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SYSTEMATIC REVIEW:
Empiric treatment with antibiotic combination therapy compared with monotherapy for adult patients with septic shock of unknown pathogen and origin

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Innhold

Key messages

The Norwegian Directorate of Health requested the Division for Health Services at the Norwegian Institute of Public Health to conduct a systematic review of effect and safety of empiric treatment with antibiotic combination therapy compared with monotherapy for adult patients with septic shock of unknown pathogen and origin.

We conducted a systematic review according to the protocol. Our systematic search identified 4086 references. We considered 15 of those as potentially relevant, and read them in full text.

We did not identify any studies comparing empiric antibiotic combination with monotherapy for adult patients with septic shock of unknown pathogen and origin. Therefore, we do not know if empiric treatment with antibiotic combination therapy is more effective than monotherapy for adult patients with septic shock of unknown pathogen and origin

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

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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:
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Last search for studies:
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External peer reviewers:
Skrede, Steinar, Ass. dep. director/professor, Med. dep. Haukeland University Clinic
Solligård, Erik, Senior physician St. Olavs Hospital HF/ professor NTNU

Executive summary (English)

Background

The 2013 Norwegian National Guidelines for antibiotic treatment of sepsis and septic shock has been debated due to uncertainty about the effectiveness and safety of currently recommended combination therapy. There is additional uncertainty among medical doctors in Norway about which alternative empiric antibiotic treatment is right or most plausible for adult patients suffering from septic shock of unknown origin, including possible consequences for antimicrobial resistance. Patients with septic shock must have immediate treatment, including rapid onset of antibiotic treatment. In the absence of a confirmed pathogen or clinical signs of the origin of the infection, empiric antimicrobial therapy becomes necessary. Empirical treatment is based on clinical reasoning in the absence of complete information.

As part of the preparation for an update of this guideline, the Norwegian Directorate of Health asked the Division for Health Services at the Norwegian Institute of Public Health to conduct a systematic review of available research about empiric treatment with antibiotic combination therapy compared with monotherapy for adult patients with septic shock of unknown pathogen and origin.

Objective

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

Method

We conducted a systematic literature search 02.12.2019 in the following databases: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and for planned and ongoing trials in clinicaltrials.gov and WHO ICTRP. We considered publications in Danish, English, German, Norwegian, and Swedish. Two persons independently read titles and abstracts to identify possibly relevant articles. We evaluated the relevance of selected publications based on our inclusion criteria:

Population	Adult patients with septic shock or suspected septic shock, with unknown origin of infection before start of treatment
Intervention	Empiric 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)
Design	Prospectively controlled studies including randomized controlled trials, non-randomized controlled trials, controlled cohort studies

Results

Of the 4086 identified references, we (two persons independently) assessed all titles and abstracts against the inclusion criteria and considered 15 as possibly relevant. We read these 15 studies in full text. None of them met the inclusion criteria. Reasons for exclusion were not relevant interventions (n=11), only abstract available (n=1), bacterial aggregated data (n=1), no primary data (n=1) and aggregated data (n=1). We excluded no studies because of language.

We did not identify any studies that compared empiric antibiotic combination therapy to that of monotherapy for adult patients with septic shock of unknown pathogen and origin.

Discussion

We did not identify published research on empiric antibiotic treatment for septic shock of unknown origin. For other patient groups there exists research on double-coverage antibiotic agents compared to monotherapy. This is reflected in the 2016 international guidelines for management of sepsis and septic shock, the foremost comprehensive evidence review of clinically relevant aspects of septic shock. This guideline reviews double-coverage antibiotic agents compared to monotherapy for septic shock collectively for origin, yet not specifically for unknown origin and unknown pathogen. We confirm with our findings that there remains a gap in available evidence.

More stratified documentation and analyses may prove useful for future research. Furthermore, our identified knowledge gap encourages new studies specifically looking at empiric treatment choices for septic shock without known origin or pathogen. A different research approach of interest may be an evaluation of local epidemiological data including resistance patterns and their possible importance for guiding empiric treatment.

Conclusion

There is an absence of published research evidence for empiric treatment with antibiotic combination therapy compared with monotherapy for adult patients with septic shock of unknown pathogen and origin. Therefore, we do not know if empiric treatment with antibiotic combination therapy is more effective than monotherapy for adult patients with septic shock of unknown pathogen and origin.

Hovedbudskap

Helsedirektoratet anmodet område for helsetjenester ved Folkehelseinstituttet om å utarbeide en systematisk oversikt om effekt og sikkerhet ved empirisk kombinasjonsbehandling med antibiotika sammenliknet med monoterapi for voksne pasienter med septisk sjokk forårsaket av ukjent patogen og ukjent opprinnelse.

Vi utarbeidet en systematisk oversikt i henhold til protokollen. Vårt systematiske søk identifiserte 4086 referanser. Vi vurderte 15 av dem som potensielt relevante, og leste dem i fulltekst.

Vi identifiserte ingen studier som sammenlignet empirisk kombinasjonsbehandling med antibiotika med monoterapi for voksne pasienter med septisk sjokk av ukjent patogen og opprinnelse. Derfor vet vi ikke om empirisk behandling med kombinasjonsbehandling med antibiotika er mer effektivt enn monoterapi for voksne pasienter med septisk sjokk forårsaket av ukjent patogen og ukjent opprinnelse.

Tittel:

Hva er effekten av empirisk kombinasjonsbehandling med antibiotika sammenlignet med monoterapi for voksne pasienter med septisk sjokk forårsaket av ukjent patogen og ukjent opprinnelse: en systematisk oversikt

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Publikasjonstype:

Systematisk oversikt

En oversikt av et klart formulert spørsmål som bruker systematiske og eksplisitte metoder for å identifisere, velge og kritisk vurdere relevant forskning, og for å samle og analysere data fra studiene som er inkludert i oversikten. Statistiske metoder (metaanalyse) kan brukes til å analysere og oppsummere resultatene fra de inkluderte studiene.

Svarer ikke på alt:

- Ekskluderer studier som faller utenfor inklusjonsskriteriene
- Ingen helseøkonomisk evaluering
- Ingen anbefalinger

Når ble litteratursøket utført?

Søk etter studier ble avsluttet i desember 2019.

Eksterne fagfeller:

Skrede, Steinar, Ass. Avd. direktør/professor, Medisinsk avd. Haukeland Universitetssykehus

Solligård, Erik, Overlege, St. Olavs Hospital HF/ professor NTNU

Sammendrag

Innledning

De norske nasjonale retningslinjene fra 2013 for antibiotikabehandling av sepsis og septisk sjokk har blitt diskutert på grunn av usikkerhet omkring effekt og sikkerhet av nåværende anbefalt kombinasjonsbehandling. Det er ytterligere usikkerhet blant leger i Norge om hvilken alternativ empirisk antibiotikabehandling som er best for voksne pasienter med septisk sjokk med ukjent opprinnelse, og mulige konsekvenser for antimikrobiell resistens. Pasienter med septisk sjokk må få behandling umiddelbart, dette inkluderer rask oppstart av antibiotikabehandling. Dersom man ikke vet hva som forårsaker infeksjonen, må man starte med empirisk behandling. Empirisk behandling er basert på klinisk erfaring og antagelser man gjør når nødvendig informasjon ikke er tilgjengelig.

Som et ledd i forberedelsene til en oppdatering av denne retningslinjen ble område for helsetjenester ved Folkehelseinstituttet bedt av Helsedirektoratet om å lage en systematisk oversikt over tilgjengelig forskning om empirisk behandling med antibiotisk kombinasjonsbehandling sammenlignet med monoterapi for voksne pasienter med septisk sjokk av ukjent patogen og opprinnelse.

Metode

Vi gjennomførte et systematisk litteratursøk 02.12.2019 i følgende databaser: Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), og for planlagte og pågående studier i clinicaltrials.gov og WHO ICTRP. Vi vurderte publikasjoner på dansk, engelsk, norsk, tysk og svensk. To personer screenet uavhengige av hverandre titler og abstrakter for å identifisere mulige relevante artikler. Vi evaluerte relevansen til utvalgte publikasjoner basert på inkluderingskriteriene våre:

Populasjon	Voksne pasienter med septisk sjokk eller mistanke om septisk sjokk, med ukjent infeksjonsopprinnelse før behandlingsstart
Intervensjon	Empirisk kombinasjonsbehandling med antibiotika inkludert følgende: • Macrolide + betalactam (alle typer) • Genta-/tobramycin (enkel daglig dose) + betalactam (ampicillin eller (benzyl) penicillin) • Genta-/tobramycin (enkel daglig dose) + betalactam (untatt ampicillin eller (benzyl) penicillin) • Amikacin (enkel daglig dose) + betalactam (ampicillin eller (benzyl) penicillin) • Amikacin (enkel daglig dose) + betalactam (untatt ampicillin eller (benzyl) penicillin)

	Planlagt behandling med aminoglykosid må inkludere dagligdose
Komparator	Monoterapi med antibiotika
Utfall	Dødelighet (30 dager) Alvorlige bivirkninger (inkludert organskader) Liggetid på sykehus (dager) Liggetid i ICU (dager) Bakteriell utryddelse (negativ blodkultur)
Studie design	Prospektive kontrollerte studier inkludert randomiserte kontrollerte studier, ikke-randomiserte kontrollerte studier, kontrollerte kohortstudier

Resultat

Av de 4086 identifiserte referansene vurderte vi (to personer uavhengig av hverandre) alle titler og abstrakt mot inklusjonskriteriene og vi vurderte 15 som mulig relevante. Vi leste disse 15 studiene i fulltekst. Ingen av dem oppfylte inklusjonskriteriene. Årsaken til eksklusjon var ikke relevante intervensjoner (n = 11), kun abstrakt (n = 1), aggregerte data, det vil si at resultatene var presentert samlet på en slik måte at vi ikke kunne isolere kun de relevante resultatene (n = 1), ingen primærdata (n = 1) og aggregerte data (n = 1). Ingen studier ble ekskludert på bakgrunn av språk.

Vi identifiserte ingen studier som sammenlignet empirisk kombinasjonsbehandling med antibiotika og monoterapi for voksne pasienter med septisk sjokk av ukjent patogen og opprinnelse.

Diskusjon

Vi fant ikke publisert studier om empirisk kombinasjonsbehandling med antibiotika for septisk sjokk av ukjent opprinnelse. Det finnes imidlertid forskning om antibiotisk kombinasjonsbehandling sammenliknet med monoterapi for andre pasientgrupper. Dette gjenspeiles i de internasjonale retningslinjene fra 2016 for behandling av sepsis og septisk sjokk, en omfattende oversikt av klinisk relevante aspekter ved septisk sjokk(1). Den retningslinjen gjennomgår dokumentasjon for effekt av kombinasjonsbehandling med antibiotika sammenlignet med monoterapi for septisk sjokk samlet, men ikke spesifikt for ukjent opprinnelse og ukjent patogen. Våre funn bekrefter at det fortsatt er et kunnskapshull i tilgjengelig dokumentasjon.

Mer stratifisert dokumentasjon og analyser kan være av nytte for fremtidig forskning. Vår gjennomgang av forskningslitteraturen bekrefter behov for nye studier som ser spesifikt på empirisk behandlingsvalg for septisk sjokk uten kjent opprinnelse eller patogen. En annen forsknings-tilnærming av interesse kan være å evaluere lokale epidemiologiske data inkludert resistensmønstre og deres mulige betydning for å informere empirisk behandling.

Konklusjon

Det mangler publiserte studier om empirisk behandling med kombinasjonsbehandling med antibiotika sammenlignet med monoterapi for voksne pasienter med septisk sjokk

av ukjent patogen og opprinnelse. Derfor vet vi ikke om empirisk behandling med kombinasjonsbehandling med antibiotika er mer effektivt enn monoterapi for voksne pasienter med septisk sjokk forårsaket av ukjent patogen og ukjent opprinnelse. Uten tilgjengelige studier, vil klinisk resonnement med hensyn til lokal epidemiologi være nødvendig for å informere behandlingen.

Preface

The 2013 Norwegian National Guidelines for antibiotic treatment of sepsis and septic shock are currently being updated. The Directorate of Health has commissioned this systematic review to compare antibiotic combination therapy with monotherapy for adult patients with septic shock of unknown pathogen and origin.

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 a narrow question (specific populations, intervention, comparison and main outcomes) that can be systematically addressed in a robust manner to inform the guideline recommendation process. The introduction and discussion chapters are accordingly brief. The Norwegian Institute of Public Health follows a common methodology as described in the handbook "How we summarize research". This means, among other things, that standard formulations are used when describing the method, the results and the discussion of the findings. Clinical experts from the guideline group are asked to perform peer review of these systematic reviews.

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this review. In addition, consulted experts have declared no conflict of interest.

The Norwegian Institute of Public Health thanks Steinar Skrede, ass. dep. director / professor, Med. dep. Haukeland University Clinic and Erik Solligård, Senior physician St. Olavs Hospital HF/ professor NTNU who have supported this project with peer reviews. The authors also thank their colleagues Signe Flottorp and Hege Kornør whom have supported this project with their constructive feedback.

Kåre Birger Hagen	Hege Kornør	Jan PW Himmels
Research director	*Department director*	*Project coordinator*

Introduction

Sepsis (*blood poisoning*) is a clinical condition that reflects a 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). A 2017 Norwegian registry study estimated that sepsis constituted 1% of the total number of somatic hospital admissions, whereof ~4% were identified to have suffered from septic shock. With a hospital mortality for sepsis admissions at an estimated 19%, septic shock admission mortality can be assumed even higher (3). Rapid and targeted treatment of sepsis, especially septic shock, is crucial towards reducing mortality. Immediate action is required, consisting of identification of the origin of the infection, securing microbiological specimens, starting effective antibiotics and providing organ supportive treatment. Patients with septic shock and 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 (4, 5). Early volume/infusion therapy and oxygen therapy has not been shown to decrease mortality. In 2018, a Norwegian report found that patients with life-threatening organ failure were put at risk due to longer initiation time for antibiotic treatment than according to standard hospital routines (6, 7). Yet, with uncertainty in microbiological origin of symptoms early initiation of antimicrobials for not infected patients is controversial (8).

Besides rapid treatment initiation of antibiotic treatment, administering the right antibiotic, dose and dosage 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 the origin of the infection, empiric antimicrobial therapy becomes necessary. Empirical treatment is 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 (9).

There is no universally *correct* antibiotic choice, antibiotics differ from each other in their mechanism of action, spectrums of effectivity, tissue distribution, pharmacokinetics and pharmacodynamics. 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) (10). 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 (11). AMR begins locally, spreads regionally and may remain country specific, yet in a globalising world, these boundaries become blurred (12).

Norway with its generally careful and prudent approach to antimicrobial use, is within Europe one of the countries with the least AMR (13). 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 (14). 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.

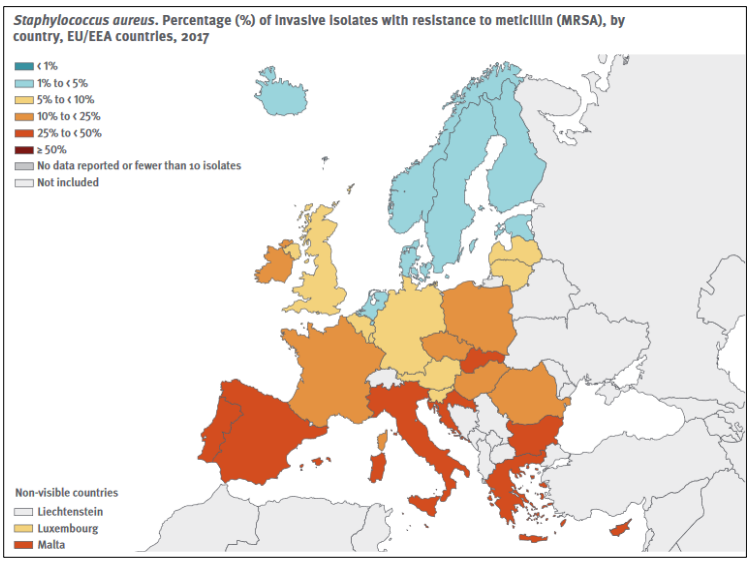

Figure 1. Exemplary map for Norway's low percentage of resistant isolates (MRSA); ECDC, Surveillance Atlas of Infectious Diseases, http://ecdc.europa.eu/en/data-tools/atlas/pages/atlas.aspx, Stockholm

There is uncertainty among medical doctors in Norway about which empiric antibiotic treatment is *right* or *most plausible* for adult patients suffering from septic shock of unknown origin. The release of the 2013 national clinical guideline 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*" (1, 15). The guideline 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 concern communicated was the known possible risk of kidney damage with aminoglycoside treatment. Nordøy and Laake claimed that many patients were referred to Oslo University Hospital, Rikshospitalet with pulmonary and kidney failure post guideline treatment (15). 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 (16). This controversial and possibly outdated recommendation in the guidelines requires revision. This review focuses on comparing currently recommended combination therapy to antibiotic monotherapy (17). The results of this review will contribute to the update process of the Norwegian national guideline for the empiric treatment of septic shock with unknown origin.

This systematic review aims to compare combination therapy with a macrolide/gentamycin (qd)/tobramycin (qd) /amikacin (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 of unknown origin. The following outcomes were considered: 30-day mortality, length of hospital/and intensive care unit (ICU) stay, bacterial eradication and serious adverse effects (including organ damage).

Method

This systematic review was conducted according to «Slik oppsummerer vi forskning» for conducting systematic reviews and the published protocol (18).

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)
Design	Prospective controlled studies including randomized controlled trials, non-randomized controlled trials, controlled cohort studies
Language	Danish, English, German, Norwegian, and Swedish

Literature search

The search strategy was developed via a series of brainstorming sessions among research team members—two researchers (GV, JH), the librarian (GH), the two individuals from the the Directorate of Health (Wang, Hege; Akselsen, Per Espen). An initial search strategy was conceptualized via expert consensus coupled with the gathering of previous literature. The search strategy is shown in Appendix 1.

We conducted a systematic literature search 02.12.2019 in the following databases:

- Medline
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)

For planned and ongoing trials, we searched in clinicaltrials.gov and WHO ICTRP.

Additionally, we checked the reference lists of included studies and other relevant literature.

Article selection

Title selection was conducted by two reviewers of the team independently, and any disagreement would have been resolved by a consensus-based discussion or by the involvement of a third independent reviewer. We utilized Rayyan for the study selection process (19). Reasons for a full text article not being selected were recorded.

Any selected studies would have been 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).

Assessing risk of bias in included studies

Two researchers would have independently assessed the risk of bias for each of the included studies in accordance with the recommendations by the Cochrane Collaboration. RCTs would have been 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, and selective outcome reporting and other risk of bias. Non-randomized controlled trials and other studies with a control group would also have been assessed for risk of bias in respect to: similarity of baseline characteristics, similarity of baseline outcome data, and contamination. All items would have been rated as high risk of bias, unclear, or low risk of bias (20).

Data extraction

One researcher would have extracted information from the included studies; another researcher would have independently checked the extraction for accuracy and relevance. Data on the following would have been extracted: full reference, location and date of study. The following patient data would have been extracted: clinical history (if available), age, sex and co-morbidities. The following intervention/comparison data would have been 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 would also have been extracted.

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

Analyses

Population: First, we would have performed a combined analysis including all patients with septic shock or suspected septic shock. We planned to collect information about the patients in each study, anonymize this information (remove link to which study), and ask the above mentioned microbiological expert to categorize the populations into different groups of similar patients that we would have sub grouped in analysis for:

- morbidity groups (co-morbidity, immunocompromised, etc.), would have been used as proxy for expected/assumed resistance pattern
- place of acquiring the infection (hospital acquired or not)
- sepsis definitions (SOFA, SIRS or others)

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

Grading
We had planned to grade our confidence in the available evidence using the GRADE approach (20).

Results

Of the 4086 identified references, we considered 15 possibly relevant (21-35). We read these 15 in full text. None matched the inclusion criteria. We were unable to identify any studies that compared empiric antibiotic combination therapy to that of monotherapy for adult patients with septic shock of unknown pathogen and origin.

Results of the literature search

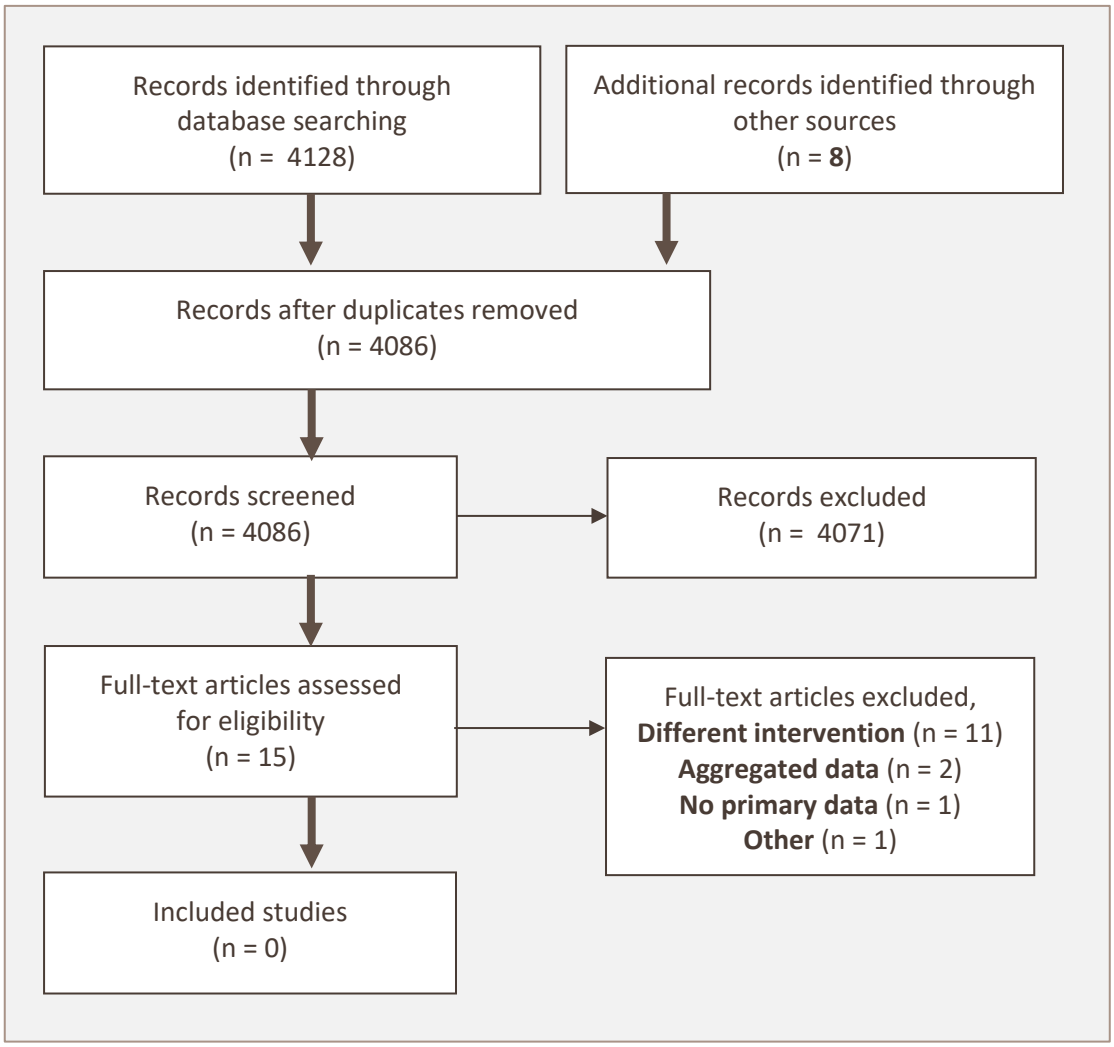

Figure 2 PRISMA flow diagram of study inclusion

Additional records identified through other sources

Eight studies were identified through other sources (reference searching of relevant articles), none of these matched the defined inclusion criteria.

Included studies

For one study we suspected that additional non-published supplementary information could have been of relevance (33). We were not able to obtain this information for rigorous evaluation from the author.

Excluded studies

The table of excluded studies is presented in appendix 2 with reasons for exclusion. Reason for exclusion were different interventions (n=11)(22, 24-32, 34), abstract only (n=1)(35), no primary data available (n=1)(21) and aggregated data only (n=2)(23, 33).

Discussion

Key findings

We did not identify relevant published studies addressing our research question: to compare the effect and safety of empiric antibiotic combination therapy with that of monotherapy for adult patients with septic shock of unknown pathogen and origin.

Although we identified 15 studies we thought potentially relevant for full text screening, none of these matched our inclusion criteria.

Strengths and weaknesses of this systematic review

Our narrowly defined research question and its strong specificity to local settings may have limited the external validity of any conclusions drawn thereof. Furthermore our research question focuses on a specific patient population with unidentified origin of infection, which may be underreported as clinical interpretations may favour a suspected origin over unknown origin.

Although we conducted a broad search, it is always possible that not all studies have been identified within our search. New studies published after our search in December 2019 would have been missed.

A thorough protocol with systematic and transparent methodology and analysis plan was compiled prior to initiation of the research. Strict quality standards were followed, two independent reviewers performed the screening process.

This systematic review has a strict focus on the exact research question (PICO), we could have considered exploding the search to look for safety information from any use of aminoglycosides for all potentially relevant patient populations.

Consistency with other reviews

There are no equivalent reviews in existence (possibly due to the lack of available evidence). The 2016 international guideline for management of sepsis and septic shock is the foremost comprehensive evidence review thoroughly addressing clinically relevant

aspects of septic shock (36). The 2016 document reviews double-coverage antibiotic agents compared to monotherapy for septic shock, yet not specifically for empiric treatment in the case of unknown origin or unknown pathogen. Therefore, their findings are not directly comparable to ours. Consistency exists so far as that the authors were equally unable to identify relevant studies for their recommendations that is directly relevant to ours. The 2016 international guideline recommends clinical judgement as follows "*several factors must be assessed and used in determining the appropriate antimicrobial regimen at each medical center and for each patient*".

Need for further research

Existing published research has not studied the specific population that our review focused on, although there has been research more generally on double-coverage antibiotic agents compared to monotherapy. Possibly more stratified documentation and analyses may provide useful evidence in the future. Our results support a call for studies looking specifically at empiric treatment options for septic shock without known origin or pathogen. Another research approach of interest may be an evaluation of local epidemiological data including resistance patterns and their possible importance for guiding empiric treatment.

Conclusion

There is an absence of evidence for empiric treatment with antibiotic combination therapy compared with monotherapy for adult patients with septic shock of unknown pathogen and origin. Therefore, we do not know if empiric treatment with antibiotic combination therapy is more effective than monotherapy for adult patients with septic shock of unknown pathogen and origin. Without robust studies available, clinical reasoning with consideration of local epidemiology will need to guide treatment.

References

1. Antibiotika i sykehus Nasjonal faglig retningslinje. Oslo; Helsedirektoratet, 2019. : Helsedirektoratet; [13.02.2020]. Available from: https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-sykehus/sepsis.
2. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
3. Knoop ST, Skrede S, Langeland N, Flaatten HK. Epidemiology and impact on all-cause mortality of sepsis in Norwegian hospitals: A national retrospective study. PLoS One. 2017;12(11):e0187990.
4. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, et al. The Timing of Early Antibiotics and Hospital Mortality in Sepsis. Am J Respir Crit Care Med. 2017;196(7):856-63.
5. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017;376(23):2235-44.
6. Sepsis – ingen tid å miste. Oppsummering av landsomfattende tilsyn i 2016–2018 med spesialisthelsetjenesten: helseforetakenes somatiske akuttmottak og deres identifise-ring og behandling av pasienter med sepsis. Rapport fra Helsetilsynet 1/2018. Oslo: Hel-setilsynet, 2018. . Report.
7. Husabo G, Nilsen RM, Flaatten H, Solligard E, Frich JC, Bondevik GT, et al. Early diagnosis of sepsis in emergency departments, time to treatment, and association with mortality: An observational study. PLoS One. 2020;15(1):e0227652.
8. Force IST. Infectious Diseases Society of America (IDSA) POSITION STATEMENT: Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines. Clin Infect Dis. 2018;66(10):1631-5.
9. Textoris J, Wiramus S, Martin C, Leone M. Antibiotic therapy in patients with septic shock. Eur J Anaesthesiol. 2011;28(5):318-24.
10. Klumper U, Recker M, Zhang L, Yin X, Zhang T, Buckling A, et al. Selection for antimicrobial resistance is reduced when embedded in a natural microbial community. ISME J. 2019.
11. Leibovici L, Paul M, Ezra O. Ethical dilemmas in antibiotic treatment. J Antimicrob Chemother. 2012;67(1):12-6.
12. Senok AC, Botta GA, Soge OO. Emergence and spread of antimicrobial-resistant pathogens in an era of globalization. Interdiscip Perspect Infect Dis. 2012;2012:286703.
13. European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA, annual epidemiological report for 2018. Stockholm: ECDC; 2019.
14. Astrup E, Elstrom E, Eriksen HM, Kacelnik O, Litleskare I. Antibiotikaresistens oppdatering av tilsvarende artikkel i Folkehelserapporten 2014: FHI; 2017 [Available from: https://www.fhi.no/nettpub/hin/smitte/resistens/.
15. Nordoy I, Laake JH. [Unjustifiable guidelines for antibiotic use in hospitals]. Tidsskr Nor Laegeforen. 2013;133(10):1056.

16. Kaspersen ER, Raeder J, Dahl V. Guidelines for treatment of sepsis. Tidsskr Nor Laegeforen. 2018;138(4).
17. Septimus EJ, Coopersmith CM, Whittle J, Hale CP, Fishman NO, Kim TJ. Sepsis National Hospital Inpatient Quality Measure (SEP-1): Multistakeholder Work Group Recommendations for Appropriate Antibiotics for the Treatment of Sepsis. Clin Infect Dis. 2017;65(9):1565-9.
18. 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.
19. Ouzzan M H, H, Fedorowicz, Z, Elmagarmid, A Rayyan — a web and mobile app for systematic reviews. Systematic Reviews. 2016;5:210.
20. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
21. Abad CL, Kumar A, Safdar N. Antimicrobial therapy of sepsis and septic shock--when are two drugs better than one? Crit Care Clin. 2011;27(2):e1-27.
22. Castano P, Plaza M, Molina F, Hincapie C, Maya W, Catano J, et al. Antimicrobial agent prescription: a prospective cohort study in patients with sepsis and septic shock. Trop Med Int Health. 2019;24(2):175-84.
23. Diaz-Martin A, Martinez-Gonzalez ML, Ferrer R, Ortiz-Leyba C, Piacentini E, Lopez-Pueyo MJ, et al. Antibiotic prescription patterns in the empiric therapy of severe sepsis: combination of antimicrobials with different mechanisms of action reduces mortality. Crit Care. 2012;16(6):R223.
24. Edwards R, Hutson R, Johnson J, Sherwin R, Gordon-Strachan G, Frankson M, et al. Severe sepsis in the emergency department - an observational cohort study from the university hospital of the West Indies. West Indian Med J. 2013;62(3):224-9.
25. Flaherty SK, Weber RL, Chase M, Dugas AF, Graver AM, Salciccioli JD, et al. Septic shock and adequacy of early empiric antibiotics in the emergency department. J Emerg Med. 2014;47(5):601-7.
26. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, Fernandez-Delgado E, Lopez-Sanchez JM. Adequate antibiotic therapy prior to ICU admission in patients with severe sepsis and septic shock reduces hospital mortality. Crit Care. 2015;19:302.
27. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med. 2003;31(12):2742-51.
28. Leone M, Bechis C, Baumstarck K, Lefrant JY, Albanese J, Jaber S, et al. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med. 2014;40(10):1399-408.
29. Leone M, Bourgoin A, Cambon S, Dubuc M, Albanese J, Martin C. Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. Crit Care Med. 2003;31(2):462-7.
30. Ploylarp Lertvipapath CP, Peerawong Werarak, Tipa Chakorn, Nasikarn Angkasekwinai, Napakadol Noppakusomboon, Apichaya Monsomboon. Association between the appropriate antimicrobial therapy and clinical outcomes in patients with sepsis. Thai Journal of Pharmaceutical Sciences. 2019;TJPS 2019, 43 (2): 110-118:9.
31. MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis. 2004;38(2):284-8.
32. Moraes RB, Guillen JA, Zabaleta WJ, Borges FK. De-escalation, adequacy of antibiotic therapy and culture positivity in septic patients: an observational study. Rev Bras Ter Intensiva. 2016;28(3):315-22.
33. Ong DSY, Frencken JF, Klein Klouwenberg PMC, Juffermans N, van der Poll T, Bonten MJM, et al. Short-Course Adjunctive Gentamicin as Empirical Therapy in

Patients With Severe Sepsis and Septic Shock: A Prospective Observational Cohort Study. Clin Infect Dis. 2017;64(12):1731-6.
34. Valles J, Rello J, Ochagavia A, Garnacho J, Alcala MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest. 2003;123(5):1615-24.
35. Jaimes F, Castaño P, Plaza M, Molina F, Hincapie C, Maya W, et al. 1470: ANTIBIOTICS PRESCRIPTION IS NOT ASSOCIATED WITH PROGNOSIS IN SEPSIS: A PROSPECTIVE COHORT STUDY. 2016;44(12):443.
36. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45(3):486-552.

Appendices

Appendix 1. Search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to November 27, 2019>
Search date: 2019-12-02

1 Shock, Septic/ or (sept*adj6 shock or toxic shock or endotox* shock or bacter* shock or toxic forward failure).ti,ab,kw,kf. **(25566)**

2 empiric*.ti,ab,kw,kf. or exp aminoglycosides/ or exp macrolides/ or anti-bacterial agents/ or amikacin/ or amoxicillin/ or amoxicillin-potassium clavulanate combination/ or ampicillin/ or azithromycin/ or azlocillin/ or aztreonam/ or carbenicillin/ or carfecillin/ or cefaclor/ or cefadroxil/ or cefamandole/ or cefatrizine/ or cefazolin/ or cefdinir/ or cefepime/ or cefixime/ or cefmenoxime/ or cefmetazole/ or cefonicid/ or cefoperazone/ or cefotaxime/ or cefotetan/ or cefotiam/ or cefoxitin/ or cefsulodin/ or ceftazidime/ or ceftibuten/ or ceftizoxime/ or ceftriaxone/ or cefuroxime/ or cephacetrile/ or cephalexin/ or cephaloglycin/ or cephaloridine/ or cephalosporins/ or cephalothin/ or cephamycins/ or cephapirin/ or cephradine/ or cilastatin, imipenem drug combination/ or ciprofloxacin/ or clarithromycin/ or cloxacillin/ or cyclacillin/ or dicloxacillin/ or doripenem/ or enoxacin/ or enrofloxacin/ or ertapenem/ or erythromycin/ or erythromycin estolate/ or erythromycin ethylsuccinate/ or floxacillin/ or fluoroquinolones/ or gatifloxacin/ or gemifloxacin/ or gentamicins/ or imipenem/ or lactams/ or levofloxacin/ or meropenem/ or methicillin/ or mezlocillin/ or moxalactam/ or moxifloxacin/ or nafcillin/ or netilmicin/ or norfloxacin/ or ofloxacin/ or oxacillin/ or pefloxacin/ or penicillin g/ or penicillins/ or piperacillin/ or piperacillin, tazobactam drug combination/ or roxithromycin/ or ticarcillin/ or tobramycin/ or beta-lactams/ or (aminoglycoside* or macrolide* or amikacin or amoxicillin* or amoxycillin* or ampicillin or azithromycin or azythromycin or azlocillin or aztreonam or azthreonam or carbenicillin or carfecillin or carphecillin or cefaclor or cefadroxil or cephadroxyl or cefamandole or cephamandole or cefatrizine or cefazolin or cephazolin or cefdinir or cefepime or cefixime or cefmenoxime or cefmetazole or cefonicid or cefoperazon* or cefotaxim* or cephotaxim*or cefotetan or cefotiam or cefoxitin or cefsulodin or ceftazidime or ceftibuten or ceftizoxime or ceftriaxon* or cefuroxime or cephuroxime or cephacetrile or cefacetrile or cephalexin or cephalexin or cephaloglycin* or cefaloglycin* or cephaloridin* or cefaloridin* or cephalosporin* or cephalothin or cefalotin or cephamycin* or cephapirin or cefapirin or cephradine or cefradine or cilastatin or ciprofloxacin or clarithromycin or cloxacillin or chloroxacillin or cyclacillin or ciclacillin or dicloxacillin or dichloroxacillin or dicloxaycline or dicloxaciclin or doripenem or enoxacin or enrofloxacin or endrofloxicin or ertapenem or erythromycin or floxacillin or fluorochloroxacillin or flucoxacillin or fluoroquinolone* or gatifloxacin* or gemifloxacin or gentamicin* or gentamycin* or imipenem or lactam* or levofloxacin or meropenem or methicillin or methicillin or mezlocillin* or meslocillin or moxalactam or la-

moxactam or moxifloxacin or nafcillin or naphthamidopenicillin or netilmicin or netromycin* or netromicin* or norfloxacin or ofloxacin* or oxacillin or oxazocilline or pefloxacin* or penicillin* or piperacillin or pipercillin or roxithromycin or ticarcillin or tobramycin or beta-lactam* or empiric*.ti,ab,kw,kf.).ti,ab,kw,kf. or (anti-bacterial or antibacterial or antibiotic* or bacteriocidal or bacteriocide*).ti,ab,kw,kf. or Drug Therapy, Combination/ or (dual therap* or dual treatment* or drug combination* or combination therap* or combination treatment* or combination drug* or polytherap* or polytherap* or multi-drug or multidrug or multiple drug*).ti,ab,kw,kf. **(1213632)**

3 (quasi experimental design or quasi experimental study or quasi experimental study design).kw. or non-randomized controlled trials as topic/ or controlled before-after studies/ or randomized controlled trial.pt. or controlled clinical trial.pt. or multicenter study.pt. or pragmatic clinical trial.pt. or (randomis* or randomiz* or randomly).ti,ab. or groups.ab. or (trial or multicenter or multi center or multicentre or multi centre).ti. or (intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or quasiexperiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat*).ti,ab. **(10267702)**

4 1 and 2 and 3 **(1470)**

Database: Embase <1974 to 2019 November 27>
Search date: 2019-12-02

1 Shock, Septic/ or (sept*adj6 shock or toxic shock or endotox* shock or bacter* shock or toxic forward failure).ti,ab,kw. **(32099)**

2 exp aminoglycosides/ or exp macrolides/ or anti-bacterial agents/ or amikacin/ or amoxicillin/ or amoxicillin-potassium clavulanate combination/ or ampicillin/ or azithromycin/ or azlocillin/ or aztreonam/ or carbenicillin/ or carfecillin/ or cefaclor/ or cefadroxil/ or cefamandole/ or cefatrizine/ or cefazolin/ or cefdinir/ or cefepime/ or cefixime/ or cefmenoxime/ or cefmetazole/ or cefonicid/ or cefoperazone/ or cefotaxime/ or cefotetan/ or cefotiam/ or cefoxitin/ or cefsulodin/ or ceftazidime/ or ceftibuten/ or ceftizoxime/ or ceftriaxone/ or cefuroxime/ or cephacetrile/ or cephalexin/ or cephaloglycin/ or cephaloridine/ or cephalosporins/ or cephalothin/ or cephamycins/ or cephapirin/ or cephradine/ or cilastatin, imipenem drug combination/ or ciprofloxacin/ or clarithromycin/ or cloxacillin/ or cyclacillin/ or dicloxacillin/ or doripenem/ or enoxacin/ or enrofloxacin/ or ertapenem/ or erythromycin/ or erythromycin estolate/ or erythromycin ethylsuccinate/ or floxacillin/ or fluoroquinolones/ or gatifloxacin/ or gemifloxacin/ or gentamicins/ or imipenem/ or lactams/ or levofloxacin/ or meropenem/ or methicillin/ or mezlocillin/ or moxalactam/ or moxifloxacin/ or nafcillin/ or netilmicin/ or norfloxacin/ or ofloxacin/ or oxacillin/ or pefloxacin/ or penicillin g/ or penicillins/ or piperacillin/ or piperacillin, tazobactam drug combination/ or roxithromycin/ or ticarcillin/ or tobramycin/ or beta-lactams/ or aminoglycoside*.mp. or macrolide*.mp. or amikacin.mp. or amoxicillin*.mp. or amoxycillin*.mp. or ampicillin.mp. or azithromycin.mp. or azythromycin.mp. or azlocillin.mp. or aztreonam.mp. or azthreonam.mp. or carbenicillin.mp. or carfecillin.mp. or carphecillin.mp. or cefaclor.mp. or cefadroxil.mp. or cephadroxyl.mp. or cefamandole.mp. or cephamandole.mp. or cefatrizine.mp. or cefazolin.mp. or cephazolin.mp. or cefdinir.mp. or cefepime.mp. or cefixime.mp. or cefmenoxime.mp. or cefmetazole.mp. or cefonicid.mp. or cefoperazon*.mp. or cefotaxim*.mp. or cephotaxim*or cefotetan.mp. or cefotiam.mp. or cefoxitin.mp. or cefsulodin.mp. or ceftazidime.mp. or ceftibuten.mp. or ceftizoxime.mp. or ceftriaxon*.mp. or cefuroxime.mp. or cephuroxime.mp. or cephacetrile.mp. or cefacetrile.mp. or cephalexin.mp. or cephalexin.mp. or cephaloglycin*.mp. or cefaloglycin*.mp. or cephaloridin*.mp. or cefaloridin*.mp. or cephalosporin*.mp. or cephalothin.mp. or cefalotin.mp. or cephamycin*.mp. or cephapirin.mp. or cefapirin.mp. or cephradine.mp. or cefradine.mp. or cilastatin.mp. or ciprofloxacin.mp. or clarithromycin.mp. or cloxacillin.mp. or chloroxacillin.mp. or cyclacillin.mp. or ciclacillin.mp. or dicloxacillin.mp. or dichloroxacillin.mp. or dicloxaycline.mp. or dicloxaciclin.mp. or doripenem.mp. or enoxacin.mp. or enrofloxacin.mp. or endrofloxicin.mp. or ertapenem.mp.

or erythromycin.mp. or floxacillin.mp. or fluorochloroxacillin.mp. or flucoxacillin.mp. or fluoroquinolone*.mp. or gatifloxacin*.mp. or gemifloxacin.mp. or gentamicin*.mp. or gentamycin*.mp. or imipenem.mp. or lactam*.mp. or levofloxacin.mp. or meropenem.mp. or methicillin.mp. or methicillin.mp. or mezlocillin*.mp. or meslocillin.mp. or moxalactam.mp. or lamoxactam.mp. or moxifloxacin.mp. or nafcillin.mp. or naphthamidopenicillin.mp. or netilmicin.mp. or netromycin*.mp. or netromicin*.mp. or norfloxacin.mp. or ofloxacin*.mp. or oxacillin.mp. or oxazocilline.mp. or pefloxacin*.mp. or penicillin*.mp. or piperacillin.mp. or pipercillin.mp. or roxithromycin.mp. or ticarcillin.mp. or tobramycin.mp. or beta-lactam*.ti,ab,kw. or empiric*.ti,ab,kw. or anti-bacterial.mp. or antibacterial.mp. or antibiotic*.mp. or bacteriocidal.mp. or bacteriocide*.ti,ab,kw. or Drug Therapy, Combination/ or (dual therap* or dual treatment* or drug combination* or combination therap* or combination treatment* or combination drug* or polytherap* or poly-therap* or multi-drug or multidrug or multiple drug).ti,ab,kw. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] **(1616659)**

3 (random* or clinical trial or quasi-experiment* or quasiexperiment* or quasi random* or quasirandom* or quasi control* or quasicontrol* or ((quasi* or experimental) adj3 (method* or study or trial or design* or controlled))).ti,ab,kw. or (effect or impact or trial or intervention).ti. or exp health care quality/ or randomized controlled trial/ or quasi experimental study/ or experimental design/ or multicenter study/ **(5686497)**

4 1 and 2 and 3 **(1907)**

Database: Cochrane Central Register of Controlled Trials
Search date: 2019-12-02

#1 MeSH descriptor: [Shock, Septic] explode all trees 829
#2 (sept* NEAR/6 shock) or "toxic shock" or (endotox* NEXT shock) or (bacter* NEXT shock) or "toxic forward failure" 3100
#3 #1 or #2 **3100**
#4 MeSH descriptor: [Aminoglycosides] explode all trees 8331
#5 MeSH descriptor: [Macrolides] explode all trees 8297
#6 MeSH descriptor: [Anti-Bacterial Agents] this term only 10349
#7 MeSH descriptor: [Amikacin] this term only 361
#8 MeSH descriptor: [Amoxicillin] this term only 2354
#9 MeSH descriptor: [Amoxicillin-Potassium Clavulanate Combination] this term only 589
#10 MeSH descriptor: [Ampicillin] this term only 994
#11 MeSH descriptor: [Azithromycin] this term only 885
#12 MeSH descriptor: [Azlocillin] this term only 44
#13 MeSH descriptor: [Aztreonam] this term only 169
#14 MeSH descriptor: [Carbenicillin] this term only 79
#15 MeSH descriptor: [Carfecillin] this term only 2
#16 MeSH descriptor: [Cefaclor] this term only 227
#17 MeSH descriptor: [Cefadroxil] this term only 85
#18 MeSH descriptor: [Cefamandole] this term only 190
#19 MeSH descriptor: [Cefatrizine] this term only 7
#20 MeSH descriptor: [Cefazolin] this term only 497
#21 MeSH descriptor: [Cefdinir] this term only 61
#22 MeSH descriptor: [Cefepime] this term only 145
#23 MeSH descriptor: [Cefixime] this term only 136
#24 MeSH descriptor: [Cefmenoxime] this term only 17
#25 MeSH descriptor: [Cefmetazole] this term only 36
#26 MeSH descriptor: [Cefonicid] this term only 43
#27 MeSH descriptor: [Cefoperazone] this term only 113

#28 MeSH descriptor: [Cefotaxime] this term only 583
#29 MeSH descriptor: [Cefotetan] this term only 109
#30 MeSH descriptor: [Cefotiam] this term only 45
#31 MeSH descriptor: [Cefoxitin] this term only 297
#32 MeSH descriptor: [Cefsulodin] this term only 6
#33 MeSH descriptor: [Ceftazidime] this term only 461
#34 MeSH descriptor: [Ceftibuten] this term only 42
#35 MeSH descriptor: [Ceftizoxime] this term only 171
#36 MeSH descriptor: [Ceftriaxone] this term only 693
#37 MeSH descriptor: [Cefuroxime] this term only 453
#38 MeSH descriptor: [Cephacetrile] this term only 6
#39 MeSH descriptor: [Cephalexin] this term only 290
#40 MeSH descriptor: [Cephaloglycin] this term only 1
#41 MeSH descriptor: [Cephaloridine] this term only 76
#42 MeSH descriptor: [Cephalosporins] this term only 1386
#43 MeSH descriptor: [Cephalothin] this term only 150
#44 MeSH descriptor: [Cephamycins] this term only 74
#45 MeSH descriptor: [Cephapirin] this term only 14
#46 MeSH descriptor: [Cephradine] this term only 78
#47 MeSH descriptor: [Cilastatin, Imipenem Drug Combination] this term only 81
#48 MeSH descriptor: [Ciprofloxacin] this term only 1109
#49 MeSH descriptor: [Clarithromycin] this term only 1399
#50 MeSH descriptor: [Cloxacillin] this term only 112
#51 MeSH descriptor: [Cyclacillin] this term only 8
#52 MeSH descriptor: [Dicloxacillin] this term only 37
#53 MeSH descriptor: [Doripenem] this term only 22
#54 MeSH descriptor: [Enoxacin] this term only 55
#55 MeSH descriptor: [Enrofloxacin] this term only 0
#56 MeSH descriptor: [Ertapenem] this term only 92
#57 MeSH descriptor: [Erythromycin] this term only 962
#58 MeSH descriptor: [Erythromycin Estolate] this term only 73
#59 MeSH descriptor: [Erythromycin Ethylsuccinate] this term only 91
#60 MeSH descriptor: [Floxacillin] this term only 79
#61 MeSH descriptor: [Fluoroquinolones] this term only 1170
#62 MeSH descriptor: [Gatifloxacin] this term only 119
#63 MeSH descriptor: [Gemifloxacin] this term only 45
#64 MeSH descriptor: [Gentamicins] this term only 1066
#65 MeSH descriptor: [Imipenem] this term only 295
#66 MeSH descriptor: [Lactams] this term only 110
#67 MeSH descriptor: [Levofloxacin] this term only 572
#68 MeSH descriptor: [Meropenem] this term only 231
#69 MeSH descriptor: [Methicillin] this term only 79
#70 MeSH descriptor: [Mezlocillin] this term only 124
#71 MeSH descriptor: [Moxalactam] this term only 110
#72 MeSH descriptor: [Moxifloxacin] this term only 737
#73 MeSH descriptor: [Nafcillin] this term only 23
#74 MeSH descriptor: [Netilmicin] this term only 147
#75 MeSH descriptor: [Norfloxacin] this term only 254
#76 MeSH descriptor: [Ofloxacin] this term only 886
#77 MeSH descriptor: [Oxacillin] this term only 49
#78 MeSH descriptor: [Pefloxacin] this term only 76
#79 MeSH descriptor: [Penicillin G] this term only 255
#80 MeSH descriptor: [Penicillins] this term only 1099
#81 MeSH descriptor: [Piperacillin] this term only 402

#82 MeSH descriptor: [Piperacillin, Tazobactam Drug Combination] this term only 144
#83 MeSH descriptor: [Roxithromycin] this term only 120
#84 MeSH descriptor: [Ticarcillin] this term only 151
#85 MeSH descriptor: [Tobramycin] this term only 583
#86 MeSH descriptor: [beta-Lactams] this term only 141
#87 (aminoglycoside* or macrolide* or amikacin or amoxicillin* or amoxycillin* or ampicillin or azithromycin or azythromycin or azlocillin or aztreonam or azthreonam or carbenicillin or carfecillin or carphecillin or cefaclor or cefadroxil or cephadroxyl or cefamandole or cephamandole or cefatrizine or cefazolin or cephazolin or cefdinir or cefepime or cefixime or cefmenoxime or cefmetazole or cefonicid or cefoperazon* or cefotaxim* or cephotaxim*or cefotetan or cefotiam or cefoxitin or cefsulodin or ceftazidime or ceftibuten or ceftizoxime or ceftriaxon* or cefuroxime or cephuroxime or cephacetrile or cefacetrile or cephalexin or cephalexin or cephaloglycin* or cefaloglycin* or cephaloridin* or cefaloridin* or cephalosporin* or cephalothin or cefalotin or cephamycin* or cephapirin or cefapirin or cephradine or cefradine or cilastatin or ciprofloxacin or clarithromycin or cloxacillin or chloroxacillin or cyclacillin or ciclacillin or dicloxacillin or dichloroxacillin or dicloxaycline or dicloxaciclin or doripenem or enoxacin or enrofloxacin or endrofloxicin or ertapenem or erythromycin or floxacillin or fluorochloroxacillin or flucoxacillin or fluoroquinolone* or gatifloxacin* or gemifloxacin or gentamicin* or gentamycin* or imipenem or lactam* or levofloxacin or meropenem or methicillin or methicillin or mezlocillin* or meslocillin or moxalactam or lamoxactam or moxifloxacin or nafcillin or naphthamidopenicillin or netilmicin or netromycin* or netromicin* or norfloxacin or ofloxacin* or oxacillin or oxazocilline or pefloxacin* or penicillin* or piperacillin or pipercillin or roxithromycin or ticarcillin or tobramycin or beta-lactam* or empiric*) 39613
#88 (anti-bacterial or antibacterial or antibiotic* or bacteriocidal or bacteriocides) 37779
#89 MeSH descriptor: [Drug Therapy, Combination] this term only 29417
#90 ((dual NEXT therap*) or (dual NEXT treatment*) or (drug NEXT combination*) or (combination NEXT therap*) or (combination NEXT treatment*) or (combination NEXT drug*) or polytherap* poly-therap* or multi-drug or multidrug or "multiple drug") 67387
#91 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 **146839**
#92 #3 and #91 in Trials **592**

Database: clinicaltrials.gov
Search date: 2019-12-02
Condition: septic shock: **424**

Database: WHO ICTRP
Search date: 2019-12-02
Condition: septic shock Title: antibiotic* OR anti-bacterial OR aminoglycosid* OR macrolid* OR ampocillin* OR penicillin*: **292**

Appendix 2. Table of excluded studies

Reference	Publication year	Cause for exclusion of study
Abad **(21)**	2011	No primary data/ Review
Castano **(22)**	2019	Different intervention
Diaz-Martin **(23)**	2012	Aggregated data
Edwards **(24)**	2013	Different intervention
Flaherty **(25)**	2014	Different intervention
Garnacho-Montero **(27)**	2003	Different intervention
Garnacho-Montero **(26)**	2015	Different intervention
Jaimes **(35)**	2016	Abstract to Castano 2019
Leone **(28)**	2014	Different intervention
Leone **(29)**	2003	Different intervention
Lertvipapath **(30)**	2019	Different intervention
MacArthur **(31)**	2004	Different intervention
Moraes **(32)**	2016	Different intervention
Ong **(33)**	2017	Aggregated data
Valles **(34)**	2003	Different intervention

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