



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Bacteria and Viruses

The Bogeymen in the Intensive Care Unit



Gerald Kayingo, PhD, MMSc, PA-C

KEYWORDS

- Bacteria • Viruses • Sepsis • Nosocomial infections • Pneumonia • Zika • Ebola
- Immunocompromised

KEY POINTS

- Infections and sepsis are the leading causes of death in noncardiac ICUs, especially in areas with a high burden of multidrug antimicrobial resistance.
- The most frequently encountered infections are pneumonia, urinary tract infections, central venous catheter-associated infections, and central nervous system infections.
- Viruses are also a major cause of morbidity in the ICU. The most commonly encountered species include influenza, respiratory syncytial virus, HIV, measles and mumps, severe acute respiratory syndrome, herpes simplex virus type 1, cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus.
- Routine handwashing, use of personal protective equipment, isolation, and surveillance can reduce the burden of ICU infections.

INTRODUCTION

Infections and sepsis are the leading causes of death in noncardiac ICUs, accounting for approximately 40% of all ICU expenditures.¹ Common infectious syndromes in the ICU are ventilator-associated pneumonia (VAP) and catheter-related bloodstream and urinary tract infections. The spectrum of infectious organisms includes nosocomial and community-acquired pathogens and the incidence of these infections is highest in burn units and surgical ICUs.

Most infections in the ICU are preventable. Population-wide immunization, prophylaxis, and infection control measures, if applied consistently, can greatly reduce the risk of acquiring infection and the associated complications. There is a need to strictly enforce routine surveillance, institutional infection control programs, at least 1 full-time infection control practitioner, a hospital epidemiologist, and routine monitoring of surgical wound infections. When an infection has occurred, health workers in ICUs need to recognize it early and manage it aggressively to prevent complications and improve outcomes.

Betty Irene Moore School of Nursing, Physician Assistant Program, University of California, Davis, 2450 48th Street, #2120, Sacramento, CA 95817, USA
E-mail address: gkayingo@ucdavis.edu

Physician Assist Clin 4 (2019) 323–332
<https://doi.org/10.1016/j.cpha.2018.11.003>

physicianassistant.theclinics.com

2405-7991/19/© 2018 Elsevier Inc. All rights reserved.

VAP is a nosocomial infection of the lung tissue that develops more than 48 hours after intubation in mechanically ventilated patients. Critically ill ventilated patients are very susceptible to pneumonia due to an impaired immune system and a breakdown of anatomic barriers that protect the lower respiratory tract. The risk of acquiring VAP increases with older age (>60 years), a history of smoking, alcoholism, prolonged stay in the ICU, and chronic comorbid conditions, such as diabetes and chronic obstructive pulmonary disease.

There are many etiologic agents for VAP. Early-onset VAP (less than 7 days of mechanical ventilation) is usually caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Staphylococcus aureus* (methicillin-sensitive). Late-onset VAP (>7 days after mechanical ventilation) is usually caused by *Pseudomonas aeruginosa*, *Acinetobacter* species, methicillin-resistant *S aureus* (MRSA), and multidrug-resistant gram-negative bacilli.²

Clinical signs and symptoms for VAP include presence of a new onset of fever, increased productive cough with sputum, leukocytosis, worsening gas exchange, and new pulmonary infiltrates on a chest radiograph. Invasive diagnosis with bronchoalveolar lavage is generally recommended to make a definitive diagnosis.

For the management of VAP, advance practice providers (APPs) should direct initial antibiotic therapy against organisms that are known to frequently cause pneumonia in the ICU. Obtain sputum and blood cultures and initiate appropriate empiric broad-spectrum without delay. Therapeutic choices include a combination of ceftazidime and ciprofloxacin, when covering *P. aeruginosa*, and carbapenems, such as imipenem-cilastatin, when covering extended-spectrum β -lactamase (ESBL)-producing pathogens, such as *Klebsiella* species. For ICUs with a high prevalence of MRSA, vancomycin should be used.

THE MOST PROBLEMATIC PATHOGENS IN THE INTENSIVE CARE UNIT

Management of infections in the ICU can be challenging due to the rise of multidrug-resistant organisms (**Box 1**). Among the most problematic pathogens are the following:

- ESBL-producing Enterobacteriaceae, such as *Klebsiella* species and *Escherichia coli*, which may be resistant to penicillins and cephalosporins
- For most ESBL-producing organisms, carbapenems, such as imipenem and meropenem, are the drugs of choice.
- *P. aeruginosa* is one of the leading causes of morbidity in ICU patients, especially those with VAP. It is also a common cause of ICU infections associated with devices and catheters, infections in the urinary tract, and surgical site infections.³
- Increasing rates of multidrug resistance have been noted, especially in immunocompromised hosts (**Box 2**), those patients with prolonged hospital stays, those patients with invasive devices or mechanical ventilation, and those patients with prior prolonged antibiotic use. Risk factors for acquiring pseudomonal infections are age, comorbidities at ICU admission (such as anemia and burns), and/or invasive devices.
- For the treatment of problematic multidrug-resistant pseudomonas, current treatment options include the following combinations:
 - Ceftolozane/tazobactam
 - Ceftazidime/avibactam
 - Piperacillin/tazobactam
 - Cefepime, ceftazidime, or a carbapenem plus an additional agent(s), such as colistin, fosfomycin, aminoglycoside, or a quinolone

Box 1**Antimicrobial resistance and optimizing antibiotic use in the ICU***Prevalence*

- The prevalence of multidrug-resistant organisms is increasing in the ICU,^{4,5} leading to increased mortality, longer hospital stays, and higher costs.
- The emergence of resistance among gram-negative bacteria has significant implications because there are not many therapeutic options.
- The most encountered resistant pathogens include MRSA, vancomycin-resistant enterococcus, Enterobacteriaceae (ESBLs), *P. aeruginosa* resistant to imipenem, and fluoroquinolones.

Risk factors

- Features that increase the risk of infection with multidrug resistant organisms in the ICU
 - Older age
 - Comorbid conditions, such as diabetes, immunodeficiency, and malignancies
 - Frequent hospitalizations and longer stays
 - Indwelling devices, such as catheters
 - Frequent utilization of antimicrobials
 - In the neonatal ICUs, infections are commonly caused by rotavirus, respiratory syncytial virus (RSV), enterovirus, hepatitis A virus, and adenovirus

Prevention

- To reduce the emergency and spread of multidrug resistant pathogens in ICU, it is critical that
 - ICU units establish strict comprehensive antimicrobial stewardship programs
 - Effective infection control measures and routine surveillance are implemented
 - Hand hygiene is implemented and motivated
 - Standard and universal precautions are encouraged
 - Patients with chlorhexidine are decolonized
 - Unnecessary use of indwelling devices, such as catheters, is limited
 - Environmental surfaces are disinfected

Optimizing antibiotic therapy in the ICU

- Principles governing antimicrobial therapy in the ICU include
 - Ensuring adequacy of the initial empiric therapy⁵
 - Timing and rapid initiation of empiric broad empiric broad antibiotics
 - Source-targeted and tissue-targeted therapy (eg, lungs, urinary tract, catheter, and abdomen)
 - Narrow antimicrobial choices based on microbiology and epidemiology data
 - Considering host factors, such as immunosuppression and comorbidities
 - Initial patient response that should guide need for further work or antibiotic duration
 - Treating for the shortest effective duration⁶
 - Avoiding unnecessary combination therapy

- APPs working in the ICU should optimize dosing, frequency, and longer infusion time. It is good practice to combine time-dependent antibiotics, including piperacillin/tazobactam, cefepime, and imipenem, with concentration-dependent antibiotics, such as ciprofloxacin or levofloxacin.
- *Acinetobacter baumannii* is also a major cause of VAP and bloodstream infections. Risk factors include longer ICU stay, recent surgery, mechanical ventilation, prior antibiotic exposure. Data from the National Nosocomial Infections Surveillance System indicate that resistance of *Acinetobacter* species is on the rise.⁸
- For the treatment of susceptible isolates of *Acinetobacter*, APPs can use
 - Broad-spectrum cephalosporins
 - β -lactam- β -lactamase inhibitor combinations
 - Carbapenems

Box 2**ICU infections in the immunocompromised patients***Increased risk*

- Critically ill and immunocompromised patients are at increased risk for community-acquired, opportunistic, and nosocomial infections.
- Immunocompromised hosts include patients with neutropenia or hematologic malignancy; those patients on corticosteroids and other forms of immunosuppressive therapy; solid transplant patients; patients with hematopoietic stem transplant, HIV/AIDS, or asplenia; and patients on biologic agents, such as tumor necrosis factor I.
- The attenuated inflammatory response in these patients make it difficult to make an early diagnosis because clinical signs and symptoms are frequently atypical and nonspecific.
- Because these patients are always put on various prophylactic antimicrobials and have multiple hospitalizations, they are also at increased risk for multidrug-resistant organisms.
- Most infections in the immunocompromised patients present in a hierarchical pattern depending on the level of immunosuppression, neutropenia, and CD4 counts.
- Because morbidity and mortality are very high, early empiric antimicrobial therapy is universally indicated.

HIV/AIDS

- Bacterial pneumonia, bacteremia, gastrointestinal (GI), and central nervous system infections occur at high frequency in HIV/AIDS patients, depending on CD4⁺ levels.
- Common pathogens include *Mycobacterium tuberculosis*, pneumocystis, *P. aeruginosa*, endemic mycoses, *Candida* species, *Histoplasma capsulatum*, *Coccidioides* species, *Toxoplasma gondii*, and *Listeria monocytogenes*.
- Pathogens frequently encountered when the CD4⁺ levels less than 50 include mycobacterium avium complex, *Cryptococcus neoformans*, CMV, herpes simplex virus (HSV), and varicella-zoster virus (VZV), although the advent of antiretroviral therapy has reduced the incidence of these pathogens.
- *S aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are the most common fatal bacterial infection in these patients irrespective of CD4⁺ levels.
- Diarrhea in HIV/AIDS patients is often caused by protozoa *Cryptosporidium parvum*.
- Immune reconstitution inflammatory syndrome, a life-threatening complication of antiretroviral therapy, may occur, leading to an exuberant inflammatory response against a pathogen that may previously been latent.

Neutropenia and other non-HIV immunocompromised hosts

- Gram-positive organisms are on the rise in neutropenia patients. These include *Staphylococcus*, *Streptococcus*, *Enterococcus*, and *Corynebacterium* species. Gram-negative bacilli include *Pseudomonas*, *Escherichia*, and *Klebsiella* species.
- Empiric therapy covering both gram-negative and gram-positive organisms is recommended for febrile neutropenic patients
- Patients who have undergone solid organ transplantation present with a broad spectrum of infections overtime.⁷ During the postoperative period, the common infections include health care-associated pneumonia, urinary tract infections, and catheter-associated and device-associated infections. The risk of opportunistic infections increases over time due to immunosuppressive therapy to prevent organ rejection.

- For multidrug-resistant *Acinetobacter* isolates, APPs can use
 - Polymyxins, such as colistin
 - Minocycline
 - Tigecycline

Table 1
Common viral illness in the ICU: clinical features, work-up, management, and prevention

Virus	Clinical Features	Investigations	Management	Precautionary Measures
Adenoviruses	Respiratory, GI, neurologic, eye	PCR on throat, nasal swabs	Supportive management	Contact and droplets precautions
Epstein-Barr virus	Upper respiratory illness, lymphadenopathy, splenomegaly	Peripheral blood smear, serology	Corticosteroids	Standard universal precautions
Ebola	Hemorrhagic symptoms	PCR, serology	Aggressive supportive care	Isolation, barrier, personal protective gear
Coronavirus	Severe upper respiratory illness	PCR, serology	Aggressive supportive care	Standard, contact, and airborne precautions
CMV	Sepsis-like illness	Serology, PCR of body fluids	Ganciclovir, foscarnet	Standard universal precautions
Enterovirus	Sepsis-like illness, meningitis, encephalitis	PCR	Supportive care, early intravenous immune globulin for neonates	Standard contact precautions
Influenza virus	Upper respiratory symptoms, fever, myalgia, arthralgia, headache, cough, pneumonia	Serology, PCR, viral culture of throat, nasal-pharyngeal swabs	Supportive care, zanamivir, oseltamivir	Standard, contact, and droplet precautions
HIV	Acute respiratory failure, pneumonia, sepsis	Serology (detection of anti-HIV antibodies and p24 antigen), PCR	Highly active antiretroviral therapy	Standard universal precautions
HSV	Respiratory tract, pneumonia, mucous membranes, genital, conjunctivitis, encephalitis	PCR, cerebral fluid analysis	Acyclovir	Standard universal precautions

(continued on next page)

Table 1 (continued)				
Virus	Clinical Features	Investigations	Management	Precautionary Measures
Measles	Prodromal illness of fever, malaise, coryza, Koplik spots	Serology, PCR	Aggressive supportive care	Contact, droplet, airborne precautions
Mimivirus	Respiratory illness, pneumonia	Serology, PCR	Supportive therapy	Standard, universal precautions
Parainfluenza	Respiratory illness, croup	PCR on throat, nasal-pharyngeal swabs	Supportive therapy, ribavirin	Contact and droplet precautions
RSV	Bronchiolitis, pneumonia	PCR on throat, nasal-pharyngeal swabs	Supportive therapy, ribavirin	Contact and droplet precautions
Rhinovirus	Severe respiratory symptoms,	PCR	Supportive therapy	Droplet, standard precautions
Severe acute respiratory syndrome–coronavirus	Severe acute respiratory syndrome, acute respiratory distress syndrome, sepsis	PCR on throat, nasal-pharyngeal swabs	Supportive management, noninvasive ventilation	Contact, droplet, and airborne precautions
VZV	Chickenpox rash, shingles, respiratory illness, pneumonia, encephalitis	PCR on throat, nasal-pharyngeal swabs, or vesicle fluid samples	Acyclovir	Contact, droplet, and airborne precautions
Zika virus	Fever, rash, joint pain, conjunctivitis, sepsis, meningoencephalitis, Guillain-Barré syndrome	PCR on serum samples, CSF, urine, saliva, amniotic fluid, and tissue Serology	Management supportive; rest, fluids, antipyretics, and analgesics	Standard precautions when dealing fluids, secretions, excretions, nonintact skin, and mucous membranes

Box 3**Nosocomial infections in the neonatal ICU***Bacterial*

- The most common nosocomial bacterial species among neonates are *Staphylococcus*, *Enterococci*, *Enterobacter*, *E coli*, and group B streptococcus.
- The bloodstream is among the most frequent site of nosocomial infection followed by nosocomial pneumonia; GI; and eye, ear, nose, and throat sites.⁸
- The major risk factors are poor umbilical handling and central intravenous catheter use.

Viral

- Outbreaks of viral infections in the neonatal ICUs are commonly caused by rotavirus, RSV, enterovirus, hepatitis A virus, and adenovirus.
- Nosocomial infections can be transmitted via droplet spread, hands of infected hospital personnel and other individuals, contaminated medical equipment, and breast milk from infected mothers. Other pathogens, such as HIV, hepatitis B/C, HSV, VZV, and CMV, can be transmitted vertically from infected mothers.
- The clinical manifestations can be severe requiring mechanical ventilation.
- Complications associated with nosocomial viral infections can be grouped into
 1. Respiratory complications, such as RSV, influenza, parainfluenza, adenoviruses, and coronaviruses
 2. GI complications, such as rotavirus (the most common GI virus for infants)
 3. Systemic disease, such as enterovirus and parechovirus

COMMON VIRAL ILLNESS

Viruses are increasingly being recognized as a major cause of morbidity in the ICU. **Table 1** shows the commonly encountered species and their clinical features, work-up, management, and prevention. In the ICU, viral illness can be community acquired or nosocomial. Viruses can lead to multiple organ system complications. The most commonly affected systems are the respiratory, GI, neurologic systems, skin, and mucous membranes, which all eventually may lead to sepsis. Viral infections are also a major source of morbidity in the neonatal ICUs (**Box 3**) and are also a leading cause of central nervous system infections (**Box 4**). Prompt diagnosis and antiviral therapy are key to good outcomes. For long-term and population-wide prevention, immunization, prophylaxis, and infection control should routinely be encouraged.

Viral community-acquired pneumonia is frequently caused by influenza followed by other respiratory viruses, such as parainfluenza, rhinovirus, adenovirus, RSV, and coronaviruses. The symptoms of viral pneumonia may vary from fever to myalgia to arthralgia headache to shortness of breath to cough and to acute respiratory distress syndrome.

APPs working in the ICU need to recognize viral community-acquired pneumonia early and manage it aggressively to prevent complications and improve outcomes. The diagnosis can be made clinically and then confirmed by serology, polymerase chain reaction (PCR), or culture. Treatment is mostly supportive. If the causative agent is influenza, oseltamivir therapy is recommended for adult patients. It can shorten the duration of symptoms and improve outcomes in severe cases. Vaccination is the best preventative measure for these viruses.

Nosocomial viral pneumonia in the ICU is frequently caused by Herpesviridae family of viruses, which include HSV and cytomegalovirus (CMV). Immunocompromised patients are particularly at high risk (see **Box 2**). HSV can be detected in the throat and

Box 4**Common infections of the central nervous system in the ICU patient***Background*

- In critically ill patients, central nervous infections, such as meningitis and encephalitis, cause significant morbidity and mortality if not diagnosed early and treated promptly.
- Bacterial infections can lead to meningitis, brain abscess, subdural empyema, and sepsis.
- Viral infections can also cause meningitis, encephalitis, optic neuritis, and poliomyelitis.

Bacterial meningitis is often caused by

- *Streptococcus pneumoniae* (the most common causative agent)
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Listeria monocytogenes*

Viral meningitis and encephalitis are often caused by

- Enteroviruses
- HSV
- West Nile virus

Clinical presentation

- Meningitis is characterized by the inflammation of the meninges surrounding the brain and the spinal cord.
- A triad of fever, nuchal rigidity, and altered mental status in most but not all patients
- Cranial nerve palsies, nausea, vomiting, headaches, and photophobia
- Positive Brudzinski and Kernig signs
- Encephalitis is inflammation within the brain parenchyma. Clinical presentation is variable depending on the brain cells affected. Patients are more likely to present with altered level of conscience or confusion, coma, and focal or generalized seizures.

Diagnosis

- Suspected patients should receive neuroimaging before lumbar puncture.⁹
- Bacterial meningitis is confirmed by cerebrospinal fluid (CSF). Positive findings for bacterial meningitis include
 - Elevated opening pressure
 - Polymorphonuclear cell predominance
 - Decreased glucose concentration
 - Elevated protein concentration
- In viral meningitis, opening pressure is usually normal, there is lymphocyte predominance, and CSF glucose is usually normal.

Treatment

- The antimicrobial agent of choice must penetrate the blood-brain barrier and should be based on patient age and risk factors.
- Vancomycin plus ceftriaxone is the preferred empiric therapy.
- Ampicillin should be added to the initial empiric therapy in children, immunocompromised hosts, and the elderly (>50 years).²
- Patients with viral encephalitis can be managed with acyclovir.

Box 5**Dealing with sepsis and systemic inflammatory response syndrome in the ICU**

- Sepsis is a systemic inflammatory response syndrome that results from an infection.
- Sepsis is described as severe if a patient develops end-organ dysfunction and hypotension that is not responsive to fluid resuscitation.
- The spectrum of sepsis causing pathogens is rapidly changing from predominantly gram-negative organisms to gram-positive organisms.
- Common clinical features for sepsis are
 - Fever ($>38.3^{\circ}\text{C}$)
 - Hypothermia ($<36^{\circ}\text{C}$)
 - Heart rate (>90 beats per minute)
 - Tachypnea
 - Altered mental status
 - Edema
 - Hyperglycemia (plasma glucose >120 mg/dL)
- Sepsis causes inflammatory, metabolic, and coagulation alterations. Laboratory evaluations may reveal²
 - Leukocytosis (white blood cell count $>12,000/\mu\text{L}$)
 - Leukopenia (white blood cell count $<4000/\mu\text{L}$)
 - Plasma C-reactive protein
 - Plasma procalcitonin
- Hemodynamic and tissue perfusion changes in a septic patient may include
 - Arterial hypotension
 - Hyperlactatemia (>1 mmol/L)
 - Decreased capillary refill
- When sepsis is suspected, clinicians should rapidly administer broad-spectrum antibiotics.
- The Surviving Sepsis Campaign bundle¹² recommends the following:
 - Measure and monitor lactate level.
 - Obtain blood cultures prior to administration of antibiotics.
 - Begin rapid administration of crystalloid to manage hypotension and elevated lactate (>4 mmol/L).
 - Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure ≥ 65 mm Hg.
- Managing a sepsis patient involves a lot of supportive care. The first few hours should be dedicated to restoring adequate perfusion, providing antibiotics, and optimizing oxygen supply and demand

respiratory secretions by PCR. HSV and CMV are responsive to treatment with acyclovir and ganciclovir, respectively. APPs should ensure universal control precautions when managing these patients.

SUMMARY

Patients in ICUs are more prone to infections and are more likely develop multidrug-resistant organisms and have poor outcomes. Multidrug resistance increases mortality and length of stay and is largely responsible for the escalating health care costs in the United States.^{10,11}

The clinical manifestations of bacterial and viral infections are highly variable in the ICU patient, ranging from severe respiratory disease to sepsis (**Box 5**). Early recognition and empiric therapy are recommended but APPs must use antibiotics wisely. ICU APPs should use appropriate initial empiric therapy and de-escalate once cultures and

susceptibility data are available. The emerging and re-emerging infectious pathogens as well as drug resistance involving Enterobacteriaceae species, *Acinetobacter baumannii*, and *Pseudomonas* should be considered a major threat to public health. There is a need for the development of new and more effective drugs. Vaccinations and effective infection control practice should be emphasized globally.

REFERENCES

1. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;302:2323.
2. Raouf S, George L, Saleh A, et al. *ACP manual of critical care*. New York: McGraw-Hill Medical; 2008.
3. El-Kholy A, Saied T, Gaber M, et al. Device-associated nosocomial infection rates in intensive care units at Cairo University hospitals: first step toward initiating surveillance programs in a resource-limited country. *Am J Infect Control* 2012;40:e216–20.
4. Kollef MH, Bedient TJ, Isakow W, editors. *The Washington manual of critical care*. Philadelphia: Lippincott Williams & Wilkins; 2008.
5. Parrillo JE, Dellinger RP. *Critical care medicine e-book: principles of diagnosis and management in the adult*. Amsterdam: Elsevier Health Sciences; 2013.
6. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003;290(19):2588–98.
7. Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med* 2007;357(25):2601–14.
8. Gaynes RP, Edwards JR, Jarvis WR, et al. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infections Surveillance System. *Pediatrics* 1996;98:357.
9. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. *Pediatrics* 2001;108(5):1169–74.
10. Spivack D. The high cost of acute health care: a review of escalating costs and limitations of such exposure in intensive care units. *Am Rev Respir Dis* 1987;136(4):1007–11.
11. Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st century. *Perspect Medicin Chem* 2014;6:25–64.
12. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Intensive Care Med* 2018;44(6):925–8.