Effect of using aminoglycosides for treatment of sepsis

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
No 3–2015
Systematic review, overwiev of systematic reviews

kunnskapssenteret
Norwegian Knowledge Centre for the Health Services

Background: Sepsis is a potentially dangerous or life-threatening medical condition, usually caused by a bacterial infection. In Norway, sepsis is usually treated with antibiotics, and a typical regimen could be to use a narrow-spectrum antibiotic, for example a beta lactam antibiotic such as benzylpenicillin in combination with a highly potent, broad-spectrum antibiotic, such as an aminoglycoside. Our aim was to systematically review the evidence on the treatment effects and harms of any antibiotic regimen with an aminoglycoside versus any antibiotic regimen without an aminoglycoside for sepsis in adults. We searched for systematic reviews, and included one systematic review that met our inclusion criteria. Based on this review which assess the clinical efficacy of beta lactam antibiotic monotherapy versus combination therapy (beta lactam + aminoglycoside-regimens) for sepsis, our main findings are: • The pooled estimate for any nephrotoxicity showed a 66 % reduction in the risk of any nephrotoxicity using beta lactam monotherapy compared with combination therapy (RR= 0.34; 95% CI [0.25, 0.46]). The quality of the evidence is low. • The *(continued)*

Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret)
PO Box 7004, St. Olavs plass
N-0130 Oslo
(+47) 23 25 50 00
www.kunnskapssenteret.no
Report: ISBN 978-82-8121-939-7 ISSN 1890-1298

no 3–2015

kunnskapssenteret

(continued from page one) pooled estimate for serious adverse events showed a statistically non-significant difference between beta lactam monotherapy and combination therapy (RR= 1.06; 95% CI [0.58, 1.91]). The quality of the evidence is low. • The pooled estimate for overall mortality showed a statistically non-significant difference between beta lactam monotherapy and combination therapy (RR= 0.89; 95% CI [0.74, 1.08]). The quality of the evidence is low. • The pooled estimate for treatment failure showed a statistically significant difference between beta lactam monotherapy and combination therapy in favor of monotherapy (RR= 0.84; 95% CI [0.72, 0.97]). The quality of the evidence is moderate.

Title Effect of using aminoglycosides for treatment of sepsis

Norwegian title Effekt av bruk av aminoglykosider i sepsisbehandling

Institution Norwegian Knowledge Centre for the Health Services
(Nasjonalt kunnskapssenter for helsetjenesten)
Nylenna, Magne, *Director*

Authors Sæterdal, Ingvil, *researcher, Norwegian Knowledge Centre for the Health Services*
Holte, Hilde H, *researcher, Norwegian Knowledge Centre for the Health Services*
Harboe, Ingrid, *research librarian, Norwegian Knowledge Centre for the Health Services*
Klemp, Marianne, *Research Director, Norwegian Knowledge Center for the Health Services*

ISBN 978-82-8121-939-7

ISSN 1890-1298

Report No. 3 – 2015

Project number 768

Type of report Systematic review, overwiev of systematic reviews (Systematisk oversikt, oversikt over systematiske oversikter)

No. of pages 39 (53 including appendices)

Client National directorate of health

Subject heading (MeSH) Sepsis, aminoclycosides, Anti-Bacterial Agents

Citation 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.

Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Norwegian Directorate for Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

We would like to thank Niels Frimodt Møller , Johan Bruun, Ingeborg Beate Lidal og Susan Munabi Babigumira for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, February 2015

Key messages

Sepsis is a potentially dangerous or life-threatening medical condition, usually caused by a bacterial infection. In Norway, sepsis is usually treated with antibiotics, and a typical regimen could be to use a narrow-spectrum antibiotic, for example a beta lactam antibiotic such as benzylpenicillin in combination with a highly potent, broad-spectrum antibiotic, such as an aminoglycoside.

Our aim was to systematically review the evidence on the treatment effects and harms of any antibiotic regimen with an aminoglycoside versus any antibiotic regimen without an aminoglycoside for sepsis in adults.

We searched for systematic reviews, and included one systematic review that met our inclusion criteria. Based on this review which assess the clinical efficacy of beta lactam antibiotic monotherapy versus combination therapy (beta lactam + aminoglycoside-regimens) for sepsis, our main findings are:

- The pooled estimate for any nephrotoxicity showed a 66 % reduction in the risk of any nephrotoxicity using beta lactam monotherapy compared with combination therapy (RR= 0.34; 95% CI [0.25, 0.46]). The quality of the evidence is low.

- The pooled estimate for serious adverse events showed a statistically non-significant difference between beta lactam monotherapy and combination therapy (RR= 1.06; 95% CI [0.58, 1.91]). The quality of the evidence is low.

- The pooled estimate for overall mortality showed a statistically non-significant difference between beta lactam monotherapy and combination therapy (RR= 0.89; 95% CI [0.74, 1.08]). The quality of the evidence is low.

Title:
Effect of using aminoglycosides for treatment of sepsis

Type of publication:

Systematic review

A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No health economic evaluation
- No recommendations

Publisher:

Norwegian Knowledge Centre for the Health Services

Updated:

Last search for systematic reviews:
April, 2014.

Peer review:

Niels Frimodt-Møller, Professor, klinikksjef, Rikshospitalet, København

Johan Bruun, Professor, overlege, Univeristetssykehuset Nord Norge, Tromsø

- The pooled estimate for treatment failure showed a statistically significant difference between beta lactam monotherapy and combination therapy in favor of monotherapy (RR= 0.84; 95% CI [0.72, 0.97]). The quality of the evidence is moderate.

The pooled evidence provided in this systematic overview, are from studies done in different settings, with different patient-groups/diagnosis, different pathogens, with different regimens (doses, intervals, length of treatment). All included studies were conducted between the years 1973 and 2006 and contains only regimens comparing beta lactam monotherapy versus aminoglycosides in combination with beta lactams. Treatment failure is defined as it was in the primary studies, and hence a mixture of definitions are included. These definitions and the interpretation of the definitions might have been assessed differently by the different study authors and might have influenced the results for treatment failure.

These aspects are important to be aware of when considering this evidence for making treatment recommendations in Norway.

Executive summary

Background

Sepsis is defined as a clinical condition that reflects a systemic inflammatory response to infection. In serious cases, sepsis can cause organ dysfunction and death. In Norway, the standard treatment for sepsis is empirical antibiotic treatment based on the diagnostic of the etiologic agent, the expected antibiotic sensitivity, as well as pharmacodynamic- and kinetic considerations. A typical regimen could be to use a narrow-spectrum antibiotic in combination with a highly potent, broad-spectrum antibiotic, such as an aminoglycoside.

Objective

To prepare an overview of systematic reviews considering the clinical effectiveness of antibiotic regimens with aminoglycosides compared to a regimen without aminoglycosides for treatment of sepsis according to a few pre-specified outcomes.

Method

We have conducted this overview of systematic reviews in accordance with the Handbook for the Norwegian Knowledge Center for the Health Services.

We performed a systematic search for literature and two review authors reviewed all citations to identify relevant publications according to pre-specified criteria. We retrieved full text copies of all potentially eligible publications and assessed whether these publications should be included based on our inclusion criteria. We assessed the methodological quality of potentially relevant systematic reviews using a checklist for systematic reviews. All assessments were conducted and agreed upon by two of the review authors working independently. One review author extracted data from the included systematic reviews for studies dealing with sepsis and entered and analyzed data using the Review Manager software. Another review author verified the data and analyses. We applied the GRADE method to assess overall quality of the evidence for each outcome.

Results

The literature search for systematic reviews on the effect of treatment of sepsis using aminoglycosides, was conducted in September 2013 and updated in April 2014. We identified 1434 references in total. After reading titles and abstracts, we considered 8 references possibly eligible and we read them in full text. Only one systematic review met our inclusion criteria, a recently updated Cochrane review written by Paul 2014 that compared beta lactam monotherapy versus beta lactam and aminoglycoside combination therapy in patients with sepsis. The Cochrane review authors designated studies that included patients with severe sepsis as "sepsis" and we have based our analyses on the 42 studies designated as sepsis and conducted in adults. Trials are pooled independent of type of beta lactam antibiotic used in the study arms.

Our main findings are:

The pooled estimate for any nephrotoxicity showed a 66 % reduction in the risk of any nephrotoxicity using beta lactam monotherapy compared with beta lactam-aminoglycoside combination therapy (RR= 0.34; 95% CI [0.25, 0.46]). The quality of the evidence is low.

The pooled estimate for serious adverse events showed a statistically non-significant difference between beta lactam monotherapy and beta lactam-aminoglycoside combination therapy (RR= 1.06; 95% CI [0.58, 1.91]. The quality of the evidence is low.

The pooled estimate for overall mortality showed a statistically non-significant difference between beta lactam monotherapy and beta lactam-aminoglycoside-combination therapy (RR= 0.89; 95% CI [0.74, 1.08]),
The quality of the evidence is low.

The pooled estimate for treatment failure showed a statistically significant difference between beta lactam monotherapy and beta lactam-aminoglycoside-combination therapy in favor of monotherapy (RR= 0.84; 95% CI [0.72, 0.97]. The quality of the evidence is moderate.

Discussion

The main results are that using a combination therapy of beta lactam and aminoglycoside may lead to more nephrotoxicity and probably leads to more treatment failure compared to using beta lactam monotherapy. Our report is based on data from one systematic review produced within the Cochrane Collaboration, Paul 2014. The Cochrane review included studies with hospitalized patients with sepsis acquired in

the community or in the hospital. Sepsis were defined as clinical evidence of infection plus evidence of systemic response to infection. The included patients might be a mixed group of patients with more or less severe sepsis depending on the definition and inclusion criteria in the original articles. The Cochrane review did not perform analysis on a sub-group of patients with septic shock.

We were not able to identify systematic reviews of high methodological quality evaluating the effect of aminoglycosides-regimen other than in combination with beta lactam antibiotic for sepsis treatment.

A limitation with our work is that we do not know how the patients were followed up during treatment with aminoglycosides. In the Norwegian guideline on sepsis treatment, it is recommended to always evaluate the risk of acute renal failure, monitor the serum level of aminoglycosides and avoid concomitant use of nephrotoxic drugs. Lack of such thorough follow up might have led to more nephrotoxicity or other failures in the included trials than will be the case today.

The decisions and monitoring of sepsis treatment are very complex processes, demanding frequent evaluations during the course, and is also dependent on available equipment and settings. The pooled evidence provided in this systematic overview, are from studies done in different settings, with different patient-groups/diagnosis, different pathogens, with different regimen (doses; intervals; length of treatment). These aspects are important to be aware of when considering this evidence for treatment recommendations in Norway.

Conclusion

The results presented in this review indicate that beta lactam-aminoglycoside combination therapy may increase the risk of nephrotoxicity compared with monotherapy. The combination therapy probably leads to more treatment failures compared with beta lactam monotherapy in adult patients. For overall mortality and serious adverse events, there may be little or no difference between monotherapy and combination therapy. The confidence in the estimates for overall mortality, nephrotoxicity and serious adverse events are limited and the true effect may be different from the estimate. We are moderately confident in the effect estimate for treatment failure; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

The pooled evidence provided in this systematic overview, are from studies done in different settings, with different patient-groups/diagnosis, different pathogens, with different regimens (doses, intervals, length of treatment). All included studies were conducted between the years 1973 and 2006 and contains only regimens comparing beta lactam monotherapy versus aminoglycosides in combination with beta lactams.

These aspects are important to be aware of when considering this evidence for making treatment recommendations in Norway.

Hovedfunn (norsk)

Blodforgiftning er en potensielt farlig og livstruende tilstand som vanligvis er forårsaket av en bakteriell infeksjon. I Norge behandles blodforgiftning vanligvis med antibiotika. Et typisk regime kan være å bruke et smalspektret antibiotika i kombinasjon med et aminoglykosid.

I denne rapporten har vi systematisk oppsummert forskning om skadevirkninger og effekt ved antibiotikaregimer med aminoglykosid versus antibiotikaregimer uten aminoglykosid for behandling av blodforgiftning hos voksne.

Vi inkluderte én systematisk oversikt som møtte våre inklusjonskriterier. Våre viktigste funn er:

- Risikoen for nyresvikt reduseres muligens med 66 prosent ved bruk av et antibiotikaregime uten aminoglykosid, sammenlignet med et antibiotikaregime med aminoglykosid. Kvaliteten på dokumentasjonen er lav.

- Resultatene for alvorlige bivirkninger er usikre og vi kan ikke konkludere om det er en forskjell mellom antibiotikabehandling med og uten aminoglykosid. Kvaliteten på dokumentasjonen er lav.

- Resultatene for totaldødelighet er usikre og vi kan ikke konkludere om det er en forskjell mellom antibiotikabehandling med og uten aminoglykosid. Kvaliteten på dokumentasjonen er lav.

- Risikoen for behandlingssvikt er trolig mindre ved bruk av et antibiotikaregime uten aminoglykosid, sammenlignet med et antibiotikaregime med aminoglykosid. Kvaliteten på dokumentasjonen er moderat.

Tittel:
Effekt av bruk av aminoglykosider i sepsisbehandling

Publikasjonstype:

Systematisk oversikt

En systematisk oversikt er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriteriene
- Ingen helseøkonomisk evaluering
- Ingen anbefalinger

Hvem står bak denne rapporten?

Kunnskapssenteret har skrevet rapporten på oppdrag fra Helsedirektoratet

---

Når ble litteratursøket utført?

Søk etter systematiske oversikter ble avsluttet april, 2014.

Fagfeller:

Niels Frimodt-Møller, Professor, klinikksjef, Rikshospitalet, København

Johan Bruun, Professor, overlege, Univeristetssykehuset Nord Norge, Tromsø

De oppsummerte resultatene i denne systematiske oversikten er fra studier som er utført i ulike settinger, med ulike pasientgrupper, ulike patogener og med ulike antibiotikaregimer (doser, intervaller, lengde av behandling). Alle studier ble utført i årene 1973 til 2006, og inneholder bare regimer som sammenlignet beta laktam monoterapi versus aminoglykosider i kombinasjon med beta laktamer.

Behandlingssvikt er definert slik det var gjort i primærstudiene, og består dermed av ulike definisjoner. Definisjonene og forståelsen av disse kan ha ført til at behandlingssvikt har blitt vurdert ulikt av forfatterne av de ulike studiene. Det er viktig å være klar over disse begrensningene når dokumentasjonen skal brukes som beslutningsgrunnlag i Norge.

Sammendrag (norsk)

Bakgrunn

Blodforgiftning (sepsis) er en potensielt farlig og livstruende tilstand som vanligvis er forårsaket av en bakteriell infeksjon. I alvorlige tilfeller kan sepsis føre til organsvikt og død. I Norge behandles sepsis vanligvis med antibiotika. Et typisk regime kan være å bruke et smalspektret antibiotika i kombinasjon med et aminoglykosid.

Problemstilling

Å utarbeide en oversikt over systematiske oversikter som vurderer effekt av antibiotikaregimer med aminoglykosider sammenlignet med et regime uten aminoglykosider for behandling av sepsis for noen forhåndsdefinerte utfall.

Metode

Vi har utarbeidet denne oversikten over systematiske oversikter i samsvar med Håndbok for Nasjonalt kunnskapssenter for helsetjenesten.

Vi utførte et systematisk søk etter litteratur, og to forfattere gjennomgikk alle referansene for å identifisere relevante publikasjoner i henhold til forhåndsdefinerte kriterier. Vi innhentet i fulltekst alle potensielt relevante publikasjoner og vurderte om disse publikasjonene skulle inkluderes basert på våre inklusjonskriterier. Vi vurderte den metodiske kvaliteten av publikasjonene ved hjelp av en sjekkliste for systematiske oversikter. Alle vurderinger ble gjort uavhengig og deretter i fellesskap med to av forfatterne. En av forfatterne hentet ut data fra studier som omhandlet sepsis fra den inkluderte litteraturen og la dette inn i Review manager-programvaren for analysering. En annen av forfatterne gjennomgikk dataene og analysene. Vi brukte GRADE-metoden for å vurdere den generelle kvaliteten på dokumentasjonen for hvert utfall.

Resultat

Vårt litteratursøk etter systematiske oversikter om effekt av bruk av aminoglykosider ved behandling av sepsis, ble utført i september 2013 og oppdatert i april 2014. Vi identifiserte totalt 1434 referanser. Etter å ha lest titler og sammendrag, vurderte vi åtte referanser som mulig relevante og vi leste disse i fulltekst. Bare én systematisk oversikt møtte våre inklusjonskriterier, en nylig oppdatert Cochrane-oversikt av Paul 2014. Denne oversikten sammenlignet beta laktam monoterapi versus beta laktam og aminoglykosid kombinasjonsbehandling for pasienter med sepsis. Cochrane-forfatterene definerte studier som inkluderte pasienter med alvorlig sepsis som "sepsis", og vi har basert våre analyser på de 42 studiene som var definert som sepsis og inkluderte voksne pasienter. Resultater fra studiene er analysert samlet, uavhengig av type beta laktam antibiotika som ble brukt i studiearmene.

Våre viktigste funn er:

- Resultatene for nyresvikt viste en 66 % reduksjon i risikoen for nyresvikt ved bruk av beta laktam monoterapi sammenlignet med kombinasjonsterapi (RR = 0,34; 95 % CI [0,25, 0,46]). Kvaliteten på dokumentasjonen er lav.

- Resultatene for alvorlige bivirkninger hendelser viste en statistisk ikke-signifikant forskjell mellom beta laktam monoterapi og kombinasjonsbehandling (RR = 1,06; 95 % CI [0,58, 1,91]). Kvaliteten på dokumentasjonen er lav.

- Resultatene for totaldødelighet viste en statistisk ikke-signifikant forskjell mellom beta laktam monoterapi og kombinasjonsbehandling (RR = 0,89; 95 % CI [0,74, 1,08]). Kvaliteten på dokumentasjonen er lav.

- Resultatene for behandlingssvikt viste en statistisk signifikant forskjell mellom beta laktam monoterapi og kombinasjonsbehandling i favør av monoterapi (RR = 0,84; 95 % CI [0,72, 0,97]). Kvaliteten på dokumentasjonen er moderat.

Diskusjon

Våre hovedfunn er at bruk av en kombinasjonsbehandling med beta-laktam og aminoglykosid kan føre til mer nyresvikt og sannsynligvis føre til mer behandlingssvikt sammenlignet med å bruke beta laktam monoterapi. Vår rapport er basert på data fra en systematisk oversikt utarbeidet av Cochrane-samarbeidet, Paul 2014. Cochrane-oversikten inkluderte studier med innlagte pasienter med sepsis ervervet i samfunnet eller på sykehuset. Sepsis ble definert som kliniske tegn på infeksjon pluss tegn på systemisk respons på infeksjon. De inkluderte pasientene kan være en

blandet gruppe av pasienter med mer eller mindre alvorlig sepsis, avhengig av definisjonen og inklusjonskriterier i de opprinnelige studiene. Cochrane-oversikten utførte ikke analyser på en undergruppe av pasienter med septisk sjokk.

Vi identifiserte ikke systematiske oversikter av høy metodisk kvalitet som evaluerer effekten av aminoglykosid gitt i kombinasjon med andre antibiotika enn beta-laktamer for sepsisbehandling.

En begrensning ved vårt arbeid er at vi ikke vet hvordan pasientene ble fulgt opp under behandling med aminoglykosider. I Norge anbefales det alltid å vurdere risikoen for akutt nyresvikt, overvåke serumnivået av aminoglykosider og unngå samtidig bruk av legemidler som kan være nyretoksiske. Mangel på en slik grundig oppfølging kan ha ført til mer nyresvikt eller behandlingssvikt i de inkluderte studiene enn det som vil være tilfelle i dag.

Beslutninger rundt behandling og monitorering av pasienter med sepsis er en kompleks prosess som krever hyppig evaluering gjennom behandlingsforløpet. De oppsummerte resultatene i denne systematiske oversikten, er fra studier som er utført i ulike settinger, med ulike pasientgrupper, ulike patogener, med ulike antibiotikaregimer (doser, intervaller, lengde av behandling). Det er viktig å være klar over disse begrensningene når dokumentasjonen skal brukes som beslutningsgrunnlag i Norge.

Konklusjon

Resultatene som presenteres i denne systematiske oversikten viser at kombinasjonsterapi med et antibiotikaregime som inneholder beta-laktam og aminoglykosid kan øke risikoen for nyresvikt sammenlignet med beta-laktam monoterapi uten aminoglykosid. Kombinasjonsbehandlingen fører sannsynligvis også til mer behandlingssvikt sammenlignet med monoterapi hos voksne pasienter. For totaldødelighet og alvorlige bivirkninger, kan det være liten eller ingen forskjell mellom monoterapi og kombinasjonsbehandling. Vår tillit til effektestimatene for nyresvikt, alvorlige bivirkninger og totaldødelighet er begrenset og den sanne effekten kan være forskjellig fra effektestimatet. Vi har moderat tillit til effektestimatet for behandlingssvikt; effektestimatet ligger sannsynligvis nær den sanne effekten, men effektestimatet kan også være vesentlig ulik den sanne effekten.

De oppsummerte resultatene i denne systematiske oversikten er fra studier som er utført i ulike settinger, med ulike pasientgrupper, ulike patogener, med ulike antibiotikaregimer (doser, intervaller, lengde av behandling). Alle studier ble utført i årene 1973 til 2006, og inneholder bare regimer som sammenlignet beta laktam monoterapi versus aminoglykosider i kombinasjon med beta laktamer. Det er viktig å være klar over disse begrensningene når dokumentasjonen skal brukes som beslutningsgrunnlag i Norge.

Table of contents

Objective

To prepare an overview of systematic reviews evaluating the clinical effectiveness including harms of antibiotic regimens with aminoglycosides compared to a regimen without aminoglycosides for treatment of sepsis. This overview will consider the following outcomes: acute renal failure, serious adverse events, overall mortality, and treatment failure.

We have not evaluated environmental consequences by using different antibiotic regimens containing aminoglycosides, such as development of antibiotic resistance.

Background

Sepsis is defined as a clinical condition that reflects a systemic inflammatory response to infection. It is a medical emergency, and treatment should take place as quickly and efficiently as possible as soon as it has been identified. Typical signs of sepsis are fever above 38 °C, *tachycardia* (rapid heart rate), *tachypnea* (rapid breathing) and poor general condition. In serious cases, sepsis can be associated with organ dysfunction/failure caused by the infection and death. When there are clinically signs of sepsis as well as persistent hypotension (low blood pressure), the condition is defined as septic shock (1). Patients with suspected sepsis are referred to immediate treatment in hospital.

The criteria for SIRS (systemic inflammatory response syndrome), are often used to define sepsis. Sepsis is defined as a condition in which individuals with known infection meet more than two of the four criteria for SIRS.
SIRS criteria :

Temperature: <36 ˚C or >38 ˚C
Heart rate: > 90/min
Respiratory rate: >20/min or $PaCO_2$ <4.3kPa (32 mmHg)
White blood cells: $<4x10^9$/L (<4000/mm^3), $\geq 12x10^9$/L (>12,000/mm^3), or 10% band cells

In Norway, the standard treatment for sepsis according to the current national guideline, is empirical antibiotic treatment based on the knowledge of the etiologic agent, the expected antibiotic sensitivity, as well as pharmacodynamic- and kinetic considerations (2). The antibiotic treatment regimen is tailored in each case, dependent on the patient's age, health status (especially considering immune status and renal function), pathogen identified through blood cultures, and the origin of the infection. The treatment is complex, and needs continuous monitoring focusing on respiratory and circulatory functions, blood glucose controls etc. to avoid organ dysfunction.

A typical antibiotic regimen could be to use a narrow-spectrum antibiotic in combination with a highly potent, broad-spectrum antibiotic, such as an aminoglycoside, with many desirable properties for the treatment of life-threatening infections. However, the guideline also includes a set of reservations for the use of aminoglycosides,

for example to always evaluate the risk of acute renal failure, monitor the serum level of aminoglycosides and avoid concomitant use of nephrotoxic drugs.

It is believed that a combination of antimicrobial therapy that includes aminoglycosides has a beneficial effect on the infection by having a broader antibiotic spectrum. Aminoglycosides act by inhibiting bacterial protein synthesis, while the beta-lactam antibiotics, kill bacteria by disrupting their cell wall. Combining these properties might possess an enhanced effect when compared to each of the antibiotics assessed separately.

There is however, an ongoing debate among infectious disease experts in Norway whether the current recommendations of using aminoglycosides for serious sepsis is acceptable due to their possible adverse effects like nephrotoxicity (3). If a regimen with the use of aminoglycosides leads to an increased number of patients with renal damage compared to treatment without aminoglycosides, the recommendations from the current national guideline should probably be reconsidered. The Norwegian Knowledge Centre for the Health Services has therefore been commissioned by the Norwegian Directorate of Health to prepare a systematic review on the effects and harms of sepsis and/or serious sepsis treatment by using a regimen with aminoglycosides compared to a regimen without aminoglycosides on selected important clinical outcomes.

Preface

The Norwegian Directorate of Health commissioned a systematic review of available research on the effect of using aminoglycosides for treatment of sepsis. This evidence review will be used as background documentation for the national guidelines for antibiotic treatment in hospitals.

The project group consisted of:

- Project leader: Dr Ingvil Sæterdal, The Norwegian Knowledge Centre for the Health Services
- Co-workers: Dr Hilde H Holte, Ms Ingrid Harboe and Dr Marianne Klemp, all The Norwegian Knowledge Centre for the Health Services

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Name	Name	Name
Gro Jamtvedt	*Marianne Klemp*	*Ingvil Sæterdal*
Head of department	*Research director*	*Project leader*

Method

This overview over systematic reviews was conducted according to a pre-specified research protocol.

Literature search

We systematically searched for relevant literature in the following databases:

- Cochrane Library: Reviews, Other reviews, Health Technology Assessments (HTA)
- Centre for Reviews and Dissemination; HTA, Database of Reviews and Dissemination (DARE)
- Ovid MEDLINE 1946 to present
- Embase (Ovid) 1980 to 2014 week 14
- PubMed e-pub ahead of print

The research librarian Ingrid Harboe planned and executed all the searches. A methodology search filter was used to limit retrieval to systematic reviews. The search filter consisted of a combination of "reviews (maximizes specificity)" or (systematic* adj1 review*) as text word (* = truncation). Studies about animals or animal experiments were removed. The complete search strategy is shown in appendix 1. Last search for studies was carried out in April 2014.

Inclusion criteria

The inclusion criteria for this systematic review were defined using the following PICO (**P**opulation, **I**ntervention, **C**ontrol, **O**utcome):

Population: Hospital admitted patients with sepsis aged 18 years and older. We have defined patients with sepsis as patients with a clinical evidence of infection, plus evidence of a systemic response to infection. We will exclude patients with neutropenic fever and immune compromised patients due to for example HIV or cancer.

Interventions: Any antibiotic regimen with an aminoglycoside

Control: Any antibiotic regimen without an aminoglycoside

Outcomes: Overall mortality
Acute renal failure (any nephrotoxicity as defined in the original articles)
Treatment failure (as defined in the original articles)
Serious adverse events

Study design: Systematic reviews of high methodological quality

Languages: No language restrictions will be applied during the literature search, but we will only include reviews written in English or in one of the Scandinavian languages.

Article selection

Two review authors (Holte and Sæterdal) independently read all the titles and/or abstracts to identify potentially relevant publications. We compared our judgments and retrieved full text copies of all potentially eligible publications. We individually and then in pair assessed whether these publications should be included based on the inclusion criteria. We resolved disagreements with discussion.

Assessment of methodological quality

We assessed the methodological quality of potentially relevant systematic reviews meeting the predefined inclusion criteria using the checklist for systematic reviews from the Handbook for the Norwegian Knowledge Centre (4). The assessment ends with a conclusion of high, moderate or low review quality. All assessments were conducted and agreed upon by two of the review authors working independently. If consensus had not been reached, we would have consulted a third person.

Data extraction and management

One review author (Holte or Sæterdal) extracted data from the included references and another review author verified the data (Holte or Sæterdal).

We captured the following data:

- Identification details of the systematic reviews and the included studies: authors, year of publication, date for literature search, study design, risk of bias of included studies, setting and funding
- Participant characteristics: gender, age, infectious disease, severity of sepsis
- Intervention and control characteristics: type of antibiotics, dose and duration of treatment
- Outcomes (outcome data/results): methods for assessing/measuring the outcome data, length of follow-up, loss to follow-up.

We found only one systematic review that met our inclusion criteria, and since this review also contained patients not matching our criteria, we re-analyzed the data from this systematic review. We included the studies that were relevant according to our inclusion criteria, i.e. studies that the authors of the included systematic reviews designated as "sepsis" and that comprised adult patients. We extracted outcome data from the included references and presented the results in GRADE evidence profiles and summary of findings tables (see below for more details). We entered and analyzed the data using the Review Manager software (RevMan). We performed the meta-analyses using a "random effect model". For dichotomous outcomes, we calculated risk ratios (RR) and associated 95% confidence interval. For all outcomes, we tried, as far as possible, to conduct each analysis according to the "intention-to-treat" principle.

Grading our confidence in the evidence

Two review authors assessed the overall quality of evidence for each outcome using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation). GRADE provides criteria for rating the quality of evidence considering study design, risk of bias, imprecision, inconsistency, indirectness, publication bias, large magnitude of effect, dose response gradient and confounding factors. We followed the GRADE guidelines and categorized our confidence in the effect estimates into four levels: high, moderate, low and very low. We present both the results from the meta-analyses (the estimate of effect) and the quality rating in "Summary of Findings" tables prepared using Guideline Development Tool (www.guidelinedevelopment.org). For more details about the GRADE system we refer to publications by the GRADE Working group (www.gradeworkinggroup.org).

GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Results

The literature search for systematic reviews of the effect of treatment of sepsis using aminoglycosides was conducted in September 2013 and April 2014. We identified 1434 references in total. After reading titles and abstracts, we considered 8 references as possibly relevant and we read them in full text. We excluded 7 references, mainly due to different intervention, comparator or population (the references are listed in appendix 2), and included one reference for the present report. A flow diagram of the selection process is shown in figure 1.

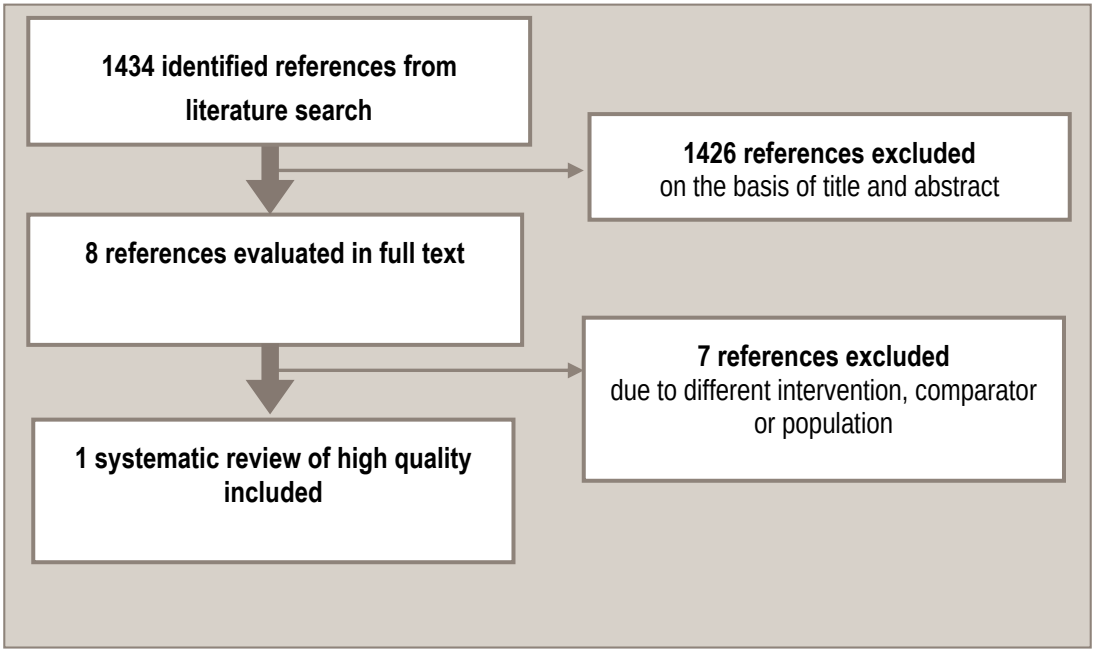

Figure 1. Flow diagram for selection of literature.

Description of included literature

We included one recently updated Cochrane review written by Paul 2014 (5) that compared beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside combination therapy in patients with sepsis. A more detailed description of the systematic review is provided in appendix 3. Their literature search was conducted in November 2013 and they included 69 randomized controlled trials. Forty-four of

these trials included participants with severe sepsis, suspected Gram-negative infection or pneumonia and the review authors designated these as “sepsis”. The other 25 trials included participants with intra-abdominal infection, urinary tract infection, gram-positive infections and staphylococcal infection. Among the 44 sepsis trials, two where conducted in children. Thus, we extracted data from Paul 2014 and have based our review and analyses on the 42 trials designated as sepsis and conducted in adults. The Cochrane review excluded studies including more than 15% neutropenic patients. We decided to base our analysis on their work although their exclusions criteria somewhat varies. We have not performed sub-group analyses based on which type of microorganism that caused the sepsis.

The 42 trials included about 5400 participants from North America (USA and Canada), South America, Europe (Austria, Belgium, France, Germany, Italy, Ireland, the Netherlands, Spain, Switzerland, and Russia), Japan, and the Philippines. The trials were performed between 1973 and 2006. The review provides results for the following outcomes relevant for our purposes: Any nephrotoxicity (acute renal failure), adverse events requiring treatment discontinuation (serious adverse events), all-cause mortality (overall mortality) and clinical failure (treatment failure).

Most trials compared sepsis treatment with one beta-lactam versus sepsis treatment with a combination of a different type of narrower-spectrum beta lactam and an aminoglycoside. A list of the beta lactams and aminoglycosides used in the 42 trials that we have based our analysis on is provided in appendix 4. Duration of therapy is also listed when presented in Paul 2014. We did not find any information in Paul 2014 about length of follow-up. The review also lacked information on whether the renal function of the participants were monitored by measuring for example serum creatinine during treatment.

Paul 2014 assessed risk of bias in all trials: 19 of the trials reported adequate random sequence generation and one reported inadequate. Allocation concealment was considered to be adequate (low risk of bias) in 14 of the trials and inadequate (high risk of bias) in one trial. Incomplete outcome data for the outcomes mortality and treatment failure was reported adequate in 15 trials and inadequate in 10 trials. No information was available for the other studies. Most trials were open and considered as high risk of bias, but for serious adverse events, acute renal failure and mortality we do not consider the lack of blinding to introduce bias.

Effects of the intervention

We summarized the results from Paul 2014 (5) for beta lactam monotherapy (monotherapy) versus beta lactam-aminoglycoside combination therapy (combination therapy) for the 42 trials designated by the review authors as “sepsis” in adult patients. We extracted data only for outcomes relevant according to our pre-specified protocol.

For the outcomes overall mortality and treatment failure, we present the results for:

- the pooled estimate for all studies reporting these outcomes (independent of which beta lactam used in the study arms).
- studies that compared beta lactam monotherapy versus the same beta lactam (same beta lactam) in combination with aminoglycoside
- studies that compared beta lactam monotherapy versus a different beta lactam (different beta lactam) in combination with aminoglycoside

For serious adverse events and acute renal failure, the results are pooled independent of which beta lactam that were used in the study arms.

Acute renal failure

We show the results from 28 studies that reported on acute renal failure measured as any nephrotoxicity.

The pooled estimate for all 28 studies, independent of which beta lactam that was used in the study arms, showed a 66% reduction in the risk of any nephrotoxicity using monotherapy compared with combination therapy (RR= 0.34; 95% CI [0.25, 0.46]), figure 2. A statistically significant increased rate of any nephrotoxicity was seen in studies administering the aminoglycoside both once daily, twice daily and trice daily. The quality of the evidence is low, due to high risk of bias and imprecision due to few events, table 1.

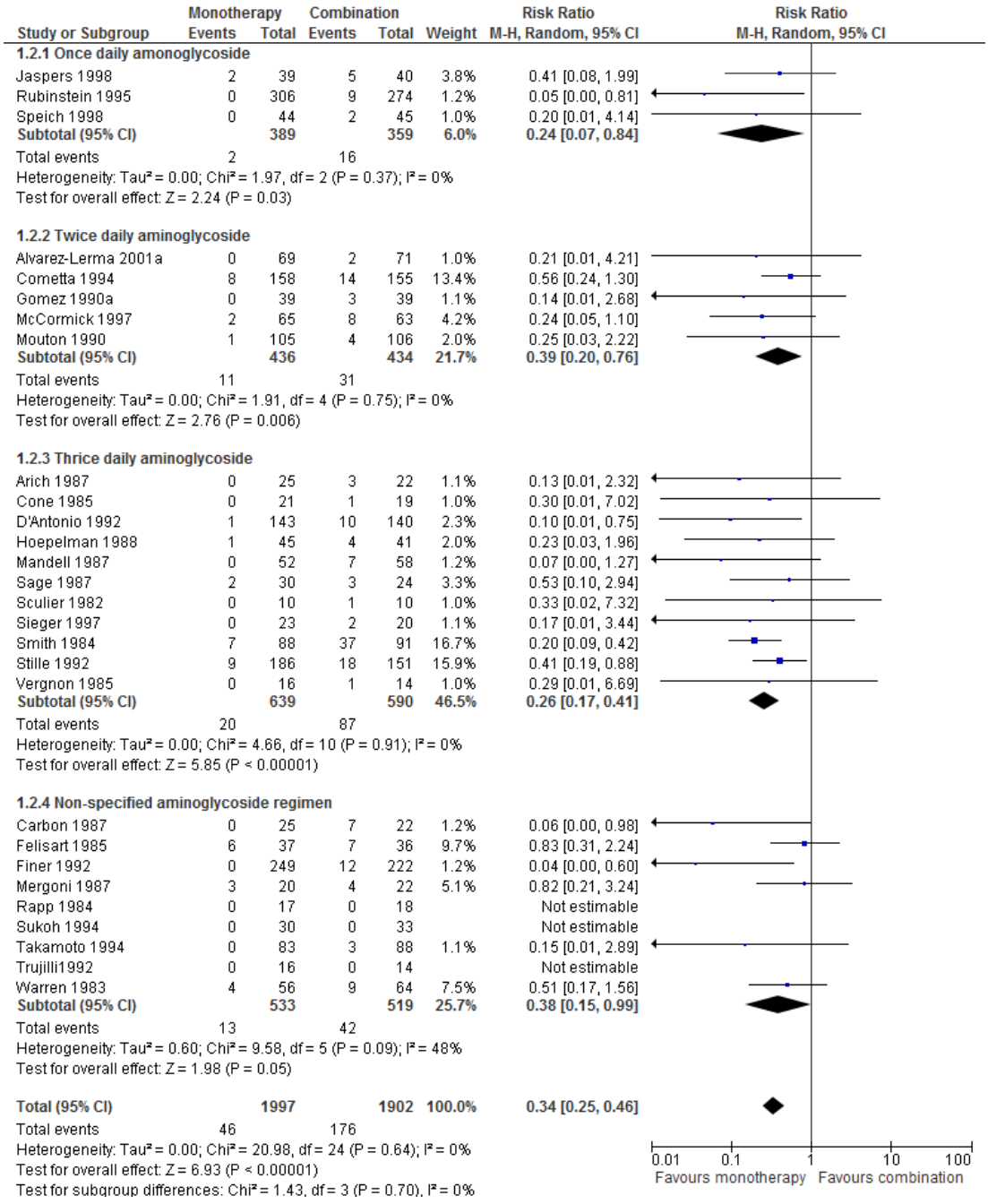

Figure 2. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy, results from all studies. Outcome: Any nephrotoxicity

Serious adverse events

Eleven studies reported results for serious adverse events (reported as adverse events requiring treatment discontinuation).

The pooled estimate for this outcome, independent of beta lactam used in the study arms, showed a statistically non-significant difference between monotherapy and

combination therapy (RR= 1.06; 95% CI [0.58, 1.91]), figure 3. The quality of the evidence is low due to high risk of bias and imprecision due to few events, table 1.

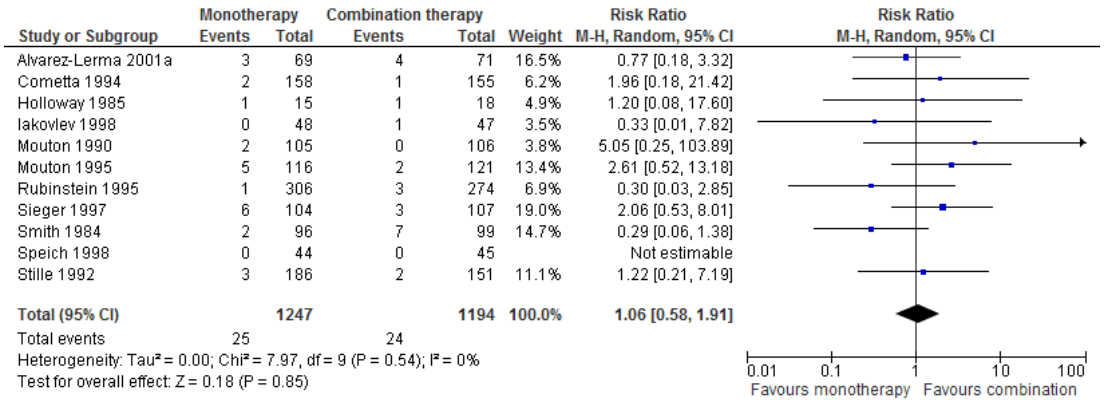

Figure 3. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy, results from all studies. Outcome: Serious adverse events

Overall mortality

For the outcome overall mortality we report results from 27 studies.

The pooled estimate for all 27 studies, independent of which beta lactam that were used in the study arms, showed a statistically non-significant difference between monotherapy and combination therapy (i.e. control) in favor of monotherapy (RR= 0.89; 95% CI [0.74, 1.08]), figure 4. The quality of the evidence is low due to high risk of bias and possible publication bias, table 1.

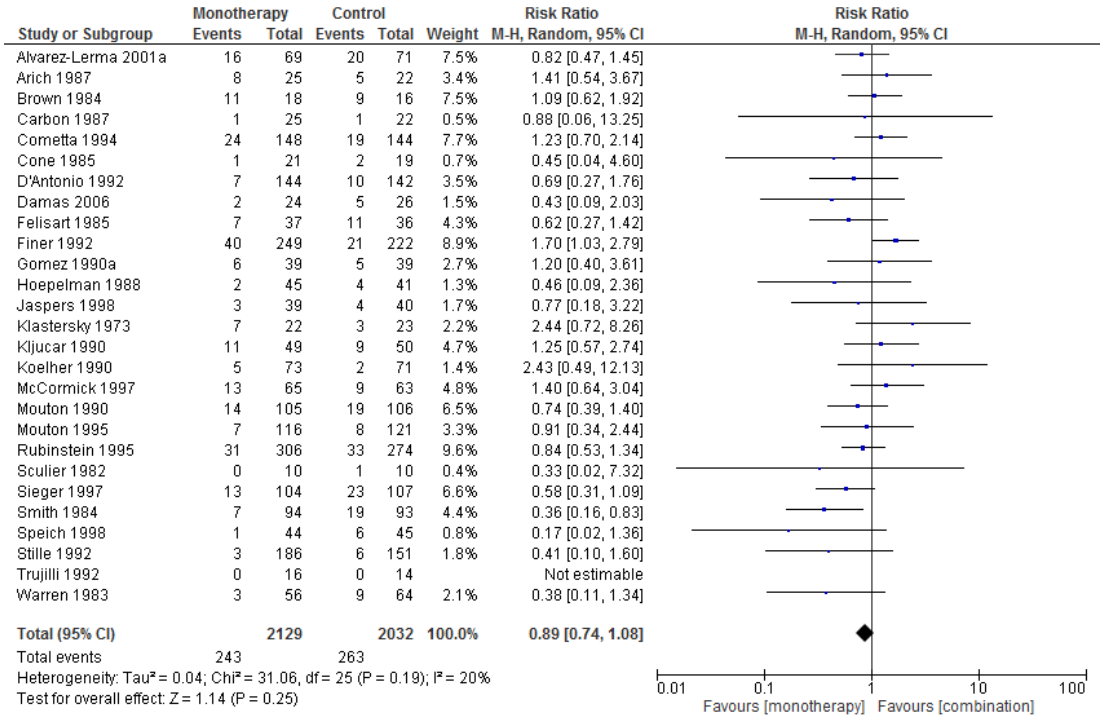

Figure 4. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy, results from all studies. Outcome: Overall mortality

The pooled estimate for overall mortality for the seven studies that used the same beta lactam in both study arms, i.e. beta lactam monotherapy versus beta lactam in combination with aminoglycoside, showed a statistically non-significant difference between monotherapy and combination therapy (RR= 1.10; 95% CI [0.76, 1.60]), figure 5. The quality of the evidence is low due to imprecision due to few events and possible publication bias, table 1.

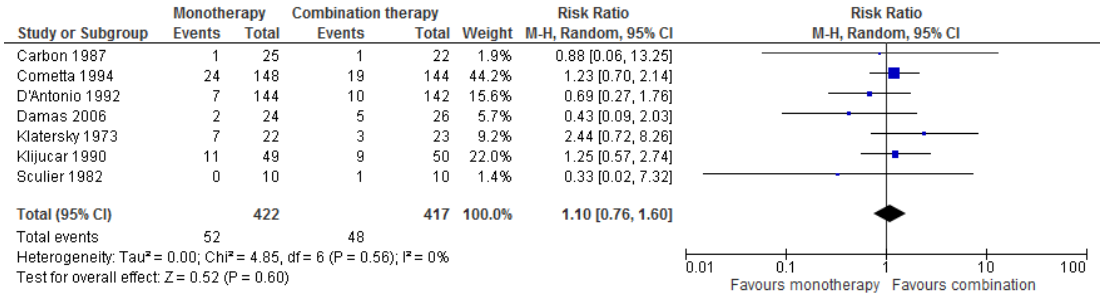

Figure 5. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy, same beta lactam. Outcome: Overall mortality

The pooled estimate for overall mortality for the 20 studies that compared beta lactam monotherapy versus a different beta lactam in combination with aminoglycoside, showed a statistically non-significant difference between monotherapy and

combination therapy in favor of monotherapy (RR= 0.84; 95% CI [0.67, 1.06]), figure 6. The quality of the evidence is low due to high risk of bias and possible publication bias, table 1.

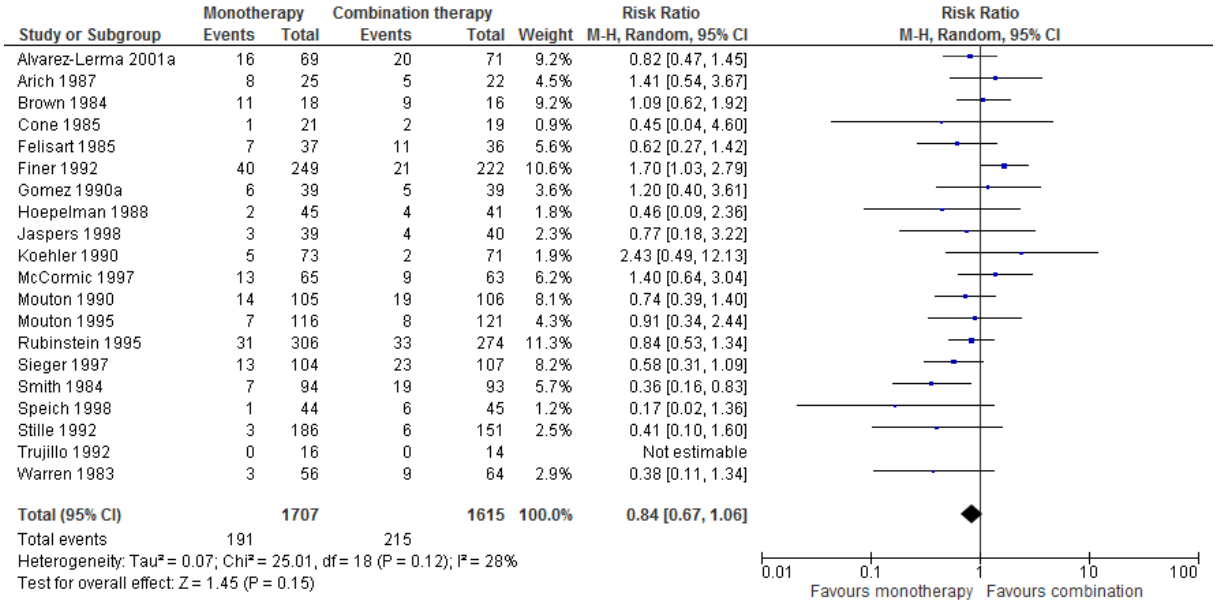

Figure 6. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy, different beta lactam. Outcome: Overall mortality

Treatment failure

For the outcome treatment failure, we report results from 41 studies.

The pooled estimate for all 41 studies independent of which beta lactam that was used in the study arms, showed a statistically significant difference between monotherapy and combination therapy in favor of monotherapy (RR= 0.84; 95% CI [0.72, 0.97], figure 7. The quality of the evidence is moderate. The quality of evidence is moderate due to high risk of bias, table 1.

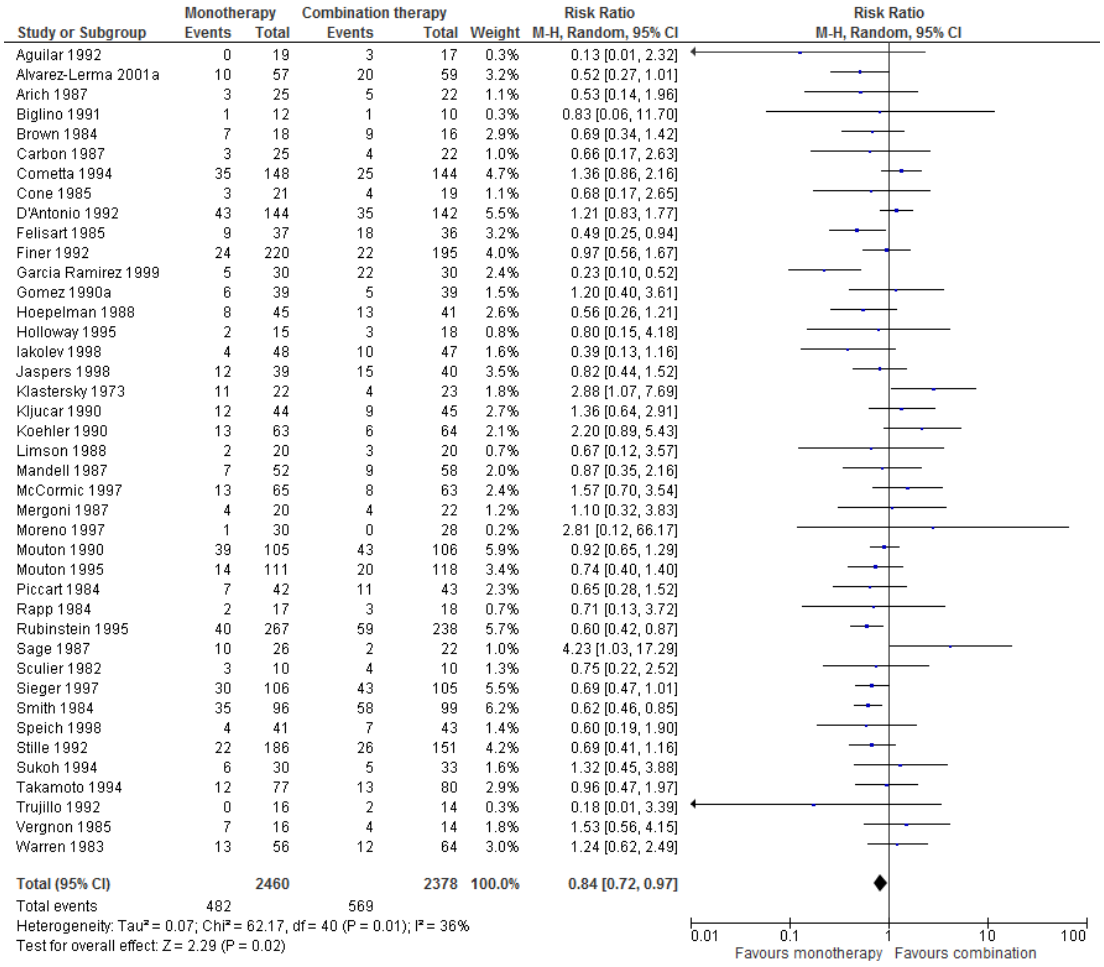

Figure 7. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy, results from all studies. Outcome: Treatment failure

The pooled estimate for treatment failure for the 12 studies that compared the same beta lactam in both study arms, i.e. monotherapy versus combination therapy with aminoglycoside, showed a non-statistically significant difference between monotherapy and combination therapy in favor of combination therapy (RR= 1.23; 95% CI [0.99, 1.53], figure 8. The quality of the evidence is low due to high risk of bias and imprecision due to few events, table 1.

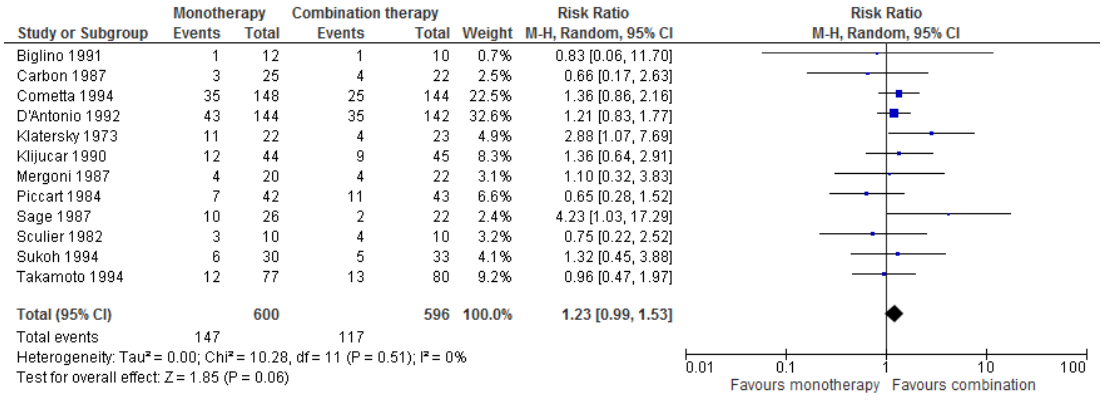

Figure 8. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy, same beta lactam. Outcome: Treatment failure

The pooled estimate for treatment failure for the 29 studies that used different beta lactam in the two study arms, showed a 27% reduction in the risk for treatment failure using monotherapy compared with combination therapy (RR= 0.73; 95% CI [0.63, 0.85], figure 9. The quality of the evidence is moderate. Downgraded from high quality due to high risk of bias, table 1.

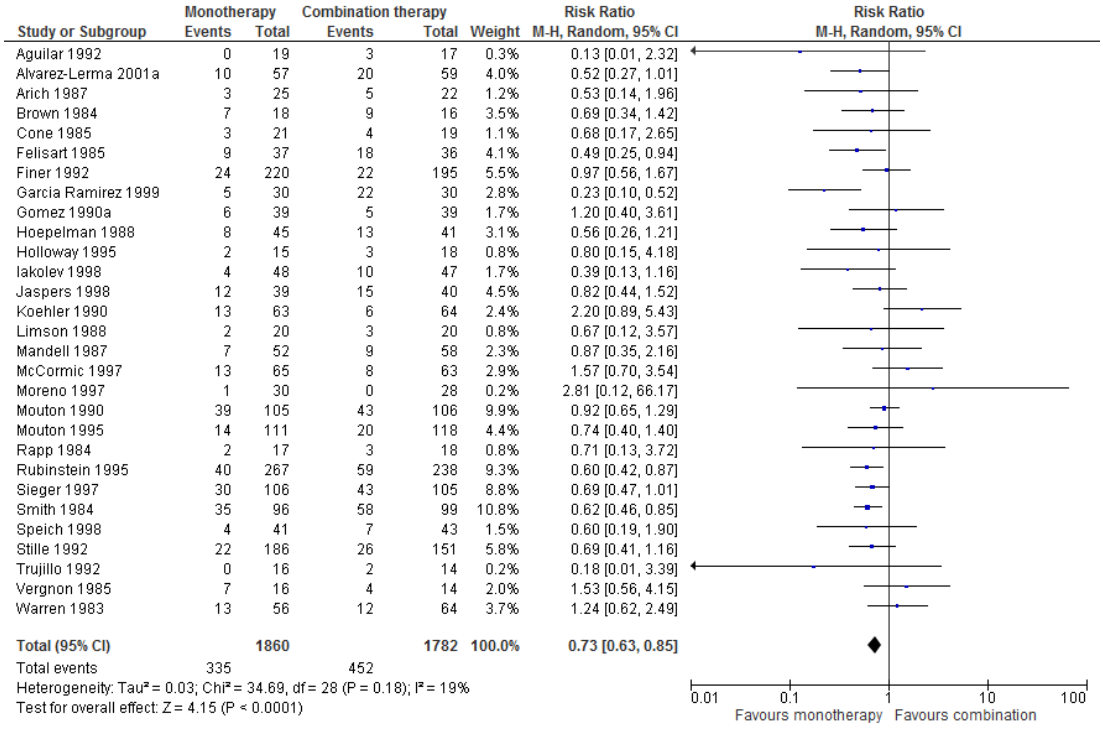

Figure 9. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy, different beta lactam. Outcome: Treatment failure

Summary of Findings

We have summarized the results for the effect of beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy of sepsis in a "Summary of Findings table", table 1. The table also presents our assessment of the quality of the evidence (i.e. the confidence we have in the results for each of the outcomes). We have presented the full evidence table in appendix 5.

Table 1 Summary of Findings: Beta lactam monotherapy compared to beta lactam-combination therapy for sepsis.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Beta lactam-aminoglycoside combination therapy	**Beta lactam monotherapy**			
Any nephrotoxicity	93 per 1000	**32 per 1000 (23 to 43)**	**RR 0.34** (0.25 to 0.46)	3891 (28 RCTs)	⊕⊕◯◯ LOW [2 4]
Serious adverse events	20 per 1000	**21 per 1000 (12 to 38)**	**RR 1.06** (0.58 to 1.91)	2441 (11 RCTs)	⊕⊕◯◯ LOW [2 4]
Overall mortality	129 per 1000	**115 per 1000 (96 to 140)**	**RR 0.89** (0.74 to 1.08)	4161 (27 RCTs)	⊕⊕◯◯ LOW [2 3]
Overall mortality, same beta lactam in treatment groups	115 per 1000	**127 per 1000 (87 to 184)**	**RR 1.1** (0.76 to 1.6)	839 (7 RCTs)	⊕⊕◯◯ LOW [1 3 7]
Overall mortality, different beta lactam in treatment groups	133 per 1000	**112 per 1000 (89 to 141)**	**RR 0.84** (0.67 to 1.06)	3322 (21 RCTs)	⊕⊕◯◯ LOW [2 3]
Treatment failure	248 per 1000	**208 per 1000 (178 to 240)**	**RR 0.84** (0.72 to 0.97)	4758 (41 RCTs)	⊕⊕⊕◯ MODERATE [6]
Treatment failure, same beta lactam in treatment groups	196 per 1000	**241 per 1000 (194 to 300)**	**RR 1.23** (0.99 to 1.53)	1196 (12 RCTs)	⊕⊕◯◯ LOW [5 6]
Treatment failure, different beta lactam in treatment groups	254 per 1000	**185 per 1000 (160 to 216)**	**RR 0.73** (0.63 to 0.85)	3642 (29 RCTs)	⊕⊕⊕◯ MODERATE [6]

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Few events. 95% confidence interval range from 24% improved survival to 60% higher risk of death with monotherapy
2. Unclear allocation concealment (risk of bias)
3. Funnel plot in the original systematic review showed that small studies favoring combination therapy might be missing (publication bias)
4. Few events
5. Large confidence interval, range from harmful to beneficial (imprecision)
6. Unclear allocation concealment and lack of blinding (risk of bias)
7. Consider risk of bias to be high due to unclear allocation concealment, but do not downgrade since we ideally would downgrade 1/2 for this (not possible technically)

Discussion

Our purposes was to systematically review the evidence on the effects of any antibiotic regimen with an aminoglycoside versus any antibiotic regimen without an aminoglycoside for the treatment of sepsis in adults.

We identified one systematic review that fulfilled our inclusion criteria. Paul 2014 (5) have evaluated beta lactam monotherapy (monotherapy) versus beta lactam-aminoglycoside combination therapy (combination therapy) for treatment of sepsis. Thus, our results are based on the findings from this review. The review included a total of 69 randomized controlled trials, whereof 42 trials conducted between 1973 and 2006 were relevant for our purposes. Our summary reports the effect of beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy in adult non-neutropenic patients with sepsis.

The main results are that using a combination therapy of beta lactam and aminoglycoside may lead to more nephrotoxicity and probably leads to more treatment failure compared to using beta lactam monotherapy. Nephrotoxicity (28 studies) occurred less frequently in the monotherapy study arm compared to the arm with aminoglycosides (RR= 0.34; 95% CI [0.25, 0.46]). The pooled effect estimate from 41 RCTs showed a 16% reduction in the risk for treatment failure using monotherapy compared with a beta lactam-aminoglycoside-combination therapy. The effect estimate for overall mortality and serious adverse events did not show any statistically significant differences between the study arms. The overall confidence in the estimates (quality of the evidence) varies between moderate and low. The main reason for lowering our confidence in the effect estimates from high to moderate and low, is the high risk of bias of the 42 RCTs due to unclear sequence generation and allocation concealment. For the outcome overall mortality, Paul 2014 presented a funnel plot analysis that showed that small studies favoring combination therapy might be missing. The majority of the studies are non-blinded which might cause bias for subjective outcomes such as treatment failure.

The Cochrane review included studies with different types of populations. The inclusion criteria were hospitalized patients with sepsis acquired in the community or in the hospital. Sepsis were defined as clinical evidence of infection plus evidence of

systemic response to infection. The Cochrane review authors labelled the studies according to site of infection (for example “abdominal” or “UTI” (urinary tract infection)). The studies that we included in our review were labelled “sepsis” and included patients with severe sepsis. This might be a mixed group of patients with more or less severe sepsis depending on the definition and inclusion criteria in the original primary articles. Our analysis for the sepsis trials are in line with the results from the original review for the assessed outcomes. Paul 2014 did not present the results for monotherapy versus combination therapy for all studies independent of which beta lactam that were used in the study arms except for the outcome any nephrotoxicity. In line with our results, Paul 2014 found that for treatment failure, the results were in favor of combination therapy when the same beta lactam was used in both study arms. This is the only outcome which is in favor of combination therapy, and it is not statistically significant. However, when different beta lactams were used in the study arms, monotherapy resulted in a 27% reduction in the risk for treatment failure in our analysis and Paul 2014 found a 23% risk reduction for treatment failure. The less treatment failure using different beta lactams in the two treatment arms might be explained by the use of a broader spectrum beta lactam in the monotherapy arm than in the combination therapy arm.

Paul 2014 included studies reporting on treatment failure as it was defined in the primary studies, and hence a mixture of definitions were included, like lack of clinical improvement, relapse, and/or modification to the antibiotic treatment. These definitions and the interpretation of the definitions might have been assessed differently by the different study authors and might have influenced the results for treatment failure.

The Cochrane review included subgroup analyses based on microorganism causing the infection. For both overall cause mortality and clinical failure they found no significant difference between monotherapy and combination therapy when analysis was restricted to participants with Gram-negative infection. We did not perform similar analysis including studies labelled sepsis. The Cochrane review did not perform analysis on a sub-group of patients with septic shock.

Our report is based on data from one systematic review produced within the Cochrane Collaboration (5). The literature search in the review was last updated in November 2013, which means that primary studies published more recently is not included. The included studies in Paul 2014 were conducted between the years 1973 and 2006, thus there seems to be a lack of new research on the effect of beta lactam-aminoglycosides-regimen. In order to ascertain new and relevant randomized controlled trials published after 2013 and up to now, we performed a systematic search after randomized controlled trials. However we did not identify any newer randomized trials that fulfilled our inclusion criteria. The equipment and settings for monitoring a complex condition like sepsis today, may be quite different from the time-

period the studies presented in this review were conducted. Since the presented evidence is of insufficient methodological quality, meaning that we do not have high confidence in the results, we suggest to conduct new RCTs in order to provide reliable answers on mortality and treatment failure.

A recent meta-analysis by Kumar 2010 (6) concludes that combination therapy improves survival of patients with septic shock compared with monotherapy. The conclusion is however based on studies of observational design in which we will have less confidence. The same study reported on harmful effects for less critically ill patients.

Our results show that the risk of any nephrotoxicity using combination therapy is almost three times as high as the risk of any nephrotoxicity using monotherapy. Most of the analysed studies administered aminoglycyside three daily doses. However, in Paul 2014 their analysis of the few studies (5 studies, 3 relevant for our review) that administered the aminoclycoside once daily was also significant in favor of monotherapy (RR=0.17; 95% CI [0.06, 0.53]).

There is a lack of systematic reviews of high methodological quality evaluating the effect of aminoglycosides-regimen other than in combination with beta lactam antibiotic for sepsis treatment. There is also a lack of systematic reviews that could provide an answer to if using aminoglycoside for a shorter time period than the standard treatment length would be beneficial, and to which doses and administration schedule that would be most beneficial. We have not performed analysis based on length or dose of treatment with aminoglycosides in the combination arm.

A limitation with our work is that we do not know how the patients were followed up during treatment with aminoglycosides. In the Norwegian guideline on sepsis treatment, it is recommended to always evaluate the risk of acute renal failure, monitor the serum level of aminoglycosides and avoid concomitant use of nephrotoxic drugs. Lack of such thorough follow up might have led to more nephrotoxicity or other failures in the analysed trials than will be the case today.

The decisions and monitoring of sepsis treatment are very complex processes, demanding frequent evaluations during the course, and is also dependent on available equipment and settings. The pooled evidence provided in this systematic overview, are from studies done in different settings, with different patient-groups/diagnosis, different pathogens, with different regimen (doses; intervals; length of treatment). These aspects are important to be aware of when considering this evidence for treatment recommendations in Norway.

Conclusion

The results presented in this review indicate that beta lactam-aminoglycoside combination therapy may increase the risk of nephrotoxicity compared with monotherapy. The combination therapy probably leads to more treatment failures compared with beta lactam monotherapy in adult patients. For overall mortality and serious adverse events, there may be little or no difference between monotherapy and combination therapy. The confidence in the estimates for overall mortality, nephrotoxicity and serious adverse events are limited and the true effect may be different from the estimate. We are moderately confident in the effect estimate for treatment failure; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

The pooled evidence provided in this systematic overview, are from studies done in different settings, with different patient-groups/diagnosis, different pathogens, with different regimens (doses, intervals, length of treatment). The majority of studies were conducted during the 80s and the 90s. These aspects are important to be aware of when considering this evidence for making treatment recommendations in Norway.

Need for further research

There is also a lack of high quality systematic reviews evaluating the effect of aminoglycoside regimens other than in combination with a beta lactam antibiotic. We searched for systematic reviews, and cannot tell whether there also is a need for conducting primary studies on the effect of other aminoglycoside regimens than we have presented in this overview of systematic reviews. For example studies on shorter length of treatment with aminoglycosides compared to standard treatment without aminoglycosides.

The most robust study design for such studies would be randomized controlled trials. The outcomes should be clinically important like; overall mortality, treatment failure, nephrotoxicity and serious adverse events. The intervention and control arm should contain the same antibiotic regimen, including dose and length of treatment, except for the addition of an aminoglycoside in one arm. The severity of sepsis

should be clearly stated and the population should be as similar as possible with regards to type of infection and the bacteria strain that causes the infection. Also how to monitor the patients during the treatment should be standardized. The studies should last long enough to be able to capture any serious side effects, at least 30 days after end of treatment. International collaboration is an advantage in order to be able to recruit enough patients, however, country specific variations in antibiotic resistance and bacterial flora has to be taken into consideration so that we will be able to apply the results in a Norwegian setting.

References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. Chest 2009;136(5 Suppl):e28.

2. Helsedirektoratet. Nasjonal faglig retningslinje for bruk av antibiotika i sykehus. http://helsedirektoratetno/sites/antibiotikabruk-i-sykehus/om/forfatterliste/Sider/defaultaspx2014.

3. Lindemann PC, Haldorsen BC, Smith I, Sjursen H, Mylvaganam H. [Aminoglycosides should still be used in empirical sepsis treatment]. TidsskrNor Laegeforen 2013;133:1054-1055.

4. Nasjonalt kunnskapssenter for helsetjenesten. Slik oppsummerer vi forskning. Håndbok for Nasjonalt kunnskapssenter for helsetjenesten. 3.2. reviderte utg.2013.

5. Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis.[Update of Cochrane Database Syst Rev. 2006;(1):CD003344; PMID: 16437452]. Cochrane Database of Systematic Reviews 2014;1:CD003344.

6. Kumar A, Zarychanski R, Light B, Parrillo J, Maki D, Simon D, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med 2010;38(9):1773-1785.

Appendix

Appendix 1 Literature search

Databases:	Cochrane Library: Database of Systematic Reviews, Other reviews, Health Technology Assessments (HTA). Centre for Reviews and Dissemination: HTA, Database of Reviews and Dissemination. Ovid MEDLINE 1946 to present. Embase (Ovid) 1980 to 2014 week 14. PubMed e-pub ahead of print.
Dates:	2013.09.12 and 2014.04.08
Study design:	Systematic review Ovid filter: "reviews (maximizes specificity)" or (systematic* adj1 review*).tw.
Results:	1434 Systematic review (460 + 974)
Comment:	Second search: “Bacterial Infections” is only included as subject heading due to too sensitive search (many irrelevant hits) when including “Bacterial Infections” as text word
Searched by:	Ingrid Harboe, research librarian

Search strategies first search
Date: 2013.09.12

Database:
Embase 1980 to 2013 Week 36,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to pres.

#	Searches	Results
1	exp sepsis/	249427
2	(sepsis or septic* or blood poisoning*).tw.	234960
3	or/1-2	361801
4	exp aminoglycoside antibiotic agent/ use emez	196349
5	exp aminoglycosides/ use prmz	130600
6	exp Anti-Bacterial Agents/ use prmz	532064
7	(anti bacterial agent* or antibacterial agent* or antibiotic* or aminoglycoside*).tw.	523063
8	(Benzylpenicillin? or Ciprofloxacin? or Piperacillin? or tazobactam? or Cefotaxim? or Cefuroxim? or Ceftriaxon? or Ceftazidim? or Klindamycin? or Erytromycin? or	

Gentamicin? or Ampicillin? or Amoxicillin? or clavulanic acid? or clavulanat? or Ciprofloxacin? or Ofloxacin? or Moxifloxacin? or Metronidazol? or Meropenem? or Imipenem? or cilastatin? or Doripenem? or Ertapenem? or Cloxacillin? or Dicloxacillin? or Flucloxacillin? or Van*omycin? or Teicoplanin?).tw.
242365
9 or/4-8
1190010
10 3 and 9
72510
11 10 and (systematic* adj1 review*).tw.
328
12 limit 10 to "reviews (maximizes specificity)"
662
13 11 or 12 [filter SR]
700
14 13 use emez
306
15 13 use prmz
394
16 remove duplicates from 14
294
17 remove duplicates from 15
313

Database: Cochrane Library
Result: 43 Cochrane reviews
42 Other reviews

#1 MeSH descriptor: [Sepsis] explode all trees
2832
#2 (sepsis or septic shock? or septicemia? or blood poisoning?):ti,ab,kw
3529
#3 #1 or #2
4856
#4 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
8535
#5 MeSH descriptor: [Aminoglycosides] explode all trees
6464
#6 (anti bacterial agent? or antibacterial agent? or antibiotic?
or aminoglycoside?):ti,ab,kw
14137
#7 (Benzylpenicillin? or Ciprofloxacin? or Piperacillin? or tazobactam? or Cefotaxim?
or Cefuroxim? or Ceftriaxon? or Ceftazidim? or Klindamycin? or Erytromycin? or
Gentamicin? or Ampicillin? or Amoxicillin? or clavulanic next acid? or clavulanat?
or Ciprofloxacin? or Ofloxacin? or Moxifloxacin? or Metronidazol? or Meropenem?
or Imipenem? or cilastatin? or Doripenemor? or Ertapenem? or Cloxacillin? or
Dicloxacillin? or Flucloxacillin? or Van?omycin? or Teicoplanin?):ti,ab,kw
6963
#8 #4 or #5 or #6 or #7
23181

#9 #3 and #8
1204

Database: Centre for Reviews and Dissemination
Result: 170 DARE/ HTA

1 MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES
363
2 (Sepsis or septic*)
697
3 #1 OR #2
823
4 MeSH DESCRIPTOR Aminoglycosides EXPLODE ALL TREES
243
5 MeSH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES
1204
6 ((anti bacterial agent* or antibacterial agent* or antibiotic* or aminoglycoside*)) 2506
7 ((Benzylpenicillin* or Ciprofloxacin* or Piperacillin* or tazobactam* or Cefotaxim* or Cefuroxim* or Ceftriaxon* or Ceftazidim* or Klindamycin* or Erytromycin* or Gentamicin* or Ampicillin* or Amoxicillin* or clavulanic acid* or clavulanat* or Ciprofloxacin* or Ofloxacin* or Moxifloxacin* or Metronidazol*
or Meropenem* or Imipenem* or cilastatin* or Doripenemor* or Ertapenem* or Cloxacillin* or Dicloxacillin* or Flucloxacillin* or Vancomycin* or Teicoplanin*)) 850
8 (#4 or #5 or #6 or #7)
2901
9 (#3 and #8)
273
10 (#3 and #8) IN DARE, HTA
170

Database: PubMed
Result: None

Search ((((((sepsis[MeSH Terms]) OR sepsis)) AND (((aminoglycosides[MeSH Terms]) OR aminoglycoside*) OR anti bacterial agent*)) AND pubstatusaheadofprint)) AND ((("review"[Publication Type])))

Second search
Date: 2014.04.08

Database:
Embase 1980 to 2014 Week 14, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to pres.

Searches
Results
1 exp Sepsis/
250410

2 Bacterial Infections/ use pmoz
59375
3 bacterial infection/ use emez
98615
4 sepsis*.tw.
146280
5 (septicemia* or septicaemia* or septic shock*).tw.
65958
6 or/1-5
471720
7 exp aminoglycoside antibiotic agent/ use emez
198237
8 exp aminoglycosides/ use pmoz
127289
9 exp Anti-Bacterial Agents/ use pmoz
526680
10 (anti bacterial agent* or antibacterial agent* or antibiotic* or aminoglycoside*).tw. 517428
11 or/7-10
1100919
12 6 and 11
104596
13 exp Animals/
35669723
14 Humans/
27807993
15 13 not (13 and 14)
7861730
16 12 not 15 [not animals]
98768
17 16 and (systematic* adj1 review*).tw.
482
18 limit 16 to "reviews (maximizes specificity)"
971
19 17 or 18 [SR]
1030
20 remove duplicates from 19
822
21 20 use pmoz [SR medline]
384
22 20 use emez [SR embase]
438

Database: Cochrane Library
Results: 163 Cochrane reviews
138 Other reviews

#1 MeSH descriptor: [Sepsis] explode all trees
3026
#2 MeSH descriptor: [Bacterial Infections] this term only
2936
#3 (sepsis*):ti,ab,kw
4005

#4 (septicemia* or septicaemia* or septic shock*):ti,ab,kw
7123
#5 #1 or #2 or #3 or #4
11156
#6 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
9158
#7 MeSH descriptor: [Aminoglycosides] explode all trees
6668
#8 (anti bacterial agent* or antibacterial agent* or antibiotic* or aminoglycoside*):ti,ab,kw
20496
#9 #6 or #7 or #8
25738
#10 #5 and #9
4693

Database: Centre for Reviews and Dissemination
Results: 229 in DARE/HTA

1 MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES
400
2 MeSH DESCRIPTOR Bacterial Infections
225
3 (sepsis* or septicemia* or septicaemia* or "septic shock*")
670
4 #1 OR #2 OR #3
1010
5 MeSH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES
1300
6 MeSH DESCRIPTOR Aminoglycosides EXPLODE ALL TREES
272
7 ("anti bacterial agent*" or "antibacterial agent*" or antibiotic* or aminoglycoside*)
2634
8 #5 OR #6 OR #7
2904
9 #4 AND #8
388
10 (#9) IN DARE, HTA
229

Database: PubMed
Result: None
Search ((((((sepsis[MeSH Terms]) OR sepsis)) AND (((aminoglycosides[MeSH Terms]) OR aminoglycoside*) OR anti bacterial agent*)) AND pubstatusaheadofprint)) AND ((("review"[Publication Type])))

Appendix 2 Excluded studies

Barochia AV, Cui X, Vitberg, D, Suffredini A F, O'Grady NP, Banks SM, Minneci P, Kern SJ, Danner RL, Natanson C, Eichacker PQ. Bundled care for septic shock: an analysis of clinical trials. *Critical Care Medicine*; 2010; 38(2): 668-678.

Gomes Silva BN, Andriolo RB, Atallah AN, Salomao R, Gomes Silva BN, Andriolo RB et al. De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. [Review]. *Cochrane Database of Systematic Reviews* 2010;(12).

Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. *Crit Care Med* 2010; 38(8):1651-1664.

Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, Leibovici L, Paul M et al. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. [Review] [162 refs]. *Cochrane Database of Systematic Reviews* 2006;(1).

Silva BN, Andriolo RB, Atallah AN, Salomao R, Silva BNG, Andriolo RB et al. De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock. [Review][Update of Cochrane Database Syst Rev. 2010;(12):CD007934; PMID: 21154391]. *Cochrane Database of Systematic Reviews* 2013; 3.

Sinert R, Bright L, Sinert R, Bright L. Evidence-based emergency medicine/systematic review abstract. Empiric antibiotic therapy for sepsis patients: monotherapy with beta-lactam or beta-lactam plus an aminoglycoside? *Ann Emerg Med* 2008; 52(5):-60, 2008.

Vidal L, Gafter-Gvili A, Borok S, Fraser A, Leibovici L, Paul M et al. Efficacy and safety of aminoglycoside monotherapy: systematic review and meta-analysis of randomized controlled trials. [Review] [110 refs]. *J Antimicrob Chemother* 2007; 60(2):-57, 2007.

Appendix 3 Characteristics of included systematic reviews

Paul 2014* **Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis**	
Date of literature search: November 2013	
Quality of the systematic review according to checklist: High **Study designs included:** Randomized controlled trials (RCTs) .	
Patients	Hospitalized participants with sepsis acquired in the community or in the hospital. They defined sepsis as clinicla evidence of infection plus evidence of a systemic response to infection. Neonates and preterm babies were excluded. They also excluded studies including more than 15% neutropenic patients.
Interventions	Any intravenous beta lactam antibiotic given as monotherapy, including: penicillins, beta lactam drugs plus beta lactamase inhibitors (e.g. co-amoxiclav), cephalosporins (e.g. ceftazidime, cefotaxime) or carbapenems (e.g. imipenem, meropenem).
Comparison	Combination therapy of a beta lactam antibiotic (as specified under interventions) with one of the following aminoglycosides antibiotics: Gentamicin, tobramycin, amikacin, netilmicin, streptomycin, isepamicin or sisomicin.
Outcomes measured	– All-cause mortality by the end of follow-up – Treatment failure defined as death/or one or more serious morbid events – Length of hospital stay – Superinfection: recurrent infections, defined as new, persistent or worsening symptoms and/or signs of infection associated with the isolation of new pathogen or the development of a new site of infection – Adverse effects: i) Life-threatning or associated with permanent disability (severe nephrotoxicity, ototoxicity, anaphylaxix, severe skin reactions ii) Serious: requiring discontinuation of therapy (other nephrotoxicity, seizures, pseudomembranous colitis, other allergic reactions iii) Any other (other gastrointestinal, other allergic reactions)

*Further details of the participants, interventions, comparisons and outcomes in each of the studies included in the review by Paul 2014 provided in the review's characteristics of studies tables.

Appendix 4

Study	Diagnose as described in Paul 2014	Intervention (monotherapy)	Control (combination therapy)
Aguilar 1992	Sepsis	Ceftizoxime 60-260 mg/kg/d	Penicillin 20-30mU/d+ gentamicin 3-5mg/kg/d
Alvares-Lerma 2001a	Sepsis; mainly pneumonia. All infections were hospital acquired.	Meropenem 1grx3 for 9.3 days	Ceftazidime 2grx3 + amikacin 7,5mg/kgx2 for 8.3 days
Arich 1987	Sepsis; enterobacteriacae bacteraemia	Cefotaxime 1grx3-4 for 17.5 dager	Cefazolin 1grx3 + tobramycin 1.5 mg/kgx3 for 10 days
Biglino 1991	Sepsis; (some immune-compromise in 73%.)	Imipenem 0.5-1grx4	Imipenem 0.5-1grx4 + netilmicin 5mg/kg
Brown 1984	Sepsis; hospital acquired pneumonia of a documented Gram-negative origin)	Moxalactam 2grx3 for 10,1 days	Carbenicillin 66 mg/kgx6 + tobramycin 1.7mg/kgx3 (following a 2-2,5mg/kg loading dose) for 10.6 days
Carbon 1987	Sepsis; enterobacteriaceae, with at least 3 positive blood cultures	Cefotaxime 1grx4 for 12.9 days	Cefotaxime 1grx4 + amikacin 7.5 mg/kg loading dose followed by a renal-function adjusted maintenance dose for 13.2 days
Cometta 1994	Sepsis; nosocomial pneumonia, nosocomial sepsis or severe diffuse peritonitis	Imipenem 500 mgx4 for 10,2 days	Imipenem 500mgx4 + netilmicin 150 mgx2 for 10.5 days
Cone 1985	Sepsis; pneumonia or bacteraemia. Pneumonia was community acquired or nosocomial. Only patients with positive bacteriological cultures were evaluated	Ceftazidime 2grx3	Ticarcillin 3grx4 + tobramycin 1mg/kgx3
D'Antonio 1992	Sepsis; 88% of patients with un-	Ceftriaxone 2grx1 for a median of 12 days	Ceftriaxone 2grx1 + amikacin 5mg/kgx3 for a median of 11 days

	derlying haematological malignancy		
Damas 2006	Sepsis; ventilator associated pneumonia	IV Cefepime 2 g every 8 hours for 8-10 days	IV cefepime 2 g every 8 hours + IV Amikacin 20 mg/kg once daily for 5 d
Felisart 1985	Sepsis; underlying advanced cirrhosis, presenting with severe bacterial infections. Most patients had spontaneous bacterial peritonitis	Cefotaxime 2grx6	Ampicillin 2grx6 + tobramycin renal adjusted maintenance dose x3/d following 1.75 mg/kg loading dose
Finer 1992	Sepsis; hospitalized with signs and symptoms of serious bacterial infections	Ceftazidime 2grx2	Ureidopenillin + aminoglycoside used routinely in specific center: piperacillin-gentamicin; amipicillin-gentamicin; mezlocillin-netilmicin; piperacillin-netilmicin
Garicia Ramirez 1999	Sepsis; nosocomial pneumonia	IV Ceftazidime	IV penicillin + amikacin
Gomez 1990a	Sepsis; patients with proven Gram-negative bacteraemia were analyzed	Ceftazidime 1grx4 for 10 days	Cefradine 1grx6 + amikacin 7.5 mg/kgx2 for 10 days
Hoepelman 1988	Sepsis; serious bacterial infections, 18% neutropenic were not analysed	Ceftriazone 2grx1	Cefuroxime 1.5grx3 + gentamicin 80 mgx3 (following by an initial 1.5 mg/kg dose)
Holloway 1995	Sepsis; blood cultures positive for a Gram-negative pathogen	Ticarcillin-clavulanic acid 3.1 grx4-6	Piperacillin 50mg/kgx4-6 + tobramycin 1-1,5 mg/kgx3-4
Iakovlev 1998	Sepsis; severe nosocomial infections	Meropenem 1grx3 for 9 days	Ceftazidime 1grx3 + amikacin 500mgx2 for 9 days
Jaspers 1998	Sepsis; sepsis syndrome and suspected bacteraemia, pneumonia, intra-abdominal sepsis, or complicated urinary tract infection	Meropenem 1grx3 for 7.5 days	Cefuroxime 1.5grx3 + gentamicin 4mg/kgx1 for 7.4 days (metronidazole 500 mgx4 added to patients receiving combination in case of abdominal sepsis (15 patients overall))
Klastersky 1973	Sepsis; disseminated cancer and life threatening infections,	Carbenicillin 10grx3 for 8.3 days	Carbenicillin 10grx3 + gentamicin 160mgx3 (IM or IV) for 9 days

	presumed gram-negative		
Klijucar 1990	Sepsis; hospitalized in the intensive care unit and ventilated, with nosocomially acquired pneumonia	Ceftazidime 2grx3	Ceftazidime 2grx3+ tobramycin 80 mgx3 Vs azlocillin 5 mgx3 + tobramycin 80 mgx3 overall for 6.6 days
Koehler 1990	Sepsis; nosocomially acquired pneumonia	Ceftazidime 1grx3	Piperacillin 4grx3 + tobramycin 80mgx3
Limson 1988	Sepsis; severe Gram-negative infections	Ceftazidime 2grx2	Ticarcillin 3grx3-4 + amikacin 500 mgx2 (or 15 mg/kgx1)
Mandell 1987	Sepsis; community acquired or nosocomial pneumonia (2/3 nosocomial)	Ceftazidime 2grx3	Cefazolin 1,5grx3 or ticarcillin 3grx4 + tobramycin 1.7 mg/kgx3
McCormick 1997	Sepsis; chronic liver disease (cirrhosis) and suspected or proven sepsis	Ceftazidime 2grx2 for 5 days	Mezlocillin 5grx3 + netilmicin 3mg/kgx2 for 4 days
Mergoni 1987	Sepsis; patients in ICU with severe infections	Azlocillin 13 + -2.2gr for 6.5 days	Azlocillin 14.1 +-1gr + amikacin 1.16+-0.027gr for 7.2 days (all in for daily doses)
Moreno 1997	Sepsis; renal or (kidneypancreas) transplant patients with fever and suspected bacterial infection	Imipenem-cilastin 500mgx4	Piperacillin 4grx3 + tobramycin 80mgx2
Mouton, 1990	Sepsis; hospitalized in intensive care unit (ICU) with respiratory tract infections	Imipenem 500mgx4 for 1.1 days	Cefotaxime 1grx4 + amikacin 5mg/kgx3 for 10,4 days
Mouton, 1995	Sepsis; community or hospital acquired serious infections, excluding intra-abdominal sepsis (urinary tract infection included)	Meropenem 1grx3 for 8.8 days	Ceftazidime 2grx3 + amikacin 5-7,5mg/kgx2-3 for 8.3 days
Piccart 1984	Sepsis; non-neutropenic, cancer patients with suspected gram-	Cefoperazone 6grx2	Cefoperazone2grx2 + amikacin 500mgx2

	negative infections		
Rapp 1984	Sepsis; hospitalized in a neurosurgial ICU, all with nosocomial pneumonia	Ceftazidime 2grx3	Ticarcillin 3grx4 + tobramycin pharmacokinetically adjusted doses after 1.75 mg/kd loading dose
Rubinstein 1995	Sepsis; serious hospital acquired infections and a diagnosis of sepsis, pneumonia or upper urinary tract infection	Ceftazidime 2grx2 for 9 days	Ceftriaxone 2grx1 + tobramycin 3-5 mg/kgx1 following 2mg/kg loading dose for 9 days
Sage 1987	Sepsis; suspected of a life threatening sepsis, thought to be caused by Enterobacteriaceae or Staphylococci	Cefotaxime 1-2 grx4 for 7.4 days	Cefotaxime 1-2 grx4 + netilmicin 2-3mg/kgx3
Sculier 1982	Sepsis; Gram-negative pneumonia in the neurosurgical ICU, radiographic bronchopneumonia, purulent sputum and gram-negative rods on sputum direct smear	Mezlocillin 10gr x 3	Mezlocillin 10grx3 + sisomicin 75 mgx3 In addition to allocated systemtic treatment, all patients received intra-tracheal sisomycin 25mgx3/d
Sieger 1997	Sepsis; hospital aquired lower respiratory tract infections. 70% intubated and 27% with severe pneumonia	Meropenem 1grx3 for 7.8 days	Ceftazidime 2grx3 + tobramycin 1mg/kgx3 (following 1.5-2 mg/kg loading dose) for 7.4 days
Smith 1984	Sepsis; suspected or proven serious infections	Cefotaxime 2grx6 + placebo x3 for 5 days	Nafcillin 1.5grx6 + tobramycin 2mg/kgx3 for 5.3 days (addition of clindamycin 600 mgx3 to both groups permitted for suspected anaerobic infections)
Speich 1998	Sepsis; severe pneumonia, community acquired in 89%	Piperacillin-tazobactam 4,5x3 for 10,2 days	Amoxicillin-clavulonic acid 2,2grx3 + gentamicin or netilmicin 3-6mg/kgx1 for 10.1 days
Stille 1992	Sepsis; non-life threatening infections, of abdominal, gynaecological or respiratory tract origin (UTI, skin,	Imipenem 500 mgx3 for 8.4 days	Cefotaxime 2grx3 + gentamicin 0.66-1 mg/kgx3 for 8.2 days (metronidazile allowed in combination treatment for group for suspected anaerobic infection)

	bone and CNS infections excluded)		
Sukoh 1994	Sepsis; respiratory tract infection and underlying respiratory disease	Cefoperazone/sulbactam 1-4gr/d for 11,7 days	Cefoperazone/sulbactam 2-6gr/d + one of several aminoglycosides in low doses (amikacin 100-400 mg/d 16 patients, tobramycin 40-180 mg/d 15 patients, isepamicin 400 mg/d 1 patient, netilmicin 200 mg/d 1 patient) for 11.1 days
Takamoto 1994	Sepsis; respiratory tract infections	Imipenem/cilastatin sodium	Imipenem/cilastatin sodium + amikacin sulfate
Trujillo 1992	Sepsis; severe skin and soft tissue or respiratory tract infections	Ceftizoxime 1-2grx3	Ampicillin 1-3grx4 + gentamicin 3-5mg/kg/d, overall for 10 days
Vergnon 1985	Sepsis; severe bronchopulmonary infections	Cefoperazone 2grx2 for 16.8 days	Ampicillin 1,5grx4 + tobramycin 1mg/kgx3 for 11.8 days
Warren 1983	Sepsis; suspected or known life-threatening infection caused by Gram-negative bacilli	Cefoperazone 1.5grx4 for a median of 9 days	Cefamandole 2grx6 + tobramycin 1.7 mg/kg loading dose, followed by drug-level-adjusted maintenance dose for a median of 8 days.

Appendix 5 GRADE Evidence Profiles

Author(s): Ingvil Sæterdal and Hilde H Holte
Date:
Question: Beta lactam monotherapy compared to beta lactam-aminoglycoside combination therapy for sepsis
Settings:
Bibliography (systematic reviews): Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD003344. DOI: 10.1002/14651858.CD003344.pub3.

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	beta lactam monotherapy	beta lactam-aminoglycoside combination therapy	Relative (95% CI)	Absolute (95% CI)	
Overall mortality											
27	randomised trials	serious [2]	not serious	not serious	not serious	publication bias strongly suspected [3]	243/2129 (11.4%)	263/2032 (12.9%)	**RR 0.89** (0.74 to 1.08)	14 fewer per 1000 (from 10 more to 34 fewer)	⊕⊕◯◯ LOW
Overall mortality, same beta lactam											
7	randomised trials	not serious [7]	not serious	not serious	serious [1]	publication bias strongly suspected [3]	52/422 (12.3%)	48/417 (11.5%)	**RR 1.1** (0.76 to 1.6)	12 more per 1000 (from 28 fewer to 69 more)	⊕⊕◯◯ LOW
Overall mortality, different beta lactam											
21	randomised trials	serious [2]	not serious	not serious	not serious	publication bias strongly suspected [3]	191/1707 (11.2%)	215/1615 (13.3%)	**RR 0.84** (0.67 to 1.06)	21 fewer per 1000 (from 8 more to 44 fewer)	⊕⊕◯◯ LOW
Treatment failure											
41	randomised trials	serious [6]	not serious	not serious	not serious	none	482/2460 (19.6%)	569/2298 (24.8%)	**RR 0.84** (0.72 to 0.97)	40 fewer per 1000 (from 7 fewer to 69 fewer)	⊕⊕⊕◯ MODERATE
Treatment failure, same beta lactam											
12	randomised trials	serious [6]	not serious [6]	not serious	serious [5]	none	147/600 (24.5%)	117/596 (19.6%)	**RR 1.23** (0.99 to 1.53)	45 more per 1000 (from 2 fewer to 104 more)	⊕⊕◯◯ LOW
Treatment failure, different beta lactam											
29	randomised trials	serious [6]	not serious	not serious	not serious	none	335/1860 (18.0%)	452/1782 (25.4%)	**RR 0.73** (0.63 to 0.85)	68 fewer per 1000 (from 38 fewer to 94 fewer)	⊕⊕⊕◯ MODERATE
Serious adverse events											
11	randomised trials	serious [2]	not serious	not serious	serious [4]	none	25/1247 (2.0%)	24/1194 (2.0%)	**RR 1.06** (0.58 to 1.91)	1 more per 1000 (from 8 fewer to 18 more)	⊕⊕◯◯ LOW
Any nephrotoxicity											
28	randomised trials	serious [2]	not serious	not serious	serious [4]	none	46/1997 (2.3%)	176/1894 (9.3%)	**RR 0.34** (0.25 to 0.46)	61 fewer per 1000 (from 50 fewer to 70 fewer)	⊕⊕◯◯ LOW

MD – mean difference, RR – relative risk

1. Few events. 95% confidence interval range from 24% improved survival to 60% higher risk of death with monotherapy

2. Unclear allocation concealment
3. Funnel plot in the original systematic review showed that small studies favouring combination therapy might be missing
4. Few events
5. Large confidence interval, range from harmful to beneficial
6. Unclear allocation concealment and lack of blinding
7. Consider risk of bias to be high due to unclear allocation concealment, but do not downgrade since we idealy would downgrade 1/2 for this (not possible technically)