- The **EURECA** Study -

(***EUR****opean study on* ***E****ncephalitis in intensive* ***CA****re*)

Sponsor number : 0008-EURECA

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1 - PROTOCOL CHANGES HISTORY

All validated versions of the protocol including a description of the modifications are listed below :

Version	Description of modifications	Date
V1.0	First Validated version of the protocol	10/01/2017
V2.0	- Major / Minor inclusion criteria unified - Procedure of non-opposition if the patient is not able to give his/her non-opposition added	15/03/2017
V3.0	- José Garnacho-Montero added in steering committee - José Garnacho-Montero deleted in country coordinators - Ricard Ferrer added in country coordinators	23/10/2017
V4.0	-Alexis Tabah added in steering committee -Jeffrey Lipman added in country coordinators	04/04/2018
V5.0	-Georgios Dimopoulos added in country coordinators -Garyphallia Poulakou added in country coordinators -Matteo Bassetti added in country coordinators	06/06/2018

2 - SUMMARY

Title	EURopean study on Encephalitis in intensive CAre
Short title	EURECA
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Introduction	Acute (meningo)-encephalitis (AE) is a severe neurological disorder associated with significant morbidity and mortality. Approximately 60% of patients with AE require ICU admission because of coma, seizures or acute respiratory failure. Determinants of neurological prognosis of these patients are not known.
Objectives	• To describe the epidemiology of patients suffering from acute meningoencephalitis who are treated in the ICU; • To identify indicators of poor neurologic outcome.

Endpoints	• Primary endpoint: Day-90 modified Rankin scale score
	• Secondary endpoints
	  ○ Day-28 mortality, in-ICU and in-hospital mortality
	  ○ Systemic complications: septic shock, hyponatremia
	  ○ Intracranial complications:
	  ▪ Documented seizures, status epilepticus
	  ▪ Diffuse cerebral edema, herniation
	  ▪ Ischemia, cerebral hemorrhage
	  ○ ICP monitoring
	  ○ Neurosurgery

Methods	Prospective observational multicenter study in European ICUs. All patients admitted to the ICU for probable or confirmed AE (2013 IDSA criteria) will be included. Factors associated with a poor prognosis will be identified by multivariate analysis using a logistic regression.
Duration of study	15 months (recruitment 12 months, follow-up 3 months).
Patients	1000 patients admitted to the ICU for AE (5 consecutive patients in each participating ICU, targeted number of ICUs in Europe : 200).

Inclusion criteria	• Age ≥ 18 years
	• non-opposition to participate in the study
	• Impaired consciousness (altered mentation, stupor, or personality changes) for a duration ≥ 24 h, without obvious explanation
	• A score on the GCS < or =13 at ICU admission
	• A CSF pleocytosis > = 5 cell / mm3
	• At least 2 of the following :
	  ○ Fever (≥ 38.0 °C) within 72 hours before or after admission
	  ○ Generalized or partial seizures non-attributable to pre-existing epilepsy
	  ○ New onset focal neurological deficit
	  ○ Parenchymal abnormalities on MRI compatible with AE
	  ○ EEG alterations compatible with AE.

Exclusion criteria	• CSF or neuroimaging not available (s) or not performed. • febrile encephalopathy associated with another diagnosis (sepsis, neurological disease with aspiration pneumonia ...)

3 - INTRODUCTION

Acute encephalitis (AE) is a serious condition associated with significant morbidity and mortality. Patients require ICU admission in 60 % of cases, mainly because of neurological symptoms (coma, seizures) or acute respiratory failure [1-3].

The etiological profile of AE has changed considerably in recent years, with the emergence of new pathogens and the description of new immune-mediated causes (acute disseminated encephalomyelitis (ADEM), autoimmune limbic encephalitis) that require urgent specific therapies [2, 4, 5]. Furthermore, despite extensive investigations, the proportion of cases of unknown cause remains high [2-4].

In-ICU care of patients with AE is a difficult task, given the diversity of etiologies and clinical presentations. Furthermore, additional studies such as magnetic resonance imaging (MRI) can be challenging to obtain [6]. Finally, there are no specific recommendations on the management and prognostic assessment of patients admitted to the ICU with AE [6, 7].

Present available data on the prognosis of patients with AE include both adult and pediatric cases, and focuses only on AE with identified causes [1, 8]. Prognosis of encephalitis in adult patients requiring ICU admission has been previously described only in retrospective single centre cohorts [4, 9, 10]. To date, no prospective multicenter study on AE has been conducted in the specific and challenging population of adult critically ill patients. Furthermore, data on the diagnostic and prognostic contributions of magnetic resonance imaging (MRI) and electroencephalography studies in these patients are lacking [6, 7].

The development of guidelines for standardized care in critically ill AE patients is needed, and will include management of early life support, prompt and exhaustive etiologic investigations, and early administration of specific treatments and assessment of neurological prognosis. This study, which will focus on prognostic evaluation of severe AE in adults, appears crucial to support the development of such guidelines.

4 - FUNDING, METHODOLOGICAL SUPPORT

The study has currently no specific funding.

Investigators from more than 50 centres in France agreed to be actively involved in the study and to recruit a minimum of 5 consecutive patients per ICU over the study period.

The principal investigator (PI) is adequately qualified for conducting this study, and has already led multicenter cohort studies on the prognosis of severe infections, with a special focus on CNS infections [11-13] . The PI is working within a group which published a high number of scientific articles on the subject in the past 5 years [4, 13-17].

The study has methodological and logistical support from the Clinical Research Unit of the department of intensive care of the Bichat-Claude Bernard University hospital (Prof. JF Timsit).

5 - POTENTIAL RISKS AND BENEFITS

5.1 Known potential risks

The study protocol does not introduce any specific procedure, neither diagnostic, treatments or surveillance. The information is extracted from the patient's record, and is based on usual care for such patients. Consequently the study does not add any risk for the patient.

5.2 Known potential benefits

The patient enrolled in the study has no direct benefit. The potential benefit of the study consists in improving the knowledge for a better medical management for similar patients in the future.

6 - RESEARCH QUESTIONS AND OBJECTIVES

6.1 Research question

What are the determinants of neurological outcome in patients admitted to the ICU for AE?

6.2 Objectives and evaluation criteria

Objectives	Endpoints
Primary objective : evaluate the correlation between mRs score and the baseline characteristics	**Primary endpoint :** Functional outcomes will be evaluated using the **modified Rankin score (mRS) score**, which is one of the most frequently used scores in acute neurological diseases [18]. **A poor outcome will be defined by a mRS score > 2** (functional dependence or death). The investigator usually evaluates this score if the patient is still in the hospital 90 days after admission. Patients discharged from hospital within 90 days following ICU admission without major disability (mRS 0, 1 or 2) are considered to have a good outcome. Patients discharged within 90 days with a disability will be classified for the study according to the latest available data. Patients will not be contacted directly by the investigator for the study purposes.
Secondary objectives : To identify additional prognosis factors : the clinical, radiological, biological and neurophysiological factors associated with poor outcome for patients admitted to the ICU with AE	• **Day 28 mortality**, in-**ICU** mortality, in-**hospital** mortality • Major **systemic complications** (septic shock, hyponatremia, nosocomial pneumonia, catheter-related BSI, overt gastroenteral bleeding, pulmonary embolism) • Major **intracranial complications during ICU stay** – Status epilepticus – Brain death – Empyema/cerebral abscess – Cerebral ischemia – Intracranial bleeding • **ICP monitoring** • **Neurosurgery** The cause of death will be categorized into 2 categories: - Systemic causes (cardiovascular failure, MOF) - Neurological cause (Diffuse neurologic injury or withdrawal of care)

7 - METHODS

This is a prospective non-interventional multicenter cohort study.

7.1 Screening

Patients admitted to ICU for a **suspicion of AE (acute encephalopathy and CSF pleocytosis > 5 cells / microliter)** will be eligible for inclusion.

7.2 Inclusion Criteria

Eligible patients will be included if they fulfil the IDSA 2013 diagnostic criteria for "probable" or "confirmed" encephalitis [6]. To be eligible, patients must meet the following criteria :

- Age ≥ 18 years
- non-opposition to participate in the study

- Impaired consciousness (altered mentation, stupor, or personality changes) for a duration ≥ 24 h, without obvious explanation
- A score on the GCS < or =13 at ICU admission
- A CSF pleocytosis > = 5 cell / mm3
- At least 2 of the following :
    - Fever (≥ 38.0 °C) within 72 hours before or after admission
    - Generalized or partial seizures non-attributable to pre-existing epilepsy
    - New onset focal neurological deficit
    - Parenchymal abnormalities on MRI compatible with AE
    - EEG alterations compatible with AE.

7.3 Exclusion criteria

i . CSF or neuroimaging not available (s) or not performed.

ii . febrile encephalopathy associated with another diagnosis

(sepsis, neurological disease with aspiration pneumonia ...)

7.4 Medical history

Patient's general information and medical history will be extracted from the patient's record, including : gender, height, weight, pre-morbid RANKIN scale score, ethnicity, immunodepression, pre-existing neurologic disease and other comorbidity.

7.5 ICU admission data

The following data will be collected within the first 24 hours following ICU admission :

Date and main reason of ICU admission, lowest and highest temperature, GCS, SOFA and SAPS 2 score, lowest and highest level of Natremia, P/F ratio, PaCO2, Blood glucose level and detailed clinical findings at admission.

7.6 Etiological investigations

In patients without an obvious etiological diagnosis, the following investigations for diagnosis is suggested to investigators, according to the most recent recommendations [6, 7]:

i . CSF analysis

- Biochemistry (Leucocytes, RBC, Lymphocytes, Polynuclear, Protein, Glucose, Concomitant blood glucose, LDH, Lactate) , Gram stain, bacterial cultures
- India ink stain, cryptococcal antigen
- PCR for HSV 1 & 2 and VZV (+ anti-VZV CSF IgG titers if available)
- Enterovirus PCR
- Fungal cultures
- Oligoclonal bands, IgG index
- VDRL
- West Nile virus

ii . Serum

- Blood cultures
- HIV status and p24 antigen
- VDRL / TPHA

iii . imaging

- Brain MRI with gadolinium injection (or CT if MRI contraindicated).
- Chest x-ray

iv . Electroencephalogram (EEG)

v . "Oriented" samples in case of non-neurological manifestations (e.g., biopsy of skin lesions, nasopharyngeal swab and/or bronchoalveolar lavage if respiratory / pulmonary signs.

7.7 Other complementary investigations

Complementary investigations will be strongly suggested in the following circumstances, in accordance with the latest recommendations (IDSA 2013) [6]:

i. Immunocompromised status

ii. Special clinical presentation: psychiatric signs / abnormal movements, limbic reached, respiratory signs ….

iii. Topography of lesions observed on neuroimaging studies.

7.8 Adjudication committee and aetiology of encephalitis

Members of the adjudication committee will review each undetermined case at the end of the study, in order to validate the diagnosis of encephalitis.

7.8.1 Definitions of probable and confirmed cases of encephalitis

A diagnostic of **confirmed encephalitis** requires one of the following:

1. **Pathologic confirmation of brain inflammation consistent with encephalitis;**
2. **Defined pathologic, microbiologic, or serologic evidence of acute infection with a microorganism strongly associated with encephalitis from an appropriate clinical specimen;**
3. **Laboratory evidence of an autoimmune condition strongly associated with encephalitis.**

Other included cases based on clinical presentation (inclusion criteria) will be given a diagnostic of **probable encephalitis**.

7.8.2 Aetiology of encephalitis

Aetiology of AE will be presented as following:

1. **Bacterial meningitis (with secondary encephalitic features)**
    a. *Streptococcus pneumoniae*
    b. *Neisseria meningitidis*
    c. *Mycobacterium tuberculosis*
    d. *Listeria monocytogenes*
2. *Fungal or parasitical meningitis*
    a. *Cryptococcus neoformans*
    b. *Toxoplasma gondii*
    c. *Aspergillus* spp.
3. **Viral encephalitis**
    a. Herpes simplex virus
    b. Varicella zoster virus

c. Enterovirus

4. **Other infectious causes of encephalitis (rare bacterial, viral or fungal causes…)**
5. **Immune-mediated causes**
    a. Acute Disseminated Encephalomyelitis
    b. Anti-NMDAR encephalitis
    c. Other immune-mediated causes
6. **Undetermined aetiology**

8 - Premature termination or suspension of study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to. If the study is prematurely terminated or suspended, the PI will promptly inform the Ethics Commitee or other local authority according to the local legislation and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination could be for instance insufficient compliance to protocol requirements from one or several sites.

Study may resume once concerns about protocol compliance and data quality are satisfactorily addressed for the sponsor and the EC.

9 - COLLECTED DATA

Data will be entered **prospectively** into a **password-protected** and **secured web-based server**.

10 - STATISTICAL METHODS

Acute encephalitis is a rare syndrome in the ICU. Retrospective single-centre studies suggest that in adult ICUs, an average number of 5-10 patients are admitted to the ICU every year [4].

Our pre-defined goal is **to include 1000 patients (5 consecutive patients / ICU, n=200 ICUs).**

Clinical, biological, neuroimaging and neurophysiological factors associated with prognosis at day 90 will be determined by uni- and multivariate analysis using a logistic regression. It is necessary to obtain approximately 10 patients meeting the primary endpoint event (i.e. mR score > 2 at D90) for each variable tested in the multivariate model. Considering that approximately 30% of patients admitted to intensive care with AE have a poor prognosis (20-year retrospective data of the Bichat university hospital, Sonneville *et al*, abstract ESICM 2013) and that approximately 5% of patients will be lost to follow-up at day 90, we aim to include a total of 1000 patients with AE in order to test 15-20 variables in the final multivariate model.

Counting on the active participation of 200 centers in Europe, **the inclusion period will last for 15 months (recruitment: 12 months, follow-up: 3 months). Data management and statistical analysis will be performed by an independent statistician .**

Handling of follow-up data (modified Rankin Score): if the patient is still in the hospital 90 days after admission, the investigator evaluates this score. Patients discharged from hospital within 90 days following ICU admission without major disability (mRS 0, 1 or 2) are considered to have a good outcome. Patients discharged within 90 days with a disability will be classified for the study according to the latest available data.

The statistical analysis will be performed using the SAS and R software.

11 - SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA / DOCUMENTS

11.1 ACCESS TO DATA

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the regulatory agencies to examine clinical records for the purposes of quality assurance reviews, audits, progress, and data validity.

11.2 SOURCE DATA

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the laboratories, and medico-technical departments involved in the study.

11.3 DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators and their staff. All medical or administrative staff with an access to the data is subject to a duty of professional secrecy. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The study monitor, other authorized representatives of the sponsor, representatives of local authorities may inspect all documents and records required to be maintained by the investigator for the participants in this study. The clinical study site will permit access to such records.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Data Manager and the Statistician of the study. This will not include the participant's contact or identifying information. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected.

12 - ETHICS / PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the Declaration of Helsinki and the ICH E6.

12.2 ETHICS COMMITTEE

The protocol and non-opposition form will be submitted to the Ethics Committee (EC) for review and approval in conformity with local existing legislation. Approval of both the protocol and the non-opposition form (if required by local authorities) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the study. All changes to the non-opposition form will be EC approved.

12.3 NON-OPPOSITION PROCESS

All participants will receive a verbal explanation in terms suited to their comprehension of the study on the study purposes, the nature of the data collected and their rights as research participants.

The non-opposition process may differ in the participating countries. The compliance to local regulation should be respected. The participants may withdraw his / her non-opposition at any time throughout the course of the study, and patient's withdrawal has no impact on the quality of care that will be provided.

If applicable, the patient will sign the non-opposition form prior to any data collected for the study. The signature of the non-opposition form will be done in two copies : the first copy of the non-opposition form will be given to the patient for his/her records and the second copy will be conserved in the trial file by investigator.

The particularity of the population of the participants is a severe neurological disorder. Therefore, in the majority of cases, the patient will not be able to understand and / or express his non-opposition to the study. If the condition of the patient do not allow to understand and / or express a non-opposition with his participation in the study, a close family member or a person of confidence (if present) will be informed about the study and sign non-opposition form for the patient. However, the patient should be informed about the study as re-sign the non-opposition form personally as soon as possible.

The rights and welfare of the participants will be protected, and it will be emphasized to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.4 MEDICAL CARE RELATED TO THE STUDY

The medical care of the participant in the study is performed as usual, without any changes compared to standard medical care. All the procedures that are suggested to the investigators are in accordance with the latest recommendations for encephalitis diagnosis and management (IDSA 2013) [6], [7]. The primary endpoint (Rankin score) is one of the most frequently used scores in acute neurological diseases [18]. Therefore, the present study is an observational study without any specific intervention.

13 - DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data will be entered into a compliant data capture system. The data system includes password protection and internal quality checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Each study site should respect the local legislation and apply for an approval to a local Data Protection Authority if necessary.

13.2 STUDY RECORD RETENTION

Study documents should be retained for a minimum of 15 years after the end of the study. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14 - RESPONSIBILITIES

14.1 Principal investigator

The role and responsibilities of the **Principal Investigator** are:

- to coordinate the study in the individual countries and identify participating countries and country coordinators
- to insure that the study is conducted in accordance to the protocol and in compliance with GCP in all participating sites and countries
- to apply for regulatory approval at a national in the coordinating country and ensure that ethical committee (EC) approvals, or waivers of EC approvals, are obtained for all the participating sites in their country prior to the initiation of the study.
- to apply for regulatory approval from a local Data Protection Authority (DP) in the coordinating country
- to assist with the translation of the study documents according to local regulations.
- to ensure good communication with the participating country coordinators, including monitoring and encouraging to achieve optimal recruitment and follow-up during the period of the study.
- to assist the monitoring committee in communicating with sites in regard to data queries
- is the main responsible of the collected data, statistical analysis, communication and publications

14.2 Country coordinators

The role and responsibilities of the **country coordinators** are:

- to advertise the study in the individual countries and identify participating sites and LPIs in their country.
- to apply for regulatory approval at a national level where applicable and ensure that ethical committee (EC) approvals, or waivers of EC approvals, are obtained for all the participating sites in their country prior to the initiation of the study.
- to apply for regulatory approval from a local Data Protection Authority (DP), where applicable
- to assist with the translation of the study protocol, non-opposition form or equivalent according to local regulations and case report form where required.
- to ensure good communication with the participating sites in their country, including monitoring and encouraging to achieve optimal recruitment and follow-up during the period of the study.
- to assist the monitoring committee in communicating with sites in regard to data queries.

14.3 Site investigators

For each participating ICU, **one local investigator should be identified.**

The role and responsibilities of the local investigators are:

- to lead the study at their site.
- to inform the respective country coordinator of their interest to participate in the study.
- to apply for ethical approval and/or local site approvals in collaboration with the country coordinator and ensure that local approvals are in place prior to the initiation of the study.
- to notify and send scanned copies of local sites approval to the country coordinator.
- to ensure accurate and timely data collection and entry in to the electronic Case Report Form (eCRF).
- to reply promptly to data queries from the country coordinator.
- to maintain effective communication with the country coordinator and coordinating centre.
- to inform the patient about his enrolment in the study and to require the patient's non-opposition according to local regulations

15 - PUBLICATION AND DATA SHARING POLICY

The data and the analysis issued of this study is under responsibility of the scientific committee, which is composed by the PI, at least one representative of the sponsor and the Biostatistician or Data Manager responsible of the study.

All publications should be based on the Statistical Analysis Report, which will report all statistical analyses performed after the end of the study by an independent Biostatistician.

15.1 Data sharing policy

The data and analysis of the study will not be shared without an assent of the scientific committee. The principal analysis will be presented on the congress of European Society if Intensive Care Medicine (ESICM). It is possible to consider that some ancillary studies could be performed on the database or a part of it. However, the ancillary studies should be approved by the scientific committee (Romain Sonneville, Jean-François Timsit), in order to insure the transparency in use of the data and to cluster some similar projects to avoid redundancies.

15.2 Publication

The authors and the order of authors of the principal publication, as well as for the ancillary publications, will be preliminarily discussed by the scientific committee. Before the publication submission, the manuscript should be validated by the scientific committee.

16 - EXPECTED IMPACT OF THE STUDY

This study will represent the first prospective multicenter international study on the epidemiology and prognosis of patients with severe forms of AE.

It will help to delineate the presentation, the epidemiological profile and the course of AE during the ICU stay. Potentially modifiable prognostic factors that will be identified will help in the design of future intervention studies aimed at improving the neurological prognosis of this disease.

This study will provide accurate data on functional outcomes of those patients.

In conclusion, this study will help in the development of diagnostic and therapeutic algorithms to provide early and standardized care for patients admitted to the ICU for AE, including the optimal management of etiological investigations and early administration of a specific therapy, if required.

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18 - Appendix 1 - ETHICAL APPROVAL

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Dr Romain SONNEVILLE
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June 5, 2015

Subject : N °15-033 : (ENCEPHALitis in Intensive Care) - *Epidemiology and prognosis of encephalitis in intensive Care*

Dear Colleague,

The "**Comité d'Evaluation de l'Ethique des projets de Recherche Biomédicale (CEERB) Paris Nord"** (Institutional Review Board **-IRB 00006477-** of HUPNVS, Paris 7 University, AP-HP), has reviewed and approved the research project entitled « **(ENCEPHALitis in Intensive Care) -** *Epidemiology and prognosis of encephalitis in intensive Care* » (**Dr Romain SONNEVILLE**, principal investigator) in 2015. This approval covers the entire period during which the project will be developed until its completion.

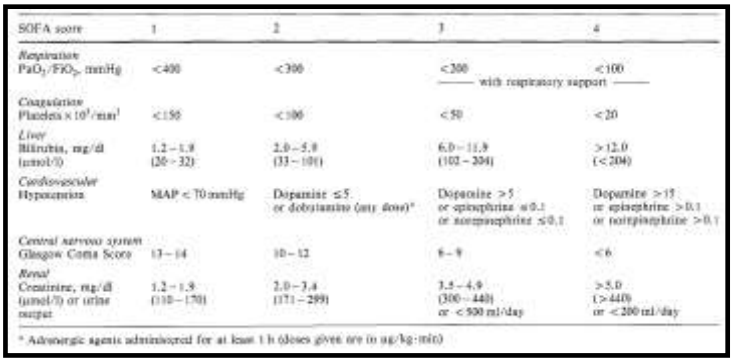
Yours sincerely.

Pr. Michel LEJOYEUX
Chair of the Institutional Review Board (IRB)

19 - APPENDIX 2: SCALES

MODIFIED RANKIN scale	
0	No symptoms
1	No significant disability Able to carry out all usual activities, despite some symptoms
2	Slight disability Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability Requires some help, but able to walk unassisted
4	Moderately severe disability Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

SOFA SCORE



SOFA score	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	<400	<300	<200 — with respiratory support —	<100 — with respiratory support —
Coagulation Platelets $\times 10^3$/mm^3	<150	<100	<50	<20
Liver Bilirubin, mg/dl (μmol/l)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (<204)
Cardiovascular Hypotension	MAP < 70 mmHg	Dopamine ≤5 or dobutamine (any dose)*	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system Glasgow Coma Score	13–14	10–12	6–9	<6
Renal Creatinine, mg/dl (μmol/l) or urine output	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or <500 ml/day	>5.0 (>440) or <200 ml/day

* Adrenergic agents administered for at least 1 h (doses given are in μg/kg·min)