Extended Prevalence of
Infection in Intensive Care

A Prospective Multicenter International 24-hour Prevalence Study

Study Protocol

version 1.0

9 June 2017

1. General information

1.1 Organization

Steering committee

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Coordinating center

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Data management

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1.2 Protocol summary

Title of the study	The Extended Study of Prevalence of Infection in Intensive Care III *(EPIC III)*
Design	Prospective, multicenter, international one day prevalence study
Target population	All patients present on or admitted to a contributing center on the study day
Interventions	None
Study objectives/ research questions	- How does the prevalence and pattern of organ dysfunction vary by global region? - What is the impact of microorganism resistance patterns on outcome? - How have the patterns of infection and of organ dysfunction changed over time from EPIC 1 through EPIC 2 to EPIC 3?
Subgroup/ Sub-study analyses	- Patterns and variations in antibiotic use - Comorbidities and relationship with prevalence and outcomes of infection - Relation of ICU and hospital organizational issues to prevalence of infection and outcome - Prevalence and outcome of infection in specific subgroups - End of life - ethical decisions
Study duration	Twenty-four hours (and 60-day follow-up in-hospital for outcome)
Follow-up period	Duration of index hospital admission censored at 60 days
Important dates	Deadline for registration: September 14, 2017 Study day: September 13, 2017 from 08:00 to September 14, 2017 at 07:59 End of follow-up period: November 13, 2017 Deadline for data entry: December 15, 2017

2. Rationale and aim of the study

Sepsis, defined as infection plus organ dysfunction, is an important problem, representing about the 10th leading cause of death in industrialized countries, and the leading cause of death in the intensive care unit (ICU). Recent years have seen several studies providing important national and international epidemiological data on the frequency, associated factors and costs of sepsis (1-7). Most of the large epidemiological studies on infection and sepsis have been conducted in North America, Europe and Australia, with relatively few data from emerging countries.

Two key measurement techniques have been used in all these studies: prevalence, i.e., the percentage of a population that has sepsis at a given time; and incidence, i.e., the number of new episodes of sepsis that commence during a specified period of time in a specified population. The different techniques, different definitions used for sepsis and different study populations can make it difficult to compare study results. Nevertheless, epidemiological data about the incidence of the disease, the type(s) of patient(s) affected, causative microorganisms, and outcomes are crucial in order to increase and maintain awareness of the impact of infection and sepsis, to help in the development of local and international policies for diagnosis and treatment, to facilitate adequate and appropriate resource allocation, and to assist in the design of interventional studies.

The European Prevalence of Infection in Intensive Care (EPIC) study (8) conducted on April 29, 1992, included data from 1417 ICUs in 17 Western European countries and provided valuable information regarding the prevalence of infection and demographics of infected critically ill patients. Fifteen years after that successful international collaboration, EPIC II, the Extended Prevalence of Infection in the ICU Study, was conducted to provide an up-to-date picture of the extent and pattern of infection in ICUs around the world (9). Demographic, infection-related and outcome data were collected from the 14,414 patients present on one of the 1265 participating units from 75 countries on the study day. Now, 10 years later, we are conducting EPIC III on **September 13, 2017** (on World Sepsis Day) to provide an update on the epidemiology and outcome of infection in ICU patients around the world. This major collaborative initiative will result in the formation of a large database, which will be useful to address a number of fundamental questions.

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3. Study outcomes

3.1 Primary outcome

The primary outcome measure is all-cause mortality at hospital discharge censored at 60 days.

3.2 Secondary outcomes

Secondary outcome measures are:

- ICU mortality
- ICU and hospital lengths of stay

4. Study description

4.1 Study design

A multicenter, international, observational, 24-hour prevalence study.

4.2 Study population

Inclusion criteria

All patients present on or admitted to a participating ICU on the study day.

Exclusion criteria

None

5. Study course

5.1 Patient enrollment

Patient enrollment will be limited to September 13 from 08:00 to September 14 at 07:59 in the local time zone.

5.2 Ethics committee approval

Where required by local legislation or regulation, the study protocol will be submitted to the local ethics committee for approval.

5.3 Therapeutic intervention

The study is purely observational with no interventions.

5.4 Data collection

Data collection includes:

- On admission: demographic characteristics, comorbidities, source of admission, primary and secondary admission diagnoses

- Study day data, including parameters used to calculate APACHE II, SAPS II and SOFA scores, and infection-related data
- Outcome at ICU and hospital discharge (or 60 days, whichever comes first)

5.5 End of follow-up period

November 12, 2017 for patients admitted on September 13, and November 13, 2017 for patients admitted on September 14.

5.6 Deadline for data entry

December 15, 2017

6. Data collection

Data can be collected on pre-printed case report forms (CRFs) by the attending intensivist or delegate (other physician or a trained research nurse/coordinator) but should be entered electronically by the investigators (centers with limited internet access may submit completed paper forms to the coordinating center for data entry if requested at registration). Access to the data entry system will be protected by a username and password, which will be provided to individual investigators during the registration process. All electronic data transfer between participating centers and the coordinating center will be username and password protected. Each center will maintain a trial file including a protocol, local investigator delegation log, ethics approval documentation etc. A patient list will be used in each participating center to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points.

The CRF will include the following sections - Form 1 must be completed once by each center; Forms 2-4 must be completed for each patient.

Form 1 - Center demography: This includes data on local hospital/unit characteristics and organization and general aspects of patient management.

Form 2 - Patient enrollment: This contains demographic information for each patient.

Form 3 - Study day variables: This form includes the variables used to calculate APACHE II, SAPS II and SOFA scores, and infection- and treatment-related data.

Form 4 - Follow up: This form should be completed at time of discharge (or at 60 days, whichever comes first).

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7 Data management and archiving

7.1 Data control

Data control will involve the following levels:

1. All participants will be provided with detailed information, including definitions of medical terms. The coordinating center will provide a rapid response for any queries (please see contact information).
2. Data plausibility checks will start at the entry level electronically, setting validity limits for each variable. Investigators will be queried in case of outliers or excessive numbers of missing values.

7.2 Data property

The individual data provided by a participating ICU remain the property of the ICU that generated the data. All investigators have the right to access their data at any time.
The aggregated study data will be jointly owned by the steering committee and the ICUs contributing data to the study.

7.3 Subsequent use of data

The steering committee, on behalf of the investigators, has the right to use all the data that are pooled in the databank for scientific purposes. Investigators will be regularly informed about ongoing study activities (see also under publication rules). All participants have the right to access the data, pooled in the databank, for research purposes after the research project has been completed, and with the approval of the steering committee.

7.4 Archiving

A copy of the electronic databank will be kept in the coordinating center and preserved for 15 years for subsequent use by the steering committee and investigators. It is recommended that a copy of the CRFs be kept at each center for future reference.

8 Publication rules

Authorship will take the following elements into account: study design, study organization, data collection, patient enrolment, data analysis, and contribution to the manuscript.

9 Sponsorship

There is no sponsorship.

10 Statistical analysis

Statistical analysis will be performed using SPSS for windows version 24.0 (Chicago, USA) and R software, version 3.2.3 (CRAN project). Categorical variables will be described as numbers and proportions. Continuous variables will be described as mean and standard deviation or median and inter-quartile range. Differences between groups in distribution of variables will be assessed using analysis of variance (ANOVA), Kruskal Wallis test, Student's t-test, Mann-Whitney test, chi-square test or Fisher's exact test as appropriate. Multivariable models using multilevel analysis (binary logistic model and/or linear regression model) will be performed to assess independent associations between prognostic factors and outcomes. Statistical significance will be set at the 5% level.

11 References

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