


# BMJ Open Impact of carbohydrate-reduced nutrition in septic patients on ICU: study protocol for a prospective randomised controlled trial

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## ABSTRACT

**Introduction** Sepsis is defined as detrimental immune response to an infection. This overwhelming reaction often abolishes a normal reconstitution of the immune cell homeostasis that in turn increases the risk for further complications. Recent studies revealed a favourable impact of ketone bodies on resolution of inflammation. Thus, a ketogenic diet may provide an easy-to-apply and cost-effective treatment option potentially alleviating sepsis-evoked harm. This study is designed to assess the feasibility, efficiency and safety of a ketogenic diet in septic patients.

**Methods and analysis** This monocentric study is a randomised, controlled and open-label trial, which is conducted on an intensive care unit of a German university hospital. As intervention enteral nutrition with reduced amount of carbohydrates (ketogenic) or standard enteral nutrition (control) is applied. The primary endpoint is the detection of ketone bodies in patients' blood and urine samples. As secondary endpoints, the impact on important safety-relevant issues (eg, glucose metabolism, lactate serum concentration, incidence of metabolic acidosis, thyroid function and 30-day mortality) and the effect on the immune system are analysed.

**Ethics and dissemination** The study has received the following approvals: Ethics Committee of the Medical Faculty of Ruhr-University Bochum (No. 18-6557-BR). Results will be made available to critical care survivors, their caregivers, the funders, the critical care societies and other researchers by publication in a peer-reviewed journal.

**Trial registration numbers** German Clinical Trial Register (DRKS00017710); Universal Trial Number (U1111-1237-2493).

## INTRODUCTION

Sepsis is a life-threatening condition characterised by a global dysregulation of the immune system: hyperinflammatory reactions, mostly mounted by innate immune cells and immunoparalysis of adaptive immune cells, can occur in an unpredictable time course, sequentially or even simultaneously.<sup>1–3</sup>

## Strengths and limitations of this study

- This is the first randomised controlled trial assessing the feasibility and safety of a low-carb nutrition in sepsis.
- Based on strong scientific reasoning derived from other patient populations, our secondary endpoints will provide first insights into the immunological impact of a ketogenic diet in critically ill septic patients.
- A strength of this clinical trial is the pragmatic nature as it uses a mainstay of patient care, that is, nutrition, as intervention with easy applicability in daily clinical care.
- Our controlled and longitudinal study design will allow us to interpret alterations over time in the intervention and control groups and will provide strong evidence for causality.
- A central limitation of this study is the mortality-related loss to follow-up and the resulting missing data points that could impact the internal validity of the results.

Despite intensive research efforts during the last decade, mortality rates of sepsis still range around 30%–50%, and causal therapies reconstituting immune homeostasis are not available so far.<sup>4</sup> In this situation, the impact of nutrition could gain importance, as metabolism has emerged as a major guiding force of immune cell functions.<sup>5</sup>

According to the European Society for Clinical Nutrition and Metabolism guideline on clinical nutrition in the intensive care unit (ICU), patients receive an enteral nutrition consisting of 1.3g of protein/kg body weight/day, 1.5g of lipids/kg body weight/day. Carbohydrate administration in the range of 4–5 mg/kg body weight/min is recommended, and insulin should be administered at blood glucose levels >180 mg/dL.<sup>6</sup> This regimen might now be reconsidered as recent experimental studies revealed that

high intake of carbohydrates and consecutive secretion of insulin induces proinflammatory reactions of innate immune cells.<sup>7</sup> In line with these findings, a number of convincing studies have recently shown that reducing carbohydrate intake significantly stabilises immune cell homeostasis and improves survival after systemic bacterial infection.<sup>8–10</sup> In these studies, the total amount of carbohydrates is reduced to approximately 10% of the overall calorie intake, whereas protein amounts are kept constant and fat amounts are increased.<sup>11 12</sup> The reduced availability of glucose results in increase of fatty acid oxidation with subsequent synthesis of ketone bodies to cover the body's energy demand and to generate sufficient amounts of adenosine triphosphate.<sup>13</sup> This evolutionary conserved mechanism results in the synthesis of beta-hydroxybutyrate (BHB).<sup>14</sup> However, it becomes increasingly clear that BHB also functions as a signalling molecule by affecting gene expression via epigenetic alterations, protein modifications and G-protein-coupled signalling.<sup>15 16</sup> In recent animal studies, BHB displayed strong anti-inflammatory effects by inhibiting the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and reducing proinflammatory cytokine secretion of innate immune cells, thus contributing to immune cell homeostasis.<sup>14 16–18</sup>

Ketogenic or low-carb diets are an established clinical tool in patients suffering from epilepsy. Here, they significantly reduce seizure frequencies without displaying significant adverse effects.<sup>19 20</sup> Also, ketogenic/low-carb nutritional regimes have recently been investigated in clinical studies enrolling overweight patients with type II diabetes<sup>21</sup> and patients suffering from glioblastoma.<sup>22</sup> These studies reported no adverse side effects, providing additional evidence that ketogenic/low-carb diets are feasible and safe.

In this prospective, randomised controlled trial, we want to assess feasibility and safety of a ketogenic diet in ICU patients suffering from sepsis. Moreover, we will investigate whether enteral administration of a low-carb/ketogenic diet induces detectable levels of ketone bodies in septic patients and whether these ketones are able to modulate immune responses during sepsis.

## METHODS AND ANALYSIS

This study is a randomised, open-label trial comparing an interventional group supplied with a low-carb diet and a control group supplied with standard enteral nutrition.

### Study population and general data acquisition

This study was reviewed and approved by the Ethics Committee of the Medical Faculty of Ruhr-University Bochum (No. 18-6657-BR) and registered in the German Clinical Trial Register prior to the inclusion of the first study patient. The study will be conducted in accordance with the Declaration of Helsinki and German laws and regulations. All patients are admitted to the ICU of University Hospital Knappschaftskrankenhaus Bochum

and are recruited from January 2020 (first patient on 22 January 2020) up to February 2021. Patients are considered eligible if study enrolment is completed within 36 hours after diagnosis of sepsis according to the current Sepsis-3 definition.<sup>23</sup>

Inclusion criteria are age  $\geq 18$  years, written informed consent of the patient or their guardian, study enrolment within 36 hours after diagnosis of sepsis and mechanical ventilation for less than 72 hours on study inclusion. Exclusion criteria are pregnancy or lactation, haemoglobin concentration  $< 80$  g/L, insulin-dependent diabetes, severe and persistently health-compromising metabolic disorders or autoimmune diseases, severe liver dysfunction or liver failure, refractory metabolic acidosis, invasive ventilation  $> 72$  hours, diagnosis of sepsis  $> 36$  hours at study enrolment and contraindications against an enteral nutrition.

After randomisation, patient data collected are depersonalised via pseudonymisation. All pseudonymised and deidentified clinical, biometrical and demographic data will be entered into an offline password-protected study database for later analysis. This data set will include pre-existing illnesses, frequently used scores such as the Simplified Acute Physiology Score II (SAPS II) or the Sepsis-related Organ Failure Assessment (SOFA) score, body mass index, need and duration of renal replacement therapy, ventilator configurations, Horowitz Index (ratio of  $\text{PaO}_2/\text{FiO}_2$ ), vital parameters (eg, heart rate, blood pressure, peripheral saturation), medications, amount and dosage of vasopressors and blood laboratory parameters.

### Patient and public involvement

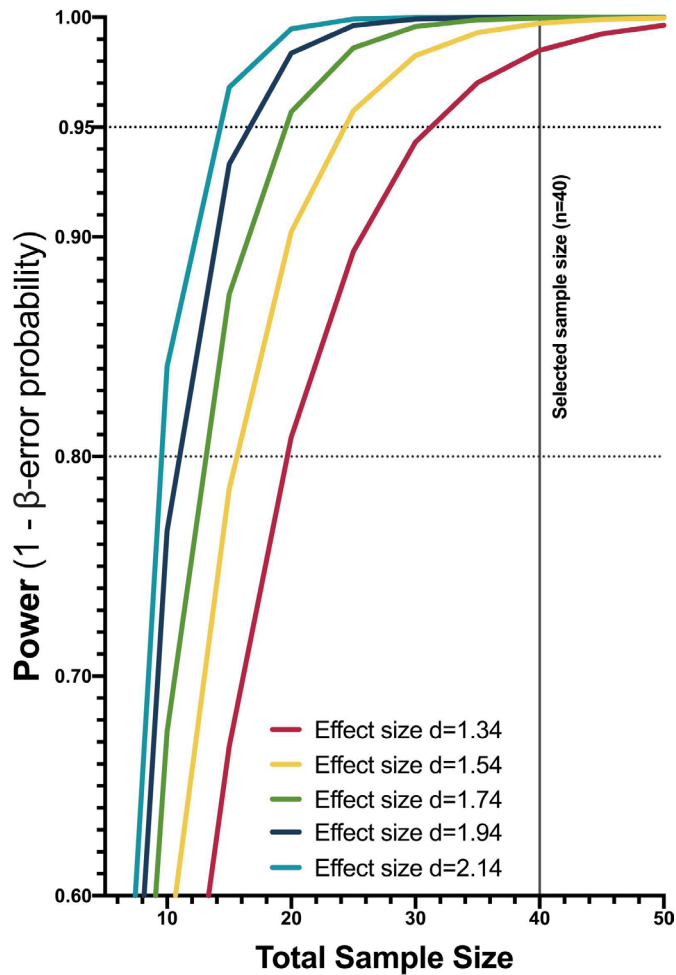
Patients were not involved in the development of the research question, outcome measures or study design.

### Sample size calculation

In this randomised controlled study, a total of 40 patients, that is, 20 patients in the intervention group and 20 patients in the control group, will be enrolled. Based on the available data on ketogenic diet regimes for healthy individuals referring to the beta-hydroxybutyric acid blood concentration<sup>11</sup> and our estimation of a clinical reasonable effect size, we assume an effect size (Cohen's *d*) between 1.34 and 2.14 as appropriate. Subsequently, we conducted sample size calculations with varying effect sizes between 1.34 and 2.14 at a level of significance of  $\alpha=0.05$ . Based on these calculations, considering the most conservative effect size of 1.34 and assuming a dropout rate of 25% as a safety margin, a total sample size of  $n=40$  ( $n=20:20$ ) presents as adequate to achieve a power of 95% (figure 1).

### Study design

The total duration of the study is planned for 18 months. It will take 12 months for recruitment of patients and collection of data. The last 6 months are scheduled for analyses. An individual study duration of 14 days is

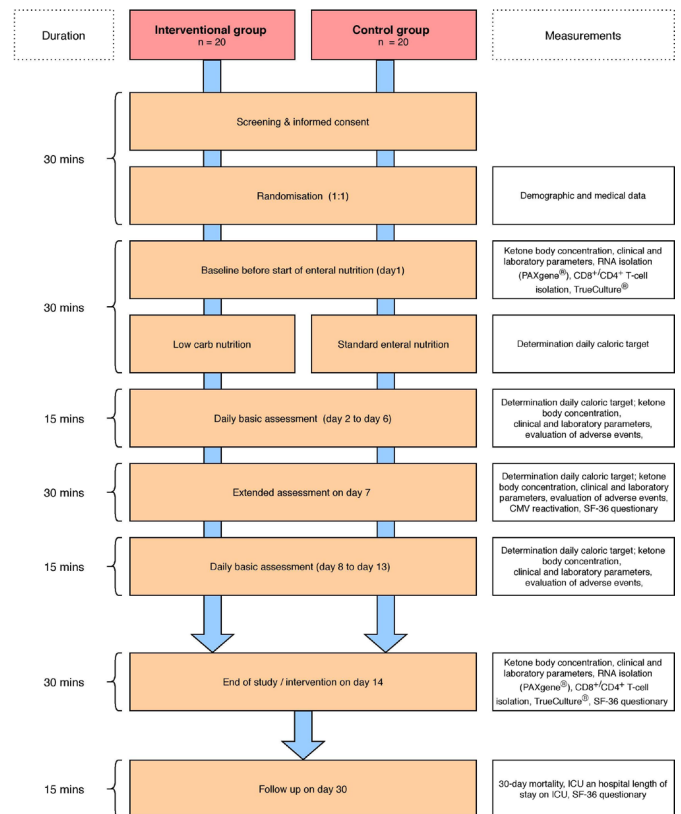


**Figure 1** Estimation results for sample sizes that were needed to receive a statistically significant change in the proportion of positive and negative outcomes via a binomial test scenario for various effect sizes (ie, Cohen's d) and power values. Each curve represents the results for one specific effect size (from left to right:  $d=2.14$ ;  $d=1.94$ ;  $d=1.74$ ;  $d=1.54$ ;  $d=1.34$ ), where  $d=2.0$  is usually considered as appropriate effect size in the literature.<sup>11</sup> For the assumed relatively low effect size of  $d=1.34$ ,  $\alpha=0.05$  and  $1-\beta=0.95$  in total about 40 patients were needed.

scheduled for each patient (figure 2). This includes study education and randomisation (30 min), data collection, intervention with accompanying data collection in both interventional and control groups (14 days). End of study is reached on day 14 (along with end of intervention) or, whatever occurred first, death or discharge from ICU. Considering secondary endpoints such as ICU length of stay, an additional observation period of 30 days is scheduled for each patient (figure 2).

### Randomisation

Block-balanced randomisation, in a 1:1 ratio ( $n=20$  ketogenic enteral nutrition;  $n=20$  conventional enteral nutrition), is computer generated by StatsDirect (StatsDirect, Cambridge, UK) with random block sizes between  $n=10$  and  $n=20$ , additionally using random permutations of treatments within each block. Investigators are blinded



**Figure 2** Flowchart of interventional procedures on intervention and control groups with duration of each step and performed measurements. CMV, cytomegalovirus; ICU, intensive care unit; SF-36, Short Form 36.

to the allocation according to the randomisation list until a patient has been included in the study.

### Interventional and study-specific procedures

After study inclusion and randomisation, the intervention group will receive a nutritional solution with a ketogenic formulation (KetoCal 4:1, Nutricia, Erlangen, Germany) with 0.61 g carbohydrates per 100 mL. The controls will receive a standard enteral nutritional solution with 17.0 g carbohydrates per 100 mL (Fresubin HP Energy, Fresenius Kabi, Bad Homburg, Germany) likewise started after randomisation. The energy expenditure to determine the daily calorie goal is estimated by using indirect calorimetry (Q-NRG+, COSMED, Rome, Italy). The enteral nutrition is commenced at an initial rate of 20 mL/hour and increased by 20 mL/hour every 6 hours in the absence of significant gastric residuals (ie,  $\geq 500$  mL), with the aim of reaching the estimated calorie goal within 24 hours after study enrolment. The attending physician is responsible for ensuring the achievement of energy targets. The exact calorie intake is electronically recorded and saved in the electronic health records.

As soon as the patients are capable of consuming oral food, the intervention group receives special ketogenic drinking solutions and an individually adapted ketogenic diet plan provided by the hospital's kitchen. The



TIMEPOINT	STUDY PERIOD							
	Enrolment		Post-allocation				End of study intervention	Close out
	Prior randomisation	Randomisation	Baseline (day 1)	Day 2 to 6	Day 7	Day 8 to 13	Day 14	Day 30
<b>ENROLMENT</b>								
- Eligibility screen	X							
- Informed consent	X							
- Randomisation		X						
<b>STUDY INTERVENTIONS</b>								
- Enteral nutrition			X	X	X	X	X	
<b>ASSESSMENTS</b>								
- Biometrical and demographic data			X					
- Clinical parameter			X	X	X	X	X	
- Ketone body concentration (in blood)			X	X	X	X	X	
- CD4 <sup>+</sup> and CD8 <sup>+</sup> T-cell isolation			X				X	
- Whole blood RNA isolation (Pax gene <sup>®</sup> )			X				X	
- Immunophenotyping (TrueCulture <sup>®</sup> )			X				X	
- Cytomegalovirus reactivation			X		X		X	
- Questionary "SF 36"			X		X		X	X
- 30-day mortality								X

**Figure 3** Schedule of enrolment, interventions and assessments—standard protocol items: recommendations for interventional trial figure. SF 36, Short Form 36.

control group will receive a standardised wholesome diet according to the hospital's menu.

All patients will be treated with a multimodal ICU concept according to the current sepsis guidelines<sup>24</sup> including analgesia and sedation, fluid therapy, lung-protective mechanical ventilation, haemodynamic monitoring and management, anticoagulation as well as antibiotic treatment and appropriate diagnostics. Most clinical, laboratory and demographic data will be collected during routine care and extracted from hospital and ICU electronic health records and merged in a common case report form (see online supplemental material 1). A comprehensive overview of the study-specific measurements, interventions, planned time points, analyses and data collections is depicted in the study flowchart adapted to Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) recommendations (figure 3).

Briefly, study-specific blood sampling is performed on day 1 (day of study inclusion) and day 14 or end of ketogenic diet. Additionally, ketone body concentration in whole blood (included in daily routine laboratory) and in urine samples will be determined daily in both groups.

Study-specific analysis comprises gene expression profiles of extracted T-cells from 15 mL of whole blood

collected in tubes containing lithium heparin (Sarstedt, Nümbrecht, Germany). Peripheral blood monocyctic cells are extracted by Ficoll density gradient centrifugation (Biochrom, Berlin, Germany) according to the manufacturer's instructions. Subsequently, T cells will be extracted by CD4/CD8 microbead separation (Miltenyi, Bergisch-Gladbach, Germany) according to the manufacturer's protocol.

Additionally, 5 mL of whole blood will be drawn into the PAXgene RNA extraction tubes (Qiagen, Venlo, The Netherlands) according to the manufacturer's instructions and stored at  $-20^{\circ}\text{C}$  until analysis. For analysis of cytokine expression profiles, 3 mL of whole blood will be drawn into TruCulture tubes (Myriad RBM, Austin, USA) and immediately incubated at  $37^{\circ}\text{C}$  for 48 hours according to the manufacturer's instructions. Afterwards, the supernatant will be aliquoted and stored at  $-80^{\circ}\text{C}$  until analysis.

### Objectives

The primary endpoint of the study is to assess whether a low-carb diet in septic patients can increase hydroxybutyric acid concentration in blood within 14 days.

The secondary objectives will be to compare the intervention group and the control group with regards to the following:

- ▶ Safety and feasibility parameters:
  - Serum cholesterol concentration.
  - Serum triglyceride concentration.
  - Acid-base balance (ie, risk of metabolic acidosis).
  - Serum aspartate transaminase and alanine transaminase activity.
  - Bilirubin concentration.
  - Blood glucose concentration and insulin requirements.
  - Catecholamine and vasopressor requirements.
  - Development of the SOFA score, SAPS II 30-day mortality.
  - ICU and hospital length of stay.
  - Short Form 36 health questionnaire.
- ▶ Immunological parameters:
  - mRNA expression profiles in T cells.
  - mRNA expression profiles from whole blood (PAXgene).
  - TruCulture whole blood stimulation (in vitro), subsequent analysis of cytokine secretion via multiplex assay.
  - Cytomegalovirus/Epstein-Barr virus reactivation rate after 7 days+14days.

### Data collection

The clinical and demographic documentation of the data will be derived from our patient data management system (Dräger ICM, Dräger Medical, Lübeck, Germany). All study-relevant data will be documented in a pseudonymised case report form (online supplementary material 1). Solely the principal investigator of this study has access to the pseudonymisation key and is capable to

deidentify the study patient in reasonable situations, for example, due to severe safety concerns. All study-relevant data will subsequently be entered in a central anonymised data source, along with study-specific measurements, for further statistical analysis. Data entered in the study data source will be monitored by an independent clinical research associate and checked for consistency and missing values ensure adequate data quality. This anonymised study data source will be made available along with the publication. All records, subjects' identities and data management will remain confidential with the General Data Protection Regulation of the European Parliament and the Council of the European Union. Furthermore, this protocol was designed following the SPIRIT (see online supplementary material 2).

### Statistical analysis

Since this is a study designed to demonstrate superiority of the primary endpoint, (increase of ketone body levels on ketogenic enteral nutrition within 14 days), we will perform an intention-to-treat analysis as recommended by the Consolidated Standards of Reporting Trials guidelines.<sup>25</sup> The per protocol population will be defined as randomised patients without major protocol deviations such as non-considerations of exclusion criteria or missing data for the primary endpoint. The per protocol analysis will also be made available along with the publication as supplementary material as appropriate. Baseline characteristics of all patients will be described per group. Qualitative data will be described as frequencies and percentages. Continuous variables are presented as mean±SD in case of normal distribution and as median and IQR (25th and 75th percentile) in case of non-normally distributed variables. Continuous variables will be compared using parametric Student's t-test or non-parametric Mann-Whitney U test. Categorical variables will be characterised by numbers with percentages and will be compared using the  $\chi^2$  test or a Fisher's exact test. Superiority will be assumed, if the 95% CI for the difference between the means excludes zero or p values are statistically significantly different at an a priori alpha error of less than 0.05. The graphical processing of variables will be performed depending on the measurement level of the variables as histograms, mean value curves with corresponding SD or box-whisker plots.

### Ethics and dissemination

A manuscript with the results of the study will be published in a peer-reviewed journal. The study has received the following approvals: Ethics Committee of the Medical Faculty of Ruhr-University Bochum (No. 18-6657-BR). The study was preregistered in the German Clinical Trial Register prior to the inclusion of the first study patient (first patient in: 22 January 2020). On completion of the trial, the primary study source data will be made public available along with the publication.

### DISCUSSION

An increasing number of experimental studies<sup>8–10 17 18</sup> revealed that different nutritional regimes can significantly affect immune cell homeostasis and modulate immune functions. Thus, nutritional interventions may provide an interesting cost-effective and easy-to-apply therapeutic approach to attenuate dysregulation of immune responses during sepsis. In particular ketogenic/very low-carb diets have been shown to inhibit overactivated innate immune cells. Such a diet is based on the restriction of carbohydrates to approximately 30g/day, which leads to the synthesis of BHB by the liver as an alternative energy source. BHB exerts anti-inflammatory effects by inhibiting the NLRP3 inflammasome, thus preventing the release of the proinflammatory cytokines interleukin-1 $\beta$  and interleukin-18.<sup>14</sup> Moreover, BHB stimulates the cellular endogenous antioxidant system and increases the efficiency of the electron transport chain.<sup>13</sup> In a ketogenic diet, not only the production of ketones but also the reduction of carbohydrates contributes to the overall anti-inflammatory effects, as high dietary intake of carbohydrates directly activates the inflammasome and increases the formation of reactive oxygen species (ROS),<sup>9 26 27</sup> which further aggravates inflammation.

Overwhelming inflammation and ROS production are considered as crucial maladaptive hallmarks in sepsis that are associated with organ dysfunction and poor outcome.<sup>28–30</sup> So far, it is completely unclear whether a ketogenic diet might enhance the immunological derailment of these patients and whether a low-carb nutrition might be an effective tool to ameliorate uncontrolled inflammation during sepsis.

Currently, state-of-the-art nutrition in critically ill patients contains more than 40% carbohydrates, thus exceeding minimal needs and preventing ketosis.<sup>6</sup> However, the need to provide amounts of glucose above minimal needs in these patients has never been demonstrated. Furthermore, during a low-carb diet in healthy adults, the controlled production of ketone bodies is known to cause a harmless (and potentially even favourable) 'substitute' physiological state known as dietary ketosis.<sup>31 32</sup> In this situation, ketone bodies are provided from the liver to extrahepatic tissues (eg, central nervous system) as alternative energetic supply.<sup>13</sup> This spares glucose metabolism via utilisation of ketone bodies as an alternative fuel. Moreover, blood glucose levels remain within the physiological range under low-carb nutrition due to glucogenic sources (glucogenic amino acids and lipolysis-derived glycerol) that are still provided in ketogenic diets.<sup>33</sup> Furthermore, hyperglycaemia and insulin resistance are more common complications during sepsis suggesting glucose deprivation as subordinate problem.<sup>34</sup>

Ketogenic diets are an established and well-tolerated clinical tool to control seizure frequencies in patients suffering from epilepsy.<sup>19 20</sup> However, in rare cases, adverse events, such as hypoglycaemia, dehydration, electrolyte alteration, metabolic acidosis, as well as gastrointestinal symptoms, including vomiting, constipation and



diarrhoea may occur. Frequency of these side effects of a ketogenic diet in critically ill patients, especially septic patients, has not been investigated yet. An alternative way that likewise could confer the beneficial effects of ketone bodies is the direct supplementation of ketone esters and salts.<sup>35</sup> However it is not clear whether the substitution of ketone bodies is capable to mimic all effects of a low-carb nutrition, for example, due to the absence of the metabolic switch.<sup>36</sup>

The current study aims at evaluating the feasibility and safety of a ketogenic diet in sepsis patients. In addition, the effects of this nutritional therapy on inflammatory reactions will be assessed.

## Outlook

This study tests the safety and practicability of a ketogenic enteral nutritional therapy in a critical care setting in patients with a severe inflammatory disease. Afterwards, larger cohorts and multicentric approaches will be needed to investigate whether ketogenic nutritional therapy represents a potential treatment strategy to improve sepsis outcome.

## Trial status

The first patient was randomised in 22 January 2020. The inclusion of participants is ongoing and is expected to continue until February 2021.

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**Contributors** TR and MH: main authors of this manuscript, written and revised the manuscript, responsible for study conceptualisation and statistical analysis plan. BK supported methodical description and laboratory experiments, participated in the design of this study and revised the manuscript. AW and K-MW contributed to study design and conceptualisation of the methodical approach, supports patient recruitment and revised the manuscript. GS supports data collection and laboratory analysis, participated in the design of this study and revised the manuscript. DE supports laboratory analysis, participated in the design of this study and revised the manuscript. MA supports data collection, reviewed the statistical analysis plan, participated in the design of this study and revised the manuscript. SK supporting study conceptualisation, drafted the design of this study, reviewed the statistical analysis plan, wrote and revised the manuscript. All authors read and approved the final manuscript.

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**Competing interests** None declared.

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## REFERENCES

- Boomer JS, To K, Chang KC, *et al*. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA* 2011;306:2594–605.
- Boomer JS, Green JM, Hotchkiss RS. The changing immune system in sepsis. *Virulence* 2014;5:45–56.
- Xiao H, Siddiqui J, Remick DG. Mechanisms of mortality in early and late sepsis. *Infect Immun* 2006;74:5227–35.
- SepNet Critical Care Trials Group. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study. *Intensive Care Med* 2016;42:1980–9.
- Jung J, Zeng H, Horng T. Metabolism as a guiding force for immunity. *Nat Cell Biol* 2019;21:85–93.
- Singer P, Blaser AR, Berger MM, *et al*. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019;38:48–79.
- Dror E, Dalmas E, Meier DT, *et al*. Postprandial macrophage-derived IL-1 $\beta$  stimulates insulin, and both synergistically promote glucose disposal and inflammation. *Nat Immunol* 2017;18:283–92.
- Choi IY, Piccio L, Childress P, *et al*. A diet mimicking fasting promotes regeneration and reduces autoimmunity and multiple sclerosis symptoms. *Cell Rep* 2016;15:2136–46.
- Hsieh P-S. Obesity-induced adipose tissue inflammation and insulin resistance. In: *Role of the adipocyte in development of type 2 diabetes*, 2011.
- Ota T. Obesity-induced inflammation and insulin resistance. *Front Endocrinol* 2014;5:204.
- Choi H-R, Kim J, Lim H, *et al*. Two-week exclusive supplementation of modified ketogenic nutrition drink reserves lean body mass and improves blood lipid profile in obese adults: a randomized clinical trial. *Nutrients* 2018;10. doi:10.3390/nu10121895. [Epub ahead of print: 03 Dec 2018].
- Zupec-Kania B, Neal E, Schultz R, *et al*. An update on diets in clinical practice. *J Child Neurol* 2013;28:1015–26.
- Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab* 2017;25:262–84.
- Youm Y-H, Nguyen KY, Grant RW, *et al*. The ketone metabolite  $\beta$ -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med* 2015;21:263–9.
- Newman JC, Verdin E.  $\beta$ -hydroxybutyrate: much more than a metabolite. *Diabetes Res Clin Pract* 2014;106:173–81.
- Newman JC, Verdin E.  $\beta$ -Hydroxybutyrate: a signaling metabolite. *Annu Rev Nutr* 2017;37:51–76.
- Goldberg EL, Asher JL, Molony RD, *et al*.  $\beta$ -Hydroxybutyrate deactivates neutrophil NLRP3 inflammasome to relieve gout flares. *Cell Rep* 2017;18:2077–87.
- Christ A, Günther P, Lauterbach MAR, *et al*. Western diet triggers NLRP3-Dependent innate immune reprogramming. *Cell* 2018;172:e14:162–75.
- Neal EG, Chaffe H, Schwartz RH, *et al*. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol* 2008;7:500–6.
- Martin-McGill KJ, Jackson CF, Bresnahan R, *et al*. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst Rev* 2018;11:CD001903.
- Yancy WS, Foy M, Chalecki AM, *et al*. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutr Metab* 2005;2:34.
- van der Louw EJTM, Olieman JF, van den Bemt PMLA, *et al*. Ketogenic diet treatment as adjuvant to standard treatment of glioblastoma multiforme: a feasibility and safety study. *Ther Adv Med Oncol* 2019;11:1758835919853958.
- Singer M, Deutschman CS, Seymour CW, *et al*. The third International consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801–10.
- Rhodes A, Evans LE, Alhazzani W, *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304–77.
- Schulz KF, Altman DG, Moher D, *et al*. Consort 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726–32.
- Vandanmagsar B, Youm Y-H, Ravussin A, *et al*. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat Med* 2011;17:179–88.
- Kitabchi AE, McDaniel KA, Wan JY, *et al*. Effects of high-protein versus high-carbohydrate diets on markers of  $\beta$ -cell function, oxidative stress, lipid peroxidation, proinflammatory cytokines, and adipokines in obese, premenopausal women without diabetes: a randomized controlled trial. *Diabetes Care* 2013;36:1919–25.
- Prauchner CA. Oxidative stress in sepsis: pathophysiological implications justifying antioxidant co-therapy. *Burns* 2017;43:471–85.

- 29 Huet O, Dupic L, Harrois A, *et al.* Oxidative stress and endothelial dysfunction during sepsis. *Front Biosci*
- 30 Esquerdo KF, Sharma NK, Brunialti MKC, *et al.* Inflammasome gene profile is modulated in septic patients, with a greater magnitude in non-survivors. *Clin Exp Immunol* 2017;189:232–40.
- 31 Feinman RD, Makowske M. Metabolic syndrome and low-carbohydrate ketogenic diets in the medical school biochemistry curriculum. *Metab Syndr Relat Disord* 2003;1:189–97.
- 32 Ravichandran M, Grandl G, Ristow M. Dietary carbohydrates impair healthspan and promote mortality. *Cell Metab* 2017;26:585–7.
- 33 Veldhorst MAB, Westerterp-Plantenga MS, Westerterp KR. Gluconeogenesis and energy expenditure after a high-protein, carbohydrate-free diet. *Am J Clin Nutr* 2009;90:519–26.
- 34 Van Cromphaut SJ, Vanhorebeek I, Van den Berghe G. Glucose metabolism and insulin resistance in sepsis. *Curr Pharm Des* 2008;14:1887–99.
- 35 Hashim SA, VanItallie TB. Ketone body therapy: from the ketogenic diet to the oral administration of ketone ester. *J Lipid Res* 2014;55:1818–26.
- 36 Marosi K, Moehl K, Navas-Enamorado I, *et al.* Metabolic and molecular framework for the enhancement of endurance by intermittent food deprivation. *Faseb J* 2018;32:3844–58.