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With editorial comments
by prof. Eldar Søreide

The Emergency Department – The missing link ?
- An update on the management of patients with severe sepsis.

In most Scandinavian hospitals, the Emergency Department (ED) is run by a system where each speciality looks after their own patients. Meaning junior doctors trying their best – mostly alone and in the middle of the night. Does this system produce better or worse outcome than a system with a designated speciality/sub-speciality working in the ED? Should emergency medicine specialists become an integrated part of the Scandinavian hospital system like in UK, Australia and Canada? Or, should we choose our own model based on what is already present? Should intensivists (anaesthesiologists) become even more involved in the ED? Too early to say obviously.

In this review of recent publications, I focus on the septic patient in the ED. The international quality improvement project - the "Surviving Sepsis Campaign" (1-6) - has brought the sub-optimal critical care management of this fragile group of patients to our attention. The first studies focused on the management in the ICU. However, critical care is a concept – not a location! All the best intensive care does not help, if initial treatment fails. What happens with these patients before they enter the ICU? The paucity of publications from Scandinavian countries indicates that we haven't start looking at the problem of severe sepsis in the ED yet! Good for us then that others have (7-9).

Dremsizov T, Clermont G, Kellum JA et al.

Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course?

Chest 2006; **129**: 968-978.

Study objectives: Most natural history studies of severe sepsis are limited to ICU populations. We describe the onset and timing of severe sepsis during the hospital course for patients hospitalized with community-acquired pneumonia (CAP). We also determine the ability of the systemic inflammatory response syndrome (SIRS) and other proposed risk stratification scores measured at emergency department (ED) presentation to predict progression to severe sepsis, septic shock, or death.

Design, setting and participants: Retrospective analysis of a prospective observational outcome study in four academic medical centers in the United States and Canada between October 1991 and March 1994. The 1,339 patients hospitalized for CAP in the PORT study cohort, and a random subset of 686 patients for whom we had information for SIRS criteria.

Interventions: None.

Measurements and results: All subjects had infection (CAP). Severe sepsis was defined as new-onset acute organ dysfunction in this cohort, using consensus criteria. Severe sepsis developed in one half of the patients (n = 639, 48%), non-pulmonary organ dysfunction developed in 520 patients (39%), and septic shock developed in 61 subjects (4.5%). Severe sepsis and septic shock were present at ED presentation in 457 patients (71% of severe sepsis cases) and 27 patients (44% of septic shock cases), respectively. While SIRS was common at presentation (82% of the subset of 686 had two SIRS criteria), it was not associated with increased odds for progression to severe sepsis (odds ratios [ORs], 0.65 and 0.89 for two or more SIRS criteria and three or more SIRS criteria, respectively), septic shock (ORs, 0.80 and 0.55), or death (ORs, 0.65 and 0.39), with poor discrimination (all receiver operating characteristic [ROC] areas under the curve < 0.5). The pneumonia severity index was associated with severe sepsis ($p < 0.001$) with moderate discrimination (ROC, 0.63).

Conclusion: Severe sepsis is common in hospitalized CAP patients, occurring early in the hospital course. SIRS criteria do not appear to be useful predictors for progression to severe sepsis in CAP.

***Commentary:**: Community-acquired pneumonia (CAP) is a common diagnosis. Most patients are treated at home, while some need hospitalization. The clinical picture varies as does the prognosis. Proper diagnosis, risk stratification and timely treatment are key topics. What this study shows is that in hospitalized CAP patients, other non-pulmonary dysfunction is common already in the ED. Not surprisingly, the more unspecific SIRS criteria were not of much use. The group with the highest mortality – those with septic shock – constitutes a relative small proportion (4.5%) of the total patients. However, almost half of them present in the ED in shock. Again, the importance of proper triage and rapid treatment is self-evident. But, does this happen in Scandinavian EDs? A Scandinavian study on the epidemiology and initial treatment of CPA and severe sepsis is obviously needed to see how far away from optimal care we are at present.*

***Bottom-line:** Pay attention to septic patients in the ED.*

Kumar A, Roberts D, Wood KE 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**: 1589-1596.

Objective: To determine the prevalence and impact on mortality of delays in initiation of effective antimicrobial therapy from initial onset of recurrent/persistent hypotension of septic shock.

Design and setting: Retrospective cohort study performed between July 1989 and June 2004 in 14 intensive care units (four medical, four surgical, six mixed medical/surgical) and ten hospitals (four academic, six community) in Canada and the United States.

Interventions: None.

Measurements and main results: The main outcome measure was survival to hospital discharge. Among the 2,154 septic shock patients (78.9% total) who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 [per hour delay], 95% confidence interval 1.103-1.136, p<.0001). Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%. By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour (odds ratio 1.67; 95% confidence interval, 1.12-2.48). In multivariate analysis (including Acute Physiology and Chronic Health Evaluation II score and therapeutic variables), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome. Median time to effective antimicrobial therapy was 6 hrs (25-75th percentile, 2.0-15.0 hrs).

Conclusions: Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock. Despite a progressive increase in mortality rate with increasing delays, only 50% of septic shock patients received effective antimicrobial therapy within 6 hrs of documented hypotension.

***Commentary:**: This study must be every epidemiology based researcher's "wet dream". The Surviving Sepsis Campaign (SSC) says that every patient should have proper antibiotics commenced within 1 hour. This was not based on RCTs or very good evidence, but on pathophysiological rationale and expert opinion. When studying four different ICU quality data bases and linking data from debut of hypotension to start antibiotics they were able to produce curves and figures linking this with survival that are almost "too good". Although their report is retrospective in nature, it will probably be the strongest evidence for this SSC recommendation of early antibiotics. And, we probably do not need stronger evidence anyway. However, I wonder if we had been able to extract similar kind of data from Scandinavian hospital data system, and if the correlations then had came out the same way?*

***Bottom line:** Hypotension definitely is a warning signal. Get your acts together and do the right stuff!*

Micek ST, Roubinian N, Heuring T et al.

Before-after study of a standardized hospital order set for the management of septic shock.

Crit Care Med 2006; **34**: 2707-2713.

Objective: To evaluate a standardized hospital order set for the management of septic shock in the emergency department.

Design and setting: Before-after study design with prospective consecutive data collection in an Emergency department of a 1,200-bed academic medical center.

Interventions: Implementation of a standardized hospital order set for the management of septic shock.

Measurements and main results: A total of 120 consecutive patients with septic shock were identified. Sixty patients (50.0%) were managed before the implementation of the standardized order set, constituting the before group, and 60 (50.0%) were evaluated after the implementation of the standardized order set, making up the after group.

Demographic variables and severity of illness measured by the Acute Physiology and Chronic Health Evaluation II (APACHE II) were similar for both groups. Patients in the after group received statistically more intravenous fluids while in the emergency department (2825 +/- 1624 mL vs. 3789 +/- 1730 mL, p = .002), were more likely to receive intravenous fluids of >20 mL/kg body weight before vasopressor administration (58.3% vs. 88.3%, p < .001), and were more likely to be treated with an appropriate initial antimicrobial regimen (71.7% vs. 86.7%, p = .043) compared with patients in the before group. Patients in the after group were less likely to require vasopressor administration at the time of transfer to the intensive care unit (100.0% vs. 71.7%, p < .001), had a shorter hospital length of stay (12.1 +/- 9.2 days vs. 8.9 +/- 7.2 days, p = .038), and a lower risk for 28-day mortality (48.3% vs. 30.0%, p = .040).

Conclusions: The implementation of a standardized order set for the management of septic shock in the emergency department was associated with statistically more rigorous fluid resuscitation of patients, greater administration of appropriate initial antibiotic treatment, and a lower 28-day mortality. These data suggest that the use of standardized order sets for the management of septic shock should be routinely employed.

Commentary: *In this study from St.Louis, Minnesota the authors looked at what happened after they implemented the SSC guidelines as standard order set minimising the variability of care in their ED. Although they correctly state that they could not define which of the measures that were most effective and to what extent the so-called Hawthorne effect (placebo effect on the system when focusing on a problem per se) could explain most of the improvement, who cares? The authors should be saluted for presenting their data showing that care of severe sepsis and septic shock can be improved without expensive drugs or solution. One problem with the SSC guidelines is said to be that they include recommendations for the use of a specific and expensive anti-inflammatory drug. Although the indication for this drug is well-studied and well documented, critical comments are many (10-12) . The last criticism is that the drug-company sponsored much of the work behind the SSC guidelines(13). Myself, I find it unfair if all the good work done around standardising and improving care of septic patients, is put in discredit because of what many consider "over-selling" by one drug-company. It is not the use of this drug that will save the majority of lives. The drug will probably play a role, but a minor one in terms of number of patients. It is whether we implement the rest of the guidelines locally and pay attention to these patients in the same manner as with trauma patients and STEMI patients! In this before-and-after study the standardisation of care according to the SSC guidelines was actually associated with less use of this costly drug. The SSC guidelines never said anything else either.*

Bottom-line: *The key to good patient care is to care for the patient.*

Flaatten H.

Epidemiology of sepsis in Norway in 1999.

Crit Care 2004; **8**: R180-184

Introduction: Little is known about the occurrence of sepsis in general hospital populations. The goal of the present study was to reveal the epidemiology of sepsis in Norwegian hospitals over 1 year.

Methods: Patients admitted to all Norwegian hospitals during 1999 (n = 700,107) were analyzed by searching the database of the Norwegian Patient Registry for markers of sepsis, using International Classification of Diseases (ICD)-10 codes for sepsis and severe infections. In patients with such diagnoses, demographic data, hospital outcome data and ICD-10 codes for organ dysfunction were also retrieved. Sepsis was further classified as primary or secondary, and severe (sepsis with vital organ dysfunction) or non-severe. The age-adjusted mortality rate, and the sepsis rates for all hospital admissions and in the Norwegian population were calculated.

Results: A total of 6665 patients were classified as having sepsis, and of these 2121 (31.8%) had severe sepsis. The most frequent failing organ system was the circulatory system, and

1562 had septic shock. Mortality increased from 7.1% (in those with no documented organ dysfunction) to 71.8% (in those with three or more organ dysfunctions). The mean mortality was 13.5%, and the mortality of severe sepsis was 27%. The incidence of sepsis was 9.5/1000 hospital admissions and 1.49/1000 inhabitants in 1999.

Conclusion: Sepsis is not uncommon in Norwegian hospitals and is associated with high hospital mortality, which is similar to recent findings from the USA. Awareness of sepsis and its appropriate treatment is mandatory in Norway if we are to reduce mortality from sepsis by 25% in the next 5 years.

Commentary*: Flaaten(14) here shows that severe sepsis is a major health care problem in Norway in the same manner as shown in other countries and in more specific population of hospitalised patients (15-26). Instead of focusing on whether to use one expansive drug or not, isn't it time to evaluate to what extent a focused, standardised approach using the SSC care bundles (1) can improve outcome in Scandinavian septic patients? Starting with proper referral, diagnosis and triage in the ED, and then onwards…………?*

Bottom line: *You cannot just look the other way and blame the industry if your sepsis patients get sub-optimal care in your institution.*

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