Antibody and B cell responses in Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli infection

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Determine the B-cell antibody response in patients with Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli bacteremia

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bacterial infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON54509

Source
ToetsingOnline

Brief title
SHMR-bacteria-1

Condition

- Bacterial infectious disorders

Synonym
Bacteraemia, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Genmab

Intervention

Keyword: B-cell, Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus

Outcome measures

Primary outcome

We will study the antibody and B cell response in patients with S. aureus, K. pneumoniae, and E. coli bacteraemia. From the blood we will isolate B cells and purify antibodies (Immunoglobulins). We have multiple approaches to identify interesting antibodies. From isolated B cells, we can: 1) select bacterium-specific B cells based on flow cytometry; 2) isolate RNA and generate yeast libraries that display the antibodies; 3) select all B cells and perform single-cell sequencing to select cells that respond to the infection. For method 1) and 2) sorted B cells will be lysed and RNA will be converted to cDNA by RT-PCR. The cDNA will be used to either amplify the variable heavy- and light-chain regions (VH/VL) of the BCR, which will be used for sequencing and cloning into antibody expression vectors or yeast display vectors. Alternatively, bulk isolated cells will be analyzed with 10x Genomics to obtain single cell immune profile data with paired BCR sequences. These sequences will be synthesized and cloned into antibody expression vectors. Cloning will be done in human embryonic kidney 293 (HEK-293) suspension cell lines to produce full-length antibodies. The supernatants, containing antibodies, will be tested for their capability to bind to bacteria and trigger complement activation and bacterial killing (either directly by complement or after phagocytosis by human neutrophils). This way we can select the B cells producing functionally relevant antibodies. The best antibodies will be produced at a larger scale and further developed towards a clinical therapeutic. A potent antibody is defined as: 1 *g/ml of purified antibody should trigger >80% phagocytosis or complement-dependent killing of bacteria. From isolate antibodies (present in serum/plasma), we will isolate specific antibodies by pull-down experiments, characterize the antibodies by mass spectrometry including de novo sequencing of the variable domains (mass spectrometry).

Secondary outcome

The serum/plasma of the patients will also be used for an initial screening

test to determine which patient has the best antibodies. In a later stage of

the project, the serum/plasma will be used to study whether the antibodies

identified in this project are better than the antibodies already present.

Also, we will isolate neutrophils (from the waste of the PBMC isolation) to

study whether the antibodies can work together with the patients* own

neutrophils.

Subject age, gender and days between bacteraemia and collection of blood for the study will be recorded. Data will be collected regarding medical history, use of medication (especially immunosuppressive therapy), baseline characteristics (among which source of infection, e.g. catheter associated sepsis, endocarditis, osteomyelitis, urinary, abdominal, other), antimicrobial therapy, laboratory, radiology, cultures (any material), morbidity, mortality within 90 days after the day of bacteraemia.

Other study parameters (if applicable)

Subject age, gender and days between bacteraemia and collection of blood for the study will be recorded. Data will be collected regarding medical history, use of medication (especially immunosuppressive therapy), baseline characteristics (among which source of infection, e.g.: catheter associated sepsis, endocarditis, osteomyelitis, urinary, abdominal, other), antimicrobial therapy, laboratory, radiology, cultures (any material), morbidity, mortality within 90 days after the day of bacteraemia.

Study description

Background summary

Staphylococcus aureus bacteraemia (SAB) is a severe bacterial infectious disease. Despite antibiotic therapy, mortality form SAB is high: upto 30% after three months. Due to the successes achieved with antibody mediated therapy in oncology, there has been a renewed interest in the role of antibodies in bacterial infections. The human complement system plays an important role in clearing bacterial infecions, and can be activated via antibodies, providing a

whole new therapeutic approach in patients with bacterial infections.

Klebsiella pneumoniae and Escherichia coli are bacteria that are found in the gut of humans. These bacteria do no harm in the intestines, but if this bacterium is found in the blood, it leads to blood poisoning. This can occur, for example, with a urinary tract infection or an abdominal infection. Blood poisoning with this bacterium can generally be treated well with antibiotics. Unfortunately, there are more and more bacteria that are resistant to antibiotics. We think that in the future, antibodies could be used to treat people with such a resistant bacteria. That is why we want to investigate whether the human body produces good antibodies (also called antibodies) after an infection against the bacterium that has made someone sick.

Study objective

Determine the B-cell antibody response in patients with Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli bacteremia

Study design

Prospective cohort study with invasive measurement.

Study burden and risks

Patients undergo one venepuncture between 7 and 90 days after the first bacteremia; a total of 45ml of blood will be drawn. Venepunctures are safe and cause only minimal discomfort. The results of this study may lead to the development of new therapeutic strategies in treating this infection.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Staphylococcus aureus, Klebsiella pneumoniae or Escherichia coli bacteraemia diagnosed during current admission
- Adult (aged 18 and over)
- able to provide informed consent

Exclusion criteria

- Informed consent for participation given 28 days after the first positive blood culture was drawn

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting

Start date (anticipated):	13-11-2019
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	03-10-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-07-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL70666.041.19