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NOSOCOMIAL INFECTIONS IN ICU- REVIEW ARTICLE

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ABSTRACT

Nosocomial Infections (NI) or Health Care Associated Infections are one of the major complications for healthcare professionals to tackle. It is a major source of morbidity, mortality, and also monetary burden on patients. Intensive Care Unit(ICU) patients are at risk for acquiring nosocomial infections. There is an ever growing importance for critical assessment of benefits and harms of various strategies for infection control and adequate control of multidrug resistant organisms in ICU setting. This review will summarize findings from some recent major publications in area of infectious diseases with emphasis on causes, preventive strategies, the role of new biomarkers and some recent updates in relation to invasive fungal infections, community acquired pneumonia and ventilator associated pneumonia in ICU patients and UTI.

Figure : 00 References : 24 Tables : 03

KEY WORDS : Intensive Care Unit (ICU), Nosocomid Inspection (NI).

Introduction

A nosocomial infection also called “hospital acquired infection” can be defined as: An infection acquired in hospital by a patient who was admitted for a reason other than that infection.An infection occurring in a patient in a hospital or other health care facility in whom the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge and also occupational infections among staff of the facility[6]. Nosocomial infections can also be defined as those occurring within 48 hours of hospital admission, 3 days of discharge or 30 days of an operation. They affect 1 in 10 patients admitted to hospital. Intensive care units (ICU) have the highest prevalence of hospital-acquired infections in the hospital setting. The European Prevalence of Infection in Intensive Care Study (EPIC), involving over 4500 patients, demonstrated that the nosocomial infection prevalence rate in ICU was 20.6%.[15] The costs of hospital-acquired (nosocomial) and other health care associated infections are great. These infections have affected as many as 1.7 million patients at a cost of approx. $28-33 billion and 99,000 lives in U.S. hospitals annually[21]. Although efforts to lower infection risks have been challenged by the numbers of immunocompromised patients, antibiotic-resistant bacteria, fungal and viral superinfections and invasive devices and procedures, a prevailing viewpoint- often termed “zero tolerance”- is that almost all health care-associated infections should be avoidable with strict application of evidence-based prevention guidelines. In fact, rates of device-related infections- historically the largest drivers of risk- have fallen steadily over the past few years. Unfortunately, antimicrobial- resistant pathogens have risen in number and are estimated to contribute to approx. 23,000 deaths in and outside of hospitals annually.

Causes of Nosocomial Infections

ICU patients are particularly at risk from nosocomial infections as a result of mechanical ventilation, use of invasive procedures and their immunocompromised status (Table 1.). Three major causes of NI’s are documented. First is antimicrobials use, long term and irrational use of antimicrobials leads to development of resistant strains of pathogens. Second, the leniency of hospital staff and infection control committee in maintaining sterility conditions. Third, the patient itself is prone to NI’s due to low immunity and

unhygienic conditions around themselves.

Gram-negative versus gram-positive pathogens, by type of ICU infection, 1986–2003

From 1986 through 2003, data on 410,503 bacterial isolates associated with nosocomial infections were submitted from ICUs in NNIS hospitals. The mean annual number of bacterial isolates reported was 24,129 (range, 10,128 in 1986 to 26,026 in 2000). The percentages of gram-negative and gram-positive bacteria associated with each of the 4 major types of infection are shown (Table 2). For pneumonia and UTI, the majority of bacterial isolates associated were gram negative, which remains stable during study period. However for surgical site infections (SSIs), the percentage of bacterial isolates that were gram negative decreased during the study period. By the middle of the 1990s, gram-positive bacterial pathogens were more commonly reported in association with SSIs than were gram-negative pathogens. Throughout the study period, gram-positive bacterial pathogens were much more commonly associated with blood stream infections (BSIs) than were gram-negative pathogens.[18]

UTI

UTI accounts for 30 to 40 % of nosocomial infections, upto 3% of bacteriuric patients develop bacteremia. These infections are reservoirs and sources for spread of antibiotic resistant bacteria. Prompts to assess a patient's need for continued use of an indwelling bladder catheter can improve removal rates and lessen the risk of UTI. Guidelines for managing postoperative urinary retention (*e.g.* with Bladder scanners) also may limit the use or duration of catheterization. Prophylactic antibiotic administration at the time of catheter removal has been reported to decrease the risk of UTI. Selective decontamination of the gut also is associated with reduced risk. Irrigation of catheter, with or without antimicrobial agents may actually increase the risk of infection. A condom catheter in men without bladder obstruction may be more useful. The most common pathogen isolated are *E.coli,* nosocomial gram negative *bacilli, enterococci* and *Staph. aureus*.[21]

Severe Pneumonia inthe ICU

Healthcare associated pneumonia: Workers[23] prospectively compared the epidemiology, antibiotic therapy and clinical outcomes between 449 patients with community acquired pneumonia (CAP), 133 health care

TABLE- 1 : Factors that predispose to nosocomial infection

Factors that predispose to nosocomial infection
Related to underlying health status
■ Advanced age
■ Malnutrition
■ Alcoholism
■ Heavy smoking
■ Chronic lung disease
■ Diabetes
Related to acute disease process
■ Surgery
■ Trauma
■ Burns
Related to invasive procedures
■ Endotracheal or nasal intubation
■ Central venous catheterization
■ Extracorporeal renal support
■ Surgical drains
■ Nasogastric tube
■ Tracheostomy
■ Urinary catheter
Related to treatment
■ Blood transfusion
■ Recent antimicrobial therapy
■ Immunosuppressive treatments
■ Stress-ulcer prophylaxis
■ Recumbent position
■ Parenteral nutrition
■ Length of stay

acquired pneumonia (HCAP) and 144 immunocompromised patients (ICP) with pneumonia admitted in 34 Spanish ICUs over 1 year period. They found that HCAP patients had more comorbidities and had a worse clinical status as compared to the two other subgroups and that both HCAP and ICP more often needed mechanical ventilation and more often underwent tracheostomy. The incidence of gram-negative pathogens, MRSA and *Pseudomonas aeruginosa* was low overall, but higher in HCAP and ICP. Inappropriate empirical antibiotic therapy was 6.5 % in CAP, 14.4 % in HCAP and 38.6 % in ICP while mortality was the highest in ICP (38.6 %) and did not differ between CAP (18.4 %) and HCAP (21.2 %). The authors concluded that empirical antibiotic regimens recommended for CAP would be appropriate for 90 % of the patients with HCAP and that consequently systematically covering multidrug-resistant pathogens in HCAP is not necessary.

Ventilator-associated pneumonia (VAP) remains the second leading cause of nosocomial infections in ICUs, associated with increased adverse outcomes and economic costs[12]. Workers[16] assessed the attributable mortality of VAP using data from 58 RCTs on VAP prevention, and estimated an attributable mortality rate of 9%. Diagnosis of ventilator-associated pneumonia (VAP) is a problem that is not yet fully solved. In fact, there have been no major advances since the last meta-analysis published by the Cochrane Collaboration.[3] Real major advances will come from rapid PCR point-of-care techniques, but these results are not yet available. In 2014, in an article in the What's New in Intensive Care section on potential innovations that could improve early recognition of VAP[4]. Those authors suggested that new techniques were promising in detecting airway colonization and pulmonary infection at the early phase. The first technique use colorimetric assays inside the endotracheal tubes to detect the type of bacteria and the pattern of resistance. The second technique is based on the detection of volatile compounds (hydrocarbons, alcohols, aldehydes, ketones and, sulfide-containing molecules) released by bacteria that cause VAP. These techniques are still in a very early clinical phase and need to be validated.

Postoperative nosocomial pneumonia is a threatening complication of major surgery (cardiovascular, thoracic and abdominal), with very high morbidity and mortality. Preoperative oral care is a non-standard prophylactic measure. Workers[2] performed a prospective study implementing several oral-hygiene measures, including a dentist visit, brushing teeth and tongue and oral rinse with chlorhexidine (0.12 %) twice a day until surgery. With these measures, they were able to reduce pneumonia from an incidence rate of 32 cases to 1000 ventilator days in the 6 months period before the study to 10 cases per 1000 days of mechanical ventilation during the 6 months following the study.

Reducing the rate of VAP often has not reduced ICU mortality. This fact suggests that this infection is a marker for patients with otherwise heightened risk of death. Early onset nosocomial pneumonia (within 4 days of hospitalization) is caused by Strep Pneumonia and Haemophilus influenza. Late onset pneumonias most commonly due to *Staph Aureus,* Aeruginosa, Klebsiella pneumonia, Enterobacter and Acinetobacter. The role of anaerobic bacteria in VAP is not well defined. One multicentre study suggests that 8 days is an appropriate duration of therapy in nosocomial pneumonia with a longer duration (15 days) when the pathogen is Acinetobacter or *P.Aeruginosa.*

Surgical Wound Infections

Wound infections account for 15-20% of nosocomial infections. These infections are usually caused by the patient's endogenous or hospital-acquired skin and mucosal flora and occasionally are due to airborne spread of skin squamous that may be shed into the wound from members of the operating team. The common risks are related to the surgeon's technical skill, the patient's underlying conditions (*e.g.* Diabetes mellitus, obesity) or advanced age and inappropriate timing of antibiotic prophylaxis. Additional risks include the presence of drains, prolonged preoperative hospital stays, shaving of operative sites by razor the day before surgery, long duration of surgery and infection at remote sites (*e.g.* Untreated UTIs). The most common pathogens are *S. aureus,* coagulase negative *staphylococci* and enteric and anaerobic bacteria. Treatment of postoperative wound infection requires drainage or surgical excision of infected of necrotic material and antibiotic therapy.

Infections Related to Vascular Access and Monitoring

Intravascular device-related bacteremias cause 10-15% of nosocomial infections; central vascular catheters (CVCs) account for most of these bloodstream infections. Catheter-related

TABLE- 2: shows most common infections and pathogen associated with them.

Pathogen	Percentage of isolates, by infection type			
	Pneumonia (n - 4365	Bloodstream infection (n = 2351)	Surgical Site infection (n = 2984)	Urinary tract infection (n = 4109)
Gram negative				
Escherichia coli	5.0	3.3	6.5	26.0
Klebsiella pneumoniae	7.2	4.2	3.0	9.8
Enterobacter species	10.0	4.4	9.0	6.9
Serratia marcescens	4.7	2.3	2.0	1.6
Pseudomonas aeruginosa	18.1	3.4	9.5	16.3
Acinetobacter species	6.9	2.4	2.1	1.6
Other	14.1	3.8	9.8	10.7
Gram positive				
Coagulase-negative staphylococci	1.8	42.9	15.9	4.9
Staphylococcus aureus	27.8	14.3	22.5	3.6
Enterococococci	1.3	14.5	13.9	17.4
Other	3.2	4.5	5.8	1.2

bloodstream infections derive largely from the cutaneous microflora of the insertion site, with pathogens migrating extraluminally to the catheter tip, usually during the first week of insertion. The common pathogens isolated include coagulase-*negative staphylococci, S.aureus, enterococci,* nosocomial gram-negative bacilli and Candida. Control measures for infections associated with vascular access include use of a chlorhexidine-impregnated patch at the skin-catheter junction; daily bathing of ICU patients with chlorhexidine; application of semitransparent access-site dressings (for ease of bathing and site infection and protection of the site from secretions); avoidance of the femoral site for catherisation because of a higher risk of infection, rotation of peripheral catheters to a new site at specified intervals (*e.g.,* every 72-96 h), which may be facilitated by use of an IV therapy team and application of aseptic technique when accessing pressure transducers or other vascular ports. These are suspected on the basis of the appearance of the catheter site or the presence of fever or bacteremia without another source in patients with vascular catheters. The diagnosis is confirmed by recovery of the same species of microorganisms from peripheral blood cultures and cultures of the vascular catheter tip.

Fungal Infections

Invasive fungal infections, notably invasive aspergillosis and candidaemia, are still a major challenge in ICUs. Some new insights about invasive aspergillosis in ICU patients were presented last year[19] and important papers have

been recently published about the management of candidaemia in critically ill patients. Workers[11] conducted a retrospective matched case-control study in the ICU of a Nebraska academic medical centre to validate and compare two clinical prediction rules aimed at identifying patients who may benefit from antifungal prophylaxis or early empiric therapy. They found an incidence of 2.3% for invasive candidiasis among 352 adult patients with an ICU stay of at least 4 days.

A systematic review of risk factors for invasive fungal disease was performed in critically ill patients[17]. Surgery, total parenteral nutrition, fungal colonization, renal replacement therapy and sepsis were found, among others, to be significantly associated with invasive fungal infections. Taken together, these approaches could be helpful for preventing unnecessary antifungal use and optimizing patient care.

However, candidaemia remains an invasive infection with a crude mortality exceeding 50%[17]. The importance of first-line antifungal agents has been evaluated in two important papers yielding concurrent results. In particular, It was found that treatment failure of first-line antifungal agents was one of the most important risk factors for mortality among ICU patients with candidaemia in four tertiary-care hospitals in Korea[8]. Indeed, an antifungal switch to second-line agents was found to be the only risk factor for longer length of stay and increased cost that could be modified, thus highlighting how the choice of an appropriate first-line antifungal agent is crucial for improved outcome.

A patient-level review of 1,915 patients extracted from seven randomized antifungal treatment trials[1] was performed and found that only removal of central venous catheters and treatment with an echinocandin were associated with improved survival and better clinical outcome than treatment with triazoles or amphotericin-B. Remarkably, the improved outcomes were evident not only for patients infected by *Candida albicans* and non-*albicans* strains but also for infection by *Candida parapsilosis*, which is usually less susceptible to echinocandins (higher MICs) due to the minor quantity of â-d-glucan - the target of echinocandins - within its cell wall.

Infection Control

The Study of the Efficacy of Nosocomial Infection Control (SENIC) demonstrated that a third of nosocomial infections might be prevented with appropriate infection control measures[10]. These comprise surveillance methods, prevention strategies and treatment programs.

Surveillance : Surveillance is the ongoing, systematic collection, analysis and interpretation of information related to health. This is essential for the planning, implementation and evaluation of public health and also the timely dissemination of information. In the UK, the Nosocomial Infection National Surveillance Service was formed in 1996[18] and is managed by the Health Protection Agency (HPA). For reliable validation, surveillance system must contain: trained personnel, criteria for nosocomial infections, risk factors, and other outcomes, sources of data for identifying infections, accurate and complete data and strategies for identifying infected patients.

Prevention Strategies : Poor hand hygiene is responsible for 40% of infections transmitted in hospitals. Surveys have shown that the improvement in compliance with hand washing reduces nosocomial infection. Accessibility of the hand washing stations and the use of alcohol gels improves compliance with hand washing. Alcohol gel dries quickly and is bactericidal, fungicidal and virucidal. Numerous studies have shown that doctors wash their hands less frequently than nurses and backs of hands, tips of fingers, web spaces and thumb are commonly missed areas. The Department of Health has produced guidelines on hand washing on their website.

Protective garments are necessary for health providers exposed to body fluids, for example sweat, oropharyngeal fluids, blood or urine. Gloves and aprons should be worn for handling body fluids. High efficiency particulate air (HEPA) filter masks are recommended for sputum smear positive patients with tuberculosis, particularly for cough-inducing procedures.Hands must be washed after glove removal as contamination of the hands can still occur.

The use of invasive procedures increases the risk of nosocomial infections. For venous access, this risk can be reduced by use of specific sites such as subclavian vein rather than internal jugular or femoral veins. Tunneling the catheter reduces the risk of nosocomial infection. Antimicrobial impregnated catheters can reduce catheter related infections. The use of a strict, aseptic technique is paramount in the insertion of

intravascular catheters. By using isolation rooms for patients with MRSA, *C. difficile*, VRE and resistant Gram-negative infections, the spread of infection can be reduced owing to improved awareness of the implementation of appropriate infection control precautions.

Treatment Strategies

Appropriate use of antibiotics is important. Upto 30% of ventilator associated pneumonias are treated inadequately. There is increasing evidence to suggest that the use of appropriate and early antibiotics improve morbidity and mortality. Appropriate antibiotic use requires a thorough knowledge of their mode of action, previous antibiotic history, local bacterial resistance profile and local pathogen prevalence. Antibiotics should be administered at the right dose and for the appropriate duration. Antibiotic-resistant bacteria prolong hospitalization, increase the risk of death and require treatment with toxic and expensive antibiotics. Empirical use of antibiotic is often necessary as laboratory results are often not available for 48 hours after the samples are sent for culture. Appropriate specimens include blood, urine, sputum, Broncho alveolar lavage, pus and wound swabs. Blood cultures are only positive for pathogens in a third of cases. Once the antibiotic profile is available, a narrow-spectrum antibiotic can be commenced. Indicators of response to treatment include temperature, leucocyte counts and C- reactive protein levels.

Any antibiotic policy or guideline should aim to limit the use of antibiotics and reduce the selective pressure for resistant microorganisms. Policies designed to encourage rational antibiotic use in ICU are an important element in quality of care, infection control and cost containment. De-escalation therapy, selective digestive decontamination (SDD), antibiotic rotation (cycling) therapy and restrictive guidelines can address these concerns.

De-escalation : involves early initiation of broad-spectrum antibiotic therapy in patients with suspected sepsis without the availability of microbiology results. The increase in antibiotic resistant pathogens such as MRSA has led some investigators to suggest broader antibiotic coverage by adding a glycopeptide to carbapenem as the initial empirical therapy. This aggressive empirical regimen is continued for 24–48 h by which time laboratory tests have confirmed the causative organisms and sensitivities. This allows for de-escalation of antibiotic therapy. De-escalation should be cautiously applied, depending on each particular patient's clinical status and considering the ICU environment as a whole.

Rotational antibiotic therapy : Rotational antibiotic therapy is a strategy to reduce antibiotic resistance by withdrawing an antibiotic or class of antibiotics, from ICU for a short period, to allow resistance rates to decrease or remain stable. The persistent use of one class of antibiotics leads to the emergence of resistant strains of bacteria; this is known as selective pressure. Rotational

TABLE - 3 : Procedure for hand wash

Routine care (minimal)	Antiseptic hand cleaning (moderate) aseptic care of infected patients	Surgical scrub (surgical care)
Hand washing with non-antiseptic soap	Hygienic hand washing with antiseptic soap following manufacturer's instructions (*e.g.* one minute)	Surgical hand and forearm washing with antiseptic soap and sufficient time and duration of contact (3-5 minutes)
Quick hygienic hand disinfection (by rubbing) with alcoholic solution	Quick hygienic hand disinfection; as previously	Surgical hand and forearm disinfection: simple hand wash and drying followed by two applications of hand disinfectant, then nub to dry for the duration of contact defined by the product.

regimens are thought to reduce this selective pressure. There is growing support for this regimen. It was demonstrated that there was a statistical decrease in nosocomial pneumonia in a large ICU after the introduction of an antibiotic rotation policy[14].

Restrictive antibiotic policies: They are less flexible and to a certain extent binding, with respect to prescribing. They require the prescriber to give written justification for any deviation from the policy. Automatic stop orders restrict prolonged antibiotic administration. In the general hospital setting, these measures have had some success with significant reductions in antibiotic resistance. However, the overall survival in ICU was unchanged.

Selective Digestive Decontamination : The concept that commensals within the bowel may provide a protective role against more virulent organisms is called colonization resistance. Translocation of Gram-negative bacteria across the intestinal wall is thought to be a major cause of nosocomial infections. SDD aims to eliminate Gram-negative aerobic bacteria by decontamination of the oral cavity and intestinal tract. There are several variations of the SDD regimen. One such regimen is non-absorbable *polymyxin E, tobramycin* and *amphotericin B* for gastrointestinal decontamination and cefotaxime for systemic prophylaxis. Cephalosporins are usually given as prophylaxis as they act on commensal respiratory flora such as *Streptococcus pneumoniae*, *Haemophilusinfluenzae* and *S. aureus*. Meta-analysis has demonstrated that SDD regimens decrease the incidence of nosocomial pneumonia but overall survival or duration of intensive care treatment is unchanged.

New insights into antibiotic treatment modalities and agents

According to recent data, BSI (blood stream infections) occurs in about 15% of ICU patients and is associated with increased mortality and morbidity. Optimization of the antimicrobial treatment duration for BSI could potentially reduce antibiotic utilization, resistance, costs and adverse events. In a systematic review, analyzed data[9] from subgroup analyses of various RCTs and have suggested equal benefit from shorter duration of therapy (<8 days) compared with longer-duration therapy regarding morbidity, mortality or microbiological cure. The authors also highlight the potential importance of having a longer duration of treatment for *S. aureus* bacteremia and thus consider it separately from other pathogens. There was very limited evidence to guide optimal treatment of catheter-related BSI, VAP, CAP, pyelonephritis and intraabdominal infections in ICU patients. The decision on the duration of therapy should thus currently be based on the clinical response rather than a specific time interval.

Tigecycline, the first representative of the glycycline class, has reported activity against a wide range of pathogens. Workers examined the efficacy of tigecycline for the treatment of adult patients with bacterial infection by conducting a systematic review of 14 RCTs, including 7,400 patients[22]. Interestingly, the authors found nonsignificantly lower success rates with tigecycline than with control antibiotics, with a more frequent rate of adverse events in the tigecycline group. They also found a nonsignificant trend towards higher all-cause mortality inthe tigecycline group. Another recent systematic review pooling non-inferiority RCTs of serious infections found an increased overall mortality associated with tigecycline therapy independent of type of infection or comparator antibiotic regimen. There is thus currently little evidence to support a superiority of tigecycline against standard antimicrobials for treatment of serious infections. In particular, tigecycline should be avoided for the treatment of severe pneumonia in critically ill patients.

Emergence of multidrug-resistant organisms has revitalised colistin, a polymyxin antimicrobial potentially useful for treatment of multidrug-resistant pathogens such as *P. aeruginosa*, *Acinetobacterbaumannii* and carbapenem-resistant *Enterobacteriaceae*. Although colistin retains *in vitro* activity against most of these Gram-negative pathogens, it is crucial to preserve its activity as a last-line drug while also minimizing the potential for adverse effects. In a retrospective cohort study of all patients receiving colistin for e”48 hours over a 5-year period, There were important safety concerns for reporting a 43% (n = 54) colistin associated nephrotoxicity[20]. Nephrotoxicity occurred in a dose-dependent manner, with higher mean colistin doses significantly increasing the risk.

In a double-blind multicenter RCT, Workers assessed the efficacy and safety of linezolid compared with a dose-optimized vancomycin strategy against MRSA nosocomial pneumonia in

448 adult participants[24]. Patients were randomized to either intravenous linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours) for 7 to 14 days with continuous dose adjustment of vancomycin. Clinical success was achieved at the end of the study in 57.6% of the linezolid group versus 46.6% of the vancomycin group (95% CI for difference, 0.5 to 21.6%; P = 0.042). There was similar all-cause mortality at 60 days (linezolid, 15.7% vs. vancomycin, 17.0%) while renal toxicity occurred more frequently with vancomycin (18.2% vs. linezolid, 8.4%). There was a similar rate of adverse events in both groups and there was no difference with regards to mortality from MRSA pneumonia.

Biomarkers

In a prospective cohort study of 191 patients with severe community-acquired pneumonia (CAP) requiring ICU admission, there were the values of different patterns of **C-reactive protein (CRP)-**ratio response to antibiotic therapy[5]. After CRP sampling every other day until day 7 of antibiotic therapy, the CRP ratio was calculated in relation to the day 1 concentration. The authors found a more rapid decrease in the CRP ratio among survivors than among nonsurvivors (P = 0.01) and they found an ability of the CRP ratio to predict ICU mortality at day 5. The ICU mortality rate varied significantly among different groups, with the individual pattern of the CRP ratio defined as fast response (4.8%), slow response (17.3%) and nonresponse (36.4%) (P <0.001). Serial evaluation of the CRP ratio may be a valuable tool for early detection of patients with severe CAP who are at risk of poor outcome.

Numerous recent publications have assessed the application of algorithms based on **procalcitonin (PCT)** as a rapid-reacting biomarker of bacterial infection for antibiotic stewardship. In a recent multicentre-randomised controlled trial (RCT), Workers randomized 1,200 critically ill patients to either a standard clinical judgement arm (blinded to PCT levels) or a PCT-guided treatment arm with a mandatory drug-escalation algorithm and antimicrobial guidance based on daily PCT measurements[13]. They failed to show any benefit on all-cause 28-day mortality in the PCT arm (31.5%, 190 of 604) compared with the control arm (32.0%, 191 of 596). More disappointingly, the length of the ICU stay increased by 1 day in the PCT arm. The rate of mechanical ventilation also increased by 4.9%. This study's findings somewhat contradicts the recent systematic reviews, which despite no indication of improved mortality showed benefits among patients with respiratory tract infection and sepsis by significantly reducing antibiotic exposure and showed a trend towards reduced costs and reduced length of ICU stay

The diagnostic value of serum PCT concentrations for discriminating among SIRS, sepsis, severe sepsis, and septic shock remains to be established. Although higher PCT concentrations suggest a systemic bacterial infection as opposed to a viral, fungal, or inflammatory etiology of sepsis, serum PCT concentrations do not correlate with the severity of sepsis or with mortality. At present, PCT concentrations are solely investigational with regard to determining the timing and appropriateness of escalation of antimicrobial therapy in sepsis. Nevertheless, serum PCT concentrations have established utility in monitoring the clinical response to medical and surgical therapy for sepsis, and in surveillance for the development of sepsis in burn and ICU patients, and may have a role in guiding the de-escalation of antibiotic therapy.

Conclusion

Nosocomial infections are associated with a great deal of morbidity, mortality and increased financial burden. Intensive care is a risk factor for the emergence of antibiotic resistant bacteria. Gram-positive bacteria have overtaken Gram-negative organisms as the predominant cause of nosocomial infections. Invasive fungal infections are still a major challenge in ICUS. Inadequate antibiotic therapy is associated with poor outcome and particularly with bacterial resistance. Infection control measures are important for the effective control, prevention and treatment of infection. Hand washing is a single best measure to prevent nosocomial infections. Knowledge of emerging biomarkers, emerging pathogens and resistance profile is essential for treatment against nosocomial infections. Shorter duration of treatment and correct dosage of antibiotic therapy is recommended to reduce the selection pressure for resistant isolates.

References

1. ANDES, D.R., SAFDAR, N., BADDLEY, J.W., PLAYFORD, G., REBOLI, A.C., REX, J.H., SOBEL, J.D., PAPPAS, P.G. AND KULLBERG, B.J. (2012) Mycoses Study Group: Impact of treatment strategy on

outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clin Infect Dis,* **54** :1110-1122.

2. BERGAN, E.H., TURA, B.R. AND LAMAS, C.C. (2014) Impact of improvement in preoperative oral health on nosocomial pneumonia in a group of cardiac surgery patients: a single arm prospective intervention study. *Intensive Care Med* **40** : 23–31.doi:10.1007/s00134-013-3049-y
3. BERTON, D.C., KALIL, A.C. AND TEIXEIRA, P.J.Z. (2014) Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator associated pneumonia. *Cochrane Database Syst Rev* **10** :CD006482 .doi:10.1002/14651858. CD006482.pub4
4. BOS, L.D.J., MARTIN-LOECHES, I. AND ARTIGAS, A. (2014) Innovations that could improve early recognition of ventilator-associated pneumonia. *Intensive Care Med* **40** : 1352–1354. doi:10.1007/s00134-014-3356-y
5. COELHO, L.M., SALLUH, J.I., SOARES, M., BOZZA, F., VERDEAL, J.C., CASTRO-FARIA-NETO, H.C., LAPA, E., SILVA, J.R., BOZZA, P.T. AND POVOA P (2012): Patterns of C-reactive protein ratio response in severe community-acquired pneumonia: a cohort study.*Crit Care*, **26** :R53
6. DUCEL, G. FABRY, J., AND NICOLLE, L. (2002) Prevention of hospital acquired infections a practical guide,2nd edition.WHO/CDS/CSR/EPH/2002.12http://www.who.int/csr/resources/publications/whocdscsreph.12.pdf; 2013
7. GARONZIK, S.M., LI, J., THAMLIKITKUL, V., PATERSON, D.L., SHOHAM, S., JACOB, J., SILVEIRA, F.P., FORREST, A. AND NATION, R.L. (2011) Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother*, **55** : 3284-3294.
8. HA, Y.E., PECK, K.R., JOO, E.J., KIM, S.W., JUNG, S.I., CHANG, H.H., PARK, K.H. AND HAN, S.H. (2012) Impact of first-line antifungal agents on the outcomes and costs of candidemia.*Antimicrob Agents Chemother,* **56** :3950-3956.
9. HAVEY, T.C., FOWLER, R.A. AND DANEMAN, N. : Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis.*Crit Care*, **15** :R267.
10. HALEY, R.W., WHITE, J.W. AND CULVER, D.H., *ET AL.*(1985) The efficacy of infection surveillance and central programs in preventing nosocomial infections in US hospitals (SENIC). *Am J Epidemiol ;* **121** : 182–205
11. HERMSEN, E.D., ZAPAPAS, M.K., MAIEFSKI, M., RUPP, M.E., FREIFELD, A.G. AND KALIL, A.C. (2011) Validation and comparison of clinical prediction rules for invasive candidiasis in intensive care unit patients: a matched case–control study. *Crit Care*, 1**5**: R198.
12. JANUEL, J.M., HARBARTH, S., ALLARD, R., VOIRIN, N., LEPAPE, A., ALLAOUCHICHE, B., GUERIN, C., LEHOT, J.J., ROBERT, M.O., FOURNIER, G., JACQUES, D., CHASSARD, D., GUEUGNIAUD, P.Y., ARTRU, F., PETIT, P., ROBERT, D., MOHAMMEDI, I., GIRARD, R., CÊTRE, J.C., NICOLLE, M.C., GRANDO, J., FABRY, J. AND VANHEMS, P. (2010): Estimating attributable mortality due to nosocomial infections acquired in intensive care units. *Infect Control Hosp Epidemiol,* **31** :388-394.
13. JENSEN, J.U., HEIN, L., LUNDGREN, B., BESTLE, M.H., MOHR, T.T., ANDERSEN, M.H., THORNBERG, K.J., LØKEN, J., STEENSEN, M., FOX, Z., TOUSI, H., SØE-JENSEN, P., LAURITSEN, A.Ø., STRANGE, D., PETERSEN, P.L., REITER, N., HESTAD, S., THORMAR, K., FJELDBORG, P., LARSEN, K.M., DRENCK, N.E., OSTERGAARD, C., KJÆR, J., GRARUP, J. AND LUNDGREN, J.D. (2011) Procalcitonin and Survival Study (PASS) Group: Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial.*Crit Care Med,* **39**:2048-2058.
14. KOLLEF, M.H., WARD, S., AND SHERMAN, G., *ET. AL.* (2000) Inadequate treatment of nosocomial infection is associated with certain empiric antibiotic choices. *Crit Care Med* ; **28** : 3456-64
15. LOUIS, V., BIHARI, M.B., AND SUTER, P., *ET AL.* (1995) The prevalence of nosocomial Infections in intensive care units in Europe. European Prevalence of infection in Intensive care (EPIC) study. *JAMA*; **274**: 639–44

16. MELSEN, W.G., ROVERS, M.M., KOEMAN, M. AND BONTEN, M.J. (2011) Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. *Crit Care Med*, **39** : 2736-2742

17. MUSKETT, H., SHAHIN, J., EYRES, G., HARVEY, S., ROWAN, K. AND HARRISON, D. (2011) Risk factors for invasive fungal disease in critically ill adult patients: a systematic review. *Crit Care*, **15** : R287.

18. Nosocomial Infection National Surveillance Service (NINSS). *Surveillance of Hospital Acquired Bacteraemia in English Hospitals 1997–2002*. London: Public Health Laboratory Service, 2002

19. PAGANI, L., AFSHARI, A. AND HARBARTH, S. (2010) Critical Care–infection.*Crit Care*, **15** :238.

20. POGUE, J.M., LEE, J., MARCHAIM, D., YEE, V., ZHAO, J.J., CHOPRA, T., LEPHART, P. AND KAYE, K.S. (2011) Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. *Clin Infect Dis,* **53**:879-884.

21. ROBERT, A. WEINSTEIN Harrison's principles of internal medicine-19th edition **131** : 1112-1120.

22. TASINA E, HAIDICH AB, KOKKALI S. AND ARVANITIDOU M (2011): Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. *Lancet Infect Dis*, **11** : 834-844.

23. VALLEìS, J., MARTIN-LOECHES, I. AND TORRES, A. *ET AL.* (2014) Epidemiology, antibiotic therapy and clinical outcomes of healthcare-associated pneumonia in critically ill patients: a Spanish cohort study. *Intensive Care Med* **40** : 572–581.doi:10.1007/s00134-014-3239-2

24. WUNDERINK, R.G., NIEDERMAN, M.S., KOLLEF, M.H., SHORR, A.F., KUNKEL, M.J., BARUCH, A., MCGEE, W.T., REISMAN, A. AND CHASTRE, J. (2012): Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis* **54** : 621-629.