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Special Article

Healthcare-associated infections in adult intensive care unit patients: Changes in epidemiology, diagnosis, prevention and contributions of new technologies

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ABSTRACT

Patients in intensive care units (ICUs) are at high risk for healthcare-acquired infections (HAI) due to the high prevalence of invasive procedures and devices, induced immunosuppression, comorbidity, frailty and increased age. Over the past decade we have seen a successful reduction in the incidence of HAI related to invasive procedures and devices. However, the rate of ICU-acquired infections remains high. Within this context, the ongoing emergence of new pathogens, further complicates treatment and threatens patient outcomes. Additionally, the SARS-CoV-2 (COVID-19) pandemic highlighted the challenge that an emerging pathogen provides in adapting prevention measures regarding both the risk of exposure to caregivers and the need to maintain quality of care. ICU nurses hold a special place in the prevention and management of HAI as they are involved in basic hygienic care, steering and implementing quality improvement initiatives, correct microbiological sampling, and aspects antibiotic stewardship. The emergence of more sensitive microbiological techniques and our increased knowledge about interactions between critically ill patients and their microbiota are leading us to rethink how we define HAIs and best strategies to diagnose, treat and prevent these infections in the ICU. This multidisciplinary expert review, focused on the ICU setting, will summarise the recent epidemiology of ICU-HAI, discuss the place of modern microbiological techniques in their diagnosis, review operational and epidemiological definitions and

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redefine the place of several controversial preventive measures including antimicrobial-impregnated medical devices, chlorhexidine-impregnated washcloths, catheter dressings and chlorhexidine-based mouthwashes. Finally, general guidance is suggested that may reduce HAI incidence and especially outbreaks in ICUs.

Implications for Clinical Practice

- Despite efforts in prevention, hospital-acquired infection remains an important source of morbidity and possibly mortality.
- COVID-19 may facilitate secondary infections such as bloodstream infection and pneumonia assumingly because of higher disease severity and excessive workload
- The proportion of preventable hospital-acquired infection depends on patient population, adherence to prevention precautions and type of infection, for example, catheter-related bloodstream infection appears highly avoidable when evidence-based prevention measures are utilised.
- Chlorhexidine-impregnated washcloths reduce the risk of Gram-positive bacteraemia but their use comes with a warning of increasing resistance against this antiseptic agent, especially by Gram-negative bacteria. Their use should therefore be reserved for outbreaks.
- The use of chlorhexidine oral care should be limited to patient groups with an evidence-based indication given its possible relationship with mortality.

Introduction

Healthcare–associated infections (HAIs) are a major public health burden (WHO, 2012). HAIs are associated with more than 140,000 deaths worldwide each year (WHO, 2011). Prevalence surveys in the United States (US) suggest that 30% of HAIs occur in intensive care units (ICUs) (Magill et al., 2014; CDC, 2016). Moreover, HAIs prolong ICU and hospital stays, increase antibiotic consumption and inflate the costs of care. The occurrence of HAIs result from a complex interplay of pathogen factors (virulence, antibiotic resistance), host factors (comorbidity, acute illness), treatment factors (invasive devices, antibiotic selection pressure), healthcare processes (staffing, prevention measures), and even climatological conditions (Myny et al., 2005; Depuydt et al., 2006a, 2006b; Guzmán-Herrador et al., 2016; Blot et al., 2021). Although most pathogens involved are of endogenous origin, microorganisms can also be acquired from human or environmental sources during the course of care (Siegel et al., 2007).

ICU nurses have a central role in the prevention and management of HAI as they are involved in basic hygienic care, clinical observation and monitoring of infection-sensitive body sites (e.g. catheter insertion sites or surgical wounds) as well as monitoring systemic signs of infection, steering and implementing quality improvement initiatives, correct microbiological sampling and aspects of antibiotic stewardship. Ongoing efforts to prevent infections have led to a significant decrease in device-associated HAIs. However, the burden of HAIs is expected to increase in the coming years, as a result of intensification of care, an ageing population, the growing prevalence of severe underlying diseases in ICU patients and the ongoing spread of multidrug resistant organisms (MDRO) in the hospital and the community (Dimopoulos et al., 2013; Blot et al., 2019a). In the meantime, the workforce is impacted by continuous shortage of highly skilled nurses (Anders, 2021). In this review, a panel of experts discusses the recent data on HAI in ICUs.

Changing epidemiology of ICU-acquired infections

Insights in epidemiology and infection dynamics are essential to identify promptly high-risk patients or potentially threatening situations. Because of the individual and collective consequences of infection and resistance, a high level of vigilance and compliance with preventive measures is required by the whole team. However, compared with other ICU clinicians, nurses have the highest exposure in terms of direct patient contact and are well-placed to ensure precautions are effectively practiced.

HAI prevalence varies among hospitals and countries (Fig. 1). Variations might be related to patient characteristics, epidemiological features and organizational factors (Rodríguez-Acelas et al., 2017). Patient-level factors include age, comorbidity (especially immunosuppression), illness severity, duration of hospitalization and exposure to invasive devices and procedures. Beside host factors, organizational factors such as heavy workload and work environment are associated with a higher risk of acquisition of HAI and MDRO (Penoyer, 2010; Kelly et al., 2013; Lee et al., 2018; Jansson et al., 2019). Quality of care, by adherence to a care bundle (Rello et al., 2013) and improving environmental cleaning appear to reduce both the risk of HAI and the risk of MDRO acquisition (Blot, 2008; Nseir et al., 2011).

The most frequent ICU-acquired infections are pneumonia (including ventilator-associated pneumonia (VAP), surgical site infections (SSI), catheter-related bloodstream infections (CRBSI) and catheter-associated urinary tract infections (CAUTI) (Vincent et al., 2009; Vogelaers et al., 2010).

Healthcare-acquired pneumonia is the most common and morbid HAI (Walter et al., 2018). In a recent multicentre international, prospective, observational study in 114 ICUs, the incidence of ventilator-associated tracheobronchitis and of VAP at baseline were similar (320 [11%; 10.2/1000 mechanically ventilated days] and 369 [12%; 8.8/1000 mechanically ventilated days], $p = 0.48$) (Martin-Loeches et al., 2015). Due to the increased use of non-invasive and high-flow ventilation, recent studies emphasize the importance of non-ventilated hospital-acquired pneumonia (HAP) found in 4.5/1000 patients-days (Saied et al., 2020).

Healthcare-acquired intra-abdominal infections (postoperative and tertiary peritonitis) account for up to 65% of all abdominal infections observed in ICU patients (WHO, 2012). Intra-abdominal infections in ICU patients highlight the issue of antibiotic resistance, which appears equally in community-acquired and in HAI (Blot et al., 2019b; Vogelaers et al., 2021), requiring early source control and appropriate antimicrobial therapy (Augustin et al., 2010; Blot et al., 2012; De Waele et al., 2014; Blot et al., 2019b). Contrary to HAI global incidence, CRBSI decreased in several countries over the last decade. Several authors report rates of 1.0/1000 catheter-days or less due to optimized processes of nursing care and technical innovation (Timsit et al., 2018; Eggimann et al., 2019).

ICU-acquired HAI rates tend to be higher and MDRO more prevalent in low- and middle-income countries compared to high-income countries (Fig. 2), particularly for Gram-negative pathogens (Sakr et al., 2018; WHO, 2011). Currently, carbapenemase-producing *Klebsiella*

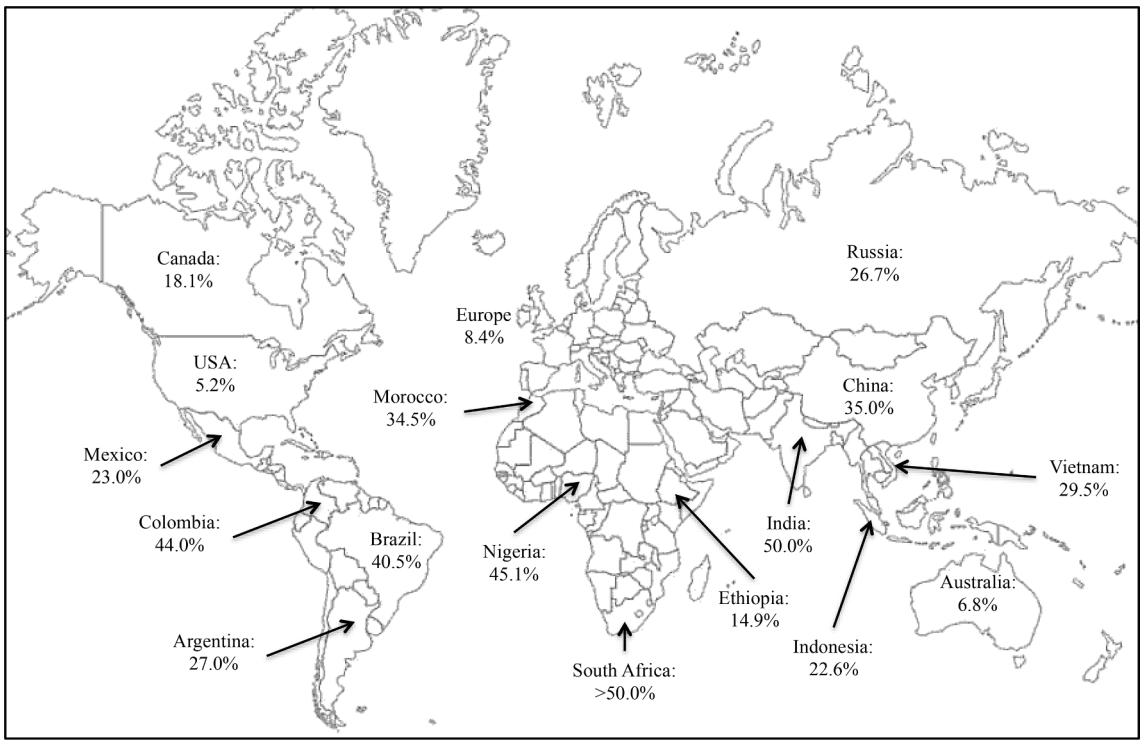

Fig. 1. Prevalence of ICU-acquired infections, 2000–2018 (ECDC, 2018; Ponce de León-Rosales et al. 2000; Rosenthal et al. 2003; Ortíz et al. 2014; Murni et al. 2015; Iwuafor et al. 2016; Mitharwal et al. 2016; Phu et al. 2016; Taylor et al. 2016; Yakovlev et al. 2016; Yallew et al. 2016; Chiang et al. 2018; Braga et al. 2019).

pneumoniae (KPCs) are endemic in Israel, Greece, Italy, Poland, China, Brazil, Argentina and Colombia, and are found in almost all European countries (Albiger et al., 2015). Similarly, *Candida auris* is now prevalent in India and the Middle East and multiple outbreaks have been reported in the US, Europe, Asia and elsewhere (Satoh et al., 2009; Jeffery-Smith et al., 2018). Infections with MDRO may increase mortality and length of stay, perhaps because of delays in starting appropriate antibiotics, but this is controversial (Tabah et al., 2012; Stewardson et al., 2016).

MDRO and *Candida* isolates are not the only pathogens acquired in ICU. Recent improvements in detection methods, helped diagnose acquired respiratory viruses in HAP. In a recent study, influenza (27%) and rhinovirus (27%) were the two most common respiratory viruses isolated from HAP in ICU (Loubet et al., 2017). ICUs are a potential high-risk areas for the transmission of such respiratory viruses (Grund et al., 2010). Finally, due to the presence of multiple risk factors, patients in ICUs are at higher risk for *Clostridium difficile* infections with a prevalence of 2% and 11% among diarrhoeic ICU patients (Karanika et al., 2016).

Impact of ICU-acquired infections on long-term outcomes

Alterations in innate and adaptive immunity following HAIs persist for a sustained period after clinical recovery. Such alterations correlate with long-term mortality (Delano and Ward 2016). Patients who recover from in-hospital sepsis have an increased risk of death for up to two years (Winters et al., 2010).

In a Taiwanese cohort of 3,070 patients with healthcare-acquired *Staphylococcus aureus* infections, infection was associated with a 20% increase in one-year mortality (Su et al., 2013). Infection was also associated with a 2.6% excess risk in dialysis dependence and a 7.3% excess risk of ventilator dependence at one year. These crude proportions are very similar to those observed in a cohort study from Europe (Stewardson et al., 2016). In 17,536 elderly patients admitted to an ICU, the long-term impact of central line-associated bloodstream infection (CLABSI) and of VAP were similar to that of sepsis and pneumonia (Dick et al., 2012). Hospital-acquired sepsis and pneumonia were associated with an increased one-year risk of death. Pneumonia was also associated with increased healthcare visits, long-term care admissions, and mortality at five years. Neurology ICU patients are another group at particularly high risk of health-acquired infections. In a large prospective cohort of ICU patients with spinal cord injury, the incidence of health-acquired pneumonia/wound infections was 47%, associated with a lower gain in functional motor autonomy at five years and an increased mortality at 10 years (Kopp et al., 2017). Similarly, post-stroke pneumonia was associated with a 50% increase in the one-year risk for death among ICU survivors (de Montmollin et al., 2019).

Immunosuppression and ICU-acquired infections

Immunosuppression related to the hospitalization in ICU

Critical illness-related immunosuppression is common in ICU patients suffering from any acute diseases (Deknuydt et al., 2013; Roquilly et al., 2017). ICU patients have functional alterations of myeloid cells (dendritic cells, monocytes and macrophages), innate-like lymphocytes (natural killer, natural killer T cells) and of conventional lymphocytes (T and B cells) (Hotchkiss et al., 2013b). ICU patients with community-acquired pneumonia or HAP have distinct transcriptional and plasma protein responses (van Vught et al., 2016) consistent with functional alterations of their immune systems. Additionally, critical illness disrupts the normal balance between the body's immunogenic and tolerogenic responses. For example, the lungs are naturally tolerant of foreign material in order to minimize acute inflammation in response to inhaled particles (Roquilly et al., 2019) but this natural tolerance is exacerbated by the immune dysfunction in critical illness leaving patients particularly susceptible to pneumonia (Fig. 3).

Interestingly, the risk of HAP is directly correlated with the severity of patients' immune alterations including: (1) the degree of decreased expression of human leukocyte antigen-DR (HLA-DR) on circulating monocytes (surrogate marker of a decreased antigenic presentation

capacity) (Hotchkiss et al., 2013a); (2) increased production of immunosuppressive cytokines such as IL-10 (Roquilly et al., 2014) and (3) depletion of the T-lymphocyte repertoire (Venet et al., 2013).

Immunosuppression related to the underlying disease

Oncology and haematology patients often require ICU admission as a result of infection, treatment toxicity and organ infiltration by underlying malignancy (Schelenz et al., 2013; Marin et al., 2014; Taplitz et al., 2018). Infectious risk among cancer patients stems from defects in innate or adaptive immunity, associated either with the malignancy *per se* or with cytotoxic effects of treatment (Fig. 4) (Talcott et al., 1988). Neutropenia, and particularly protracted neutropenia (>7 days), is a major risk factor for infection and call for protective isolation (Freifeld et al., 2011). Other factors may also play an important role (Table 1) (Freifeld et al., 2011; Taplitz et al., 2018). Acute hematological malignancies and myelodysplastic syndromes have an enhanced infectious risk due to marrow infiltration by malignancy. Chemotherapy and graft-versus-host disease facilitate opportunistic infection through disruption of mucosal integrity (Freifeld et al., 2011; Taplitz et al., 2018). Solid tumors are more associated with local complications, related or not with tumor resection surgery, rather than marrow failure or cytotoxic effects of the treatment (Table 2) (Talcott et al., 1988; Freifeld et al., 2011; Taplitz et al., 2018). Finally, immunocompromised patients, whatever the cause, require specific measures to control the risk of HAI (Table 2).

The role of COVID-19 infection in the risk of HAIs

COVID-19 has highlighted the challenge of adapting prevention measures to protect caregivers and patients against exposure while maintaining an optimal quality of care standard (Jansson et al., 2020). Any healthcare-associated outbreak, whether among clinicians or patients, should prompt for a route-cause investigation (Mongin et al., 2021; Vuichard-Gysin et al., 2021). Initially, the basis of prevention lies in the knowledge of the mode of contamination. Certain actions such as aerosol-generating procedures expose an inherent transmission risk and call for upgraded prevention measures (Tran et al., 2012; Lormans et al., 2021). Like other respiratory viruses, direct transmission seems to predominate for SARS-CoV-2, however, surfaces seem to be contaminated in 27 to 45% of cases with need for specific cleaning (Mendes et al., 2021).

COVID-19 considerably increased the incidence of VAP with a pooled estimated incidence of 45.4% (95% confidence interval [CI] 37.8–53.2%) (Ippolito et al., 2021). COVID-19 related acute respiratory distress syndrome (ARDS) is associated with more profound hypoxia than ARDS from other origins resulting in longer duration of mechanical ventilation and more application of prone positioning, factors affecting the risk of HAIs and CRBSI (Luyt et al., 2020; Razazi et al., 2020; Maes et al., 2021; Rouzé et al., 2021). COVID-19 amplifies the risk of HAI due to multiple factors: less rigorous use of standard prevention strategies, disease and therapy-associated immune impairment, prolonged duration of mechanical ventilation and sedation, more frequent prone ventilation and higher risk for pulmonary infarction with associated superinfection. ICU overcrowding the use of suboptimal trained healthcare personnel may have reduced compliance with HAI prevention programs (Reper et al., 2020; Arabi et al., 2021; Reper et al., 2021; Wicky et al., 2021).

Assessing the role of microbiota composition in the risk of HAI

Recent advances in microbiology and metagenomics (i.e., sequencing of all the nucleic acids in a sample) have led to a better understanding of patients' microbiota, its changes during an ICU stay, and how this can affect the probability and nature of ICU-HAIs. Understanding the microbiota of the skin and oral cavity, especially when it comes to the use of antiseptic agents potentially diminishing

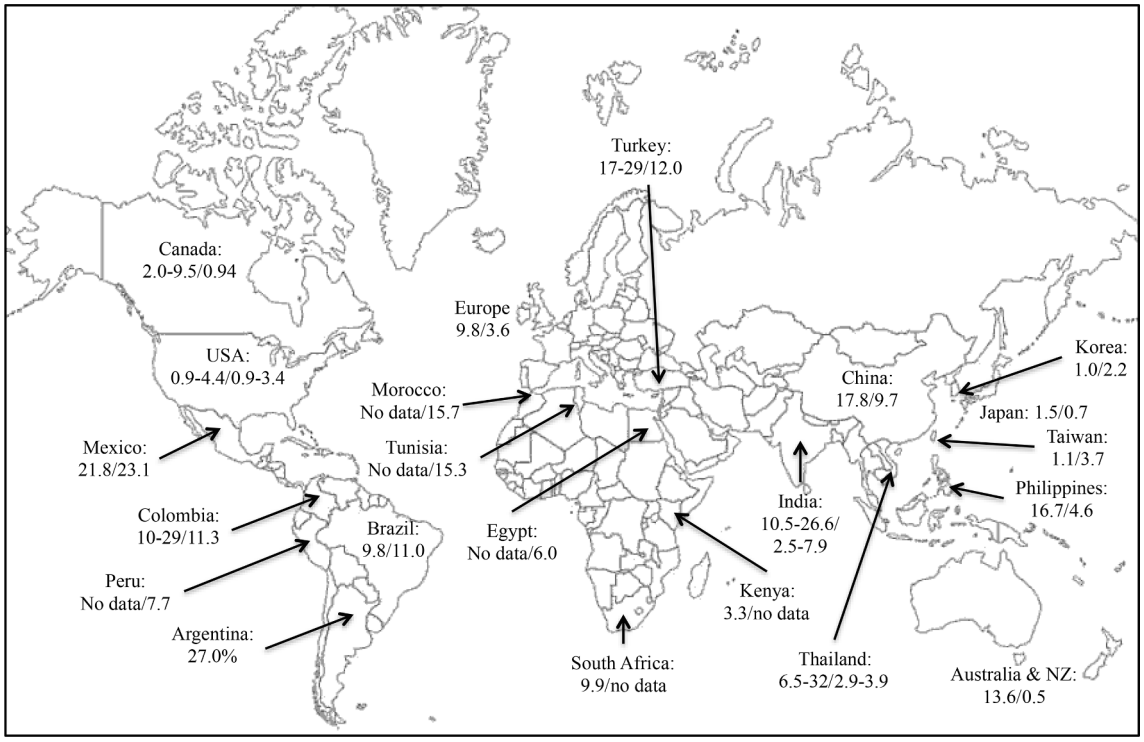

Fig. 2. Rates of ventilator-associated pneumonia per 1000 days of intubation and ICU-central line-associated bloodstream infections per 1000 catheter days, respectively (2000–2018) (PHAC, 2014; Lobo et al. 2005; Moreno et al. 2006; Rosenthal et al. 2006; Hajdu et al. 2007; Leblebicioglu et al. 2007; Mehta et al. 2007; Arabi et al. 2008; Korbkitjaroen et al. 2011; Navoa-Ng et al. 2011; Ramirez et al. 2011; Son et al. 2012; Charles et al. 2013; Dudeck et al. 2013; Medell et al. 2013; Leblebicioglu et al. 2013a, 2013b; Ndegwa et al. 2014; Behari and Kalafatis 2015; Dasgupta et al. 2015; Elliott et al. 2015; Entesari-Tatafi et al. 2015; Singh et al. 2015; Malek et al. 2018).

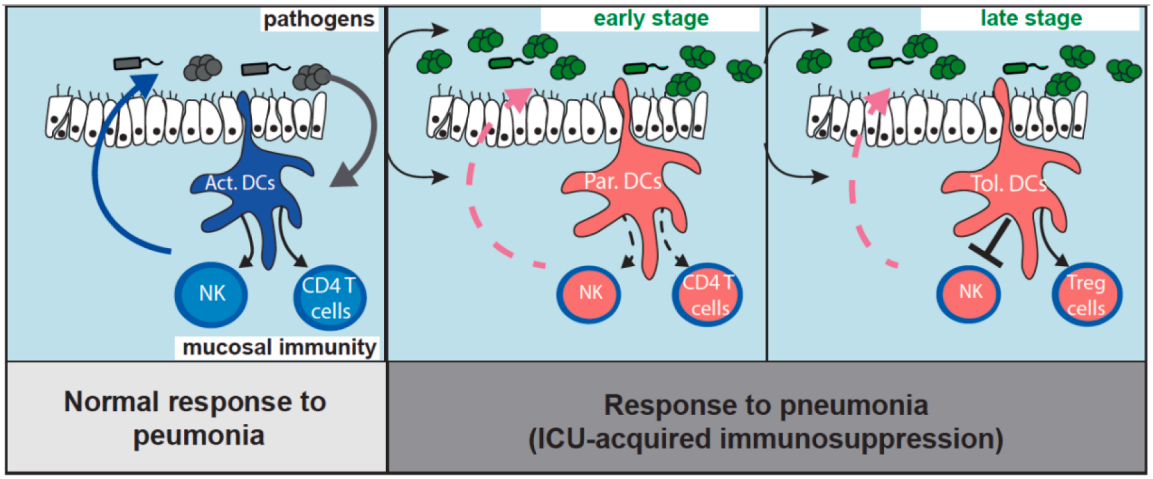

Fig. 3. A reappraisal of the immunological effects of ICU acquired immunosuppression on respiratory defenses against pathogens. Normal response of Dendritic cell during primary pneumonia (left panel), and after immunosuppression-induced pneumonia (middle and right panel). The stimulation of dendritic cells activated by pathogen-associated molecular patterns (Act DCs) induces the production of inflammatory cytokines (such as Interleukin-12) which stimulate NK cells (innate-like lymphocyte) and prime naive CD4 T cells to fight against bacteria. During sepsis-induced immunosuppression (middle and right panels), bacterial clearance is decreased as compared to what is observed during "normal response" to pneumonia. (middle) Early after the first hit (sepsis, severe trauma) causing ICU-acquired immunosuppression, DCs are paralyzed (Par DC) and unable to respond to subsequent pathogens. Par DC also fail to produce cytokines and to prime new CD4 T cells or NK cells. (right) Lately, newly formed DCs locally acquire a tolerogenic phenotype (Tol. DCs). Upon stimulation by pathogens, Tol-DCs do not activate NK cells but induce the local accumulation of Treg cells that maintain an immunosuppressive milieu.

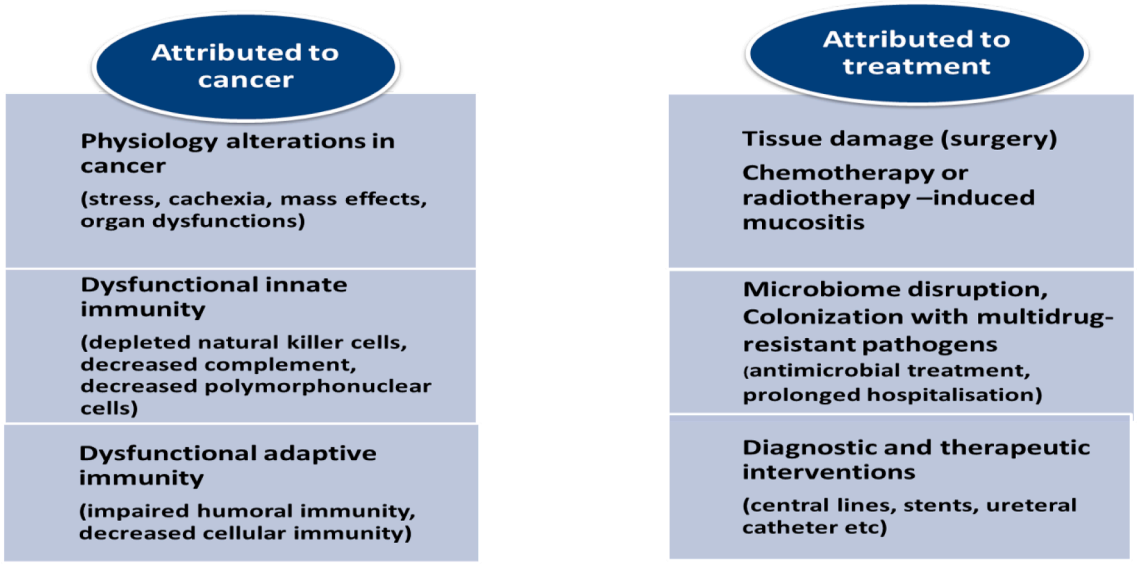

Fig. 4. Immune response alterations in cancer patients (ECDC, 2018; Smith et al. 2015; Taplitz et al. 2018).

colonization resistance with MDRO, is particularly relevant for nursing practice. Yet, little is known about the role of commensal skin and oral flora in the dynamics of ICU-HAI.

The gut and lung microbiota have been the most investigated in ICU patients. The gut microbiota serves as a defense against colonization and persistence of MDRO and helps to prevent infections (Vollaard and Clasener, 1994; Buffie and Pamer, 2013; Gosalbes et al., 2016; Caballero et al., 2017; Leo et al., 2019). The gastrointestinal tract is the primary reservoir for most bacterial pathogens associated with HAIs (Sommerstein et al., 2019). Rectal colonization with Gram-negative bacteria is an independent risk factor for both respiratory tract colonization and new Gram-negative infection in the ICU (Frencken et al., 2018). Indeed, Gram-negative organisms from the gut gain access to the oropharynx following intubation and rapidly outgrow the commensal members of the oropharynx, thus increasing risk for VAP (Freedberg et al., 2018; Sommerstein et al., 2019).

Also the lung has a normal microbiota that varies in health and disease. Ventilated patients have less diversity in lower and upper respiratory tract samples compared to healthy subjects which may include a risk for pneumonia (Kelly et al., 2016; Langelier et al., 2018; Emonet et al., 2019).

Diagnosis of HAIs: evaluating the gap between epidemiological and bedside definitions

The first step in the fight against HAIs in the ICU consists of implementing a reliable surveillance system to track infections and identify the risk factors associated with HAIs. Two definitions focused on different targets coexist for all HAIs, epidemiological definitions for surveillance purposes and clinical definitions for bedside decision-

Table 1
Factors that contribute to the development of healthcare-acquired infection in patients with solid tumors and hematologic malignancies (adapted from Deknuydt et al., 2013; van Vught et al., 2016; Roquilly et al., 2019).

Risk factor	Comments
Neutropenia	Chemotherapy, radiation therapy, bone marrow infiltration by malignant cells, adverse effects of concomitant medications (e.g., ganciclovir, cotrimoxazole)
Disruption of anatomic barriers (e.g., skin, mucosal surfaces)	Chemotherapy (mucositis), radiation therapy, graft versus host disease (GVHD), urinary catheters, central venous catheters, long term venous access devices (port-a-cath or Hickman catheters), percutaneous endoscopic gastrostomy tubes, stenting (e.g.., tracheal or bronchial, biliary etc.), other surgical/diagnostic procedures, fistula formation (e.g., broncho-pleural or trachea-oesophageal)
Obstruction due to primary or metastatic tumor or lymph node block	Respiratory: post-obstructive pneumonia, pleural effusion, lung abscess, empyema Biliary tract: ascending cholangitis, hepatic and pancreatic abscess Abdominal cavity and intestines: obstruction, necrosis, perforation, ileus, peritonitis, haemorrhage, fistula formation, abscesses Urinary tract: ureteral obstruction, hematuria, urinary tract infections, renal or prostatic abscess
Prosthetic devices and procedures	Surgical procedures: surgical site infections, anastomosis leakages, wound dehiscence, abscess formation Shunts: disseminated infection (bacteremia) shunt-related infections such as meningitis/ventriculitis Prosthetic devices (stents, catheters and drains, vascular grafts): infected prosthesis, osteomyelitis and/or septic arthritis, local abscess formation, fistula formation, rupture, hepato-biliary infections, complicated urinary tract infections, disseminated infection, endocarditis or endarteritis
Miscellaneous factors	Age, co-morbidities (diabetes mellitus, chronic obstructive pulmonary disease, uremia, etc.), poor nutritional status, dietary restrictions, loss of gag reflex Multiple antibiotic exposures and multiple hospitalizations leading to colonization by multidrug-resistant pathogens, disruption of the microbiome Corticosteroid systemic use Presence of immunomodulating viruses (i.e. Epstein Barr Virus, Cytomegalovirus, Human Immunodeficiency Virus, etc.)

making. Epidemiological data are devised to inform effective infection prevention and control programs. They can also be used as stand-alone quality indicators for benchmarking. Clinical definitions are designed to facilitate rapid and accurate recognition of HAIs for timely treatment decisions at the bedside. Intelligent information technology may serve as a meaningful tool to reconcile the expectations and requirements for both definitions and serve the needs of different users. Such tools could simplify and limit the variability of the surveillance process and could enhance efficiency in early detection of patients developing HAI. However, viewing the same entity from different angles may perpetuate the ongoing confusion between surveillance and clinical diagnosis.

Diagnosis of ventilator-associated lower respiratory tract infections

Ventilator-associated lower respiratory tract infections comprises VAP and ventilator-associated tracheobronchitis (Timsit et al., 2017). VAP is universally accepted with defined guidelines for diagnosis and treatment as an infection of the lung parenchyma that occurred at least 48 h after the onset of mechanical ventilation. Ventilator-associated tracheobronchitis represents an intermediate process from colonization to VAP. Current diagnosis of ventilator-associated tracheobronchitis is based on the absence of chest X-ray infiltrates and the presence of signs consistent with respiratory inflammation along with at least one microbiologic criterion. Clinical criteria for ventilator-associated lower respiratory tract infections are subjective (e.g. radiographic infiltrates) and both clinical and microbiological criteria correlate poorly with histology leading to high rates of over-diagnosis and overtreatment (Tejerina et al., 2010; Nussenblatt et al., 2014; Kalil et al., 2016).

Diagnosis of catheter-related bloodstream infections (CRBSI)

A definitive diagnosis of CRBSI requires microbiological confirmation that an intravascular catheter is the source of bacteremia and ruling out alternative foci of infection (Mermel et al., 2009). This definition puts an emphasis on specificity, but is complicated to use and requires specialized microbiological testing that is not universally available. At the bedside, a diagnosis of CRBSI is often marred by uncertainty regarding whether intravascular lines are the source of infection and the required distinction between contaminating and infecting skin commensals (Tomlinson et al., 2011; Cherifi et al., 2013). Appropriate observation of the insertion site by the nurse during catheter maintenance is important as $\geq$1 local sign (either redness, non-purulent or discharge) increases the probability of CRBSI in the first seven days of catheter maintenance (Buetti et al., 2021).

For surveillance purposes, the US Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC-NHSN) proposed the simplified concept of CLABSI (CDC, 2019). CLABSI diagnosis is more readily retrieved from patient charts and is amenable to automated querying but leads to overdiagnosis of the true incidence of CRBSI (CDC, 2019; Woeltje et al., 2008; Tomlinson et al., 2011; Dixon-Woods et al., 2012).

Diagnosis of surgical site infections (SSIs)

The CDC-NHSN definitions for SSIs (superficial incisional, deep incisional and organ/space) are the most frequently used in published literature (Horan et al., 1992). Direct nursing observation is pivotal. The criteria for SSI are localized swelling or erythema, purulent discharge from the surgical wound and organisms isolated from a wound. The WHO stated that there is no single, objective gold standard test for surgical wound infection (Allegranzi et al., 2016). SSI may also indicate ongoing abdominal sepsis following abdominal surgery (Pusajó et al., 1993). Patients with soft-tissue infections (including SSI) in an ICU are at high risk of misdiagnosis and underdiagnosis, resulting in a doubling of the in-hospital mortality (Abe et al., 2019). There is no perfect tool for early diagnosis of SSI in ICU patients. There are limited post-operative SSI prevention measures that pertain to the ICU. Key measures include discontinuation of surgical prophylaxis, daily wound inspection and appropriate wound care without exogenous contamination.

Differentiating between colonization and infection

The presence of potentially pathogenic and MDRO in microbiological samples, particularly from non-sterile body sites, is not proof of infection. The interpretation of a microbiological result will rely on five factors: (1) the clinical context (signs of infection?), (2) the sampling site (sterile site?), (3) the microbial species (pathogenic or possible contaminant?), (4) the suspected site of infection (frequently colonized

Table 2
Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: 2019 recommendations by ASCO and IDSA (adapted from Taplitz et al., 2018).

Type of prophylaxis	Population	Recommendation	Strength of recommendation	Period of prophylaxis
Antibacterial	Patients at high risk of febrile neutropenia or profound, protracted neutropenia[1,2]	Fluoroquinolone as prophylaxis however serious concerns exist (see foot note)[3]	Evidence quality: high; Strength of recommendation: moderate	During expected neutropenia
Antifungal	Patients at high risk of febrile neutropenia or profound, protracted neutropenia[1,2,4] Patients with GVHD	Oral triazole or parenteral echinocandin; a mold-active triazole when the risk of invasive aspergillosis is > 6% [5]	Evidence quality: intermediate; Strength of recommendation: moderate	During expected neutropenia
Antifungal	Patients receiving chemotherapy regimens associated with > 3.5% risk for pneumonia from *Pneumocystis jirovecii* [6]	Prophylaxis with oral trimethoprim-sulfamethoxazole or alternatives (such as dapsone, aerosolized pentamidine, or atovaquone in case of hypersensitivity to sulfonamides or cotrimoxazole intolerance	Evidence quality: high; Strength of recommendation: strong	Until myeloid reconstitution or engraftment after stem-cell transplantation, particularly during post-engraftment severe immunosuppression
Antiviral	HSV-seropositive patients undergoing HSCT or leukemia induction therapy	Antiviral prophylaxis with a nucleoside analog (eg, acyclovir)	Evidence quality: high; Strength of recommendation: strong	Until recovery of the WBC count or resolution of mucositis, whichever occurs later; duration can be extended for persons with frequent recurrent HSV infections or those with GVHD, or can be continued as VZV prophylaxis for up to 1 year
Antiviral	Patients at substantial risk of reactivation of HBV infection[6]	Treatment with a nucleoside reverse transcription inhibitor (eg, entecavir or tenofovir)	Evidence quality: intermediate; Strength of recommendation: moderate	
Antiviral	All persons treated with chemotherapy for malignancy and their family and household contacts[7]	Inactivated influenza vaccine (patients, household contacts and health care providers)	Evidence quality: intermediate; Strength of recommendation: moderate	Annual immunization is recommended Optimal timing of vaccination for patients being treated for cancer is not established, but serologic responses may be best between chemotherapy cycles (>7 days after the last treatment or >2 weeks before initiation of chemotherapy) In HSCT recipients better response if vaccinated >6 months after transplantation
Antiviral	Immunosuppressed adult oncology patients	The ASCO Expert Panel also supports other vaccination recommendations for immunosuppressed adult oncology patients that are contained within the IDSA guideline for vaccination of the immunosuppressed host[7]	Evidence quality: intermediate; Strength of recommendation: moderate	
Additional precautions to reduce the risk for aerosol- and direct or indirect contact–based transmission of pathogenic microorganisms	All health care workers	Health care workers should comply with hand hygiene and respiratory hygiene/cough etiquette guidelines	Evidence quality: intermediate; Strength of recommendation: strong	Not applicable
Additional recommended precautions	Outpatients with neutropenia from cancer therapy	Outpatients with neutropenia from cancer therapy should avoid prolonged contact with environments that contain high concentrations of airborne fungal spores[7]	Evidence quality: intermediate; Strength of recommendation: strong	Not applicable
Precautions no longer recommended	Footwear exchange, protected environments, air filtration, respiratory or surgical masks, neutropenic diet, or nutritional supplements	Evidence of clinical benefit is lacking for these interventions, therefore they are no longer recommended	Evidence quality: strong; Strength of recommendation: strong	Not applicable

1. Patients with AML/MDS or HSCT treated with myeloablative conditioning regimens, or during treatment of GVHD. Antibiotic prophylaxis is not routinely recommended for patients with solid tumors.

2. Antibacterial and antifungal prophylaxis would generally not be indicated when CSF prophylaxis effectively reduces the depth and duration of neutropenia.
3. On November 15, 2018, EMA finalised a review of serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics given by mouth, injection or inhalation. Among other restrictions recommended for this drug class, the committee stated that they should not be used for preventing traveller's diarrhoea or recurring lower urinary tract infections or in the treatment of mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.
The authors of the current review express their serious concerns on the potential use of quinolones as antibacterial chemoprophylaxis in neutropenic patients.
https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products.
4. Grade III or IV mucositis entails a great risk for invasive candidiasis.
5. Patients with AML/MDS or during treatment of GVHD.
6. Those with $\geq$ 20 mg prednisone equivalents daily for $\geq$ 1 month or those on the basis of purine analogs.
7. Live viral vaccines should not be administered during immunosuppression period.
8. Construction and demolition sites, intensive exposure to soil through gardening or digging, or household renovation.
AML/MDS; acute myeloid leukemia/myelodysplastic syndrome, ASCO; American Society of Clinical Oncology, CSF; colony stimulating factor, GVHD; Graft versus host disease, HSV; Herpes simplex virus, HBV; Hepatitis B virus, HSCT; Hematopoietic stem-cell transplantation, IDSA; Infectious Diseases Society of America, VZV; varicella-zoster virus.

Table 3
Arguments pro and against systematic bacteriological samples in ICU patients.

PRO	CON
Surrogate for lack of diagnostic cultures	Not representative for focus of infection
Immediately available microbiological information as compared to new diagnostic cultures (take 48–72 h turnaround time)	Outdated information if rapidly changing microbiome
Increased emphasis on antibiotic therapy covering all likely pathogens	Increased emphasis on antibiotic therapy selectively covering causative pathogens
Allows quick antibiotic response to emerging resistance	Leads to unnecessarily antibiotic escalation

site?), (5) the sensitivity and specificity of microbial cultures considering prior exposure to antibiotics, specimen source and microbiological technique. Increased microbiological sampling without a clearly defined clinical indication may lead to antibiotic overuse (Tambyah and Maki, 2000; Nussenblatt et al., 2014). However, when used judiciously with antibiotic restraint, regular sampling for microbiological surveillance purposes may offer up-to-date and personalized data to guide empirical antibiotic prescription (Table 3) (Depuydt et al., 2008; Brusselaers et al., 2013; Zahar et al., 2019).

Evolving role of the microbiological lab in the diagnosis and follow up of HAIs

Bacteriology laboratories are undergoing dramatic changes. Laboratory automation enables real-time reading of culture plates: samples set-up in the morning may have viable results by the afternoon with an antibiogram available the next morning. Another point of evolution is multiplexed, automated and fast polymerase chain reaction (PCR) assays. These are now available, and referred to as "syndromic testing" because they target not only bacteria but also viruses, parasites and fungi relevant to the context (Ramanan et al., 2018). These tests tend to require minimal hands-on-time and promise fast turn-around times (Fig. 5), allowing for the possibility of point-of-care testing or syndromic testing for early identification of HAIs, and early susceptibility results enabling to promptly administer appropriate antibiotics. Yet, the profusion of targets raises the issue of testing the "unwanted". For instance, clinicians must wrestle with how to interpret the presence of viruses when a bacterial VAP is initially suspected, especially in light of studies associating positive tests for viruses with poor outcome (Loubet et al., 2017). A close dialogue between intensivists and microbiologists should accompany the deployment of syndromic tests.

Even more complex will be the emergence of clinical metagenomics. This refers to the sequencing of the nucleic acids present in a clinical sample in order to identify pathogens and to infer their susceptibility to antimicrobials (Chiu and Miller, 2019). Metagenomic sequencing identifies many more bacteria than conventional cultures where microbiologists only report the most-likely pathogens. Those unreported bacteria, as well as the host's response, could be of help to improve the diagnosis of lower respiratory tract infections. Metagenomic sequencing combined with machine-learning tools providing (*1*) the most likely pathogenic bacteria, (*2*) the diversity of the surrounding bacterial community and (*3*) the host's response (via the transcriptome) can accurately predict the occurrence of pneumonia (Langelier et al., 2018).

Viruses in samples: pathogens or passengers?

The detection of viruses via molecular methods when HAIs are suspected is common. However, determining their clinical significance is challenging. Because of immunoparalysis following the initial pro-inflammatory response to aggression, latent viruses such as *Herpesviridae* may reactivate in ICU patients (Hotchkiss et al., 2013a). *Herpes simplex* virus, cytomegalovirus but also Epstein-Barr virus are frequently recovered in lung or blood of ICU patients (up to 50%), and their recovery is associated with increased morbidity and mortality (Luyt et al., 2007; Limaye et al., 2008; Coisel et al., 2012; Libert et al., 2015; Ong et al., 2017; Li et al., 2018). The exact significance of these reactivations is debated. These viruses may have true pathogenicity and cause organ damage thereby having a direct role in the morbidity and mortality observed with their reactivation. However, they also may be bystanders with reactivation being only secondary to disease severity. The question remains unanswered as data regarding a potential advantage of antiviral treatment are inconclusive. Respiratory viruses (rhinovirus, influenza, adenovirus and others) have recently been implicated in HAIs in ventilated or non-ventilated patients (Vincent et al., 2009; Nseir et al., 2011; Loubet et al., 2017; Shorr et al., 2017). The presence of viruses in HAP requiring ventilation is associated with poor outcomes (Grund et al., 2010). Cross-transmission of respiratory viruses such as influenza is now well identified by PCR and may be responsible for 10% of ICU admissions for influenza (Alvarez-Lerma et al., 2017) and for a growing number of episodes of severe respiratory distress, particularly in hospitalized immunocompromised patients. However, their global impact on morbidity and mortality is unknown.

Preventability of HAIs in ICU

Most experts agree that large proportions of device-related infections can be prevented with the use of evidence-based recommendations and prevention bundles succeeding to optimize provider adherence (Blot et al., 2014; van der Kooi et al., 2018; Labeau, 2020). A first systematic review covering 1990–2002 evaluated the proportion of HAIs that are potentially preventable HAI per multi-modal intervention studies (Harbarth et al., 2003). An evaluation of 30 reports suggested that great potential exists to decrease HAI rates, from a minimum reduction effect of 10% to a maximum effect of 70%, depending on the setting, study

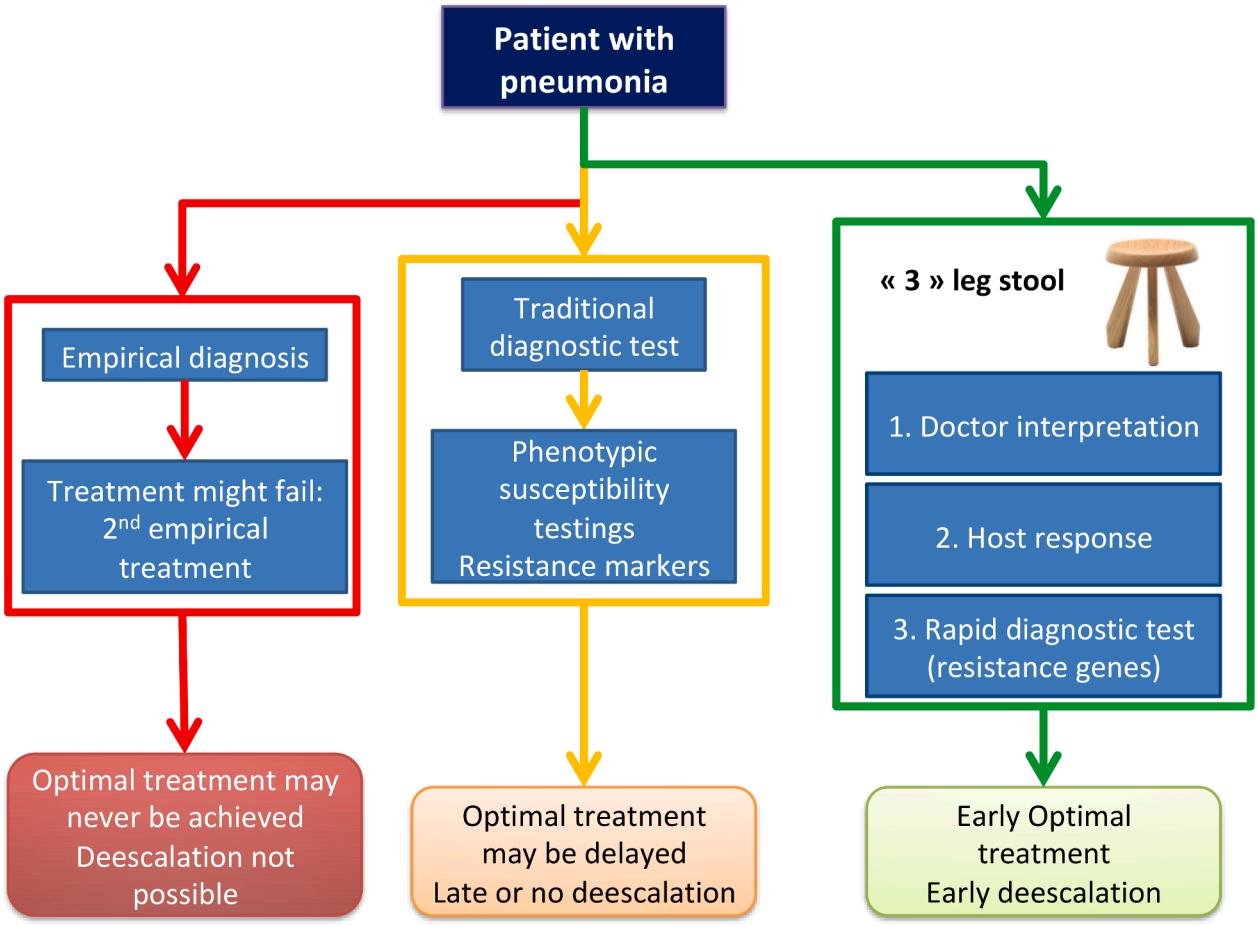

Fig. 5. Illustration of the role of the laboratory in the management of hospital-acquired pneumonia.

design, baseline infection rates and type of infection. The most important reduction effect was identified for CRBSI. In 2011, a second systematic review argued that as many as 65%–70% of cases of CLABSI and CAUTI and 55% of cases of VAP and SSI may be preventable with current evidence-based strategies, estimates that caused some debate (Umscheid et al., 2011). More recently, a systematic review (Schreiber et al., 2018) of studies published between 2005 and 2016 yielded somewhat lower proportions of preventable infections. None of the mentioned systematic reviews stratified their analyses by type of microorganisms; thus, there is ongoing uncertainty about the potential to prevent exogenous cross-infection by different MDROs.

Educational programs for healthcare workers imbedded in a comprehensive quality improvement program are the cornerstone for any prevention approach (Fig. 6). Regarding device-associated infections, particular attention should be given on reducing exposure and dwell time of invasive devices (Buetti and Timsit, 2019) and their necessity must be evaluated daily (Vazquez Guillamet and Kollef, 2018).

Should we use active antiseptic/antibiotic compounds for preventing HAIs?

Numerous studies have correlated the occurrence of HAIs to prior colonization and in some situations to the overgrowth of endogenous pathogenic bacteria (Johanson et al., 1979; Blot et al., 2005; Brusselaers et al., 2012; Frencken et al., 2018).

The use of antiseptics (mainly chlorhexidine) and antibiotics for preventing HAI in ICU has shown a potential benefit, despite concerns about increasing rates of bacterial resistance. Several studies have addressed the interest of cutaneous, digestive and oro-pharyngeal decolonization in reducing the risk of HAI in ICU and have highlighted that rational use of these interventions in specific contexts can be helpful if thoughtfully implemented.

The role of chlorhexidine gluconate for HAI prevention in ICU

Chlorhexidine gluconate (CHG) has broad antimicrobial action and prolonged residual effect. It is available as pre-packaged CHG-impregnated washcloths, as antiseptic soaps or solutions and mouthwashes.

CHG washcloths significantly reduce Gram-positive bacteremia, but not Gram-negative bacteremia (Afonso et al., 2016; Eggimann et al., 2019). Their use is associated with an increased risk of infections caused by bacteria with reduced susceptibility to CHG. No clinical consequences have been noted to date (Afonso et al., 2016) but the implementation of CHG-based universal skin decolonization warrants careful consideration. There is a need for trials exploring the safety, cost-efficiency and impact of systematic washcloth use for patients at high-risk for Gram-negative infections (Dray et al., 2019). Given the threat of growing CHG-resistance, the use of CHG-impregnated washcloths may be reserved for controlling outbreaks rather than in daily routine.

Both CHG-impregnated sponges and CHG–gel dressings have been used for the care of indwelling intravascular devices and have resulted in an up to a 60% decrease in the risk of intravascular infections, including CRBSI (Timsit et al., 2009, 2012; Ullman et al., 2016; Eggimann et al., 2019). Their use has been recommended in high-risk adult patients when the risk of infection remains high despite the application of an appropriate catheter care bundle.

CHG oral care is widespread in ICUs for intubated patients albeit that its value for reducing pneumonia risk is only been proven in cardiosurgical patients (Labeau et al., 2011; Klompas et al., 2014). Its use has been recently challenged. Firstly, a 2% CHG mouthwash appeared a

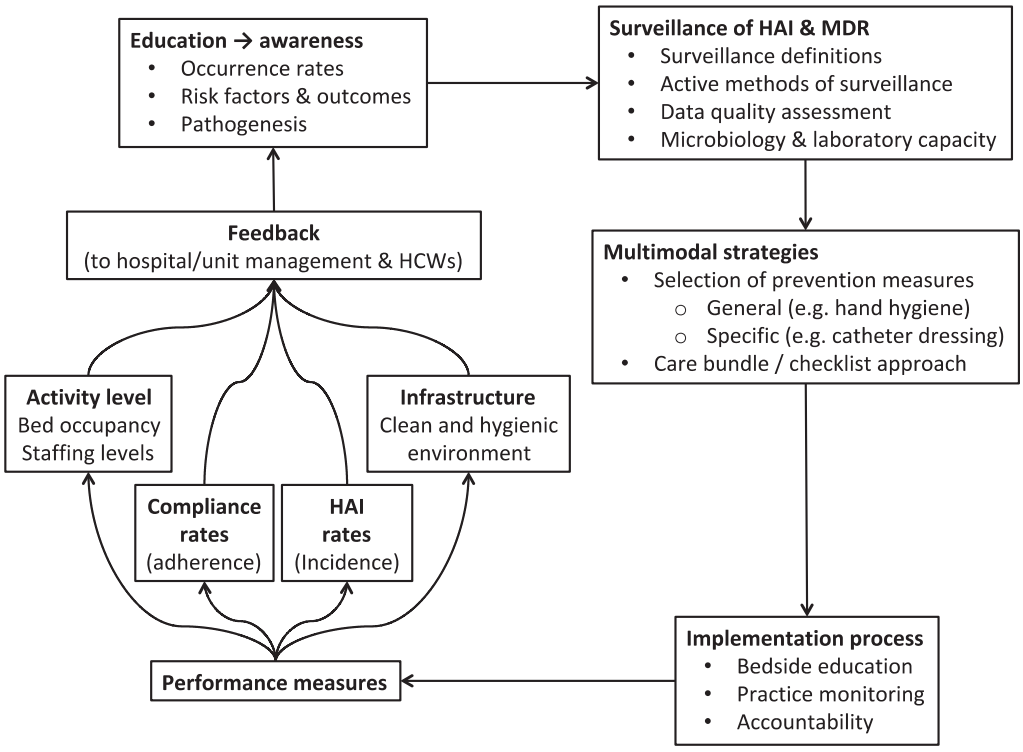

Fig. 6. Global rules for hospital-acquired infection prevention programs in the ICU. HAI, hospital-acquired infection. MDR, multidrug resistance. HCWs, healthcare workers. Education awareness: must target all healthcare workers, including support staff (e.g. logistics, cleaning). Infection preventionists and nurse-practitioners can bridge communication between various stakeholders and fine-tune educational materials to target specific groups. Multimodal strategies: (1) reducing exposure and duration of invasive procedures, the need for invasive procedures must be evaluated on a daily basis. (2) Development and application of multimodal evidence-based prevention measures. Implementation within a care bundle or checklist is positively associated with adherence. Implementation process: During the implementation period, infection preventionists and/or nurse-practitioners must provide continual bedside education and support, and trigger a culture of accountability. Determinants and prevention measures for HAIs as well as outcomes need to be monitored with close feedback to unit leaders and bedside personnel to fuel constant quality improvement. These include reports on compliance with recommendations (adherence rates) and correlation with HAI rates (outcomes). Feedback is crucial to fine-tune prevention programs and to optimize the motivation of stakeholders.

trigger for (reversible) oral mucositis in 9.8% of patients (Plantinga et al., 2016). Secondly, recent meta-analyses suggested that oral CHG increased the risk of death (Klompas et al., 2014; Price et al., 2014). Additionally, a large hospital-wide observational cohort study showed that CHG oral care was associated with increased mortality (Deschepper et al., 2018). In a large cohort of ICU patients from 186 hospitals, CHG oral care was also found to be an independent risk factor for sepsis and death (Parreco et al., 2020). It has been hypothesized that eradicating the oral microbiome with use of oral antiseptics results in a state of defective nitric oxide bio-availability thereby putting patients at risk for life-threatening complications such as ischaemic heart events and sepsis (Blot, 2021). If this hypothesis proves sound, the deleterious effect would be valid for all antiseptic mouthwash solutions and not exclusively those based on CHG. While awaiting more insights it seems wise to limit the use of CHG mouthwash to evidence-based indications. Moreover, a recent study demonstrated that omitting CHG mouthwashes from the oral care routine does not impact ICU mortality while improving oral health scores (Dale et al., 2021).

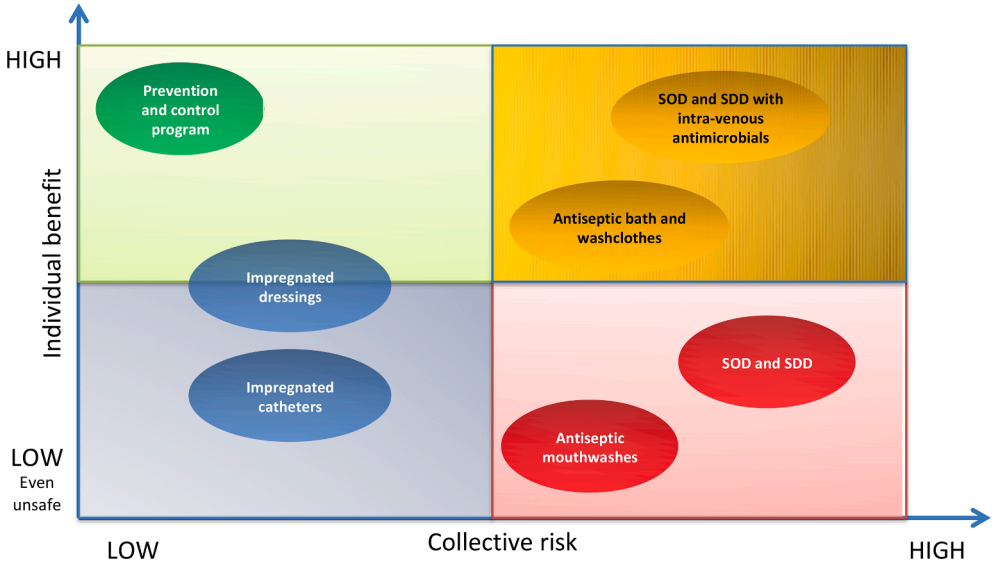

Fig. 7. Individual benefits and collective risks of active prevention measures in ICU-hospital-acquired infections. Rational use active antiseptic/antibiotic compounds for preventing nosocomial infections. Right upper quadrant: Prerequisites: prevention and control of multidrug resistant organisms (MDRO) spread, hand hygiene, and surveillance of nosocomial infections are prerequisites. If unobserved, any attempts in implementing prevention strategies using antiseptics or antibiotics will be futile. Right lower quadrant: To consider in high risk patients or when the risk of infection remains high despite the implementation of the prerequisites. Left upper quadrant: To consider when the prevalence of MDRO is low or if the evidence of spread of infections caused by MDRO is low. Left lower quadrant: Not to consider until further available data.

Is there any role for anti-infective impregnated materials?

Anti-infective impregnated materials have been proposed to prevent VAP, CRBSI, and CAUTI. A meta-analysis of 27 randomized controlled clinical trials evaluating the clinical effectiveness of central venous catheters treated with anti-infective agents reported a significant reduction in CRBSI in comparison to uncoated catheters (Hockenhull et al., 2009). Antimicrobial-impregnated catheters seem particularly appropriate when the background rate of CRBSI is high despite adherence to a comprehensive infection prevention bundle strategy (Timsit et al., 2018).

The role of selective digestive and oral decontamination (SDD and SOD)

A recent meta-analysis based on studies performed in settings with a low prevalence of antibiotic resistance, concluded that SOD and SDD with intravenous antimicrobials was associated with lower mortality rates, fewer HAIs, and less carriage of MDROs (Wittekamp et al., 2018, 2020). These results appear to only apply in settings with low baseline levels of MDROs. The use of SOD and SDD without intravenous antimicrobials was not associated with decreases in neither the rate of bacteremia due to MDRO nor 28-day ICU mortality in countries where the prevalence of MDRO was higher (Wittekamp et al., 2018).

The use of anti-infective agents to prevent infection requires a careful benefit-risk assessment both for the patient and the community. Fig. 7 offers a risk–benefit assessment in comparison to prevention and control program considered as the gold standard in infection control.

Is there any risk related to the environment?

The hospital environment facilitates the transmission of several pathogens such as VRE, MRSA, *C difficile, Acinetobacter* spp., and viruses (Mitchell et al., 2015). Several studies suggested an increased risk of acquisition when patients were hospitalized in a room previously occupied by a patient known to be colonized or infected with these bacterial pathogens (Dancer, 2014). Surfaces are frequently contaminated and contribute for bacteria cross-transmission and patient colonization/infection. Several factors are associated with a higher risk of hand contamination such as: positive environmental cultures, time spent in a room, physical examination and contact with the ventilator. ICUs should be considered as high-risk environments. Therefore, bio-cleaning must be rigorously performed in routine practice, must include detergent and disinfection phases and be carried out at least daily. Quaternary ammonium and bleach are the most commonly used products for environmental cleaning. However, for *C. difficile,* only bleach is effective to control the risk.

Conclusion

HAIs in ICU remain a cause of high mortality and morbidity, and prevention a core measure in hospitals. Patients' advanced age, co-morbidity and immunocompromised status explain the perpetuation in increases of ICU-acquired HAIs in some centers. While "Zero-HAI" is not achievable, our objective should be to reach the lowest thresholds described in the literature. Additionally, the high prevalence of MDROs perpetuates the worldwide persistence of HAIs. Their decrease requires further implementation of prevention bundles coupled with antimicrobial stewardship programs.

Growing knowledge about microbiotas will probably make it possible in the future to introduce new types of preventive measures. These measures could be based on respecting commensal flora (Hamilton and Behal 2020), the administration of better defined probiotics or the manipulation of microbiotas (Young, 2016). New diagnostic tools will help us to better identify infected patients. They will however, require rigorous evaluation before being implemented. Finally, decontamination and decolonization strategies will probably have to be limited to high-risk populations to minimize selection for antiseptic-resistant infections. The future of prevention in ICUs will likely be based on our ability to adapt policies and emerging technologies to specific risk profiles.

Conflicts of interests

JFT declares research grants from Pfizer, Merck, 3M, Astellas, Biomerieux; scientific Board participation with Merck, Bayer pharma, Gilead; lecture fees for Merck, Pfizer, Biomerieux. GP declares Speaker's Honoraria by Merck, Angellini, Biorad, Pfizer; research grants by Merck, Pfizer, Roche. CE declares scientific board participation and lecture fees for Correvio, Menarini, Merck and Pfizer. PD received fees from Belgian Health Care Knowledge Centre. SH declares SAB fees from Sandoz. SB declares conflict of interest with Pfizer, Halyard and 3M.CEL declares research grants from Bayer Healthcare and Maquet; scientific board participation with Bayer Healthcare, ThermoFischer Brahms, Carmat, Faron; lecture fees from Merck, Biomérieux. JR declares consultancy and speakers bureau fees for Pfizer and Nebriva. MK declares receiving research grants from the US Centers for Disease Control and Prevention and royalties from UpToDate Inc. CE declares scientific board participation and lecture fees for Correvio, Menarini, Merck and Pfizer. IML declares lecture fees from accelerate, MSD and Gilead. PP declares lectures fees from Pfizer and Orion. JRZ declares research grants from Pfizer, Merck; scientific Board participation with Merck, BioMerieux, Eumedica, Pfizer; lecture fees for Merck, Pfizer, Correvio, Gilead. No other conflicts of interests to declare.

References

Abe, T., Tokuda, Y., Shiraishi, A., Fujishima, S., Mayumi, T., Sugiyama, T., et al., 2019. In-hospital mortality associated with the misdiagnosis or unidentified site of infection at admission. Crit Care. BioMed Central 23 (1), 202–209.

Afonso, E., Blot, K., Blot, S., 2016. Prevention of hospital-acquired bloodstream infections through chlorhexidine gluconate-impregnated washcloth bathing in intensive care units: a systematic review and meta-analysis of randomised crossover trials. Euro. Surveill. 21 (46), 30400.

Albiger, B., Glasner, C., Struelens, M.J., Grundmann, H., Monnet, D.L., European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) working group, 2015. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill. European Centre for Disease Prevention and Control 20 (45), 30062.

Allegranzi, B., Zayed, B., Bischoff, P., Kubilay, N.Z., de Jonge, S., de Vries, F., et al., 2016. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect. Dis. 16 (12), e288–e303.

Alvarez-Lerma, F., Marín-Corral, J., Vilà, C., Masclans, J.R., Loeches, I.M., Barbadillo, S., et al., 2017. Characteristics of patients with hospital-acquired influenza A (H1N1) pdm09 virus admitted to the intensive care unit. J. Hosp. Infect. 95 (2), 200–206.

Anders, R.L., 2021. Patient safety time for federally mandated registered nurse to patient ratios. Nurs. Forum. John Wiley & Sons Ltd.

Arabi, Y., Al-Shirawi, N., Memish, Z., Anzueto, A., 2008. Ventilator-associated pneumonia in adults in developing countries: a systematic review. Int. J. Infect. Dis. 12 (5), 505–512.

Arabi, Y.M., Azoulay, É., Al-Dorzi, H.M., Phua, J., Salluh, J., Binnie, A., et al., 2021. How the COVID-19 pandemic will change the future of critical care. Intensive Care Med. Springer Berlin Heidelberg 47, 282–291.

Augustin, P., Kermarrec, N., Muller-Serieys, C., Lasocki, S., Chosidow, D., Marmuse, J.-P., et al., 2010. Risk factors for multidrug resistant bacteria and optimization of empirical antibiotic therapy in postoperative peritonitis. Crit. Care. BioMed Central Ltd 14 (1), R20.

Behari, A., Kalafatis, N., 2015. Incidence and outcome of ventilator-associated pneumonia in Inkosi Albert Luthuli and King Edward VIII Hospital surgical intensive care units. South Afr. J. Crit. Care 31 (1), 16–18.

Blot, S., 2008. Limiting the attributable mortality of nosocomial infection and multidrug resistance in intensive care units. Clin. Microbiol. Infect. 14 (1), 5–13.

Blot, S., 2021. Antiseptic mouthwash, the nitrate-nitrite-nitric oxide pathway, and hospital mortality: a hypothesis generating review. Intensive Care Med. Springer Berlin Heidelberg 47, 28–38.

Blot, K., Bergs, J., Vogelaers, D., Blot, S., Vandijck, D., 2014. Prevention of central line-associated bloodstream infections through quality improvement interventions: A systematic review and meta-analysis. Clin. Infect. Dis. Oxford University Press 59 (1), 96–105.

Blot, S., Depuydt, P., Vogelaers, D., Decruyenaere, J., De Waele, J., Hoste, E., et al., 2005. Colonization status and appropriate antibiotic therapy for nosocomial bacteremia

caused by antibiotic-resistant gram-negative bacteria in an intensive care unit. Infect. Control Hosp. Epidemiol. 26 (6), 575–579.
Blot, S., De Waele, J.J., Vogelaers, D., 2012. Essentials for selecting antimicrobial therapy for intra-abdominal infections. Drugs. Springer International Publishing 72 (6), e17–e32.
Blot, S., Antonelli, M., Arvaniti, K., Blot, K., Creagh-Brown, B., de Lange, D., et al., 2019b. Epidemiology of intra-abdominal infection and sepsis in critically ill patients: "AbSeS", a multinational observational cohort study and ESICM Trials Group Project. Intensive Care Med. Springer Berlin Heidelberg 45, 1703–1717.
Blot, K., Hammami, N., Blot, S., Vogelaers, D., Lambert, M.-L., 2019a. Increasing burden of Escherichia coli, Klebsiella pneumoniae, and Enterococcus faecium in hospital-acquired bloodstream infections (2000–2014): A national dynamic cohort study. Infect. Control. Hosp. Epidemiol. Cambridge University Press 40 (6), 705–709.
Blot, K., Hammami, N., Blot, S., Vogelaers, D., Lambert, M.-L., 2021. Seasonal variation of hospital-acquired bloodstream infections: A national cohort study. Infect. Control. Hosp. Epidemiol. Cambridge University Press 1–7.
Braga IA, Campos PA de, Batistão DWDF, Gontijo Filho PP, Ribas RM. Using point prevalence survey to define burden of antimicrobial use among 35 adult intensive care units in Brazil. Infect Dis (Lond). Taylor & Francis; 2019;51(6):459–462.
Brusselaers, N., Logie, D., Vogelaers, D., Monstrey, S., Blot, S., 2012. Burns, inhalation injury and ventilator-associated pneumonia: value of routine surveillance cultures. Burns 38 (3), 364–370.
Brusselaers, N., Labeau, S., Vogelaers, D., Blot, S., 2013. Value of lower respiratory tract surveillance cultures to predict bacterial pathogens in ventilator-associated pneumonia: systematic review and diagnostic test accuracy meta-analysis. Intensive Care Med. Springer-Verlag 39 (3), 365–375.
Buetti, N., Timsit, J.-F., 2019. Management and prevention of central venous catheter-related infections in the ICU. Semin. Respir. Crit. Care Med. 40 (4), 508–523.
Buetti, N., Ruckly, S., Lucet, J.-C., Mimoz, O., Souweine, B., Timsit, J.-F., 2021. Factors influencing local signs at catheter insertion site regardless of catheter-related bloodstream infections. Crit. Care. BioMed Central 25 (1), 71–73.
Buffie, C.G., Pamer, E.G., 2013. Microbiota-mediated colonization resistance against intestinal pathogens. Nat. Rev. Immunol. Nature Publishing Group 13 (11), 790–801.
Caballero, S., Kim, S., Carter, R.A., Leiner, I.M., Sušac, B., Miller, L., et al., 2017. Cooperating commensals restore colonization resistance to vancomycin-resistant Enterococcus faecium. Cell Host Microbe 21 (5), 592–594.
Centers for Disease Control and Prevention. National and State Healthcare-associated Infections Progress Report, 2016. Available from: https://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf. 2016.
Centers for Disease Control and Prevention. Bloodstream Infection Event (central line-associated bloodstream infection and non-central line associated bloodstream infection). 2019. https://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf.
Charles, M.P., Easow, J.M., Joseph, N.M., Ravishankar, M., Kumar, S., Umadevi, S., 2013. Incidence and risk factors of ventilator associated pneumonia in a tertiary care hospital. Australas Med J. 6 (4), 178–182.
Cherifi, S., Mascart, G., Dediste, A., Hallin, M., Gerard, M., Lambert, M.-L., et al., 2013. Variations in catheter-related bloodstream infections rates based on local practices. Antimicrob. Resist. Infect. Control. BioMed Central 2 (1), 10–14.
Chiang, C.-H., Pan, S.-C., Yang, T.-S., Matsuda, K., Kim, H.B., Choi, Y.H., et al., 2018. Healthcare-associated infections in intensive care units in Taiwan, South Korea, and Japan: recent trends based on national surveillance reports. Antimicrob. Resist. Infect. Control. BioMed Central 7 (1), 129–212.
Chiu, C.Y., Miller, S.A., 2019. Clinical metagenomics. Nat. Rev. Genet. Nature Publishing Group 20 (6), 341–355.
Coisel, Y., Bousbia, S., Forel, J.-M., Hraiech, S., Lascola, B., Roch, A., et al., 2012. Cytomegalovirus and herpes simplex virus effect on the prognosis of mechanically ventilated patients suspected to have ventilator-associated pneumonia. PLoS ONE Public Library of Science 7 (12), e51340.
Dale, C.M., Rose, L., Carbone, S., Pinto, R., Smith, O.M., Burry, L., et al., 2021. Effect of oral chlorhexidine de-adoption and implementation of an oral care bundle on mortality for mechanically ventilated patients in the intensive care unit (CHORAL): a multi-center stepped wedge cluster-randomized controlled trial. Intensive Care Med. Springer Berlin Heidelberg 47, 1295–1302.
Dancer, S.J., 2014. Controlling hospital-acquired infection: focus on the role of the environment and new technologies for decontamination. Clin. Microbiol. Rev. American Society for Microbiology Journals 27 (4), 665–690.
Dasgupta, S., Das, S., Chawan, N.S., Hazra, A., 2015. Nosocomial infections in the intensive care unit: Incidence, risk factors, outcome and associated pathogens in a public tertiary teaching hospital of Eastern India. Indian J. Crit. Care Med. 19 (1), 14–20.
de Montmollin, E., Ruckly, S., Schwebel, C., Philippart, F., Adrie, C., Mariotte, E., et al., 2019. Pneumonia in acute ischemic stroke patients requiring invasive ventilation: Impact on short and long-term outcomes. J. Infect. 79 (3), 220–227.
De Waele, J., Lipman, J., Sakr, Y., Marshall, J.C., Vanhems, P., Barrera Groba, C., et al., 2014. Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome. BMC Infect. Dis. BioMed Central Ltd 14 (1), 420.
Deknuydt, F., Roquilly, A., Cinotti, R., Altare, F., Asehnoune, K., 2013. An in vitro model of mycobacterial granuloma to investigate the immune response in brain-injured patients. Crit. Care Med. 41 (1), 245–254.
Delano, M.J., Ward, P.A., 2016. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunol. Rev. John Wiley & Sons, Ltd 274 (1), 330–353.
Depuydt, P., Benoit, D., Vogelaers, D., Claeys, G., Verschraegen, G., Vandewoude, K., et al., 2006a. Outcome in bacteremia associated with nosocomial pneumonia and the impact of pathogen prediction by tracheal surveillance cultures. Intensive Care Med. 32 (11), 1773–1781.
Depuydt, P., Benoit, D., Vogelaers, D., Decruyenaere, J., Vandijck, D., Claeys, G., et al., 2008. Systematic surveillance cultures as a tool to predict involvement of multidrug antibiotic resistant bacteria in ventilator-associated pneumonia. Intensive Care Med. 34 (4), 675–682.
Depuydt, P.O., Blot, S.I., Benoit, D.D., Claeys, G.W., Verschraegen, G.L., Vandewoude, K. H., et al., 2006b. Antimicrobial resistance in nosocomial bloodstream infection associated with pneumonia and the value of systematic surveillance cultures in an adult intensive care unit. Crit. Care Med. 34 (3), 653–659.
Deschepper, M., Waegeman, W., Eeckloo, K., Vogelaers, D., Blot, S., 2018. Effects of chlorhexidine gluconate oral care on hospital mortality: a hospital-wide, observational cohort study. Intensive Care Med. Springer Berlin Heidelberg 44, 1017–1026.
Dick, A., Liu, H., Zwanziger, J., Perencevich, E., Furuya, E.Y., Larson, E., et al., 2012. Long-term survival and healthcare utilization outcomes attributable to sepsis and pneumonia. BMC Health Serv. Res. BioMed Central 12 (1), 432–510.
Dimopoulos, G., Koulenti, D., Blot, S., Sakr, Y., Anzueto, A., Spies, C., et al., 2013. Critically ill elderly adults with infection: analysis of the extended prevalence of infection in intensive care study. J. Am. Geriatr. Soc. 61 (12), 2065–2071.
Dixon-Woods, M., Leslie, M., Bion, J., Tarrant, C., 2012. What counts? An ethnographic study of infection data reported to a patient safety program. Milbank Q. John Wiley & Sons, Ltd 90 (3), 548–591.
Dray, S., Forel, J.-M., Papazian, L., 2019. What's new in the prevention of healthcare-associated infections using chlorhexidine gluconate-impregnated washcloths. Intensive Care Med. Springer Berlin Heidelberg 45, 249–251.
Dudeck, M.A., Horan, T.C., Peterson, K.D., Allen-Bridson, K., Morrell, G., Anttila, A., et al., 2013. National Healthcare Safety Network report, data summary for 2011, device-associated module. Am. J. Infect. Control 41 (4), 286–300.
Eggimann, P., Pagani, J.-L., Dupuis-Lozeron, E., Ms, B.E., Thévenin, M.-J., Joseph, C., et al., 2019. Sustained reduction of catheter-associated bloodstream infections with enhancement of catheter bundle by chlorhexidine dressings over 11 years. Intensive Care Med. Springer Berlin Heidelberg 45 (6), 823–833.
Elliott, D., Elliott, R., Burrell, A., Harrigan, P., Murgo, M., Rolls, K., et al., 2015. Incidence of ventilator-associated pneumonia in Australasian intensive care units: use of a consensus-developed clinical surveillance checklist in a multisite prospective audit. BMJ Open British Medical Journal Publishing Group 5 (10), e008924.
Emonet, S., Lazarevic, V., Leemann Refondini, C., Gaïa, N., Leo, S., Girard, M., et al., 2019. Identification of respiratory microbiota markers in ventilator-associated pneumonia. Intensive Care Med. Springer Berlin Heidelberg 45, 1082–1092.
Entesari-Tatafi, D., Orford, N., Bailey, M.J., Chonghaile, M.N.I., Lamb-Jenkins, J., Athan, E., 2015. Effectiveness of a care bundle to reduce central line-associated bloodstream infections. Med. J. Aust. John Wiley & Sons, Ltd 202 (5), 247–250.
European Centre for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units. In: ECDC. Annual epidemiological report for 2016. Stockholm: ECDC; 2018.
Freedberg, D.E., Zhou, M.J., Cohen, M.E., Annavajhala, M.K., Khan, S., Moscoso, D.I., et al., 2018. Pathogen colonization of the gastrointestinal microbiome at intensive care unit admission and risk for subsequent death or infection. Intensive Care Med. Springer Berlin Heidelberg 44 (8), 1203–1211.
Freifeld A.G., Bow E.J., Sepkowitz K.A., Boeckh M.J., Ito J.I., Mullen C.A., et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases Society of America. Vol. 52, Clinical Infectious Diseases. 2011. pp. e56–93.
Frencken, J.F., Wittekamp, B.H.J., Plantinga, N.L., Spitoni, C., van de Groep, K., Cremer, O.L., et al., 2018. Associations between enteral colonization with Gram-negative bacteria and intensive care unit-acquired infections and colonization of the respiratory tract. Clin. Infect. Dis. 66 (4), 497–503.
Gosalbes, M.J., Vázquez-Castellanos, J.F., Angebault, C., Woerther, P.-L., Ruppé, E., Ferrús, M.L., et al., 2016. Carriage of enterobacteria producing extended-spectrum β-lactamases and composition of the gut microbiota in an Amerindian Community. Antimicrob. Agents Chemother. American Society for Microbiology Journals 60 (1), 507–514.
Grund, S., Roggendorf, M., Schweiger, B., 2010. Outbreak of influenza virus A/H1N1 in a hospital ward for immunocompromised patients. Arch. Virol. Springer Vienna 155 (11), 1797–1802.
Guzmán-Herrador, B., Molina, C.D., Allam, M.F., Navajas, R.-F.-C., 2016. Independent risk factors associated with hospital-acquired pneumonia in an adult ICU: 4-year prospective cohort study in a university reference hospital. J. Public Health (Oxf) 38 (2), 378–383.
Hajdu, A., Samodova, O.V., Carlsson, T.R., Voinova, L.V., Nazarenko, S.J., Tjurikov, A.V., et al., 2007. A point prevalence survey of hospital-acquired infections and antimicrobial use in a paediatric hospital in north-western Russia. J. Hosp. Infect. 66 (4), 378–384.
Hamilton, L.A., Behal, M.L., 2020. Altering routine intensive care unit practices to support commensalism. Nutr. Clin. Pract. John Wiley & Sons, Ltd 35 (3), 433–441.
Harbarth, S., Sax, H., Gastmeier, P., 2003. The preventable proportion of nosocomial infections: an overview of published reports. J. Hosp. Infect. 54 (4), 258–266 quiz321.
Hockenhull, J.C., Dwan, K.M., Smith, G.W., Gamble, C.L., Boland, A., Walley, T.J., et al., 2009. The clinical effectiveness of central venous catheters treated with anti-infective agents in preventing catheter-related bloodstream infections: a systematic review. Crit. Care Med. 37 (2), 702–712.
Horan, T.C., Gaynes, R.P., Martone, W.J., Jarvis, W.R., Emori, T.G., 1992. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC

definitions of surgical wound infections. Infect. Control Hosp. Epidemiol. 13 (10), 606–608.
Hotchkiss, R.S., Monneret, G., Payen, D., 2013a. Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect. Dis. 13 (3), 260–268.
Hotchkiss, R.S., Monneret, G., Payen, D., 2013b. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat. Rev. Immunol. Nature Publishing Group 13 (12), 862–874.
Ippolito, M., Misseri, G., Catalisano, G., Marino, C., Ingoglia, G., Alessi, M., et al., 2021. Ventilator-associated pneumonia in patients with COVID-19. A systematic review and meta-analysis. Antibiotics (Basel) 10 (5).
Iwuafor A.A., Ogunsola F.T., Oladele R.O., Oduyebo O.O., Desalu I., Egwuatu C.C., et al. Incidence, clinical outcome and risk factors of intensive care unit infections in the Lagos University Teaching Hospital (LUTH), Lagos, Nigeria. PLoS ONE. Public Library of Science; 2016;11(10):e0165242.
Jansson, M., Liao, X., Rello, J., 2020. Strengthening ICU health security for a coronavirus epidemic. Intensive Crit. Care Nurs. 57, 102812.
Jansson, M.M., Syrjälä, H.P., Ala-Kokko, T.I., 2019. Association of nurse staffing and nursing workload with ventilator-associated pneumonia and mortality: a prospective, single-center cohort study. J. Hosp. Infect. 101 (3), 257–263.
Jeffery-Smith, A., Taori, S.K., Schelenz, S., Jeffery, K., Johnson, E.M., Borman, A., et al., 2018. Candida auris: a Review of the Literature. Clin. Microbiol. Rev. American Society for Microbiology Journals 31 (1).
Johanson, W.G., Woods, D.E., Chaudhuri, T., 1979. Association of respiratory tract colonization with adherence of gram-negative bacilli to epithelial cells. J. Infect. Dis. 139 (6), 667–673.
Kalil A.C., Metersky M.L., Klompas M., Muscedere J., Sweeney D.A., Palmer L.B., et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Vol. 63, Clinical Infectious Diseases. 2016. pp. e61–e111.
Karanika, S., Paudel, S., Zervou, F.N., Grigoras, C., Zacharioudakis, I.M., Mylonakis, E., 2016. Prevalence and clinical outcomes of Clostridium difficile infection in the intensive care unit: A systematic review and meta-analysis. Open Forum Infect. Dis. 3 (1), ofv186.
Kelly, B.J., Imai, I., Bittinger, K., Laughlin, A., Fuchs, B.D., Bushman, F.D., et al., 2016. Composition and dynamics of the respiratory tract microbiome in intubated patients. Microbiome BioMed Central 4 (1), 7–13.
Kelly, D., Kutney-Lee, A., Lake, E.T., Aiken, L.H., 2013. The critical care work environment and nurse-reported health care-associated infections. Am. J. Crit. Care 22 (6), 482–488.
Klompas, M., Speck, K., Howell, M.D., Greene, L.R., Berenholtz, S.M., 2014. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. JAMA Intern. Med. American Medical Association 174 (5), 751–761.
Kopp, M.A., Watzlawick, R., Martus, P., Failli, V., Finkenstaedt, F.W., Chen, Y., et al., 2017. Long-term functional outcome in patients with acquired infections after acute spinal cord injury. Neurology. Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology 88 (9), 892–900.
Korbkitjaroen, M., Vaithayapichet, S., Kachintorn, K., Jintanothaitavorn, D., Wiruchkul, N., Thamlikitkul, V., 2011. Effectiveness of comprehensive implementation of individualized bundling infection control measures for prevention of health care-associated infections in general medical wards. Am. J. Infect. Control 39 (6), 471–476.
Labeau, S.O., 2020. Recommendation and protocol compliance: “Yes, I do” may not be true; the complexity of measuring provider adherence. Intensive Crit. Care Nurs. 60, 102890.
Labeau, S.O., Van de Vyver, K., Brusselaers, N., Vogelaers, D., Blot, S.I., 2011. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. Lancet Infect. Dis. 11 (11), 845–854.
Langelier, C., Kalantar, K.L., Moazed, F., Wilson, M.R., Crawford, E.D., Deiss, T., et al., 2018. Integrating host response and unbiased microbe detection for lower respiratory tract infection diagnosis in critically ill adults. Proc. Natl. Acad. Sci. U.S. A. National Academy of Sciences 115 (52), E12353–E12362.
Leblebicioglu, H., Rosenthal, V.D., Arikan, O.A., Ozgültekin, A., Yalcin, A.N., Koksal, I., et al., 2007. Device-associated hospital-acquired infection rates in Turkish intensive care units. Findings of the International Nosocomial Infection Control Consortium (INICC). J. Hosp. Infect. 65 (3), 251–257.
Leblebicioglu, H., Öztürk, R., Rosenthal, V.D., Akan, Ö.A., Sirmatel, F., Ozdemir, D., et al., 2013a. Impact of a multidimensional infection control approach on central line-associated bloodstream infections rates in adult intensive care units of 8 cities of Turkey: findings of the International Nosocomial Infection Control Consortium (INICC). Ann. Clin. Microbiol. Antimicrob. BioMed Central 12 (1), 10.
Leblebicioglu, H., Yalcin, A.N., Rosenthal, V.D., Koksal, I., Sirmatel, F., Unal, S., et al., 2013b. Effectiveness of a multidimensional approach for prevention of ventilator-associated pneumonia in 11 adult intensive care units from 10 cities of Turkey: findings of the International Nosocomial Infection Control Consortium (INICC). Infection Springer-Verlag 41 (2), 447–456.
Lee, Y.S.H., Stone, P.W., Pogorzelska-Maziarz, M., Nembhard, I.M., 2018. Differences in work environment for staff as an explanation for variation in central line bundle compliance in intensive care units. Health Care Manage. Rev. 43 (2), 138–147.
Leo, S., Lazarevic, V., Gaïa, N., Estellat, C., Girard, M., Matheron, S., et al., 2019. The intestinal microbiota predisposes to traveler’s diarrhea and to the carriage of multidrug-resistant Enterobacteriaceae after traveling to tropical regions. Gut Microbes. Taylor & Francis 10 (5), 631–641.
Li, X., Huang, Y., Xu, Z., Zhang, R., Liu, X., Li, Y., et al., 2018. Cytomegalovirus infection and outcome in immunocompetent patients in the intensive care unit: a systematic review and meta-analysis. BMC Infect. Dis. BioMed Central 18 (1), 289–310.
Libert, N., Bigaillon, C., Chargari, C., Bensalah, M., Muller, V., Merat, S., et al., 2015. Epstein-Barr virus reactivation in critically ill immunocompetent patients. Biomed. J. 38 (1), 70–76.
Limaye, A.P., Kirby, K.A., Rubenfeld, G.D., Leisenring, W.M., Bulger, E.M., Neff, M.J., et al., 2008. Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA. American Medical Association 300 (4), 413–422.
Lobo, R.D., Levin, A.S., Gomes, L.M.B., Cursino, R., Park, M., Figueiredo, V.B., et al., 2005. Impact of an educational program and policy changes on decreasing catheter-associated bloodstream infections in a medical intensive care unit in Brazil. Am. J. Infect. Control 33 (2), 83–87.
Lormans, P., Blot, S., Amerlinck, S., Devriendt, Y., Dumoulin, A., 2021. COVID-19 acquisition risk among ICU nursing staff with patient-driven use of aerosol-generating respiratory procedures and optimal use of personal protective equipment. Intensive Crit. Care Nurs. 63, 102993.
Loubet, P., Voiriot, G., Houhou-Fidouh, N., Neuville, M., Bouadma, L., Lescure, F.-X., et al., 2017. Impact of respiratory viruses in hospital-acquired pneumonia in the intensive care unit: A single-center retrospective study. J. Clin. Virol. 91, 52–57.
Luyt, C.-E., Combes, A., Deback, C., Aubriot-Lorton, M.-H., Nieszkowska, A., Trouillet, J.-L., et al., 2007. Herpes simplex virus lung infection in patients undergoing prolonged mechanical ventilation. Am. J. Respir. Crit. Care Med. American Thoracic Society 175 (9), 935–942.
Luyt, C.-E., Sahnoun, T., Gautier, M., Vidal, P., Burrel, S., Pineton de Chambrun, M., et al., 2020. Ventilator-associated pneumonia in patients with SARS-CoV-2-associated acute respiratory distress syndrome requiring ECMO: a retrospective cohort study. Ann. Intensive Care. SpringerOpen 10 (1), 158–210.
Maes, M., Higginson, E., Pereira-Dias, J., Curran, M.D., Parmar, S., Khokhar, F., et al., 2021. Ventilator-associated pneumonia in critically ill patients with COVID-19. Crit. Care. BioMed Central 25 (1), 25–111.
Magill, S.S., Edwards, J.R., Bamberg, W., Beldavs, Z.G., Dumyati, G., Kainer, M.A., et al., 2014. Multistate point-prevalence survey of health care-associated infections. N. Engl. J. Med. Massachusetts Medical Society 370 (13), 1198–1208.
Malek, A.M., Abouseif, H.A., Elaziz, K., Allam, M.F., Fahim, H.I., 2018. Incidence of central line-associated bloodstream infections in intensive care units in a private hospital (Cairo, Egypt). Open Public Health J. 11, 562–571.
Marin, M., Gudiol, C., Ardanuy, C., Garcia-Vidal, C., Calvo, M., Arnan, M., et al., 2014. Bloodstream infections in neutropenic patients with cancer: differences between patients with haematological malignancies and solid tumours. J. Infect. 69 (5), 417–423.
Martin-Loeches, I., Póvoa, P., Rodriguez, A., Curcio, D., Suárez, D., Mira, J.-P., et al., 2015. Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study. Lancet Respir. Med. 3 (11), 859–868.
Medell, M., Hart, M., Duquesne, A., Espinosa, F., Valdés, R., 2013. Nosocomial ventilator-associated pneumonia in Cuban intensive care units: bacterial species and antibiotic resistance. MEDICC Rev. 15 (2), 26–29.
Mehta, A., Rosenthal, V.D., Mehta, Y., Chakravarthy, M., Todi, S.K., Sen, N., et al., 2007. Device-associated nosocomial infection rates in intensive care units of seven Indian cities. Findings of the International Nosocomial Infection Control Consortium (INICC). J. Hosp. Infect. 67 (2), 168–174.
Mendes, M., Andrade Oliveira, A., Pires, O., Branca, F., Beirão, M., Santa-Cruz, A., et al., 2021. Sampling methods and risk stratification regarding environmental contamination by SARS-CoV-2. Acta Med. Port. 34 (13).
Mermel L.A., Allon M., Bouza E., Craven D.E., Flynn P., O’Grady N.P., et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Vol. 49, Clinical infectious Diseases. Oxford University Press; 2009. pp. 1–45.
Mitchell, B.G., Dancer, S.J., Anderson, M., Dehn, E., 2015. Risk of organism acquisition from prior room occupants: a systematic review and meta-analysis. J. Hosp. Infect. 91 (3), 211–217.
Mitharwal, S.M., Yaddanapudi, S., Bhardwaj, N., Gautam, V., Biswal, M., Yaddanapudi, L., 2016. Intensive care unit-acquired infections in a tertiary care hospital: An epidemiologic survey and influence on patient outcomes. Am. J. Infect. Control 44 (7), e113–e117.
Mongin, D., Catho, G., Iten, A., Harbarth, S., Courvoisier, D.S., 2021. Incidence of healthcare-associated coronavirus disease 2019 (COVID-19) in the state of Geneva. Infect. Control Hosp. Epidemiol. Cambridge University Press 1–3.
Moreno, C.A., Rosenthal, V.D., Olarte, N., Gomez, W.V., Sussmann, O., Agudelo, J.G., et al., 2006. Device-associated infection rate and mortality in intensive care units of 9 Colombian hospitals: findings of the International Nosocomial Infection Control Consortium. Infect. Control Hosp. Epidemiol. Cambridge University Press 27 (4), 349–356.
Murni, I.K., Duke, T., Kinney, S., Daley, A.J., Soenarto, Y., 2015. Reducing hospital-acquired infections and improving the rational use of antibiotics in a developing country: an effectiveness study. Arch. Dis. Child. BMJ Publishing Group Ltd 100 (5), 454–459.
Myny, D., Depuydt, P., Colardyn, F., Blot, S., 2005. Ventilator-associated pneumonia in a tertiary care ICU: analysis of risk factors for acquisition and mortality. Acta Clin. Belg. 60 (3), 114–121.
Navoa-Ng, J.A., Berba, R., Galapia, Y.A., Rosenthal, V.D., Villanueva, V.D., Tolentino, M.C.V., et al., 2011. Device-associated infections rates in adult, pediatric, and neonatal intensive care units of hospitals in the Philippines: International Nosocomial Infection Control Consortium (INICC) findings. Am. J. Infect. Control 39 (7), 548–554.

Ndegwa, L.K., Katz, M.A., McCormick, K., Nganga, Z., Mungai, A., Emukule, G., et al., 2014. Surveillance for respiratory health care-associated infections among inpatients in 3 Kenyan hospitals, 2010–2012. Am. J. Infect. Control 42 (9), 985–990.
Nseir, S., Blazejewski, C., Lubret, R., Wallet, F., Courcol, R., Durocher, A., 2011. Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit. Clin. Microbiol. Infect. 17 (8), 1201–1208.
Nussenblatt, V., Avdic, E., Berenholtz, S., Daugherty, E., Hadhazy, E., Lipsett, P.A., et al., 2014. Ventilator-associated pneumonia: overdiagnosis and treatment are common in medical and surgical intensive care units. Infect. Control Hosp. Epidemiol. Cambridge University Press 35 (3), 278–284.
Ong, D.S.Y., Bonten, M.J.M., Spitoni, C., Verduyn Lunel, F.M., Frencken, J.F., Horn, J., et al., 2017. Epidemiology of multiple herpes viremia in previously immunocompetent patients with septic shock. Clin. Infect. Dis. 64 (9), 1204–1210.
Ortíz, G., Dueñas, C., Rodríguez, F., Barrera, L., Rosa, L.a., de, G., Dennis, R., et al., 2014. Epidemiology of sepsis in Colombian intensive care units. Biomedica 34 (1), 40–47.
Parreco, J., Soe-Lin, H., Byerly, S., Lu, N., Ruiz, G., Yeh, D.D., et al., 2020. Multi-center outcomes of chlorhexidine oral decontamination in intensive care units. Surg. Infect. (Larchmt) sur.2019.172.
Penoyer, D.A., 2010. Nurse staffing and patient outcomes in critical care: a concise review. Crit. Care Med. 38 (7), 1521–1528 quiz1529.
Phu, V.D., Wertheim, H.F.L., Larsson, M., Nadjm, B., Dinh, Q.-D., Nilsson, L.E., et al., 2016. Burden of hospital acquired infections and antimicrobial use in Vietnamese adult intensive care units. PLoS ONE. Public Library of Science 11 (1), e0147544.
Plantinga, N.L., Wittekamp, B.H.J., Leleu, K., Depuydt, P., Van den Abeele, A.-M., Brun-Buisson, C., et al., 2016. Oral mucosal adverse events with chlorhexidine 2% mouthwash in ICU. Intensive Care Med. Springer Berlin Heidelberg 42, 620–621.
Ponce de León-Rosales, S.P., Molinar-Ramos, F., Domínguez-Cherit, G., Rangel-Frausto, M.S., Vázquez-Ramos, V.G., 2000. Prevalence of infections in intensive care units in Mexico: a multicenter study. Crit. Care Med. 28 (5), 1316–1321.
Price R., MacLennan G., Glen J., SuDDICU Collaboration. 2014. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. BMJ. BMJ Publishing Group; 348(mar31 2):g2197–7.
Public Health Agency of Canada, 2014. Central Venous Catheter-Associated Blood Stream Infections in Intensive Care units in Canadian Acute-Care Hospitals: Surveillance Report January 1, 2006 to December 31, 2006 and January 1, 2009 to December 31, 2011. Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada.
Pusajó, J.F., Bumaschny, E., Doglio, G.R., Cherjovsky, M.R., Lipinszki, A.I., Hernández, M.S., et al., 1993. Postoperative intra-abdominal sepsis requiring reoperation. Value of a predictive index. Arch Surg. American Medical Association 128 (2), 218–222 discussion 223.
Ramanan, P., Bryson, A.L., Binnicker, M.J., Pritt, B.S., Patel, R., 2018. Syndromic panel-based testing in clinical microbiology. Clin. Microbiol. Rev. American Society for Microbiology Journals 31 (1).
Ramirez, M., Fernandez, B., Cruz, A., Jardines, E., Bermudez, Y., 2011. Comportamiento de las infecciones nosocomiales en Unidad de Cuidados Intensivos en un quinquenio (2005–2009). MediSur 9 (5), 467–473.
Razazi, K., Arrestier, R., Haudebourg, A.F., Benelli, B., Carteaux, G., Decousser, J.-W., et al., 2020. Risks of ventilator-associated pneumonia and invasive pulmonary aspergillosis in patients with viral acute respiratory distress syndrome related or not to Coronavirus 19 disease. Crit Care. BioMed Central 24 (1), 699–711.
Rello, J., Afonso, E., Lisboa, T., Ricart, M., Balsera, B., Rovira, A., et al., 2013. A care bundle approach for prevention of ventilator-associated pneumonia. Clin. Microbiol. Infect. 19 (4), 363–369.
Reper, P., Bombart, M.A., Leonard, I., Payen, B., Darquennes, O., Labrique, S., 2020. Nursing Activities Score is increased in COVID-19 patients. Intensive Crit. Care Nurs. 60, 102891.
Reper, P., Delaere, S., Yimbou, J.J., Labrique, S., Massaut, J., 2021. Not only intensive care unit workload and activities but also quality indicators are influenced by the COVID-19 epidemic. Intensive Crit. Care Nurs. 63, 103008.
Rodríguez-Acelas, A.L., de Abreu, A.M., Engelman, B., Cañon-Montañez, W., 2017. Risk factors for health care-associated infection in hospitalized adults: Systematic review and meta-analysis. Am. J. Infect. Control 45 (12), e149–e156.
Roquilly, A., Broquet, A., Jacqueline, C., Masson, D., Segain, J.P., Braudeau, C., et al., 2014. Hydrocortisone prevents immunosuppression by interleukin-10+ natural killer cells after trauma-hemorrhage. Crit. Care Med. 42 (12), e752–e761.
Roquilly, A., McWilliam, H.E.G., Jacqueline, C., Tian, Z., Cinotti, R., Rimbert, M., et al., 2017. Local modulation of antigen-presenting cell development after resolution of pneumonia induces long-term susceptibility to secondary infections. Immunity 47 (1), 135–145.
Roquilly, A., Torres, A., Villadangos, J.A., Netea, M.G., Dickson, R., Becher, B., et al., 2019. Pathophysiological role of respiratory dysbiosis in hospital-acquired pneumonia. Lancet Respir Med. 7 (8), 710–720.
Rosenthal, V.D., Guzman, S., Orellano, P.W., 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.
Rosenthal, V.D., Guzman, S., Crnich, C., 2006. Impact of an infection control program on rates of ventilator-associated pneumonia in intensive care units in 2 Argentinean hospitals. Am. J. Infect. Control 34 (2), 58–63.
Rouzé, A., Martin-Loeches, I., Póvoa, P., Makris, D., Artigas, A., Bouchereau, M., et al., 2021. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. Intensive Care Med. Springer Berlin Heidelberg 47 (2), 188–198.
Saied, W.I., Martin-Loeches, I., Timsit, J.-F., 2020. What is new in non-ventilated ICU-acquired pneumonia? Intensive Care Med. Springer Berlin Heidelberg 46, 488–491.
Sakr, Y., Jaschinski, U., Wittebole, X., Szakmany, T., Lipman, J., Ñamendys-Silva, S.A., et al., 2018. Sepsis in intensive care unit patients: worldwide data from the intensive care over nations audit. Open Forum. Infect. Dis. Intensive Care Med. Springer Berlin Heidelberg 5 (12), ofy313.
Satoh, K., Makimura, K., Hasumi, Y., Nishiyama, Y., Uchida, K., Yamaguchi, H., 2009. Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol. Immunol. John Wiley & Sons, Ltd 53 (1), 41–44.
Schelenz, S., Nwaka, D., Hunter, P.R., 2013. Longitudinal surveillance of bacteraemia in haematology and oncology patients at a UK cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. J. Antimicrob. Chemother. 68 (6), 1431–1438.
Schreiber, P.W., Sax, H., Wolfensberger, A., Clack, L., Kuster, S.P., Swissnoso, 2018. The preventable proportion of healthcare-associated infections 2005–2016: Systematic review and meta-analysis. Infect. Control Hosp. Epidemiol. Cambridge University Press 39 (11), 1277–1295.
Shorr, A.F., Zilberberg, M.D., Micek, S.T., Kollef, M.H., 2017. Viruses are prevalent in non-ventilated hospital-acquired pneumonia. Respir. Med. 122, 76–80.
Siegel, J.D., Rhinehart, E., Jackson, M., Chiarello, L., Health Care Infection Control Practices Advisory Committee, 2007. Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am. J. Infect. Control 35, S65–S164.
Singh, S., Goyal, R., Ramesh, G.S., Ravishankar, V., Sharma, R.M., Bhargava, D.V., et al., 2015. Control of hospital acquired infections in the ICU: A service perspective. Med. J. Armed Forces India 71 (1), 28–32.
Smith T.J., Bohlke K., Lyman G.H., Carson K.R., Crawford J., Cross S.J., et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. Vol. 33, Journal of Clinical Oncology. American Society of Clinical Oncology; 2015. pp. 3199–212.
Sommerstein, R., Merz, T.M., Berger, S., Kraemer, J.G., Marschall, J., Hilty, M., 2019. Patterns in the longitudinal oropharyngeal microbiome evolution related to ventilator-associated pneumonia. Antimicrob. Resist. Infect. Control. BioMed Central 8 (1), 81–110.
Son, C.H., Daniels, T.L., Eagan, J.A., Edmond, M.B., Fishman, N.O., Fraser, T.G., et al., 2012. Central line-associated bloodstream infection surveillance outside the intensive care unit: a multicenter survey. Infect. Control Hosp. Epidemiol. Cambridge University Press 33 (9), 869–874.
Stewardson, A.J., Allignol, A., Beyersmann, J., Graves, N., Schumacher, M., Meyer, R., et al., 2016. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. Euro Surveill. European Centre for Disease Prevention and Control 21 (33), 30319.
Su, C.-H., Chang, S.-C., Yan, J.-J., Tseng, S.-H., Chien, L.-J., Fang, C.-T., 2013. Excess mortality and long-term disability from healthcare-associated staphylococcus aureus infections: a population-based matched cohort study. PLoS ONE. Public Library of Science 8 (8), e71055.
Tabah, A., Koulenti, D., Laupland, K., Misset, B., Valles, J., Bruzzi de Carvalho, F., et al., 2012. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med. Springer-Verlag 38 (12), 1930–1945.
Talcott, J.A., Finberg, R., Mayer, R.J., Goldman, L., 1988. The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. Arch. Intern. Med. 148 (12), 2561–2568.
Tambyah, P.A., Maki, D.G., 2000. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. Arch Intern Med. American Medical Association 160 (5), 678–682.
Taplitz R.A., Kennedy E.B., Bow E.J., Crews J., Gleason C., Hawley D.K., et al. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. Vol. 36, Journal of Clinical Oncology. American Society of Clinical Oncology; 2018. pp. 3043–54.
Taylor, G., Gravel, D., Matlow, A., Embree, J., LeSaux, N., Johnston, L., et al., 2016. Assessing the magnitude and trends in hospital acquired infections in Canadian hospitals through sequential point prevalence surveys. Antimicrob. Resist. Infect. Control. BioMed Central 5 (1), 19–27.
Tejerina, E., Esteban, A., Fernández-Segoviano, P., Frutos-Vivar, F., Aramburu, J., Ballesteros, D., et al., 2010. Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings. J. Crit. Care 25 (1), 62–68.
Timsit, J.-F., Schwebel, C., Bouadma, L., Geffroy, A., Garrouste-Orgeas, M., Pease, S., et al., 2009. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. JAMA. American Medical Association 301 (12), 1231–1241.
Timsit, J.-F., Mimoz, O., Mourvillier, B., Souweine, B., Garrouste-Orgeas, M., Alfandari, S., et al., 2012. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. Am. J. Respir. Crit. Care Med. American Thoracic Society 186 (12), 1272–1278.
Timsit, J.-F., Esaied, W., Neuville, M., Bouadma, L., Mourvllier, B., 2017. Update on ventilator-associated pneumonia. F1000Res. F1000 Research Limited 6 (2061), 2061.
Timsit, J.-F., Rupp, M., Bouza, E., Chopra, V., Karpanen, T., Laupland, K., et al., 2018. A state of the art review on optimal practices to prevent, recognize, and manage complications associated with intravascular devices in the critically ill. Intensive Care Med. Springer Berlin Heidelberg 44, 742–759.

Tomlinson, D., Mermel, L.A., Ethier, M.-C., Matlow, A., Gillmeister, B., Sung, L., 2011. Defining bloodstream infections related to central venous catheters in patients with cancer: a systematic review. Clin. Infect. Dis. 53 (7), 697–710.
Tran, K., Cimon, K., Severn, M., Pessoa-Silva, C.L., Conly, J., 2012. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS ONE. Public Library of Science 7 (4), e35797.
Ullman, A.J., Cooke, M.L., Mitchell, M., Lin, F., New, K., Long, D.A., et al., 2016. Dressing and securement for central venous access devices (CVADs): A Cochrane systematic review. Int. J. Nurs. Stud. 59, 177–196.
Umscheid, C.A., Mitchell, M.D., Doshi, J.A., Agarwal, R., Williams, K., Brennan, P.J., 2011. Estimating the proportion of healthcare-associated infections that are reasonably preventable and the related mortality and costs. Infect. Control Hosp. Epidemiol. 32 (2), 101–114.
van der Kooi, T., Sax, H., Pittet, D., van Dissel, J., van Benthem, B., Walder, B., et al., 2018. Prevention of hospital infections by intervention and training (PROHIBIT): results of a pan-European cluster-randomized multicentre study to reduce central venous catheter-related bloodstream infections. Intensive Care Med. Springer Berlin Heidelberg 44, 48–60.
van Vught, L.A., Scicluna, B.P., Wiewel, M.A., Hoogendijk, A.J., Klein Klouwenberg, P.M. C., Franitza, M., et al., 2016. Comparative analysis of the host response to community-acquired and hospital-acquired pneumonia in critically ill patients. Am. J. Respir. Crit. Care Med. American Thoracic Society 194 (11), 1366–1374.
Vazquez Guillamet, C., Kollef, M.H., 2018. Is zero ventilator-associated pneumonia achievable?: Practical approaches to ventilator-associated pneumonia prevention. Clin. Chest Med. 39 (4), 809–822.
Venet, F., Filipe-Santos, O., Lepape, A., Malcus, C., Poitevin-Later, F., Grives, A., et al., 2013. Decreased T-cell repertoire diversity in sepsis: a preliminary study. Crit. Care Med. 41 (1), 111–119.
Vincent, J.L., Rello, J., Marshall, J., Silva, E., Anzueto, A., Martin, C.D., et al., 2009. International study of the prevalence and outcomes of infection in intensive care units. JAMA. American Medical Association 302 (21), 2323–2329.
Vogelaers, D., De Bels, D., Forêt, F., Cran, S., Gilbert, E., Schoonheydt, K., et al., 2010. Patterns of antimicrobial therapy in severe nosocomial infections: empiric choices, proportion of appropriate therapy, and adaptation rates–a multicentre, observational survey in critically ill patients. Int. J. Antimicrob. Agents 35 (4), 375–381.
Vogelaers, D., Blot, S., Van den Berge, A., Montravers, P., 2021. Antimicrobial lessons from a large observational cohort on intra-abdominal infections in intensive care units. Drugs. Springer International Publishing 1–14.
Vollaard, E.J., Clasener, H.A., 1994. Colonization resistance. Antimicrob. Agents Chemother. American Society for Microbiology Journals 38 (3), 409–414.
Vuichard-Gysin, D., Abbas, M., Harbarth, S., 2021. In-hospital COVID-19 outbreak investigation: A practical approach to root cause analysis. Intensive Crit. Care Nurs. 67, 103132.
Walter, J., Haller, S., Quinten, C., Kärki, T., Zacher, B., Eckmanns, T., et al., 2018. Healthcare-associated pneumonia in acute care hospitals in European Union/European Economic Area countries: an analysis of data from a point prevalence survey, 2011 to 2012. Euro Surveill.. European Centre for Disease Prevention and Control 23 (32), 1700843.
WHO, 2011. Report on the Burden of Endemic Health Care-associated Infection Worldwide - Clean Care is Safer Care. Word Health Organization.
WHO (2012). WHO, Prevention of hospital-acquired infections - A practical guide, 2nd edition, in: W. H. Organization (Ed.).
Wicky, P.-H., Niedermann, M.S., Timsit, J.-F., 2021. Ventilator-associated pneumonia in the era of COVID-19 pandemic: How common and what is the impact? Crit. Care. BioMed Central 25 (1), 153–163.
Winters, B.D., Eberlein, M., Leung, J., Needham, D.M., Pronovost, P.J., Sevransky, J.E., 2010. Long-term mortality and quality of life in sepsis: a systematic review. Crit. Care Med. 38 (5), 1276–1283.
Wittekamp, B.H.J., Oostdijk, E.A.N., Cuthbertson, B.H., Brun-Buisson, C., Bonten, M.J. M., 2020. Selective decontamination of the digestive tract (SDD) in critically ill patients: a narrative review. Intensive Care Med. Springer Berlin Heidelberg 46, 343–349.
Wittekamp, B.H., Plantinga, N.L., Cooper, B.S., Lopez-Contreras, J., Coll, P., Mancebo, J., et al., 2018. Decontamination strategies and bloodstream infections with antibiotic-resistant microorganisms in ventilated patients: A randomized clinical trial. JAMA. American Medical Association 320 (20), 2087–2098.
Woeltje, K.F., Butler, A.M., Goris, A.J., Tutlam, N.T., Doherty, J.A., Westover, M.B., et al., 2008. Automated surveillance for central line-associated bloodstream infection in intensive care units. Infect. Control Hosp. Epidemiol. Cambridge University Press 29 (9), 842–846.
Yakovlev, S.V., Suvorova, M.P., Beloborodov, V.B., Basin, E.E., Eliseev, E.V., Kovelenov, S.V., et al., 2016. Multicentre study of the prevalence and clinical value of hospital-acquired infections in Emergency Hospitals of Russia: ERGINI Study Team. Antibiot Khimioter. Antibiot. Khimioter. 61 (5–6), 32–42.
Yallew, W.W., Kumie, A., Yehuala, F.M., 2016. Point prevalence of hospital-acquired infections in two teaching hospitals of Amhara region in Ethiopia. Drug Healthc. Patient Saf. Dove Press 8, 71–76.
Young, V.B., 2016. Therapeutic manipulation of the microbiota: past, present, and considerations for the future. Clin. Microbiol. Infect. 22 (11), 905–909.
Zahar, J.-R., Blot, S., Nordmann, P., Martischang, R., Timsit, J.-F., Harbarth, S., et al., 2019. Screening for intestinal carriage of extended-spectrum beta-lactamase-producing enterobacteriaceae in critically ill patients: expected benefits and evidence-based controversies. Clin. Infect. Dis. 68 (12), 2125–2130.