Diagnostic, prognostic and therapeutic strategies in critically ill COVID–19 patients

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CHAPTER

Practice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019 (PRoAcT–COVID) – rationale and protocol for a national multicenter observational study in The Netherlands

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ABSTRACT

Background

Many patients with coronavirus disease 2019 (COVID–19) need hospitalization for supplemental oxygen, and a substantial number of them even need intensive care unit (ICU) admission for escalation of care. Practice of adjunctive and supportive treatments remain uncertain and may vary widely between countries, within countries between hospitals, and possibly even within ICUs. We aim to investigate practice of adjunctive and supportive treatments, and the effects on outcome, in COVID–19 patients in ICUs in the Netherlands.

Methods

PRoAcT–COVID ('study of PRactice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019') is an investigator–initiated national, multicenter observational study to be undertaken in ICUs in The Netherlands. Consecutive COVID–19 patients aged 18 years or older, who receive care in the participating ICUs, are to be enrolled during a 3–months period, with a daily follow–up of 28 days. The primary endpoint is a combination of adjunctive treatments, including types of oxygen support, ventilatory support and rescue therapies for refractory hypoxemia during invasive ventilation, other adjunctive and supportive treatments, and experimental therapies. We will also collect tracheostomy rate, duration of mechanical ventilation and ventilator–free days and alive at day 28 (VFD–28), duration of ICU and hospital stay, and ICU, hospital and 90–day mortality.

Discussion

PRoAcT–COVID will be an observational study that will combine high density treatment data and major outcomes. There is urgent need for a better understanding of treatment practices, and the effects of treatments on outcomes in COVID–19 patients. The results of PRoAcT–COVID will be rapidly disseminated through electronic presentations, such as webinars and electronic conferences, publications in international peer–reviewed journals, and reports on the PRoAcT–COVID website. Access to source data will be made available on request, through local, regional and national anonymized datasets, and after agreement of the PRoAcT–COVID steering committee.

Trial Registration

PRoAcT–COVID is registered at clinicaltrials.gov (identifier NCT04719182).

Keywords
SARS–CoV–2; coronavirus disease 2019 (COVID–19); critical care; intensive care; oxygen support; oxygen therapy; supplemental oxygen; ventilation; adjunctive treatment; pharmacologic management; fluid strategy; antiviral treatments; immunomodulating treatments; experimental supportive care; ventilator–free days; mortality

INTRODUCTION

The Netherlands is currently facing a new surge of coronavirus disease 2019 (COVID–19) patients. Patients with COVID–19 are frequently hospitalized and a substantial number of them end up in an intensive care unit (ICU) for organ support (1).

Many patients with COVID–19 develop hypoxemia. Hypoxemia may respond well to simple oxygen support, like supplementary oxygen through interfaces like a nasal prong or cannula, and non–rebreather or Venturi masks—this type of support is usually provided on a normal ward. Patients with severe COVID–19 may develop 'refractory' hypoxemia, for which more intense oxygen support is needed, like continuous positive airway pressure (CPAP) or high–flow nasal oxygen (HFNO)—these types of support usually mandate admission to an ICU. If oxygenation does not improve, so–called 'awake proning' has been suggested as one rescue therapy, but non–invasive ventilation and eventually invasive ventilation may become necessary. Even with invasive ventilation hypoxemia may persist (2-5). Rescue therapies for persistent hypoxemia may include higher airway pressures and prone positioning, at times in combination with continuous or intermitted muscle paralysis. In certain cases, extracorporeal membrane oxygenation (ECMO) may even be necessary. Other adjunctive treatments in patients with COVID–19 can include intensified thromboprophylaxis, and in cases of suspected or proven deep venous thrombosis or pulmonary embolism, full anticoagulation. Also, various antiviral and immunomodulating strategies have been advocated (6). Experimental supportive care may consist of various types of minerals or vitamins, and other pharmacological interventions (7-10).

Care for patients with COVID–19 varies widely between countries and regions, and probably also within the Netherlands. It is very well possible that differences in care are amplified by a lack of consensus on best care for COVID–19. They all could affect outcome, though. We aim to investigate practice of adjunctive and supportive treatments in COVID–19 patients in ICUs in the Netherlands. For this, PRoAcT–COVID ('study of PRactice of Adjunctive Treatments in Intensive Care Unit Patients with Coronavirus Disease 2019') is to be undertaken. We also wish to determine associations with patient–centered outcomes. This study may form an important step towards creating a guideline for standard care in patients with COVID–19. Standardization and implementation of guidelines has the potential to improve outcome of COVID–19 patients.

METHODS

Design and settings

PRoAcT–COVID is an investigator–initiated, multicenter, national, observational study in patients with COVID–19 admitted to participating ICUs in the Netherlands. PRoAcT–COVID will capture high density data in up to 20 hospitals. PRoAcT–COVID is registered at www.clinicaltrials.gov (trial identification number NCT04719182). The study protocol (version 1.0 30-11-2020) is approved by the local Institutional Review Board of the Amsterdam University Medical Centers, location 'AMC' (W20_526 # 20.583). Figure 1 shows the study flow chart.

Study population

At least 1,000 patients with severe COVID–19 admitted to participating ICUs in the Netherlands from October 2020 through December 2020 (i.e. during the first 3 months of the second surge of COVID–19 patients). This study will not be restricted to 'physical' ICUs, as patients may also receive accelerated care provided by intensivists at other locations within a hospital during the pandemic—whether a patient outside the ICU will count as an 'ICU patient' is to be decided by the local physicians. Since a substantial number of patients will be transported between ICUs within The Netherlands when hospitals get overwhelmed, we may not be able to collect data of a subset of patients from start of ICU care (i.e., when a patient is admitted to an ICU that does not participate in PRoAcT–COVID), or during ICU care (i.e., when ICU care will continue in an ICU that does not participate in PRoAcT–COVID). In all patients, however, outcome data including duration of ventilation and mortality can and will be captured (i.e., even if transported to or from an ICU that does not participate in in PRoAcT–COVID) through contacts with healthcare providers at the final destination.

Inclusion criteria of PRoAcT–COVID are: COVID–19 is confirmed by reverse transcriptase–polymerase chain reaction (RT–PCR) for SARS–Coronavirus–2, and COVID–19 being the reason for ICU admission. Patients who need ICU care for another reason than severe COVID–19 (i.e., patients who are infected with SARS–Coronavirus–2, but do not have COVID–19, or COVID–19 pneumonia) are excluded, as are patients aged < 18 years. PRoAcT–COVID has no other exclusion criteria.

Study conduct

Study sites are recruited through direct contact by steering committee members of PRoAcT–COVID. Study coordinators will contact local doctors, and trained data collectors will assist local doctors in collecting the data. Study coordinators will monitor the study according to the International Conference on Harmonization Good Clinical Practice–guidelines and ensure integrity and timely completion of data collection.

Local doctors screen patients with COVID–19. Data collection will start as of end–February 2020 and will continue until the mid–April.

Data to be collected

Baseline and demographic variables will be collected from the first day of stay in ICU in each participating center, including sex, age, weight and height, medication and comorbidities. In addition, date of start of complaints, date of diagnosis, hospital admission and date of ICU admission, Simplified Acute Physiology Score (SAPS) II, and Sequential Organ Failure Scores (SOFA).

The following treatment variables will be collected daily:

- Types of oxygen support (including oxygen supplementation via nasal prong or nasal canula, non–rebreather or Venturi masks, continuous positive airway pressure (CPAP), high–flow nasal oxygen (HFNO), non–invasive ventilation (NIV) and invasive ventilation); practice of awake proning; characteristics of invasive ventilation; rescue therapies for refractory hypoxemia (including prone positioning, higher positive–end expiratory pressure (PEEP)), continuous or intermitted muscle paralysis, and extracorporeal membrane oxygenation (ECMO);
- Practice of thromboprophylaxis, antiplatelet therapy, and practice of full anticoagulation in patients with suspected or confirmed deep venous thrombosis (DVT) or pulmonary embolism (PE); practice of stress ulcer prophylaxis; practice of sedatives and muscle paralysis;
- Practice of antiviral treatments (including, but not restricted to remdesivir, lopinavir–ritonavir, baloxavir marboxil, barunavir–cobicistat, favipiravir, sofosbuvir–daclatasvir, triazavirin, umifenovir and practice of immunomodulating treatments (including, but not restricted to corticosteroids, chloroquine or hydroxychloroquine, interferon, aprepitant,

colchicine, immunoglobulin, ivermectin, ruxolitinib, telmisartan, tocilizumab and convalescence plasma);

- Practice of aerosolized medication (including, but not restricted to salbutamol, ipratropium and acetylcysteine);
- Practice of experimental supportive care (including, but not restricted to minerals or vitamins, and other pharmacologic agents, like zinc, N–acetylcysteine, and vitamins);
- Daily cumulative fluid balances and cumulative urine production; development of acute kidney injury (AKI) and use of renal replacement therapy (RRT); and
- Proven DVT or PE; incidence of gastrointestinal (GI) bleeding;
- Place where care was provided (i.e., in an ICU or at other locations within a hospital during the pandemic)
- Definitive follow–up data will be collected at days 28 and 90:
- Duration of ventilation in survivors; number of ventilator–free days and alive at day 28 (VFD–28); and incidence of tracheostomy; and
- Duration of ICU and hospital stay; and ICU, hospital and 90–day mortality.

In addition, on ICU level, data on standard ventilator care including, but not restricted to active or passive humidification, tracheal suctioning procedures and manual hyperinflation will be collected.

Workflow of data collection is represented in **Figure 2**.

STUDY ENDPOINTS

Study endpoints are a combination of adjunctive treatments, including types of oxygen support, ventilatory support and rescue therapies for refractory hypoxemia during invasive ventilation (primary), adjunctive and supportive treatments and experimental therapies. Other endpoints include duration of ventilation and ventilator–free days and alive at day 28 (VFD–28) and tracheostomy rate, complication rates, including DVT and PE, GI bleeding, AKI and use of RRT, and duration of ICU and hospital stay, and ICU, hospital and 90–day mortality.

Definitions

VFD–28 is defined as the number of days the patient has been completely liberated from the ventilator and alive during the first 28 days from the start of invasive

ventilation in a participating center. DVT and PE are defined as a proven DVT with a duplex ultrasound and/or proven PE with computerized tomography pulmonary angiography. GI bleeding is defined as observed blood from the gastric tube or melena, eventual confirmed by gastroscopy or coloscopy. AKI is defined using the KDIGO definition (11), and RRT is defined by the usage of continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodialysis without filtration (CVVHD), hemodialysis or peritoneal dialysis. Duration of ICU and hospital stay is calculated from the first day of admission to the ICU or hospital and ICU discharge from ICU or hospital, respectively. All–cause ICU or 90–day mortality is defined as any death occurring in the ICU or within 90 days of admission to a participating center, respectively.

Data management

Data will be collected from locally used electronic patient data management systems. Local investigators and trained data collectors from the Amsterdam UMC, location AMC, will transcribe the collected data directly into a pseudo–anonymized online electronic case report form (eCRF) (Castor Electronic Data Capture; https://castoredc.com), which is protected by a personalized username and password.

Study sites

The following hospitals already agreed to participate in PRoAcT–COVID: Department of Intensive Care, University Medical Center Groningen, Groningen (1); Medical Center Leeuwarden, Leeuwarden, The Netherlands (2); Department of Intensive Care, ISALA hospital, Zwolle, The Netherlands (3); Department of Intensive Care, Rijnstate hospital, Arnhem, The Netherlands (4); Department of Intensive Care, Gelderse Vallei, Ede, The Netherlands (5); Department of Intensive Care, Gelre hospitals, Apeldoorn (6); Department of Intensive Care, University Medical Centers Utrecht, Utrecht, The Netherlands (7); Department of Intensive Care, Antonius hospital, Nieuwegein, The Netherlands (8); Department of Intensive Care, Amsterdam University medical centers (AMC), Amsterdam, The Netherlands (9); Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands (10); Department of Intensive Care, Spaarne hospital, Hoofddorp, The Netherlands (11); Department of Intensive Care, Dijklander hospital, Hoorn, The Netherlands (12); Department of Intensive Care, HAGA hospital, Den Haag, The Netherlands (13); Department of Intensive Care, Haaglanden Medical Centers, Den Haag, The Netherlands (14); Department of

Intensive Care, Reinier de Graaf hospital, Delft, The Netherlands (15); Department of Intensive Care, Catharina hospital, Eindhoven, The Netherlands (16); Department of Intensive Care, Amphia hospital, Breda, The Netherlands (17); Department of Intensive Care, Zuyderland Hospital, Heerlen, The Netherlands (18); Department of Intensive Care, Maastricht University Medical Center, Maastricht, The Netherlands (19); Department of Intensive Care, Flevo Hospital, Almere, The Netherlands (20).

With these hospitals participating, we expect to include over 40% of critically ill patients with COVID–19 in the Netherlands.

Preliminary statistical analysis plan

Descriptive statistics will be reported as number and relative proportions for categorical variables and median (quartile 25% – quartile 75%) for continuous variables. For baseline characteristics, the groups will be compared using Fisher exact tests for categorical variables and Wilcoxon rank–sum test for continuous variables. The impact of adjunctive therapies on outcomes will be assessed through regression modelling according to the distribution of each outcome. Time–to–event outcomes will be reported in Kaplan–Meier curves and compared using appropriate statistical tests. For each analysis of impact on outcomes, there will be an updated analysis plan before assessing the data, in which it is explained how to control the confounders.

It is also planned to compare care for COVID–19 patients provided in the ICU, and at other locations within a hospital during the pandemic.

All analyses are planned to be conducted in R v.4.0.2 and a P value < 0.05 is considered statistically significant.

An updated and finalized statistical analysis plan will be published online on the PRoAcT–COVID website (12).

Study organization

The Steering Committee is composed of selected members of the PRoAcT–COVID investigator group, involved in the design of the study and the analysis of the data. Data collection onsite and submission into the eCRF will performed either by trained data collectors from the Amsterdam UMC, location AMC, or the local doctors. Incomplete or incorrectly entered eCRFs will be signaled in the online eCRF, to be corrected and completed by the collecting investigators.

Patient and public involvement

Patients and public are currently not directly involved in the study.

Ethics and dissemination

PRoAcT–COVID is conducted in accordance with the Declaration of Helsinki (revision Fortaleza, Brazil, October 2013). The Institutional Review Board of the Amsterdam University Medical Centers, location 'AMC' sees this study as a service review. Since no research–related interventions will take place, and because the study collects pseudo–anonymous data, which can no longer be attributed to a specific data subject, there were no ethical concerns and there is no concern for informed consent. According to Dutch law, participating centers will submit the study protocol to their local Institutional Review Board for judgment of feasibility. The results of PRoAcT–COVID will be rapidly disseminated through electronic presentations, such as webinars and electronic conferences, and reports on the PRoAcT–COVID website. The results of PRoAcT–COVID will also be published in a peer–reviewed journal. After publication, access to source data will be made available by providing anonymized datasets on request and after agreement of the steering committee of PRoAcT–COVID.

DISCUSSION

PRoAcT–COVID is designed and is to be conducted to compare practices regarding adjunctive treatments in COVID–19 patients in ICUs in the Netherlands, and to determine whether differences in adjunctive treatments have an independent association with patient–centered outcomes. The findings of PRoAcT–COVID will serve as a basis for suggestions and recommendations in national, and also international guidelines for critically ill COVID–19 patients.

The results of PRoAcT–COVID will be available within weeks after completion of data–capturing, thus allowing fast optimization of adjunctive treatment practices in ICUs that care for COVID–19 patients. Both academic and non–academic hospitals will participate, covering all counties in the Netherlands, and we will expect to collect data of approximately 40% of patients with COVID–19 in the Netherlands—thus allowing a thorough national insight in care for critically ill COVID–19 patients.

Practice of care for COVID–19 patients remains based on evidence from a small set of randomized clinical trials performed over the last 12 months, e.g., for

thromboprophylaxis (13), use of remdesivir (14-18), lopinavir–ritonavir (16, 19-21), hydroxychloroquine (16, 22, 23), hydrocortisone, methylprednisolone and dexamethasone (24-29), interleukin 6 receptor antagonists (30-34), vitamin D (7, 35) and convalescent plasma (36-38). Some of these trials lack statistical power. To our best knowledge there have been no published trials of other treatments yet. PRoAcT–COVID will be the first study that combines epidemiology with adjunctive treatment practices and outcomes in critically ill COVID–19 patients.

Strengths of this study include its size (PRoAcT–COVID will be one of the largest studies of adjunctive treatment practices and outcomes in COVID–19) and its high granularity (PRoAcT–COVID will collect daily data through the first 28 days after ICU admission, and have a final follow–up at day 90). Limitations of this study include its retrospective design, and conclusions drawn of associations between practices. Outcomes should be interpreted with caution.

The results of PRoAcT–COVID are highly relevant for care in critically ill COVID–19 patients. Instant generation and rapid implementation of recommendations for adjunctive treatments in COVID–19 patients have the potential to improve their outcomes, and may increase ICU capacity if such treatments lead to a more rapid ICU discharge.

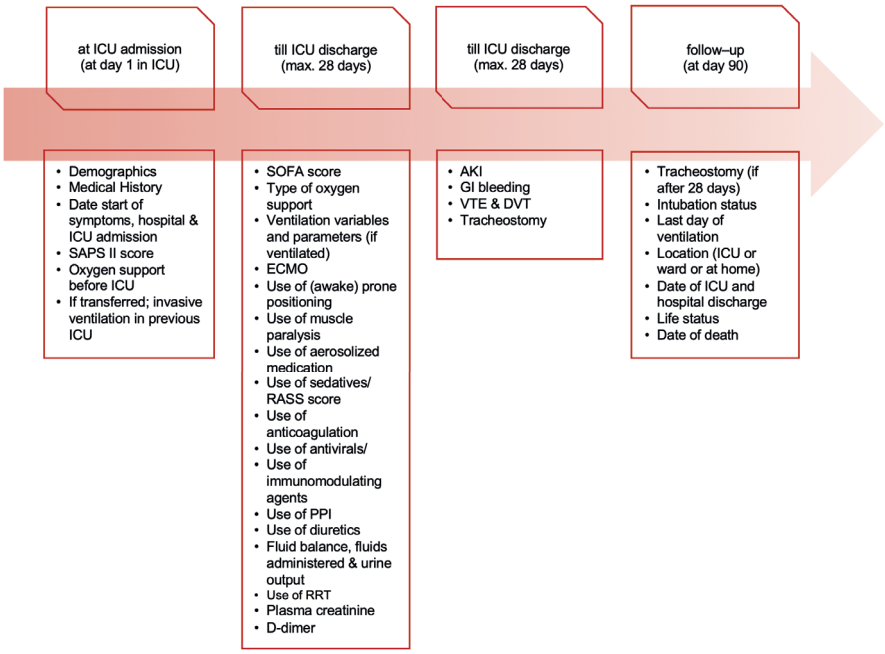
PRoAcT–COVID is the successor of PRoVENT–COVID, a service review into ICU care during the first 3 months of COVID–19 pandemic in the Netherlands (39). In the first 3 months of the pandemic, nearly all patients who needed ICU care did so because of invasive ventilation—consequently, PRoVENT–COVID focused on ventilation management and clinical outcomes in invasively ventilated patients. In the first 3 months of the second and current surge, many more ICU patients do not receive invasive ventilation—thus, ventilatory support will be different, but also other aspects of care may differ. Together, PRoVENT–COVID and PRoAcT–COVID will provide insights into (changes in) epidemiology, management, and outcome in patients with COVID–19 Therefore, the databases of PRoVENT–COVID and PRoAcT–COVID can and will be merged for additional analyses.

Strengths and limitations of this study

- The database of PRoAcT–COVID will contain high density data of adjunctive treatments and clinical outcomes in COVID–19 ICU patients in the Netherlands;

- PRoAcT–COVID will have a large sample size which allows for a robust analysis of adjunctive therapies, and associations between these therapies and major outcomes;
- The data generated by this study will rapidly provide guidance to practice in COVID–19 ICU patients in absence of randomized clinical trials; and
- PRoAcT–COVID is limited by the observational nature and the national character; and
- PRoAcT–COVID is a successor of PRoVENT–COVID, and analyses of the combined databases will help to understand whether, and how epidemiology, management, and outcome in patients with COVID–19 has changed in the Netherlands.

Figure 1. Sequence of data collection.



Abbreviations: ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA score, Sequential Organ Failure Assessment score; ECMO, extracorporeal membrane oxygenation; RASS score, Richmond Agitation–Sedation score; PPI, proton pump inhibitors; AKI, acute kidney injury; RRT, renal replacement therapy; GI, gastrointestinal; VTE, venous thromboembolism; DVT, deep venous thrombosis.

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