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De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock (Review)  
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De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock

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ABSTRACT

Background

Mortality rates among patients with sepsis, severe sepsis or septic shock are highly variable throughout different regions or services and can be upwards of 50%. Empirical broad-spectrum antimicrobial treatment is aimed at achieving adequate antimicrobial therapy, thus reducing mortality; however, there is a risk that empirical broad-spectrum antimicrobial treatment can expose patients to overuse of antimicrobials. De-escalation has been proposed as a strategy to replace empirical broad-spectrum antimicrobial treatment by using a narrower antimicrobial therapy. This is done by reviewing the patient's microbial culture results and then making changes to the pharmacological agent or discontinuing a pharmacological combination.

Objectives

To evaluate the effectiveness and safety of de-escalation antimicrobial treatment for adult patients diagnosed with sepsis, severe sepsis or septic shock caused by any micro-organism.

Search methods

In this updated version, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 10); MEDLINE via PubMed (from inception to October 2012); EMBASE (from inception to October 2012); LILACS (from inception to October 2012); Current Controlled Trials; bibliographic references of relevant studies; and specialists in the area. We applied no language restriction. We had previously searched the databases to August 2010.

Selection criteria

We planned to include randomized controlled trials (RCTs) comparing de-escalation (based on culture results) versus standard therapy for adults with sepsis, severe sepsis or septic shock. The primary outcome was mortality (at 28 days, hospital discharge or at the end of the follow-up period). Studies including patients initially treated with an empirical but not adequate antimicrobial therapy were not considered for inclusion.
Data collection and analysis

Two authors planned to independently select and extract data and to evaluate methodological quality of all studies. We planned to use relative risk (risk ratio) for dichotomous data and mean difference (MD) for continuous data, with 95% confidence intervals. We planned to use the random-effects statistical model when the estimate effects of two or more studies could be combined in a meta-analysis.

Main results

Our search strategy retrieved 493 studies. No published RCTs testing de-escalation of antimicrobial treatment for adult patients diagnosed with sepsis, severe sepsis or septic were included in this review. We found one ongoing RCT.

Authors’ conclusions

There is no adequate, direct evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis or septic shock. This uncertainty warrants further research via RCTs and the authors are awaiting the results of an ongoing RCT testing the de-escalation of empirical antimicrobial therapy for severe sepsis.

PLAIN LANGUAGE SUMMARY

Adjustment of antimicrobial agents for adults with sepsis, severe sepsis or septic shock

Broad-spectrum antimicrobial treatment is defined as the use of an antibiotic or a combination of antibiotics which act against a wide range of disease-causing bacteria. Broad-spectrum antimicrobial treatment can reduce mortality rates in patients with sepsis, severe sepsis or septic shock. Sepsis is a serious medical condition which is characterized by an inflammatory response to an infection that can affect the whole body. The patient may develop this inflammatory response to microbes in their blood, urine, lungs, skin or other tissues. However, there is a risk that empirical broad-spectrum antimicrobial treatment can expose patients to overuse of antimicrobials and increase the resistance of micro-organisms to treatment. De-escalation has been proposed as a means of adjusting initial, adequate broad-spectrum treatment by changing the antimicrobial agent or discontinuing an antimicrobial combination according to the patient's culture results (a means of identifying the microbe causing the infection). In this updated Cochrane review we searched the databases until October 2012. We found no published randomized controlled trials (RCTs). We found one ongoing RCT. There is no adequate or direct evidence on whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis or septic shock. Appropriate studies are needed to investigate the potential benefits proposed by de-escalation treatment.

BACKGROUND

Description of the condition

Sepsis is defined as a systemic inflammatory response to an infection (Bone 1992). Acute organ dysfunction caused by the infection is defined as severe sepsis, which when combined with persistent hypotension causes a condition defined as septic shock (Dellinger 2008). There are clinical and laboratory characteristics to be considered in the diagnosis of sepsis, severe sepsis or septic shock. These include fever, hypothermia, level of consciousness and inflammatory parameters (Levy 2003).

Irrespective of geographic and socio-economic circumstances, sepsis, severe sepsis or septic shock have been associated with mortality. In a cohort study involving 3147 patients admitted to intensive care units (ICU) in 24 European countries, the rate of sepsis was 37% (mortality rate 27%); 30% had severe sepsis (mortality rate 32%) and 15% had septic shock (mortality rate 54%) (Vincent 2006). Similar findings could be seen in North America (from 1993 to 2003) (Dombrovskiy 2007). In the latter study an alarming prevalence of 2,857,476 cases of severe sepsis was found among more than eight million patients with sepsis. Higher mortality rates have been observed in other countries, for example in Brazil (Silva 2004; Teles 2008). Moreover, other studies from different countries have shown that the most prevalent infectious agents responsible for sepsis and severe sepsis are Staphylococcus.
Before commencing antimicrobial therapy, it is necessary to obtain appropriate cultures in order to identify the pathogens responsible for the septic conditions. Factors that should be taken into account are that sampling should not delay the antimicrobial treatment in patients with severe sepsis; rapid sterilization of blood cultures can occur within a few hours after the first antibiotic dose (Dellinger 2008); and previous or concomitant antimicrobial administration can impair the culture results (Darby 1997). A broad-spectrum antimicrobial treatment is usually used to achieve adequate antibiotic therapy as soon as possible. This is because early and adequate antimicrobial therapy reduces mortality rates (ATS IDSA 2005; Harbarth 2003; Kumar 2006; Micek 2005; Proulx 2005). Unfortunately this approach can expose individuals to an overuse of antimicrobials. This is mainly because of emerging resistant pathogens, which increase the risk of inappropriate therapy (Leone 2007; Niederman 2006). Large pharmaceutical companies have recently decreased their antibiotic discovery efforts resulting in a dearth of resources being invested to target antibiotic resistance (IDSA 2004).

Strategies have been developed to solve the problems associated with the overuse of antimicrobials. For instance, a Cochrane systematic review offered favourable evidence for monotherapy (beta-lactam alone) as compared to combination antibiotic therapy (beta-lactam combined with aminoglycosides) (Paul 2006). According to Leone 2008, "restricting the use of antibiotics should remain the common rule" in order to minimize the chances for the emergence of multiresistant bacteria; and de-escalation is one such strategy.

Description of the intervention

De-escalation has been proposed by Kollef (Kollef 2006) and consists of the following.

1. Beginning treatment with an empirical broad-spectrum antimicrobial therapy, aiming to cover the probable infectious agent(s).
2. Changing the empirical and appropriate broad-spectrum antimicrobial to a narrower-spectrum antimicrobial therapy by one of two ways:
   • changing the antimicrobial agent;
   • discontinuing an antimicrobial combination.
3. A further strategy is to shorten the course of the antimicrobial therapy.

Culture results are a prerequisite for the use of de-escalation for patients with sepsis, severe sepsis or septic shock (Dellinger 2008; Höflken 2002) but the decision to de-escalate has to also be based on the clinical evolution of the patient.

Some evidence on antibiotic de-escalation is available for ventilator-associated pneumonia (ATS IDSA 2005; Singh 2000). However antibiotic de-escalation has been suggested by the ‘Surviving Sepsis Campaign’ for patients with sepsis, severe sepsis or septic shock based on poor quality evidence (Dellinger 2008).

How the intervention might work

Adequate antimicrobial therapy is associated with lower mortality rates in patients with sepsis, severe sepsis or shock septic (Harbarth 2003; McArthur 2004; Vallès 2003). The overuse of antimicrobials, usually characterized by broad spectrum antimicrobial therapies, may be related to adverse events, extra costs (Glowacki 2003) and the emergence of bacterial resistance (Leone 2008). Thus the use of an initial broad-spectrum antimicrobial regimen with appropriate coverage would need to be balanced against the withdrawal of unnecessary drugs. Therefore, de-escalation is essentially a proposed approach to minimize antimicrobial exposure, avoid the overuse of antibiotics, and to consequently minimize the adverse events and emergence of resistant micro-organisms (Rello 2004).

Why it is important to do this review

The main guideline on sepsis, the ‘Surviving Sepsis Campaign’ (Dellinger 2008), has suggested de-escalation as an option to avoid undesired manifestations associated with the overuse of antimicrobials. In view of the probable increase in de-escalation of antimicrobial therapy, the authors of this current systematic review intended to combine all existing evidence in order to improve the directions for future trials involving patients with sepsis, severe sepsis or septic shock caused by any micro-organism. The aim of this review was to assess the evidence from available randomized studies in order to improve practice in the area of sepsis.

OBJECTIVES

To evaluate the effectiveness and safety of antimicrobial de-escalation when compared with the maintenance of broad-spectrum therapy for adult patients diagnosed with sepsis, severe sepsis or septic shock caused by any micro-organism.

METHODS

Criteria for considering studies for this review
Types of studies
We planned to include randomized or quasi-randomized controlled trials.

Types of participants
We planned to include adult patients (aged 18 years and older) with sepsis, severe sepsis or septic shock caused by any microorganism.

Types of interventions
Our comparison groups of interest were as follows.
1. De-escalation: defined as changing an initially appropriate antimicrobial therapy from an empirical broad-spectrum characteristic to a narrower-spectrum one (by either changing the antimicrobial agent or by discontinuing an eventual antimicrobial combination, or both) according to culture results (Kollef 2001; Leone 2007; Niederman 2006) or clinical conditions.
2. Standard therapy: defined as the maintenance of an initial empirical broad-spectrum antimicrobial therapy (independent of whether the antimicrobial therapy was a combination or a single agent).
We also considered de-escalation defined as the shortening of the time course of the antimicrobial therapy (for example short-course versus long-course antimicrobial therapy), trial by trial, to see whether it fulfilled the conditions for this review.
We planned to consider comparison arms for analysis irrespective of the types of antimicrobial agents and possible combinations. Studies in which the patients were previously treated with an empirical but not adequate antimicrobial therapy were not considered for inclusion.

Types of outcome measures

Primary outcomes
1. Mortality at day 28
2. Mortality at hospital discharge or at the end of the follow-up period

Secondary outcomes
1. Hospital length of stay
2. Intensive care unit (ICU) length of stay
3. Adverse events (e.g., hepatotoxicity, nephrotoxicity)
4. Individual antimicrobial resistance
5. Environmental antimicrobial resistance (de Jonge 2003)
6. Re-infection

Search methods for identification of studies

Electronic searches
In our original review we searched the databases to August 2010. In this updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 9); MEDLINE via PubMed (from inception to October 2012); EMBASE (from inception to October 2012); and LILACS (from inception to October 2012).
We used the search terms and synonyms for “sepsis”, “severe sepsis”, “septic shock” (clinical conditions of interest), “antimicrobial therapy” and “de-escalation” (intervention of interest) together with specialized filters for randomized controlled trials for MEDLINE and EMBASE (Appendix 1; Appendix 2; Appendix 3).
We searched for ongoing trials on the Current Controlled Trials website (www.controlled-trials.com/).
We did not apply any language restriction.

Searching other resources
We searched the bibliographic references of relevant studies, irrespective of study design (narrative reviews, retrospective studies, etc) with the intention of finding cited randomized studies to be included in this review; as well as conference proceedings of relevant scientific societies, published in their official journals.
We contacted authors of relevant studies in the area for information on additional unpublished studies.

Data collection and analysis

Selection of studies
Two authors (BNGS and RBA) independently assessed the titles and abstracts of the identified articles to determine their potential relevance. We planned to resolve any disagreements by discussion with a third author (RS); this was not necessary for the first version of this systematic review. We planned to use the Kappa coefficient to formally test concordance between observers (Lattour 1997).

Data extraction and management
Two authors (BNGS and RBA) planned to independently extract data from each study using a data extraction form (see Appendix 4). We planned to resolve any disagreements by discussion with a third author (RS), but this was not necessary during preparation of the first version of this systematic review.
Assessment of risk of bias in included studies

Two authors (BNGS and RBA) planned to independently assess the methodological quality of included studies according to the study design, using the following items.

Selection bias
- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Were there systematic differences between the baseline characteristics of the groups that were compared?

Performance bias
- Were there systematic differences between groups in the care that was provided, or in exposure to factors other than the interventions of interest?

Detection bias
- Were there systematic differences between groups in how outcomes were determined?

Attrition bias
- Were incomplete outcome data adequately addressed?

Selective reporting bias
- Were reports of the study free of suggestion of selective outcome reporting?

Other bias
Was the study apparently free of other problems that could put it at a high risk of bias?

For each one of the above items, we planned to classify studies according to their risk of systematic error
- High risk: when the appropriate method to avoid systematic error (bias) was not met
- Moderate risk: when the appropriate method to avoid systematic error (bias) was not described or the information was not acquired by contacting the authors of the primary studies
- Low risk: when the appropriate method to avoid systematic error (bias) was met

Measures of treatment effect

For dichotomous variables, we planned to calculate the risk ratio (RR). For continuous variables, we planned to calculate the mean difference (MD) if the studies reported their results through the same variables measured with the same instruments (same units of measurement). On the other hand, when continuous data were relative to the same aspect in the patients but were measured with different instruments (and were not interchangeable units of measurement) it was intended to pool them by using standardized mean difference (SMD). The 95% confidence interval (95% CI) was to be determined for all statistical methods.

Unit of analysis issues

The unit of analysis was to be based on the individual patient. We had expected to find only parallel group study designs, not crossover studies. This is because of the natural history of sepsis, severe sepsis or septic shock. That is, the need to resolve the condition within a short time frame.

Dealing with missing data

For dichotomous data, we planned to use intention-to-treat analyses (ITT) by including all participants randomized to the intervention groups. For continuous data, we planned to try to contact the authors of the primary studies to supply missing information for participants who withdrew from the studies. We planned to analyse data based on the last individual data before the withdrawal. If we were unsuccessful in obtaining the missing data from the study authors, then we planned to perform available case analysis. If any studies did not report withdrawals, then we planned to assume that there were no withdrawals.

Assessment of heterogeneity

We planned to assess statistical heterogeneity using the $I^2$ statistic (Higgins 2002). We planned to assume a statistically significant heterogeneity between estimated effects of included studies when $I^2 > 50%$. We planned to use the random-effects model if significant heterogeneity was found.

Assessment of reporting biases

If there were a sufficient number of available studies, we had planned to assess publication bias by preparing a funnel plot. However, we were aware that asymmetry in the funnel plot can be associated with other reasons than publication bias (for example chance; real heterogeneity; clinical particularities inherent to each one of the included studies, such as patients at high risk of the outcome; etc).
**Data synthesis**

**Qualitative data**
We planned to synthesize and present qualitative information relative to methods, risk of bias, description of participants and outcomes measures and present them in the table 'Characteristics of included studies'.

**Quantitative data**
Irrespective of the nature of the data we planned to use the random-effects model because substantial clinical and methodological heterogeneities were expected, which by themselves could generate substantial statistical heterogeneity. When data from primary studies were not parametric (for example effects reported as medians, quartiles, etc) or are without sufficient statistical information (for example standard deviations, number of patients, etc) we planned to insert them into an 'Additional table'.

**Subgroup analysis and investigation of heterogeneity**
We intended to carry out subgroup analyses by type of de-escalation (guided by culture, stopping one drug of a combination, or guided by clinical signs). We planned to perform subgroup analysis according to: the type of infectious agent, fungi or bacteria; and site of infection (for example gastrointestinal, urinary, respiratory, abdominal, and surgical focus). We planned that heterogeneity in both the direction and length of estimate effect between subgroups would be assumed as a suspected causal relationship between them (the subgroup characteristic and the estimate effect).

**Sensitivity analysis**
We planned to use sensitivity analyses to examine the effects of study quality and any trials that were only reported as abstracts. This will be performed in updated versions of this systematic review.

**RESULTS**

**Description of studies**
See: Characteristics of excluded studies; Characteristics of ongoing studies.

**Results of the search**
Our sensitive search strategy yielded 158 references in MEDLINE (PubMed), 52 in EMBASE, 302 in The Cochrane Library, 12 studies in Current Controlled Trials, and two in LILACS; and one ongoing trial by contacting the specialists in the area. We did not retrieve any studies in the reference lists of the main articles. After discarding duplicates we identified 493 publications. Because of the lack of suitable studies in this area the two authors (BNGS and RBA), after screening the references by title and abstract, initially selected 71 studies. Although most were not RCTs they expressed the idea of a 'more restrictive' or 'rational' use of antimicrobial regimens or made suggestions about adjustment of an initial and empirical broad-spectrum antimicrobial therapy to a narrowed-spectrum antimicrobial therapy, irrespective of their inclusion criteria (participants) and study design. Of these 71 studies, 59 were not considered suitable because of their study design (Appendix 5). The 59 studies were comprised of 22 observational studies (cohort, case-control, or prevalence studies), one an in vitro study, one a guideline, and 34 narrative or systematic reviews (including the previous version of this own systematic review). We did not calculate the Kappa coefficient because none of these studies met our inclusion criteria. For more details, see Figure 1.
Figure 1. Study flow diagram.

- Number of records identified through database searching:
  - Current Controlled Trials: 12
  - EMBASE: 52
  - LILACS: 2
  - MEDLINE (PubMed): 156
  - The Cochrane Library: 302

- Additional records identified through other sources:
  - Reference lists of the main articles: 0
  - Contacting specialists in the area: 1

- Number of records after duplicates removed: n=493

- Number of records screened: n=493

- Publications either referring or suggesting the idea of "a more restrictive antimicrobial regimen" (including the de-escalation of antimicrobial therapy): n=71

- Full-text articles excluded:
  - Intervention not of interest: n=6
  - Intervention and clinical condition not of interest: n=5
  - Ongoing randomized controlled trials: n=1

- Randomized controlled trials assessed for eligibility: n=12

- Studies included in qualitative and quantitative synthesis: n=0
Included studies
We did not include any studies in this updated review.

Excluded studies
We excluded the remaining 12 references either because their interventions were not of interest (Bailey 1996; Bouadma 2010; Mahasa 2009; Masaoka 2000; Roberts 2009; Schroeder 2009) or because their interventions and inclusion criteria (clinical conditions) were not of interest to this review (Christ-Crain 2004; Horisberger 2004; Jensen 2008; van den Anker 1995; Vuori-Holopainen 2000) (see Characteristics of excluded studies). One study is an ongoing randomized controlled trial on the de-escalation of empirical antimicrobial therapy for severe sepsis (Leone 2012) and the authors of this systematic review are awaiting its results. Of the 12 studies we had paid special attention to, four studies (Bouadma 2010; Christ-Crain 2004; Jensen 2008; Schroeder 2009) were excluded because they randomized the patients to either:
1. monitoring by procalcitonin (inflammatory marker) levels, or
2. a control group.
The patients’ antibiotics were commenced or ceased based on procalcitonin concentrations. The patients were not randomized to have an initial empirical, broad-spectrum antimicrobial therapy which was adjusted according to their culture results or clinical condition. Therefore, these four studies were not considered suitable for inclusion in this review.

Risk of bias in included studies
There was no eligible study.

Allocation
This category was not evaluated since no eligible study was found.

Blinding
This category was not evaluated since no eligible study was found.

Incomplete outcome data
This category was not evaluated since no eligible study was found.

Selective reporting
This category was not evaluated since no eligible study was found.

Other potential sources of bias
This category was not evaluated since no eligible study was found.

Effects of interventions
There was no eligible study.

DISCUSSION

Summary of main results
We found no adequate, direct evidence as to whether de-escalation of antimicrobial agents is effective and safe for adults with sepsis, severe sepsis or septic shock.

Overall completeness and applicability of evidence
We hope the information available in this systematic review will encourage researchers and specialists to test the de-escalation of antimicrobial agents with the methodological rigour inherent in randomized controlled trials. Currently, there is no available evidence to recommend or not the de-escalation of antimicrobial agents in clinical practice for septic patients. This lack of evidence justifies future randomized controlled trials or cohort studies. However, some clinical and methodological particularities should be considered (for example new infectious focus, recurrence, any intercurrent event needing changes in the antimicrobial therapy, or unavailability of microbiological culture) to avoid additional risks of harms (for example worsening of clinical condition, mortality). We offer a simplified model of patient flow for future randomized trials in this area, see Figure 2.
Figure 2. A simplified patients’ flow for future randomized controlled trials testing the de-escalation of antimicrobial therapy for septic patients. Adapted with kind permission of David Moher from the figure in Moher 2005.
We suggest sample sizes for two hypothesis.

**Absence of difference in mortality between comparison groups (de-escalation versus control)**

- Baseline risk of 27% for mortality among septic patients (Vincent 2006)
- Assumed relative risk reduction of 10% for mortality in the de-escalation group, corresponding to 24% of mortality (risk difference between comparison groups 3%)

4599 patients would be needed for each one of the comparison groups, according to the formula \( n = \left[2P_C \cdot (1-P_C) \cdot (Z\alpha + \beta) \right]^2 \cdot (P_E - P_C)^{-2} \) (Pocock 1983), where \( P_C = 27\% \); \( P_E = 24\% \); \( Z\alpha = 1.96 \); \( Z\beta = 1.28 \).

**Reduction of mortality in the de-escalation group (indirect evidence obtained from observational study in ventilator-associated pneumonia)**

- Baseline risk of 27% for mortality among septic patients (Vincent 2006)
- Indirect evidence of relative risk reduction of 28% for mortality in the de-escalation group in patients with ventilator-associated pneumonia, corresponding to a mortality rate of 19% in the de-escalation group (risk difference between comparison groups of 8%) (Kollef 2006)

323 patients would be needed for each one of the comparison groups, according to the formula \( n = \left[P_E - (1-P_E) \cdot (Z\alpha + \beta)^2 \right] \cdot (P_E - P_C)^{-2} \) (Pocock 1983), where \( P_C = 27\% \); \( P_E = 19\% \); \( Z\alpha = 1.96 \); \( Z\beta = 1.28 \).

**Quality of the evidence**

We found a complete absence of direct evidence regarding the de-escalation of antimicrobial agents for adults with sepsis, severe sepsis or septic shock.

**Potential biases in the review process**

The high sensitivity of the search strategy we used in this systematic review should guarantee a low probability that we have missed any randomized controlled trials which would fulfil our inclusion criteria. Language bias was prevented by not imposing any language restriction. Other methodological issues of this review, such as data collection and analysis, cannot be judged since no adequate study could be found.

**Agreements and disagreements with other studies or reviews**

The World Health Organization and other health organizations have been encouraging the selection of interventions to minimize microorganisms that are resistant to antimicrobial agents, with important implications for world health and the economy (IDSA 2006; WHO 2002). Thus, several authors support the de-escalation of antibiotics as a reasonable strategy to achieve this aim besides the minor adverse events and costs (Heenen 2012; Masterton 2011; Morel 2010; Shime 2011). In a narrative review, Deresinski 2007 suggests the de-escalation of antimicrobial antibiotics in ICUs according to patients’ culture results and their clinical evolution. Available guidelines, specifically the ‘Surviving Sepsis Campaign’, have also suggested de-escalation of antimicrobial agents for adults with sepsis, severe sepsis or septic shock based on specialists’ opinions or indirect evidence (Dellinger 2008).

**Authors’ conclusions**

**Implications for practice**

There is no adequate evidence as to whether de-escalation of antimicrobial agents is, or is not, effective and safe for adults with sepsis, severe sepsis or septic shock.

**Implications for research**

The information available in this systematic review should encourage researchers and specialists to test the de-escalation of antimicrobial agents with the methodological rigour inherent in randomized controlled trials. This lack of information justifies future randomized controlled trials or cohort studies considering ethical, epidemiological and economical points of views. However, several clinical particularities as well as operational or methodological circumstances have to be better understood. Specific inclusion criteria and reasons for protocol deviations may be adopted to avoid additional risks of harms. Future trials can test for two hypothesis:

1. absence of difference in mortality between the de-escalation and the control groups (maintained empirical broad-spectrum antimicrobial therapy) \( (n \simeq 4600 \text{ patients for each of the comparison groups}) \);

2. relative risk reduction of 28% for mortality in the de-escalation group, considering the mortality baseline risk of 27% \( (n \simeq 323 \text{ for each of the comparison groups}) \).

The authors of this review are awaiting the results of an ongoing randomized controlled trial by Leone 2012.
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Douglas MD, Christianson K, Johnson J. The role of prophylactic antibiotics in reducing the incidence of surgical site infection.

Dreskena 2008

Erlandsson 2007

Filius 2002
Filius PM, Gyssens IC. Impact of increasing antimicrobial resistance on wound management.

Filius 2003
Filius PM, Gyssens IC. Impact of increasing antimicrobial resistance on wound management.

Fluckiger 2000

Galal 2010

Garnacho-Montero 2003

Glowacki 2003
De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock (Review)

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Gomes Silva 2010

Guillon 2010

Harbarth 2003

Heenen 2012

Higgins 2002

Higgins 2011

Hitt 1997

Höffken 2002

IDSA 2004

IDSA 2006
De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock (Review)

Moher 2005

Mol 2006

Morse 2010

Mutlu 2006

Napolitano 2009

Niederman 2006

Paul 2006

Pea 2009

Pocock 1983

Proulx 2005

Raich 1988
Raich DW, Bootman JL, McGhan WF. Association of length of stay and total hospital charges with antimicrobial use in an unspecified sepsis is an antimicrobial stewardship program (ASP). European Journal of Clinical Microbiology & Infectious Diseases 2011;30(7):853–5. [PUBMED: 21279532]

Liew YX, Chlebicki MP, Lee W, Hsu LY, Kwa AL. Use of procalcitonin (PCT) to guide discontinuation of antibiotic use in an unspecified sepsis is an antimicrobial stewardship program (ASP). European Journal of Clinical Microbiology & Infectious Diseases 2011;30(7):853–5. [PUBMED: 21279532]
De-escalation of antimicrobial treatment for adults with sepsis, severe sepsis or septic shock (Review)

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Rello 2004

RevMan 5.1

Richards 2005

Rodloff 2006

Sanchez 1997

Schierbeck 2007

Schuler 1994

Shani 2009

Shime 2011

Silva 2004

Singh 2000

Spies 2009

Teles 2008

Textoris 2011

Tripathi 2012

Vallés 2003

Vincent 2006

Welte 2004

West 2008

WHO 2002

Zaragoza 2008
empirical, preemptive or targeted therapy, which is the best in the different hosts? Therapeutics and Clinical Risk Management 2008;4(6):1261–80. [PUBMED: 19337433]

References to other published versions of this review

Silva 2010

* Indicates the major publication for the study
### Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey 1996</td>
<td>Intervention not of interest: single large iv dose (10 mg/kg) of gentamicin with a standard multiple dose regimen of gentamicin</td>
</tr>
<tr>
<td>Bouadma 2010</td>
<td>Intervention not of interest, patients were randomized to:</td>
</tr>
<tr>
<td></td>
<td>• group I, to be monitored by an inflammatory marker (procalcitonin), and thus the antibiotics were started or stopped based on predefined cut-off ranges of procalcitonin concentrations;</td>
</tr>
<tr>
<td></td>
<td>• group II, control group (antibiotics according to present guidelines). The patients were not randomized to have an initial empirical and broad-spectrum antimicrobial therapy, adjusted according to the culture results or clinical condition</td>
</tr>
<tr>
<td>Christ-Crain 2004</td>
<td>Intervention not of interest: patients randomized to be monitored by inflammatory marker (procalcitonin) or control group. The patients were not randomized to have their antimicrobial therapy adjusted according to the culture results or clinical condition</td>
</tr>
<tr>
<td></td>
<td>Clinical condition out of area of interest: ICU patients with no obvious site of Infection</td>
</tr>
<tr>
<td>Horisberger 2004</td>
<td>Interventions not of interest: routine sepsis work up versus intervention strategy with additional cytokine measurements</td>
</tr>
<tr>
<td></td>
<td>Clinical condition not of interest: paediatric patients.</td>
</tr>
<tr>
<td>Jensen 2008</td>
<td>Interventions not of interest: procalcitonin measurements.</td>
</tr>
<tr>
<td></td>
<td>Clinical condition out of area of interest: ICU patients.</td>
</tr>
<tr>
<td>Mabasa 2009</td>
<td>Intervention out of area of interest: participants with septic shock were randomized to have renally adjusted dosage of antibiotics</td>
</tr>
<tr>
<td>Masaoka 2000</td>
<td>Interventions out of area of interest: intravenous immunoglobulin in combination therapy with antibiotics versus antibiotics monotherapy</td>
</tr>
<tr>
<td>Roberts 2009</td>
<td>Intervention out of area of interest: different daily doses of piperacillin-tazobactam by bolus dosing or continuous infusion</td>
</tr>
<tr>
<td>Schroeder 2009</td>
<td>Intervention out of area of interest, patients were randomized to:</td>
</tr>
<tr>
<td></td>
<td>1. be monitored by inflammatory marker (procalcitonin).</td>
</tr>
<tr>
<td></td>
<td>2. control group (absence of monitoring by inflammatory markers).</td>
</tr>
<tr>
<td>van den Anker 1995</td>
<td>Intervention not of interest (once-daily versus twice-daily administration of ceftazidime), clinical condition not of interest (preterm infants).</td>
</tr>
<tr>
<td>Vuori-Holopainen 2000</td>
<td>Interventions out of area of interest: procaine penicillin intramuscularly (narrow-spectrum antimicrobial) versus cefuroxime intravenously (broad-spectrum antimicrobial) for 4 to 7 days</td>
</tr>
<tr>
<td></td>
<td>Clinical condition out of area of interest: common infections of childhood</td>
</tr>
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</table>
### Characteristics of ongoing studies  
*ordered by study ID*

**Leone 2012**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>De-escalation of Empirical Antimicrobial Therapy Study in Severe Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Open label randomized controlled trial</td>
</tr>
</tbody>
</table>
| Participants        | - Major subject.  
                      | - Subject having a sepsis engraves (burns) defined according to the following criteria during the initiation of the probability antibiotic treatment:  
                      |   - criteria of SIRS \[14\], and  
                      |   - a suspected infection, and  
                      |   - a failure of organ: low blood pressure, respiratory failure, coma, hepatic insufficiency, renal insufficiency, thrombopenia, spontaneous extension of the TCA.  
                      | - Subject for which an antibiotic treatment was begun within 6 hours following the diagnosis of sepsis engraves (burns).  
                      | - Subject for which taking the microbiological aim was made within 48 hours following the diagnosis of sepsis. |
| Interventions       | 1. Experimental: a strategy based on de-escalation intervention. Procedure: streamlining of the empirical antimicrobial therapy  
                      | 2. Active comparator: a conservative strategy intervention. Procedure: continuation of the empirical antimicrobial therapy |
| Outcomes            |                                                                 |
| Starting date       | October 2011                                                          |
| Contact information | Marc Leone marc.leone@ap-hm.fr                                       |
| Notes               |                                                                       |
DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search for MEDLINE (via PubMed)

#1 (Sepsis [Mesh]) OR (Septicemia) OR (Blood stream infection) OR (Septic shock) OR (Endotoxic Shock) OR (Toxic Shock) OR (Severe sepsis)

#2 (Anti-Bacterial agents [Mesh]) OR (antibiotic therapy) OR (Anti Bacterial) OR (Antibacterial) OR (Anti-Mycobacterial) OR (Bacterial) OR (Anti-Mycobacterial) OR (Anti Mycobacterial) OR (Antimycobacterial) OR (Antibiotics) OR (Antibiotic) OR (Bacteriocidal) OR (Bacteriocides) OR (Antifungal agents [Mesh]) OR (Anti-fungal) OR (Antifungic) OR (Anti-fungal) OR (Fungicides) OR (Chemotherapies) OR (Chemotherapy) OR (Drug Therapies) OR (Drug Therapy [Mesh]) OR (Pharmacotherapies) OR (Pharmacotherapy)

#3 (Adequacy) OR (Adequate) OR (Extended-spectrum) OR (Appropriate) OR (Empiric) OR (Empirical) OR (Broad-spectrum) OR (Broad spectrum)

#4 (De-escalation) OR (De escalation) OR (Deescalate) OR (Narrow spectrum) OR (Narrow-spectrum) OR (Narrowed spectrum) OR (Narrowed-spectrum) OR (Narrowing) OR (Adjustment) OR (Adjust) OR (Tailoring) OR (Tailored) OR (Tailor) OR (Downgrading) OR (Discontinue) OR (discontinuing)

#5 ((randomized controlled trial [pt]) OR (controlled clinical trial [pt]) OR (randomized [tiab]) OR (placebo [tiab]) OR (drug therapy [sh]) OR (randomly [tiab]) OR (trial [tiab]) OR (groups [tiab])) AND (humans[mh])

#6 #1 AND #2 AND #3 AND #4 AND #5

Appendix 2. EMBASE via Ovid

1 sepsis[emtree]/exp OR sepsis OR ‘septicemia’/exp OR septicemia OR (‘blood’/exp OR blood AND stream AND (‘infection’/exp OR infection)) OR (septic AND (‘shock’/exp OR shock)) OR (endotoxic AND (‘shock’/exp OR shock)) OR (toxic AND (‘shock’/exp OR shock)) OR (severe AND (‘sepsis’/exp OR sepsis))

2 ‘antiinfective agent[emtree]’ OR ‘anti bacterial’ OR (‘antibiotic’ OR ‘antibiotic’/exp OR antibiotic AND (‘therapy’ OR ‘therapy’/exp OR therapy)) OR (anti AND bacterial) OR antibacterial OR bactericidal OR ‘antimycobacterial’ OR (anti AND mycobacterial) OR (anti mycobacterial) OR antimycobacterial OR ‘antibiotics’ OR ‘antibiotics’/exp OR antibiotics OR ‘antibiotic’ OR ‘antibiotic’/exp OR antibiotic OR bactericidial OR bacteriocides OR ‘antifungal’ OR ‘antifungal’/exp OR antifungal OR ‘antifungal’ OR antifungic OR ‘antifungal’ OR fungicides OR chemotherapy OR ‘chemotherapy’/exp OR chemotherapy OR (‘drug’ OR ‘drug’/exp OR drug AND therapies) OR (‘drug’ OR ‘drug’/exp OR drug AND (‘therapy’ OR ‘therapy’/exp OR therapy)) OR pharmacotherapies OR ‘pharmacotherapy’/exp OR pharmacotherapy

3 adequacy OR adequate OR ‘extended spectrum’ OR appropriate OR empiric OR empirical OR ‘broad spectrum’ OR (broad AND (‘spectrum’/exp OR spectrum))

4 narrow AND (‘spectrum’/exp OR spectrum) OR ‘narrow spectrum’ OR (narrower AND (‘spectrum’/exp OR spectrum)) OR ‘narrower spectrum’ OR ‘narrowed spectrum’ OR (narrowed AND (‘spectrum’/exp OR spectrum)) OR (de AND escalation) OR narrowing ORdesescalate OR ‘de escalation’ OR ‘adjustment’/exp OR adjustment OR adjust OR tailoring OR tailored OR tailor OR downgrading OR discontinue OR discontinuing OR switch

5 (random$) OR (factorial$) OR (crossover$) OR (cross over$) OR (cross-over$) OR (placebo$) OR (double$ adj blind$) OR (single$ adj blind$) OR (assign$) OR (allocat$) OR (volunteer$) OR (crossover-procedure) OR (double-blind procedure) OR (randomized controlled trial) OR (single-blind procedure)

6 #1 and #2 and #3 and #4 and #5
Appendix 3. Search strategy for LILACS (via Bireme)

#1 (Sepsis) OR (Septicemia) OR (Blood stream infection) OR (Septic shock) OR (Endotoxic Shock) OR (Toxic Shock) OR (Severe sepsis)

#2 ((Anti-Bacterial agents) OR (antibiotic therapy) OR (Anti Bacterial) OR (Antibacterial) OR (Anti-Mycobacterial) OR (Bactericidal) OR (Anti-Mycobacterial) OR (Anti Mycobacterial) OR (Antimycobacterial) OR (Antibiotics) OR (Antibiotic) OR (Bacteriocidal) OR (Bacteriocides) OR (Antifungal agents) OR (Anti-fungal) OR (Antifungic) OR (Anti-fungic) OR (Fungicides) OR (Chemotherapies) OR (Chemotherapy) OR (Drug Therapies) OR (Drug Therapy) OR (Pharmacotherapies) OR (Pharmacotherapy) AND ((Adequacy) OR (Adequate) OR (Extended-spectrum) OR (Appropriate) OR (Empiric) OR (Empirical) OR (Broad-spectrum) OR (Broad spectrum))

#3 (De-escalation) OR (De escalation) OR (Deescalate) OR (Narrow spectrum) OR (Narrow-spectrum) OR (Narrower spectrum) OR (Narrower-spectrum) OR (Narrowed-spectrum) OR (Narrowed spectrum) OR (Narrowing) OR (Adjustment) OR (Adjust) OR (Tailoring) OR (Tailored) OR (Tailor) OR (Downgrading) OR (Discontinue) OR (discontinuing)

#4 #1 and #2 and #3

Appendix 4. Data extraction form

Study Selection, Quality Assessment & Data Extraction Form

<table>
<thead>
<tr>
<th>First author</th>
<th>Journal/Conference Proceedings etc</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Study eligibility**

<table>
<thead>
<tr>
<th>RCT/Quasi-randomized</th>
<th>Participants with sepsis, severe sepsis or septic shock</th>
<th>De-escalation*</th>
<th>Relevant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes / No / Unclear</td>
<td>Yes / No / Unclear</td>
<td>Yes / No / Unclear</td>
<td>Yes / No / Unclear</td>
</tr>
</tbody>
</table>

* De-escalation, as defined by the changing the empirical and adequate broad spectrum to a narrower spectrum antimicrobial therapy by changing the antimicrobial agent or discontinuing an antimicrobial combination

Do not proceed if any of the above answers are ‘No’. If study to be included in ‘Excluded studies’ section of the review, record below the information to be inserted into ‘Table of excluded studies’
Freehand space for comments on study design and treatment:

References to trial (Secondary references)

Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one Study ID in RevMan.

<table>
<thead>
<tr>
<th>Code each paper</th>
<th>Author(s)</th>
<th>Journal/Conference Proceedings etc</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><em>The paper listed above</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td><em>Further papers</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Participants and trial characteristics

**Participant characteristics**

<table>
<thead>
<tr>
<th>Further details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, median, range, etc)</td>
</tr>
<tr>
<td>Sex of participants (numbers / %, etc)</td>
</tr>
<tr>
<td>Disease status / type, etc (if applicable)</td>
</tr>
<tr>
<td>Undelying disease</td>
</tr>
<tr>
<td>% of appropriate empirical antibiotic treatment</td>
</tr>
<tr>
<td>Setting</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

**Trial characteristics**

Methodological quality
### Allocation of intervention

State here method used to generate allocation and reasons for grading

<table>
<thead>
<tr>
<th>Grade (circle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate (Random)</td>
</tr>
<tr>
<td>Inadequate (e.g. alternate)</td>
</tr>
<tr>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Concealment of allocation

Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding

State here method used to conceal allocation and reasons for grading

<table>
<thead>
<tr>
<th>Grade (circle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate</td>
</tr>
<tr>
<td>Inadequate</td>
</tr>
<tr>
<td>Unclear</td>
</tr>
</tbody>
</table>

### Blinding

Person responsible for participants care

<table>
<thead>
<tr>
<th>Yes / No</th>
</tr>
</thead>
</table>

Participant

<table>
<thead>
<tr>
<th>Yes / No</th>
</tr>
</thead>
</table>

Outcome assessor

<table>
<thead>
<tr>
<th>Yes / No</th>
</tr>
</thead>
</table>

Other (please specify)

<table>
<thead>
<tr>
<th>Yes / No</th>
</tr>
</thead>
</table>

### Intention-to-treat (consider each one of the outcomes)

An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants entering trial</td>
</tr>
<tr>
<td>15% or fewer excluded</td>
</tr>
<tr>
<td>More than 15% excluded</td>
</tr>
</tbody>
</table>
Not analysed as ‘intention-to-treat’

Unclear

**Were withdrawals described?**  Yes ?  No ?  not clear ?

Discuss if appropriate

**Data extraction**

**Outcomes relevant to your review**
Copy and paste from ‘Types of outcome measures’

<table>
<thead>
<tr>
<th>Reported in paper (circle)</th>
</tr>
</thead>
</table>

**Primary outcomes**

1) mortality.  
2) hospital length stay;  
3) intensive care unit (ICU) length stay

<table>
<thead>
<tr>
<th>Yes / No</th>
</tr>
</thead>
</table>

**Secondary outcomes**

1) adverse events (e.g., hepatotoxicity, nephrotoxicity);  
2) individual antimicrobial resistance;  
3) environmental antimicrobial resistance  
4) re-infection

<table>
<thead>
<tr>
<th>Yes / No</th>
</tr>
</thead>
</table>
### For Continuous data

<table>
<thead>
<tr>
<th>Code of paper</th>
<th>Outcomes (rename)</th>
<th>Unit of measurement</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Details if outcome only described in text</th>
</tr>
</thead>
<tbody>
<tr>
<td>A etc</td>
<td>1) Mean time to mortality.</td>
<td></td>
<td>n Mean (SD)</td>
<td>n Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2) Mean hospital length stay;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Mean intensive care unit (ICU) length stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### For Dichotomous data

<table>
<thead>
<tr>
<th>Code of paper</th>
<th>Outcomes (rename)</th>
<th>Intervention group (n)</th>
<th>Control group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n = number of participants, not number of events</td>
<td>n = number of participants, not number of events</td>
</tr>
</tbody>
</table>

**Primary outcomes**

1) mortality.

2) hospital length stay

3) intensive care unit (ICU) length stay

**Secondary outcomes**

1) adverse events (e.g., hepatotoxicity, nephrotoxicity)

2) individual antimicrobial resistance

3) environmental antimicrobial resistance
(Continued)

| 4) re-infection |

Other information which you feel is relevant to the results
Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review.

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports of potentially eligible trials not already identified for this review?

<table>
<thead>
<tr>
<th>First author</th>
<th>Journal / Conference</th>
<th>Year of publication</th>
</tr>
</thead>
</table>

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list contact name and details

Trial characteristics

<table>
<thead>
<tr>
<th>Single centre / multicentre</th>
<th>Further details</th>
</tr>
</thead>
</table>

| Country / Countries | |
|---------------------||
### Appendix 5. Studies referring to the idea of 'de-escalation' of antimicrobial agents for diverse clinical conditions

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
</tr>
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<tbody>
<tr>
<td>1 Adukauskiene 2006</td>
<td>Narrative review</td>
</tr>
<tr>
<td>2 Alexandraki 2008</td>
<td>Observational study</td>
</tr>
<tr>
<td>3 Apisarnthanarak 2004</td>
<td>Observational study</td>
</tr>
<tr>
<td>4 Bagshaw 2009</td>
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<td>Balk 2004</td>
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<td>Berild 2006</td>
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</table>
53 Shime 2011 Observational study
54 Spies 2009 Observational study
55 Teotoris 2011 Narrative review
56 Tripathi 2012 Narrative review
57 Welte 2004 Narrative review
58 West 2008 Narrative review
59 Zaragoza 2008 Narrative review

WHAT'S NEW
Last assessed as up-to-date: 31 October 2012.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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<tbody>
<tr>
<td>18 February 2013</td>
<td>New citation required but conclusions have not changed</td>
<td>We found no published randomized controlled trials (RCTs). We found one ongoing RCT (Leone 2012).</td>
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<tr>
<td>18 February 2013</td>
<td>New search has been performed</td>
<td>In the previous version (Silva 2010) we searched the databases until August 2010. In this updated version, we reran the searches until October 2012</td>
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</tbody>
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CONTRIBUTIONS OF AUTHORS
Conceiving the review: Brenda NG Silva (BGNS), Reinaldo Salomão (RS)
Co-ordinating the review: BNGS
Screening search results: BNGS, Régis B Andriolo (RBA)
Organizing retrieval of papers: BNGS
Screening retrieved papers against inclusion criteria: BNGS, RBA, RS
Appraising quality of papers: BNGS, RBA, Álvaro N Atallah (ANA)
Abstracting data from papers: BNGS, RBA
Writing to authors of papers for additional information: BNGS
Providing additional data about papers: BNGS
Obtaining and screening data on unpublished studies: BNGS, RS
Data management for the review: BNGS
Entering data into Review Manager (RevMan 5.1): BNGS, RBA
RevMan statistical data: BNGS, RA, ANA
Other statistical analysis not using RevMan: RBA
Interpretation of data: BNGS, RBA, ANA
Statistical inferences: BNGS, RBA
Writing the review: BNGS, RS, ANA
Guarantor for the review (one author): BNGS
Person responsible for reading and checking review before submission: BNGS, RS, ANA

DECLARATIONS OF INTEREST
Brenda NG Silva: none known
Régis B Andriolo: none known
Álvaro N Atallah: none known
Reinaldo Salomão: none known

SOURCES OF SUPPORT

Internal sources
• CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brazil.

External sources
• No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
We inserted two new items in the Assessment of risk of bias in included studies according to the updated Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011): selective reporting bias and other bias.

The comparison group was inserted into the objective. Thus, the objective was changed from 'To evaluate the effectiveness and safety of antimicrobial de-escalation for adult patients diagnosed with sepsis, severe sepsis or septic shock caused by any micro-organism' to 'To evaluate the effectiveness and safety of antimicrobial de-escalation when compared with the maintenance of broad-spectrum therapy for adult patients diagnosed with sepsis, severe sepsis or septic shock caused by any micro-organism'.

The filter for randomized controlled trials previously planned to be used in the LILACS database was removed from the search strategy.
INDEX TERMS

Medical Subject Headings (MeSH)
*Withholding Treatment; Anti-Bacterial Agents [*administration & dosage]; Sepsis [*drug therapy]; Shock, Septic [drug therapy]

MeSH check words
Adult; Humans