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Route of antibiotic prophylaxis for prevention of cerebrospinal fluid-shunt infection (Protocol)

Arts SHHMJ, Boogaarts HD, van Lindert EJ

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Route of antibiotic prophylaxis for prevention of cerebrospinal fluid-shunt infection.
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[Intervention Protocol]

Route of antibiotic prophylaxis for prevention of cerebrospinal fluid-shunt infection

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effect of different routes of antibiotic prophylaxis (i.e. oral, intravenous, intrathecal, topical and via antibiotic-impregnated shunt catheters) on CSF-shunt infection rates in individuals treated for hydrocephalus using internalised CSF shunts.

BACKGROUND

Description of the condition

Hydrocephalus is a condition in which cerebrospinal fluid (CSF) accumulates in the cerebral ventricles and subarachnoid spaces, resulting in dilatation of the ventricular system and an increase in intracranial pressure (Rekate 1999). There are two basic forms of hydrocephalus: non-communicating and communicating. Non-communicating hydrocephalus is caused by structural blockage of the CSF within the ventricular system and is the most common form of hydrocephalus in children. Communicating hydrocephalus can be caused either by the excessive production of CSF by the plexus choroideus or by inadequate resorption of CSF by the subarachnoid villi. Treatment of hydrocephalus comprises the drainage of excessive CSF through the implantation of shunts, external drains or an endoscopic third ventriculostomy. The choice of treatment and its efficacy differ according to he individual's age and the aetiology of the condition (Fu 2002; Hebb 2001; Limbrick 2014). The main complication of CSF-shunt surgery is the incidence of CSF-shunt infection (average rate 3% to 20%) (Borgbjerg 1995; Drake 1998; James 2014; Kestle 2011; Kestle 2016; Konstantelias 2015; Simon 2009; Greenberg 2010); the highest infection rate is seen in infants (Bondurant 1995; Casey 1997). The symptoms associated with a shunt infection can be very non-specific (e.g. fever, nausea, lethargy, anorexia or irritability). Symptoms of shunt infections in children tend to be more distinctive (e.g. high fever, with or without concomitant meningitis, and rapid neurological deterioration). Up to 29% of individuals presenting with shunt malfunction have been shown to have a shunt infection, as confirmed by positive cultures (Greenberg 2010). Shunt infections can be treated by the administration of long-term antibiotics, but in most cases shunt revision is required (Simon 2010; Greenberg 2010). Both, antibiotics and shunt revision can lead to longer hospital stays, additional complications and greater associated costs (Attenello 2010; Sciubba 2007). Hence,

minimising shunt infections would be beneficial to both patients and to the healthcare system.

Description of the intervention

Currently, antibiotics used for the prevention of shunt infections can be administered in five ways: orally, intravenously, intrathecally, topically and via the implantation of antibiotic-impregnated shunt catheters. Antibiotics given via the oral route are used as add-on therapy in the treatment of CSF-shunt infections, but are rarely used to prevent CSF-shunt infections (Frame 1984).

Intravenous pre-operative antibiotics are widely used as shunt infection prophylaxis, and appear to lower the risk of such infections (Klimo 2014); however, these systemic antibiotics infiltrate the central nervous system poorly, and so intravenous antibiotics are often combined with antibiotics administered via one of the other routes in order to increase their impact on the shunt infection rate. Ragel 2006 found that the addition of intrathecal gentamycin and vancomycin to intravenous cefazolin reduced the shunt infection rate to 0.42% (from 5.4% in the intrathecal gentamicin plus intravenous cefazolin (control) group).

Intrathecal antibiotics are usually administered intraoperatively; however, Moussa 2016 used a shunt containing a reservoir in which a prophylactic antibiotic was injected. They showed that an additional administration of antibiotics one week after surgery resulted in a lower shunt infection rate than intra-operative administration alone. Although this technique essentially eliminated shunt infection, it did not significantly differ from single dose administration (Moussa 2016). Another option is the administration of topical antibiotics. This route is partly similar to intrathecal administration but provides the opportunity of covering the entire drainage route (including the extracranial pathway).

A relatively new technique in the field of shunt infection prevention is the antibiotic-impregnated shunt catheter. These catheters, which are impregnated with two antibiotic agents, which they release slowly over a period of days, have been shown to significantly reduce the rate of shunt infections (Konstantelias 2015). However, such catheters are relatively expensive when compared with the previously mentioned administration routes. In addition, Konstantelias 2015 found that antibiotic-impregnated shunt catheters had a higher probability of colonisation by strains more virulent than coagulase-negative staphylococci (CoNS), which can result in a more severe infection. Another concern regarding the use of antibiotic-impregnated shunt catheters was noted by James 2014, who found that individuals who needed shunt replacement after the implantation of an antibiotic-impregnated shunt catheter were more prone to infections than those who were initially treated with other types of shunt.

How the intervention might work

Foreign materials, such as a shunt or external drain, when placed in the body are prone to infection, and once a foreign material is infected that infection can be hard to manage. Antibiotic agents have a bactericide or bacteriostatic function that helps to eliminate bacterial infections. These functions are also useful when the prevention of bacterial colonisation is the aim. Although a ventricular-peritoneal shunt can be in situ for years, most shunt infections occur within two months of surgery (Greenberg 2010). The source of the infection is usually bacteria from the individual's own skin (Yogev 1985). Hence, contamination of the shunt takes place during, or early after, surgery, which suggests that the perioperative administration of antibiotic prophylaxis could be effective in the prevention of shunt infections.

Why it is important to do this review

CSF-shunt infection is a major problem in individuals (including children) with hydrocephalus, with a reported infection rate of 3% to 20% (Greenberg 2010). Shunt infections have a very high impact, both clinically (repeat surgery, prolonged hospitalisation, neurological deterioration) and economically (we estimate that each infection is associated with incremental costs equating to EURO30,000). Hence, a reduction in the shunt infection rate is urgently needed. Prophylactic antibiotics are currently the main preventative strategy in use; however, the best route of administration for the prevention of shunt infection remains to be determined (Ratilal 2008). This Cochrane Review has the potential to establish whether antibiotic prophylaxis has a positive effect on the CSF-shunt infection rate and could direct which route of administration is the most effective. Some other aspects of antibiotic treatment (duration of treatment, dose and intervals between doses) are also unknown, but due to the potentially wide variety in these three factors, we will not be including them in our review.

OBJECTIVES

To determine the effect of different routes of antibiotic prophylaxis (i.e. oral, intravenous, intrathecal, topical and via antibiotic-impregnated shunt catheters) on CSF-shunt infection rates in individuals treated for hydrocephalus using internalised CSF shunts.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised and quasi-randomised controlled trials that studied the effect of antibiotic prophylaxis for the prevention of CSF-shunt infection. We will consider cluster randomised trials and cross-over trials as eligible for inclusion but will exclude studies in which participants received more than one shunt simultaneously.

Types of participants

All individuals, of any age and gender, who underwent any type of internalised CSF-shunt placement for the treatment of hydrocephalus. We will impose no restrictions with respect to the aetiology of hydrocephalus. We will include studies that enrolled only a subset of relevant participants; we will present the data from these studies only for the relevant subset. If data on the subset of relevant participants cannot be obtained, we will exclude the study. We will exclude individuals treated with external drains or temporary shunts.

Types of interventions

We will include all types of antibiotics administered in any dose, frequency and intensity and for any duration of therapy. We will include studies investigating any of five different administration routes of antibiotic prophylaxis: oral, intravenous, topical, intrathecal and via antibiotic-impregnated shunt catheters.

Types of outcome measures

Primary outcomes

1. Overall CSF-shunt infection rate
2. Shunt infection rate per administration route (i.e. oral, intravenous, intrathecal, topical and via antibiotic-impregnated catheters)

We will define shunt infection as: clinical and biochemical signs of infection in combination with a positive CSF culture. We will report the shunt infection rate as counts and percentages.
All outcomes need to occur within two years of shunt placement.

Secondary outcomes

1. Infection rate in children
2. Infection rate in adults
3. Infection rate associated with each individual type of antibiotic agent

All outcomes need to occur within two years of shunt placement. We will report infection rates at one month, three months, six months, one year and two years after shunt placement, with a minimum follow-up of six weeks.

Search methods for identification of studies

We will conduct a systematic electronic search without restrictions on language, date or publication type, in line with the advice given in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefevbre 2011). If we identify studies published in a language other than English, we will ask a professional translator to translate the text.

Electronic searches

The Information Specialist will search the Trials Register of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group, which, among other sources, contains trials from:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2017; most recent issue);
- MEDLINE (PubMed) (1966 to date);
- Embase (Embase.com) (1974 to date);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) (1981 to date);
- Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to date);
- ClinicalTrials.gov (clinicaltrials.gov/); and
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

We will use the following keywords to search for trials for this review: {cerebrospinal fluid shunting} OR {CSF-shunt} OR {ventriculoperitoneal shunt} OR {shunt} OR {catheter} AND {antibiotic prophylaxis} OR {infection prevention} OR {infection}. Information on the Group's Trials Register and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group's module.
In addition, we will search three of the above databases separately in order to ensure that no relevant trials are missed.

- CENTRAL (2017; most recent issue) (Appendix 1).
- MEDLINE (PubMed) (1966 to date) (Appendix 2).
- Embase (Embase.com) (1974 to date) (Appendix 3).

We will search for the terms in the title, abstract, keywords and controlled vocabularies.

Searching other resources

We will then search the following other resources.

- The reference lists of all retrieved articles, texts and other reviews on the topic.
- The ISRCTN registry (isrctn.com/), to identify any unpublished data.
- WebOfScience (webofknowlegde.com), for forward citation search.

We will also attempt to contact authors of the included studies to obtain key missing data as needed.

Data collection and analysis

Selection of studies

The three review authors (SA, HB and EvL) will independently screen titles and abstracts for inclusion with regard to our eligibility criteria, which we will store in a reference management software system. We will obtain full text versions of the articles that meet the eligibility criteria. The three review authors (SA, HB and EvL) will again independently screen these articles and will list those that do not meet the inclusion criteria based on a full text review in a 'Characteristics of excluded studies' table. We will resolve disagreements by discussion or by referral to an independent researcher within our department when necessary.

Data extraction and management

Two review authors (SA and EvL) will independently extract the following data from included studies.

- Date and location of study.
- Study design.
- Number of participants.
- Demographic data.
- Inclusion and exclusion criteria.
- Antibiotic prophylaxis (administration route, antibiotics used, frequency and doses).
- Primary and secondary outcomes.
- Methodological quality.

We will summarise all studies that meet the inclusion criteria in a 'Characteristics of included studies' table provided in Review Manager 5.3 (RevMan 2017) and will include details related to design, participants, interventions and outcomes.

Assessment of risk of bias in included studies

Two review authors (SA and EvL) will independently assess the risk of bias in the included studies using the Cochrane 'Risk of bias' tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will assess the following domains of bias.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other biases.

After this independent assessment of risk of bias, we will resolve any disagreements by discussion with a third review author (HB).

Measures of treatment effect

We are planning to perform meta-analyses on both the primary and secondary outcomes. Since our outcomes are dichotomous and we expect the study designs of included studies to differ considerably, we will use the risk ratio in our meta-analyses as described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Unit of analysis issues

We will consider any of the following designs of included studies as having high potential for unit of analysis issues.

- Cluster-randomisation.
- Cross-over trial or simultaneous treatment of multiple sites on each individual.
- Repeated measurements (i.e. recurring infections in the same participant).

When appropriate controls were not used, we will request and re-analyse data according to Chapters 9 (Deeks 2011) and 16 (Higgins 2011b) in the *Cochrane Handbook for Systematic Reviews of Interventions* . Hence, for cluster-randomised trials, we will first check whether an effective sample size can be calculated. If this is not possible, then we will exclude the study. If a proper calculation of the effective sample size can be performed, we will include the study in the meta-analysis using the generic inverse-variance method. In cross-over trials we will first check whether the data required to perform a paired analysis are available. If not, we will exclude the study. Otherwise, we will include the study in the meta-analysis using the generic inverse-variance method. We will obtain the data for individual participants of studies that included repeated measurements. After obtaining such data, we will carry out an analysis that includes the whole follow-up period for each participant (e.g. a time-to-event analysis).

Dealing with missing data

In the case of missing data we will first contact the authors and request their database. In this way we hope to receive missing data or determine whether the data are randomly or structurally missing. First, we will perform sensitivity analyses to assess how sensitive the results are to reasonable changes in the assumptions that are made. If the data are missing at random we will analyse only the available data. However, if data are not missing at random we will consider one of the following options.

- Imputing the missing data with replacement values and treating these as if they are observed.
- Imputing the missing data and accounting for the fact that these are imputed with uncertainty.

- Using statistical models to allow for missing data and making assumptions about their relationship with the available data.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by critically appraising the included studies. When clinical and methodological heterogeneity is unlikely, we will assess statistical heterogeneity by performing a meta-analysis. First, we will assess heterogeneity using the confidence interval of the forest plot; thereafter we will take the Chi^2 and I^2 tests into account (Higgins 2011c). We will interpret the I^2 statistic as follows.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: represents considerable heterogeneity.

When heterogeneity is detected, we will assess the individual study in order to find the origin of the heterogeneity.

Assessment of reporting biases

We will build a funnel plot in order to assess publication bias. However, for a funnel plot at least 10 studies need to be included per outcome. We will assess selective outcome bias by critically appraising the included studies.

Data synthesis

Since our research question is broad we will use a random-effects model for our meta-analyses, though we may use a fixed-effect model in subgroup analysis when heterogeneity is low. If substantial statistical heterogeneity is present and the direction of effect is inconsistent across studies, we will not combine data in meta-analysis but will present a narrative summary. We will use RevMan 5.3 to perform analyses (RevMan 2017).

Subgroup analysis and investigation of heterogeneity

When sufficient data are available we will perform subgroup analyses according to the route of antibiotic administration, type of antibiotic agent, aetiology of hydrocephalus and demographic parameters (e.g. age and gender). We will conduct an indirect comparison analysis.

Sensitivity analysis

If statistical heterogeneity is detected or if the eligibility of some studies in the meta-analysis is dubious because they do not contain full details, we plan to conduct sensitivity analyses in order to check whether particular decisions or missing information that significantly influences the outcomes of this review can be identified, as described in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011c). For example:

- we will analyse the results after exclusion of studies that were scored as high risk of bias; and
- when moderate heterogeneity is detected we will perform both fixed-effect and random-effects model meta-analyses.

Overall quality of the body of evidence: 'Summary of findings' table

We will summarise the evidence for all outcomes in 'Summary of findings' tables, according to the GRADE approach (GRADEprofiler 2011; Guyatt 2008). For each comparison, two review authors (SA and EvL) will rate the quality of evidence as 'high', 'moderate', 'low', or 'very low' using GRADEprofiler 2011. We will present a 'Summary of findings' table for each outcome that we have analysed. We will resolve any disagreements by discussion or by referral to a third review author (HB) when necessary. If we are unable to perform a meta-analysis, we will summarise the results in a narrative 'Summary of findings' table.

ACKNOWLEDGEMENTS

None

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Library

#1hydrocephal*:ti,ab,kw

#2MeSH descriptor: [Hydrocephalus] explode all trees

#3aqu?ductal stenos?s:ti,ab,kw

#4#1 or #2 or #3

#5MeSH descriptor: [Cerebrospinal Fluid Shunts] explode all trees

#6(shunt* or catheter*):ti,ab,kw

#7#5 or #6

#8#4 and #7

#9MeSH descriptor: [Anti-Bacterial Agents] explode all trees

#10antibiotic* or anti-bacterial or antibacterial or anti near/4 bacterial:ti,ab,kw

#11MeSH descriptor: [Antibiotic Prophylaxis] explode all trees

#12MeSH descriptor: [Vancomycin] explode all trees

#13vancomycin:ti,ab,kw

#14vancomicin:ti,ab,kw

#15MeSH descriptor: [Rifampin] explode all trees

#16rifampicin:ti,ab,kw

#17rifampin:ti,ab,kw

#18MeSH descriptor: [Gentamicins] explode all trees

#19gentam?cin:ti,ab,kw

#20MeSH descriptor: [Methicillin] explode all trees

#21methicillin or meticillin or methycillin or metycillin:ti,ab,kw

#22MeSH descriptor: [Cefazolin] explode all trees

#23cephazolin*:ti,ab,kw

#24cefazolin*:ti,ab,kw

#25#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

#26[mh staphylococcus] or [mh streptococcus]

#27s. aureus:ti,ab,kw

#28st. aureus:ti,ab,kw

#29staphylococcus aureus:ti,ab,kw

#30s. epidermidis:ti,ab,kw

#31st. epidermidis:ti,ab,kw

#32staphylococcus epidermidis:ti,ab,kw

#33bacterial infection*:ti,ab,kw

#34bacterem*:ti,ab,kw

#35(gram-negative bacterial infection*):ti,ab,kw

#36(gram negative bacterial infection*):ti,ab,kw

#37(gram-positive bacterial infection*):ti,ab,kw

#38(gram positive bacterial infection*):ti,ab,kw

#39staphylococ* infection*:ti,ab,kw

#40streptococ* infection*:ti,ab,kw

#41(catheter-related infection* or catheter-associated infection* or catheter* infection or prosthes*-related infection* or prosthes* infection*):ti,ab,kw

#42(shunt-related infection* or shunt-associated infection* or shunt* infection*):ti,ab,kw

#43MeSH descriptor: [Infection] this term only

#44MeSH descriptor: [Catheter-Related Infections] this term only

#45MeSH descriptor: [Prosthesis-Related Infections] explode all trees

#46MeSH descriptor: [Sepsis] explode all trees

#47sepsis or blood poisoning or shock or toxemia* or circulatory failure or pyohemia* or pyemia or pyaemia or septicemia or circulatory collapse:ti,ab,kw

#48MeSH descriptor: [Bacterial Infections] explode all trees

#49#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

#50#8 and #25 and #49

Appendix 2. MEDLINE

1 hydrocephal*.ti,ab,kf. (23714)

2 hydrocephalus/ or dandy-walker syndrome/ or hydrocephalus, normal pressure/ (21817)

3 aqu?ductal stenos?s.ti,ab,kf. (674)

4 cerebrospinal fluid shunts/ or ventriculoperitoneal shunt/ (9913)

5 (shunt* or catheter*).ti,ab,kf. (235894)

6 exp Anti-Bacterial Agents/ (636809)

7 exp Vancomycin/ (12005)

8 van?om?cin.ti,ab,kf,rn. (25325)

9 exp Rifampin/ (16257)

10 rifamp??in.ti,ab,kf,rn. (26494)

11 exp Gentamicins/ (18172)

12 gentam#cin.ti,ab,kf,rn. (24315)

13 exp Methicillin/ (3675)

14 met??cillin*.ti,ab,kf,rn. (29932)

15 exp Cefazolin/ (2584)

16 ce??azolin*.ti,ab,kf,rn. (4945)

17 (antibiotic* or anti-bacterial or antibacterial or (anti adj4 bacterial)).ti,ab,kf. (333911)

18 exp Antibiotic Prophylaxis/ (11911)

19 exp Staphylococcus/ or exp streptococcus/ (157073)

20 (staphylococcus epidermidis or staphylococcus aureus).ti,ab,kf. (90371)

21 (s? aureus or s? epidermidis).ti,ab,kf. (34110)

22 (bacterial adj5 infection*).ti,ab,kf. (46788)

23 bacterem*.ti,ab,kf. (22597)

24 (gram-negative adj4 bacterial adj4 infection*).ti,ab,kf. (1021)

25 (gram-positive adj4 bacterial adj4 infection*).ti,ab,kf. (465)

26 staphylococ* infection*.ti,ab,kf. (6916)

27 ((shunt* or prosthes* or catheter*) adj4 infection*).ti,ab,kf. (10617)

28 pyohemia*.ti,ab,kf. (8)

29 py?emia*.ti,ab,kf. (161)

30 blood poisoning*.ti,ab,kf. (25)

31 (circulatory adj3 (collaps or failure)).ti,ab,kf. (2252)

32 shock.ti,ab,kf. (159681)

33 sepsis.ti,ab,kf. (80390)

34 toxemia*.ti,ab,kf. (5853)

35 septic?emia*.ti,ab,kf. (19623)

36 bacterial infections/ or meningitis, bacterial/ or gram-negative bacterial infections/ or gram-positive bacterial infections/ or staphylococcal infections/ or streptococcal infection/ or infection/ or catheter-related infections/ or prosthesis-related infections/ or sepsis/ or bacteremia/ or endotoxemia/ or shock, septic/ (284371)

37 1 or 2 or 3 (31047)

38 4 or 5 (238246)

39 37 and 38 (10565)

40 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 (802056)

41 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 (636632)

42 39 and 40 and 41 (397)

Appendix 3. Embase

1 hydrocephal*.ti,ab,kw. (30549)

2 aqu?ductal stenos?s.ti,ab,kw. (889)

3 brain ventricle peritoneum shunt/ or cerebrospinal fluid shunting/ (12536)

4 (shunt* or catheter*).ti,ab,kw. (327207)

5 hydrocephalus/ or brain aqueduct stenosis/ or brain ventricle dilatation/ or communicating hydrocephalus/ or congenital hydrocephalus/ or costello syndrome/ or dandy walker syndrome/ or normotensive hydrocephalus/ or obstructive hydrocephalus/ or walker warburg syndrome/ (43875)

6 exp antibiotic agent/ (1189546)

7 (antibiotic* or anti-bacterial or antibacterial or (anti adj4 bacterial)).ti,ab,kw. (425175)

8 exp vancomycin/ or vancomycin derivative/ (75963)

9 van?om?cin.ti,ab,kw,rn. (80189)

10 exp rifampicin/ (80059)

11 rifamp??in.ti,ab,kw,rn. (83132)

12 exp gentamicin/ (95859)

13 gentam#cin.ti,ab,kw,rn. (99462)

14 exp meticillin/ (22727)

15 met??cillin*.ti,ab,kw,rn. (45463)

16 exp cefazolin/ (23856)

17 ce??azolin*.ti,ab,kw,rn. (24421)

18 exp antibiotic prophylaxis/ (26990)

19 exp staphylococcus/ or exp streptococcus/ (279482)

20 (staphylococcus aureus or staphylococcus epidermidis).ti,ab,kw. (110835)

21 s? aureus.ti,ab,kw. (40211)

22 s? epidermidis.ti,ab,kw. (5419)

23 (bacterial adj5 infection*).ti,ab,kw. (62753)

24 bacterem*.ti,ab,kw. (28575)

25 ((gram-negative adj4 bacterial adj4 infection*) or (gram-positive adj4 bacterial adj4 infection*)).ti,ab,kw. (1765)

26 staphylococ* infection*.ti,ab,kw. (4619)

27 ((catheter* or shunt* or prosthes*) adj4 infection*).ti,ab,kw. (15124)

28 sepsis.ti,ab,kw. (120941)

29 pyohemia*.ti,ab,kw. (4)

30 py?emia*.ti,ab,kw. (115)

31 septic?emia.ti,ab,kw. (21677)

32 blood poisoning*.ti,ab,kw. (25)

33 (circulatory adj3 (collaps or failure)).ti,ab,kw. (3161)

34 shock.ti,ab,kw. (199561)

35 toxemia*.ti,ab,kw. (3996)

36 bacterial infection/ or infection/ or bacterial meningitis/ or gram negative infection/ or gram positive infection/ or staphylococcus infection/ or streptococcus infection/ or endotoxemia/ or exp device infection/ (742628)

37 bacteremia/ or sepsis/ or septic shock/ or septicemia/ (216240)

38 1 or 2 or 5 (48510)

39 3 or 4 (331237)

40 38 and 39 (14764)

41 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 (1371513)

42 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 (1302104)

43 40 and 41 and 42 (909)

CONTRIBUTIONS OF AUTHORS

SA drafted the protocol. All authors participated in reviewing and editing the protocol.

DECLARATIONS OF INTEREST

SA - None

HB - None

EvL - None

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External sources

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