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# BMJ Open Prevention of early ventilation-acquired pneumonia (VAP) in comatose brain-injured patients by a single dose of ceftriaxone: PROPHY-VAP study protocol, a multicentre, randomised, double-blind, placebo-controlled trial

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## ABSTRACT

**Introduction** Ventilator-associated pneumonia (VAP) is the first cause of healthcare-associated infections in intensive care units (ICUs) and brain injury is one of the main risk factors for early-onset VAP. Antibiotic prophylaxis has been reported to decrease their occurrence in brain-injured patients, but a lack of controlled randomised trials and the risk of induction of bacterial resistance explain the low level of recommendations. The goal of this study is to determine whether a single dose of ceftriaxone within the 12 hours postintubation after severe brain injury can decrease the risk of early-onset VAP.

**Methods and analysis** The PROPHY-VAP is a French multicentre, randomised, double-blind, placebo-controlled, clinical trial. Adult brain-injured patients (n=320) with a Glasgow Coma Scale  $\leq 12$ , requiring mechanical ventilation for more than 48 hours, are randomised to receive either a single dose of ceftriaxone 2g or a placebo within the 12 hours after tracheal intubation. The primary endpoint is the proportion of patients developing VAP from the 2nd to the 7th day after mechanical ventilation. Secondary endpoints include the proportion of patients developing late VAP (>7 days after tracheal intubation), the number of ventilator-free days, VAP-free days and antibiotic-free days, length of stay in the ICU, proportion of patients with ventilator-associated events and mortality during their ICU stay.

**Ethics and dissemination** The initial research project was approved by the Institutional Review Board of OUEST III (France) on 20 October 2014 (registration No 2014-001668-36) and carried out according to the principles of the Declaration of Helsinki and the Clinical Trials Directive 2001/20/EC of the European Parliament relating to the Good Clinical Practice guidelines. The results of this study will be presented in national and international meetings and published in an international peer-reviewed journal.

**Trial registration number** NCT02265406; Pre-results.

## Strengths and limitations of this study

- This trial will be the first randomised, double-blind, placebo-controlled multicentre study adequately powered to determine whether antibiotic prophylaxis could prevent early-onset ventilator-associated pneumonia in brain-injured patients. It has the potential to change international recommendations on the field.
- Emergence of resistant micro-organisms will be checked using only pulmonary microbiological results performed in routine during the monitoring timeline. The impact of antibiotic prophylaxis on gastrointestinal microflora will be addressed in only two intensive care units (ICUs) from faecal swab cultures performed in routine.
- Another limitation of the trial is the absence of surveillance of all other ICU-acquired infections, including ventilator-acquired tracheobronchitis.

## INTRODUCTION

### Background and rationale

Ventilator-associated pneumonia (VAP) is the first cause of healthcare-associated infections in intensive care unit (ICU) and more than half of antibiotics prescriptions in ICU are due to VAP.<sup>1</sup> Brain-injured patients are particularly exposed to this infection, with incidence ranging from 22% to 71% depending on studies.<sup>2 3</sup> In patients with severe trauma, brain injury is an independent factor (OR 11.9; 95% IC 2.6 to 52.6) for the development of VAP.<sup>4</sup> Micro-organism inhalation and immune suppression observed in the initial course

of most severe brain-injured patients partially explain the high incidence of VAP and their precocity.<sup>5–7</sup> According to the American Thoracic Society (ATS), two types of VAP are described, early and late VAP, with a cut-off at day 5 following the start of mechanical ventilation (MV); late VAP (ie, occurring after the 5th day of MV) is frequently due to multidrug resistant (MDR) organisms and requires broad-spectrum empirical treatment.<sup>5</sup> In brain-injured patients, this cut-off is controversial as coma at ICU admission is a factor of lower risk of MDR VAP (OR 0.21; 95% CI 0.08 to 0.52), with VAP due to susceptible micro-organisms being the majority until a median of 7 days; thus a delayed cut-off at day 7 has been proposed for brain-injured patients by some authors.<sup>8–10</sup> In addition to increased antibiotic prescription as well as a risk of bacterial resistance, a longer stay in ICU and higher cost of hospitalisation, early-onset VAP could alter outcome in brain-injured patients.<sup>11–12</sup> VAP prevention is consequently essential in ICU patients and a bundle of measures, applicable to brain-injured patients as well, have shown their efficacy: orotracheal route for tracheal intubation, tracheal cuff pressure maintained between 25 and 30 cm H<sub>2</sub>O, strategies to shorten MV, sedation–analgesia algorithm to facilitate early weaning from MV, head of bed elevation, decontamination of nasal and oropharyngeal cavity through suitable mouth care and starting enteral nutrition as early as possible.<sup>13</sup> Most of these measures aim to decrease colonisation of the upper airways tract by oropharyngeal micro-organisms. With the same goal in mind, antibiotic prophylaxis has been proposed through several routes of administration including selective oral or digestive tract decontamination or systemic antibiotic prophylaxis at tracheal intubation.<sup>2 14–16</sup> While such prophylaxis was shown in a recent meta-analysis to decrease the incidence of early VAP and mortality, the lack of controlled randomised trial and the risk of induction of bacterial resistance explain the low level of recommendations.<sup>13 17 18</sup>

Only two randomised studies have explored the efficacy of systemic antibiotic administration at tracheal intubation in brain-injured patients.<sup>15 16</sup> The first one included 100 brain-injured patients with a Glasgow Coma Scale (GCS) below 12 receiving or not receiving cefuroxime 1.5g two times at 12 hours interval after tracheal intubation. Administration of antibiotic prophylaxis significantly reduced the incidence of early-onset VAP from 36% to 16% and overall VAP in ICU from 50% to 24%.<sup>15</sup> The second study compared two groups of 19 patients each with GCS <8 receiving or not receiving ampicillin–sulbactam 3g every 6 hours for 3 days. Incidence of early-onset VAP was significantly lower in the antibiotic group (27% vs 57% in the controlled group).<sup>16</sup> More recently, another study showed a decrease of early-onset VAP in comatose patients receiving an early single dose of ceftriaxone 2g compared with an historical group of patients, 22.4% and 2.8%, respectively.<sup>2</sup> No impact in length of MV

and outcomes was noted in these studies probably by lack of power. Similarly, none of them were placebo controlled and applied all the recommended preventive measures. Moreover, they provided no description of any increase of MDR bacteria in treated groups, and patient follow-up was too short to allow the authors to draw any conclusions about resistance. Several works have shown that prophylactic antibiotics could influence the susceptibility of late-onset VAP bacteria.<sup>19 20</sup> The limitations of published studies and the risk of bacterial resistance seemed to justify performance of a double-blind randomised placebo-controlled study to determine whether antibiotic prophylaxis can decrease early-onset VAP incidence in brain-injured patients.

## Study aims and objectives

### Primary objectives

The goal of this study is to assess the ability of ceftriaxone 2g infused within 12 hours after tracheal intubation to decrease the risk of early-onset VAP in brain-injured patients receiving all other recommended methods of VAP prevention.

### Secondary objectives

To assess the efficacy of ceftriaxone 2g within the 12 hours after tracheal intubation on late-onset VAP occurrence, susceptibility of micro-organism-induced VAP, exposure to MV and to antibiotics and on neurological outcome.

### Ancillary study

To assess the impact of ceftriaxone 2g infused within 12 hours after tracheal intubation on acquired cephalosporin-resistant gram-negative bacteria occurrence at ICU discharge.

This ancillary study is performed in two centres routinely, practising faecal swabs cultures on selective media on admission and at ICU discharge, in order to detect potential changes in intestinal flora after antibiotic treatment (Centre Hospitalier Universitaire, CHU of Angers and CHU of Rennes).

### Expected benefits

The expected individual benefits are shorter duration of MV and length of stay in the ICU, and a better outcome, in patients receiving antibiotic prophylaxis. At a collective level, the cost of hospital stay should be reduced by decreasing the number of days on antibiotics, MV length and length of stay in ICU.

### Trial design

The PROPHY-VAP trial is a multicentre, randomised, double-blind, placebo-controlled, clinical trial. The primary endpoint is the proportion of patients developing VAP in the ICU from the 2nd to the 7th day (included) after MV. Randomisation will be carried out through a secure web-based randomisation system, stratified by centre and severity of coma at the time of inclusion (GCS lower or equal to 8 and 9–12).

## METHODS: PARTICIPANTS, INTERVENTION AND OUTCOMES

### Participants

Brain-injured patients can be included in the PROPHY-VAP study after checking for inclusion and exclusion criteria. After allocation in one of the two groups of the study, patients will receive 2g of ceftriaxone or placebo within the 12 hours after tracheal intubation, and all other recommended methods of VAP prevention.

### Inclusion criteria

- ▶ Patients aged more than 18 years.
- ▶ Brain-injured patients with a GCS  $\leq 12$ .
- ▶ Tracheal intubation via oral route for less than 12 hours.
- ▶ Expected duration of MV more than 48 hours.
- ▶ Participating in a social security scheme or benefiting from such a scheme by means of a third party.
- ▶ Patient's legal surrogate written consent when possible or emergency inclusion if next of kin cannot be informed in the maximal delay for inclusion.

### Exclusion criteria

- ▶ Patient with a high risk of death within the first 48 hours after admission.
- ▶ Tracheal intubation 48 hours or more after admission.
- ▶ Tracheal tube with functional subglottic secretion drainage.
- ▶ Patient with a tracheotomy.
- ▶ Coma due to a tumour, an infectious disease or cardiac arrest.
- ▶ Previous hospitalisation within the last month before admission for coma.
- ▶ Contraindication or an allergy to beta-lactams.
- ▶ Receiving antibiotics on admission for a previous infection.
- ▶ Antibiotic prophylaxis expected within the 24 hours after randomisation.
- ▶ Patient or family refuse to be involved in the study.
- ▶ Participating in another research protocol in connection with an anti-infective treatment or which could affect the infectious risk or with a potential drug interaction.
- ▶ Benefiting from reinforced protection or persons deprived of freedom subsequent to a legal or administrative decision, majors under legal protection.

### Control

In the control arm, patients will receive all other recommended methods of VAP prevention and a blinded intravenous injection of saline over 30 min, within the 12 hours following the tracheal intubation.

The standard methods of VAP prevention are the following:

- ▶ No systematic changes of the respirator circuits.
- ▶ Preferential use of heat and humidity exchange filters, changed only when soiled.
- ▶ Head-of-bed elevation of 30°, monitored every 4 hours.

- ▶ Hand washing prior to any treatment and following isolation measures.
- ▶ Mouth care every 8 hours, at a minimum, according to the protocol observed in the unit.
- ▶ Tracheal aspiration carried out using sterile equipment, only when required.
- ▶ Preferential oral insertion of feeding tubes.
- ▶ Starting enteral feeding as soon as possible.
- ▶ Systematic application of a glucose monitoring protocol with blood sugar level measured every 4 hours, according to the protocol observed in the unit.
- ▶ Prevention of ulcer disease in accordance with the protocol observed in the unit.
- ▶ Monitoring of tracheal cuff pressure of the tracheal tube every 8 hours to maintain pressure between 25 and 30 cm H<sub>2</sub>O.
- ▶ According to the protocol observed in the unit, extubation should be considered as soon as possible in order to avoid non-scheduled extubations.

### Interventions

In the intervention arm, patients will receive standard methods of VAP prevention and an intravenous injection of ceftriaxone 2g within the 12 hours following the tracheal intubation.

### Study outcomes

#### Primary endpoint

Proportion of patients developing early-onset VAP, defined in our study by a VAP from the 2nd to the 7th day (included) after MV.<sup>8-10</sup> The diagnosis of VAP follows the ATS definition, except for the time of occurrence and will be confirmed by microbiological culture (box 1).<sup>21</sup>

#### Secondary endpoints

Compare the two strategies at day 28 or at discharge from ICU on:

- ▶ Proportion of patients developing late-onset VAP, defined in our study as a VAP after the 7th day of

### Box 1 2005 American thoracic society definition for ventilator-associated pneumonia (VAP)

VAP diagnosis is based on an association, 48 hours after the start of mechanical ventilation, of at least:

- ▶ Two clinical signs among the following:
  - Fever  $\geq 38.0^{\circ}\text{C}$  or hypothermia  $\leq 36.0^{\circ}\text{C}$ .
  - Purulent endotracheal aspirations.
  - Hyperleucocytosis ( $\geq 12\,000/\text{mL}$ ) or leucopenia ( $\leq 4000/\text{mL}$ ).
- ▶ One radiological sign such as:
  - A new radiographic condensation.
  - Modification of a previously existing radiographic condensation.
- ▶ And a positive bacterial analysis of the respiratory tract with cultures of at least:
  - 103 cfu/mL for a brush by fibroscopy or blind protected distal sampling.
  - 104 cfu/mL for bronchoalveolar lavage.
  - 106 cfu/mL for tracheal aspirates.

MV.<sup>8-10</sup> The diagnosis of VAP follows the ATS definition, except for the time of occurrence and will be confirmed by microbiological culture (box 1).<sup>21</sup>

- ▶ Proportion of patients developing VAP during ICU period, according to the ATS definition.<sup>21</sup>
- ▶ Proportion of patients developing ventilator-associated events (VAE) during ICU period, according to the Centers for Disease Control and Prevention (CDC) definition.<sup>21 22</sup>
- ▶ Comparison of global incidences of VAP according to the ATS and the CDC definitions respectively.<sup>21 22</sup>
- ▶ Type of bacteria and their susceptibility to early-onset or late-onset VAP.
- ▶ Number of VAP-free days.
- ▶ Number of antibiotic-free days (AFDs).
- ▶ Number of ventilator-free days (VFDs).
- ▶ Time between inclusion and the first spontaneous ventilation test.
- ▶ Proportion of patients that die during their ICU stay. Compare the two strategies at day 28 and day 60 (without exceeding 60 days after inclusion) on:
  - ▶ Neurological prognosis according to Glasgow Outcome Scale (GOS) and modified Rankin scale.
  - ▶ Proportion of patients that die
  - ▶ Length of stay in ICU.
  - ▶ Number of ICU-free days.
  - ▶ Length of stay at the hospital.

Compare the two strategies on the proportion of acquired cephalosporin-resistant gram-negative bacteria at discharge from ICU, in the two centres involved in the ancillary study.

### Patient monitoring and timeline

Every day until ICU discharge, without exceeding 28 days following inclusion: VAP sign detection will be performed, while patient is under MV according to the established ATS definition.<sup>21</sup>

The following parameters will be followed: sedation, ventilation parameters, extubation, intubation or tracheotomy, occurrence of intracranial hypertension and treatments, occurrence of any type of surgery, indication and length of any prescribed antibiotic. For each suspected VAP, the modified Clinical Pulmonary Infection Score will be calculated, and clinical and radiological signs, susceptibility to micro-organism-induced VAP, type and length of antibiotics will be monitored. Each diagnosed VAP during follow-up will be reviewed by two assessors masked to the group assignment and will classify the case report according to the ATS and CDC definitions.<sup>21 22</sup>

At ICU discharge, without exceeding 28 days, will be evaluated: The number of VAP-free days, AFDs and VFD, and the neurological prognosis according to GOS and modified Rankin scale. When rectal swab is being performed, microbiological data will be collected.

At hospital discharge, without exceeding 60 days, will be evaluated: Date of ICU discharge and hospital discharge.

At day 28 and day 60, the neurological prognosis will be evaluated.

Any patient or next of kin can exit the study if requested, without any justification and with no modification of quality of care, and in the final analysis the outcome will not be taken into account.

### Sample size calculation

The sample size of each group (n=160) is based on the mean incidence of early-onset VAP of 30% in the control group, with the hypothesis that it could be reduced by half in the intervention group (15%), with a study power of 90% and p value of 5% in bilateral situation. VAP incidence in the control group was chosen on the basis of published incidence in randomised studies in brain-injured patients. Because of the wide variability of results in literature, we chose a low incidence.

According to the expected recruitment of participating centres and protocol constraints, the expected inclusion duration was set at 24 months.

### Recruitment

Brain-injured patients, admitted into the ICUs of eight French University Hospitals, are screened and enrolled by the attending physicians, within 12 hours after tracheal intubation.

### Assignment of interventions and masking protocol

A computer-generated numbered list was provided by a statistician not involved in either the screening of patients or the assessment of outcomes. Randomisation will be carried out using a secure web-based randomisation system with stratification by centre and severity of unconsciousness at the time of inclusion (GCS <8 or ≥8), to account for differences in patient treatment between centres and heightened VAP risk in patients with a GCS lower than 8. Patients will be randomly assigned (1:1) to one of the two treatment groups, based on the treatment administered, ceftriaxone or placebo. All participants and ICU staff will be blinded for the treatment.

### Data collection, confidentiality, storage and archiving of study documents

In each participating hospital, independent clinical research assistants help with running of the study and data collection. Study documents will be de-identified and stored for 15 years, as per the protocol for non-clinical trial notification interventional studies. Data will be electronically stored on double password-protected computers. Hard copies of data (clinical research files) will be stored in a locked, secure office. All personnel involved in data analysis will be masked. Only the principal investigators and the statisticians will have access to the final data set.

### Statistical methods

Analyses will be performed following the intention-to-treat principle (all randomised patients except those who shall have withdrawn consent). Statistical analyses will take into account the stratified randomisation (centre and GCS <8 or ≥8), as recommended in the 2010

Consolidated Standards of Reporting Trials guidelines and other studies reported in the literature.<sup>23 24</sup>

The categorical variables will be reported as numbers and percentages, while continuous variables will be summarised using means ( $\pm$ SD) or medians (IQR) for normally and non-normally distributed data, along with their respective 95% CIs.

Analyses of the primary endpoint and secondary endpoints related to VAP incidence will use logistic regression models adjusted for stratification factors and covariates significantly imbalanced between groups.

The cumulative event curves (time until first VAP diagnosis) will be estimated using the Kaplan-Meier procedure. An adjusted Cox model taking of stratification factors and covariates into account will be used to estimate adjusted HRs.

The number of VFD is the number of days for which the patient is successfully weaned from MV until the endpoint at day 28 (or day 60). This is defined as follows: VFD=0 for patients who died within 28 (or 60) days or required MV for 28 (or 60) or more days; VFDs = (28 (or 60) - x) for patients successfully weaned off MV within 28 (or 60) days, where x is the number of days on MV.

The number of AFD is the number of days during which the living patient did not receive antibiotics over 28 (or 60) days.

The VFD and AFD will be assessed in the same manner, and will be compared between groups using regression models allowing adjustment for stratification factors. The other categorical secondary endpoints will be compared between groups using logistic regression models. Statistical analyses will all be conducted using SAS V.9.3 software.

Missing data will be described as the number and corresponding percentage for each group. The presence of any imbalance in the proportion of missing data between treatment groups will be evaluated using logistic regression models. To assess the robustness of the results in the case of missing data, sensitivity analyses will be performed with imputation of missing data (worst value such as failure, death, etc) and multiple imputation.

### Monitoring

Clinical research associates will ensure that patient inclusion, data collection, registry and rapport are in line with the protocol, and that the study is conducted in accordance with the Good Clinical Practice guidelines. Furthermore, he or she will verify the following variables: patient initials, date of birth, sex, signed consent form, eligibility criteria, date of randomisation, treatment assignment, adverse events and study endpoints. The trial will be monitored by the research monitoring officer of Poitiers University Hospital.

### Patient and public involvement

The ethical committee, composed of patients' representatives, considered if the research is conformed to patients' priorities, experience and preferences. Each patient,

admitted in a participating ICU, is screened and enrolled by the attending physicians according to the protocol. As patients are in coma, the burden of the intervention cannot be assessed by patients themselves. Each patient, after the end of the study, will have the opportunity to obtain the results if they are interested, all information is provided at inclusion in consent and information forms.

### ETHICS AND DISSEMINATION

The clinical trial will be carried out in line with the principles of the Declaration of Helsinki and according to the Clinical Trials Directive 2001/20/EC of the European Parliament on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practices in the conduct of clinical trials on medicinal products for human use.

#### Consent

Patient's legal surrogate provides written consent for participation when possible. Patients are eligible to be enrolled without the provision of legal surrogate consent, if next of kin cannot be informed in the maximal delay for inclusion, emergency inclusion is possible. Patients who recover sufficient capacity to provide consent are asked to agree to continue in the trial.

#### Confidentiality

People with direct access to the data will take all necessary precautions to maintain confidentiality. All data collected during the study will be rendered anonymous. Only initials and inclusion number will be registered.

#### Dissemination policy

The results of the study will be released to the participating physicians, referring physicians and medical community no later than 1 year after completion of the trial, through presentation at scientific conferences and publication in peer-reviewed journals. The principal investigator (CD-F), the scientific expert (OM) and the statistician (DF) will write the first draft of the manuscript. All the coauthors (investigators having carried out no less than less than 20 inclusions) will append and approve the final manuscript before submission. No professional writer will be used.

### DISCUSSION

This study is the first double-blind, randomised placebo-controlled study designed to assess the impact of ceftriaxone prophylaxis on the incidence of early-onset VAP, in severe brain-injured patients. At an individual level, the expected benefits are shorter duration of MV and stay in the ICU, and a better outcome in patients receiving antibiotic prophylaxis. At a collective level, the cost of hospital stay should be reduced by decreasing the number of days on antibiotics, of MV and length of stay in ICU.

We include patients with moderate to severe brain injury (GCS 3–12) since in many cases patients with moderate brain injury (GCS 9–12) require MV for associated respiratory failure. Even if early-onset VAP has been primarily and extensively described in traumatic brain-injured patients,<sup>4 9 25 26</sup> we have decided, given the fact that VAP physiopathology, responsible microbial agents and consequences on outcome are somewhat equivalent,<sup>10 27 28</sup> to also include ischaemic stroke, parenchyma or subarachnoid haemorrhage. Moreover, all of the prospective studies published on antibiotic prophylaxis of early-onset VAP have enrolled all types of comatose patients requiring MV for more than 48 hours.<sup>2 15 16</sup>

We defined the incidence of early-onset VAP as the primary endpoint, as brain-injured patients are particularly exposed to it.<sup>9</sup> VAP incidence is determined on the basis of 2005 ATS criteria (except for the time of occurrence), as they are commonly used in the literature and so as to be able to compare our results to those of previous studies published on this topic.<sup>2 15 16 21</sup> We will also record VAE according to the CDC criteria and compare the ATS and CDC definitions for VAP.<sup>22</sup>

The choice of ceftriaxone is based on the microbial agents responsible for early-onset VAP. Moreover, its spectrum and prolonged half-life allow a single injection for a simplified antibiotic prophylaxis. Previous studies on this topic also studied cephalosporins administered to prevent VAP in comatose patients.<sup>2 15 16</sup> Finally, as third-generation cephalosporin could be involved in potential resistance emergence, we are performing an ancillary study to compare the intestinal flora between the two groups of patients, in centres which routinely perform rectal swabs at admission and discharge from ICU.

Several limitations should be acknowledged according to the design of the study. First, patients with subglottic secretion drainage, one of the more efficient measures to prevent VAP, were excluded because this device is exceptionally used in emergency departments and prehospital settings in France. Whether the use of this device may interfere with the efficacy of antibiotic prophylaxis will require further evaluation. Second, because we chose to follow only VAP during all the ICU stay, we will not be able to assess the impact of antibiotic prophylaxis on other ICU-acquired infections including ventilator-acquired tracheobronchitis. However, this analysis may be done after the study is completed, as data can easily be collected retrospectively. Third, we will study the impact of ceftriaxone use on emergence of MDR organism in VAP only. Finally, the impact of ceftriaxone on gastrointestinal microbiome will be studied in only two participating centres, and the power of this ancillary study will be probably insufficient to conclude.

This study is the first multicentre, randomised, controlled study adequately powered to explore in double blind the protective effect of a single dose of antibiotic on early-onset VAP in MV comatose patients. If its results are supportive of systemic ceftriaxone prophylaxis, this study could change future practices.

## Participating centres

University Hospital of Poitiers (Professor Claire DAHY-OT-FIZELIER), University Hospital of Angers (Professor Sigismond LASOCKI), University Hospital of Nantes (Professor Karim ASEHNOUNE), University Hospital of Nantes (Professor Bertrand ROZEC), University Hospital of Montpellier (Dr Pierre-François PERRIGAULT), University Hospital of Toulouse (Professor Thomas GEERAERTS), University Hospital of Rennes (Professor Philippe SEGUIN), University Hospital of Tours (Dr Djilali ELAROUSSI), University Hospital of Bordeaux (Dr Vincent COTTENCEAU).

## Trial status

The trial is currently in progress, and the inclusion process started in October 2015. At the time of manuscript submission, 189 patients had been included. As the last patient is expected to be recruited in June 2019, a protocol's amendment to extend inclusion until October 2019 was submitted and accepted by the ethic committee.

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**Contributors** CD-F conceived the study, coordinated its design and drafted the manuscript. CD-F and OM wrote the manuscript. SL, KA, P-FP, TG, PS, BR, DE, VC, CG, DB and A-LG read and were involved in critical appraisal and revision of the manuscript. DF provided statistical expertise. All authors approved the final manuscript prior to submission.

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