# Time course of epigenetic, metabolic and endocrine alterations during critical illness

Submission date	Recruitment status No longer recruiting	[X] Prospectively registered		
08/12/2015		Protocol		
Registration date	Overall study status Ongoing Condition category	Statistical analysis plan		
09/12/2015		Results		
Last Edited		Individual participant data		
04/08/2025	Other	[X] Record updated in last yea		

#### Plain English summary of protocol

Background and study aims

Critically ill patients suffer from vital organ failure, undergo remarkable endocrine (hormonal) and metabolic changes, and frequently develop muscle weakness. Patients who survive a critical illness often face continuing debilitating physical and psychological problems after their stay in an intensive care unit (ICU). The exact mechanisms leading to the changes that occur during a critical illness and the long-term consequences that follow remain largely unknown. Recent data has shown that disturbances in stress responses (how the body responds to a stressful situation) may play a crucial role. Furthermore, there is evidence to suggest that changes in what genes are switched on or off (epigenetics) may also be involved in causing the long-term consequences of critical illness. For a long time, it has been known that critical illness has a remarkable time course. In that regard, hormonal changes during a prolonged critical illness differ from those present in the acute (short term) phase of critical illness. So far, however, the dynamics of the metabolic, hormonal and epigenetic changes during a stay in ICU have not been thoroughly studied. In view of finding the right timing for starting certain treatments (interventions) in critically ill patients, this is nevertheless crucial. Indeed, insight in when epigenetic, metabolic and endocrine changes develop may identify a "time window of opportunity" for future interventions and may to an important extent contribute to the planning of future intervention studies. The aim of this study is to map the time course of the epigenetic, metabolic and endocrine changes during critical illness (i.e. find out when these changes happen). In the intensive care units of the University Hospitals of Leuven we will collect blood, mouth mucosa (inside of the mouth), hair and urine samples as well as a muscle and fat biopsy from adult patients. In this way, human samples will be obtained at different stages of a critical illness, from the acute phase of illness until recovery. The results will be compared with demographically matched controls (people who are not critically ill). The levels of stress hormones and how they are being used by the body and any epigenetic changes will be studied and there will be tests looking at muscle function.

#### Who can participate?

Adults in ICU and matched controls. The matched control group is made up of volunteers who have not been critically ill but have similar health issues.

What does the study involve?

Biological samples are collected from both patients and controls in order to look at epigenetic, metabolic and endocrine changes that occur during a critical illness. This includes the sampling of blood, mouth mucosa, hair, urine, and/or muscle and fat biopsies. These analyses will be complemented with muscle force measurement (checking the strength of the muscles) and electrophysiological tests.

What are the possible benefits and risks of participating?

There is no direct personal benefit for the participating patients, but they can contribute to obtaining new information on the impact of critical illness. This can be important in the future for the treatment of critically ill patients during and after ICU stay and can provide new medical insight. There is no risk to participating.

Where is the study run from?

Five intensive care units (ICUs) at the University Hospital of Leuven (Belgium)

When is the study starting and how long is it expected to run for? September 2015 to August 2027

Who is funding the study?

- 1. Methusalem program funded by the Flemish Government through the University of Leuven
- 2. European Research Council Advanced Grant from the Ideas Programme of the European Union's Seventh Framework Programme
- 3. Research Foundation-Flanders (FWO) Belgium

Who is the main contact? Professor Greet Van den Berghe

# Contact information

# Type(s)

**Public** 

#### Contact name

Prof Greet Van den Berghe

#### Contact details

Clinical Division and Laboratory of Intensive Care Medicine Department Cellular and Molecular Medicine, KU Leuven Herestraat 49 Leuven Belgium 3000

# Additional identifiers

EudraCT/CTIS number

**IRAS** number

ClinicalTrials.gov number

#### Secondary identifying numbers

S58533

# Study information

#### Scientific Title

The dynamics of epigenetic, metabolic and endocrine alterations during critical illness: a prospective cross-sectional study

#### Acronym

**CROSS** 

#### Study objectives

Critically ill patients suffer from vital organ failure, are characterized by remarkable endocrine and metabolic alterations, and frequently develop muscle weakness. Patients who survive critical illness are often confronted with sustained debilitating physical and psychological problems after ICU stay, including persistent muscle weakness and long-term neurocognitive impairment. This condition is referred to as "the legacy of critical illness". The exact pathophysiology of these alterations during critical illness and the legacy of critical illness remain largely unknown. The aim of this study is to gain insight in the pathophysiology of critical illness and its long-term consequences. As primary objective, we will study in detail in preset time windows of ICU stay the time course of the epigenetic, metabolic and endocrine alterations that develop in response to critical illness and to unravel potential underlying processes involved in these changes. Secondary objectives include a reanalysis of the time course of the alterations described in the primary objective as well as a longitudinal analysis of within-subjects changes in time for those patients who participate multiple times.

#### Ethics approval required

Old ethics approval format

#### Ethics approval(s)

Medical Ethics Committee (Institutional Review Board) of the University Hospitals Leuven, 16/10 /2015, ref: S58533

# Study design

Single-center prospective observational cross-sectional study

# Primary study design

Observational

# Secondary study design

Cross sectional study

# Study setting(s)

Hospital

# Study type(s)

Other

#### Participant information sheet

Not available in web format, please use contact details to request a patient information sheet

#### Health condition(s) or problem(s) studied

Critical illness

#### **Interventions**

Biological samples will be collected from patients and controls after informed consent in order to perform the detailed studies as described. This includes the sampling of blood, mouth mucosa, hair, urine, and/or muscle and fat biopsies. These analyses will be complemented with muscle force measurement and electrophysiological tests. The data obtained from these analyses will be correlated with available demographic and clinical data.

#### **Intervention Type**

Other

#### Primary outcome measure

To study in detail, in preset time windows of ICU stay, the time course of the epigenetic, metabolic and endocrine alterations that develop in response to critical illness and to unravel potential underlying processes involved in these changes

#### Secondary outcome measures

- 1. Reanalysis of the time course of the alterations described in the primary objective
- 2. Within-subjects longitudinal analysis of changes for those patients who participate multiple times

#### Overall study start date

01/09/2015

#### Completion date

31/08/2027

# **Eligibility**

#### Key inclusion criteria

1. Patients:

All adult/senior patients at the surgical and medical intensive care units are eligible

#### 2. Controls:

A control group of volunteers who have not been critically ill, but have similar comorbidities as the critically ill patients will be recruited to match demographically with the patient group

#### Participant type(s)

Mixed

#### Age group

Mixed

#### Sex

Both

#### Target number of participants

Patient recruitment will continue until preset sample numbers (120 per group for blood analyses and 60 per group for biopsy analyses) will have been obtained in four groups based on time in ICU within the first 28 days time window with a comparable distribution of ICU admission categories. At that time, recruitment of patients in a fifth group (> day 28) will also stop. In addition, we will recruit controls who never stayed in the ICU until 120 matched controls have been included for blood analyses and 60 for biopsy analyses

#### Total final enrolment

374

#### Key exclusion criteria

- 1. Patients:
- 1.1. General:
- 1.1.1. Age younger than 18 years
- 1.1.2. Readmission to ICU (unless within 48 hrs)
- 1.1.3. Declined participation
- 1.1.4. DNR code
- 1.1.5. Patients with HIV
- 1.1.6. Chronic systemic treatment with glucocorticoids prior to ICU admission (added 12/09/2018: patients who did receive chronic systemic treatment with glucocorticoids prior to ICU admission will be recruited separately to allow investigation of the impact of prior chronic systemic glucocorticoid treatment)
- 1.2. Blood sampling: absence of arterial line
- 1.3. Mouth mucosa sampling: normal mouth mucosa not accessible (e.g. post-tumor resection)
- 1.4. Neuromuscular evaluation:
- 1.4.1. General:
- 1.4.1.1. Patients with neuromuscular disorders identified prior to ICU admission / unable to walk without assistance (wheelchair, walking stick, arm support) prior to ICU admission
- 1.4.1.2. Patients with a neuromuscular disorder as reason for ICU admission
- 1.4.2. Muscle biopsy: increased bleeding risk
- 1.4.2.1. Platelet count below 50000/mm3 and/or PT below 40%
- 1.4.2.2. Known coagulation disorders
- 1.4.2.3. Use of anti-coagulation or thrombolytic agents
- 1.4.3. Muscle force by MRC sum score:
- 1.4.3.1. No muscle biopsy
- 1.4.3.2. Patient not awake/cooperative (\*)
- 1.4.4. Hand grip strength
- 1.4.4.1. No muscle biopsy
- 1.4.4.2. Patients not awake/cooperative (\*)
- 1.4.4.4. Medical Research Council (MRC) score for forearm flexion or wrist extension below 3
- 1.4.5. Electromyography / nerve conduction studies / direct muscle stimulation
- 1.4.5.1. No muscle biopsy
- (\*) patients who give a biopsy but are not awake/cooperative at the time of sampling will be screened for awakening/cooperation up until two days later for MRC sum scoring and hand grip strength
- 1.5. Fat biopsy: increased bleeding risk:
- 1.5.1. Platelet count below 50000/mm3 and/or PT below 40%
- 1.5.2. Known coagulation disorders
- 1.5.3. Use of anti-coagulation or thrombolytic agents

- 2. Controls:
- 2.1. General
- 2.1.1. Age younger than 18 years
- 2.1.2. Previous ICU stay (except coronary care unit stay)
- 2.2. Blood sampling: known severe coagulation disorders (e.g. hemophilia)
- 2.3. Mouth mucosa sampling: normal mouth mucosa not accessible (e.g. post-tumor resection)
- 2.4. Muscle and fat biopsy:
- 2.4.1. Controls with acute or chronic neuromuscular disorders or unable to walk without assistance (wheelchair, walking stick, arm support) will be excluded for muscle biopsy
- 2.4.2. Increased risk of bleeding:
- 2.4.2.1. Known coagulation disorders
- 2.4.2.2. Use of anti-coagulation
- 2.5. Muscle force / electrophysiology / direct muscle stimulation: no muscle biopsy

#### Date of first enrolment

11/01/2017

#### Date of final enrolment

03/09/2020

# Locations

#### Countries of recruitment

Belgium

# Study participating centre KU Leuven University Hospital

Leuven Belgium 3000

# **Sponsor information**

#### Organisation

**KU** Leuven

#### Sponsor details

c/o Professor Dr. Ir. Koenraad Debackere Managing Director University Administration and Central Services Krakenstraat 3 - box 5500 Leuven Belgium 3000

#### Sponsor type

University/education

#### **ROR**

https://ror.org/05f950310

# Funder(s)

#### Funder type

Government

#### **Funder Name**

Methusalem program funded by the Flemish Government through the University of Leuven (METH08/07 and METH14/06)

#### **Funder Name**

European Research Council Advanced Grant from the Ideas Programme of the European Union's Seventh Framework Programme (AdvG-2012-321670)

#### **Funder Name**

Fonds Wetenschappelijk Onderzoek

#### Alternative Name(s)

Research Foundation Flanders, Flemish Research Foundation, FWO

#### **Funding Body Type**

Government organisation

#### Funding Body Subtype

Local government

#### Location

Belgium

# **Results and Publications**

#### Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal, date to be confirmed later.

#### Intention to publish date

31/08/2028

## Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to preserving patient confidentiality. Prof. Greet Van den Berghe will on request detail the restrictions and any conditions under which access to some data may be provided.

#### IPD sharing plan summary

Not expected to be made available

## **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Interim results article		15/05/2022	17/08/2023	Yes	No