

The pre-symptomatic detection of early extreme response to an infection (sepsis)

Submission date 26/10/2020	Recruitment status No longer recruiting	☐ Prospectively registered ☐ Protocol
Registration date 28/10/2020	Overall study status Completed	☐ Statistical analysis plan ☒ Results
Last Edited 14/07/2022	Condition category Infections and Infestations	☐ Individual participant data

Plain English summary of protocol

Background and study aims

We are trying to develop a blood test which would allow us to predict whether (and when) patients will go on to develop the severe complications of infection. We call severe infection "sepsis", which can cause people to become very ill and need intensive care.

Who can participate?

Adults aged between 18 and 80 who are undergoing elective surgery.

What does the study involve?

- Taking blood samples (15 ml) and urine samples from participants before their operation and each day afterwards for a week or until they leave hospital or develop an infection.
- Noting details of medical background
- Noting details such as pulse and blood pressure, each day
- Use of blood and urine to measure various things including which genes are activated in any response to infection
- Collection of some follow up details from hospital records
- Use of these data in this study and possibly use of the data and samples in future studies

What are the benefits and risks of participating?

Developing a blood test to predict the onset of these problems would allow us to start treatment very early and early treatment is more effective and saves lives. The study may have major implications for patients in the future, though it will not be of immediate benefit to the participant. There are no risks involved in the study. The only inconvenience is that of having a daily blood test over and above the normal blood tests normally needed. We will try to ensure these samples are taken together to minimize the inconvenience to the participant.

Where is the study run from?

1. Defence Science and Technology Laboratory (Dstl) Porton Down (UK)
2. Centre for Intensive Care Medicine, Department of Medicine & Wolfson Institute for Biomedical Research, University College London (UK)

When is the study starting and how long is it expected to run for?

Who is funding the study?

1. Ministry of Defence (UK)
2. Defense Threat Reduction Agency (USA)

Who is the main contact?

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Contact information

Type(s)

Scientific

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Public

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Additional identifiers

Protocol serial number

S167-01

Study information

Scientific Title

A multi-centre study to investigate immune modulators for the early diagnosis of sepsis in patients undergoing major elective surgery

Acronym

MASH

Study objectives

Patterns of host biomarker expression in the blood of patients undergoing high-risk elective surgery predict which patients will and will not go onto develop sepsis before the onset of clinical symptoms of infection.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 22/02/2007, Southampton & South West Hampshire Research Ethics Committee (A) (1st Floor Regents Park Surgery, Park Street, Shirley, Southampton, Hampshire, SO16 4RJ, UK; +44 203 8036 2466; hampshirea.rec@hra.nhs.uk), ref: 06/Q1702/152

Primary study design

Observational

Study design

Observational case control

Study type(s)

Diagnostic

Health condition(s) or problem(s) studied

Prediction of sepsis in elective surgery patents

Interventions

Demographic and clinical data will be gathered daily along with blood samples for immune modulators and urine samples. Some patients will have a straightforward perioperative course (non-septic group) and some will develop sepsis (sepsis group). Blood and urine samples will be taken daily for up to 7 days in all patients (or until discharge for the non-sepsis group and until the time of development of sepsis in the sepsis group). Standard blood biochemistry and haematology assays will be run. Appropriate microbiological analysis of a variety of clinical matrices (e.g. blood, urine, swab and sputum) will be undertaken when there is a clinical suspicion of infection.

Expression of host genes in the transcriptomes of patients that go on to develop sepsis that differentiates patient groups who do and do not go onto develop sepsis. Gene expression will be measured using microarray and reverse transcriptase quantitative polymerase chain. Gene expression (RT-qPCR) will be analysed in blood samples taken before surgery and then on each day following surgery for 7 days or until the patient developed sepsis, or until the patient is discharged earlier than 7 days post-surgery.

Intervention Type

Other

Primary outcome(s)

Original primary outcome:

1. Development of sepsis, measured using the “sepsis 2” criteria which is a Systemic Inflammatory Response Syndrome (SIRS) characterised by 2 of the following (measured daily for 7 days after surgery):
 - 1.1. Temperature >38 or $<36^{\circ}\text{C}$ measured by clinical observation
 - 1.2. Respiratory rate $>20/\text{min}$ or $\text{PCO}_2 <4.3$ or the need for ventilation measured by clinical observation
 - 1.3. Tachycardia $>90/\text{min}$ after fluid resuscitation measured by clinical observation
 - 1.4. White cell count >10 or $<4 \times 10^9/\text{l}$, or $>10\%$ immature forms measured by blood testA clinical adjudication panel sifted blinded patient data (including all relevant patient observations and clinical data) to determine which patients adhered to this criteria and which did not.

The definition of the study’s primary outcome (SEPSIS) was later changed to be defined as organ dysfunction (characterised by an increase in daily Sequential Organ Failure Assessment (SOFA) score of 2 or more from one day to the next) caused by an infectious agent. Sufficient clinical data was collected during the study to enable identification of patients who achieved the new “sepsis 3” criteria. The parameters for SOFA score include (measured using standard clinical biochemistry and haematology assays, daily for up to 7 days after surgery):

- 1.1. Respiratory system function (PO_2/FiO_2 mmHg/kPa >400 to <100)
- 1.2. Coagulation (Platelets $\times 10^3$ >150 to <20)
- 1.3. Liver function (Bilirubin levels <1.2 to >12.0 mg/dl)
- 1.4. Cardiovascular system function (MAP or medication to maintain MAP)
- 1.5. Central nervous system function (Glasgow Coma Score)
- 1.6. Renal system function (Creatinine levels <1.2 to >5.0 mg/dl)

2. Biomarkers in whole blood samples (collected daily for 7 days) of patients who go on to develop sepsis, assessed using gene expression measured using microarray and RT-qPCR

Key secondary outcome(s)

1. The time point at which sepsis occurred judged by a clinical advisory panel using the information collected for the primary outcome measures
2. Identification of alternative biomarkers such as proteins and metabolomic by-products was enabled through the collection of patient sera at the same time points as whole blood. Secondary analysis of protein expression by immunoassay in serial serum samples will enable identification of biomarker signatures that do not rely on RT-qPCR

Completion date

28/02/2017

Eligibility

Key inclusion criteria

1. Patients aged between 18 and 80 years
2. Ability to give written informed consent prior to study participation
3. Patients undergoing elective high-risk surgery (e.g. aortic vascular surgery, cardio-thoracic surgery, colonic surgery, gastrectomy, oesophago-gastrectomy, Whipple’s procedure, biliary or urological procedures)
4. ASA grades 1, 2, 3

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 Years

Sex

All

Total final enrolment

4385

Key exclusion criteria

1. Pregnant patients
2. Immunosuppressed patients (e.g. HIV disease, anti-rejection medication)

Date of first enrolment

01/11/2007

Date of final enrolment

20/02/2017

Locations**Countries of recruitment**

United Kingdom

England

Germany

Study participating centre

Heartlands Hospital

Bordesley Green E

Birmingham

United Kingdom

B9 5SS

Study participating centre

University College Hospital

University College London Hospitals NHS Foundation Trust
235 Euston Road
Bloomsbury
London
United Kingdom
NW1 2BU

Study participating centre**The Royal Liverpool University Hospital**

Royal Liverpool & Broadgreen University Hospitals NHS Trust
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre**St James's University Hospital**

Beckett Street
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Leeds
United Kingdom
LS9 7TF

Study participating centre**Bristol Royal Infirmary**

University Hospitals Bristol and Weston NHS Foundation Trust
Upper Maudlin Street
Bristol
United Kingdom
BS2 8HW

Study participating centre**Queen Elizabeth Hospital**

University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
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United Kingdom
B15 2TH

Study participating centre**St. Thomas' Hospital**

Guy's and St Thomas's NHS Foundation Trust
Westminster Bridge Road
London
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Study participating centre**University Hospital Frankfurt**

Theodor-Stern-Kai 7
Frankfurt am Main
Germany
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Sponsor information

Organisation

Defence Science and Technology Laboratory

ROR

<https://ror.org/04jswqb94>

Funder(s)

Funder type

Government

Funder Name

Ministry of Defence

Alternative Name(s)

MOD

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Funder Name

Defense Threat Reduction Agency

Alternative Name(s)

U.S. Defense Threat Reduction Agency, DOD Defense Threat Reduction Agency, United States Defense Threat Reduction Agency, US DoD Defense Threat Reduction Agency, Defense Special Weapons Agency, Defense Nuclear Agency, Defense Atomic Support Agency, Armed Forces Special Weapons Project, Manhattan Project, DTRA, US DTRA, AFSWP

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United States of America

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study will be stored in a publically available repository.

All raw data is derived following the anonymisation of participating patients. Transcriptomic data will be uploaded to a publicly available GEO database. Individual patient metadata will not be publicly available but will be available to individual patients on a case by case basis.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		13/07/2022	14/07/2022	Yes	No