



Cochrane
Library

Cochrane Database of Systematic Reviews

Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults (Review)

Siddiqui S, Razzak J

Siddiqui S, Razzak J.

Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults.

Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD007081.

DOI: [10.1002/14651858.CD007081.pub2](https://doi.org/10.1002/14651858.CD007081.pub2).

www.cochranelibrary.com

Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults
(Review)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

| | |
|---|----|
| ABSTRACT | 1 |
| PLAIN LANGUAGE SUMMARY | 2 |
| BACKGROUND | 3 |
| OBJECTIVES | 3 |
| METHODS | 3 |
| RESULTS | 4 |
| Figure 1. | 5 |
| DISCUSSION | 5 |
| AUTHORS' CONCLUSIONS | 6 |
| ACKNOWLEDGEMENTS | 6 |
| REFERENCES | 7 |
| APPENDICES | 7 |
| WHAT'S NEW | 11 |
| HISTORY | 11 |
| CONTRIBUTIONS OF AUTHORS | 11 |
| DECLARATIONS OF INTEREST | 12 |
| SOURCES OF SUPPORT | 12 |
| DIFFERENCES BETWEEN PROTOCOL AND REVIEW | 12 |
| INDEX TERMS | 12 |

[Intervention Review]

Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults

Shahla Siddiqui¹, Junaid Razzak²

¹Department of Anesthesiology, Aga Khan University Hospital, Karachi, Pakistan. ²Department of Emergency Medicine, Aga Khan University Hospital, Karachi, Pakistan

Contact: Shahla Siddiqui, Department of Anesthesiology, Aga Khan University Hospital, Stadium Road, PO Box 3500, Karachi, 74800, Pakistan. shahlasi@yahoo.com.

Editorial group: Cochrane Emergency and Critical Care Group.

Publication status and date: Edited (no change to conclusions), published in Issue 12, 2018.

Citation: Siddiqui S, Razzak J. Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD007081. DOI: [10.1002/14651858.CD007081.pub2](https://doi.org/10.1002/14651858.CD007081.pub2).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Severe sepsis and septic shock have recently emerged as particularly acute and lethal challenges amongst critically ill patients presenting to the emergency department (ED). There are no existing data on the current practices of management of patients with severe sepsis comparing early versus late administration of appropriate broad spectrum antibiotics as part of the early goal-directed therapy that is commenced in the first few hours of presentation.

Objectives

To assess the difference in outcomes with early compared to late administration of antibiotics in patients with severe sepsis in the pre-intensive care unit (ICU) admission period. We defined early as within one hour of presentation to the ED.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2009); MEDLINE (1990 to February 2010); EMBASE (1990 to February 2010); and ISI web of Science (February 2010). We also searched for relevant ongoing trials in specific websites such as www.controlled-trials.com; www.clinicalstudyresults.org; and www.update-software.com. We searched the reference lists of articles. There were no constraints based on language or publication status.

Selection criteria

We planned to include randomized controlled trials of early versus late broad spectrum antibiotics in adult patients with severe sepsis in the ED, prior to admission to the intensive care unit.

Data collection and analysis

Two authors independently assessed articles for inclusion.

Main results

We found no studies that satisfied the inclusion criteria.

Authors' conclusions

Based on this review we are unable to make a recommendation on the early or late use of broad spectrum antibiotics in adult patients with severe sepsis in the ED pre-ICU admission. There is a need to do large prospective double blinded randomized controlled trials on the efficacy of early (within one hour) versus late broad spectrum antibiotics in adult severe sepsis patients. Since it makes sense to start

Early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults (Review)

1

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

antibiotics as soon as possible in this group of seriously ill patients, administering such antibiotics earlier as opposed to later is based on anecdotal suboptimal evidence.

PLAIN LANGUAGE SUMMARY

To assess the optimal of timing of administering antibiotics to sepsis patients in the emergency department

Sepsis is a serious medical condition characterized by an inflammatory response to an infection that can affect the whole body. The patient may develop an inflammatory response to microbes in their blood, urine, lungs, skin, or other tissues. Sepsis is a serious condition with a very high death rate if left untreated. Most sepsis patients require antibiotics and admission to an intensive care unit (ICU). How soon broad spectrum antibiotics should be delivered is as yet unclear. Broad spectrum antimicrobial treatment is defined as a combination of antibiotics which act against a wide range of disease-causing bacteria, used to reduce mortality rates in patients with sepsis, severe sepsis or septic shock. We carried out a systematic review of the literature by searching key databases for high quality published and unpublished material on the timing of antibiotics in the emergency department prior to ICU admission. Our searches revealed no randomized controlled trials (RCTs) on the timing of broad spectrum antibiotic treatment in this population. We conclude that there is a need to carry out observational cohort studies, in the absence of RCTs, even if they lack the precision of RCTs. We also conclude that the earlier the antibiotics are administered the better. It is important to realize that the clock starts ticking when the patient arrives in the ED and stops once the antibiotic is started. The pre-intensive care unit period is the time spent in the ward or ED prior to being admitted to the ICU, where most patients with severe sepsis are admitted. The review was purposefully very specific as it is focused only on patients with severe sepsis and in finding only RCTs. The absence of these may imply, in itself, the complicated nature of the study question as it may be ethically wrong to randomize such patients to a seemingly inferior treatment arm.

BACKGROUND

The mortality rate for patients with severe sepsis is generally high. The principles of treatment and the approach to sepsis are timely recognition and early treatment. Appropriate antibiotics and source control are the cornerstones of treatment.

Patients who are admitted to the emergency department (ED) with severe sepsis are often not given appropriate broad spectrum antibiotics, as set out in the Surviving Sepsis Guidelines (Dellinger 2008) developed by the Society of Critical Care Medicine. These patients subsequently arrive in the intensive care unit (ICU) in a moribund state with profound shock and multi-organ failure (Besselink 2009). A variety of factors may contribute to this state. These include how long the infection has been present, other host factors (such as age, general health status etc.) and how long it takes to reach an ED. Better understanding of the pathophysiology of sepsis has led to several recommendations aimed at early and aggressive management as an integral part of improving outcomes (Nguyen 2006). The biggest challenge with complicated infections is early recognition of the problem (Bochud 2004).

Standardized regimens using either monotherapy or combination therapy have proven their efficacy, as shown in recent recommendations from large-scale prospective studies done in western countries (Adler 2005; Blot 2005). More recent literature points at worse outcomes when appropriate broad spectrum antibiotics are delayed, that is after the first hour of admission (Kumar 2006). This evidence is for septic shock patients, however, and not those with severe sepsis. We set out to review the literature for evidence in patients with severe sepsis. Patients who are admitted with severe sepsis may eventually arrive in ICU in a non-salvageable state, partly due to a delay in administration of antibiotics (Tsolia 2003). The Surviving Sepsis Campaign (Dellinger 2008; Rivers 2006) was created in 2004 and incorporated evidence-based guidelines to reduce mortality from severe sepsis and septic shock (Morimatsu 2004). Our review specifically looked at the timing of administration of antibiotics.

As the mechanisms of sepsis become better defined, many evidence-based recommendations centred on pathophysiological principles indicate that early, systematic supportive therapy can improve outcomes, most notably goal-directed therapy that includes early identification, aggressive fluid resuscitation and broad spectrum antibiotics (Morimatsu 2004). The recommendations for low-dose hydrocortisone and activated protein C (Grimaldi 2004) to disrupt inflammatory cascades and favourably influence the course of the disease may be impractical and expensive in developing countries. Efforts are required to better define nationwide epidemiology and treatment practices for severe sepsis (Dellinger 2004). We planned to look at the timing of administration of broad spectrum antibiotics in the pre-intensive care setting to see if early (within one hour of presentation), appropriate broad spectrum antibiotics changed the mortality rate of patients with severe sepsis (Fadel 2008; Kula 2009). The economic aspect of such studies and decisions are also an integral part of the outcomes for this review.

OBJECTIVES

The objective of this review was to assess the difference in outcomes with early compared to late administration of antibiotics

in patients with severe sepsis. We defined 'early' as within one hour of presentation to the emergency department (ED).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs).

Only those studies in which the difference between the two arms was the timing of antibiotics, and not any other aspect of intervention, were to be included.

Types of participants

We planned to include all patients above the age of 16 years presenting to ED with 'severe sepsis' diagnosed according to the current Society of Critical Care Medicine (SCCM) definitions (Montravers 2006), that is the systemic inflammatory response syndrome (SIRS) criteria plus organ failure or haemodynamic instability.

We planned to exclude paediatric patients and pregnant women as other confounding factors such as microbial heterogeneity may obscure the results. Also, the surviving sepsis guidelines differ for a paediatric population. We also excluded 'septic shock' and 'early sepsis' patients as early broad spectrum antibiotics are a foregone conclusion in one and not recommended so soon in another.

Types of interventions

Early (within one hour of ED admission) versus late (defined as greater than one hour after admission) administration of broad spectrum antibiotics.

Late administration of antibiotics was independent of microbiology cultures, waiting for cultures, or both.

We did not study the types of antibiotics used.

Types of outcome measures

Primary outcomes

1. Mortality at 28 days
2. Length of stay in hospital

Secondary outcomes

1. Development of multi-organ failure (such as renal failure, hepatic insufficiency, coma etc)
2. Length of ICU stay

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 6), see [Appendix 1](#); Ovid MEDLINE (from 1990 to February 2010), see [Appendix 2](#); EMBASE via Ovid (1990 to February 2010), see [Appendix 3](#); and the ISI Web of Science (1990 to February 2010) see [Appendix 4](#). We started the searches from 1990 as the 'Surviving Sepsis' campaign formulated the guidelines of early, goal-directed therapy then, which included early antibiotics. Literature from before then would have been out of date with regard to current guidelines.

For our subject search we combined the "terms for severe sepsis" AND "terms for antibiotics" AND "timing" and "terms for ICU" AND (RCT filter). We combined the MEDLINE search strategy with the Cochrane highly sensitive search strategy for identifying RCTs, contained in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

We searched for relevant ongoing trials on specific websites:

- 1) www.controlled-trials.com;
- 2) www.clinicalstudyresults.org;
- 3) www.update-software.com.

Searching other resources

We identified trials by manually searching abstracts of relevant conference proceedings; checking the reference list of relevant articles; contacting relevant trial authors to identify any additional studies; and contacting relevant hospitals and pharmaceutical companies for published and unpublished reports.

We did not apply language or publication restrictions.

Data collection and analysis

Trial identification

We (SS and JR) independently scanned the titles and abstracts of reports identified by the electronic searches, manual handsearching, and through contact with experts and trial authors.

Trial selection

We independently selected trials that met the inclusion criteria using a checklist designed specifically for this purpose.

Quality assessment

We judged the quality of trials by following the guidelines set out in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008), on the basis of the following.

1. Method of randomization.
2. Method of allocation concealment:
 - i. low risk of bias - adequate allocation concealment i.e. central randomization or equivalent, described fully;
 - ii. moderate risk of bias - unclear allocation concealment, the author did not give details of concealment (randomization);
 - iii. high risk of bias - inadequate allocation concealment, such as changes to randomization.
3. Blinding of treatment or outcome assessment.
4. Completeness of follow up.

Data extraction

We (SS and JR) planned to independently extract data using the data extraction form given in Grimaldi 2004 (see Appendix

5). We planned to resolve any disagreements by discussion. We were not blinded with regard to the names of the study authors, investigators, institutions and results. We intended to identify the excluded trials and list the reasons for exclusion.

Statistics

With help from the Statistics Department of Aga Khan University, Pakistan, we were to review the data extracted from the trials on population, intervention and outcomes first qualitatively and then quantitatively using the Cochrane Collaboration's software Review Manager (RevMan 5.0).

We planned to base quantitative analyses on intention-to-treat results. In the case of clinical heterogeneity we would not pool the results.

We planned to explore clinical and statistical heterogeneity (the latter using the I^2 statistic) (Higgins 2008).

We planned to perform a meta-analysis with a sensitivity analysis based on trial quality. We planned to undertake the following subgroup analyses based on:

1. site of infection;
2. type of pathogen;
3. whether patients had already received antibiotics outside the hospital;
4. comorbidities that lead to immunosuppression, such as diabetes mellitus.

Patients with intra-abdominal sepsis are often taken to the operating room straight away and so may not receive antibiotics until during the procedure. Patients who received antibiotics outside the hospital may not be given a repeat dose or may have microbiological cultures that are misrepresentative.

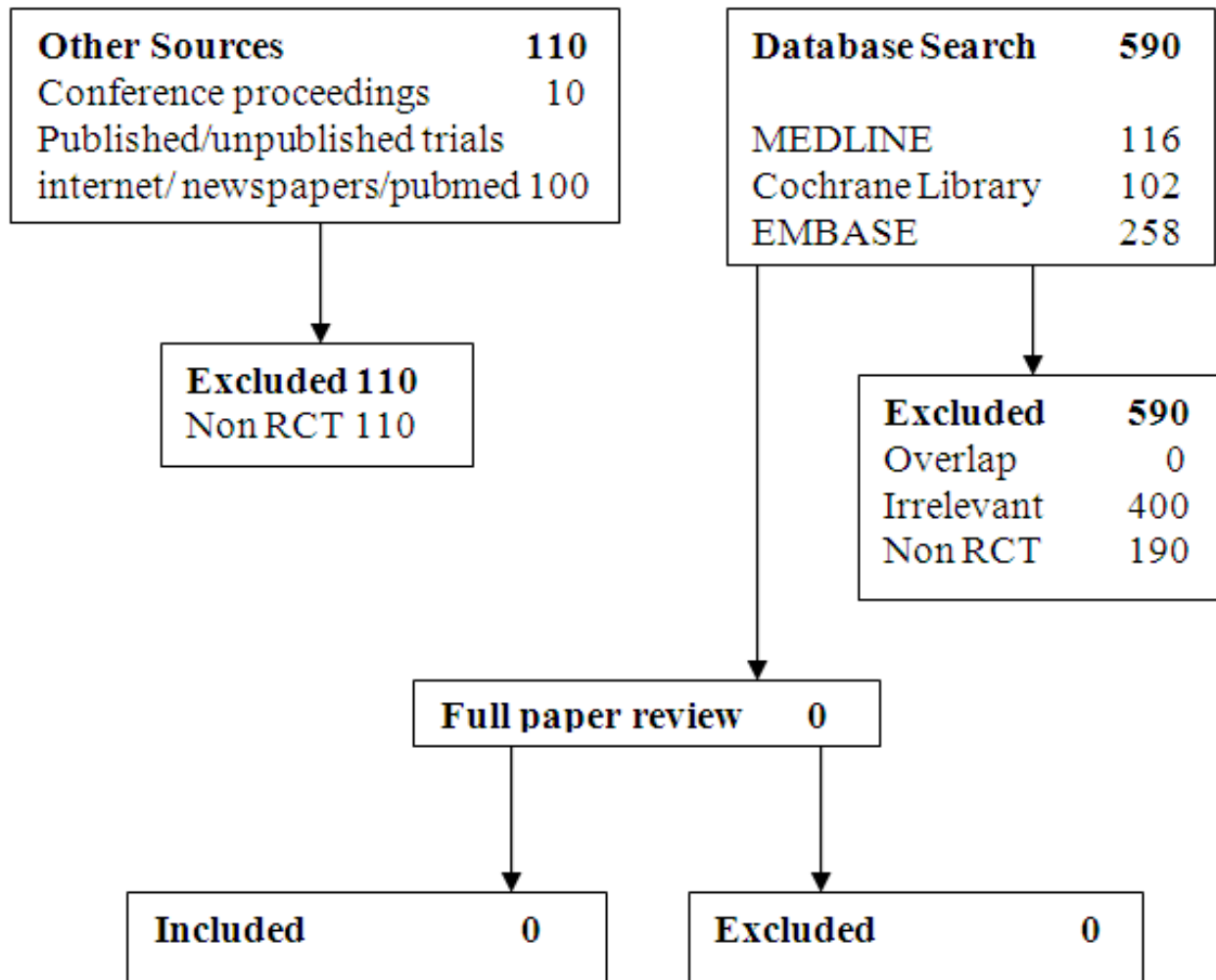
For dichotomous outcomes we intended to calculate relative risk (RR) and 95% confidence intervals (CIs). We planned to calculate the standardized difference in means for continuous outcomes.

RESULTS

Description of studies

We searched the databases (to February 22nd 2010). Our search yielded 590 hits (see Figure 1). After scrutiny of the study abstracts, no study fulfilled the inclusion criteria. They were either not relevant or not RCTs. We looked at newspapers and conference proceedings but this showed only 10 hits, which failed to contribute any relevant published or unpublished studies. The search of the Internet (PubMed, Yahoo and Google) using 'severe sepsis' and 'antibiotics' and 'timing' as a keyword identified 100 articles, all of which were excluded as they were either not RCTs or were not relevant.

Figure 1. Searching flow diagram



Risk of bias in included studies

There were no eligible studies.

Effects of interventions

There were no eligible studies.

DISCUSSION

This review failed to uncover any evidence from prospective, randomized or quasi-randomized trials on the effectiveness of early broad spectrum antibiotics in adult patients with severe sepsis, before admission into the ICU. This is an important question to review, to see if the literature exists to support a recommendation for the use of pre-intensive care broad spectrum antibiotics and to determine if there is a need for such literature, as is clearly demonstrated by our review. Given the severity of the condition, the high mortality rate (Fadel 2008) and the haste in delivering antibiotics, this lack of evidence on the timing of antibiotics is perhaps unsurprising (Besselink 2009). Despite modern day advances in therapeutics and diagnostic tests, severe sepsis remains a serious condition with a high mortality rate. Treatment

focuses on early goal-directed therapy, with antibiotics as part of source control. However, the optimal timing of antibiotic delivery is yet to be ascertained. It makes sense to administer them as early as possible but other considerations, whilst awaiting objective evidence such as microbial cultures, such as spread of resistance with unnecessary broad spectrum antibiotics, cost and side effects as well as reduction in immunity may hamper this hypothesis. We endeavoured to find level 1 evidence from randomized controlled double blinded trials in this field, however we could not find any such studies.

Initiating effective antibiotic therapy is proven to lead to better outcomes in severe sepsis and shock. The Surviving Sepsis Campaign, developed in 2004, incorporated evidence-based guidelines to reduce mortality from severe sepsis and septic shock (Dellinger 2008). These guidelines include the early initiation of broad spectrum antimicrobials, that is within one hour of recognition of sepsis (Kumar 2006). However, too early use of antibiotics can lead to excessive, unnecessary use as many other disease states such as myocardial infarction or pulmonary embolism can mimic severe sepsis. The biggest challenge in sepsis is early recognition of the problem. The presentation of severe

sepsis and septic shock can initially be non-specific but can progress within hours to fulminant multiple organ failure and death. Patients presenting to the emergency department with sepsis may not receive timely or appropriate antibiotics since the diagnoses of systemic inflammatory response syndrome (SIRS) and sepsis are often missed. Delays in the identification, transfer and management of critically ill patients during the first six hours after admission have been associated with higher mortality rates and increased utilization of hospital resources (Ruokonen 2009). Antimicrobial selection is often random and erratic.

Delaying antibiotic administration may be related to worsened clinical outcomes. Patients eventually arrive in the intensive care unit in a moribund state with profound shock and multi-organ failure. Better understanding of the pathophysiology of sepsis has led to recommendations that target both early and goal-directed management to improve outcomes. The timeliness of treatment became apparent after Rivers et al showed a significant mortality benefit when haemodynamic optimization was provided within the first few hours of disease presentation (Rivers 2006). These ideals have been incorporated into the Surviving Sepsis Campaign, a multi-national initiative which recommends a 24-hour sepsis pathway that includes a critical six-hour course of action. Results of studies, predominantly from Europe and North America, document the mortality and morbidity benefits of both early and appropriate antimicrobials. Kollef et al, in their landmark paper on 2000 patients with both community-acquired and nosocomial infections, demonstrated that inadequate antimicrobial treatment of infection was the most important independent determinant of hospital mortality for the entire patient cohort (adjusted odds ratio 4.27; 95% CI 3.35 to 5.44; $P < 0.001$) (Kumar 2006). Observational studies suggest a significant reduction in mortality when antibiotics are administered within four to eight hours of hospital presentation ($P < 0.01$). In these studies they were able to demonstrate a statistically significant relationship between early administration of antibiotics and survival, the crude odds ratio of 0.70 (95% CI 0.63 to 0.98; $P = 0.04$) indicated a protective effect when antibiotics were given early. Kumar conducted a study (Kumar 2006) which showed a 5% to 10% mortality. This was a multi-centre, retrospective study which only looked at hypotensive patients. Since our review focuses on all severe sepsis patients, and not just patients in shock, the Kumar study may not encompass our cohort. The basis for the timing of antibiotics in the Surviving Sepsis Guidelines (Dellinger 2008) is this study, which is for septic shock patients and is appropriate given the ethics involved and the urgency of the situation. The guidelines for severe sepsis state 'within six hours of presentation' and are based on non-RCT studies.

Unfortunately guidelines are not always immediately incorporated. There are delays in recognition of disease states and in institution

of therapy, especially in the emergency room setting where patient volumes and time constraints put additional burdens on the care providers. Since there may be serious ethical issues involved with implementing an RCT on this topic, as randomizing a patient to a potentially harmful intervention (late administration of antibiotics) in a potentially fatal condition such as severe sepsis may not be a feasible option, we suggest a review of non-randomized, observational cohort trials in the future. There are many barriers to commencement of treatment for such patients, such as physician failure, system delays and work-up delays as well as recognition of the pathophysiology. Treatment should ideally be started prior to admission in order to save time. Timely intervention is key, thereby decreasing mortality and morbidity.

AUTHORS' CONCLUSIONS

Implications for practice

We found no relevant evidence for early use of broad spectrum antibiotics in severe sepsis. We are, therefore, unable to make any recommendations based on the findings of this review.

Implications for research

Given the seriousness of the condition and high associated mortality, there is a need for further studies. Non-RCTs may be acceptable to show any improvement in outcomes. Any future trials would need to look at the appropriate sample size, ethics of randomization and appropriate outcome measures. We also recommend research on quality improvement strategies to facilitate timely administration of antibiotics in the emergency department. Research on implementing the sepsis bundle of care is the other direction for research into.

ACKNOWLEDGEMENTS

We would like to thank Dr Karen Hovhannisyan (Trials Search Co-ordinator, Cochrane Anaesthesia Review Group (CARG)) for help in running the searches and Jane Cracknell (Managing Editor, CARG) for her expert guidance.

We would like to thank Mr Iqbal Azam of the Department of Statistics, Aga Khan University in Pakistan, who will help with statistical analyses not included in Review Manager and will be available for statistical help with the meta-analysis, such as calculating relative risks, confidence intervals and odds ratios.

We would like to thank Dr Nicola Petrucci (content editor), Dr Marissa M Alejandria, Dr Mazen Bader (peer reviewers), Nathan Grimm and Karl Gallegos (Cochrane Consumer Network) for their help and editorial advice during the preparation of the systematic review.

REFERENCES

Additional references

Adler 2005

Adler G, Woehrle H. Diagnosis and therapy of acute pancreatitis. *Internist* 2005;**46**(2):131-44. [MEDLINE: 15655685]

Besselink 2009

Besselink MG, van Santvoort HC, Boermeester MA, Nieuwenhuijs VB, van Goor H, Dejong CH, et al. Timing and impact of infections in pancreatitis. *The British Journal of Surgery* 2009;**96**(3):267-73.

Blot 2005

Blot S, DeWaele JJ. Critical issues in the clinical management of complicated intra-abdominal infections. *Drugs* 2005;**65**(12):1611-20. [MEDLINE: 16060697]

Bochud 2004

Bochud PY, Bonten M, Marchetti O, Calandra T. Antimicrobial therapy for patients with severe sepsis and septic shock: an evidence-based review. *Critical Care Medicine* Nov 2004;**32**:495-512. [MEDLINE: 15542958]

Dellinger 2004

Dellinger RP, Carlet JM, Gerlach H, Ramsey G, Levy M. The surviving sepsis guidelines: not another "groundhog day". *Intensive Care Medicine* 2004;**32**:1601-2. [MEDLINE: 15241108]

Dellinger 2008

Dellinger RP, Vincent JL. The Surviving Sepsis Campaign: sepsis change bundles and clinical practice. *Critical Care* 2008;**9**:653-4. [MEDLINE: 16356261]

Fadel 2008

Fadel MV, Repka JC, Cunha CL, Leão MT. Inadequate timing between corticosteroid and antibiotics applications increases mortality due to sepsis. *The Brazilian Journal of Infectious Diseases* 2008;**12**(5):416-22. [MEDLINE: 19219282]

Grimaldi 2004

Grimaldi D, Caille V, Vieillard-Baron A, Bossi P. [Treatment of severe sepsis and septic shock]. *La Presse Médicale* 2004;**33**(4):265-8.

Higgins 2008

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Kula 2009

Kula R, Chylek V, Szturz P, Sklienka P, Sukenik P, Tichy J, et al. A response to infection in patients with severe sepsis--do we need a "stage-directed therapy concept"? *Bratislavské Lekárske Listy* 2009;**110-8**:459-64. [MEDLINE: 19750981]

Kumar 2006

Kumar A, Roberts D, Wood K E, Light B, Parrillo J E, Sharma S, et al. Duration of hypotension before initiation of effective. *Critical Care Medicine* 2006;**34**(6):1589-96. [MEDLINE: 16625125]

Montravers 2006

Montravers P, Quintard H, Piednoir P. [Activated proteine C]. *Annales Françaises d'Anesthésie et de Réanimation* 2006;**25**:270-4. [MEDLINE: 16387470]

Morimatsu 2004

Morimatsu H, Singh K, Uchino S, Bellomo R, Hart G. Early and exclusive use of norepinephrine in septic shock. *Resuscitation* 2004;**62**(2):249-54. [MEDLINE: 15294412]

Nguyen 2006

Nguyen HB, Corbett SW, Menes K, Cho T, Daugharthy J, Klein W, et al. Early goal-directed therapy, corticosteroid, and recombinant human activated protein C for the treatment of severe sepsis and septic shock in the emergency department. *Academic Emergency Medicine* 2006;**13**(1):109-13. [MEDLINE: 16365336]

RevMan 5.0 [Computer program]

Cochrane Collaboration. Review Manager (RevMan). Version 5.0. Copenhagen: Cochrane Collaboration, 2008.

Rivers 2006

Rivers EP, McIntyre, L Morro DC, Rivers KK. The outcome of patients presenting to the emergency department with severe sepsis or septic shock. *Critical Care* 2006;**10**(4):154.

Ruokonen 2009

Ruokonen E, Hovilehto S, Loisa P, Perttilä J, Pettilä V, Puurunen M, et al. Update on current care guidelines. Treatment of severe sepsis in adults. *Duodecim* 2009;**125**:2402-3. [MEDLINE: 19999665]

Tsolia 2003

Tsolia MN, Kafetzis D, Danelatou K, Astral H, Kallergi K, Spyridis P, et al. Epidemiology of respiratory syncytial virus bronchiolitis in hospitalized infants in Greece. *European Journal of Epidemiology* 2003;**18**(1):55-61. [MEDLINE: 12705624]

APPENDICES

Appendix 1. Search strategy for CENTRAL, The Cochrane Library

- #1 . MeSH descriptor Antibiotic Prophylaxis explode all trees
- #2 . (broad spectrum) near antibiotic*
- #3 . MeSH descriptor Anti-Bacterial Agents, this term only
- #4 . MeSH descriptor Cephalosporins, this term only
- #5 . MeSH descriptor Aminoglycosides, this term only

- #6 . MeSH descriptor Vancomycin explode all trees
- #7 . MeSH descriptor Carbapenems explode all trees
- #8 . carbapenem* or vancomycin
- #9 . (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
- #10 . MeSH descriptor Sepsis explode all trees
- #11 . MeSH descriptor Shock, Septic explode all trees
- #12 . MeSH descriptor Systemic Inflammatory Response Syndrome explode all trees
- #13 . (septic* or sepsis*);ti,ab
- #14 . Severe near sepsis
- #15 . shock near septic
- #16 . (#10 OR #11 OR #12 OR #13 OR #14 OR #15)
- #17 . (#9 AND #16)
- #18 . MeSH descriptor Intensive Care explode all trees
- #19 . MeSH descriptor Intensive Care Units explode all trees
- #20 . MeSH descriptor Emergency Medical Services explode all trees
- #21 . MeSH descriptor Emergency Medicine explode all trees
- #22 . MeSH descriptor Emergency Service, Hospital explode all trees
- #23 . (emergency near department*)
- #24 . (intensive near (care or unit))
- #25 . (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
- #26 . (#17 AND #25)
- #27 . ("child*" not ("adult*" and "child*"))
- #28 . (#26 AND NOT #27)

Appendix 2. MEDLINE (Ovid SP) search strategy

- 1 . exp Antibiotic Prophylaxis/
- 2 . (broad spectrum adj3 antibiotic*).mp.
- 3 . Anti-Bacterial-Agents/
- 4 . Cephalosporins/ or Aminoglycosides/
- 5 . exp Vancomycin/ or vancomycin.mp.
- 6 . exp Carbapenems/ or carbapenem*.mp.
- 7 . 1 or 2 or 3 or 4 or 5 or 6
- 8 . exp Sepsis/ or exp Shock, Septic/ or exp Sepsis-Syndrome/ or exp Septicemia/
- 9 . (septic* or sepsis*).ti,ab.
- 10 . (Severe adj3 sepsis).mp.
- 11 . (shock adj3 septic).mp.
- 12 . 8 or 11 or 10 or 9
- 13 . 7 and 12
- 14 . exp Intensive-Care/ or exp Intensive-Care-Units/ or exp Emergency-Medical-Services/ or Emergency-Medicine/ or Emergency-Service-Hospital/
- 15 . (emergency adj3 department*).mp.
- 16 . (intensive adj3 (care or unit)).mp.
- 17 . 16 or 15 or 14
- 18 . 13 and 17
- 19 . ("child*" not ("adult*" and "child*")).sh,kw.
- 20 . 18 not 19
- 21 . ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
- 22 . 21 and 20

Appendix 3. Search strategy for EMBASE (Ovid SP)

- 1 . exp Antibiotic Prophylaxis/
- 2 . (broad spectrum adj3 antibiotic*).mp.
- 3 . Antiinfective Agent/
- 4 . Cephalosporins/ or Aminoglycosides/
- 5 . exp Vancomycin/ or vancomycin.mp.
- 6 . exp Carbapenems/ or carbapenem*.mp.
- 7 . 1 or 2 or 3 or 4 or 5 or 6
- 8 . exp Sepsis/
- 9 . exp Septic Shock/
- 10 . exp Septicemia/

- 11 . (septic* or sepsis*).ti,ab.
- 12 . (Severe adj3 sepsis).mp.
- 13 . (shock adj3 septic).mp.
- 14 . 8 or 11 or 13 or 10 or 9 or 12
- 15 . 7 and 14
- 16 . exp Intensive Care/
- 17 . exp Intensive Care Unit/
- 18 . exp Emergency Health Service/
- 19 . exp Emergency Medicine/
- 20 . (emergency adj3 department*).mp.
- 21 . (intensive adj3 (care or unit)).mp.
- 22 . 21 or 18 or 19 or 16 or 17 or 20
- 23 . 22 and 15
- 24 . ("child*" not ("adult*" and "child*")).sh,tw.
- 25 . 23 not 24
- 26 . (RANDOMIZED-CONTROLLED-TRIAL/ or RANDOMIZATION/ or CONTROLLED-STUDY/ or MULTICENTER-STUDY/ or PHASE-3-CLINICAL-TRIAL/ or PHASE-4-CLINICAL-TRIAL/ or DOUBLE-BLIND-PROCEDURE/ or SINGLE-BLIND-PROCEDURE/ or (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER* or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).ti,ab.) not (animals not humans and animals).sh.
- 27 . 25 and 26

Appendix 4. Search strategy for ISI Web of Science

- #1. TS=(Antibiotic SAME Prophylaxis) or TS=((broad spectrum) SAME antibiotic*) or TS=(Cephalosporin* or Aminoglycoside* or vancomycin or carbapenem*)
- #2. TS=(septic* or sepsis*)
- #3. #2 AND #1
- #4. TS=(intensive SAME (care or unit)) or TS=emergency
- #5. #4 AND #3
- #6. TS=child* NOT TS=(adult* and child*)
- #7. #5 NOT #6
- #8. (TS=random* or TS=((clinical or controlled) SAME trial) or TS=((CONTROLLED or MULTICENTER) SAME STUDY) or TS=(CROSSOVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) or TS=((SINGL* or DOUBL* or TREBL* or TRIPL*) SAME (BLIND* or MASK*))) NOT (TS=(animal* not (human* and animal*)))
- #9. #8 AND #7

Appendix 5. Data extraction form

MEDLINE Journal ID: (as per article)

Year of publication

Language:

Type of study: RCT CCT CS

Comments on design of study:

Quality of randomization/concealment:

D

Allocation was not concealed (e.g. quasi randomization)

C

Allocation concealment was inadequate

B

Methods of concealment not stated clearly

A

Concealment adequate (e.g. numbered, sealed opaque envelopes drawn non consecutively, or computerized block randomization).

Inclusion/ exclusion criteria not clearly defined in methods.

Yes/ no

Outcomes of patients dropped or excluded after allocation were stated separately OR included in intention to treat analysis OR the text stated there were no exclusions.

Yes/ no

Treatment and control groups were NOT adequately described at the beginning

Yes/ no

A minimum of 4 admission details were described

Yes/no

Methods:

Yes/No/Unclear

Subject blinded

Physician blinded

Outcome assessor blinded

Participants:

No. of eligible participants: No. enrolled in study:

No. of males: No. of females:

Severity of sepsis: SIRS severe sepsis septic shock

Intervention:

abxdose time of administration route

(hrs)

Early antibiotics group

(treatment group 1) <1 hour

Late treatment group

(treatment group 2) > 1 hour

Comment on treatment and timing:

(Prior antibiotic use Yes/No)

Withdrawals: Yes No Unclear

Outcomes:

LOS (days, mean) Mortality

(n, %) Morbidity

(n, %) Cost- if given

(\$)

Treatment Group 1

Treatment Group 2

Changes in protocol: Yes / No

Contact with author: Yes/ No

Other comments:

Data extraction form

DY:

Quality of randomization/concealment:

D

Allocation was not concealed (e.g. quasi randomization)

C

Allocation concealment was inadequate

B

Methods of concealment not stated clearly

A

Concealment adequate (e.g. numbered, sealed opaque envelopes drawn non consecutively, or computerized block randomization).

Inclusion/ exclusion criteria not clearly defined in methods.

Yes/ no

Outcomes of patients dropped or excluded after allocation were stated separately OR included in intention to treat analysis OR the text stated there were no exclusions.

Yes/ no

Treatment and control groups were NOT adequately described at the beginning

Yes/ no

A minimum of 4 admission details were described

Yes/no

WHAT'S NEW

| Date | Event | Description |
|------------------|---------|--|
| 14 December 2018 | Amended | Editorial team changed to Cochrane Emergency and Critical Care |

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 10, 2010

| Date | Event | Description |
|---------------|---------|--------------------------|
| 17 April 2012 | Amended | Contact details updated. |

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Shahla Siddiqui (SS), Junaid Razzak (JR)

Designing the review: SS, JR

Co-ordinating the review: SS

Undertaking manual searches: SS, JR

Screening search results: SS

Organizing retrieval of papers: SS

Screening retrieved papers against inclusion criteria: SS

Appraising quality of papers: SS, JR

Abstracting data from papers: SS, JR

Writing to authors of papers for additional information: SS

Providing additional data about papers: SS

Obtaining and screening data on unpublished studies: SS

Data management for the review: SS

Entering data into Review Manager ([RevMan 5.0](#)): SS, JR

RevMan statistical data: SS

Other statistical analysis not using RevMan: Mrlqbal Azam, Dept of Statistics, AKUH, Pakistan

Double entry of data: (data entered by person one: SS)

Interpretation of data: SS, JR

Statistical analysis: SS, Mrlqbal Azam, Dept of Statistics, AKUH

Writing the review: SS

Securing funding for the review: SS, JR

Performing previous work that was the foundation of the present study: SS

Guarantor for the review (one author): SS

Person responsible for reading and checking review before submission: SS, JR

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Department of Anaesthesia and Critical Care, AKUH, Karachi, Pakistan.
- Mr Iqbal Azam, department of statistics, AKUH, Karachi, Pakistan.

External sources

- The Aga Khan University, Pakistan.

Non-monetary support in the form of computer access, personnel for help and software access.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not search the LILACS database as stated in the published protocol. This was due to the difficulty in accessing it.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; Anti-Bacterial Agents [*administration & dosage]; Drug Administration Schedule; Intensive Care Units; Sepsis [*drug therapy]; Time Factors; Treatment Outcome

MeSH check words

Adult; Humans