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

Submission date
26/10/2020

Recruitment status
No longer recruiting

Registration date
28/10/2020

Overall study status
Completed

Last Edited
14/07/2022

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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?
Prof. Mervin Singer, m.singer@ucl.ac.uk

Contact information

Type(s)
Scientific

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

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

Study design
Observational case control

Primary study design
Observational

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°C measured by clinical observation
1.2. Respiratory rate >20/min or PCO2 <4.3 or the need for ventilation measured by clinical observation
1.3. Tachycardia >90/min after fluid resuscitation measured by clinical observation
1.4. White cell count >10 or < 4 x10(9)/l, or >10% immature forms measured by blood test
A 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 (PO2/FiO2 mmHg/kPa >400 to <100)
1.2. Coagulation (Platelets x 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

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B9 5SS

Study participating centre
University College Hospital
University College London Hospitals NHS Foundation Trust
235 Euston Road
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Study participating centre
The Royal Liverpool University Hospital
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Prescot Street
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Study participating centre
St James's University Hospital
Beckett Street
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LS9 7TF

Study participating centre
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BS2 8HW

Study participating centre
Queen Elizabeth Hospital
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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, DTRA, US DTRA

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
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes