Effect of Immediate Administration of Antibiotics in Patients With Sepsis in Tertiary Care

A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: This review sought to synthesize existing evidence to establish if patients who present to the Emergency Department (ED) and are administered antibiotics immediately (within 1 hour) or later (>1 hour) and then subsequently diagnosed with a sepsis illness have different outcomes (mortality).

Methods: *Data sources.* A search of Pubmed, Embase, Cochrane CENTRAL and CINAHL, using MeSH descriptors 'sepsis', 'systemic inflammatory response syndrome', 'mortality', 'emergency' and 'antibiotics', was performed to identify studies reporting time to antibiotic administration and mortality outcome in patients with sepsis.

Study selection. Included studies (published in English between 1990-2016) listed patient mortality based on time to antibiotic administration.

*Data extraction***.** Studies were evaluated for methodological quality and data were extracted using a data extraction form tailored to this study.

*Data synthesis***.** From an initial pool of 582 potentially relevant studies, eleven studies met our inclusion criteria of which ten had quantitative data for meta-analysis.

Analytical methods. Three different models; a random effects (RE), a bias adjusted quality-effects (synthetic bias; QE), and its bias unadjusted variant inverse variance heterogeneity (IVhet) model, were used to undertake the meta-analysis.

Findings: Pooled results suggest a significant 33% reduction in mortality odds for immediate (within 1 hour) compared to later (>1 hour) antibiotic administration (OR 0.67; 95% CI 0.59 – 0.75).

Implications: Immediate antibiotic administration (<1 hour) appeared to reduce patient mortality. There was some minor negative asymmetry suggesting that the

evidence may be biased towards the direction of effect. Nevertheless, this study provides strong evidence for early, comprehensive, sepsis management in the ED.

INTRODUCTION

It is estimated that there are 18 million cases of sepsis per year worldwide. More than 17,000 of those episodes are in Australia and that number is projected to grow at a rate of 1.5% per year [1]. Sepsis has high mortality rate and results in significant morbidity [2].

Sepsis arises when the body's immune response to infection causes a widespread inflammatory response. Often described under the umbrella term "sepsis", there is an acknowledged continuum now assessed using a sequential [sepsis-related] organ failure assessment[3] and sometimes assessed using a staging score[4]. Each form of sepsis is progressively more severe, with a higher mortality rate. Septic shock (with acute organ dysfunction) has a mortality rate up to 46% [5]. Sepsis is a time sensitive illness where rapid, relatively uncomplicated treatment (including the administration of antibiotics) can translate into lives saved [6].

International consensus guidelines recommend initiating broad-spectrum antibiotic coverage immediately (within the first hour) once a diagnosis of severe sepsis and septic shock is considered [7]. This recommendation is largely based on one large retrospective study by Kumar et al and expert consensus [8]. Kumar et al. [8] estimated that mortality rate increases by 7.6% with every hour delay in starting antimicrobial therapy in the first 6 hours after hypotension onset. Further, it was demonstrated that effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in septic shock [8].

A Cochrane review of 'early versus late pre-intensive care unit admission broad spectrum antibiotics for severe sepsis in adults' did not locate any randomized controlled trials [9]. They were, therefore, unable to make any specific recommendations other than that there is a need for large prospective double blind RCTs examining the efficacy of immediate (within 1 hour) versus later broad spectrum antibiotics in adult severe sepsis patients [9]. In the interim, research derived from other (less rigorous) study types incorporating broader (additional) sepsis diagnoses may be useful to guide practice in the emergency setting [10].

The aim of this systematic review and meta-analysis was to review and assess the current evidence regarding patients who present to the ED and are diagnosed with a Sepsis illness (i.e. Systemic inflammatory syndrome (SIRS), sepsis, severe sepsis, sepsis with septic shock and sepsis with organ dysfunction) in terms of in-hospital mortality outcomes for those who are administered antibiotics immediately (within 1 hour) or later (>1 hour).

METHODS

Identification of studies

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11]. Ethical review is not required for a review study. We searched EMBASE, MEDLINE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL). All terms were mapped to the appropriate MeSH/EMTREE/CINAHL headings and "exploded". Search terms used included: 'sepsis', 'systemic inflammatory response syndrome', 'mortality', 'emergency' and 'antibiotic agent'. Additional search strategies (i.e. Pubmed, google,

reference lists of articles, forward and backwards reference chaining) were used to identify further articles for potential inclusion[12, 13].

Study selection

Studies were included if they were published in English language during 1990-2016, as the 'surviving sepsis' campaign was formulated in 1990 and guidelines of early, goal-directed therapy (which included early antibiotics) were produced at that time. All original research studies that included the term 'sepsis', included associated with EDs as a setting for antibiotic administration, and described outcomes that include mortality pertaining to early (<1 hour) versus late (>1 hour) administration of broad spectrum antibiotics were included[11, 13]. Studies were excluded if they were qualitative in nature, did not include an assessment of early versus late antibiotic administration and did not include some measure of mortality as an outcome [14].

Data extraction and quality assessment

Two authors (JCl & AJ) independently undertook the initial screen for article inclusion using the Rayyan platform to facilitate study selection[15]. Clarification of inclusion was resolved by discussion with other authors. The article selection process is displayed in Figure 1. Data extracted from each study included author, year and country of publication, sample size, study design, main outcomes measured and results (see Tables 1 and 2).

The quality of articles that met inclusion criteria were independently reviewed and assessed by two authors (AJ, VS) with clarification resolved using a third author (JC). Included studies were assessed by careful reading of the manuscripts for their methodological quality using National Health and Medical Research Council

(NHMRC) guidelines[16] and a generic scale created by the authors (presented in Table 3). The latter includes 17 questions (with subsections to total 25 in all) divided into 5 components that explore potential design bias, selection bias, information bias, potential for confounding and analytical bias[17]. One point was given for each study criterion cited in the study that limited bias; up to a maximum of 25 points, and this was summed into a univariate quality score out of 25. The proforma for the generic quality assessment scale is included in the supplemental material. This score was used to rank studies for use with the quality effects model [18].

Statistical analysis and data synthesis

The in-hospital mortality odds ratios for early versus late antibiotic administered groups were pooled using three different meta-analytic models [17-20]. Hazard ratios reported in some studies were interpreted as odds ratios in this analysis. Of the three models, two were the quality-effects model (QE) and the inverse variance heterogeneity model (IVhet) which both use a quasi-likelihood based variance structure without distributional assumptions. The latter thus have coverage probabilities for the CI at the 95% nominal level and have been documented to have a better performance when compared to the conventional third model we used: the random effects (RE) model [17, 18]. Cochran's Q test and I^2 were used to assess heterogeneity amongst studies. I^2 >50% was considered to indicate practically significant heterogeneity. Publication bias was assessed via funnel plot asymmetry. All meta-analyses were conducted using MetaXL version 5.2 [21].

RESULTS

Application of the study inclusion/exclusion process (Figure 1) resulted in 11 articles. Data for the 11 studies were developed between 2005 and 2013 with subsequent publication dates ranging from 2009 to 2016 (see Table 1). The trials were conducted in various countries: five in USA (including one multi-continent study including Europe)[6, 22-25], one included a broad grouping 'Europe'[26], and one each in Korea[27], Canada[28], The Netherlands[29], Australia[30] and Iran[31] (see Table 1). The population of each study varied and included SIRS, sepsis, severe sepsis and septic shock. The number of patients included in the study varied between 85 and 17,990. In terms of study type, one was a randomized control trial [22], six were retrospective cohort studies [6, 24, 27-30], three were prospective cohort studies [23, 26, 31] and one was a pre-post observational study[25]. Eight of the studies were set exclusively in the emergency department [6, 22, 24, 25, 27, 29-31]; and while all involved patients had an ED episode of care, two were the result of data collected eventually from the ICU [23, 26] and one from data collected from general medical, general surgical and ICU areas [28] following ED administration of antibiotics.

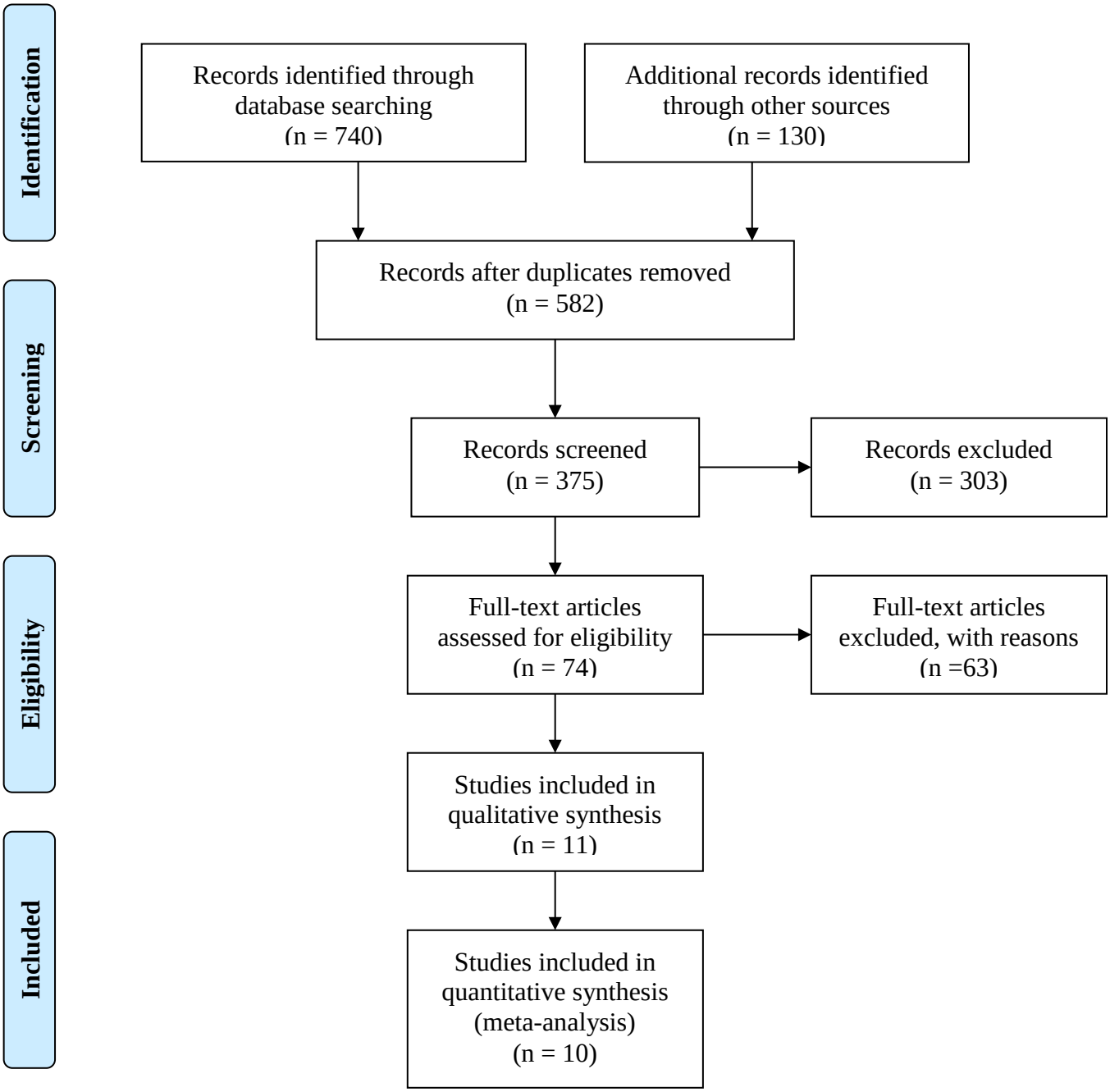

Figure 1. PRISMA 2009 Flow Diagram Article database source and schematic representation of the search processes with application of inclusion/exclusion criteria. The numbers of articles included in each step are shown numerically in each component of the process.

Table 1. Characteristics of studies included in the review

Authors, Year, Reference	When Trial Conducted	Country	Population Type	Sepsis classification and definition used	No. of Patients	Study Type	Trial setting where sepsis outcome was identified
Ferrer et al., 2009[26]	**2005 - 2007**	**Europe**	**SS SK**	SS: sepsis associated with organ dysfunction unexplained by other causes S: respiratory dysfunction (bilateral pulmonary infiltrates with PaO2/FIO2 <300), renal dysfunction (urine output <0.5 ml/kg/hr for at least 2 hours or creatinine >2.0 mg/dl), coagulation abnormalities (International Normalized Ratio [INR] >1.5 or a partial thromboplastin time [PTT] >60 seconds), thrombocytopenia (platelet count <100,000/uL), hyperbilirubinemia (total plasma bilirubin >2.0 mg/dl), hypoperfusion (lactate >18 mg/dl), or hypotension (systolic blood pressure <90 mm Hg, mean arterial pressure <65 mm Hg, or a reduction in systolic blood pressure >40 mm Hg from baseline measurements). SK acute circulatory failure (systolic blood pressure <90 mm Hg, mean arterial pressure <65 mm Hg, or a reduction in systolic blood pressure >40 mm Hg from baseline) despite adequate volume resuscitation.	**2796**	**Prospective Cohort**	**ICU**
Gaieski et al., 2010[6]	**2005 - 2006**	**USA**	**SS SK**	As per Surviving Sepsis Guidelines [7]	**261**	**Retrospective Cohort**	**ED**
Puskarich et al., 2011[22]	**2007 - 2009**	**USA**	**SK**	SK: the patient developed two or more SIRS criteria and either a systolic blood pressure 90 mmHg after a minimum of 20-mL/kg rapid volume	**291**	**RCT†**	**ED**

				challenge or a blood lactate concentration of at least 4 mmol/L.			
O'Neill et al., 2012[24]	**2008-2009**	**USA**	**SS SK**	As per Surviving Sepsis Guidelines [7]	**85**	**Retrospective Cohort**	**ED**
Jalili et al., 2013[31]	**2007 - 2009**	**Iran**	**S**	S: presence of at least two criteria of SIRS and procalcitonin levels ≥2 μg/l	**145**	**Prospective Cohort**	**ED**
Ferrer et al., 2014[23]	**2005 - 2010**	**USA South America Europe**	**SS**	SS: having a suspected site of infection, two or more SIRS criteria, and one or more organ dysfunction criteria [3, 34]	**17990**	**Prospective Cohort**	**ICU**
Ryoo et al 2015[27]	**2010-2012**	**Korea**	**SK**	SK: refractory hypotension, specifically, systolic blood pressure <90 mm Hg or mean arterial pressure <70 mm Hg requiring vasopressors despite adequate fluid therapy, or a blood lactate concentration of at least 4 mmol/L	**426**	**Retrospective Cohort**	**ED**
De Groot et al., 2015[29]	**2011-2013**	**The Netherlands**	**S**	As per Surviving Sepsis Guidelines[7] segregated by PIRO scores[4]	**1168**	**Prospective observational cohort**	**ED**
Wisdom et al., 2015[30]	**2012**	**Australia**	**S SS**	As per International Sepsis definitions conference[36]	**220**	**Retrospective Cohort**	**ED**
Narayanan et al., 2016[25]	**2012-2013**	**USA**	**SS SK**	As per Surviving Sepsis Campaign[7]	**214**	**Pre-Post observational**	**ED**
Mok, Christian et al., 2014[28]	**2009-2010**	**Canada**	**SS SK**	SS: sepsis associated with organ dysfunction, hypoperfusion, or hypotension. SK: sepsis with hypotension despite adequate fluid resuscitation	**100**	**Retrospective Cohort**	**Hospital-wide**

ED, Emergency Department; ICU, Intensive Care Unit; PIRO, predisposition, infection (or insult), response and organ dysfunction (PIRO) staging of sepsis; S, Sepsis; SIRS, systemic inflammatory response syndrome; SS, severe sepsis; SK, septic shock; SSC, surviving sepsis campaign[48]; †Detailed methodology for this study[27] was outlined elsewhere[38].

Table 2. Summary of Study Results

Authors, Reference	Type of Antibiotic used AU, appropriateness of antibiotic measured AA (Yes/No)	Number of patients AB ≤1 hour group	Number of patients in AB >1 hour group	In hospital Mortality (AB ≤1 hour) N (%)	In hospital Mortality (AB >1 hour) N (%)	OR	95% CI	p
Ferrer et al., 2009[26]	AU (N), AA (N)	510 (18.2)	1851 (81.5)	175 (34.3%)	792 (42.8%)	0.67	0.5-0.9	0.001¥
Gaieski et al., 2010[6]	AU (N), AA (Y)	41 (15.7%)	220 (84.3%)	8 (19.5%)	73 (33.2%)	0.3	0.11-0.83	0.02‡
Puskarich et al., 2011[22]	AU (N), AA (Y)	65 (22.3%)	226 (77.7%)	11 (16.9%)	44 (19.5%)	^0.55	0.23-1.35	0.69‡
O'Neill et al., 2012[24]	AU (N), AA (N)	65 (77.4%)	19 (22.6)	15 (23.1%)	4 (21.1)	0.89	0.31-2.55	NS¥
Jalili et al., 2013[31]	AU (N), AA (Y)	26 (17.9%)	118 (81.3%)	1 (3.8%)	30 (25.4%)	0.12	0.02-0.90	0.05‡
Ferrer et al., 2014[23]	AU (Y), AA (N)	4728 (26.3%)	13265 (73.7%)	1508 (31.9%)	4112 (31%)	^0.66	0.59-0.74	0.001§
Ryoo et al 2015[27]	AU (N), AA (Y)	150 (35.2%)	276 (64.8)	29 (19.3%)	121 (19.3%)	0.81	0.45-1.45	NS€

de Groot et al., 2015[29]	**AU(Y)** **AA(Y)**	**--**	**--**	**--**	**--**	**^**0.68** **^**0.98** **^**0.71**	**0.5-0.95a** **0.72-1.33b** **0.43-1.19c**	
Wisdom et al., 2015[30]	**AU(Y)** **AA(Y)**	**--**	**--**	**--**	**--**	**^**0.57**	**0.2-1.33**	**0.08**
Narayanan et al., 2016[25]	**AU(Y)** **AA(Y)**	**133 (62%)**	**81 (38%)**	**--**	**--**	**0.64**	**0.26-1.57**	**<0.001**
Mok, Christian et al., 2014[28]	**AU (Y)** **AA (Y)**	**6 (6.0%)**	**94 (94.0%)**	**N/A**	**N/A**	**-**	**-**	**∫-**

Captions and abbreviations used: AU, antibiotics used; AA, appropriateness of antibiotics; OR, Odds ratio of in-hospital mortality for cases where AB is given >1 hour; CI, Confidence Interval; p, probability-values

‡ Times given are for triage ("door") to antibiotic administration

§ For patients enrolled from the ED, time is defined as the time of triage to antibiotic administration. For patients admitted to the ICU from medical and surgical wards and for patients in ICU at time of diagnosis, time is determined by chart review for the diagnosis of septic shock to antibiotic administration.

¥ Time is defined as time from noted diagnosis to antibiotic administration

€ Time is defined as time from initial assessment to antibiotic administration

∫ Time is defined as time from onset of sepsis/septic shock to antibiotic administration

^data reversed for analysis

**Hazard ratios reported

a,b,c refer to three groupings of PIRO[4] (predisposition, infection (or insult), response and organ dysfunction) staging scores; a = 1-7, b = 8-14, c = >14 PIRO[4]

Results of the study quality assessment tools applied indicated that the included studies varied somewhat, but generally rated as mid- to high quality. There was only one randomized controlled trial (level II NHMRC). The remainder ranged in strength from III-2 to IV[12]. The Quality Scale provided some degree of study quality discrimination with scores ranging from 13 to 21.5[18] (see Table 3)..

Table 3. Results of the quality assessment measures applied to the studies that were used to inform the review

Authors, Reference	Loss to follow up	Adjustment for Confounders	NHMRC level of evidence	Quality score
Ferrer et al., 2009[26]	**<15%**	**Yes**	**III-3**	**19/25**
Gaieski et al., 2010[6]	**-**	**Yes**	**III-2**	**17/25**
Puskarich et al., 2011[22]	**<5%**	**Yes**	**II**	**21.5/25**
O'Neill et al., 2012[24]	**<15%**	**Yes**	**III-S**	**14/25**
Jalili et al., 2013[31]	**<15%**	**Yes**	**III-2**	**16/25**
Ferrer et al., 2014[23]	**~32%**	**Yes**	**III-3**	**20/25**
Ryoo et al 2015[27]	**-**	**Yes**	**III-3**	**13/25**
De Groot et al., 2015[29]	**-**	**Yes**	**III-2**	**18/25a,b,c***
Wisdom et al., 2015[30]	**-**	**Yes**	**III-3**	**17/25**
Narayanan et al., 2016[25]		**Y**	**III-3**	**16/25**
Mok, Christian et al., 2014[28]	**-**	**N/A**	**IV**	**13/25**

Captions and abbreviations used: NHMRC; National Health and Medical Research Council (Australia); *a = 1-7, b = 8-14, c = >14 using the PIRO

Our primary outcome of interest was in-hospital mortality for immediate versus later administration of antibiotics. One study [28] only reported overall mortality rate, not differentiating between those administered antibiotics within or greater than 1 hour and was excluded from the quantitative synthesis. The remaining ten studies compared in-hospital mortality between patients who had immediate (<1 hour) antibiotics, or not, given in the ED. These ten studies reported in-hospital mortality of between 4-34% for patients administered antibiotics immediately and between 19-43% mortality for patients administered antibiotics later (see Table 2). All studies contributing data for meta-analysis [6, 22-27, 29-31], reported an odds ratio of less than one, indicating that administration of antibiotics within 1 hour may make a difference in terms of mortality. Statistically significant impacts of time to antibiotic administration were reported in five of the ten studies [6, 23, 25, 26, 31]. One study reported a range of odds ratios based on a predefined illness severity score [4, 29].

While all 10 studies had a time to antibiotic of one hour or less as the exposure (see Table 2), the control for analysis varied from >1h to >6h [6, 22, 23, 27, 28, 31]. Five studies reported on the type [23, 25, 28-30], and eight on the 'appropriateness' [6, 22, 25, 27-31], of the antibiotic administered with another stating that 'antibiotic appropriateness' had been established [31]. In general, the studies considered antimicrobial therapy to be appropriate if the bacteria identified in blood culture was susceptible to at least one of the antibiotics administered empirically in the ED, based on the culture results taken at this point.

Quantitative synthesis

While three different models were used to undertake the meta analysis, only QE results are presented because the other results essentially concurred. The QE model

indicated an estimated 33% reduction in mortality odds with immediate antibiotic administration (OR 0.67; 95% CI: 0.59 – 0.75). Cumulative forest plots with a sensitivity analysis excluding two influential studies (see Figure 2), demonstrate that significance of the results is not driven by the two largest studies (Ferrer et al. [23, 26]) and without them the pooled odds for immediate vs. delayed antibiotic use was 0.70 (95% CI 0.57, 0.87). There was no heterogeneity of effects seen across studies (I^2=9%; Q=12.13; p=0.35).

Funnel and Doi plots [32] in Figure 3 indicated that there was minor negative asymmetry and therefore there may be some degree of publication related or small study bias favouring studies supporting early antibiotic administration. However asymmetry was minor and thus the effect reported is not likely to be grossly exaggerated.

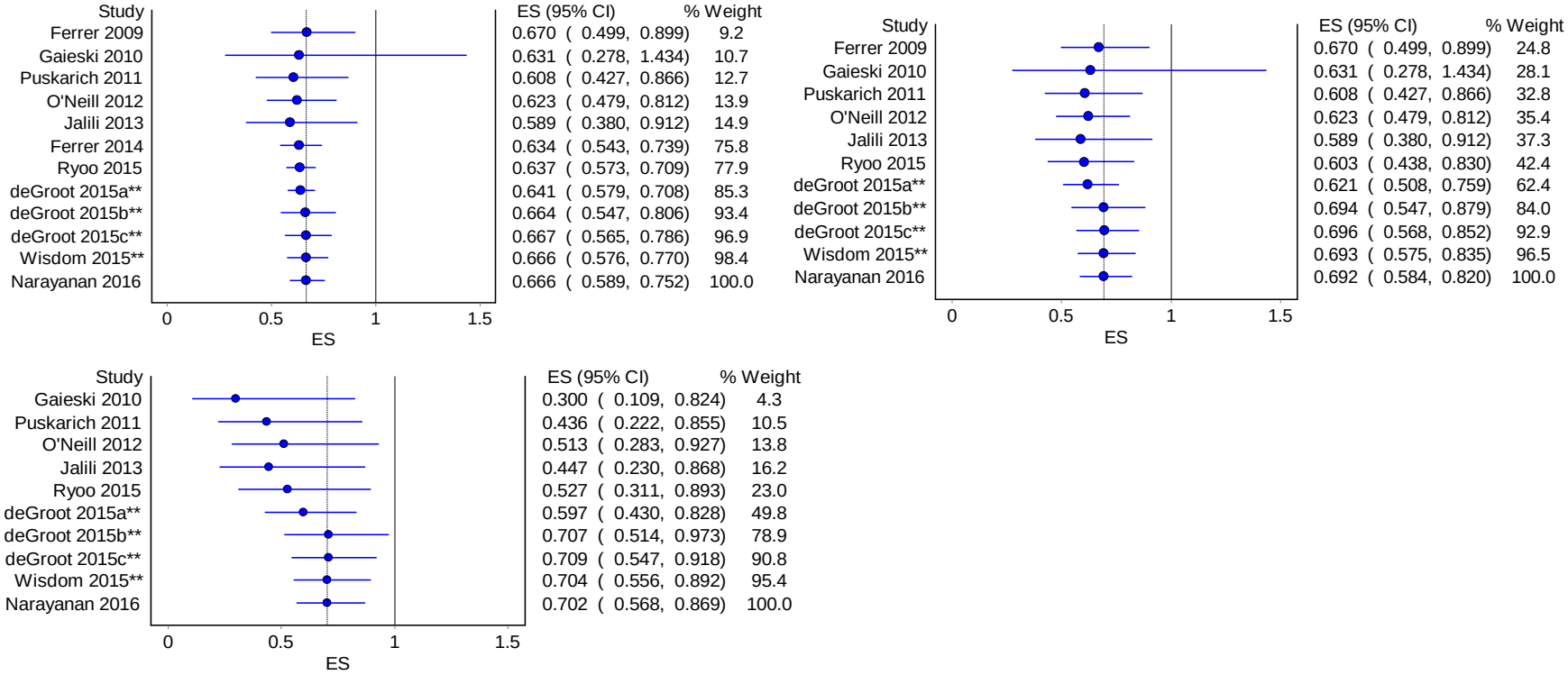

Figure 2. Cumulative Forest plots using the QE method including all studies (top left), excluding the Ferrer et al 2014[23] study only (top right) and excluding both Ferrer et al 2014 and 2009[23, 26] studies (bottom left). CI, confidence interval; ES, effect size (all odds ratios except ** indicate hazard ratios).

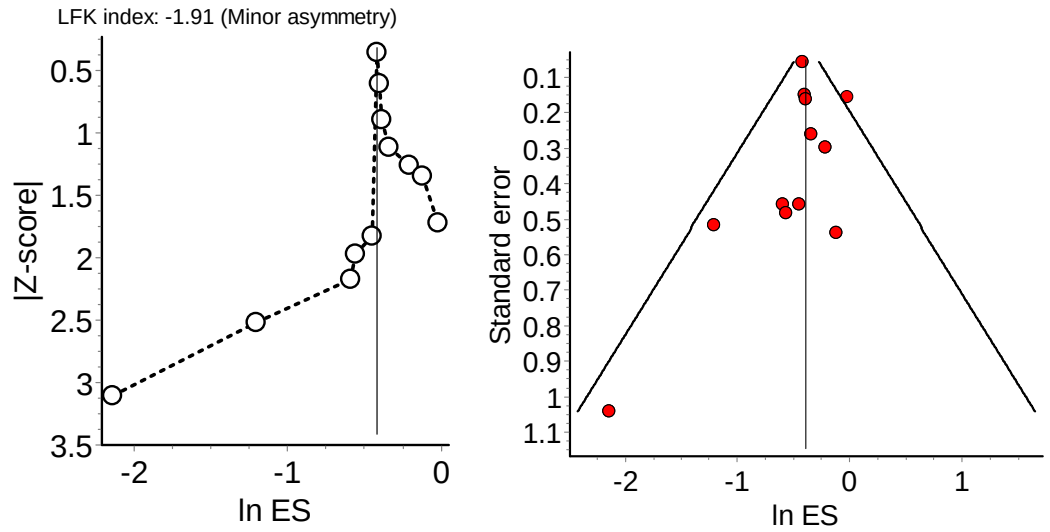

Figure 3. Publication bias assessed via the Doi plot (left panel) and Funnel plot (right panel). Minor negative asymmetry, suggesting some publication bias is evident. ln, natural log; ES, effect size.

DISCUSSION

The meta-analysis of the studies included in this review suggest that immediate antibiotic commencement can decrease the mortality odds from sepsis by up to an estimated 33% (OR 0.67; 95% CI 0.59 – 0.75). The largest study showed a strong effect [23] with a confidence interval that ranged between 26 and 41% decrease in odds of mortality [23]. All included studies, provided more or less similar effect sizes in this study because the quality rank of the studies were not very variable and study effects were homogenous (I^2=9%)[12, 32]. The Doi plot (figure 3) shows only minor asymmetry and therefore the pooled odds ratio of 0.67 is probably a robust estimate. Thus, the overall data suggests a real clinical impact of early (ED) administration of antibiotics on patient mortality, supporting the earlier assertions of Kumar [8].

This finding provides strong support for evidence-based guidelines that advocate earlier management with antibiotics of patients with sepsis. Although the 'Surviving Sepsis Campaign' international consensus guidelines recommend administering a broad-spectrum antibiotic within the first hour of recognizing severe sepsis and septic shock [7], this was largely based on expert opinions and a retrospective study [8, 34] and does not consider the time variations between arrival at hospital and recognition of sepsis. However this meta-analysis indicates that irrespective of the start point, earlier antibiotics are typically better for patients. It is possible that delay for clinical screening tools and confirmatory biochemical markers (such as lactate levels[35]) may compromise outcomes.

The results of this meta-analysis do not provide a resolution to the optimal time frame beyond which delaying antibiotics can be deleterious for patients with sepsis but strongly suggest that antibiotics be administered as early as is feasibly possible.

Such timing is challenging because recording the initial time point (detection) is inconsistently defined within the literature. Starting time points used to determine time to antibiotic administration included time from; arrival, diagnosis, detection, recognition, and admission. This was possibly due to the settings in which the sepsis studies were undertaken. For example, in broad-based studies, patients recruited from ED often had the triage time logged as time of presentation whereas patients in the same studies that were recruited from general wards or ICU a chart review or equivalent was used to determine time of diagnosis and presentation [28, 30]. Thus, studies undertaken in the ED were primarily focused on the *early detection* of sepsis, whereas studies undertaken in the ICU setting were focused more on the *effectiveness* of early goal directed therapy and could draw on additional information not typically available in the ED setting (such as APACHE II score) to guide care delivery.

Five of the ten studies included in this review indicated a significantly reduced mortality when antibiotics were given within one hour (of arrival, from diagnosis, from detection, from recognition, from admission) compared to delayed administration of antibiotics (>1hr). The other six studies (including the study that did not contribute data to the meta analysis [28]) showed no significant benefit of antibiotic administration within an hour but the pooled effects suggest that the latter could have been under-powered to detect such a benefit. Studies showing non-significant effects also varied in quality from the highest included to lower rated studies, so non-significance was not just an effect of a poor study.

There are two other issues that evidence suggests may be considered as important as that of timing and thus must be considered. First is the notion of ‘appropriate

antibiotic therapy'. Appropriateness usually means that the organism identified from culture was sensitive to the initial antibiotics administered. [36, 37]. One study that did not show any reduction in mortality in early antibiotic administration arm (≤1hour) did not measure the "appropriateness" of the antibiotics that were given in the ED [24], however other studies were contradictory such that the appropriateness of the antibiotic administered was associated with either no significant [28] or significant [6] benefits of timing of administration <1 hour. Further research in this area is required to enhance not only the early recognition but also the appropriateness of treatment, including antibiotics, provided. Indeed, antibiotic appropriateness is becoming an increasing focus of sepsis studies, guided by local antibiotic stewards.

The second critical issue to note regarding sepsis is the overall care bundle provided. Care bundles [38, 39] are generally guided by a specific protocol and examples include the Surviving Sepsis Campaign guidelines [7], ProCESS [39, 40] and, most recently, ARISE [41]. Based on early goal-directed therapy, the outcomes from studies using these guidelines are not necessarily conclusive in whether early goal-directed therapy improves outcomes and is cost effective [42], however these overall analyses suggest that early goal-directed therapy can improve patients' outcomes.

Strengths and limitations

A strength of our study is that we used several analytic approaches and they all concurred because heterogeneity was not seen across studies. Nevertheless we should point out that the conventional approach using the random effects (RE) model [19] is known to underestimate the statistical error which can lead to an overconfidence in the result when heterogeneity is present [43]. The two other statistical approaches used

have been documented to have a better performance when compared to the RE method [18].

There are several limitations to our study. The dominance by a single primary author (the two Ferrer et al papers[23, 26]) accounting for 74% of the weight from the 10 studies included is a relative limitation. However, exclusion of these studies in a sensitivity analysis did not make a difference to the pooled estimate (see Figure 2). Our search strategy was carefully planned, and article exclusion criteria were strictly adhered to, perhaps limiting the scope of included evidence [44]. Our main outcome of interest was in-hospital mortality. Other outcomes that reflect care quality may also be useful to consider when undertaking reviews such as this one. Another limitation was the varied definitions of timing, as discussed above. There were also varying definitions, 'grades' of sepsis used for study inclusion and varying sepsis detection processes within these studies. While some studies included patients with severe sepsis and septic shock [6, 26], others included only patients with septic shock [22]. However, the pattern of results from these studies did not vary widely. In studies that compared wards where sepsis was detected, a higher mortality rate was noted in the 'ward groups' versus the 'ED groups'[28]. Additionally, the study settings had varying sepsis detection processes, with multi-site studies consistently demonstrating that in hospital mortality from detection of sepsis in the ward compared to ED increased [23, 28, 37].

CONCLUSIONS

The evidence base assessed here indicates that administering appropriate antibiotics immediately sepsis is recognized appears to reduce mortality in patients with sepsis and severe sepsis. Recognizing the signs of sepsis early can be sometimes difficult. On the basis of this evidence implementation of international standardized guidelines for ED clinician's regarding i) early detection and ii) appropriate early treatment of sepsis is required.

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Supplementary material

Pubmed

("Anti-Bacterial Agents"[Mesh] OR Antibacterial[tiab] OR Antibacterials[tiab] OR Antibiotics[tiab] OR Antibiotic[tiab] OR Antimicrobial[tiab] OR Antimicrobials[tiab])
AND
("Sepsis"[Mesh] OR Sepsis[tiab] OR “Septic shock”[tiab] OR “Systemic inflammatory response syndrome”[tiab] OR Septicemia[tiab] OR Septicemias[tiab])
AND
("Mortality"[Mesh] OR “Survival Rate"[Mesh] OR "Survival Analysis"[Mesh] OR Mortality[tiab] OR Death[tiab] OR Deaths[tiab] OR Survival[tiab])
AND
("Emergency Service, Hospital"[Mesh] OR “Emergency service”[tiab] OR “Emergency services”[tiab] OR “Emergency department”[tiab] OR “Emergency departments”[tiab] OR “Emergency Units”[tiab] OR “Emergency Unit”[tiab] OR ED[tiab] OR "Intensive Care Units"[Mesh] OR "Intensive Care Units"[tiab] OR "Intensive Care Unit"[tiab] OR ICU[tiab] OR ICUs[tiab])
AND
("Time-to-Treatment"[Mesh] OR Timing[tiab] OR “Time to”[tiab] OR Hour[tiab] OR Hours[tiab])
AND
(Administration[tiab] OR Appropriate[tiab] OR Appropriateness[tiab] OR Compliance[tiab])
AND
(“randomized controlled trial”[pt] OR “controlled clinical trial”[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "Epidemiologic Studies"[Mesh] OR “case-control studies”[Mesh] OR “Cohort Studies”[Mesh] OR “case control”[tiab] OR Cohort[tiab] OR “Follow up”[tiab] OR Observational[tiab] OR longitudinal[tiab] OR Prospective[tiab] OR retrospective[tiab] OR “cross sectional”[tiab] OR “Cross-Sectional Studies”[Mesh] OR Investigated[tiab] OR Analysis[tiab])
NOT
(Animals[Mesh] not (Animals[Mesh] and Humans[Mesh])

Cochrane CENTRAL

([mh "Anti-Bacterial Agents"] OR Antibacterial:ti,ab OR Antibacterials:ti,ab OR Antibiotics:ti,ab OR Antibiotic:ti,ab OR Antimicrobial:ti,ab OR Antimicrobials:ti,ab)
AND
([mh Sepsis] OR Sepsis:ti,ab OR "Septic shock":ti,ab OR "Systemic inflammatory response syndrome":ti,ab OR Septicemia:ti,ab OR Septicemias:ti,ab)
AND
([mh Mortality] OR [mh "Survival Rate"] OR [mh "Survival Analysis"] OR Mortality:ti,ab OR Death:ti,ab OR Deaths:ti,ab OR Survival:ti,ab)
AND
([mh "Emergency Service, Hospital"] OR "Emergency service":ti,ab OR "Emergency services":ti,ab OR "Emergency department":ti,ab OR "Emergency departments":ti,ab OR "Emergency Units":ti,ab OR "Emergency Unit":ti,ab OR ED:ti,ab OR [mh "Intensive Care Units"] OR "Intensive Care Units":ti,ab OR "Intensive Care Unit":ti,ab OR ICU:ti,ab OR ICUs:ti,ab)

AND
([mh Time-to-Treatment] OR Timing:ti,ab OR “Time to”:ti,ab OR Hour:ti,ab OR Hours:ti,ab)
AND
(Administration:ti,ab OR Appropriate:ti,ab OR Appropriateness:ti,ab OR Compliance:ti,ab)

Embase
('antiinfective agent'/exp OR Antibacterial:ti,ab OR Antibacterials:ti,ab OR Antibiotics:ti,ab OR Antibiotic:ti,ab OR Antimicrobial:ti,ab OR Antimicrobials:ti,ab)
AND
('Sepsis'/exp OR Sepsis:ti,ab OR "Septic shock":ti,ab OR "Systemic inflammatory response syndrome":ti,ab OR Septicemia:ti,ab OR Septicemias:ti,ab)
AND
('mortality'/exp OR 'Survival Rate'/exp OR 'survival'/exp OR Mortality:ti,ab OR Death:ti,ab OR Deaths:ti,ab OR Survival:ti,ab)
AND
('emergency health service'/exp OR “Emergency service”:ti,ab OR "Emergency services":ti,ab OR "Emergency department":ti,ab OR "Emergency departments":ti,ab OR "Emergency Units":ti,ab OR "Emergency Unit":ti,ab OR ED:ti,ab OR 'intensive care unit'/exp OR "Intensive Care Units":ti,ab OR "Intensive Care Unit":ti,ab OR ICU:ti,ab OR ICUs:ti,ab)
AND
('time to treatment'/exp OR Timing:ti,ab OR “Time to”:ti,ab OR Hour:ti,ab OR Hours:ti,ab)
AND
(Administration:ti,ab OR Appropriate:ti,ab OR Appropriateness:ti,ab OR Compliance:ti,ab)
AND
(randomized:ti,ab OR randomised:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab OR 'epidemiology'/exp OR “case control”:ti,ab OR Cohort:ti,ab OR "Follow up":ti,ab OR Observational:ti,ab OR longitudinal:ti,ab OR Prospective:ti,ab OR retrospective:ti,ab OR "cross sectional":ti,ab OR Investigated:ti,ab OR Analysis:ti,ab)

CINAHL
((MH "Antiinfective Agents+") OR Antibacterial OR Antibacterials OR Antibiotics OR Antibiotic OR Antimicrobial OR Antimicrobials)
AND
((MH "Sepsis+") OR Sepsis OR "Septic shock" OR "Systemic inflammatory response syndrome" OR Septicemia OR Septicemias)
AND
((MH "Mortality+") OR "(MH "Survival+") OR Mortality OR Death OR Deaths OR Survival)
AND
((MH "Emergency Service+") OR (MH "Intensive Care Units+")

OR "Emergency service" OR "Emergency services" OR "Emergency department" OR "Emergency departments" OR "Emergency Units" OR "Emergency Unit" OR "Intensive Care Units" OR “Intensive Care Unit" OR ICU OR ICUs)
AND
(Timing OR Time OR Hour OR Hours)
AND
(Administration OR Appropriate OR Appropriateness OR Compliance)
AND
(randomized OR randomised OR placebo OR randomly OR trial OR groups OR (MH "Epidemiology+") OR “case control” OR Cohort OR "Follow up" OR Observational OR longitudinal OR Prospective OR retrospective OR "cross sectional" OR Investigated OR Analysis)

Table Liu-Doi Quality Scale

Item	Questions	Score
		1=Yes/Not applicable, 0=No/Unclear
	Design bias	
1	What was the type of design? a) randomized and allocation concealed – 3 points b) randomized only – 2 points c) prospective cohort – 1 point d) retrospective cohort or case control – 0 point [note of b)：1. Was the study described as randomized (this includes words such as randomly, random, and randomization)? Yes=1, No=0 2.Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)? Yes=1, No=0]	
2	Was the duration of active treatment appropriate for the demonstration of study outcome (e.g. >= 6 months for neurological recovery of SCI)*?	
	Selection bias	
3	Did the inclusion/exclusion criteria remain consistent across the comparison groups of the study? [*Abstractor: to use this question for studies with* ***one group****, the focus of the question on comparison groups and related response categories would need to be changed to individuals*]	
4	Was the strategy for recruitment into the study the same across comparison groups (e.g. not from same populations or both groups were not recruited over the same time period)? *[Abstractor: in case-control studies were the controls randomly selected from the source population for cases over the same time period? To use this question for studies with one group, the focus of the question on comparison groups and related response categories would need to be changed to individuals]*	
5	Was the interval between the start of intervention and outcome the same across comparison groups, or if different, were appropriate analyses used to equalize this (e.g. time-to-event analyses)? *[Abstractor: in case-control studies, was the interval between the start of intervention and outcome the same for cases and controls? To use this question for studies with one group, the focus of the question on comparison groups and related response categories would need to be changed to individuals]*	
6	Was attrition < 20%, or if not, was follow-up done for these subjects to ensure their loss was not related to outcome? *[Abstractor: in case-control and cross-sectional studies the non-response rate is used instead of attrition.]*	
	Information bias	
7	Were the outcomes of interest in the study pre-specified?	
8	Were reproducible measures (clear name of predefined scale or clear details of non-predefined scale were presented) of study outcomes	

	implemented in the same way across comparison groups? *[Abstractor: for case-control studies the focus is on case definition. To use this question for studies with one group, the focus of the question on comparison groups and related response categories would need to be changed to individuals.]*	
9	Were the outcome assessors blinded to the nature of intervention or control (e.g. Qigong, acupuncture or usual medical care)?	
10	Were the subjects blinded to the nature of intervention or control (e.g. Qigong, acupuncture or usual medical care)?	
11	Apart from blinding, were any other safeguards described and used for assuring the reliability of study outcomes (e.g. any of validated instruments, duplicated measurement, independent assessment)?	
12	Were data assessed and recorded in the same way for both comparison groups and across time points? *[Abstractor: to use this question for studies with one group, the focus of the question on comparison groups and related response categories would need to be changed to individuals at two time points]*	
13	Were interventions/exposures clearly defined (all essential components were described) and implemented in the same way across both study groups? *[Abstractor: to use this question for studies with one group, the focus of the question on comparison groups and related response categories would need to be changed to individuals]*	
	Confounding bias	
14	Were the groups similar at baseline in key confounding variables or if not were steps taken to achieve comparability of key confounders (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)? a) age b) duration of disease c) level of lesion d) severity of SCI e) gender *[Abstractor: to use this question for studies with one group, the focus of the question on comparison groups and related response categories would need to be changed to temporal trends in these variables and related co-interventions over time for the individuals]*	
	Analytical bias	
15	Were effect sizes based on the data available at post assessment or pre-defined subgroups rather than a post hoc portion of the data?	
16	Was intention-to-treat analyses conducted for the outcome of interest?	
17	Were all data available (i.e. they did not need to be estimated from results)?	

*****Please make a decision based on the target health condition in your study

******Please make a decision on the important confounder (s) in your study (maximum 5 founders recommended); 1 point if the answer is YES to each question/confounder, otherwise 0 point.

1. **Was the study described as randomized (this includes words such as randomly, random, and randomization)?**
   Yes=1, No=0
2. **Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?**
   Yes=1, No=0
3. **Was the study described as double blind?**
   Yes=1, No=0
4. **Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?**
   Yes=1, No=0
5. **Was there a description of withdrawals and dropouts?**
   Yes=1, No=0
6. **Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (e.g. patients were allocated alternately, or according to date of birth, hospital number, etc).**
   Described but inappropriate = -1, Described and appropriate = 0
7. **Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet vs. injection with no double dummy).**
   Described but inappropriate = -1, Described and appropriate = 0