EUROBACT II

Epidemiology and determinants of outcomes of Hospital Acquired Blood Stream Infections in the Intensive Care.

A multinational cohort study by the ESICM infection section.

STUDY PROTOCOL
V 1.21
5/12/2019

Eurobact II is endorsed by:

The ESICM Infection Section
The ESICM Trials Group
ESCMID Study Group for Infections in Critically Ill Patients – ESGCIP
Asia Pacific Association of Critical Care Medicine - APACCM

Title	Epidemiology and determinant of outcomes of hospital acquired Blood Stream Infections in the intensive care. (Eurobact II)
Design	Prospective observational multinational, multicenter cohort study.
Target pop.	Patients with a Hospital acquired blood stream infection treated in the ICU.
Interventions	None
Study objectives/ research questions	**Primary outcome measure** Day 28 mortality in patients with HA-BSI **Secondary outcome measures** Progress of organ failures at day 7 Days free of RRT/MV/Vasopressors/ICU **Objectives** • To describe the organisation of microbiology processing o Communication, changes with day/night/weekend. o Use of rapid testing for resistance patterns (VRE, CPE, others) o Use of Maldi-Tof for rapid identification. • To describe the determinants of outcomes of HA-BSI, specifically the effects o Source o Microorganisms. ▪ Species and antibiogram ▪ Resistance and "difficult to treat" status ▪ Mechanism of resistance and specific enzymes (ESBL, Carbapenemase producers, VRE…) ▪ MICs for Difficult to treat pathogens. o Antimicrobial therapy ▪ Timing, Spectrum and adequacy ▪ Combination therapy ▪ Dose and Mode of administration ▪ Modifications including escalation and de-escalation. o Source control, including timing and adequacy. o Patient specific factors o Severity of shock, organ failures and lactate levels o Organisational factors • To assess the respective impact of the source the microorganism and the components of therapy on outcomes. • To describe the determinants of management of HA-BSI, including o Diagnostic methods and how they influence starting and modifying therapy (MALDI-TOF and molecular vs traditional methods for identification, speciation and susceptibility reporting) o Type, dosing and duration of antimicrobial therapy o Source control o Other treatments for sepsis (steroids) • To describe epidemiological changes since the Eurobact study.
Study duration	3 months or 10 included patients per center.
Follow-up period	28 days or hospital discharge.

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Rationale:

Sepsis is recognised as one of the leading causes of mortality and has become a global healthcare priority. It is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. In a large multinational study Infections were thought to be present in 51% of ICU patients, of which 30% were culture negative [2].
Blood stream infection (BSI) is defined as the presence of a pathogen in the blood stream of a patient. As such, and once contaminants are excluded, BSI is the only cause of sepsis where the presence of an infection and the pathogen are known with certainty. This makes BSI the perfect model of infection to study the effects of the micro-organism on the patient, and the effects of the antibiotics and other treatments on survival.
The Eurobact 1 study collected multinational data on HA-BSI in 2010-11 as part of a large multicentric collaboration coordinated by the infection section of the ESICM [3]. By including 1156 patients with HA-BSI from 162 ICUs in 24 countries this was the largest and most cited study of HA-BSI treated in the ICU. It has been topical in describing the relationship between antimicrobial resistance (AMR) and increased delays in effective drug therapy and how resistance is independently associated with mortality.
While growing AMR and sepsis makes the headlines of mainstream media, the problematic of growing AMR was recently highlighted in a joint roundtable hosted by the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the World Alliance Against Antimicrobial Resistance (WAAAR) [4]. The panel published a list of 6 recommendations, of which 1 was to make AMR a priority in research activities, 2 to document Gram Negative AMR infection from a global perspective and 4 to collect data on treatment and outcome of XDR/PDR infections. Furthermore recent changes in the overall management of patients with sepsis and shock and a reported change in prognosis makes it urgent to obtain current data on HA-BSI in the critically ill [5, 6].
Eurobact 2 was developed by the infection section of the ESICM to specifically answer those questions and recommendations. By targeting HA-BSI in a large multinational study we will obtain granular data and investigate how management and outcomes of patients with severe hospital acquired infections may have changed while there has been a worldwide increase in AMR.

Objectives and outcome measures:

Primary outcome measure

Day 28 mortality in patients with HA-BSI

Secondary outcome measures

Progress of organ failures at day 7

Days free of RRT/MV/Vasopressors/ICU

Objectives

- To describe the epidemiology and determinants of outcome of HA-BSI treated in the ICU
- To describe the organisation of microbiology processing
    - Communication, changes with day/night/weekend.
    - Use of rapid testing for resistance patters (VRE, CPE, others)
    - Use of Maldi-Tof for rapid identification.
- To describe the determinants of outcomes of HA-BSI and specifically the effects of:
    - Source
    - Microorganisms.
        - Species and antibiogram
        - Resistance and difficult to treat status
        - Mechanism of resistance and specific enzymes (ESBL, Carbapenemase producers, VRE…)
        - MICs for Difficult to treat pathogens.
    - Antimicrobial therapy
        - Timing
        - Spectrum and adequacy
        - Combination therapy
        - Dose
        - Mode of administration
        - Modifications including escalation and de-escalation.
    - Source control, including timing and adequacy.
    - Patient specific factors
    - Severity of shock, organ failures and lactate levels
    - Organisational factors
- To describe the determinants of management of HA-BSI, including
    - Diagnostic methods and how they influences starting and modifying therapy (MALDI-TOF and molecular vs traditional methods for identification, speciation and susceptibility reporting.)
    - Type, dosing and duration of antimicrobial therapy
    - Source control
    - Other treatments for sepsis (steroids)
- To describe epidemiological changes since the Eurobact study.

Design:

Prospective observational multicenter cohort study.

Intervention:

none

Patient Inclusion criteria:

All adult (Age > 18 Years) patients with a Hospital Acquired Bloodstream Infection (HA-BSI) treated in the ICU.
HA-BSI is defined as a positive blood culture (BC) sampled after 48 hours following hospital admission.

For CNS and common contaminants (coagulase-negative staphylococci, Corynebacterium species, Bacillus species, Propionibacterium species, Aerococcus species, Micrococcus species), 2 blood cultures with the same antimicrobial susceptibility profile are mandatory or strong clinical grounds that it is not a contaminant. One example is infected material proven as a source for the HA-BSI.

Treated in the ICU is defined as the BC has been sampled in the ICU or the patient has been transferred to the ICU for the treatment of the BSI.

Exclusion criteria:

Community acquired BSI = Blood culture sampled before 48 hours following hospital admissions.
Patient not treated in the ICU.
Patients that had a positive blood culture in the hospital and transferred to ICU for a different reason than specific treatment of the causes or consequences of HA-BSI.
Patients less than 18 years of age.

Duration of the study:

3 consecutive months or 10 consecutive hospital-acquired bacteraemia per intensive care unit, whichever comes first.
Inclusions beyond 3 months or for more than 10 patients is possible on request of the participating ICU or National Coordinator.
A flexible start of the inclusion period will be allowed for each ICU to facilitate participation in the study.

Unit participation criteria:

Definitions of Intensive Care vary over the world. Any department specifically designed to manage patients with organ failures within a health facility and able to provide invasive mechanical ventilation for a duration of more than 24 hours is defined as ICU for this study.

Ethical considerations.

Eurobact 2 is a prospective observational study. All data will be collected from the patient's chart. There is no requirement for any diagnostic test or intervention additional to what the patient is receiving s part of their treatment.
All data will be anonymously collected on a secured webserver by the operational committee. No identifying data will be collected.
Ethical requirements for data collection vary within countries and jurisdictions. Where appropriate, ethical approval and requirement or waiver for consent of participation will be obtained for each country by the country coordinator and where required by the local primary investigator at each site.

Timeline

- March 2018:
    - First announcement of the study.
    - A team of experts constitutes the organisational committee.
    - Country coordinators are recruited.
    - Protocol and data requirements are designed.
    - An e-crf is designed.
- October 2018:
    - The study has been awarded the ESICM Trials Group award.
    - National Coordinators recruitment ongoing
- November-June
    - Expressions of interest are sought from prospective participating centres
    - Ethical requirements are completed by country coordinators
    - E-CRF setup and testing
- September 2019
    - Study commencement.
- September 2019 – September 2020
    - Flexible 3 months commencement period
- October 2020
    - Preliminary results presented at ESICM LIVES 2020
    - Completion of 28 days follow-up
    - Data-quality controlled and tidying-up the database.
- Late 2020
    - Data analysis and write up of the core epidemiological description of the database.
- Early 2021
    - Publication of the core paper
    - Analysis and write up of ancillary analysis.

Data to record:

- Center data: Single entry for each participating ICU.
    - To collect adjustment variables and define center effect.
    - To define the effect of specific microbiology processing techniques on outcomes.
        - Type of hospital/ICU/specific recruitment
        - Staffing variables
        - Scoring systems used
        - Stewardship practices.
            - Infectious diseases specialist availability within and outside of the ICU.
            - Specific ID or Stewardship rounds and/or Phone advise
            - Timings (daily vs specific day vs on demand)
            - Written protocols and common practices for administration and modification of antimicrobial therapy (modality of infusion, use of TDM, MIC based adjustments)
            - Restricted antibiotics/preauthorization/use of computerized prescription systems
        - Microbiological lab specifics
            - Organization and communication with the ICU
                - Opening times and reporting delays
                - Communication mode (phone, internet, proprietary software, fax, in person, email, paper mail)
                - Techniques used
                - availability of novel rapid diagnostic techniques
                - Reporting to the clinicians and stewardship specialists (if different)
                    - Sensitive vs resistant status
                    - Reporting of MICs, resistance mechanisms, specific enzymes
                - Availability of TDM for each class of antibiotics and use of pharmacodynamic principles for dose adjustment of antimicrobials
        - MDR prevalence.
        - Type and frequency of screening for MDR colonisation.
        - Number of patients and severity for the study period.
- Patient data: once per patient
    - Admission data
        - Dates of ICU and Hospital admission
        - Reason for admission
        - Co-morbid conditions
        - Severity score: APACHE II
        - Frailty and treatment limitation orders.
    - Infection data (day of bacteraemia)
        - Source
        - Severity of shock
            - SOFA score

        - Lactate levels
        - Organ supportive therapy (MV/RRT/Vasoactive)
    - Specific / other treatments
        - steroids
- Microbiological data
    - Center questionnaire will determine what data and timings each centre can provide and adjust to those
    - Date-time of sampling / positivity
    - Date-time of Gram stain / antibiogram where available
    - Rapid testing if used
    - Antibiogram / molecular methods
    - Mechanism of resistance if known
        - ESBL, CPE, MRSA, VISA, VRE
          Specific enzyme
    - MICs
- Treatment data
    - Antibiotics already present at onset of bacteraemia
    - Antibiotics given for the infection
        - Date / time of start
        - Date / time of changes and reasons
        - Date time of stop
        - Dose / route / mode of admin (II as default, CI if used…)
        - TDM. Change of antibiotic doses based on TDM results
- Follow up data
    - Censored at d28
    - Duration of MV/RRT/Vasoactive agents
    - SOFA score at day 7.
    - Dates of ICU and Hospital discharge
    - Vital status and cause of death

Operational considerations

Principal investigators

To design the study, coordinate all actors and take primary responsibility for the conduct of the study.

Steering (organisational) committee:

To design the study, including protocol, data collected and scientific protocol.
To participate in the analysis of the data and preparation of the manuscript.
To analyse the data, results and content of the manuscript.

Operational committee:

To coordinate all actors and ensure smooth conduct of the study according to the principles defined in this document. They will report to the organisational committee.

National Coordinator:

National Coordinators (NCs) will be appointed by the Organisational Committee and will have a key role in the conduction of the study in the individual countries as leaders of the project. The role/responsibilities of the NC include the following:

- Advertise the study in the individual countries and identify participating hospitals and local investigators in their country.
- Apply for regulatory approval in a national level where applicable and ensure that ethical committee (EC) approvals or waivers for all the participating hospitals in the country are in place prior to the initiation of the study. The NC will receive scanned copies of the EC approvals from all centers, will check them and report to the Principal Investigator (PI). The checked by the NC scanned copies of the EC approval will be sent altogether to the PI prior to the initiation of the study.
- Assist with the translation of the study protocol/CRF where required.
- Ensure the distribution of study material to the centers (protocol, CRF, instruction manuals etc.) and that the local investigators are familiar to the study material prior to the start date.
- Ensure good communication with the participating sites in the respective country and to animate local investigators to achieve optimal recruitment and follow up during the period of the study. During the period of database quality control (data 'cleaning') the NC should animate the individual to reply in possible queries.
- They are invited to participate in data analysis and preparation of the manuscript.

Local Primary Investigators (LPI)

There will be one local investigator per ICU with the following role/responsibilities:

- Lead the study in their hospital.
- Communication with the NC and OC for each issue that may arise.
- Apply for ethical review where applicable in accordance with the requirements for each jurisdiction.
- Ensure accurate data collection and accurate and timely eCRF completion.
- Reply promptly to possible queries during the period of database quality control
- Maintain a patient list to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points.
- Guarantee the integrity, consistency and quality of data collection and ensure that the EC approval, the patient list and the paper CRFs will be kept in a safe and locked place for the period of time set in the study protocol.

Electronic data capture:

The case report file and the electronic version will follow these principles:

- Anonymity.
- Data security and encryption of internet communications.
- Minimisation of the data required to answer the primary and secondary objectives.
- Ease of use.
- Reliability.

Data will be collected on an electronic CRF (eCRF, secured website). The patient file or a local copy of the Paper/PDF versions of the center form and the patient's CRF will be considered as source data.

Financial considerations

A grant of 25 000 euros has been awarded by the ESICM Trials Group for operational management of the study and eCRF management.
A grant of 30 000 euros has been awarded by the ESCMID for operational management of the study and statistical analysis.
A grant of 5000 Australian dollars has been awarded by the Norva Dahlia foundation specifically to facilitate patient inclusions in Australia.
Support will be provided in kind by the primary investigators at their institutions.

Sponsor and Legal considerations

The Outcomerea organization is the sponsor, data-custodian and responsible for data security, management and statistical analysis. Where required the Outcomerea organization will provide with data transfer agreements between them and participating centres.

Security, confidentiality and data quality processes

All data will be collected by the LPI at each site. A list of included patients will only be kept locally by the LPI at each site. Confidentiality must be kept at all times and the file should be kept in a locked environment or digitally encrypted in a secure fashion.
Data will be collected to a secure webserver.
No identifying data will be transferred at any time.

The eCRF will contain consistency checks to avoid typing errors and capture of implausible data. Efforts will be made to accommodate different unit systems and harmonise data in the back-end. Routine data consistency checks will be operated by the statistical team and any inconsistencies will be returned to the operational committee to be discussed with the NC and LPI. Every case report will be reviewed manually by the operational committee and queries discussed by the LPI.
In extreme cases of inconsistencies and unavailable data case reports may be excluded from the study.

All study records at local sites should be kept for at least 3 years by the local investigators.

Once all data has been collected and queries resolved the electronic CRF and working database will be taken offline. Pseudonymised data and the webserver database will be kept by the sponsor for 5 years to ensure all queries can be resolved, then securely destroyed.

Once all queries have been resolved and prior to analysis the database will be transformed in an anonymised data matrix which will be securely stored for 20 years for scientific purposes.

Use of data and property

The data pooled in the databank will be the collective property of the investigators and maintained by the Outcomerea organization and the primary investigators to be used for scientific purposes.

An initial description of the data will be provided by the statistical team to describe the database and answer the primary and secondary objectives of the study.
Any requests for subsequent analysis will be reviewed by the steering committee, on behalf of the investigators. Validity, overlap and scientific interests will be taken in account before a decision is made and a supplementary analysis is provided or not.

Statistical analysis

Statistical analyses will be performed using SAS (SAS institute, NC USA), R (R project Vienna Austria) and additional software where appropriate. 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 will be described with the appropriate statistical test accordingly. Multivariable hierarchical models will be used to investigate the independent associations within collected variables and mortality.
Models for causal inferences (propensity score or inverse probability of treatment weighting) will be used for the appropriate determinants of outcome.

Rules for publication and authorship

After the study and data monitoring are completed and the database has been closed, the statistical team will provide a comprehensive analysis. The principal investigators will prepare a draft manuscript and submit to the organisational committee and prospective authors for discussion, analysis and editing. They will form the Writing Committee. From each submission a period of 2-3 weeks will be allowed for comments and discussion before a revised manuscript is prepared. The process is to be repeated until a satisfactory scientific manuscript is obtained. In case of disagreements on the scientific content, adjudication will be obtained by voting within prospective authors. In extreme cases adjudication will be done by the principal investigators.

Authorship will be defined according to the guidelines published by the international Committee of Medical Journal Editors (ICMJE) which can be summarized in the following 4 principles to define an author [7].

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Substantial coordination efforts will also be considered for authorship.
It is expected that most members of the organization committee and country coordinators may fulfil the above criteria according to their contribution.
Group authorship will be defined as “The Eurobact 2 study group”. All research publications will be reported as: “the authors, the Eurobact 2 study group on behalf of the infection section of the ESICM.”
We will list all PI at each center as collaborators as allowed by the publishing journal. All collaborators will be listed in the acknowledgement section of each publication according to their contribution.

Pre-Planned subgroup and ancillary analysis.

- The effects of combination therapy and aminoglycosides in high severity patients.
- Timing of source control

Protocol registration

Clinicaltrials.gov registration number NCT03937245

Organization

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Outcomerea is a non-profit nongovernmental organization, collaborative of researchers to promote and develop research and education in critical care. Outcomerea maintains the e-rhrea multicentre database of ICU admissions and has a strong track record in ICU research.

Outcomerea is the data custodian for the Eurobact II database on behalf of the investigators. It will provide with the CRF, data hosting and security, data management and statistical analysis for the Eurobact II study.

References

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7. ICMJE (2017) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. ICMJE 1–17

Version record

CRF
1.08-19-09-2019 Added Bilirubin to scoring variables for: Time of BSI for ICU diagnosed infections and at Day 7. CRP/PCT was added to a timepoint where it was missing. These variables were already recorded at different time points and those time points were added for consistency.

Sections have been renumbered, renamed and some parts reordered to facilitate data capture where it is done on paper and secondarily transferred to the e-CRF – no changes to the data collected.
1.07-25/07/2019
Added some separator headings to the table of co-morbid conditions (no change in collected data)
Re-arranged the wording of a sentence describing suspected blood culture contaminants (meaning not changed)
Added some explanatory text to the GCS score and modified the way delirium is captured to increase quality of the data.
Added a question on antibiotic levels
Modified to table of source control interventions to capture if it was effective or not for each group of interventions and a question regarding positivity of microbiological specimens from the source.
1.06-13/06/2019
Added the possibility to enter spine as modality for investigations
1.05-03/05/2019
Added PET-Scan to investigations (7.3)
Added mediastinitis and surgical site infection to sources (3.3)
Changed the ordering of source control interventions (7.2) to match sources as entered in 3.3
Removed days of High-Flow Nasal Canula oxygen therapy from day28 follow up.
1.04-15/04/2019
Corrected typographic errors in subsections numbering.
1.03 –28/02/2019
Simplified admission categories to medical and surgical elective or emergency
Clarified Co-morbidities to allow for Charlson score calculation but also APACHE II ROD.
Re-organised scoring data to simplify data capture and avoid duplicate entry of the same values if cases have a date of ICU admission = date of BSI. Data captured is the same.
Added the variables: CRP, Procalcitonin, Lymphocyte count.
Added a section to inform on previous MDR colonisation and antibiotics received in the 7 days prior to the index BSI.
Clarified definitions for withhold or withdraw life-sustaining treatment.
1.02 – 21 /01/2019 added information about antimicrobial loading dose (Yes/No).
Added version number to footer
1.01 – 03/01/2019
Added details on haematological malignancies on co-morbid conditions (2.5)
Added high flow nasal canula, levosimendan, terlipressin to severity assessment and day 7 status (2.7, 5)
Added neutrophil count additionally to White blood cell count that was already recorded (2.7, 3.5, 5)
Added Tracheobronchitis as an option for possible sources for BSI (3.3)
Added once daily dose as an option for antibiotic administration (4.0)
Added the option of withdrawing treatment as a reason to stop the antibiotic (4.0)
Added G-CSF, INF-γ and blood purification techniques as other treatments for sepsis (4.3)
Added bronchoscopy as investigations (now section 4.4)
Removed the section where the investigator could enter other pre-calculated scores as this is not required anymore (2.8, removed)

Added detail to which type of ventilation (Invasive, non-invasive, high flow) to day 28 follow up (6).

Center Form
1.1 27/06/2019
added question 2.11 on dosing strategies for steroids for sepsis/septic shock

Protocol
1.22 5/12/2019 Added Jean Aldo Rodríguez Díaz as the National Coordinator for Cuba.
1.21 26/11/2019 Added Phunsup Wonhsurakiat as the National Coordinator for Thailand and Dr Bui Van Cuong as a National Coordinator for Vietnam.
1.20 13/11/2019 Added Dr Dmitriy Viderman as National coordinator for Kazakhstan and Dr Bashir El Sanousi as a National Coordinator for Sudan
1.19 4/11/2019 Typo corrected and wording of the inclusion criteria adjusted to match all other study documents where it reads: "mandatory OR and not mandatory for."
1.18 30/10/2019 added Pr. Philippe Montravers and Dr. Niccolo Buetti to the Steering committee, Dr Abdullah Tarık Aslan as NC for Turkey and Drs Andrea Kwa and Qing Yuan Goh as National coordinators for Singapore.
1.17 17/10/2019 added the possibility to continue inclusions beyond 3 months or for more than 10 patients as this was required by some participating centers and some countries have planned to include beyond 3 months.
Added Drs. Ho Yeh Li and Maria Luisa N. Moura as NC for Brazil
1.16 26/09/2019 added Dr Lowell Ling as the NC for Hong Kong.
1.15 21/09/2019 added Pr Farid Zand as the NC for Iran.
1.14 19/09/2019 added Dzana Spahic as a member of the scientific committee and Liana Valeanu as a National Coordinator for Romania.
1.13 11/09/2019 added Dr David Obada as a NC for Kenya
1.12 5/7/2019 Timeline adjusted to the new start-up date in September.
1.11 27/06/2019 added Prof. Tony Yu-Chang Yeh as NC for Taiwan.
1.10 13/06/2010 clarified data storage durations.
1.09 23/05/2019 added Dr. Raihan Rabbani as NC for Bangladesh.
1.08-21/05/2019 added Prof. Pierre Singer as NC for Israel.
1.07-07/05/2019
Changed Trials group to infection section on the title page
Added information on clinicaltrials.gov registration.
1.06-19/04/2019
Added Prof. Anand Kumar (sc) and Prof. Wendy Sligl (NC) for Canada
1.05-17/04/2019
Added Dr. Haibo Qiu as NC for China and Dr. Alexey Gritsan as NC for the Russian Federation
1.04- 15/04/2019
Added Dr. Adel Alsisi as NC for Egypt and Dubai
1.03– 28/03/2019
Clarified the role of the Outcomerea organization as the sponsor and data custodian for the study.
Mention of the ESCMID grant.
1.02 Added Dr. Pedro Povoa to the steering committee.
1.01 11/01/2019
Added Dr Ross Freebairn as NC for New Zealand.

1.01– 03/01/2019
Added Dr Muhammed Elhadi as a NC for Libya
Added page numbers to protocol
Clarified the electronic data capture requirements
Corrected typographic errors.
3/1/2019 : added changes to version record for CRF
Changed file naming convention from file-date.extension to file-version.extension