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A trial of using antibiotics to prevent infection in patients with advanced liver disease

Submission date 29/04/2020	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 29/04/2020	**Overall study status** Completed	
Last Edited 14/02/2025	**Condition category** Digestive System	

Plain English summary of protocol

Background and study aims
Liver disease is a common cause of death and the three major causes are excessive alcohol drinking, obesity or infection with viral hepatitis. It develops over 15-30 years and causes irreversible liver scarring, cirrhosis. Some patients develop features of advanced liver disease - yellow skin, vomiting of blood or fluid in their abdomen and this affects 6000 people a year in Britain. They are very vulnerable to infection with bacteria because of their weak immune systems. These infections almost always require hospital admission and worsen their liver disease. A strategy of prevention of infection may be better than cure. The researchers will look at whether giving these people antibiotics when they do not have an infection for 18 months prevents development of SBP and improves overall survival. This is called prophylaxis and has been shown to work but only in small numbers of people and for short time frames. The researchers do not know if this would work across a wider population in the long term. Also antibiotic prophylaxis may cause harm. During antibiotic treatment bugs can find ways to stop antibiotics from killing them, antimicrobial resistance. These resistant bugs are even more dangerous as the researchers have fewer antibiotics that work against them. The researchers therefore need to test our approach in a clinical trial.

Aims:
Patients who have advanced liver disease are at high risk of suffering infection, hospital admission and death and it is preferable to prevent infection in the first place. The researchers are targeting a specific infection that affects fluid that builds up in the abdomen (known as ascites) of advanced liver disease patients, called Spontaneous Bacterial Peritonitis (SBP). Preventing SBP could help people with liver disease live longer, healthier lives.

Who can participate?
Adults over 18 years, with liver cirrhosis and ascites.

What does the study involve?
The researchers will recruit 432 people with cirrhosis and ascites but no SBP from 30 hospitals. Each will be given a pill once a day. These pills will look identical but half of patients will take an antibiotic whilst the other half will take an inactive tablet, a placebo. The antibiotic is co-trimoxazole, commonly used for urine infections. Neither patients nor doctors will know which is

which, a double-blind trial. Patients and investigators know which pill they are taking otherwise this can affect results even with an inactive drug, the placebo effect. Participants will take the medication for 18 months and meet research nurses every 3 months to determine if they have developed SBP or required admission to hospital. Information on liver function and quality of life will be collected and participants tested for antimicrobial resistance.

What are the possible benefits and risks of participating?
Co-trimoxazole causes significant side effects in 1 of every 100 patients, usually skin rashes. Very rarely (1-7 cases per million people per year) a severe dangerous skin rash develops, Stevens-Johnson, which people will be taught to look out for. High blood potassium levels can also occur and will be monitored by 3 monthly blood testing. Information will be stored securely so that participants cannot be identified and analysed by statisticians to inform us if co-trimoxazole prophylaxis prevents SBP effectively and safely.

Patient and public involvement
An infection in cirrhosis patient group has been set up to inform about concerns e.g. safety or adverse effects. The researchers will meet before the trial to design the protocol, consent forms, patient information sheets and a lay FAQ sheet for patients.

Where is the study run from?
Royal Free Hospital (UK)

When is the study starting and how long is it expected to run for?
September 2019 to May 2025

Who is funding the study?
National Institute for Health and Care Research (UK)

Who is the main contact?
Prof. Alastair O'Brien (scientific), a.o'brien@ucl.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04395365

Clinical Trials Information System (CTIS)
2019-000581-38

Integrated Research Application System (IRAS)
262176

Protocol serial number
CTU/2017/308, , HTA 176701

Study information

Scientific Title
Primary Antibiotic prophylaxis using co-trimoxazole to prevent SpontanEous bacterial PeritoniTIs in Cirrhosis

Acronym
ASEPTIC

Study objectives
Current study hypothesis as of 13/05/2021:
The primary objective of ASEPTIC is to determine whether primary antibiotic prophylaxis with co-trimoxazole reduces the incidence of spontaneous bacterial peritonitis compared to placebo in adults with cirrhosis and ascites over an 18-month trial period.

Previous study hypothesis:
The primary objective of ASEPTIC is to determine whether primary antibiotic prophylaxis with co-trimoxazole reduces the incidence of spontaneous bacterial peritonitis compared to placebo in adults with cirrhosis and ascites over a 2-year trial period.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/06/2019, South Central - Oxford B Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)2071048046; oxfordb.rec@hra.nhs.uk), ref: 19/SC/0311

Study design
Multicentre placebo-controlled randomized double-blind trial

Primary study design

Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Spontaneous Bacterial Peritonitis (SBP) in adults with liver cirrhosis and ascites

Interventions
Current interventions as of 13/05/2021:
This multicentre placebo-controlled randomised double-blind trial assesses efficacy, cost-effectiveness and safety of the use of co-trimoxazole for two years to prevent SBP in patients with cirrhosis.

Co-trimoxazole OR Placebo, 960mg capsules orally consumed daily for 18 months.
Patients randomised using Sealed Envelope online database.

Previous interventions:
This multicentre placebo-controlled randomised double-blind trial assesses efficacy, cost-effectiveness and safety of the use of co-trimoxazole for two years to prevent SBP in patients with cirrhosis and a low ascitic fluid protein count (<2.0 g/dL).

Co-trimoxazole OR Placebo, 960mg capsules orally consumed daily for 24 months.
Patients randomised using Sealed Envelope online database.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Co-trimoxazole

Primary outcome(s)
Current primary outcome measure as of 13/05/2021:
Overall survival measured using patient records at 18 months

Previous primary outcome measure:
Time to first incidence of spontaneous bacterial peritonitis up to 24 months following randomisation measured using patient records

Key secondary outcome(s))
Current secondary outcome measures as of 13/05/2021:
The following will be measured for a minimum period of 18 months from randomisation:
1. Time to first incidence of spontaneous bacterial peritonitis (SBP) (SBP is defined as per the standard guidelines: ascitic fluid polymorphonuclear (PMN) cell count >250/mm^3 with either positive or negative ascitic fluid culture without an evident intra-abdominal surgically treatable source of infection. A white cell count >500 cell/mm2 or positive microbial culture may be considered as evidence of previous SBP if the site PI considers this was in the context of a likely clinical diagnosis of SBP)

2. Hospital admission rates
3. Incidence of C. difficile-associated diarrhoea
4. Incidence of infections other than SBP that require hospital admission
5. Incidence of other cirrhosis related events (e.g. variceal haemorrhage)
6. Incidence of renal dysfunction with creatinine >133 µmol/L (1.5mg/dL) at any point during hospital admission
7. Incidence of anti-microbial resistance
8. Incidence of liver transplantation
9. Progression of liver disease assessed by increase in MELD score between baseline and end of trial follow up
10. Safety and treatment-related serious adverse events
11. Treatment adherence (assessed by MARS questionnaire)
12. Health-related quality of life assessed using EQ-5D-5L questionnaire
13. Health and social care resource use assessed using Hospital Episode Statistics (HES) database
14. Mean incremental cost per quality adjusted life year gained (QALY)
15. Incidence of resolution of ascites with diuretic treatment not required for 6 months
16. Incidence of Transjugular intrahepatic portosystemic shunt (TIPS) insertion

Previous secondary outcome measures:
The following will be measured up to 24 months from randomisation using patient records unless otherwise stated:
1. All-cause mortality
2. Incidence of spontaneous bacterial peritonitis infection
3. Hospital admission rates
4. Incidence of C. difficile-associated diarrhoea
5. Incidence of infections other than spontaneous bacterial peritonitis with hospital admission.
6. Incidence of other cirrhosis related events (e.g. variceal haemorrhage)
7. Incidence of renal dysfunction with creatinine >133 µmol/L (1.5mg/dL) at any point during hospital admission
8. Incidence of liver transplantation
9. Progression of liver disease assessed by increase in MELD score between baseline and end of trial follow up.
10. Safety and treatment-related adverse events
11. Treatment adherence (assessed by MARS questionnaire)
12. Health-related quality of life assessed using EQ-5D-5L questionnaire
13. Health and social care resource use assessed using Hospital Episode Statistics (HES) database
14. Mean incremental cost per quality-adjusted life year gained (QALY)
15. Incidence of resolution of ascites with diuretic treatment not required for 6 months

Completion date
31/05/2025

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 13/05/2021:
1. Liver cirrhosis and ascites persisting for >3 months despite standard treatment
2. Aged ≥18 years
3. Documented informed consent to participate

Previous participant inclusion criteria:
1. Liver cirrhosis and ascites with ascitic fluid protein count <2.0 g/dL (from sample taken within <12 weeks prior to randomisation)
2. Ascitic polymorphonuclear count <250 cells/mm3 and negative microbial culture at 5 days (on the last sample sent within <12 weeks prior to randomisation)
3. At least 18 years of age
4. Documented informed consent to participate

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
442

Key exclusion criteria
Current participant exclusion criteria as of 13/05/2021:
1. Current or previous Spontaneous Bacterial Peritonitis (defined as ascitic polymorphonuclear cell count >250/mm^3 with either positive or negative ascitic fluid culture without an evident intra-abdominal surgically treatable source of infection. A white cell count >500 cell/mm^2 or positive microbial culture may be considered as evidence of previous SBP if the site PI considers this was in the context of a likely clinical diagnosis of SBP)
2. Receiving palliative care with a life expectancy of <8 weeks
3. Allergic to co-trimoxazole, trimethoprim or sulphonamides
4. Pregnant or lactating mothers
5. Enrolled in a clinical trial of investigational medicinal products (IMPs) that would impact on their participation in the study
6. Serum potassium (>5.5 mmol/l) related to pre-existing kidney disease which cannot be reduced
7. Receiving antibiotic prophylaxis (except for rifaximin)
8. Long-term ascites drains
9. Women of child-bearing potential and males with a partner of child-bearing potential without effective contraception for the duration of trial treatment
10. Patients with pathological blood count changes:
10.1. Haemoglobin (Hb) <70 g/l
10.2. Granulocytopenia defined as absolute neutrophil counts of less than 500 cells per microliter
10.3. Severe thrombocytopenia with a platelet count <30 x10^9/l
11. Severe renal impairment, with eGFR <15 ml/min
12. Skin conditions: exudative erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis and drug eruption with eosinophilia and systemic symptoms

13. Congenital conditions: congenital glucose-6-Phosphate dehydrogenase deficiency of the erythrocytes, haemoglobin anomalies such as Hb Köln and Hb Zürich
14. Acute porphyria
15. Any clinical condition which the investigator considers would make the patient unsuitable for the trial

As some investigations may change in patients with cirrhosis and long-term ascitic drains may be removed, patients can be re-screened for eligibility if this occurs.

Previous participant exclusion criteria:
1. Previous Spontaneous Bacterial Peritonitis (SBP)
2. Receiving palliative care with an expected life expectancy of <8 weeks
3. Allergic to co-trimoxazole, trimethoprim or sulphonamides
4. Pregnant or lactating mothers
5. Enrolled in a clinical trial of investigational medicinal products (IMPs) that would impact on their participation in the study
6. Persistent hyperkalaemia (>6.5 mmol/L) related to pre-existing kidney disease with reduction not possible
7. Receiving antibiotic prophylaxis (except for rifaximin)
8. Long-term ascites drains
9. Women of child bearing potential and males with a partner of child bearing potential without effective contraception for the duration of trial treatment
10. Pathological blood count changes (granulocytopenia, megaloblastic anaemia)
11. Severe thrombocytopenia with a platelet count <30 x109 /L
12. Severe renal impairment, with eGFR <15 ml/min
13. Skin conditions: exudative erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis and drug eruption with eosinophilia and systemic symptoms
14. Congenital conditions: congenital glucose-6-Phosphate dehydrogenase deficiency of the erythrocytes, haemoglobin anomalies such as Hb Köln and Hb Zürich
15. Acute porphyria
16. Any clinical condition which the investigator considers would make the patient unsuitable for the trial

Date of first enrolment
28/09/2019

Date of final enrolment
31/08/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Free hospital
Pond St

Hampstead
London
United Kingdom
NW3 2QG

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Not defined

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version v3.0	13/08/2019	29/04/2020	No	No
Protocol file	version 4.0	25/08/2020	13/05/2021	No	No