folkehelseinstituttet

Protocol for empiric treatment with antibiotic combination therapy compared with monotherapy for adult patients with septic shock of unknown pathogen and origin: a systematic review

Project number :	RL 035
Protocol prepared :	November 2019

Short title Septic shock and empirical antimicrobial therapy

Short summary

The Norwegian National Guideline for use of antibiotics in hospitals was published in 2013, and is currently under revision(1). This systematic review will compare effect and safety of antibiotic combination therapy with monotherapy for adult patients with septic shock of unknown pathogen and origin. The results will feed into the developing of recommendations, adjusted to Norwegian conditions, for patients suffering from septic shock

Norsk:

Hva er effekten av empirisk behandling med kombinasjonsbehandling med antibiotika sammenlignet med monoterapi for voksne pasienter med septisk sjokk forårsaket av ukjent patogen og ukjent plassering: en systematisk oversikt. Nasjonal faglig retningslinje for bruk av antibiotika i sykehus ble utgitt i 2013, og er nå under revisjon (1). Denne systematiske oversikten skal sammenlikne effekt og sikkerhet av kombinasjonsbehandling med monoterapi for antibiotikabehandling hos voksne pasienter med septisk sjokk. Resultatene vil inngå i arbeidet med å oppdatere anbefalinger, tilpasset norske forhold, for pasienter som lider av septisk sjokk.

Project category and commissioner	
Product:	Systematic review
Thematic area:	Intensive care treatment in the hospital
Commissioner:	Hege Wang, Helsedirektoratet
Projectmanagement and participants	
Project leader:	Jan Himmels og Gunn Vist
Responsible for the project:	Gunn Vist og Hege Kornør
Internal project participants:	Gyri Hval Liv Giske Helene Arentz- Hansen
Plan for replacement if project participants drop out:	Will be decided by the person responsible for the project

The commission

The 2013 Norwegian National Guidelines for antibiotic treatment of sepsis and septic shock are under debate due to uncertainty about the effectiveness and safety of currently recommended combination therapy. This systematic review will compare antibiotic combination therapy with monotherapy for adult patients with septic shock.

In collaboration, the Directorate of Health and the Division for Health Services at the Norwegian Institute of Public Health have developed an accelerated process providing relevant up-to-date systematic reviews of direct usefulness to a specific recommendation for a National Guideline in Norway. This agreement focuses on defining narrow questions (specific populations, intervention, comparison and main outcomes) that will inform the guideline recommendation process. As the deciding guideline panel's members include clinical experts in the field, these systematic reviews have only short introductions, discussions and rarely include a glossary. Clinical experts from the guideline group perform peer review of these systematic reviews.

The aim

The aim of this systematic review is to compare the effect and safety of empiric antibiotic combination therapy to that of monotherapy for adult patients with septic shock of unknown pathogen and origin.

Introduction

Sepsis (*septicaemia, blood poisoning*) is a clinical condition that reflects the patient's systemic response to infection. Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone (2). Rapid and targeted treatment of sepsis, especially septic shock, is crucial towards reducing mortality. Immediate action is required, consisting of identification of infection origin, securing microbiological specimens, starting effective antibiotics and providing organ supportive treatment. Patients with septic shock and pronounced organ failure must have immediate life-saving treatment specifically aimed at the circulatory and respiratory failure. In addition, antibiotics should be administered as soon as possible, preferably after blood cultures have been taken. More timely initiation of effective antibiotic treatment has been linked to decreased mortality (3, 4). Early volume and oxygen therapy has not been shown to decrease mortality. In 2018, a Norwegian report found that patients with life-threatening reduced organ function were put at risk due to too long initiation time for antibiotic treatment (5).

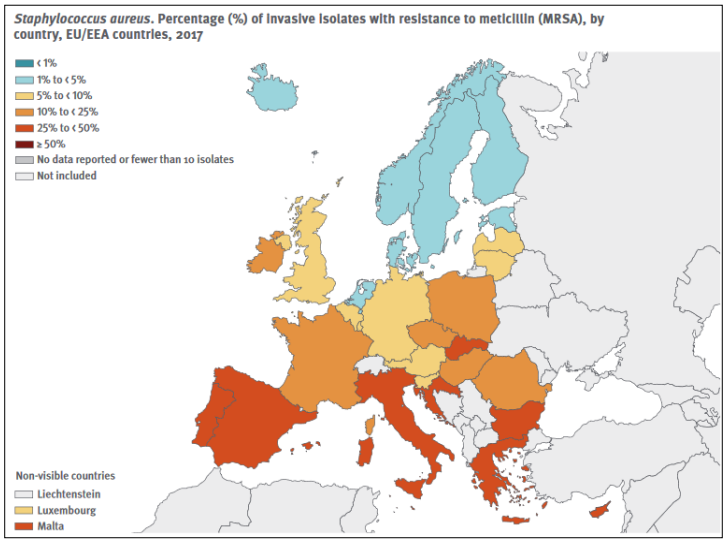

Figure 1. Exemplary map for Norway's low percentage of resistant isolates (MRSA); ECDC, Surveillance Atlas of Infectious Diseases, http://ecdc.europa.eu/en/data-tools/atlas/pages/atlas.aspx,Stockholm

Besides rapid treatment initiation, administering the right antibiotic is essential for the eradication of the bacterial pathogen, and therefore a prerequisite for tackling the underlying cause of sepsis. In the absence of a confirmed pathogen or clinical signs of infection origin, empiric antimicrobial therapy becomes necessary. Empirical treatment is treatment based on clinical reasoning in the absence of complete information. Empiric antimicrobial therapy aims to cover all plausible bacterial pathogens, including their regional resistance patterns; it will inherently be broader than necessary for the individual patient and yet not be broad enough for all. The acute nature of septic shock requires rapid initiation of empiric treatment with no time to await microbiological test results. Empiric therapy may fail when there is a mismatch between antimicrobial agent and bacterial sensitivity (6).

There is no universally *right* antibiotic choice, antibiotics differ from each other in their mechanism of action and have varying spectrums of effectivity. Bacterial diversity is even greater and brings with it the inherent necessity for different antibiotics. Besides intrinsic resistance to antimicrobial agents, bacteria are also capable of developing/acquiring broader resistance. This adaptation process contributes to bacterial survival, and is accelerated under bacterial stress (such as exposure to antibiotics) (7). Since the initiation

of antibiotic treatment, antimicrobial resistance (AMR) has accompanied their use and reduced their effectivity with time. Wide use favours further AMR. Treatment choice is influenced by effectiveness, risk of side effects and the risk for increased antimicrobial resistance. Broader or combination antibiotics may be more effective, without necessarily causing more side effects, but may contribute disproportionally to AMR. Balancing these aspects is ultimately an ethical question (8). AMR begins locally spreads regionally and may remain country specific, yet in a globalising world, these boundaries become blurred (9).

Norway with its generally careful and prudent approach to antimicrobial use, is within the EEA one of the countries with the least AMR. This is fortunate for Norway, in contrast to declining effects in most of Europe and the rest of the world many antibiotics continue to be effective (10). Other Scandinavian countries have similarly favourable conditions. Therefore, the most *plausible* choice for empiric antibiotic treatment/ septic shock treatment for patients in Norway is reliant on the epidemiological situation of Norway/ possibly Scandinavia. Evidence from other epidemiological settings beyond Scandinavia may nonetheless provide beneficial insights into treatment tolerance, side effects and a broader understanding of probable future treatment options in a more AMR afflicted Norway.

There is uncertainty among medical doctors in Norway on which empiric antibiotic treatment is *right* or *most plausible* for adult patients suffering from septic shock of unknown origin. The release of the 2013 guidelines for antibiotic use in hospitals recommending "*Benzylpenicillin iv 3g x 4 + Gentamicin iv 5-7 mg/kg x 1"*, were met with claims of "*unjustifiable guidelines for antibiotic use in hospitals*" (11, 12). The recommendations did not differentiate between "sepsis" and "septic shock". The critique did not address differing regional resistance patterns or varying patient population needs. A major communicated concern was the known possible risk of kidney damage with aminoglycoside treatment. Nordøy and Laake claimed that many patients were referred to Rikshospitalet with pulmonary and kidney failure post guideline treatment (11). A 2018 study looking at adherence to the guideline in Norway found that only Rikshospitalet refrained from the use of aminoglycosides in all patients with sepsis and septic shock (13). This controversial and possibly outdated recommendation in the guidelines requires revision. This review focuses on comparing currently recommended combination therapy to antibiotic monotherapy (14). This review aims to contribute its results to the update process of the Norwegian guidelines for the empiric treatment of septic shock of unknown origin.

Within the possibility of a systematic review and if the data allows a meta-analysis we aim to compare combination therapy with a macrolide/gentamycin (qd)/tobramycin(qd) + any betalactam/ (ampicillin or (benzyl) penicillin) / betalactam except (ampicillin or (benzyl) penicillin) versus any type of antibacterial monotherapy for the empiric treatment of septic shock with unknown focus. We will look at 30-day mortality, length of hospital/and intensive care unit (ICU) stay, bacterial eradication and serious adverse effects.

Methods

We will conduct a systematic review in accordance with the Handbook used at the Division for Health Services at the Norwegian Institute of Public Health (15).

Inclusion criteria

We will use the following inclusion criteria:

Population: Adult patients with septic shock or suspected septic shock, with unknown origin of infection before start of treatment

Intervention: Antibiotic combination therapy including the following:

- Macrolide + any betalactam
- Genta/tobramycin (single daily dose) + betalactam (ampicillin or (benzyl) penicillin)
- Genta/tobramycin (single daily dose) + betalactam (except ampicillin or (benzyl) penicillin)
- Amikacin (single daily dose) + betalactam (ampicillin or (benzyl) penicillin)
- Amikacin (single daily dose) + betalactam (except ampicillin or (benzyl) penicillin)

Planned aminoglycoside treatment should include daily doses

Comparison: Antibiotic monotherapy

Outcomes: Mortality (30 days)
Serious adverse events (including organ damage)
Length of stay in hospital (days)
Length of stay in ICU (days)
Bacterial eradication (negative blood culture)

Study design: Prospectively controlled studies including randomized controlled trials (RCTs), non-randomized controlled trials, controlled cohort studies

Languages: We will include studies published in the following languages: Danish, English, German, Norwegian, and Swedish.

Literature search

Our librarian (GH) will develop and conduct the literature search. She will search for published trials in the following databases:

- Cochrane Central Register of Controlled Trials
- Medline (Ovid)
- Embase (Ovid)

and for planned and ongoing trials in

- clinical.trials.gov
- WHO ICTRP

Another librarian will peer review this process.

The electronic search will be checked for duplicates in EndNote (ref). Additionally, we plan to check the reference lists of included studies and other relevant literature.

Study selection

Two researches will, using the above defined inclusion criteria independently carry out title and abstract screening. Two researches will independently perform full text screening for all potentially eligible studies. We will be utilize Rayyan for the study selection process (16).

The selected studies will be assessed by an expert in the field, in order to ensure that the included studies are applicable in the current Norwegian setting (issues such as dosage, length of treatment, therapeutic drug monitoring (TDM) and AMR epidemiology are of paramount importance to consider).

Assessment of risk of bias

Two researchers will independently assess the risk of bias for each of the included studies in accordance with the recommendations by the Cochrane Collaboration.

RCTs will be assessed for risk of bias in respect to: sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessor, incomplete outcome data, selective outcome reporting and other risk of bias. Non-randomized controlled trials and other studies with a control group will also be assessed for risk of bias in respect to: similarity of baseline characteristics, similarity of baseline outcome data, and contamination. All items will be rated as high risk of bias, unclear, or low risk of bias.

Data extraction and analysis

One researcher will extract information from the included studies; another researcher will independently check the extraction for accuracy and relevance. Data on the following will be extracted: full reference, location and date of study. The following patient data will be extracted: clinical history (if available), age, sex and co-morbidities. The following intervention/comparison data will be extracted: pharmaceutical agent/s, dose, dose regiment, treatment length (for empiric treatment and the treatment following pathogen identification) and type of monotherapy (comparison). Outcomes measured and follow-up times will also be extracted.

Dichotomous outcomes will be presented as risk ratios (RRs) with 95% confidence intervals (CIs). Continuous outcomes will be presented as mean difference between the groups with 95% CIs. Where different scales are used to measure the same outcome, we will calculate standardized mean difference with a 95% CI. We plan to use Review Manager (RevMan 5.3) software to generate forest plots and conduct meta-analysis if relevant. Attrition will be handled using intention-to-treat analysis. We will use random effects model and evaluate statistical heterogeneity using the Q test and I^2 statistic.

Analysis plan:
Population: First, combined analysis including all patients with septic shock or suspected septic shock. We plan to collect information about the patients in each study, anonymize this information (remove link to which study), and ask the above mentioned clinical expert to categorize the populations into different groups of similar patients that we will sub group in analysis:

- morbidity groups (co-morbidity, immunocompromised, etc), will be used as proxy for expected/assumed resistance pattern
- place of acquiring the infection (hospital acquired or not)
- sepsis definisjoner (SOFA, SIRS eller annet)

Intervention: First, we plan a combined analysis with all combination therapy compared to monotherapy, and then we plan to look at subgroups separately according to the bullet points in the inclusion criteria.

Judgements about our certainty in the evidence, GRADE
We plan to use the Grading of Recommendations Assessment, Development and Evaluation (17) method to assess our confidence in the evidence for each outcome.

Starting date (for FHI.no):
29th October 2019

End date
Planned date of publication for this systematic review is 29th April 2020.

Publication
The planned product of this project is a systematic review published as a report in series of the Norwegian Institute of Public Health and made available on www.fhi.no. We may consider writing a short description of the results from this systematic review (omtale) in Norwegian.

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Indexing for the homepage

(Septic shock, antibiotic dual treatment, antibiotic monotherapy, antimicrobiotic ressistance (AMR)

Related projects or publications

Sæterdal I, Holte HH, Harboe I, Klemp M. Treatment of sepsis using aminoglycosides. Report from Kunnskapssenteret no. 3–2015. Oslo: Norwegian Knowledge Centre for the Health Services, 2015.

Sæterdal I, Akselsen PE, Berild D, Harboe I, Odgaard-Jensen J, Reinertsen E, Vist GE, Klemp M. Antibiotikabehandling i sykehus, peroral versus intravenøs behandling. Rapport fra Kunnskapssenteret nr 2–2010. Oslo: Nasjonalt kunnskapssenter for helsetjenesten, 2010.