ICU MANAGEMENT & PRACTICE

ICU Volume 5 - Issue 1 - Spring 2005 - Features

German Competence Network for the Study of Severe Sepsis and Septic Shock (SepNet)

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Drs Brunkhorst and Reinhart provide an update on the SepNet infrastructure and two scientific projects, which it supports, VISEP and PREVALENCE.

SepNet

Faced with therapeutic stand-still and limited results of former trials in the field of sepsis, the major objective of SepNet was to establish an efficient infrastructure for sepsis research in Germany and to develop and initiate independent, innovative, internationally competitive, prospective clinical trials. Due to the limited funding awarded, the goals of SepNet are restricted to the establishment of the network structure with the following central facilities:

1. 23 regional study centres throughout Germany for the recruitment of patients for clinical trials within the network;

2. a SepNet office for all management and steering issues;

3. a Centre for Study, Coordination, Biometry and Telematics (CSCBT) to provide professional assistance for the planning, conduct and analysis of scientific projects and to provide an appropriate telematic infrastructure (remote data entry, communication, data management);

4. a central sample bank for serum, plasma and DNA samples of septic patients as a basis for future research projects.

Scientific projects funded by the German Ministry of Education and Research (BMBF) and by additional thirdparty support from the industry include:

a) A randomized controlled interventional multi-centre trial to investigate the role of colloids vs. cristalloids for Volume substitution and the role of conventional vs. intensive Insulin therapy in the treatment of severe SEPsis and septic shock ("VISEP-Study").

b) A national epidemiologic study for the estimation of the prevalence of sepsis including assessment of treatment habits and related costs, and information on the current organization and structure of Intensive Care Medicine in a representative sample of German ICUs ("PREVALENCE Study").

VISEP

The VISEP trial was bifactorially designed to prospectively assess the choice of fluid resuscitation (hydroxyethylstarch 10% vs. lactated Ringer solution) and the quality of blood glucose adjustment by insulin treatment (conventional vs. intensive insulin treatment) on the mortality of patients with severe sepsis or septic shock (sample size: 600 patients). The primary endpoints are a reduction in the mean SOFA-Score (1.2 points) and a 10% reduction in the 28 and 90 day mortality rate, respectively (adaptive two-phase study design). Secondary endpoints are the frequency of renal failure in patients treated with colloids, the reduction in the occurrence of critical illness polyneuropathy in patients treated with intensive insulin therapy, time to haemodynamic stabilization, ventilator-free days and length of stay in the ICU. In 2002, the protocol, the case report forms, the working instructions and the applications for the ethics committees were prepared. The protocol was discussed and modified in collaboration with all SepNet members during the following General Assemblies. Since the VISEP-study was not part of the BMBF funding, SepNet obtained industrial funding to undertake this trial. The start of the VISEP study (originally scheduled for January 2003) was delayed since

the quality of whole blood glucose measurements was not consistent enough among SepNet centres to satisfy scientific and safety needs. A uniform methodology for blood glucose measurement at the bedside needed to be established in all regional SepNet centres. HemoCue® (HemoCue AB, Ängelholm, Sweden) was the only device to fulfil such criteria. A quality control system was established by the SepNet Office together with the central laboratory of the network. The results of this quality control system revealed a high quality device, comparable with daily routine results in the central laboratory. An IT-infrastructure (eResearch Network from eResearch Technologies) for the central data base, remote data entry and central data and quality management was implemented successfully. Completeness, plausibility and consistency of data is checked by automated procedures on a daily basis with generation of corresponding query reports, which are communicated electronically to the trial sites. First patient visits for the VISEP trial began on April 1, 2003. In July, 2003, an amendment to the protocol became necessary to change the procedure for the diagnosis of the critical illness polyneuropathy, which is a secondary study endpoint. Since the start of the study, 428 patients have been enrolled.

Sample Bank

A centralized Sample Bank facility has been established. With the goal to guarantee optimal homogeneity of sample quality with respect to pre-analytical conditions and long-term storage, Standard Operating Procedures(SOPs) were created addressing all relevant steps of sampling, processing of primary samples, and sample transport. Dedicated order forms were provided for contributing centres linking sample ID (bar-code label on samples sent to Sample Bank and order form submitted to data collection centre) and patient ID (order form sent to data collection centre); patient data were coded with pseudonyms and a data trustee ensures confidentiality of patient data.

Ascertaining homogenous sample quality allowed focus on obtaining samples of pre-defined, well-controlled, and homogenous rather than optimized quality; to this end, emphasis was placed on minimizing pre-analytical steps and sample handling outside the central Sample Bank facility. Pre-defined quality assurance procedures were detailed to and discussed with staff of contributing centres during dedicated, regular study meetings. A special “lab package”, containing order forms, primary and secondary sample containers and a return envelope for EDTA samples for DNA preparation, was provided for each individual patient to be included in the study. To minimize the risk of sample mix-up, bar-coded labels were provided to transfer sample ID to all secondary samples after centrifugation. Centrifuged serum samples were frozen at the site of the contributing centre and sent batch-wise to the central Sample Bank. Our quality management helped to ensure that a vast majority of samples were obtained following these procedures.

The application procedure for use of banked samples obtained through the study was set out prior to sample acquisition. Researchers both from within and outside the SepNet study can apply to the central study board of SepNet; following approval by the board, the central Sample Bank will provide sets of sample aliquots according to (approved) user specifications. To implement logistics and quality management procedures for sample retrieval, compilation of aliquot sets and shipping is, thus, another goal for the upcoming phase of the project.

PREVALENCE Study

Although a large number of epidemiological sepsis studies have been performed in Europe and the US in the past years, sound data for Germany is lacking so far. In the study "Prevalence of severe sepsis and septic shock in Intensive Care Units in Germany”, a prospective observational cross-sectional study, the network gathered data from 454 randomly selected ICUs in 310 hospitals in Germany and screened 3,877 patients - according to the ACCP/SCCM Consensus Conference criteria - by local one-day visits of trained physicians from SepNet´s 17 regional study centres. Visits were randomly distributed over a one year period (2003) to allow assessment of seasonal variations of sepsis prevalence. The ICU sample was taken from a registry of all German hospitals with ICUs (1380 hospitals with 2075 ICUs). Paediatric ICUs were not included. The study was completed in January 2004 and the data base closed on May 31. 7% of ICUs were situated in universities, 34% were university-affiliated and 53% in general hospitals. 56% of ICU directors were anaesthesiologists and 26% internists. An infection was microbiologically documented in 22% and diagnosed by clinical criteria alone in 12% of screened patients. Respiratory tract infections were most common (52%), followed by intra-abdominal (15%) and urogenital infections (7%). Gramnegative and grampositive infections were nearly equally distributed (33% vs 35%); in 16% a fungal infection was suspected. The prevalence of sepsis was 12%, infection without SIRS 7%, and severe sepsis/septic shock 11%. There were significant differences in the prevalence of severe sepsis/ septic shock over one year with the highest prevalence in May/June 2003 (18%). The infection was ICU acquired in 37%, hospital acquired in 20% and community acquired in 35.5%. ICU mortality in patients with severe sepsis/septic shock was 47% and hospital mortality 54%. Based on these findings the incidence of severe sepsis/septic shock in German ICUs can be estimated to 75,000 cases per year (110 per 100,000 inhabitants), comparable with the incidence of acute myocardial infarction (143 per 100,000 inhabitants).

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Incidence and mortality rate of severe sepsis and septic shock in German ICUs are higher than reported in recent studies. This may be due to the representative sample size, the more standardized diagnostic criteria and a lower inter-observer variability.

To increase the public awareness for sepsis, the German Sepsis Society (GSS, www.sepsis-gesellschaft.de) was

founded on November 2001 among a group of SepNet members. The chair of the GSS (Prof. Reinhart) is the speaker of SepNet, and the board members are almost all SepNet members. The GSS fulfils different, but complementary tasks: whereas SepNet is a platform for clinical and

basic research, the GSS is the scientific society for sepsis and responsible for all public relation and educational activities of SepNet. The GSS has defined recommendations for the diagnosis and treatment of severe sepsis and septic shock. These recommendations have been developed in accordance with the recommendations of the International Sepsis Forum (Intensive Care Med 2001; 27 Suppl 1: S1-134) and the Surviving Sepsis Campaign (Crit Care Med 2004; 32: 858-872). A Continuing Medical Education (CME) about sepsis was offered to all hospitals, which have been visited during the PREVALENCE Study and a promotion campaign has been started at national congresses and meetings. The organization of the CME is funded by the GSS and is free of charge for the attended hospital. For each presentation, SepNet and the GSS chose a speaker from the working group who is committed to the content of the prepared presentation. The GSS organizes a biannual international sepsis congress. The first congress “Sepsis and Multiorgan Dysfunction” was attended by 1100 visitors from 22 countries. Furthermore, the research prizes of the GSS, the Hugo-Schottmüller-prize and the Roger-Bone-prize have been awarded since 2002. The 2nd International Congress on “Sepsis and Multiorgan Dysfunction” will be held from Sept. 7 – 10, 2005 in Weimar.

Published on : Thu, 15 Aug 2013