Update: sepsis and septic shock

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Severe sepsis and septic shock are common causes of death in intensive care units (ICU). The incidence of sepsis has been increasing over the past two decades, and is expected to continue rising during the next few years. Despite the fact that we know much about the complex pathophysiologic alterations that occur in severe sepsis and septic shock, patients with sepsis remain at a high risk of death. However, in the last few years, new treatment strategies have significantly improved patient outcome. This article reviews nine major studies published during 2004 and 2005: two deal with incidence rates, distribution of pathogens and trends in antibiotic resistance among ICU patients with sepsis; two discuss selected aspects of antibiotic therapy, the usefulness of combination therapy for sepsis in immunocompetent patients and the impact of empirical treatment in *Pseudomonas aeruginosa* bloodstream infections; two consider the usefulness of risk assessment in the management of sepsis and the importance of dynamic clinical evolution of critically ill patients with infection. The remaining three studies analyze adjunctive therapy in severe sepsis: the effect of an intensive glucose-management protocol on the outcome of critically ill patients; the evaluation of relative adrenal insufficiency and the variability of cortisol plasma concentrations over a 24-hour period; and the use of Drotrecogin alfa (Activated) for adults with severe sepsis and a low risk of death.

Key words: **Sepsis, Septic Shock, Nosocomial infections, Management.**

Actualización: sepsis y shock séptico

La sepsis grave y el shock séptico son causas frecuentes de fallecimiento en las unidades de cuidados intensivos (UCI). La incidencia de sepsis se ha incrementado durante los 2 últimos decenios y se considera que lo va a seguir haciendo durante los próximos años. A pesar de que actualmente poseemos mucha más información acerca de las complejas alteraciones fisiopatológicas que tienen lugar en la sepsis grave y en el shock séptico, los pacientes con sepsis siguen presentando un elevado riesgo de muerte. Sin embargo, durante los últimos años la introducción de nuevas estrategias terapéuticas ha mejorado significativamente el pronóstico de estos pacientes. En este artículo se revisan nueve estudios de gran envergadura publicados en 2004 y 2005: en dos de ellos se abordan las tasas de incidencia, la distribución de los patógenos y las tendencias en la resistencia frente a los antibióticos en los pacientes con sepsis atendidos en la UCI; en otros dos artículos se exponen diversos aspectos seleccionados del tratamiento antibiótico, la utilidad del tratamiento de combinación en los cuadros de sepsis que presentan los pacientes inmunocompetentes y el impacto del tratamiento empírico en los cuadros de sepsis causados por *Pseudomonas aeruginosa*; en otras dos publicaciones se consideran la utilidad de la evaluación del riesgo en el tratamiento de la sepsis y la importancia de una evaluación clínica dinámica en los pacientes con infección y en situación clínica crítica. En los tres estudios restantes se analiza el tratamiento complementario en la sepsis grave: el efecto de un protocolo de control intensivo de la glucemia sobre la evolución de los pacientes en situación clínica crítica; la evaluación de la insuficiencia suprarrenal relativa y de la variabilidad de las concentraciones plasmáticas de cortisol durante un período de 24 horas, y el uso de drotrecogina alfa (activada) en los adultos con sepsis grave y riesgo bajo de muerte.

Palabras clave: **Sepsis. Shock séptico. Infecciones nosocomiales. Tratamiento.**

State of the art (Dr. Mercedes Palomar)

In the last few years, sepsis has emerged as one of the leading causes of death among hospitalised patients. The real incidence is unknown, but recent data estimate that sepsis accounts for about 3% of hospital admissions and

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for up to 10% in the ICU[1]. As the population is ageing and invasive procedures, chemotherapy and immunosuppressive drugs become more common, these figures are expected to grow.

According to Martin[2], the incidence of sepsis in the United States has increased over the last two decades, growing from 82.7 cases per 100,000 people to 240.4 cases per 100,000, which represents an annual increase of 8.7%. Causative agents have also changed. Sepsis caused by fungi has increased by 207%, with gram-positive bacteria becoming the predominant pathogens after 1987. On the contrary, mortality rates declined significantly—by about 10%—during the study period, although the increasing incidence of sepsis results in almost three times the number of in-hospital deaths related to sepsis (21.9 deaths per 100,000 people in 1979 to 43.9 per 100,000 in 2000). The decline in mortality is attributed to improvements in intensive care management, but other factors such as diagnostic criteria and coding practices could also play a role.

Most patients with sepsis are admitted to the ICU. A large number of cases are community-acquired, and most nosocomial cases are ICU-acquired. According to a multicenter European sepsis database, about one-fifth of all patients present infection on admission to the ICU, whereas half of these patients develop an infection during their stay in the ICU[3]. Respiratory, digestive, urinary tract-related and primary bloodstream infections represent about 80% of all sites. Half of the infections are associated with severe sepsis and septic shock. Hospital-acquired and ICU-acquired infections are microbiologically documented more frequently than community-acquired infection (71% and 86% respectively vs. 55%). Crude hospital mortality rates range from 16.9% in non-infected patients to 53.6% in patients with either hospital-acquired infections at the time of ICU admission or those acquiring infection during the ICU stay. In comparison with non-sepsis cases, patients with sepsis present more severe organ dysfunction, longer ICU and hospital lengths of stay, and higher mortality rates. The severity of septic patients depends on the number of organs failing, and those with at least two organ dysfunctions should be analyzed separately.

The definition of sepsis has been quite controversial and has been tackled in many papers and consensus conferences. A lack of accurate, harmonized definitions has made it difficult to compare studies. In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened the first Consensus Conference, in order to "provide a conceptual and a practical framework to define the systemic inflammatory response to infection"[4]. The general definitions resulting from this meeting have been widely used in practice, and have served as inclusion criteria in numerous clinical trials. In 2001, and thanks to the support and sponsorship of the SCCM, the European Society of Intensive Care Medicine (ESICM), the ACCP, the American Thoracic Society (ATS) and the Surgical Infection Society (SIS), a group of experts and opinion leaders revisited the 1992 sepsis guidelines, and found that, apart from expanding the list of signs and symptoms of sepsis needed to reflect clinical bedside experience, no evidence existed to support a change in the definitions[5]. This lack of evidence served to underscore the challenge still present for clinicians and researchers when diagnosing sepsis, and provided the basis for a new sepsis classification system, the PIRO, as a model for future research.

PIRO stands for p*redisposition, infection, response, and organ dysfunction*. It is hoped that, by defining the septic process through a detailed analysis of each of its integrating parts, the development of sepsis will be better understood and thus help improve therapeutic interventions in the future. The PIRO model should be directly tested, both in the laboratory and in clinical trials, in order to determine its practical value[6-9].

Infection is a key component of the definition of sepsis and another source of variability in clinical trials. Consensus definitions of infection have recently been developed for the six most frequent causes of infection in septic patients: pneumonia, bloodstream infections (including infective endocarditis), intravascular catheter-related sepsis, intra-abdominal infections, urosepsis, and surgical wound infections. The use of these definitions in clinical trials should help to improve the quality of sepis-oriented clinical research[10].

The pathogenesis of sepsis is an extremely complex process involving multiple interactions between the host and the etiologic microorganism[11]. Considerable progress has been made in understanding the processes through which the initial interaction of pathogen recognition by the innate immune system becomes a cascade of events that results in cellular injury, and finally in organ failure. The detection of invading microorganisms is mediated by pattern recognition receptors, which are expressed on the surface of innate immune cells. When a pathogen-associated molecular pattern binds to a pattern-recognition receptor, it activates several intracellular signaling pathways, resulting in the activation of transcription factors that control the expression of immune response genes and the release of numerous effector molecules, such as cytokines. Cytokines control both pro-inflammatory and anti-inflammatory host responses. Unbalanced inflammatory and immune reactions can result in either uncontrolled microbial growth or devastating inflammatory responses with tissue injury and vascular collapse. Circulatory alterations (including microcirculatory alterations) and cellular energy production-related alterations play a prominent role in the pathogenesis of organ dysfunction.

During the past 5 years, and after decades of frustrating failures, the progress in our basic understanding of sepsis has led to successful new therapies. These new treatment strategies have significantly improved patient outcome[12]. Nevertheless, antimicrobial therapy is still probably the most influential factor. Prompt initiation of antibiotic therapy that is active against the causative pathogen is one of the most important outcome predictors[13]. The impact of inappropriate antibiotic treatment on the final outcome of septic patients increases in relation to the severity of the immune response. Patients with community-acquired bacteremia in septic shock and receiving inappropriate treatment present survival rates below 20%[14]. On the other hand, the chance of having uncovered pathogens is higher in the sickest patients.

More effective supportive therapies with early, goal-oriented treatments including volume resuscitation, catecholamine therapy and transfusion improve survival in cases of septic shock[12,15]. Novel endocrine management,

with hydrocortisone replacement therapy against relative adrenal insufficiency in septic shock patients and strict blood glucose control, provides survival advantages in critically ill patients. Nutritional support and ventilation protocols with low tidal volumes have now been shown to benefit septic patients. In 2001, Van den Berghe et al[16] demonstrated that maintaining blood sugar between 80 and 110 mg/dl through intensive insulin therapy reduced ICU mortality from 8 to 4.6% in a large surgical ICU population. The protocol resulted in a low incidence of hypoglycemia. Institutions such as the Institute for Healthcare Improvement and other organizations such as the Surviving Sepsis Campaign[17] are promoting a care "bundle" for severe sepsis that also includes intensive control of glycemia. However, the VISEP trial[18], a multicenter German study that randomized 600 subjects with medical or surgical severe sepsis to conventional or intensive insulin therapy, was halted after recruitment of 488 subjects, because no difference was found in the intensive insulin therapy arm with regards to mortality and frequent hypoglycemia (2.1 vs 12.1%, $p < 0.001$). The use of steroids in patients with septic shock has been controversial for many years, although recent studies show benefits from lower doses of corticosteroids for more prolonged periods and, based on the Annane study[19], their use has increased enormously. The possible adverse effects of corticosteroids and the diagnosis of adrenal insufficiency in septic patients is a cause for concern.

Finally, human recombinant activated protein C (drotrecogin alfa), an anticoagulant which ameliorates sepsis-induced disseminated intravascular coagulation and exerts several other favorable effects on endothelial cells, is the first anti-inflammatory agent that has been shown to reduce mortality in patients with severe sepsis[20]. Nevertheless, extended use of activated protein C is controversial, due to potential adverse effects, the definition of the population that can benefit from it, and the cost.

As sepsis-derived mortality remains unacceptably high, 11 organizations, including the European and American Societies of Intensive Care Medicine, have jointly developed management guidelines for severe sepsis and septic shock[17]. The Surviving Sepsis Campaign is an international effort to reduce mortality related to severe sepsis and septic shock. The campaign created evidence-based guidelines sponsored and endorsed by 11 international organizations. Based on these guidelines, sepsis care bundles for initial resuscitation (6 hours) and management (24 hours) were created as a performance improvement tool. Management includes early targeted resuscitation, broad empiric antibiotic coverage and source control, effective shock evaluation and treatment, adjuvant therapy with recombinant human activated C protein, moderate-dose hydrocortisone in selected patients, and comprehensive supportive care. The consensus committee created a dynamic electronic Web-based guidelines.

http://www.survivingsepsis.org/; http://www.sepsisforum.org/

On the basis of newly discovered pathophysiological mechanisms of sepsis, several other adjuvant therapies for sepsis are in various stages of preclinical and clinical development. Individualized and optimal supportive cares with efforts to reverse the precipitating cause of sepsis remain the mainstay of therapy for severe sepsis. How these new and often expensive regimens will fit into the standard treatment approach to sepsis has yet to be defined.

Several genetic polymorphisms have been identified in patients with sepsis and severe sepsis. These include the tumor necrosis factor-alpha (TNF-alpha) and TNF-beta genes, the interleukin-1 (IL-1) family, IL-6, IL-10, CD-14, and Toll-like receptors, plasminogen activator inhibitor type 1, and the factor V 1691G-A mutations. Identifying people who are at increased risk of sepsis may anticipate future benefits from targeted immunomodulatory therapies[21,22].

Literature review

Nine major articles published during 2004 and 2005 were selected for discussion: two deal with incidence rates, distribution of pathogens and trends in antibiotic resistance among ICU patients with sepsis; two discuss selected aspects of antibiotic therapy; two consider the usefulness of risk assessment in the management of sepsis; and the remaining three analyze the efficacy of several adjunctive treatments in severe sepsis.

Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial Bloodstream Infections in US Hospitals: Analysis of 24,179 Cases from a Prospective Nationwide Surveillance Study. CID. 2004;39:309-17[23].

In this study, data from the SCOPE Project were used to examine traditional trends in the epidemiology and microbiology of nosocomial bloodstream infection (BSI). The SCOPE Project is based at Virginia Commonwealth University in Richmond, and includes 49 hospitals of various sizes from across the US. The study began in 1995; clinical data were collected prospectively by local IPCs, using a standardized case report form and then forwarded to the coordinating center, along with each microbial isolate.

The study detected 24,179 cases of nosocomial BSI over a 7-year period (60 cases per 10,000 hospital admissions), which were distributed as follows: Gram-positive organisms 65%, Gram-negative organisms 25%, and fungi 9.5%. The crude mortality rate was 27%. The most common organisms were coagulase-negative staphylococci (CoNS) (31%), *Staphylococcus aureus* (20%), enterococci (9%) and *Candida* species (9%). Approximately half of the BSI episodes were in ICU patients. *S. aureus* and *E. coli* were more likely to be isolated from patients in non-ICU wards, whereas CoNS and *Candida* spp. were more commonly isolated from ICU patients. In this setting, *Pseudomonas aeruginosa* was the most frequent Gram-negative pathogen, associated with a crude mortality as high as 47.9%. Other Gram-negative bacilli more likely to cause infection in this patient population were *Enterobacter* spp. *Serratia* spp. and *Acinetobacter* spp. In ICU patients, the longest mean interval between admission and infection was seen in *Candida*, enterococcal and *Acinetobacter* infections.

Methicillin resistance was detected in 75% of CoNS isolates. The proportion of methicillin-resistant *S. aureus* in-

creased from 22% in 1995 to 57% in 2001 ($p < 0.001$). Among enterococcal isolates, vancomycin resistance was found in only 2% of *E. faecalis*, but in 60% of *E. faecium*. For *E. coli* and *K. pneumoniae* isolates, third-generation cephalosporins, aminoglycosides, fluorquinolones, aztreonam and imipenem were active against > 80% of the isolates tested. Of the *P. aeruginosa* isolates, 11%, 14%, and 16% were resistant to piperacillin, imipenem, and ceftazidime, respectively. Of note, the proportion of isolates resistant to ceftazidime increased from 12% in 1995 to 29% in 2001 ($p < 0.001$). Resistance to ciprofloxacin was seen in 20% of the isolates tested.

This study is of special significance because it is based on one of the largest databases of patients with nosocomial bacteremia. It is a clinically-oriented surveillance project, collecting data on defined infections, not on culture results alone. However, the design of the study (1 single blood culture for CoNS) might have led to an overestimation of BSIs due to this organism. The proportion of BSIs due to enterococci and fungi was higher than that seen in European series. Similarly, the rate of resistance to vancomycin among *E. faecium* isolates and the rate of resistance to methicillin among *S. aureus* are also higher.

One striking feature of the study is the demonstration that half of all nococomial BSIs occur in the critical-care setting, where a large number of patients present late onset infections due to opportunistic pathogens, including some Gram-negative organisms. The authors claim that the proportion of BSIs caused by antibiotic-resistant organisms is clearly increasing in US hospitals.

Gaynes R, Edwards JR, the National Nosocomial Infections Surveillance System. Overview of Nosocomial Infections caused by Gram-negative Bacilli. CID. 2005;41:848-54[24].

Data from the the National Nosocomial Infections Surveillance (NNIS) System for the 1986-2003 period were analyzed to determine the epidemiology of Gram-negative bacilli causing pneumonia, surgical site infections, urinary tract infections (UTI) and bloodstream infections in the ICU. A total of 410,503 bacterial isolates associated with nosocomial infections in the ICUs were submitted to the NNIS. The percentage of Gram-negative bacteria causing pneumonia and UTI remained stable (between 70 to 80%) throughout the study period, but decreased from around 60% to 40% as a cause of surgical site infection. However, Gram-positive bacteria were more often associated (approx. 70%) with bloodstream infection and also remained stable during the study period. The proportion of ICU pneumonia episodes associated with *Acinetobacter* spp. increased from 4% in 1986 to 7% in 2003. Similarly, *K. pneumoniae* and *Acinetobacter* spp. increased significantly, although they only accounted for 9.8% and 1.6%, respectively, of UTI isolates in 2003. The distribution of Gram-negative bloodstream infection in ICUs changed very little, with a general increase in antimicrobial resistance. *E. coli* and *K. pneumoniae* resistance to third-generation cephalosporins increased, as did resistance to ceftazidime and imipenem in *P. aeruginosa* and *Acinetobacter* spp.

In conclusion, Gram-negative bacilli are commonly associated with hospital-acquired infections in ICUs. The proportion of *Acinetobacter* species associated with ICU pneumonia increased significantly.

Although molecular typing to exclude the possibility of epidemics or clonal spread of bacteria was not performed, the overall data most probably represent the current situation in many ICUs. In addition, the data on pathogen distribution and antimicrobial resistance of Gram-negative organisms causing infections in ICUs were as expected. With regard to distribution, it is obvious that Gram-negative pathogens are still the most prevalent microorganisms causing UTI, since the main reservoir of these uropathogens is the intestinal tract. Of note is the shift toward Gram-positive pathogens as the predominant etiologic agents of surgical site infections, which the authors associate with antimicrobial prophylaxis and increased use of laparoscopy. Nonetheless, other factors such as the change in type of surgery performed, e.g., orthopedic device infections, may also play an important role.

The ICU is a unique scenario in which different factors favoring the increase in antimicrobial resistance may converge. These units have seriously ill patients in confined environments where antibiotic use is extremely common. In fact, excessive use of broad-spectrum antimicrobial agents in ICUs has been directly correlated with the emergence of antimicrobial resistance. In this study, it is surprising that the authors did not mention the trend toward quinolone-resistance in *P. aeruginosa* reported by other authors in similar surveillance studies.

Finally, infections due to *Acinetobacter* sp. have increased steadily and are now a cause for concern, mainly due to the multi-resistance presented by this microorganism, making therapeutic options very limited. In conclusion, the increase in the prevalence of multi-resistant Gram-negative bacilli as a cause of nosocomial infections is a serious health problem. Therefore, therapeutic strategies should attempt to minimize this increase in antimicrobial resistance.

Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibivici L. β lactam monotherapy versus β lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. BMJ. 2004;328: 668-72[25].

A major objective when choosing empiric antibiotic therapy for a severe infection is to achieve an antimicrobial spectrum that is wide enough to cover most potentially causative microorganisms. In order to meet this goal, hospital physicians use combination therapy.

Due to their demonstrated in vitro synergism and wide antimicrobial spectrum, β lactam-aminoglycoside combinations are the most commonly used. Nevertheless, there is no evidence that any β lactam-aminoglycoside combination is better than β lactam monotherapy in most clinical scenarios. Besides, several studies have demonstrated similar effectiveness in neutropenic fever.

In order to analyze this topic in immunocompetent patients, the authors performed a systematic review and

meta-analysis of randomized trials comparing β lactam-aminoglycoside combination therapy with β lactam monotherapy for severe infections in patients without neutropenia.

The authors defined severe infection as clinical evidence of infection, plus evidence of a systemic response, and excluded studies with neonates, pre-term babies, a dropout rate above 30%, and more than 15% of patients with neutropenia.

The primary outcome assessed was all-cause fatality by the end of study and follow-up, and up to a maximum of 30 days. The secondary outcomes included treatment failure, defined as death, non-resolving primary infection, any modification to allocated antibiotics, bacteriological failure, adverse events and length of hospital stay.

In order to make results more homogeneous, studies comparing the same β lactam were separated from studies that compared different β lactams. Similarly, for *P. aeruginosa* infections, subgroup analyses of Gram-negative infection, bacteremia, and specific sources of infection were carried out separately.

Of the 64 randomized clinical trials that reached the required quality criteria, 41 involved patients with severe sepsis, pneumonia or Gram-negative infections, 11 involved abdominal infections, 7 urinary tract infections, and 5 Gram-positive infections. The same β lactam was compared in 20 trials, while all other trials compared one β lactam to a different narrower-spectrum β lactam combined with an aminoglycoside. The trials included 7586 patients, nearly all of whom were adults, and were performed between 1968 and 2001.

There was no significant difference in fatality rates between monotherapy and combination therapy, or in those studies comparing the same β lactam, or among studies comparing different β lactams. In addition, the authors found no differences between monotherapy and combination therapy in subgroups with *P. aeruginosa* infections, Gram-negative infection, bacteremia, non-urinary tract infections, Gram-positive infections and endocarditis. Nevertheless, nephrotoxicity was more common with combination therapy in almost all studies. The authors did not find bias induced by any of the measures assessed, but they admitted that the overall quality of the studies included in the meta-analysis was poor, and they could not obtain data on all-cause fatality in 33% of the trials.

The study also presents important limitations such as the low number of trials with Gram-positive infections, low number of bacteriologically documented *P. aeruginosa* infections, scarce mention of specific locations such as endocarditis, and no mention of dose or duration of therapy.

Even assuming these biases and the intrinsic limitations of any meta-analysis, the authors clearly demonstrate the following: first, there is no difference between empirical treatment with β lactam monotherapy or a β lactam-aminoglycoside combination to treat patients with sepsis; second, the addition of an aminoglycoside does not seem to improve the prognosis of patients with severe infections treated with an appropriate β lactam; third, nephrotoxicity is significatively higher with the β lactam-aminoglycoside combination; and finally, novel β lactams should not be compared with older β lactams or penicillins combined with aminoglycosides.

Micek ST, Lloyd AE, Ritchie DJ, Richard RM, Fraser VJ, Kollef MH. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrobial Agents and Chemotherapy. 2005;49:1306-11[26].

The use of beta-lactam monotherapy is widely accepted, even in the empirical treatment of febrile neutropenic patients, where *Pseudomonas aeruginosa* is an important pathogen. In a retrospective cohort analysis, Micek et al studied the importance of appropriate initial antimicrobial treatment in *P. aeruginosa* bloodstream infections. The main objectives of the study were i) to determine whether the administration of appropriate initial antimicrobial treatment was associated with better clinical outcome, and ii) to examine the relationship between the empirical administration of combination Gram-negative antimicrobial therapy and appropriate treatment for *P. aeruginosa* bloodstream infections. A total of 596 consecutive patients with bloodstream infections due to *P. aeruginosa* were evaluated and only 305 patients were finally included in the study (see below). Hospital mortality was statistically greater ($p = 0.018$) for patients receiving inappropriate initial treatment, compared with those receiving appropriate initial treatment (30.7% vs 17.8%). This conclusion—lower mortality with appropriate initial treatment—was reinforced in the multivariate analysis, which identified the administration of inappropriate treatment as an independent determinant of hospital mortality. Interestingly, inappropriate initial antimicrobial therapy was statistically more likely ($p = 0.011$) to occur among patients receiving monotherapy against Gram-negative bacteria than in those receiving combination therapy (34.5% vs 20.6%). The appropriateness of initial antimicrobial therapy was higher in patients receiving ceftazidime or cefepime than in those receiving ciprofloxacin.

The limitations of this study included the absence of patient stratification according to length of hospital stay or prior antimicrobial therapy. Moreover, nearly 40% of patients were excluded from the analysis due to the presence of polymicrobial infection, and 11% were excluded due to incomplete treatment information. It is important to note that, of the patients excluded, 20% presented higher mortality rates than those receiving appropriate or inappropriate treatment.

Previously published studies had demonstrated that when implementing empirical combination therapy against *P. aeruginosa* bacteremia until receipt of the antibiogram, survival rates were better than those recorded for monotherapy. The authors demonstrated that inappropriate initial antimicrobial treatment of *P. aeruginosa* bloodstream infection was associated with statistically higher mortality when compared with initial treatment with an antimicrobial regimen to which bacteria were susceptible. The study also showed that initial treatment with a combination of antimicrobial agents against *P. aeruginosa* was statistically more likely to provide appropriate treatment than monotherapy. Moreover, regimens with fluoroquinolones were associated with a statistically greater likelihood of inappropriate initial treatment, while therapy with expanded-spectrum cephalosporins was statistically more likely to be associated with appropriate therapy. In summary, the authors concluded that increas-

ing the use of combination antimicrobial treatment could minimize inappropriate empirical antimicrobial treatment of *P. aeruginosa* bloodstream infection.

Guidet B, Aegerter P, Gauzit R, Meshaka P, Dreyfuss D, on behalf of the CUB-Réa Study Group. Incidence and Impact of Organ Dysfunctions Associated With Sepsis. CHEST. 2005;127:942-51[27].

Patients with severe sepsis present a high risk of death compared with critically-ill non-septic patients. As new, effective, and costly therapeutic agents are becoming available, epidemiologic data must be updated to better understand the incidence and pathophysiology of the disease, and to plan rational treatment.

The objective of this study was to assess the incidence and severity of organ dysfunction associated with sepsis in a large database. The authors hypothesized that, in a non-selected population, septic patients with at least two organ dysfunctions during the ICU stay, would have an intermediate severity compared with septic patients with only one organ failure, a subgroup of patients considered not severe enough to be candidates for newer, more expensive drugs, and patients with septic shock and a mortality close to 60%. All patients hospitalized in 35 Parisian ICUs for > 24 hours and meeting the criteria for septic shock, with one organ dysfunction (SS1; n = 5675) or two or more organ dysfunctions (SS2; n = 12,598), were compared with all other patients hospitalized for > 24 hours in the ICU, during the same period (n = 47,637). Community-acquired septic shock and nosocomial septic shock were analyzed altogether.

Most patients with septic shock had two organ dysfunctions, the three most frequent being the respiratory system, circulatory system and kidneys. The most common sites of infection were the lungs, abdomen and cardiovascular system. Infection was documented in 49.8% of SS1 patients and in 60.9% of SS2 patients. The incidence of SS2 was double in patients admitted for unscheduled surgery than in those admitted for scheduled surgery or on medical grounds ($p < 0.001$). It was also higher in patients admitted to surgical ICUs than in those admitted to medical or medico-surgical ICUs ($p < 0.001$). Patients with SS were significantly older and more frequently men ($p < 0.001$), and were also more often admitted by external transfer and for surgical procedures ($p < 0.001$).

According to multivariate analyses, respiratory and cardiovascular dysfunctions were the strongest independent risk factors for ICU death, with 5.64-fold and 4.35-fold increased risks, respectively. Age and Charlson-Deyo score (which takes into account the number and the severity of comorbidities) were also independently related to ICU death. Fungal infection and *Pseudomonas* spp. were predominant. Urinary tract infections were associated with a lower risk of death. Comparable data were found in the subset with one organ failure, and in outcome (hospital discharge).

The authors of the study focused on a specific group of patients who were particularly likely to benefit from the new therapies for septic shock. The definition of septic shock used in the present study was closer to "real life", as it did not use SIRS and included patients with infection, regardless of whether this was documented or not. As the microbiologic characteristics suggest that a part of SS2 is ICU-acquired, it seems that SS2 may be at least partially preventable. Moreover, prompt diagnosis and appropriate treatment could help prevent progression to SS2, and, therefore, on mortality. The authors conclude that, when designing clinical trials, septic patients with at least two organ dysfunctions should probably be considered separately from patients with only one organ dysfunction.

Alberti C, Bruin-Buisson C, Chevret S et al, for the European Sepsis Study Group. Systemic Inflammatory Response and Progression to Severe Sepsis in critically ill Infected Patients. Am J Respir Crit Care Med. 2005;171:461-8[28].

The classification of sepsis in three groups of increasing severity (sepsis or SIRS, severe sepsis, and septic shock) proposed by the American College of Chest Physicians / Society of Critical Care Medicine (ACCP/SCCM), has been widely used in the last few years in the critical-care setting, especially in epidemiological studies or clinical trials. Although one of the main purposes of this classification was the early identification of patients with sepsis (especially in SIRS / infection stages), it does not estimate the progression of these SIRS patients to a more severe situation during ICU stay, whereas the SOFA Score daily calculation (delta SOFA) does. Moreover, it does not predict which patients are at risk of complicated evolution.

Alberti C and the European Sepsis Study Group recently published a very interesting paper in the *American Journal of Respiratory and Critical Care Medicine*, using the European Sepsis Database and trying to resolve the lack of sensitivity of the SIRS definition for detecting patients at risk of a poor evolution during their ICU stay. The main objectives of this important study were to examine the incidence and risk factors of exacerbation of sepsis in infected patients (SIRS patients according to the ACCP/SCCM classification), in order to develop a risk score for worsening sepsis (RISSC). This in turn would facilitate early identification of cases and initiation of therapy, and allow us to establish a prognosis. A prospective, one-year cohort study was conducted (May 1997 - April 1998) in 28 ICUs in eight European countries, Canada and Israel. Of 14,364 ICU admissions, 1531 patients who presented a first sepsis episode on ICU admission or during ICU stay were finally enrolled. Patients with severe sepsis and septic shock were excluded. The variables associated with progression of infection/sepsis to severe sepsis or septic shock were analyzed using the regression model for the sub-distributions of competing risks developed by Fine and Gray (http://biowww.dfci.harvard.edu/~gray).

Almost a quarter of the SIRS-infection patients progressed to a more severe clinical stage, developing severe sepsis (11%) and septic shock (13%), and the mortality rates of these patients ranged from 47% to 97%. Twelve variables were selected in the final multivariate model (RISCC), including six physiologic variables (temperature, heart rate, systolic blood pressure, platelet count, serum sodium, and bilirubin), mechanical ventilation (used in place of respiratory rate in patients on a ventilator), three

infection sites (pneumonia, peritonitis and primary bacteremia), and two categories of microorganisms (gram-positive cocci, anaerobic gram-negative bacilli). Mechanical ventilation and primary bacteremia were the most powerful variables. In order to simplify the score for clinical use, this information was summarized in four risk strata: the "low" (score 0-8) and "moderate" (score 8.5-16) risk groups, for which the cumulative estimated risk of progression to severe sepsis was 9% and 17%, and the "high" (score 16.5-24) and "very high" risk (score > 24) groups, with a risk of progression to severe sepsis of 31% and 55%, respectively. Patients with a "very high" risk had the highest mortality rates, ranging from 42.8% to 55%, depending on the day of evaluation.

This paper demonstrates the importance of dynamic clinical evolution of critically ill patients with infection, and not only the initial clinical presentation of infection as a prognostic factor; it also reveals the weakness of the sepsis severity classification when determining specific outcome in these patients.

However, the study is limited in that the data were collected eight years ago, and current management of these patients has been harmonized (Surviving Sepsis Campaign), so the results might not accurately reflect the current scenario. Moreover, attributable mortality rates of community-acquired and nosocomial infections might be different. Finally the incorporation of biochemical markers of infection might add more accuracy to this score.

In spite of these limitations, the RISCC is now a valid score for early recognition of worsening patients, and it should be used in clinical practice for rapid initiation of therapy in risk patients.

Krinsley JS. Effect of an intensive glucose-management protocol on the mortality of critically ill patients. Mayo Clin Proc. 2004;79:992-1000[29].

Recently, it has been acknowledged that critically ill patients who experience high levels of glucose during their disease present higher risks of morbidity and mortality. Insulin therapy (under continuous perfusion if necessary) is associated with lower mortality. In a randomized trial published in 2001, Van de Berghen et al detected a reduction in mortality (20.2% vs 10.6%) in patients in the ICU for more than 5 days, and additional reductions of over 30% were registered for complications such as sepsis, renal failure, need for blood transfusions, and polyneuropathy. Most patients in this series had previously undergone heart surgery. Subsequent analyses conclude that glucose control, and not insulin, improves protection. Nevertheless other questions must be answered: Can the results of this clinical trial be compared with those of patients suffering from other diseases? Which glucose level provides the greatest benefits and lowest risks of hypoglycemia? Which is the mechanism of action that protects patients from death?

This study approaches the first question. It is a prospective trial comparing 800 patients who underwent a protocol for the control of glycemia, with another 800 patients previously collected when implementing the protocol. Patients were recruited from a 14-bed polyvalent ICU (24% surgery and trauma patients). The protocol aimed to maintain glycemia levels under 140 mg/dl, and began intravenous insulin perfusion if glucose exceeded 200 mg/dl during two consecutive determinations.

The two groups were of similar composition regarding age, gender, race, presence of diabetes mellitus, and levels of APACHE II scores on admission. A significant reduction in mean glycemia levels was detected in the protocol group (152 vs 130.7 mg/dl; $p < 0.001$) and an additional reduction of 56% was registered in the percentage of glycemia values under 200 mg/dl in those patients monitored through a strict glucose control. The rate of hypoglycemia was 0.35% during the pre-intervention period and 0.34% during the intervention period. The incidence of renal failure fell by 75% ($p = 0.03$) and the percentage of patients requiring blood transfusion also fell by 18.7% ($p = 0.04$). Finally, the length of ICU stay was 10.8% shorter (mean of 3.58 days vs 3.19 days; $p = 0.01$).

Hospital mortality fell from 20.9% to 14.8% in the protocol group, with a relative reduction of 29.3% ($p = 0.002$). The relative reduction in mortality reached 44.9% in septic shock patients (60.4% vs 33.3%; $p = 0.02$) and 59.5% in neurological patients (21 vs 8.5%; $p = 0.007$). The highest mortality was observed among less severe patients (73% of relative reduction in the APACHE II < 15 group), while patients with an APACHE II over 35 did not experience a reduction.

The authors conclude that the implementation of a protocol aimed at maintaining glycemia levels below 140 mgr/dl is related to a reduction in mortality and morbidity in a wide variety of critically-ill patients.

This study is limited by its historical controls, and its single-center focus. The authors use clinical arguments to justify the maintenance of the same diagnostic and therapeutic protocols during the 22 months of the study. There is no mention of new strategies showing a reduction in mortality (protective ventilation, activated C protein, etc) among septic shock patients. If both groups are really comparable, then the conclusions are adequate (even though this is not a randomized trial), although it is doubtful whether the comparison could be applied to all units.

The reduction in mortality and morbidity (complications and hospital stay) in both groups is striking. It would be interesting to better describe the group of septic shock patients (baseline group: 34 patients, mean age 73 years, APACHE II 28, mortality 60.4%; and treatment group: 41 patients, mean age 72 years, APACHE II 25, mortality 33.3%), taking into account the difference in mortality rates according to the infection site, suitability of antibiotic treatment, timeliness of therapy, etc. It seems that those levels determined as objective do not relate to a higher rate of hypoglycemia. The authors stress that an ideal scenario would involve a multi-center, randomized trial.

Venkatesh B, Mortimer RH, Couchman B, Hall J. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. Anaesth Intensive Care. 2005;33:201-9[30].

Venkatesh et al performed sequential 24-hour plasma total cortisol measurements in 21 critically ill patients

with sepsis. The patients were studied on days 3 to 4 after admission and assessment included presence or absence of stability and reception (or not) of glucocorticoid therapy. The mean APACHE II score was 21 (range 6 to 36), mean SOFA score was 7 (range 2 to 14) and hospital mortality was 10%. Seven patients (33%) were in septic shock (noradrenaline infusion) and 16 (76%) required mechanical ventilation.

Mean plasma cortisol level reached 16.6 µg/dl (range 10.4 to 28.8 µg/dl), with hourly variations from 8 to 30%, and no circadian rhythm. The low-dose corticotropin test, performed at the end of the 24-hour study protocol, showed a mean increase in cortisol concentrations of 5.5 and 4.9 µg/dl at 30 and 60 minutes, respectively. Four patients presented increases within the normal range at 30 minutes, and 2 patients had normal increases at 60 minutes. The mean maximum spontaneous rise in cortisol level over the 24 hours of observation was significantly greater than the response to exogenous corticotropin. ACTH concentrations were unrelated to plasma cortisol levels and urinary free cortisol excretion.

Use of different cortisol level diagnostic criteria for relative adrenal insufficiency provided a variable range of the incidence of hypoadrenalism: 3 (14.3%) patients had at least one value < 7.25 µg/dl, 16 (76.2%) patients showed increases < 9 µg/dl at 30 or 60 minutes on the corticotropin test, and in 17 (81%) patients most values were < 20 µg/dl. None of the patients had relative adrenal insufficiency by the criteria mentioned above presented hemodynamic instability or other features of hypoadrenalism. Plasma cortisol variability, but not mean plasma cortisol, showed significant negative linear correlations with APACHE II and SOFA scores.

Venkatesh et al's study evaluates one of the most controversial and unclear aspects of the main indication for steroid therapy in septic states: relative adrenal insufficiency. The authors provide valuable information on the wide variability of total plasma cortisol concentrations over a period of 24 hours, without detecting a circadian rhythm. Their data will generate reasonable doubt about the value of random plasma cortisol measurements to guide steroid therapy, as is current practice in many ICUs. Venkatesh et al also confirm previous findings, which show a poor correlation of plasma cortisol and ACTH concentrations.

It is important to note, however, that the group of patients studied differs markedly from those receiving steroid therapy. Actually, the efficacy of steroids in patients with sepsis and severe sepsis has not been proven and its use is not recommended. The main inclusion criterion in recent randomized steroid trials is the presence of septic shock. For example, Annane et al required all patients to be vasopressor-dependent, to have renal and/or respiratory dysfunction and abnormal lactate levels, and to be on mechanical ventilation for inclusion in their multi-center trial. Only 33% of the patients in Venkatesh's study needed a noradrenaline infusion. In fact, patients with renal failure or surgery were specifically excluded and a more "stable" phase was sought for the purposes of the study. A hospital mortality of 10% also reflects important differences in patient characteristics.

Cortisol concentrations may not only vary over a 24 hour time period, but also over the first days of severe sepsis. The time point chosen by the authors appears to be more than 72 hours apart from measurements in other trials, where inclusion had to be completed within 3 hours of the onset of septic shock.

In view of the uncertainties still existing in the area of sepsis and the potential benefit of steroid therapy, efforts such as those of Venkatesh et al are badly needed. The authors should be congratulated for highlighting the need for consensus in defining adrenal insufficiency.

Abraham E, Laterre PF, Garg R, Levy H, Talmar D, Trzaskoma BL et al. Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death. N Engl J Med. 2005;353:1332-41[31].

After the approval of drotrecogin alfa (activated) (DrotAA) for adults with severe sepsis and a high risk of death, the Food and Drug Administration (FDA) demanded a trial to evaluate the efficacy of DrotAA for adults who had severe sepsis and a low risk of death.

Overall, 2640 patients were enrolled, and data were collected for 2613 of them (1297 in the placebo group and 1316 in the DrotAA arm). There were no differences in 28-day mortality (17.0% in placebo vs 18.5% in DrotAA group; p = 0.34). There was more serious bleeding in the DrotAA group than in the placebo group (3.9% vs 2.2%; p = 0.002). In the ADDRESS study, no benefit was observed in patients with an APACHE II score lower than 25. In addition, there was an increase in the incidence of serious hemorrhage.

The ADDRESS study shows us that the results from any trial can only be applied to patients with similar characteristics. The PROWESS study showed an absolute reduction in mortality of 6.1% at 28 days. After 720 patients had been enrolled, the sponsor amended the study protocol. Entry criteria were modified, and the population had less severe underlying disease and more acute infectious illnesses. In addition, a new placebo was introduced. Subgroup analyses showed no benefit for patients who had undergone surgery, or for patients with failure of a single organ. Patients treated with heparin had no benefit either. The pediatric population was evaluated in a new study, and DrotAA presented no benefit, with a higher risk of intra-cerebral hemorrhage. The benefit of the drug is reduced to 4% in patients with severe community-acquired pneumonia and appropriate treatment.

To date, only one study (PROWESS) has exhibited a significant reduction in the risk of death for patients with severe sepsis (APACHE II score higher than 25) treated with DrotAA. In the other patients studied, subgroup analyses have not detected any benefit in comparison with placebo, and thus the administration of DrotAA in these groups might be harmful.

References

1. Angus D, LindeZwirble WT, Lidicke J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated cost of care. Crit Care Med. 2001;29:1303-10.
2. Martin CG. The Epidemiology of Sepsis in the United States from 1979 through 2000. New Engl J Med. 2003;348:1546-54.
3. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Int Care Med. 2002;2:108-21.

4. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP-SCCM Consensus Conference: Definitions of sepsis and multiple organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20:864-74.
5. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D et al. International Sepsis Definitions Conference 2001 SCCM/ESIMC/ACCP/ATS/SIS International Sepsis Conference. Int Care Med. 2003;29:530-8.
6. Angus DC, Burgner D, Wunderink R, Mira JP, Gerlach H, Wiedermann CJ et al. The PIRO concept: P is for predisposition. Crit Care. 2003;7:248-251.
7. Vincent JL, Opal S, Torres A, Bonten M, Cohen J, Wunderink R. The PIRO concept: I is for infection. Crit Care. 2003;7:252-5.
8. Gerlach H, Dhainaut JF, Harbarth S, Reinhart K, Marshall JC, Levy M. The PIRO concept: R is for response. Crit Care. 2003;7:256-9.
9. Vincent JL, Wendon J, Groeneveld J, Marshall JC, Streat S, Carlet J. The PIRO concept: O is for organ dysfunction. Crit Care. 2003;7:260-4.
10. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med. 2005;3: 1538-48.
11. Bochud PV, Calandra T. Pathogenesis of sepsis: new concepts and implications for future treatment BMJ. 2003;326:262-6.
12. Marik PE, Varon J. Goal-directed therapy for severe sepsis. N Engl J Med. 2002;346:1025-6.
13. Garnacho Montero J, García Garmendia JL, Barrero Almodóvar AE, Jiménez Jiménez FJ, Pérez Paredes C, Ortiz Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the ICU with sepsis. Crit Care Med. 2003;31:2742-51.
14. Vallés J, Rello J, Ochagavía A, Garnacho J, Alcalá MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest. 2003;23:1615-24.
15. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368-77.
16. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359-67.
17. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J et al. Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock. Intensive Care Med. 2004;30:536-55.
18. Brunkhorst FM, Kuhnt E, Engel C, Meier-Hellmann A, Ragaller M, Quintel M et al. Intensive insulin therapy in patients with severe sepsis and septic shock is associated with an increased rate of hypoglycemia - results from a randomized multicenter study (VISEP) [abstract]. Infection. 2005;33:19-20.
19. Annane D, Sébille V, Charpentier C, Bollaert PE, Francois B, Korach JM et al. Effects of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862-71.
20. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, López Rodríguez A et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344:699-709.
21. Reid CL, Perrey C, Pravice V, Hutdinson IV, Campbell IT. Genetic variation in proinflammatory and anti-inflammatory cytokine production in multiple organ dysfunction syndrome. Crit Care Med. 2002;30:2216-21.
22. Watanabe E, Hirasawa H, Oda S, Matsuda K, Hatano M, Tokulisa T. Extremely high interleukin-6 blood levels and outcome in the critically ill are associated with tumor necrosis factor- and interleukin-1-related gene polymorphisms. Crit Care Med. 2005;33:89-97.
23. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial Bloodstream Infections in US Hospitals: Analysis of 24.179 Cases from a Prospective Nationwide Surveillance Study. Clin Infectious Dis. 2004;39:309-17.
24. Gaynes R, Edwards JR and the National Nosocomial Infections Surveillance System. Overview of Nosocomial Infections caused by Gram-negative Bacilli. CID. 2005;41:848-54.
25. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibivici L. β lactam monotherapy versus β lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. BMJ. 2004;328:668-72.
26. Micek ST, Lloyd AE, Ritchie DJ, Richard RM, Fraser VJ, Kollef MH. Pseudomonas aeruginosa bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrob Agents Chemother. 2005;49: 1306-11.
27. Guidet B, Aegerter P, Gauzit R, Meshaka P, Dreyfuss D, on behalf of the CUB-Réa Study Group. Incidence and Impact of Organ Dysfunctions Associated With Sepsis. CHEST. 2005;127:942-51.
28. Alberti C, Bruin-Buisson C, Chevret S et al. for the European Sepsis Study Group. Systemic Inflammatory Response and Progression to Severe Sepsis in critically ill Infected Patients . Am J Respir Crit Care Med. 2005;171:461-8.
29. Krinsley, JS. Effect of an intensive glucose-management protocol on the mortality of critically ill patients. Mayo Clin Proc. 2004;79:992-1000.
30. Venkatesh B, Mortimer RH, Couchman B, Hall J. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. Anaesth Intensive Care. 2005;33:201-9.
31. Abraham E, Laterre PF, Garg R, Levy H, Talmar D, Trzaskoma BL et al. Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death. N Engl J Med. 2005;353:1332-41.