PERIODICUM BIOLOGORUM
VOL. 124, No 3–4, 85–95, 2022
DOI: 10.18054/pb.v124i3-4.23316

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Review Article

Common infections acquired in intensive care: Microbiological aspects and risk factors

SAID OULKHEIR[1,2]*
KHADIJA OUNINE[3]
ASMAE LAMRANI HANCHI[4]
AMINE RKHAILA[3]
KHALID AROUYA[5]
JAOUAD MOSTAFI[6]
SMAIL CHADLI[1]

[1] Team of Biotechnology, Health and Environment Laboratory of Sciences of Health and Environment, Higher Institute of Nursing Professions and Health Techniques, Agadir, Morocco

[2] Laboratory of Microbial Biotechnology and Plant Protection. Team of Microbiology Applied to the Environment and Agrifood. Department of Biology, Faculty of Sciences, Ibn Zohr University, Agadir, Morocco

[3] Laboratory of Plant, Animal and Agro-Industry Productions, Department of Biology, Faculty of Sciences, University Campus, Ibn Tofail University, Kenitra, Morocco

[4] Faculty of Medicine and Pharmacy, University Cadi Ayyad, Marrakech, Morocco

[5] Laboratory of Organic Chemistry, Catalysis and Environment, Faculty of Sciences, University Campus, Ibn Tofail University, Kenitra, Morocco

[6] Department of Biology, Faculty of Sciences, University Campus, Ibn Tofail University, Kenitra, Morocco

***Correspondence:**
Said Oulkheir
E-mail address: oulkheirs@gmail.com

Keywords: nosocomial infections; intensive care unit; risk factors; quality public healthcare

Received September 23, 2022
Revised February 9, 2023
Accepted February 10, 2023

Abstract

Nosocomial infections are a serious health problem resulting in an enormous burden of morbidity and mortality rates, and high health care costs. The various microorganisms implicated in nosocomial infections were not known for causing recalcitrant nosocomial infections, they are opportunistic pathogens and hence pose a challenge to patients especially those with immunocompromised conditions. Patients at the intensive care unit are the most at risk of these hospital-acquired infections The infections usually encountered in intensive care unit (ICU) include urinary tract infection, pneumonia, tuberculosis, gastroenteritis. The main risk factors for these infections can be divided into three key groups: those related to patient characteristics and underlying diseases, those related to the acute disease process, and those related to the use of invasive diagnostic or therapeutic procedures. Incidence of ICU-acquired infections vary between hospitals and according to the type of population studied, being highest in burn units and surgical and trauma ICUs and lowest in coronary care units.

The major preventive effort to reducing the risk of nosocomial infections should be focused on hospitals and other health care facilities. The responsible health authority should develop a national (or regional) programme to support hospitals. Such programmes must assess and promote good health care, appropriate isolation, sterilization, and other practices, staff training, and epidemiological surveillance should be developed.

INTRODUCTION

Nosocomial infection, also known as hospital-based infection or health care-associated infection, is a serious global public health issue, causing the suffering of 1.4 million people across the world at any given time *(1)*. Studies have indicated that nosocomial infections occurred in 5–10% of all hospitalized patients in Europe and North America and in more than 40% in parts of Asia, Latin America, and sub-Saharan Africa *(2,3)*.

The various microorganisms implicated in nosocomial infections can be classified as pathogenic or normal microbial flora of the human body. Bacteria are the most common of these micro-organisms. Several species of microorganisms have been isolated from different hospitals across the world *(4)*. Even though some of these organisms were not known for causing recalcitrant nosocomial infections, they are opportunistic pathogens and hence pose a challenge to patients especially those with immunocompromised conditions. Nosocomial infections usually encountered include urinary tract infection, pneumonia, tuberculosis, gastroenteritis and legionnaire's disease *(5)*. Microorganisms usually implicated in these infections include among others *Pseudomonas aeru-*

ginosa, Escherichia coli, Staphylococcus aureus, Klebsiella species, *Mycobacterium tuberculosis*, and *Clostridium difficile*, which are rapidly gaining resistance because of the broad-spectrum antibiotics used in an attempt to control them. Most of these organisms are usually contaminants on the surfaces of most materials such as doors, beds, instruments and on care providers. They are therefore easily transmitted to patients when adequate hygienic practices are not followed regularly. Patients at the Intensive Care Unit (ICU) are the most at risk of these hospital-acquired infections *(6,7)*. The prevalence of hospital-acquired infections (HAI) in ICU has been reported to be more than twofold compared to other wards *(8,9)*, indicating the considerable importance of hospital-acquired infections in the ICU population. The proportion of infected patients on ICU admission has varied from 21.1% to 38.5%, depending on the country *(10,11,12)*. Alberti et al. *(10)* and Legras et al. *(11)* reported that 11.9%–21% of patients had Community-acquired Infection (CAI) and 8.3–9.2% HAI. In a French study, the proportion of infected patients was 10% higher if only the patients who had an ICU length of stay over 24 hours were taken into account *(10)*. Higher figures were also reported from the large British National Prevalence Survey, where 21% of ICU patients had CAI and 43% had HAI *(8)*. Indeed, nosocomial infection rates in adult and pediatric ICUs are approximately three times higher than elsewhere in hospitals. The sites of infection and the pathogens involved are directly related to treatment in ICUs. In these areas, patients with invasive vascular catheters and monitoring devices have more bloodstream infections due to coagulase-negative staphylococci. Studies have shown that cases of occult bacteremia in ICU patients are probably due to vascular access-related infections *(13)*.

The high rates of infection are not surprising in view of the fact that the patients treated in the ICU are the sickest patients in the hospital. Advanced medicine with its new treatment modalities and organ replacement therapies has allowed successful treatment of patients with more severe illnesses in ICU. However, these patients are often susceptible to infection because of the impairing effects of their underlying diseases and therapies on the immune system as well as the consequences of surgery *(14)*. The purpose of these study was to provides an literature review of infections acquired in intensive care with a particular focus on microbiological aspects, and risk factors.

Microbiological aspects of infections treated in ICU

Colonization of the host by potentially pathogenic micro-organisms is the first step towards the further development of most ICU-acquired infections, and it may occur from exogenous or endogenous sources *(14,15)*. Bacterial colonization is associated with the hospital stay, and critically ill patients are especially susceptible due to treatments such as immunosuppressive medications or long-term or repeated courses of antimicrobials or the use of invasive devices. Antimicrobials can cause selective pressure on the patients´ own bacterial flora, modifying it to select potential pathogenic colonisers to the bacterial flora of the skin or the oropharyngeal or gastrointestinal tract, from which many ICU-acquired infections are assumed to arise. Exogenous colonisation arises from cross-contamination either via direct contact from the hands of the medical staff or by transmission of exogenous microbes via contaminated equipment *(16,17)*. Colonisation is often difficult to differentiate from infection, but it should also be noted that not all patients with clinical infection have positive cultures: the earlier literature has reported that, of the infected patients treated in ICU, 30% had no microbiological documentation.

Of all ICU-acquired infections, 85.8% were microbiologically documented, while only 54.8% of community-acquired infection (CAIs) had such documentation *(10)*. The authors suggested that many instances of CAI could not be documented because of the antimicrobial therapy administered prior to ICU admission. Due to the many events during the ICU stay, such as fever due to tissue trauma or corticosteroids, which confound the infection parameters, the clinical diagnosis of ICU infection may be more difficult to ascertain than CAI, and microbiological samples may therefore be more likely to be obtained during the ICU stay.

The causal micro-organisms differ, depending on the origin and source of infection. In a French study, gram-negative rods predominated (49% of isolates), followed by grampositive cocci (37%) and fungi (9.7%) in ICU-acquired infections, while the corresponding results were 35, 39 and 9% in community-acquired infections and 48, 35 and 10.4% in hospital-acquired infections *(10)*. In a multicentre sepsis study, 62% of infections were microbiologically documented, while gram-positive cocci accounted for 37% of CAIs and 47% of ICU-acquired infections and gram-negative rods for 34% and 53%, respectively *(18)*. The proportion of fungal infections (17%) in their series was exceptionally high. A similar predominance of gramnegative rods in ICU-acquired infections has also been reported in other studies *(11,12)*. In one study, microbiological culture results were available for 85% of the patients with ICU-acquired infections; 55% of the infections were polymicrobial. Gram-negative rods (most often *Pseudomonas aeruginosa, E.coli* and *Klebsiella*) have been shown to predominate in respiratory and urinary tract infections, while grampositive organisms (most often coagulase-negative staphylococci (CNS), *Staphylococcus aureus* and enterococci) mainly cause catheter-related, bloodstream and surgical site infections *(12,19)*. The number of gram-positive infections has increased, particularly those caused by coagulase-negative staphylococci *(20,21)*. Fungal infections by especially candida species have become increasingly common (*22*). A continuous shift towards more resistant strains has also

been reported by NNIS: the proportion of methicillin-resistant *Staphylococcus aureus* isolates is over 60% and that of vancomycin-resistant Enterococci over 25%, and there was also a nearly 50% increase in *Klebsiella pneumoniae* isolates nonsusceptible to 3rd generation cephalosporins between 2002 and 2003 *(23,24)*. However, the proportions of isolates resistant to most pathogens have been lower in Northern European countries than in US ICUs *(25)*. The favourable resistance situation was also reported in the Finnsepsis study, where no multidrug-resistant microbes causing infections were found *(26)*. It should be noted that the precise pattern of causative microbes varies between countries and ICUs, reflecting the case mix, antibiotic protocols and local ecology and resistance patterns *(21)*.

Risk factors for ICU-acquired infections

The severity of illness on admission as assessed based on the Acute Physiologic and Chronic Health Evaluation (APACHE II) or some other score has been associated with the development of ICU infections *(27,28)*. Contrariwise, Appelgren et al. *(29)* reported that APACHE II did not correlate with infection, suggesting that patients with high APACHE II scores may die from their underlying disease before they have developed an infection. It has further been found that more severe organ dysfunction during the ICU stay and longer stay were more common among the patients who acquired an ICU infection *(12)*. Similarly, in a case-control study, the severity of illness scores (APACHE II, Simplified Acute Physiology (SAPS) score) and the TISS, Therapeutic Intervention Scoring System scores were significantly higher for cases than controls at three days after ICU admission and at one day before the onset of nosocomial infection. This result suggesting that case patients required a higher level of therapeutic activity between their ICU admission and the day of infection *(30)*. It is often difficult to assess whether the prolonged stay is due to infection, or the infection is due to prolonged stay, and controversial results have therefore been obtained on the importance of the length of ICU stay *(19,31,32)*. Neurologic failure on admission *(19,32)* or certain diagnostic categories such as trauma *(29,32)* have increased the infection risk. Infection rate has also been reported to vary according to infection status on admission, being 1.5-fold in patients infected on admission compared to noninfected patients *(10)*.

Other studies, however, reported that the most risk factors of ICU-acquired infection have been exogenous, including central venous or urinary catheterisation and mechanical ventilation *(33)*. Results of Richards et al. *(20)* indicate that the device-associated rates did not correlate with the length of ICU stay, the size of the hospital or the number of beds in the ICU. ICU-acquired infections at the most frequent infection sites were usually associated with the use of an invasive device: 86% of pneumonias were ventilatorassociated, 87% of BSIs central catheter-associated and 95% of UTIs urinary catheterassociated. De Leon-Rosales et al. *(32)* reported that the risk has been increase when the total number of therapeutic or diagnostic interventions increases. Medications or procedures that promote gastric colonisation by potential VAP pathogens or increase the risk of aspiration have also been reported as risk factors *(19,28,32,33)*. Intensive treatment of hyperglycemia has been found to reduce the BSI rate *(34)*. Early enteral nutrition has been shown to significantly reduce the infection complication rates compared to parenteral nutrition, although it has not been shown to have impact on mortality *(35)*.

Many outbreaks of nosocomial infections are often linked to aseptic breaks or failure to follow infection control guidelines. Aseptic breaks are frequently associated with overcrowded and understaffed units, and admission during a period of low nurse-to-patient ratio has been associated with an increased risk of infection *(36,37)* or cross-transmission of nosocomial pathogens (38).

Although length of stay is relatively simple to measure and often routinely collected in surveillance data bases, several factors complicate these analyses. Study design, study population, type of HAI, and approach to statistical analysis can lead to wide variations in estimating excess length of stay.

The study design, population under investigation, type of HAI, and approach to statistical analysis can result in large variations on estimates of excess LOS. The potential for time-dependent bias, is not always accounted for in studies estimating the additional LOS due to HAI *(39)*. Time-dependent bias occurs when a patient's entire hospital stay, or even the entire period after the patient develops HAI, is attributed as additional LOS due to the HAI, and this may lead to inflated estimates in excess LOS linked with HAI. Despite these issues being well documented there are still a wide range of analytical approaches used to estimate the excess attributable LOS due to HAI that fail to address this issue *(40,41,42,43,44,45)*.

The common analytical approaches compare LOS in HAI and non-HAI groups, matching HAI and non-HAI patients using characteristics that may affect LOS, with and without accounting for time of infection, survival analyses, and multi-state modelling *(39)*. There is considerable heterogeneity in both study designs and analytical approaches that prevent the use of meta-analysis or the use of these data to inform IPC priorities and interventions.

Many observational reports have studied the impact of NI on length of stay by using different statistical methods. When evaluating the prolonged LOS of NI, the timing of NI plays an important role to distinguish between pre-infection time and consequence of NI. Several studies showed the magnitude of the so-called time-dependent (aka immortal-time) bias which occurs if the timing of infection is not adequately addressed or rather ignored in

the analysis *(46,47)*. Multi-state models or time-dependent matching techniques account for the timing of NI to avoid the time-dependent bias *(46,47,42)*. However, there exist fundamentally different estimands to quantify this prolonged LOS associated with NI.

Common infections treated in ICU

Most studies on infections necessitating ICU treatment have concentrated on sepsis, severe sepsis or septic shock *(18,48,49,50,51)*. In sepsis studies, respiratory tract infection has been the most common infection focus, followed by urinary tract infections, intra-abdominal and surgical site infections or primary bloodstream infections *(48)*. However, their distributions in patients with community- or hospital-acquired infections have not always been reported separately. In Finland, severe sepsis was diagnosed in only 10.5% of all ICU admissions and the incidence of severe sepsis was 0.38/1000 adults per year *(26)* while in a prospective study conducted in Australia and New Zealand, severe sepsis was present in 11.8% of ICU admissions, and the incidence was 0.77/1000 adults *(52)*. The lower percentage in Finland may be related to a low proportion of resistant bacteria or early hospital admission. In the Finnsepsis study, infection was community-acquired in 58% of cases and nosocomial in 38%. Similar proportions of CAI and HAI were reported in a French study, but 42% of the patients in this survey met the criteria for severe sepsis on admission *(53)*. This higher percentage may reflect a different case mix and the use of a 48-hour or longer ICU stay as an inclusion criterion in the latter study. In this study, the total ICU cost of community-acquired severe sepsis was significantly lower than that of hospital- or ICU-acquired severe sepsis. In a large multicentre sepsis study, 37% of patients admitted to ICU had sepsis, and 76.3% of them had sepsis present on admission or developed it on the second day of admission, while only 23.7% of the cases of sepsis were really ICU-acquired *(18)*. In patients with ICU-acquired sepsis, the site of infection was more commonly the respiratory tract, catheter-related or the urinary tract and less commonly abdominal compared to patients with non-ICU acquired sepsis. Septic infections necessitating ICU treatment are associated with high mortality. In a Brazilian sepsis study, the mortality rate of patients with systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock increased progressively from 24.3% to 34.7%, 47.3% and 52.2%, respectively. Patients with SIRS without infection had a mortality rate of 11.3% *(54)*. In a large British study of intensive care unit admissions that met the criteria for severe sepsis in the first 24 hours, 35% of patients died before discharge from intensive care, and 47% died during their hospital stay *(50)*. Hospital mortality ranged from 17% in the age group of 16–19 years to 64% in those aged > 85 years. In a Swiss study, the 28-day fatality rate among bacteremic sepsis patients was 37% and the two most powerful predictors of 28-day mortality in this study remained the APACHE II score and the number of evolving organ dysfunctions *(55)*. Similar results have been published in other sepsis studies *(18,49,52)*, while lower results were reported in the Finnsepsis study (ICU mortality 15.5%, hospital mortality 28.3%) *(26)*. According to results of Kumar et al. *(56)*, mortality from septic shock is dependent on the time between the administration of effective antimicrobials and the identification of septic shock, being only 25% if antimicrobial medication was initiated within the first hour and 89% if it was initiated within six to nine hours.

Taking into account the high mortality rates, the international Surviving Sepsis Campaign published in 2004 severe sepsis guidelines with the aim to improve the prognosis of severe sepsis and to reduce the mortality from severe sepsis by 25% in 5 years *(57)*. The interventions recommended included the maintenance of blood glucose levels<8.3 mmol/l, stress-dose steroid therapy for septic shock; administration of recombinant activated protein C to patients with severe sepsis and high risk for death; a semirecumbent bed position unless contraindicated; and protocols for weaning.

Community and Hospital-acquired pneumonia

Community-acquired pneumonia (CAP) is a common illness, and up to 42% of these patients require hospital admission *(58)*. In a multicentre study, 12.7% of pneumonia inpatients were admitted into ICU, with the ICU admission rates ranging from 8.8 to 26.1% across the participating centres *(59)*. In a British survey, admissions into ICU due to CAP increased by 128% during the years 1994–2004 *(60)*. Severe CAP is considered a distinct clinical entity, which usually requires ICU management and has a particular epidemiology and a somewhat different distribution of etiological pathogens compared with the less severe forms of communityacquired pneumonia *(61)*. *Streptococcus pneumoniae* has been reported to be the most common bacterial aetiology for severe CAP *(62)*.

The mortality rates were almost fourfold in ICU-treated patients compared to non-ICU patients *(59)*. However, in a multicentre study, there was no difference in ICU mortality between patients with or without CAP requiring mechanical ventilation *(63)*. A similar mortality rate (43%) was reported in a French study, where *Klebsiella pneumoniae* as the bacterial etiology and a positive blood culture as well as the initial severity of illness were independent risk factors for death *(64)*. The severity of illness on admission and sepsis or septic shock have also been associated with high mortality in other studies *(63,65)*. In the British survey, higher mortality was seen among those who were admitted into ICU later during their hospital stay *(60)*. In addition to having high mortality, ICU treated pneumonia patients had slower recovery and a

lower proportion of the patients had resumed work or their usual activities one month after admission *(59)*.

However, Earlier literature on hospital-acquired pneumonias (HAP) necessitating ICU admission is rare. In a French study, pneumonias accounted for 38% of the hospital-acquired infections treated in ICU *(10)*. Patients with HAP admitted into ICU had high mortality (53%), especially those with septic shock and chronic obstructive pulmonary disease (COPD) *(66)*. Gram-negative rods predominated in the bacterial etiology of HAP *(10)*; *Pseudomonas aeruginosa* being the most frequent pathogen isolated *(66)*.

Ventilator-associated pneumonia (VAP)

Studies of VAP have often provided contradictory results due to the absence of standardized criteria for its diagnosis and the wide variation of the patient populations studied. The frequency of VAP varied from 4% to 48% even within the same study population, depending on the selected definition criteria *(67)*. VAP is generally the most frequent nosocomial infection in the ICU, accounting for 25–46.9% of ICU-acquired infections and the VAP incidence varies from 6.8% to 22.3% *(68,69,70,71,72,73,74,75)*. Incidence densities per 1000 patient days have varied from 12 to 19 and those per 1000 ventilator days from 3.7 up to 50. The pooled cumulative incidence of VAP in patients receiving mechanical ventilation was 9.7% in one analysis, which covered 38 prospective cohort or nonrandomized studies with 48 112 patients, and 22.8% when 51 prospective randomized trials with 4802 patients were pooled *(76)*. VAP was diagnosed clinically almost twice as often as it was microbiologically confirmed. However, it has been shown that microbiological confirmation of the diagnosis by invasive techniques usually does not add any prognostic information *(77)*. There is only one randomised study where an invasive strategy was associated with reduced mortality *(78)*. Otherwise, controversial opinions have been published *(79,80)*. In one recent survey, too, two diagnostic strategies for VAP – bronchoalveolar lavage (BAL) with a quantitative culture of the BAL fluid and endotracheal aspiration with a nonquantitative culture of the aspirate – were associated with similar clinical outcomes and similar use of antibiotics *(81)*, but there were methodological problems in, for example, the exclusion criteria of that survey *(82)*. It has been demonstrated that the National Nosocomial Infections Surveillance (NNIS) criteria introduced for epidemiological purposes are not suitable for a bedside diagnosis of VAP and will lead to less well targeted treatment of these patients, i.e., undertreatment of some patients (up to 20% of patients) and overtreatment of some others *(83)*. To sum up, an invasive diagnostic approach may be beneficial, but further studies are needed. In the pathogenesis of VAP, bacterial colonization of the oral cavity and subsequent aspiration of oropharyngeal fluids along the endotracheal tube are of major importance *(84)*. Interventions that reduce the concentrations of oral microbial flora, such as topical chlorhexidine, have been beneficial in preventing VAP *(85,86)*. The role of the gastrointestinal tract as a source of oropharyngeal and tracheal colonization is more controversial *(87)*. Nasal sinuses are also potential sources of infected secretions *(88)*. Most risk factors associated with VAP, apart from mechanical ventilation, appeared to predispose the patient to either colonization of the aerodigestive tract with pathogenic microbes (e.g., prior use of antibiotics *(72)*) or aspiration (e.g., witnessed aspiration, paralytic agents *(70)*, supine positioning *(72)*). Male gender, organ system failure *(72)*, admission diagnosis of burns, trauma, CNS disease and respiratory or cardiac disease *(72,89)* have been reported to be other risk factors. Cook et al. *(69)* found that, although the cumulative risk of VAP increased over time, the daily hazard rate decreased after day five. It is noteworthy that the risk factors were the same regardless of the pneumonia definition used. The microbiological aetiology of VAP differs according to the patient population studied, the lengths of stay in hospital and ICU and the specific diagnostic methods used. In 24 studies with altogether 1689 VAP episodes, where the aetiology of VAP was investigated bronchoscopically, gram-negative bacilli (GNB) accounted for 58% of the organisms recovered *(90)*. The most common GNB were *Pseudomonas aeruginosa, Acinetobacter* species and *Enterobacteriaceae. Staphylococcus aureus* was the most common gram-positive bacterium recovered, being present in 20% of the cases. In VAP diagnosed during the first days of admission, i.e., early-onset VAP, the causative agents are usually the endogenous oropharyngeal flora and high rates of *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus* and antibiotic-sensitive *Enterobacteriaceae*. In late-onset VAP, the causative organisms are usually exogenous organisms such as *Pseudomonas aeruginosa, Acinetobacter* species, *Stenotrophomonas* or other antibiotic-resistant GNB or MRSA *(88,91)*.

The current literature on the impact of VAP on outcome is controversial. Prospective cohort studies have reported attributable mortality rates from 21% to 34% *(29,92)*. Several interventional studies of selective digestive decontamination or semirecumbent positioning have shown reduced VAP rates, but the influence of that on mortality has been controversial *(93,94,95)*. In a small case-control study of case patients who died and control patients who were discharged from ICU, similar proportions (36%) of both groups developed VAP, and VAP was not an independent risk factor for death in multivariate analysis *(96)*. A similar finding was also reported in an earlier cohort study *(72)*. A study using data from a large US inpatient database reported significantly longer ICU and hospital stays for patients with VAP, while hospital mortality did not differ significantly between cases and matched controls *(89)*. In a study where specific invasive techniques were used to diagnose pneumonia, nosoco-

mial pneumonia was independently associated with mortality *(70)*, and a similar finding was reported in a large case-control study with a strict matching process *(97)*. Mortality associated with VAP also differs by bacterial aetiology, being higher with resistant microbes such as *Pseudomonas aeruginosa or Acinetobacter* species *(90)*. The treatment of VAP is also an important determinant of outcome; inappropriate initial antibiotic treatment has been associated with excessive hospital mortality *(98,99)*.

Intra-abdominal infections.

In a French study, the digestive tract or peritoneum was the infection focus in 17.5% of CAIs and 32.7% of HAIs in patients admitted into ICU. Over half of all infections were polymicrobial *(10)*. Among patients with septic shock on ICU admission, intra-abdominal infection was the focal infection in 29.3%: bowel perforation was the most common cause (8.3%), followed by ischaemic bowel (6.1%) *(56)*. Reports on ICU-acquired intra-abdominal infections are rare, while the incidence of these infections has varied from 2% in surgical ICU patients *(27)* to 8.5% in a french multicentre study *(10)*. In a British study, 4.4% of patients admitted into ICU after abdominal surgery underwent relaparotomy for suspected intraperitoneal sepsis at a median of five days after the initial procedure *(100)*. In a prospective study from 1991-2002, the incidence of intra-abdominal infection treated in ICU was 5.75%, and *de novo* infection accounted for 71.8% of cases and nosocomial infection for 28.2% of cases *(101)*. In this study, 73.7% of patients developed organ dysfunction, and mortality was 22.6%. Surprisingly, many studies of ICU-acquired infections did not report the proportion of these infections at all *(19,28)*.

ICU-acquired bloodstream infections

Bloodstream infections (BSIs) account for 3.5–30% of ICU-acquired infections, and their incidence density has varied within 2.0–4.6 per 1000 central catheter days. The intravascular device associated with the greatest risk if BSIs is the central venous catheter *(15)*, and infections derive from the cutaneous bacterial flora at the insertion site. The subclavian route of insertion has been recommended *(102)*. However, the incidence of central venous catheter infection and colonization was not different at three sites (i.e., internal jugular, subclavian or femoral) in a study where the optimal insertion sites were selected, experienced operators inserted the catheters, a strictly sterile technique was observed, and trained intensive care unit nursing staff performed catheter care *(103)*. Ultrasound-guided catheterisation was recently reported in a randomised study to prevent CR-BSIs *(104)*.

The most common microbial aetiologies were *Staphylococcus aureus*, viridans group *streptococci* and coagulase-negative staphylococci in a survey where one third of infections were secondary *(105)*. The impact of BSIs on mortality and length of stay is controversial, with some studies reporting 10–25% increased mortality and prolongation of hospital stay, while some other studies report no attributable mortality *(29,106,107,108)*. In a multicentre study, the risk for death associated with primary infections and CR-BSIs appeared much lower than that due to secondary BSIs *(107)*. A casecontrol study of 57 patients with catheter-related infection revealed no significant difference in hospital mortality between cases and controls, while the length of hospital stay was increased by 19.6 days *(109)*. It should be noted that the majority of infections in this series were caused by coagulase-negative staphylococci. In contrast to that, there are three matched studies with larger patient populations, where ICU-acquired BSI was associated with significant attributable mortality *(105,110)*. It is noteworthy that BSIs were not restricted to catheter-related ones in those studies. When adjusted for risk exposure time and severity on admission and during the ICU stay, BSI was associated with increased mortality, but considerable variation occurred across the BSI subgroups *(110)*. The attributable mortality due to BSI was highest in patients with less severe illness, while the impact of BSI on mortality was lower in patients with higher initial severity *(111)*. In another study, CR-BSI was associated with increased mortality even when adjusted for severity factors on ICU admission *(108)*. However, after adjustment for severity factors during the ICU stay and before the infection, there was only a trend toward CR-BSI attributable mortality. In addition to attributable mortality, BSIs have also been associated with increased health care costs *(105,112)*.

Urinary tract infections

Urinary tract infection (UTI) is a common type of infection: 14.2% of hospitalized patients have been reported to have community-acquired UTI and 23.2% hospital-acquired UTI *(8)*. It is, however, rarely a cause for ICU admission. In a French study, UTI represented 7.2% of CAIs and 8.2% of HAIs treated in the ICU, and in a European multicentre study, the urinary tract was the infection focus in 12% of sepsis patients admitted into ICU *(10,18)*. UTIs account for 7.8–23.6% of ICU-acquired infections, and the incidence densities vary from 1.7 to 8.5 episodes per 1000 urinary catheter days. An incidence density of 9.6 was reported in a survey with 111 ICU-acquired UTIs, where the most common etiologies were Enterococcus species (24%), *Candida albicans* (31%) and *Escherichia coli* (15%) *(113)*.

In the ICU are usually related to urinary catheters or invasive urinary tract procedures, and their pathophysiology is characterized by colonization by microorganisms from the colonic flora. Female sex, length of ICU stay, prior use of antibiotics, severity score on admission and duration of catheterization have been reported as independent risk factors for catheter-associated bacteriuria *(114)* and female sex and length of stay for UTI *(113)*.

Development of ICU-acquired UTI was associated with significantly higher crude ICU-related mortality, but after controlling for other significant variables, ICU-acquired UTI was not independently associated with death *(113)*. Attributable mortality of 5.7% in patients with UTI was reported in a cohort study which figure was much lower than that for VAP or BSIs *(92)*.

CONCLUSION

Nosocomial infections is difficult to address because it is such a complex problem with diverse underlying causes. Even though several measures have been put in place by hospital officials to prevent these infections by ensuring strict sanitation, hygienic principles and rational antibiotic use, the incidence of nosocomial infections still keep. Howver, approximately one third of nosocomial infections are preventable. To achieve this level of prevention the institutional policies and practices must be developed and adhered to, especially in the developing nations where nosocomial infections are a devastating problem that impacts many vulnerable groups. A system must also be developed for the surveillance of nosocomial infections that occur outside the hospitals and other health care providing facilities after the patients are discharged.

REFERENCES

1. WHO: 10 Facts on Patient Safety. Retrieved October 17, 2007, from http://www.who.int/features/factfiles/patient_safety/en/index.html
2. LYNCH P, JACKSON M, PRESTON G.A, SOULE B.M 1997 Infection Prevention with Limited Resources. Chicago: ETNA Communications.
3. NATIONAL NOSOCOMIAL INFECTIONS SURVEILLANCE (NNIS): System Report, data summary from January 1992 through June 2004. American Journal of Infection Control; 32: 470–485 (2004).
4. MARKOVIC-DENIC L 2009 Nosocomial infections prevalence study in a Serbian university hospital. Vojnosanit Pregl, 66(11): 868–75.
5. SHEARS P 2007 Poverty and infection in the developing world: healthcare-related infections and infection control in the tropics. Journal of Hospital Infections; 67: 217–224. https://doi.org/10.1016/j.jhin.2007.08.016
6. GUNSEREN F, MAMIKOGLU L, OZTURK S, YUCESOY M, BIBEROGLU K, YULUG N, DOGANAY M, SUMERKAN B, KOCAGOZ S, UNAL S, CETIN S, CALANGU S, KOKSAL I, LEBLEBICIOGLU H, GUNAYDIN M 1999 A surveillance study of antimicrobial resistance of gram-negative bacteria isolated from intensive care units in eight hospitals in Turkey. Journal of Antimicrobial Chemotherapy; 43: 373–378. https://doi.org/10.1093/jac/43.3.373
7. KUCUKATES E 2005 Antimicrobial resistance among Gram-negative bacteria isolated from intensive care units in a Cardiology Institute in Istanbul Turkey. Japanese Journal of Infectious Diseases; 58: 228–231.
8. EMMERSON AM, ENSTONE JE, GRIFFIN M, KELSEY MC, SMYTH ET 1996 The Second National Prevalence Survey of infection in hospitals-overview of the results. J Hosp Infect 32(3): 175–190. https://doi.org/10.1016/s0195-6701(96)90144-9
9. METINTAS S, AKGUN Y, DURMAZ G, KALYONCU C 2004 Prevalence and characteristics of nosocomial infections in a Turkish university hospital. Am J Infect Control 32(7): 409–413. https://doi.org/10.1016/j.ajic.2004.05.001
10. ALBERTI C, BRUN-BUISSON C, BURCHARDI H, MARTIN C, GOODMAN S, ARTIGAS A, SICIGNANO A, PALAZZO M, MORENO R, BOULME R, LEPAGE E, LE GALL R 2002 Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med 28(2): 108–121. https://doi.org/10.1007/s00134-001-1143-z
11. LEGRAS A, MALVY D, QUINIOUX AI, VILLERS D, BOUACHOUR G, ROBERT R, THOMAS R 1998 Nosocomial infections: prospective survey of incidence in five French intensive care units. Intensive Care Med 24(10): 1040–1046. https://doi.org/10.1007/s001340050713
12. VOSYLIUS S, SIPYLAITE J, IVASKEVICIUS J 2003 Intensive care unit acquired infection: a prevalence and impact on morbidity and mortality. Acta Anaesthesiol Scand 47(9): 1132–1137. https://doi.org/10.1034/j.1399-6576.2003.00230.x
13. FRIDKIN SK, WELBEL SF, WEINSTEIN R A 1997 Magnitude and prevention of nosocomial infections in the intensive care unit. Infectious Disease Clinics of North America; 11: 479–96. https://doi.org/10.1016/s0891-5520(05)70366-4
14. EGGIMANN P, PITTET D 2001 Infection Control in the ICU. Chest 120(6): 2059–93. https://doi.org/10.1378/chest.120.6.2059
15. WEINSTEIN RA, MAKI DG 2004 Prevention of Infection in ICU Patients. In: Cohen J & Powderly W (eds) Infectious Diseases. Second Edition London Elsevier Limited
16. GRUNDMANN H, BARWOLFF S, TAMI A, BEHNKE M, SCHWAB F, GEFFERS C, HALLE E, GOBEL UB, SCHILLER R, JONAS D, KLARE I, WEIST K, WITTE W, BECK-BEILECKE K, SCHUMACHER M, RUDEN H, GASTMEIER P 2005 How many infections are caused by patient-to-patient transmission in intensive care units? Crit Care Med 33: 946–95. https://doi.org/10.1097/01.ccm.0000163223.26234.56
17. WEIST K, POLLEGE K, SCHULZ I, RUDEN H, GASTMEIER P 2002 How many nosocomial infections are associated with cross-transmission? A prospective cohort study in a surgical intensive care unit. Infect Control Hosp Epidemiol 23: 127–132. https://doi.org/10.1086/502021
18. VINCENT JL, SAKR Y, SPRUNG CL, RANIERI VM, REINHART K, GERLACH H, MORENO R, CARLET J, LE GALL JR, PAYEN D 2006 Sepsis Occurrence in Acutely Ill Patients Investigators. : Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 34(2): 344–353. https://doi.org/10.1097/01.ccm.0000194725.48928.3a
19. ERBAY H, YALCIN AN, SERIN S, TURGUT H, TOMATIR E, CETIN B, ZENCIR M 2003 Nosocomial infections in intensive care unit in a Turkish university hospital: a 2-year survey. Intensive Care Med 29(9): 1482–1488. https://doi.org/10.1007/s00134-003-1788-x
20. RICHARDS MJ, EDWARDS JR, CULVER DH, GAYNES RP 2000 Nosocomial infections in combined medical-surgical intensive care units in the United States. Infect Control Hosp Epidemiol 21(8): 510–515. https://doi.org/10.1086/501795
21. VINCENT JL 2003 Nosocomial infections in adult intensive-care units. Lancet 361(9374): 2068–2077. https://doi.org/10.1016/S0140-6736(03)13644-6
22. EDGEWORTH JD, TREACHER DF, EYKYN SJ 1999 A 25-year study of nosocomial bacteremia in an adult intensive care unit. see comment. Crit Care Med 27(8): 1421–1428. https://doi.org/10.1097/00003246-199908000-00002
23. JARVIS WR 2004 The state of the science of health care epidemiology, infection control, and patient safety. Am J Infect Control 32(8): 496–503. https://doi.org/10.1016/j.ajic.2004.09.00

24. KLEVENS RM, EDWARDS JR, TENOVER FC, MCDONALD LC, HORAN T, GAYNES R 2006 Changes in the Epidemiology of Methicillin-Resistant Staphylococcus aureus in Intensive Care Units in US Hospitals, 1992–2003. Clin Infect Dis 42(3): 389–391. https://doi.org/10.1086/499367

25. MEYER E, SCHWAB F, GASTMEIER P, RUEDEN H, DASCHNER FD 2006 Surveillance of Antimicrobial Use and Antimicrobial Resistance in German Intensive Care Units (SARI): A Summary of the Data from 2001 through 2004. Infection 34(6): 303–309. https://doi.org/10.1007/s15010-006-6619-x

26. KARLSSON S, VARPULA M, RUOKONEN E, PETTILA V, PARVIAINEN I, ALA-KOKKO TI, KOLHO E, RINTALA EM 2007 Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. Intensive Care Med 33 (3): 435–433. https://doi.org/10.1007/s00134-006-0504-z

27. CRAVEN DE, KUNCHES LM, LICHTENBERG DA, KOLLISCH NR, BARRY MA, HEEREN, TC, MCCABE WR 1988 Nosocomial infection and fatality in medical and surgical intensive care unit patients. Arch.Intern.Med. 148(5): 1161–1168. https://doi.org/10.1001/archinte.1988.00380050165024

28. FERNANDEZ-CREHUET R, DIAZ-MOLINA C, DE IRALA J, MARTINEZ-CONCHA D, SALCEDO-LEAL I, MASACALLES J 1997 Nosocomial infection in an intensive-care unit: identification of risk factors. Infect Control Hosp Epidemiol 18(12): 825–830.

29. APPELGREN P, HELLSTROM I, WEITZBERG E, SODERLUND V, BINDSLEV L, RANSJO U 2001 Risk factors for nosocomial intensive care infection: a long-term prospective analysis. Acta Anaesthesiol Scand. 45(6): 710–719. https://doi.org/10.1034/j.1399-6576.2001.045006710.x

30. GIROU E, STEPHAN F, NOVARA A, SAFAR M, FAGON JY 1998 Risk factors and outcome of nosocomial infections: results of a matched case-control study of ICU patients. Am J Respir Crit Care Med 157(4 Pt 1): 1151–1158. https://doi.org/10.1164/ajrccm.157.4.9701129

31. GRAVES N, WEINHOLD D, TONG E, BIRRELL F, DOIDGE S, RAMRITU P, HALTON K, LAIRSON D, WHITBY M 2007 Effect of healthcare-acquired infection on length of hospital stay and cost. Infect Control Hosp Epidemiol 28: 280–292. https://doi.org/10.1086/512642

32. DE LEON-ROSALES SP, MOLINAR-RAMOS F, DOMINGUEZ-CHERIT G, RANGEL-FRAUSTO MS, VAZQUEZ-RAMOS VG 2000 Prevalence of infections in intensive care units in Mexico: A multicenter study. Crit Care Med 28(5): 1316–1321. https://doi.org/10.1097/00003246-200005000-00010

33. VINCENT J., BIHARI, DJ., SUTER, PM., BRUINING, HA., WHITE, J., NICOLAS-CHANOIN, M., WOLFF, M., SPENCER RC, HEMMER M 1995 The Prevalence of Nosocomial Infection in Intensive Care Units in Europe: Results of the European Prevalence of Infection In Intensive Care (EPIC) Study. JAMA 274(8): 639–644.

34. VAN DEN BERGHE G, WOUTERS P, WEEKERS F, VERWAEST C, BRUYNINCKX F, SCHETZ M, VLASSELAERS D, FERDINANDE P, LAUWERS P, BOUILLON R 2001 Intensive insulin therapy in the critically ill patients. N Engl J Med 345(19): 1359–1367. https://doi.org/10.1056/NEJMoa011300

35. PETER JV, MORAN JL, PHILLIPS HUGHES J 2005 A meta-analysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients .Review. Crit Care Med 33(1): 213–220. https://doi.org/10.1097/01.ccm.0000150960.36228.c0

36. HUGONNET S, CHEVROLET JC, PITTET D 2007 The effect of workload on infection risk in critically ill patients. Crit Care Med 35(1): 76–81. https://doi.org/10.1097/01.CCM.0000251125.08629.3F

37. ROBERT J, FRIDKIN SK, BLUMBERG HM, ANDERSON B, WHITE N, RAY SM, CHAN J, JARVIS WR 2000 The influence of the composition of the nursing staff on primary bloodstream infection rates in a surgical intensive care unit. Infect Control Hosp Epidemiol 21(1): 12–17. https://doi.org/10.1086/501690

38. HALWANI M, SOLAYMANI-DODARAN M, GRUNDMANN H, COUPLAND C, SLACK R 2006 Cross transmission of nosocomial pathogens in an adult intensive care unit: incidence and risk factors. J Hosp Infect 63(1): 39–46. https://doi.org/10.1016/j.jhin.2005.10.012

39. MANOUKIAN S, STEWART S, DANCER S, GRAVES N, MASON H, MCFARLAND A, ROBERTSON C, REILLY J 2018 Estimating excess length of stay due to healthcare-associated infections: a systematic review and meta-analysis of statistical methodology J Hosp Infect, 100: 222–235. https://doi.org/10.1016/j.jhin.2018.06.003

40. BARNETT AG, BEYERSMANN J, ALLIGNOL A, ROSENTHAL VD, GRAVES N, WOLKEWITZ M 2011 The time-dependent bias and its effect on extra length of stay due to nosocomial infection Value Health 14: 381–386. https://doi.org/10.1016/j.jval.2010.09.008

41. BEYERSMANN J, GASTMEIER P, WOLKEWITZ M, SCHUMACHER M 2008 An easy mathematical proof showed that time-dependent bias inevitably leads to biased effect estimation J Clin Epidemiol 61: 1216–1221. https://doi.org/10.1016/j.jclinepi.2008.02.008

42. BEYERSMANN J, KNEIB T, SCHUMACHER M, GASTMEIER P 2009 Nosocomial infection, length of stay, and time-dependent bias Infect Control Hosp Epidemiol 30: 273–276. https://doi.org/10.1086/596020

43. DE ANGELIS G, MURTHY A, BEYERSMANN J, HARBARTH S 2010 Estimating the impact of healthcare-associated infections on length of stay and costs Clin Microbiol Infect 16: 1729–1735. https://doi.org/10.1111/j.1469-0691.2010.03332.x

44. SCHUMACHER M, ALLIGNOL A, BEYERSMANN J, BINDER N, WOLKEWITZ M 2013 Hospital-acquired infections – appropriate statistical treatment is urgently needed! Int J Epidemiol 42: 1502–1508, https://doi.org/10.1093/ije/dyt111

45. WOLKEWITZ M, ALLIGNOL A, HARBARTH S, DE ANGELIS G, SCHUMACHER M, BEYERSMANN J 2012 Time-dependent study entries and exposures in cohort studies can easily be sources of different and avoidable types of bias J Clin Epidemiol 65: 1171–1180. https://doi.org/10.1016/j.jclinepi.2012.04.008

46. BARNETT AG, BEYERSMANN J, ALLIGNOL A, ROSENTHAL VD, GRAVES N, WOLKEWITZ M 2011 The Time-Dependent Bias and its Effect on Extra Length of Stay due to Nosocomial Infection. Value Health 14: 381–386. https://doi.org/10.1016/j.jval.2010.09.008

47. NELSON RE, NELSON SD, KHADER K, PERENCEVICH EL, SCHWEIZER ML, RUBIN MA, GRAVES N, HARBARTH S, STEVENS VW, SAMORE MH 2015 The Magnitude of Time-Dependent Bias in the Estimation of Excess Length of Stay Attributable to Healthcare-Associated Infections. Infect Control Hosp Epidemiol. 36(9): 1089–1094. https://doi.org/10.1017/ice.2015.129

48. ANGUS DC, LINDEZWIRBLE WT, LIDICKER J, CLERMONT G, CARCILLO J, PINSKY MR 2001 Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 29(7): 1303–1310. https://doi.org/10.1097/00003246-200107000-00002

49. BRUN-BUISSON C, MESHAKA P, PINTON P, VALLET B 2004 EPISEPSIS Study Group: EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 30(4): 580–588. https://doi.org/10.1007/s00134-003-2121-4

50. PADKIN A, GOLDFRAD C, BRADY AR, YOUNG D, BLACK N, ROWAN K 2003 Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. Crit Care Med 31(9): 2332–2338. https://doi.org/10.1097/01.CCM.0000085141.75513.2B

51. VAN GESTEL A, BAKKER J, VERAART C, VAN HOUT B 2004 Prevalence and incidence of severe sepsis in Dutch intensive care units. Crit Care 8(4): 153–162. https://doi.org/10.1186/cc2858

52. FINFER S, BELLOMO R, LIPMAN J, FRENCH C, DOBB G, MYBURGH J 2004 Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med 30(4): 589–596. https://doi.org/10.1007/s00134-004-2157-0

53. ADRIE C, ALBERTI C, CHAIX-COUTURIER C, AZOULAY E, DE LASSENCE A, COHEN Y, MESHAKA P, CHEVAL C, THUONG M, TROCHE G, GARROUSTE-ORGEAS M, TIMSIT JF 2005 Epidemiology and economic evaluation of severe sepsis in France: age, severity, infection site, and place of acquisition (community, hospital, or intensive care unit) as determinants of workload and cost. J Crit Care 20(1): 46–58. https://doi.org/10.1016/j.jcrc.2004.10.005

54. SILVA E, PEDRO M, SOGAYAR A, MOHOVIC T SILVA C, JANISZEWSKI M, CAL R, DE SOUSA E, ABE T, DE ANDRADE J, DE MATOS J, REZENDE E, ASSUNCÃO M, AVEZUM A, ROCHA P, DE MATOS G, BENTO A, CORRÊA A, VIEIRA P, KNOBEL E 2004 Brazilian Sepsis Epidemiological Study (BASES study). Crit Care 8(4): 251–260. https://doi.org/10.1186/cc2892

55. HUGONNET S, HARBARTH S, FERRIERE K, RICOU B, SUTER P, PITTET D 2003 Bacteremic sepsis in intensive care: Temporal trends in incidence, organ dysfunction, and prognosis. Crit Care Med 31(2): 390–394. https://doi.org/10.1097/01.CCM.0000045026.81584.6F

56. KUMAR A, ROBERTS D, WOOD KE, LIGHT B, PARRILLO JE, SHARMA S, SUPPES R, FEINSTEIN D, ZANOTTI S, TAIBERG L, GURKA D, KUMAR A, CHEANG M 2006 Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34(6): 1589–1596. https://doi.org/10.1097/01.CCM.0000217961.75225.E9

57. DELLINGER RP, CARLET JM, MASUR H, GERLACH H, CALANDRA T, COHEN J, GEA-BANACLOCHE J, KEH D, MARSHALL JC, PARKER MM, RAMSAY G, ZIMMERMAN JL, VINCENT JL, LEVY MM 2004 Surviving Sepsis Campaign Management Guidelines,Committee : Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32(3): 858–873. https://doi.org/10.1097/01.ccm.0000117317.18092.e4

58. JOKINEN C, HEISKANEN L, JUVONEN H, KALLINEN S, KARKOLA K, KORPPI M, KURKI S, RONNBERG PR, SEPPA A, SOIMAKALLIO S 1993 Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. Am J Epidemiol 137(9): 977–988. https://doi.org/10.1093/oxfordjournals.aje.a116770

59. ANGUS DC, MARRIE TJ, OBROSKY DS, CLERMONT G, DREMSIZOV TT, COLEY C, FINE MJ, SINGER DE, KAPOOR WN 2002 Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. Am J Respir Crit Care Med 166(5): 717–723. https://doi.org/10.1164/rccm.2102084

60. WOODHEAD M, WELCH C, HARRISON D, BELLINGAN G, AYRES J 2006 Community-acquired pneumonia on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC Case Mix Programme Database. Critical Care 10(Suppl 2): S1. https://doi.org/10.1186/cc4927

61. COHEN J, BRUN-BUISSON C, TORRES A, JORGENSEN J 2004 Diagnosis of infection in sepsis: an evidence-based review. Crit Care Med 32(11 Suppl): S466–94. https://doi.org/10.1097/01.ccm.0000145917.89975.f5

62. RELLO J, BODI M, MARISCAL D, NAVARRO M, DIAZ E, GALLEGO M, VALLES J 2003 Microbiological testing and outcome of patients with severe community-acquired pneumonia. Chest 123(1): 174–180. https://doi.org/10.1378/chest.123.1.174

63. TEJERINA E, FRUTOS-VIVAR F, RESTREPO MI, ANZUETO A, PALIZAS F, GONZALEZ M, APEZTEGUIA C, ABROUG F, MATAMIS D, BUGEDO G, ESTEBAN A 2005 International Mechanical Ventilation Study Group : Prognosis factors and outcome of community-acquired pneumonia needing mechanical ventilation. J.Crit.Care 20(3): 230–238. https://doi.org/10.1016/j.jcrc.2005.05.010

64. PAGANIN F, LILIENTHAL F, BOURDIN A, LUGAGNE N, TIXIER F, GENIN R, YVIN JL 2004 Severe community-acquired pneumonia: assessment of microbial aetiology as mortality factor. Eur Respir J 24(5): 779–785. https://doi.org/10.1183/09031936.04.00119503

65. YOSHIMOTO A, NAKAMURA H, FUJIMURA M, NAKAO S 2005 Severe community-acquired pneumonia in an intensive care unit: risk factors for mortality. Intern Med 44(7): 710–716. https://doi.org/10.2169/internalmedicine.44.710

66. VALLES J, MESALLES E, MARISCAL D, DEL MAR FERNANDEZ M, PENA R, JIMENEZ JL, RELLO J 2003 A 7-year study of severe hospital-acquired pneumonia requiring ICU admission. Intensive Care Med 29(11): 1981–1988. https://doi.org/10.1007/s00134-003-2008-4

67. MINEI JP, HAWKINS K, MOODY B, UCHAL LB, JOY K, CHRISTENSEN LL, HALEY RW 2000 Alternative case definitions of ventilator-associated pneumonia identify different patients in asurgical intensive care unit. Shock 14(3): 331–336. https://doi.org/10.1097/00024382-200014030-00016

68. BERCAULT N, BOULAIN T 2001 Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: a prospective case-control study. Crit Care Med 29(12): 2303–2309. https://doi.org/10.1097/00003246-200112000-00012

69. COOK DJ, WALTER SD, COOK RJ, GRIFFITH LE, GUYATT GH, LEASA D, JAESCHKE RZ, BRUN-BUISSON C 1998 Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 129(6): 433–440. https://doi.org/10.7326/0003-4819-129-6-199809150-00002

70. FAGON JY, CHASTRE J, VUAGNAT A, TROUILLET JL, NOVARA A, GIBERT C 1996 Nosocomial pneumonia and mortality among patients in intensive care units. JAMA 275(11): 866–869.

71. HUGONNET S, EGGIMANN P, BORST F, MARICOT P, CHEVROLET J, PITTET D 2004 Impact of ventilator-associated pneumonia on resource utilization and patient outcome. Infect Control Hosp Epidemiol 25(12): 1090–1096. https://doi.org/10.1086/502349

72. KOLLEF MH 1993 Ventilator-associated pneumonia. A multivariate analysis. JAMA 270(16):1965–1970.

73. PAPAZIAN L, BREGEON F, THIRION X, GREGOIRE R, SAUX P, DENIS JP, PERIN G, CHARREL J, DUMON JF, AFFRAY JP, GOUIN F 1996 Effect of ventilator-associated pneumonia on mortality and morbidity. Am J Respir Crit Care Med 154(1): 91–97. https://doi.org/10.1164/ajrccm.154.1.8680705

74. ROSENTHAL VD, GUZMAN S, MIGONE O, SAFDAR N 2005 The attributable cost and length of hospital stay because of nosocomial pneumonia in intensive care units in 3 hospitals in Argentina: a prospective, matched analysis. Am J Infect Control 33(3): 157–161. https://doi.org/10.1016/j.ajic.2004.08.008

75. WARREN DK, SHUKLA SJ, OLSEN MA, KOLLEF MH, HOLLENBEAK CS, COX MJ, COHEN MM, FRASER VJ 2003 Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center.

Crit Care Med 31(5): 1312–1317. https://doi.org/10.1097/01.CCM.0000063087.93157.06

76. SAFDAR N, DEZFULIAN C, COLLARD HR, SAINT S 2005 Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. Crit Care Med 33(10): 2184–2193. https://doi.org/10.1097/01.ccm.0000181731.53912.d9

77. TIMSIT JF, CHEVRET S, VALCKE J, MISSET B, RENAUD B, GOLDSTEIN FW, VAURY P, CARLET J 1996 Mortality of nosocomial pneumonia in ventilated patients: influence of diagnostic tools. Am J Respir Crit Care Med 154(1): 116–123. https://doi.org/10.1164/ajrccm.154.1.8680666

78. FAGON JY, CHASTRE J, WOLFF M, GERVAIS C, PARER-AUBAS S, STÉPHAN F, SIMILOWSKI T, MERCAT A, DIEHL JL, SOLLET JP, TENAILLON A 2000 Invasive and Noninvasive Strategies for Management of Suspected Ventilator-Associated Pneumonia: A Randomized Trial. Ann Intern Med 132(8): 621–630. https://doi.org/10.7326/0003-4819-132-8-200004180-00004

79. CHASTRE J LUYT CE COMBES A, TROUILLET JL 2006 Use of quantitative cultures and reduced duration of antibiotic regimens for patients with ventilator-associated pneumonia to decrease resistance in the intensive care unit. Clin Infect Dis 43(Suppl): 2: S75–81. https://doi.org/10.1086/504483

80. FUJITANI S, YU VL 2006 Quantitative Cultures for Diagnosing Ventilator- Associated Pneumonia: A Critique. Clin Infect Dis 43: 106–113. https://doi.org/10.1086/504488

81. THE CANADIAN CRITICAL CARE TRIALS GROUP 2006 A Randomized Trial of Diagnostic Techniques for Ventilator-Associated Pneumonia. N Engl J Med 355(25): 2619–2630. https://doi.org/10.1056/NEJMoa052904

82. MARIN H, KOLLEF MD 2006 Diagnosis of Ventilator-Associated Pneumonia. N Engl J Med 355(25): 2691–2693. https://doi.org/10.1056/NEJMe068231

83. MILLER PR, JOHNSON JC 3RD, KARCHMER T, HOTH JJ, MEREDITH JW, CHANG MC 2006 National nosocomial infection surveillance system: from benchmark to bedside in trauma patients. J Trauma 60(1): 98–103. https://doi.org/10.1097/01.ta.0000196379.74305.e4

84. AMERICAN THORACIC SOCIETY 2005 Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. Am J Respir Crit Care Med 171(4): 388–416. https://doi.org/10.1164/rccm.200405-644ST

85. CHLEBICKI MP, SAFDAR N 2007 Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. Crit Care Med 35(2): 595–602. https://doi.org/10.1097/01.CCM.0000253395.70708.AC

86. KOEMAN M, VAN DER VEN ANDRE A J, HAK E, JOORE HC, KAASJAGER K, DE SMET AG, RAMSAY G, DORMANS TP, AARTS LP, DE BEL EE, HUSTINX WN, VAN DER TWEEL I, HOEPELMAN AM, BONTEN MJ 2006 Oral Decontamination with Chlorhexidine Reduces the Incidence of Ventilator-associated Pneumonia. Am J Respir Crit Care Med 173(12): 1348–1355. https://doi.org/10.1164/rccm.200505-820OC

87. BONTEN MJ, GAILLARD CA, DE LEEUW PW, STOBBERINGH EE 1997 Role of colonization of the upper intestinal tract in the pathogenesis of ventilator-associated pneumonia. Clin Infect Dis 24(3): 309–319. https://doi.org/10.1093/clinids/24.3.309

88. HERNANDEZ G, RICO P, DIAZ E, RELLO J 2004 Nosocomial lung infections in adult intensive care units. Microbes & Infection 6(11): 1004–1014. https://doi.org/10.1016/j.micinf.2004.05.019

89. RELLO J, OLLENDORF DA, OSTER G, VERA-LLONCH M, BELLM L, REDMAN R, KOLLEF MH, VAP 2002 Outcomes Scientific Advisory,Group: Epidemiology and outcomes of ventilator associated pneumonia in a large US database. Chest 122(6): 2115–2121. https://doi.org/10.1378/chest.122.6.2115

90. CHASTRE J, FAGON J 2002 Ventilator-associated Pneumonia. Am J Respir Crit Care Med 165(7): 867–903. https://doi.org/10.1164/ajrccm.165.7.2105078

91. RELLO J, DIAZ E, ROQUE M, VALLES J 1999 Risk factors for developing pneumonia within 48 hours of intubation. Am J Respir Crit Care Med 159(6): 1742–1746. https://doi.org/10.1164/ajrccm.159.6.9808030

92. ROSENTHAL VD, GUZMAN S, ORELLANO PW 2003 Nosocomial infections in medical-surgical intensive care units in Argentina: attributable mortality and length of stay. Am J Infect Control 31(5): 291–295. https://doi.org/10.1067/mic.2003.1

93. D'AMICO R, PIFFERI S, LEONETTI C, TORRI V, TINAZZI A, LIBERATI A 1998 Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. BMJ 316(7140): 1275–1285.

94. DRAKULOVIC MB, TORRES A, BAUER TT, NICOLAS JM, NOGUE S, FERRER M 1999 Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet 354(9193): 1851–1858. https://doi.org/10.1136/bmj.316.7140.1275

95. VAN NIEUWENHOVEN CA, VANDENBROUCKE-GRAULS C, VAN TIEL F H, JOORE HC, VAN SCHIJNDEL RJ, VAN DER TWEEL I, RAMSAY GB, BONTEN MJ 2006 Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: A randomized study. Crit Care Med 34(2): 396–402. https://doi.org/10.1097/01.ccm.0000198529.76602.5e

96. BREGEON F, CIAIS V, CARRET V, GREGOIRE R, SAUX P, GAINNIER M, THIRION X, DRANCOURT M, AUFFRAY JP, PAPAZIAN L 2001 Is ventilator-associated pneumonia an independent risk factor for death? Anesthesiology 94(4): 554–560. https://doi.org/10.1097/00000542-200104000-00005

97. BERCAULT N, BOULAIN T 2001 Mortality rate attributable to ventilator-associated nosocomial pneumonia in an adult intensive care unit: a prospective case-control study. Crit Care Med 29 (12): 2303–2309. https://doi.org/10.1097/00003246-200112000-00012

98. LUNA C, VUJACICH P, NIEDERMAN M, VAY C, GHERARDI C, MATERA J, JOLLY E 1997 Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 111(3): 676–685. https://doi.org/10.1378/chest.111.3.676

99. LUNA CM, ARUJ P, NIEDERMAN MS, GARZON J, VIOLI D, PRIGNONI A, RIOS F, BAQUERO S, GANDO S, FOR THE GRUPO ARGENTINO DE ESTUDIO DE LA NEUMONIA ASOCIADA AL RESPIRADOR (GANAR) GROUP 2006 Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. Eur Respir J 27(1): 158–164. https://doi.org/10.1183/09031936.06.00049105

100. HUTCHINS RR, GUNNING MP, LUCAS DN, ALLENMERSH TG, SONI NC 2004 Relaparotomy for suspected intraperitoneal sepsis after abdominal surgery. World J Surg 28(2): 137–141. https://doi.org/10.1007/s00268-003-7067-8

101. BARIE PS, HYDO LJ, EACHEMPATI SR 2004 Longitudinal outcomes of intra-abdominal infection complicated by critical illness. Surg Infect 5(4): 365–373. https://doi.org/10.1089/sur.2004.5.365

102. O'GRADY NP, ALEXANDER M, DELLINGER EP, GERBERDING JL, HEARD SO, MAKI DG, MASUR H, MCCORMICK RD, MERMEL LA, PEARSON ML, RAAD II RANDOLPH A, WEINSTEIN RA 2002 Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep 51(RR-10): 1–29. https://doi.org/10.1086/502007

103. DESHPANDE KS, HATEM C, ULRICH HL, CURRIE BP, ALDRICH TK, BRYAN-BROWN CW, KVETAN V 2005 The incidence of infectious complications of central venous catheters at the subclavian, internal jugular, and femoral sites in an intensive

care unit population. Crit Care Med 33(1): 13–20. https://doi.org/10.1097/01.ccm.0000149838.47048.60

104. KARAKITSOS D, LABROPOULOS N, DE GROOT E, PATRIANAKOS AP, KOURAKLIS G, POULARAS J, SAMONIS G, TSOUTSOS DA, KONSTADOULAKIS MM, KARABINIS A 2006 Real-time ultrasound-guided catheterisation of the internal jugular vein: a prospective comparison with the landmark technique in critical care patients. Critical Care 10(6): R162. https://doi.org/10.1186/cc5101

105. LAUPLAND KB, LEE H, GREGSON DB, MANNS BJ 2006 Cost of intensive care unit-acquired bloodstream infections. J Hosp Infect 63(2): 124–132. https://doi.org/10.1016/j.jhin.2005.12.016

106. DIGIOVINE B, CHENOWETH C, WATTS C, HIGGINS M 1999 The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. Am J Respir Crit Care Med 160(3): 976–981. https://doi.org/10.1164/ajrccm.160.3.9808145

107. RENAUD B, BRUN-BUISSON C, ICU-BACTEREMIA STUDY GROUP 2001 Outcomes of primary and catheterrelated bacteremia. A cohort and case-control study in critically ill patients. Am J Respir Crit Care Med 163(7): 1584–1590. https://doi.org/10.1164/ajrccm.163.7.9912080

108. SOUFIR L, TIMSIT JF, MAHE C, CARLET J, REGNIER B, CHEVRET S 1999 Attributable morbidity and mortality of catheter-related septicemia in critically ill patients: a matched, risk-adjusted, cohort study. Infect Control Hosp Epidemiol 20(6): 396–401. https://doi.org/10.1086/501639

109. RELLOR J, OCHAGAVIA A, SABANES E, ROQUE M, MARISCAL D, REYNAGA E, VALLES J 2000 Evaluation of outcome of intravenous catheter-related infections in critically ill patients. Am J Respir Crit Care Med 162(3 Pt 1): 1027–1030. https://doi.org/10.1164/ajrccm.162.3.9911093

110. GARROUSTE-ORGEAS M, TIMSIT JF, TAFFLET M, MISSET B, ZAHAR J, SOUFIR L, LAZARD T, JAMALI S, MOURVILLIER B COHEN Y, DE LASSENCE A, AZOULAY E, CHEVAL C, DESCORPS-DECLEREA, ADRIE, C, DE BEAUREGARD MC, CARLET J 2006 Excess Risk of Death from Intensive Care Unit–Acquired Nosocomial Bloodstream Infections: A Reappraisal. Clin Infect Dis 42(8): 1118–1126. https://doi.org/10.1086/500318

111. KIM PW, PERL TM, KEELAGHAN EF, LANGENBERG P, PERENCEVICH EN, HARRIS AD, SONGX, ROGHMANN MC 2005 Risk of mortality with a bloodstream infection is higher in the less severely ill at admission. Am J Respir Crit Care Med 171(6): 616–620. https://doi.org/10.1164/rccm.200407-916OC

112. WARREN DK, QUADIR WW, HOLLENBEAK CS, ELWARD AM, COX MJ, FRASER, VJ 2006 Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. Crit Care Med 34(8): 2084–2089. https://doi.org/10.1097/01.CCM.0000227648.15804.2D

113. LAUPLAND KB, ZYGUN DA, DAVIES HD, CHURCH DL, LOUIE TJ, DOIG CJ 2002 Incidence and risk factors for acquiring nosocomial urinary tract infection in the critically ill. J Crit Care 17(1): 50–57. https://doi.org/10.1053/jcrc.2002.33029

114. LEONE M, ALBANESE J, GARNIER F, SAPIN C, BARRAU K, BIMAR MC, MARTIN C 2003 Risk factors of nosocomial catheter-associated urinary tract infection in a polyvalent intensive care unit. Intensive Care Med 29(7): 1077–1080.