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Management of Infections in Critically Ill Patients

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Abstract

Background: Critically ill patients have an increased risk of developing infections and infectious complications, sometimes followed by death. Despite a substantial investment of resources in outcomes improvement, optimum treatment for such patients remains unclear for practicing intensivists.
Methods: We conducted a review that highlights the most recent developments in the prevention, diagnosis, and management of infection and the evaluation of its outcomes. The review examines the prevention of infection, such as through daily bathing with chlorhexidine and the addition of probiotics to treatment regimens, and questions the previous standards of care, including the monitoring of gastric residuals and treatment of severely ill patients with drotrecogin alfa (activated). It also discusses novel approaches to the treatment of severely ill infected patients with extra-corporeal membrane oxygenation and the earlier normalization of body temperature.
Results: The development of new antibiotics continues at a slow pace, with the likelihood that alternative approaches to the management of infection, including changes in the quality of patient care, are producing needed improvements.
Conclusions: Clinical outcomes of infection are improving slowly as medical teams strive for better patient care. Lack of reimbursement is unnecessary as a punitive approach to infectious diseases.

Infection, sepsis, and septic shock continue to be the leading causes of morbidity and mortality in the intensive care unit (ICU), with a great many resources dedicated to their prevention, diagnosis, and treatment and to the evaluation of their outcomes. Improvements in the management of infection in patients at high risk for complications and adverse outcomes will most likely have roots in better quality of care, the development of new models for evaluating outcomes data, questioning of the currently accepted standards of care, the development of original ideas and design of novel trials, and the application of new treatment modalities and treatment tactics, rather than in the development of new ''wonder'' drugs. We reviewed some of the most advanced research reported during the past 12–18 months with regard to progress in the understanding and management of infectious disease.

Pathophysiology and Epidemiology

With rapid technologic advances, the development of sophisticated models for evaluating infectious processes, through genetics and statistical modeling, will be the key to evaluating properly and ultimately improving outcomes of infectious disease.

Pathogens

The prevention and control of multi-drug-resistant organisms has become a national priority, with continuing efforts being made to reduce infection and prevent the spread of drug-resistant microorganisms. Recent evidence has suggested that whole-genome sequencing may offer advantages over traditional epidemiologic methods in both of these fields of endeavor. Snitkin et al., using whole-genome sequencing [1], demonstrated the complex transmittal of carbapenemase-resistant *Klebsiella pneumoniae*, and Koser et al. [2] performed similar surveillance in the real-time tracking of methicillin-resistant *Staphylococcus aureus* (MRSA) in neonates. These techniques also show the limitations of current methods, such as antibiogram matching, in which only a minority of cases involve isolates with distinct antibiograms, with the additional problem of these isolates not always being related genetically or involved in the same transmission event.

Immune response

Despite the evolutionary distance between mice and human beings, with differences in the species' cell compositions and different temporal spans of recovery from disease, mouse models of disease have continued to dominate the scientific literature. Seok et al. [3] compared genes expressed in human conditions such as trauma, burns, infections, sepsis, and acute respiratory distress syndrome (ARDS) with those in the murine models of these conditions and found that murine models do not reflect human disease accurately, but often show a minimal or even an inverse correlation with

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such disease. Thus, for example, although there was a high degree of correlation between human trauma and human burns ($r^2 = 0.91$, 97%), and moderate correlation between endotoxemia and injuries ($r^2 = 0.47$, 88%), there was a low degree of correlation of changes in gene expression between human and mouse genes in any condition ($r^2 \leq 0.09$, 47%–63%). Mice appear to have an attenuated response to disease, being highly resilient to inflammatory change, which may result in genomic responses that are completely different from human responses. It appears as though new approaches, with a specific focus on responses to disease at the molecular level, may be required to create adequate models that could be used to reproduce human disease.

Morbidity and mortality

Ventilator-associated pneumonia (VAP) is the infection reported most commonly in the ICU, with a mean incidence exceeding 30%. It has recently been proposed as an indicator of quality of care, although efforts to reduce its incidence may sometimes be misdirected if it does not contribute to mortality in the ICU in certain populations.

Several studies have attempted to quantify the attributable mortality of ventilator associated pneumonia (VAP), yielding estimates ranging from 0–60% in critically ill patients. Melsen et al. [4] developed a new approach, labeled ''patient data meta-analysis,'' in which raw data from prospectively obtained, published trials of means for preventing VAP was used to estimate the relative risk reduction (RRR) for mortality in VAP. This eliminated confounding cluster effects for which adjustment had been made, and allowed sensitivity analysis to assess the effect of VAP. Mortality attributable to VAP was found to be 13%; however, this varied greatly for different subgroups, being 69% in surgical patients and 36% in those with illness of intermediate severity. Unexpectedly, VAP in trauma patients, medical patients, and patients with low or high Acute Physiology and Chronic Health Evaluation (APACHE) II scores had an attributable mortality of zero. Instead, a longer ICU stay, with possibly increased rates of nosocomial infections and complications secondary to invasive procedures, was found to contribute to mortality. The use of tactics for preventing VAP did not seem to affect overall mortality.

Prevention

It is crucial that cost-effective, uncomplicated interventions be identified for preventive health care.

Chlorhexidine

Blood stream infections (BSI) are a major cause of mortality and morbidity in children and adults. Bathing with chlorhexidine gluconate (CHG), with its antiseptic capabilities for decreasing microbial colonization of the skin, is a novel strategy for preventing blood stream infection. Milstone et al. [5] demonstrated a 36% decrease in the incidence of bacteremia in children given daily CHG bathing, with most of the decrease seen in patients with catheter-associated infections (32%). Climo et al. [6] in a multicenter, randomized controlled trial of bathing with CHG in adults, found a reduction of 28% in the risk of hospital-acquired infection, as well as a 31% lower rate of primary BSI and a 90% reduction in catheter-associated infections, in comparison with the rates of these conditions in a control group (0.89 with CHG bathing vs. 1.76 in the control group, $p = 0.05$). In BSI, there was a significant reduction in numbers of gram-positive organisms with CHG bathing (46% in children and 56% in adults), and such bathing also significantly reduced colonization with vancomycin-resistant enterococci (VRE) and MRSA in adults. Given the low cost of this intervention, CHG baths seem a reasonable approach to preventing BSI.

Surveillance and intervention bundles for ventilator-associated pneumonia

With VAP considered a substantial cause of morbidity and mortality, surveillance and intervention bundles have been reported as effective tools for reducing its incidence. Implementation by Rosenthal et al. [7] of the multi-dimensional approach to VAP of the International Nosocomial Infection Control Consortium (INICC) produced notable differences in the incidence of VAP (a 55.8% reduction) in both developed and developing countries, with rates three- to five-fold lower in health care settings with limited resources after the program was implemented. Multi-faceted approaches were the most successful, although without regular reinforcement efforts, the gains they produced were short-lived. Unfortunately, integration of guidelines for the prevention, diagnosis, and treatment of VAP into daily practice, has been difficult, as shown by Sinuff et al. [8], with a rate of guideline concordance at 24 mo of only 58.7% and a mean change in concordance of only 8% before commencement of the program. Instead of the one-size fits all approach to multiple institutions, perhaps a more individualized approach, with locally tailored interventions to allow for improved infection-prevention efforts, will be more successful.

Gastrointestinal tract/nutrition

The role of the gastro-pulmonary route in the pathogenesis of VAP continues to be called into question, and the hypothesis that VAP results from leakage of pooled pharyngeal bacteria around the cuff of the endotracheal tube used during assisted ventilation may be just as plausible as the gastro-pulmonary hypothesis. In either case, the overgrowth of opportunistic pathogens in critically ill patients is probably related to VAP. This ''intestinal dysbiosis'' could potentially be corrected through the administration of probiotics, including strains of *Bifidobacterium* and *Lactobacillus*. A meta-analysis done by Petrof et al. [9] showed that critically ill patients treated with probiotics had lower rates of infection (RR 0.82), including VAP (0.75), than those not so treated. Additionally, there was a trend toward decreased ICU mortality with the use of probiotics; however, no effect was found on in-hospital mortality or on ICU or hospital length of stay.

Glutamine supplementation was hoped to improve survival in critically ill patients by enhancing immunocompetence and decreasing the expression of mediators of oxidative stress. However, in a recent randomized trial Heyland et al. [10] found that glutamine supplementation resulted in significantly increased patient mortality, at 32.4% vs. 27.2% for a control population. The incidence of VAP remained unchanged in patients treated with glutamine supplements,

although there was a trend toward a decreased incidence of ICU-acquired pneumonia with the administration of antioxidants.

Monitoring of gastric residual volume has been the standard of care in critically ill patients undergoing mechanical ventilation who are at risk for regurgitation, aspiration, and VAP. Yet Reigner et al. [11] showed that gastric volume monitoring in patients receiving enteral nutrition resulted only in a decreased administration of calories rather than in any reduction in the incidence of pneumonia. In their study, although the proportion of patients who vomited was higher in the group without residual gastric monitoring than in the patients in whom such monitoring was done, the incidence of VAP in the two groups was similar, arguing against the gastropulmonary mechanism of VAP.

As a further point, nutritional support has played an integral part in the recovery of critically ill patients. When the gastrointestinal tract is functioning, enteral nutrition (EN) is recommended, yet when EN is not tolerated, it is unclear when parenteral nutrition (PN) should be initiated. Heidegger et al. [12] added PN on day 4 after admission to the treatment regimen of non-infected patients to achieve nutritional goals, and found an overall decrease in the development of nosocomial infections (27%, vs. 38% without PN, HR = 0.65), number of days of antibiotic therapy, and days on mechanical ventilation, without an increase in BSI. Parenteral nutrition as an intervention may become a strategy for improving outcomes in patients in the ICU, although the exact timing of its use remains unclear, given other data suggesting that PN may increase overall mortality.

Punitive approach

An approach taken sometimes to reducing hospital-acquired infections (HAI) is to reduce payments to healthcare systems for these events. Lee et al. [13] analyzed changes in the rates of central venous catheter-associated BSI and catheter-associated urinary tract infection (UTI) at 398 hospitals in the National Healthcare Safety Network (NHSN) before and after the implementation of a Centers for Medicare and Medicaid Services (CMS) policy denying additional payments to hospitals for these complications. They found rates comparable to those of VAP, which was not subject to the CMS policy. No evidence was found that the CMS policy had any effect on the rates of HAI either in the study hospitals or when these hspitals were compared with 1,166 hospitals not participating in the NHSN. These data indicate that a punitive approach to reducing hospital-acquired infections is not useful.

Diagnosis

Excessive use of antibiotics has been associated with the development of multi-drug-resistant organisms and complications associated with antibiotic use, including infection with *Clostridium difficile*. Proper diagnosis and the delay of antibiotic administration until objective evidence confirms infection may decrease morbidity and mortality.

Ventilator-associated pneumonia

In 2003, the U.S. Centers for Disease Control and Prevention (CDC) issued new guidelines for the diagnosis of ventilator-associated events and VAP (www.cdc.gov/nhsn/PDFs/pscManual/10- VAE_FINAL.pdf). The definitions of these events and of VAP have been designed to be objective and derived easily from the electronic health record. In brief, a ventilator-associated condition (VAC) occurs when a patient has a new deficit in oxygenation after more than 2 d of mechanical ventilation. An infection-related ventilator-associated complication (IVAC) is a VAC with general, objective evidence of infection/inflammation. An IVAC with appropriate laboratory/microbiologic testing constitutes a possible or probable VAP. Possible VAP converts to probable VAP with the appropriate level of quantified micro-organism growth, positive pleural cultures, histopathology, or any findings of *Legionella* species or positive results of virologic testing. Notably, imaging (radiologic or bronchoscopic) is excluded from these definitions. Although these new definitions and the required reporting will increase available data regarding ventilator management and ventilator-associated complications, they probably do not in fact represent the ever-elusive gold standard for the true diagnosis of VAP.

Procalcitonin

Although early initiation of antibiotic therapy is the cornerstone of treatment for bacterial infections, the overuse of antibiotics has been associated with increased drug resistance, high cost, and adverse drug reactions. The differentiation of infectious from non-infectious causes of systemic inflammation is difficult, because early signs of sepsis, such as fever, tachycardia, and leukocytosis, are non-specific. Procalcitonin (PCT) has emerged recently as a promising marker of bacterial infection because higher concentrations of this peptide are observed in bacterial infections but not in viral or non-specific inflammatory diseases. Meta-analyses by Schuetz et al. [14] and Wacker et al. [15] showed that the use of PCT in settings that ranged from the emergency department (ED) to primary-care facilities to the ICU decreased antibiotic exposure through reduced rates of prescription of these drugs and caused no change in overall mortality according to an algorithm based on PCT. Both Schuetz et al. and Wacker et al. found shorter durations of antibiotic therapy in the ED and ICU for patients with community-acquired pneumonia and VAP when PCT was considered in clinical decision-making.

Timing of antibiotic therapy

Choosing a time for the initiation of antibiotic therapy requires a complex weighing of whether to start treatment immediately after obtaining cultures (aggressive approach), knowing that this may result in the unnecessary administration of antibiotics to many uninfected patients, versus withholding antibiotics until infection is confirmed by objective data (conservative approach), knowing that this may lead to potentially harmful delays in the treatment of many patients. Hranjec et al. [16] found that, in normotensive patients with signs of ICU-acquired infection, starting antibiotic therapy only after the acquisition of objective data confirming infection reduced mortality as compared with a tactic in which antibiotic therapy was begun immediately upon the suspicion of infection. Furthermore, the latter, aggressive approach was associated with prolonged use of antibiotics, inappropriate

antibiotic administration, and other adverse effects, such as *C. difficile* infection.

Management

Some innovative treatments, such as extra corporeal membrane oxygenation (ECMO) and cooling, are proving useful in refractory septic shock, whereas the use of drotrecogin alfa has been proved ineffective even in the most severely ill infected patients.

Overall treatment

The most recent version of the guidelines of the Surviving Sepsis Campaign was published by Dellinger et al. in 2012 [17]. These guidelines should be familiar to all medical personnel who manage critically ill patients with infections. The guidelines underwent many changes since their 2008 version, including changes related to the use of corticosteroids, intensive insulin therapy, and recombinant human activated drotrecogin alfa (activated).

Drotrecogin alfa (activated)

Several studies, beginning with the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, found a decrease in mortality in patients with septic shock when they were given recombinant human drotrecogin alfa (activated), with this decrease being as large as a 6.1% in absolute mortality and 19.4% in relative mortality. A meta-analysis reported by Kalil et al. [18] in 2012 confirmed these results, with an 18% decrease in relative risk of mortality. Subsequently, however, two studies, performed by Annane et al. [19] and Ranieri et al. [20], respectively, showed that drotrecogin alfa (activated) provided no benefit in critically patients with septic shock and increased the severity of their illness. The use of drotrecogin alfa (activated) can no longer be recommended in the management of sepsis, no matter what its degree of severity.

Extracorporeal membrane oxygenation

The benefits of ECMO in rescuing patients with respiratory or cardiovascular collapse have been examined recently in adults. Mechanical circulatory assistance has been suggested for profound myocardial dysfunction, which occurs during bacterial septic shock in approximately 20% of patients. Brechot et al. [21] demonstrated that veno-arterial (VA)-ECMO was able to rescue 70% of patients who were unresponsive to conventional treatment (for whom the predicted mortality is 79%), with good results. Although several of the patients so rescued experienced the long-term consequences of limb and toe amputation, this did not seem to affect their long-term health. Moreover, ECMO did require a high degree of ICU resource utilization or a highly experienced surgical team. Veno-venous (VV)-ECMO appeared to be not as successful as VA-ECMO in reducing mortality in patients with respiratory collapse from H_1N_1-associated influenza in a cohort study done by Pham et al. [22]. In their study, survival in ECMO-treated patients was the same as in a matched group of patients treated with ECMO. Given that younger ECMO-treated patients with severe respiratory illness did have a 50% lower mortality rate in the ICU than the older group of patients in the study of Pham et al., as well as the possibility of ultra-protective ventilation strategies with a Pplat of 25 mm Hg during VV-ECMO, ECMO remains a possible treatment option for future respiratory rescue in appropriate subgroups of severely ill patients with infection.

Cooling

Fever occurs in approximately two-thirds of patients with severe sepsis. It is a direct result of tissue injury or infection, leukocyte activation, and the release of pyrogenic cytokines. To restore tissue oxygenation, external cooling of patients in the ICU has been suggested. Schortgen et al. [23] showed that reversal of shock was more common in febrile patients with septic shock when they were cooled to 36.5°– 37.0°C than in patients without cooling, with an absolute difference of 13%. A decreased need for vasopressor support was even more pronounced in patients with the highest baseline doses of such drugs. Survival was greatest at 14 d (OR 0.36) after admission in the group that underwent cooling, although no difference was seen in mortality at discharge from the ICU or hospital. Normalization of body temperature early in the course of sepsis seems to allow for earlier hemodynamic and cardiovascular oxygenation, with a potential consequent decrease in multiple organ dysfunction syndrome.

Outcomes

The Surviving Sepsis Campaign Guidelines of 2004 and 2008 promoted the bundling of appropriate elements of care for patients with sepsis into two bundles, for resuscitation and maintenance, respectively, for the purpose of standardizing interventions and reducing unintended variation in critically ill septic patients. A multi-hospital quality improvement project reported by Miller et al. [24] revealed a significant reduction in hospital mortality, from 21.2% in 2004 to 8.7% in 2010, as compliance with bundled care increased from 4.9%–73.4%. Interestingly, Levy et al. [25] documented the ways in which critical care in Europe differs from that in the United States, with significant differences in compliance with all elements of resuscitation in sepsis and bundled practices for maintenance. Yet the outcomes in Europe and the United States, when adjusted for severity of illness, suggest similar mortalities in groups of critically ill, septic patients in both locations.

Conclusion

We have reviewed some of the most important recent articles in the field of infectious diseases, especially as they pertain to critically ill patients. We have addressed advances in epidemiology, including data collection, the appropriateness of animal models, and new statistical analyses; preventive strategies with VAP bundling and the need for adequate nutrition; proper diagnosis in the face of a continuing lack of gold standards for the diagnosis of common infections including pneumonias; and the benefits to treatment of delaying antibiotic administration, providing ECMO or active cooling, and many other measures. In an era in which strict CMS policies provide financial disincentives for the failure to reduce rates of infection, these medical advances show the inherent desire of medical practitioners to improve medical care and strive for better patient outcomes. In the future, and in view of the benefits of oversight, establishment of strict protocols, and the appropriate collection

and assessment of data, punitive action against hospitals with subpar outcomes may not be needed if they implement plans for improving the management and outcomes of infection.

Author Disclosure Statement

The authors declare no conflicts of interest.

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