Update on infections in ICU patients

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Studies carried out in 2006 on severe community-acquired pneumonia or nosocomial pneumonia requiring admission to the ICU are numerous and of a high quality. Among studies of community-acquired pneumonia, the most relevant are those focused on the development and evaluation of systems for the identification of patients with severe pneumonia, analysis of the impact of the initial inflammatory response on the course of the disease, and level of adherence to therapeutic guidelines proposed by different scientific societies. Among studies of nosocomial pneumonia, those involving ventilator-associated pneumonia and health care-associated pneumonia should be emphasized. The reliability of different respiratory sampling methods for the etiological diagnosis of pneumonia, the impact of different etiological agents, and the efficacy of prophylactic measures have been the object of different investigations. Important aspects of these studies include the assessment of different strategies in the use of antimicrobial agents to decrease the selection of multiresistant pathogens. Moreover, early identification of patients at risk of invasive fungal infections, as well as preemptive treatment of these infections in selected patients have been topics of increasing interest.

Key words: **Infections. ICU. Update.**

Actualización sobre infecciones en pacientes de la UCI

Los estudios realizados en 2006 sobre la neumonía extrahospitalaria grave o la neumonía nosocomial que requieren el ingreso en la UCI son numerosos y de gran calidad. Entre los trabajos sobre la neumonía extrahospitalaria, los más relevantes son los que se basan en el desarrollo y la valoración de los sistemas para identificar a los pacientes con neumonía grave, en el análisis del impacto de la respuesta inflamatoria inicial sobre el curso de la enfermedad, y en el nivel de seguimiento de las normas terapéuticas propuestas por diferentes sociedades científicas. Entre los estudios sobre la neumonía nosocomial, cabe destacar los relacionados con la neumonía asociada al respirador o a la asistencia sanitaria. La fiabilidad de los distintos métodos para obtener muestras respiratorias con el fin de establecer el diagnóstico etiológico, el impacto de los diferentes agentes etiológicos, y la eficacia de las medidas profilácticas, han sido objeto de diversas investigaciones. Entre los aspectos importantes de estos estudios se halla la valoración de las diferentes estrategias para el uso de los agentes antimicrobianos con el fin de reducir la selección de los gérmenes plurirresistentes. Además, la identificación precoz de los pacientes con riesgo de infecciones micóticas invasivas, así como el tratamiento precoz de estas infecciones en determinados pacientes, han sido otros tantos temas de interés general.

Palabras clave: **Infecciones. UCI. Actualización.**

State of the art

In 2006, many studies on community- and nosocomially-acquired infections affecting critically ill patients[1-27] were published. Their objective was to improve the clinical management of patients with infections in order to reduce

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infection-related mortality and morbidity. All of the studies focus on the following: *a)* designing strategies for early identification of patients with infection using infection markers, particularly in infections associated with high mortality (pneumonia, bacteremia)[1,2,6-8,11,19-22]; *b)* establishing and evaluating recommendations to optimize the management of patients with severe sepsis or septic shock[3-5,16-18]; *c)* improving the use of antimicrobials to diminish the selection pressure on multidrug-resistant pathogens[13-15], and *d)* evaluating preventive measures to reduce the incidence of nosocomial infections caused by bacteria or fungi[9,10,12,23-27].

Identification of an infection in a critically ill patient implies the initiation of empirical therapy with 1 or more antibiotics. Diagnosis of infection is sometimes difficult, as the expression of the signs and symptoms of infection might not be clear enough or might be caused by a noninfectious process. However, when a severe infection does exist, early administration of empirical therapy and appropriateness of the antimicrobials selected are related to improved survival. The availability of infection markers that are sensitive and specific enough would aid decision-making–particularly in the more complex cases in which diagnosis is uncertain–and could help to avoid unnecessary delays in the prescription of antimicrobial therapy. Studies using markers such as procalcitonin and C reactive protein are an important starting point that might be useful not only for the initiation of empirical therapy, but also for the evaluation of the response and for deciding when to stop or change antimicrobial therapy[19-22]. However, more studies are needed to find a suitable place for such markers in daily clinical practice and to demonstrate that their use on a routine basis is really of benefit to infected patients. In other scenarios, such as invasive fungal infections (candidemia, systemic candidosis), in which such markers do not help decision-making, risk indexes such as the *Candida* score have been developed. This index, based on clinical and microbiological data, establishes the risk of fungal infection for individual patients and proposes that antifungal therapy be initiated as pre-emptive therapy in the highest-risk groups, even before the fungal infection has been proven[12]. This score should be validated prospectively, and its real clinical usefulness has yet to be demonstrated.

The development of guidelines for the treatment of infections represents an important improvement in the management of critically ill patients. The adaptation of the guidelines to local epidemiology (center and unit) further increases the probability that patients will receive appropriate therapy. The impact of adherence to these guidelines has recently been proved in patients with ventilator-associated pneumonia and community-acquired pneumonia[3,4]. However, the management of infection in the presence of severe sepsis or septic shock involves measures that go beyond the scope of antimicrobial therapy. A set of therapeutical measures has recently been proposed for these patients. Some should be administered during the first 6 hours, and the rest during the first 24 hours after diagnosis of the infectious process. These recommendations are original in that they are accompanied by a campaign–the Surviving Sepsis Campaign–aimed at the diffusion and implementation of the measures in hospitals, with the objective of reaching a 25% reduction in the mortality of severely infected patients. Some studies performed to evaluate the application of the campaign are now being published, and relevant benefits in terms of mortality, hospital and ICU stay, and costs are being observed[16,18]. In parallel, severity indexes that allow stratification of the risk of death based on clinical data on admission are being developed for some syndromes, such as community-acquired pneumonia[1]. These indexes help to select which patients would benefit from a more aggressive approach from the onset of infection.

The main risk for antimicrobial use in critically ill patients is multidrug resistance. The risk for the development of resistance in certain bacteria increases when the same antimicrobial or family of antimicrobials is used for long periods of time and when dosing is suboptimal (subinhibitory concentrations at the focus of infection). Duration of antimicrobial therapy is not well established for most types of severe infection. Thus, antimicrobials are often administered for 2 or 3 weeks, particularly in the case of bacteremia, abscesses, empyema, etc. The use of sympathicomimetic drugs (dopamine, noradrenaline) and diuretics increases the clearance of antibiotics, while many other circumstances increase the distribution volume for most drugs. In both cases, there is a high probability that the concentration of antimicrobials at the focus of infection is suboptimal if antimicrobials are administered at current recommended doses. Recognition of the need to use pharmacokinetic and pharmacodynamic parameters to adjust dosing in the most severely ill patients is one of the most significant recent improvements in the management of infection. Regrettably, the possibility of using plasma concentrations is limited to aminoglycosides and vancomycin in the case of antimicrobials, while blood level motoring is used only used in research protocols for the other most common antimicrobials but not as a clinical tool. In order to minimize the risk of resistance associated with overuse of a specific family of antimicrobials, cycling strategies have been proposed. Even though the rationale for such an approach is reasonable, the studies performed to evaluate their efficacy are confusing and not very reassuring. Antibiotic cycling has been proposed in different ways (successive restriction of a certain family over a period of several months, preferred use of a specific antimicrobial for different periods, consecutive changes of antimicrobials) with diverse levels of adherence[13-15]. Criteria used to evaluate the intervention have not been homogeneous, and, when the rate of multidrug-resistant pathogen has been used as an outcome measure, the results indicate that the strategy does not control the imported resistant pathogens (not covered by the antibiotic policy in the ICU) or the cross-transmission of these pathogens, which are frequent in ICUs. At present, this strategy cannot be recommended in routine clinical practice and should be limited to well-designed research protocols that evaluate its potential.

Between 10 and 15% of critically ill patients may develop a new infection during their hospital stay. Ventilator-associated pneumonia and primary catheter-related bloodstream infections are the most frequent. The fact that these infections are associated with high morbidity and mortality explains why different preventive strategies to reduce their frequency are being investigated. Oropharyngeal decontamination with antiseptic solutions (chlorhexidine) and the use of topical nonabsorbable antimicro-

bials (tobramycin, polymyxin B, and amphotericin B deoxycholate) have been the most frequently studied[23-25]. Accordingly, there is evidence that this measure is effective in reducing both VAP and other nosocomial infections. Regrettably, the implementation of this measure has not been generalized in ICUs, probably because of difficulties with their routine use, such as the lack of commercial preparations and the need for in-house preparation, the need for surveillance cultures to evaluate their efficacy and detect resistant organisms early, the data concerning the emergence of resistant gram-positive bacteria, and the absence of data that unequivocally demonstrate an impact on mortality. Some centers that have been using this strategy for years have reported that nonabsorbable antibiotic solutions did not select resistant flora, and even that the strategy has favored the emergence of resistance[25]. Persistent rates of VAP above 10 episodes per 1,000 mechanical ventilation days should prompt a review of the procedures followed in patients under mechanical ventilation, and, in the case of no improvement, the possibility of implementing this preventive strategy should be evaluated. The use of systemic antibiotics or antifungals to prevent infections is only indicated if the risk of infection is high and the number needed to treat or prevent a case is low, e.g. in patients with a low level of consciousness who need intubation, or in patients with multifocal colonization with Candida who have a long hospital stay and receive broad-spectrum antimicrobials[27].

The most relevant articles of the last year, selected for discussion were the following:

Community-acquired pneumonia

España PP, Capelastegui A, Gorordo I, Esteban C, Oribe M, Ortega M, et al. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. Am J Resp Crit Care Med. 2006;174:1249-56.

In this study, a clinical prediction rule for identifying patients evolving to severe community-acquired pneumonia (SCAP) (mortality, need for mechanical ventilation, septic shock) after evaluation in the emergency department was developed and validated in an internal cohort and in an external multicenter cohort. The variables associated with SCAP in the multivariate analysis were pH < 7.30, systolic blood pressure < 90 mm Hg, respiratory rate > 30 breaths per minute, altered mental status, blood urea nitrogen > 30 mg/dl, oxygen arterial pressure < 54 mm Hg or ratio of arterial oxygen pressure to fraction of inspired oxygen < 250 mm Hg, age ≥ 80, and multilobar/bilateral lung involvement. The multivariate model results were used to assign a score to each variable. The rule showed better prediction for SCAP than previous rules.

Comments

This study provided a rule that proved useful for identifying patients with an increased risk of developing SCAP. The 8 parameters in the rule can be used easily when evaluating patients with community-acquired pneumonia. While previous rules (CURB-65, PSI) identified patients at risk of death, this rule adds clinically useful information because it may identify patients who would benefit from more aggressive management.

Dremsizov T, Clermont G, Kellum JA, Kalassian KG, Fine MJ, Angus DC. Severe sepsis in community-acquired pneumonia. When does it happen, and do systemic inflammatory response syndrome criteria help predict course? Chest. 2006;129:968-78.

The ability of the systemic inflammatory response syndrome (SIRS) at presentation to predict progression to severe sepsis, septic shock or death, and onset and timing of severe sepsis (new onset acute organ dysfunction) during hospitalization in patients with community-acquired pneumonia (CAP) was investigated in a multicenter cohort study; 34% of patients presented at the emergency department with severe sepsis and 2% with septic shock; 48% and 4.4% of patients had severe sepsis and septic shock at some point during hospitalization, respectively. SIRS on admission was present in 82% of patients, but it was not associated with increased risk of progression to severe sepsis, shock, or death.

Comments

These results suggest that the presence of SIRS on admission does not predict subsequent severe sepsis, septic shock or death in CAP, and challenge the importance of early identification and management of patients with SIRS. However, clinical management might be an uncontrolled confounder in this study (patients with SIRS might have been more aggressively managed). It is remarkable that severe sepsis was present on admission in one third of patients who were admitted with CAP.

Mortensen EM, Restrepo MI, Anzueto A, Pugh JA. Antibiotic therapy and 48-hour mortality for patients with pneumonia. Am J Med. 2006;119:859-64.

The authors analyzed the impact of guideline-concordant antibiotic therapy (GCAT) on mortality during the first 48 hours after admission in patients with CAP in a retrospective cohort study. Mortality at 48 hours was 2.5%. After adjusting for potential confounders, including a propensity score for receiving GCAT, the use of GCAT was significantly associated with decreased mortality at 48 hours.

Comments

While most previous studies evaluating the impact of antimicrobial therapy in patients with CAP evaluated crude or in-hospital mortality, this observational study is the first to show that prescribing antibiotic therapy following the ATS/IDSA guidelines is associated with a significant benefit in terms of very early mortality, and further reinforces the need for careful choice of antimicrobial therapy in these patients.

Shorr AF, Bodi M, Rodríguez A, Sole-Violan J, Garnacho-Montero J, Rello J, for the CAPUCI Study Investigators. Impact of antibiotic guideline compliance on duration of mechanical ventilation in critically ill patients with community-acquired pneumonia. Chest. 2006; 130: 93-100.

A cohort of surviving patients with SCAP (admitted to the ICU because of CAP) was retrospectively evaluated to assess the impact of antimicrobial therapy (compliant or not with IDSA guidelines) on the duration of mechanical ventilation (MV). After controlling for confounders in a multivariate hazard model, noncompliance with IDSA regimens was associated with longer duration of MV. The adjusted duration of MV in patients receiving a regimen that did not adhere to IDSA recommendations was 3 extra days.

Comments

The results of this limited study emphasize the benefits of following IDSA guidelines in the treatment of SCAP beyond the impact on survival. The effect is probably associated with more adequate pathogen coverage, but the fact that following the guidelines is a surrogate marker for a higher quality of care cannot be ruled out.

Health care-associated pneumonia

Clec'h C, Jauregui F, Hamza L, Karoubi P, Fosse JP, Hamdi A, et al. Agreement between quantitative cultures of postintubation tracheal aspiration and plugged telescoping catheter, protected specimen brush, or BAL for the diagnosis of nosocomial pneumonia. Chest. 2006;130:956-61.

The authors compared the usefulness of quantitative cultures (threshold, 105 cfu/ml) of postintubation tracheal aspiration (PITA) with the reference methods (RM) (protected specimen brush, bronchoalveolar lavage, or plugged telescoping catheter procedures) in the diagnosis of nosocomial pneumonia in 44 non-mechanically-ventilated patients needing intubation. The concordance of PITA with RM results was 0.71 (k-statistic). The sensitivity, specificity, positive and negative likelihood ratios of PITA and RM were 77 and 75%, 84 and 88%, 4.80 and 6.25, 0.27 and 0.28, respectively.

Comments

This is the first study evaluating PITA. It proved to be a useful, simple, cheap, and readily available tool in this specific subset of patients with nosocomial pneumonia needing intubation. While this technique merits further evaluation, it would also be very interesting to assess whether rapid results from PITA (e.g, Gram stain) would be useful for guiding empirical antimicrobial therapy.

Jeffres MN, Isakow W, Doherty JA, McKinnon PS, Ritchie DJ, Micek ST, et al. Predictors of mortality for methicillin-resistant *Staphylococcus aureus* health-care-associated pneumonia. Specific evaluation of vancomycin pharmacokinetic indices. Chest. 2006;130:947-55.

The impact of vancomycin pharmacokinetic parameters (trough levels and AUC values) on the mortality of patients with pneumonia due to MRSA was retrospectively evaluated in 102 patients diagnosed by BAL and treated with vancomycin in monotherapy. In-hospital mortality was 34%. There were no significant differences between survivors and non-survivors in terms of pharmacokinetic parameters; stratification of vancomycin trough concentrations and AUC values did not show any relationship with mortality.

Comments

Data from observational studies and randomized trials show a high mortality rate in patients treated with vancomycin. Limited tissue concentration of vancomycin in the lungs, slow bactericidal activity, and higher MICs for MRSA have been proposed to explain these results, and a dose-adjusting approach to achieve serum trough concentrations of 15-20 µg/mL has been recommended. The results of this retrospective study, which includes patients diagnosed with MRSA pneumonia using BAL and treated with standard vancomycin dosing, do not support the idea that adjusting the dose of vancomycin to achieve higher serum concentrations is associated with improved prognosis. Another interesting result is the huge variability in the pharmacokinetic parameters of vancomycin in patients.

Shorr AF, Combes A, Kollef MH, Chastre J. Methicillin-resistant *Staphylococcus aureus* prolongs intensive care unit stay in ventilator-associated pneumonia, despite initial appropriate antibiotic therapy. Crit Care Med. 2006;34:700-6.

This study analyzes whether ventilator-associated pneumonia (VAP) due to methicillin-resistant *S. aureus* (MRSA) is associated with prolonged ICU stay in comparison with methicillin-susceptible *S. aureus* (MSSA). Surviving patients included in different randomized trials of VAP who received appropriate therapy within 24 hours of bronchoscopy were included and retrospectively analyzed; 107 patients were studied, 69 with MSSA and 38 with MRSA. Patients with MRSA were treated with vancomycin. Using a Cox proportional hazard model and controlling for potential confounders, the authors associated VAP due to MRSA with double the probability of needing continued ICU care.

Comments

The results of this study, which adequately controlled many potential confounders (including appropriate antimicrobial treatment) and included only patients with *S. aureus* VAP diagnosed by bronchoscopic techniques, further confirm that MRSA is more commonly associated with increased morbidity than MSSA and underline that controlling MRSA is very relevant from both clinical and financial perspectives. As all patients with MRSA were treated with vancomycin, the results might also be interpreted in the sense that therapy of VAP due to MRSA with vancomycin is unsatisfactory.

Bloodstream infections and catheter-related infections

Garrouste-Orgeas M, Timsit JF, Tafflet M, Misset B, Zahar JR, Soufir L, et al. Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. Clin Infect Dis. 2006;42:1118-26.

This multicenter prospective matched cohorts study investigated the impact of ICU-acquired bloodstream infection (BSI) on hospital mortality. Exposed patients were those with BSI after 3 days of ICU admission; unexposed patients were those who did not have BSI. Matching criteria included the TRIO score on admission and the previous length of ICU stay. Attributable mortality was 24.8%; the adjusted OR for hospital mortality was 3.02 (95% CI, 2.17-4.22). The ORs varied substantially according to microorganisms, timing of BSI, source, and appropriateness of therapy; catheter-related BSI and coagulase-negative staphylococci had no impact on mortality.

Comments

The results of this large, well-designed study have many implications. First, ICU-acquired BSI is associated with a 3-fold increase in the risk of death. Most studies on the prevention of BSI in ICU patients examine catheter-related BSI. However, considering that the impact is relevant for non-catheter-related BSI, efforts aimed at understanding and prevention should also be directed towards other sources of BSI. Second, the adjusted OR for mortality in patients receiving inappropriate empirical therapy was higher than in patients receiving appropriate therapy. And third, some microorganisms had a greater impact on mortality. Thus, these results emphasize the fact that the prognosis of BSI in ICU patients is heterogeneous according to source, microorganism, and timing.

Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc. 2006;81:1159-71.

This systematic review of 200 prospective studies evaluates the risk of infection with various types of intravascular devices (IVDs). The risk of BSI for every type of IVD differed substantially if expressed as the number of BSI per 100 IVDs or per 1000 IVD-days. Incidence-density rates of BSI were higher in the following types: peripheral IV catheters, steel needles, and venous cutdown catheters; short-term central venous catheters, pulmonary artery catheters, silver-impregnated catheters, and benzalkonium chloride catheters; hemodialysis catheters, temporary, non-cuffed catheters; and intra-aortic balloon pumps.

Comments

Even considering the heterogeneity of populations, potential impact of confounding factors, and other limitations, this study provides useful benchmarking data for specific types of IVD.

Staphylococcus aureus

Huang SS, Yokoe DS, Hinrichsen VL, Spurchise LS, Datta R, Miroshnik I, et al. Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2006;43:971-8.

This study retrospectively evaluated the effect of 4 consecutive infection control interventions on the rate of MRSA bacteremia in ICU patients during a 9-year period using an interrupted time series design and segmented regression analysis. The interventions were promotion of compliance with maximum sterile barrier precautions for placement of central venous catheter, institution of alcohol-based hand rubs, a hand hygiene campaign, and the institution of nares surveillance cultures for MRSA in all patients admitted to ICUs and weekly thereafter (positive cultures resulting in the initiation of contact isolation precautions). While the first 3 interventions were not associated with significant changes in the rate of MRSA bacteremia, active surveillance cultures and consequent isolation precautions resulted in a 67% reduction in the incidence density of MRSA bacteremia both in ICU and non-ICU patients, while the incidence density of MSSA bacteremia remained unchanged.

Comments

The results of this study indicate that significant reductions in MRSA in bacteremia could only be achieved by the implementation of active surveillance–a specific measure aimed at controlling MRSA–and not by other general measures. It is remarkable that this measure, although only performed in ICUs, also caused a reduction in MRSA bacteremia rates outside ICUs, thus underlining the strategic role of the ICU in nosocomial MRSA. At present, active surveillance for MRSA in all ICU patients is considered standard of care.

Oztoprak N, Cevik MA, Akinci E, Korkmaz M, Erbay A, Eren SS, et al. Risk factors for ICU-acquired methicillin-resistant Staphylococcus aureus infections. Am J Infect Control. 2006;34:1-5.

Risk factors for acquisition of MRSA infection in the ICU were investigated in a cohort of 249 patients who underwent surveillance cultures on admission and weekly thereafter; 23.7% of patients became colonized in the ICU, and 8.4% developed an infection due to MRSA (> 50% had been detected as previously colonized). Multivariate analysis disclosed the following independent risk factors: length of ICU stay, central venous catheter insertion, previous antibiotic use, and presence of > 2 colonized patients at the same time.

Comments

"Colonization pressure" (the percentage of colonized patients) has been noted as a very relevant risk factor for acquisition of colonization by MRSA and other antibiotic-resistant organisms in previous studies. In this study, colonization pressure (measured as a dichotomous variable

using a threshold of > 2) was a risk factor for MRSA infection. These data provide further evidence for the need to control MRSA.

Candida

León C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Álvarez-Lerma F, et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med. 2006;34:730-7.

This multicenter prospective cohort study investigated the incidence rates for *Candida* colonization (detected by surveillance cultures of tracheal aspirates, pharyngeal exudates, gastric aspirates, and urine, which were performed weekly) and infection, and the variables associated with increased risk for proven *Candida* infection. *Candida* colonization was detected in 51.9% of patients and *Candida* infection was proven in 5.7%. Four variables were independently associated with *Candida* proven infection: multifocal colonization, parenteral nutrition, surgery, and severe sepsis. A scoring system with a sensitivity of 81% and a specificity of 74% was developed.

Comments

This study provides an interesting prediction rule for *Candida* infection in ICU patients that might be useful when considering early antifungal therapy. However, the rule should be validated in an external cohort. The need to perform weekly surveillance cultures to detect multifocal colonization is a problem; as this practice is time-consuming and costly, it would be necessary to investigate whether the use of this rule has a significant impact on mortality, morbidity and/or cost.

Montravers P, Dupont H, Gauzit R, Veber B, Auboyer C, Blin P, et al. *Candida* as a risk factor for mortality in peritonitis. Crit Care Med. 2006;34:646-52.

The role of *Candida* in the prognosis of peritonitis was investigated in this study using a matched case-control design. Mortality in cases (patients with isolation of *Candida* during surgery for peritonitis) was compared with controls (patients without *Candida*), matched by age, SAPS II, community or nosocomial acquisition, and length of stay. Mortality was similar among cases and controls with community-acquired peritonitis, but was significantly higher among cases with nosocomial peritonitis. Presence of *Candida* was a risk factor for mortality in nosocomial peritonitis in the multivariate analysis, although antifungal therapy did not show any protective effect.

Comments

The role of some microorganisms in intraabdominal mixed infections is controversial. The results of this study suggest that, as is the case with enterococci, isolation of *Candida* is associated with worse prognosis only in patients with nosocomial peritonitis; however, antifungal treatment did not show a beneficial effect. More studies are needed to assess the role of *Candida* and to evaluate the real need for antifungal therapy in these patients.

Strategies in antibiotic policy to decrease the selection of multiresistant pathogens

Martínez JA, Nicolás JM, Marco F, Horcajada JP, García-Segarra G, Trilla A, et al. Comparison of antimicrobial cycling and mixing strategies in two medical intensive care units. Crit Care Med. 2006; 34:329-36.

This prospective, open-label, and comparative study analyzes the impact of mixing vs. cycling strategies with 4 antibiotic families that are active against P*seudomonas aeruginosa* in the selection of resistance in gram-negative bacilli in patients admitted to 2 medical ICUs. Cycling was accomplished by prescribing 1 of these antibiotics for 1 month each. Mixing was accomplished by using the same order of antibiotic administration on consecutive patients. Surveillance samples were obtained 3 times a week. Differences in the rates of ICU-acquired infection or infections caused by potentially resistant gram-negative pathogens were not observed. The finding of a higher proportion of cefepime-resistant *P. aeruginosa* in the mixing strategy leads the authors to conclude that cycling of the antibiotics for 1 month each is a better strategy.

Comments

Although the conclusion drawn by the authors is based on significant differences in the presence of cefepime-resistant *P. aeruginosa* strains, it should be accepted with caution. Adherence to antibiotic recommendations was limited (particularly in the cycling phase), the study period is limited to 8 months, the number of patients is small (n = 346), and 2 different ICUs of the same hospital participated in the study. Furthermore, molecular studies confirming the selection and excluding invasion of a *P. aeruginosa* strain with a resistance pattern different from the initial resistance pattern were not performed.

Sandiumenge A, Díaz E, Rodríguez A, Vidaur L, Canadell L, Olona M, et al. Impact of diversity of antibiotic use on development of antimicrobial resistance. J Antimicrob Chemother. 2006;57:1157-204.

Over a 44-month study period, 4 different strategies of empirical antibiotic administration for the treatment of ventilator-associated pneumonia were compared, and the impact on the development of resistance to 4 different microorganisms was assessed. Strategies for the homogenization of antibiotics by restriction or prioritization of specific drugs have been associated with an increase in the isolation of multiresistant pathogens.

Comments

This study demonstrates that the best strategy to limit the selection of multiresistant pathogens is diversification of antibiotics in order to avoid the predominance of 1 particular drug in daily use. In addition, the study shows the difficulties in controlling other factors that may influ-

ence the results, such as invasion of multiresistant pathogens from other hospital areas or other centers.

Merz LR, Warren DK, Kollef MH, Fridkin SK, Fraser VJ. The impact of an antibiotic cycling program on empirical therapy for Gram-negative infections. Chest. 2006;130:1672-80.

It is unknown whether application of antibiotic cycling strategies every 3 or 4 months to prevent the selection of multiresistant pathogens may affect inappropriate empirical treatment of gram-negative infections acquired in a medical ICU. Over a surveillance period of 28.5 months, the authors demonstrate that the rates of inappropriate empirical treatment were similar for the pre-cycling and cycling periods (15 vs. 10%, $P = 0.4$).

Comments

This study shows once again the effect of inappropriate treatment of ICU-acquired gram-negative infections on mortality (67 vs. 32%, $P < 0.001$). Differences in inappropriate treatment between a baseline phase and a phase in which the cycling strategy was used were not found, although the number of infections assessed is very small (less than 200 cases overall for both periods).

Optimization of treatment of severe sepsis and septic shock

Micek ST, Roubinian N, Heuring T, Bode M, Williams J, Harrison C, et al. Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med. 2006;34:2707-13.

This study was conducted to assess the impact of standardization of treatment for septic shock in an emergency department. Using a before-and-after design in 120 consecutive patients with septic shock, the authors observed an improvement in the management of these patients (administration of fluids, use of appropriate antibiotics) in the second period, which resulted in a shorter hospital stay (12.1 ± 9.2 vs. 8.9 ± 7.2 days; $P = 0.038$) and lower risk of 28-day mortality (48.3 vs. 30%; $P = 0.040$).

Comments

This study shows the importance of implementing an order set for the management of septic shock in an emergency department. Although this was a single-center study and not all aspects of treatment were improved, the results obtained allowed the authors to recommend implementing the order set in daily practice to optimize the general and multidisciplinary treatment of patients with septic shock.

Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589-96

The authors retrospectively reviewed a total of 2731 patients with septic shock diagnosed in 14 ICUs and 10 hospitals in Canada and the United States between 1989 and 2004. The main objective was to assess the duration of hypotension before starting effective antimicrobial treatment and to establish a relationship with survival during hospitalization. The administration of effective treatment within the first hour of hypotension was associated with 79.9% survival. For each hour of delay in administering effective therapy, hospital survival decreased by 7.6%. In this study, only 50% of patients received effective antimicrobial treatment within the first 6 hours.

Comments

There is a clear relationship between duration of hypotension, effective antibiotic treatment, and hospital mortality. The information provided by this study confirms the need for early and effective antibiotic treatment in septic shock-associated infections. Although this is a retrospective multicenter study, probably with differences in the management of shock between the participating hospitals, timely administration of antibiotics as a crucial aspect in the management of patients with septic shock is a very relevant conclusion.

Trzeciak S, Dellinger RP, Abate NL, Cowan RM, Stauss M, Kilgannon JH, et al. Translating research to clinical practice. A 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. Chest. 2006; 129:225-32.

The authors analyzed the use of early goal-directed therapy (EGDT) for septic shock in the emergency department in a collaborative study between the emergency medicine and critical care services. In 20 of the 22 patients with septic shock treated according to EGDT, all endpoints in the first 6 hours were achieved. In a comparison of these results with 16 historical control cases, there was a nonsignificant decrease in mortality (43.8 vs. 18.2%; $P = 0.09$) and in ICU pulmonary artery catheter utilization.

Comments

This study demonstrates that collaboration between emergency medicine and critical care services achieves fulfillment of more than 90% of endpoints of septic shock therapy within the first 6 hours. This has an important impact on posterior treatment in the ICU. The low number of cases included in the study and the retrospective comparison with historical control cases are the main limitations. The conclusion, however, is relevant for clinicians.

Markers of sepsis

Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med. 2006;34:1996-2003.

The objective of this meta-analysis was to determine the usefulness of procalcitonin as a diagnostic marker of sep-

sis, severe sepsis, or septic shock in adult patients admitted to the ICU or in post-surgical or post-trauma patients. The secondary objective of the study was to compare the diagnostic reliability of procalcitonin and C-reactive protein. Based on data collected from 15 studies, the diagnostic accuracy of procalcitonin (OR = 15.7, 95% CI 9.1 ± 27.1) was higher than that of C-reactive protein (OR = 5.4, 95% CI 3.2 ± 9.2) ($P < 0.001$); the difference was even higher when only blinded studies were considered.

Comments

Procalcitonin is a good biological marker of sepsis, severe sepsis, or septic shock, better in this clinical setting than C-reactive protein. Accordingly, this marker should be included in diagnostic protocols of sepsis in ICU clinical practice. The main limitation is the definition of the cut-off values and the low implementation in emergency laboratories. The usefulness of procalcitonin in decision-making has yet to be assessed.

Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med. 2006;34:596-602.

This observational study prospectively assessed the usefulness of serum procalcitonin levels as a predictor of mortality in critically ill patients. A total of 472 patients undergoing daily measurements of procalcitonin were included in the study. It was observed that high levels of procalcitonin and increasing levels from the first measurement were independent predictors of all-cause of mortality in a 90-day follow-up period after admission to the ICU. The relative risk for mortality in ICU increases for every day that procalcitonin increases. Levels or increases in C-reactive protein and white blood cell count do not seem to predict mortality.

Comments

According to the results of this study, an increase in procalcitonin > 1 ng/mL can identify patients at high risk of death in a 90-day follow-up period. Daily assessment of procalcitonin may allow the intensivist to identify patients with high-risk infections before the development of serious complications. However, new prospective intervention studies are needed to demonstrate the possibility of decreasing mortality by means of targeted antibiotic treatment according to procalcitonin levels.

Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia. A randomized trial. Am J Resp Crit Care Med. 2006;174:84-93.

This intervention and randomized study assessed the value of serum procalcitonin levels as a guide for the initiation and duration of antibiotic therapy in community-acquired pneumonia. A group of 151 patients treated with antibiotics according to usual practice was compared with a group of 151 patients in which antibiotics were only administered if the procalcitonin level was > 0.25 µL and antibiotic use was discontinued when procalcitonin levels were lower than 10% of baseline values. Although the clinical result was similar in both groups (3%), in the serum-level group, there was a reduction in total exposure to antibiotics (relative risk 0.52, 95% CI, 0.48 ± 0.55; $P < 0.001$), antibiotic prescriptions on admission (85 vs. 99%; $P < 0.001$), and antibiotic treatment duration (median, 5 vs. 12 days; $P < 0.001$) compared with patients treated according to the guidelines.

Comments

Antimicrobial treatment of community-acquired pneumonia guided by serum concentrations of procalcitonin is associated with a decrease in the use of antibiotics because of the possibility of stopping treatment early. Although this therapeutic strategy may have important clinical and public health implications, a careful clinical assessment can never be substituted by determination of serum procalcitonin levels. It is necessary to design multicenter studies with a large population to validate these results.

Charles PE, Dalle F, Aho S, Quenot JP, Doise JM, Aube H, et al. Serum procalcitonin measurement contribution to the early diagnosis of candidemia in critically ill patients. Intensive Care Med. 2006;2: 577-83.

The value of serum procalcitonin levels for early differentiation of bacteremia from candidemia in non-neutropenic critically ill patients admitted to the ICU was studied in a low number of patients. Procalcitonin levels were found to be markedly higher in patients with bacteremia than in those with candidemia. Moreover, a low procalcitonin value was found to be an independent predictor of candidemia in the study population. A procalcitonin level greater than 5.5 ng/mL yielded a 100% negative predictive value and a 65.2% positive predictive value for candidemia-related sepsis.

Comments

Although the results of this study suggest that procalcitonin values can be used as an alternative in the suspicion/exclusion diagnosis of candidemia, the characteristics of the study (retrospective, small number of patients, high number of patients excluded, and single center) are important limitations for the applicability of results.

Prevention of nosocomial infections

Segers P, Speekenbrink RG, Ubbink DT, van Ogtrop ML, de Mol BA. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial. JAMA. 2006; 296:2460-6.

In a prospective, randomized, double-blind, controlled trial, the authors have assessed the efficacy of perioperative decontamination of the nasopharynx and oropharynx

with 0.12% chlorhexidine gluconate for reduction of nosocomial infection after cardiac surgery. The incidence of nosocomial infection in the chlorhexidine gluconate group and placebo group was 19.8 and 26.2%, respectively (P = 0.002). In particular, lower respiratory tract infections and deep surgical site infections were less common in the chlorhexidine gluconate group than in the placebo group (P = 0.002). For 1 episode of nosocomial infection to be prevented, 16 patients had to be treated with chlorhexidine gluconate.

Comments

Decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate seems effective for reducing nosocomial infections after cardiac surgery, particularly pneumonia and surgical wound infection. Given that this method is safe and inexpensive, it can be recommended for use in daily practice in patients undergoing heart surgery.

Koeman M, van der Ven AJ, Hak E, Joore HC, Kaasjager K, de Smet AGA, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Resp Crit Care Med. 2006;173:1348-55.

The authors evaluated whether oral decontamination with chlorhexidine (CHX, 2%) or CHX/colistin (CHX/COL, 2%/2%) would reduce and postpone development of ventilator-associated pneumonia and oral and endotracheal colonization. The daily risk of ventilator-associated pneumonia was reduced in both treatment groups compared with placebo: 65% for CHX (P = 0.012) and 55% for CHX/COL (P = 0.030). CHX/COL provided significant reduction in oropharyngeal colonization with both gram-negative and gram-positive microorganisms, whereas CHX mostly affected gram-positive microorganisms. Endotracheal colonization was reduced for CHX/COL patients and to a lesser extent for CHX patients. No differences in duration of mechanical ventilation, ICU stay, or ICU survival could be demonstrated.

Comments

The results of this study demonstrate the effectiveness of chlorhexidine 2% alone or combined with colistin in reducing the incidence of ventilator-associated pneumonia, so that application of oral decontamination with these products every 6 h should be recommended in clinical practice. It should be noted that a decrease in the duration of mechanical ventilation, ICU stay, or ICU mortality was not observed, although these were not endpoints of the study.

Heininger A, Meyer E, Schwab F, Marschal M, Unertl K, Krueger WA. Effects of long-term routine use of selective digestive decontamination on antimicrobial resistance. Intensive Care Med. 2006;32: 1569-76.

Over a period of 5 years, this study compared the distribution of different species of bacteria and their multiresistance markers identified in an ICU in which selective digestive decontamination had been implemented with that used in the participating ICUs of the "Surveillance of Antimicrobial Use and Antimicrobial Resistance in German Intensive Care Units" project. The authors concluded that the routine use of selective digestive decontamination in the study ICU was not associated with an increase in gram-negative rods and that it was even lower for Pseudomonas aeruginosa, whereas a relative increase in vancomycin-resistant enterococci and coagulase-negative staphylococci was observed. Methicillin-resistant Staphylococcus aureus remained stable.

Comments

The results of this study show that the use of selective digestive decontamination protects against and even decreases the presence of multiresistance in gram-negative rods, although there is an increase in gram-positive cocci. The implementation of surveillance and control of methicillin-resistant *Staphylococcus aureus* in an ICU in which selective decontamination was used prevented an increase in the presence of this pathogen. The use of selective digestive decontamination forces surveillance studies to be carried out for early detection of multiresistant pathogens.

Lorente L, Lecuona M, Jiménez A, Mora ML, Sierra A. Tracheal suction by closed system without daily change versus open system. Intensive Care Med. 2006;32:538-44.

The objective of this prospective and randomized study was to assess the incidence of ventilator-associated pneumonia and tracheal suctioning costs using a closed tracheal aspiration system without the need for complete daily exchange and an open system. There were no significant differences between the study groups (236 with a closed system and 221 with an open system) in the number of ventilator-associated pneumonia per 1000 days of mechanical ventilation (14.1 vs. 14.6). There were no significant differences in tracheal suctioning costs per patient/day. However, when length of mechanical ventilation was lower than 4 days, the cost was higher with the closed system.

Comments

The main contribution of this study is that the use of a closed tracheal aspiration system in mechanically ventilated patients did not influence the rate of ventilator-associated pneumonia. Cost changes depending on the duration of mechanical ventilation should be treated with caution since the closed system did not involve the need for a complete daily change.

Playford EG, Webster AC, Sorrell TC, Craig JC. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. Cochrane Database Syst Rev. 2006 Jan 25 (1);CD004920.

In order to assess the effects of antifungal prophylaxis in non-neutropenic critically ill adult patients on all-cause mortality and the incidence of invasive fungal infections, data from 12 trials (8 comparing fluconazole and 4 keto-

conazole with no antifungal or a nonabsorbable agent) involving 1606 randomized patients were analyzed. Although no differences were found in the individual studies, combined analysis revealed that prophylaxis with fluconazole or ketoconazole in critically ill patients reduces invasive fungal infections by one half and total mortality by one quarter. Although no significant increase in azole-resistant Candida species associated with prophylaxis was demonstrated, trials were not sufficiently powerful to exclude such an effect.

Comments

Although this meta-analysis presents promising results, most studies analyzed included highly heterogeneous populations with a small number of cases. A protective effect on mortality was demonstrated in only 1 study. Further studies are warranted to define those patient groups in which this strategy may be beneficial, as well as to define doses, duration of prophylaxis, and antifungal agents of choice.

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