an $ScvO_2$ of > 65% and a urine output of 0.5 mL/kg/h.

CSF: cerebrospinal fluid
CVP: central venous pressure
MAP: mean arterial pressure
$ScvO_2$: central venous oxygen saturation
SvO_2: mixed venous oxygen saturation

EXHIBIT 37-3

THE SEPSIS MANAGEMENT BUNDLE

Intervention	Notes
Fluid therapy	Give 1,000 mL/500 mL fluid challenges with crystalloid/colloid respectively to achieve a CVP of 8 mm Hg.
Vasopressors	Use norepinepherine or dopamine to achieve an MAP of 65 mm Hg. Vasopressin 0.03 units/min. Add epinephrine if hemodynamics are deteriorating.
Inotropic therapy	Use dobutamine in presence of myocardial dysfunction (as demonstrated on trans-thoracic echo when deployed).
Steroids	Add hydrocortisone to a maximum dose of 300 mg/day.
Recombinant human activated protein C	Consider in adult patients with multiple organ failure and no contraindications.

CVP: central venous pressure
MAP: mean arterial pressure

EXHIBIT 37-4

OTHER SUPPORTIVE THERAPY

Intervention	Notes
Blood product administration	Target hemoglobin of 7.0–9.0 g/dL. Only correct deranged clotting with fresh frozen plasma if bleeding or invasive procedures are planned.
Mechanical ventilation	Nurse patient with the head up 45°. Provide a tidal volume at 6 mL/kg (predicted body weight) with a peak pressure of ≤ 30 cm H_2O. Tolerate hypercarbia. Use a sedation and weaning protocol including sedation holds and spontaneous breathing trials.
Glucose control	Keep blood glucose < 150 mg/dL (8.3 mmol/L).
DVT prophylaxis	Use a mechanical prophylactic device if low molecular or unfractionated heparin is contraindicated.
Stress ulcer prophylaxis	A proton pump inhibitor may be preferable to an H_2 blocker in thrombophilia.

DVT: deep vein thrombosis

obtaining a meaningful result, although this should not be allowed to delay antibiotic administration unduly. Cross-sectional imaging may be required when the source of sepsis is not obvious.

Antibiotics are a vital and time critical intervention that must be a priority for the managing clinicians; mortality in patients with septic shock increases by 7% per hour that administration of appropriate antibiotics is delayed.[24] The choice of antibiotic should be protocol driven, but will initially be broad spectrum with the aim of deescalating to more targeted therapy once culture results become available. The choice of antimicrobial agents will be determined by local epidemiology of disease and microbial resistance patterns, and by the availability of drugs in the deployed formulary.

The resuscitation targets are derived from a study examining early goal-directed resuscitation protocols, which showed a reduction in 28-day mortality (30.5% vs 46.5%) and less organ dysfunction in the treatment group.[25] In ventilated patients or in those with intraabdominal hypertension, the CVP target should be revised upward to at least 12 mm Hg. Invasive cardiac output monitoring is not currently available in most deployed settings; transthoracic echo may be available and can provide useful information about volume status and cardiac performance.

The guidelines support the use of crystalloid and colloid equally, and a mixture of a balanced salt solution and synthetic colloid is often used. If despite perceived adequate fluid resuscitation the central venous oxygen saturation remains below 65%, then oxygen delivery should be augmented through transfusion of packed red blood cells to reach a hematocrit of 30% or alternatively by starting a dobutamine infusion (3–20 μg/kg/min). An epinephrine infusion (0.04–0.4 μg/kg/min) is an acceptable alternative to adding dobutamine to a preexisting norepinephrine infusion. The guidelines support the use of dopamine (1–20 μg/kg/min) as an alternative to norepinephrine, although the increased incidence of arrhythmias should be noted.

The Sepsis Management Bundle

Noncompliance with the sepsis management bundle of hemodynamic support and adjunctive therapy results in a significant increase in mortality.

Fluid challenges targeting central venous pressure and lactate should continue while the patient's central venous pressure remains fluid responsive, and the mean arterial pressure should be maintained at 65 mm Hg or above. Intravenous hydrocortisone (50 mg, every 6 hours) should be added in the presence of an increasing vasopressor requirement. An adrenocorticotropic hormone test is no longer recommended and not practical in the deployed environment.

Vasopressin (an antidiuretic hormone) causes vasoconstriction via activation of V1 receptors on vascular smooth muscle while also mediating coronary, renal, pulmonary, and cerebral vasodilatation in low doses. Plasma vasopressin levels fall rapidly in septic shock. Vasopressin administration improves blood pressure and renal function, but the only large randomized control trial completed so far found no difference in mortality when compared to norepinephrine.[26] It did, however, demonstrate a synergistic effect when vasopressin and steroids are combined, which resulted in both a statistically and clinically significant reduction in mortality. At doses exceeding 0.04 units per minute, vasopressin decreases cardiac output and causes myocardial ischemia and renal vasoconstriction.

Other Measures

Although not in the Surviving Sepsis guidelines, high-dose intravenous immunoglobulin and methylene blue are occasionally used in some facilities in cases of severe sepsis. Polyclonal immunoglobulin may suppress the inflammatory response to infection, although it may remain impractical until the casualty reaches a homeland facility. Dose is preparation dependent and outlined in Table 37-1. Methylene blue (2 mg/kg bolus followed by an infusion of 1 mg/kg/h for 12 hours) inhibits nitric oxide-mediated vasodilation and may have a vasopressor-sparing action. The evidence base for its use is currently scanty.

TABLE 37-1

DOSES OF INTRAVENOUS IMMUNOGLOBULIN

Preparation	Dose
Intraglobin	250 mg/kg over 2 days
Sandoglobin	400 mg/kg/day for 3 days
Endobulin	1 gm/kg on day 1, then 500 mg/kg on days 2 and 3
Pentaglobin (IgM enriched)	1,300 mL within 72 h

Septic patients occasionally demonstrate tachyphylaxis to vasopressor agents, requiring alternative use of agents and the addition of agents not normally used in this context such as phenylephrine (0.5–5.0 μg/kg/min).

TAILORING THERAPY

It is possible to develop generic guidelines for all aspects of clinical management of patients in deployed medical facilities, and for most aspects of care, including antimicrobial therapy, this is entirely appropriate.[27] However, geography, environment, and operational context have significant impact on the range of potential pathogens, and in most cases theater-specific guidance is required that reflects local microbial resistance patterns and disease epidemiology. In turn, this mandates that microbiological laboratory support now forms an integral element of deployed medical care, both for early insertion and enduring military operations.

Laboratory Support

Early insertion operations or those with a small medical footprint are generally planned to deploy without discrete laboratory facilities; the medical plan requires immediate evacuation of casualties once stabilized. Any laboratory support required is provided by point-of-care testing and undertaken by either laboratory scientists or medical personnel. In a forward environment the primary role is provision of blood and blood products, and the requirement for microbiological support is limited; patients are not held at the location pending investigations, and those investigations deemed critical are provided by point-of-care testing technology (eg, rapid malaria diagnostics).

For mature and enduring operations the situation is different. Although critically ill casualties will still be evacuated as soon as possible, there is now the requirement to provide extended care. This care might be for Allied forces, local police and military personnel, homeland civilian contract personnel, and local civilians. Intensive care support is most likely to be sited with this level of medical provision. The laboratory requirement is significantly different compared to the light role, with the need for both infectious disease diagnostic capability and appropriate bacteriological support. It is clear from recent operational experiences that "appropriate bacteriological support" is at a much

higher level than previously considered, reflecting the high quality of care now delivered, the increasingly complex resistance patterns of endemic bacteria, and the need to accurately direct antimicrobial therapy.

Antibiotic Guidelines

For deployed medical facilities, antibiotic guidelines are generally divided into trauma-related and non-trauma-related components. For trauma, guidelines recommend the use of particular antimicrobials depending on the area of the body injured, type of injury, level of care (ie, prehospital or hospital), and the time since injury. These are evidence based when possible and kept under regular review.[28] For non-trauma-related infections, guidelines give recommendations based on the differential diagnosis and likely pathogens involved.[27]

Several factors must be considered when developing local guidelines suitable for use in a deployed ICU. In civilian settings ICU guidelines can be tailored to local resistance patterns based on data gathered over many years and adjusted as required by the microbiology or infectious diseases senior consultants. In contrast, no local data will initially be available to inform military guidelines for the deployed hospital, and the guidelines must be adaptable to a wide range of environments and a wide variety of microbial resistance patterns. Deployed hospitals will often lack a deployed specialist microbiologist or infectious diseases specialist to advise on appropriate alternatives.

There are also other constraints not encountered in civilian practice. For example, therapeutic monitoring of drug levels is often unavailable, and there may be difficulties with supply chains for pharmaceuticals. Classes of antibiotics used daily in civilian ICUs include aminoglycosides (such as gentamicin) and glycopeptides (such as vancomycin) that have a narrow therapeutic index, with dose-related side effects. In the absence of monitoring and given the potential for drug toxicity, an alternative antimicrobial with similar cover should be considered (eg, teicoplanin rather than vancomycin). Logistic restraints limit the variety of antibiotics on the formulary. It is easier to maintain stock levels and supply lines for a small number of drugs that are regularly used, sometimes requiring that a suitable rather than ideal option is chosen.

A further requirement is that clinicians must find the guidelines easy to adopt on joining a deployed unit. The drugs in the UK and US guidelines are commonly used in civilian departments and will be familiar to all intensivists. Antibiotic guidelines and prescriptions for operational theaters must also allow for the variation in antibiotic preference and licensing seen between different coalition partners. Different national guidelines will recommend different antibiotics at different points in a patient's treatment. Licensing differences are a common occurrence; eg, the UK Medicines and Healthcare Products Regulatory Agency may not have approved a drug that has been approved by the US Food and Drug Administration (Center for Drug Evaluation and Research). In Afghanistan the International Security Assistance Force contains more than 45 different nations' troops, with two to three nations' medical staff in the deployed hospital at Bastion at any one time. As an example of the potential complexities, a 2006 review of antimalarial chemoprophylaxis of North Atlantic Treaty Organization forces in Afghanistan indicated that every nation had a different policy.[29]

It is now widely accepted that in the face of dwindling numbers of new antibiotics and increasing resistance, antibiotic use must be monitored and controlled. The term often used for this control is antibiotic stewardship, and its aims are to reduce the unintended consequences of antimicrobial use such as toxicity and emergence of resistance.[30] In the deployed setting the use of broad-spectrum antibiotics, and the selection pressure caused by this practice, has been implicated in the increased isolation of MDR organisms from patients. One military study showed that reducing the surgical antibiotic prophylaxis given in an Air Force theater hospital in Iraq to that recommended in US military guidelines reduced the number of VAP cases with MDR organisms.[12] This reflects findings from civilian practice, with studies showing an increased mortality associated with inappropriate antibiotic prescription in patients on a civilian intensive care unit[31] and increased mortality in patients with severe sepsis and shock-complicating gram-negative bacteremia who had recent antibiotic exposure.[32]

The emergence of novel MDR strains of bacteria from central Asia remains a cause for concern, and is subject to active surveillance.[33] One such strain may be actively selected for by widespread use of carbapenem antimicrobials in North Atlantic Treaty Organization forces.[34]

A number of antibiotic stewardship strategies can be used to control antibiotic use and prevent the development of resistance. Although clinician education is important, the main method of stewardship in a deployed setting with rotating personnel is the strict use of antibiotic guidelines. Military guidelines are designed to restrict the use of broad-spectrum antibiotics to situations when they are required, and adherence to the guidelines is essential to prevent the selection pressure that leads to the colonization of patients with resistant organisms. Other options such as telephone approval, antibiotic cycling, heterogeneity of antimi-

crobial use, prior-approval programs, and automatic stop orders either currently lack supporting evidence or would not be practical in a deployed setting because of logistic and communication constraints.[30]

SUMMARY

Infection control in deployed medical facilities is perhaps more important today than ever before because the consequences of failure can be significant and readily visible to a wide audience. The effects may include operational impact, with loss of one or more medical facilities as a result of an outbreak or the control measures employed,[35] and exportation of MDRs to civilian medical facilities in the homeland.[36] The subject is discussed in more detail in Chapter 40, Multidrug-Resistant Organisms and Infection Control Practice in the US Military Medical System. Revised guidance has been recently produced by a joint US-UK group.[37]

In the ICU setting, infection control is important at all times and in the operational setting may be subject to additional pressures. Different patient populations may be managed alongside each other, with some patients rapidly transferring to home countries on evacuation after initial care, while others remain for extended periods.

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