Supplemental Methods

This systematic review, prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist (1), was registered in the PROSPERO database (2017:CRD42017080258) on 12/18/2017.

Data sources and searches

We searched PubMed, EMBASE, Scopus, Web of Science, and Clinicaltrials.gov (see Appendix-1 for search strategies). The electronic searches were conducted without language restrictions from each database's inception to 03/15/2018 and used the same search terms as those employed previously to examine the evidence for CMS's SEP-1 bundle and its components (2). We also examined all supplementary data from studies including that which was available electronically and when applicable that data was included in our analysis. Finally, we scanned the references of relevant studies from the searches.

Study selection

We included randomized and observational studies of adult patients (≥16 years old) with sepsis, severe sepsis, or septic shock that compared mortality rates between patients receiving *versus* not receiving a focused sepsis bundle that included: antibiotic administration and/or fluid infusion, with or without vasopressors if needed. We excluded studies with bundles that used components of the volume status and tissue perfusion assessment no longer required with SEP-1 in 2018 (i.e., a clinician's focused exam with vital signs, cardiopulmonary, capillary refill, peripheral pulse and skin examination, CVP measurements, $ScvO_2$ measurements, bedside cardiovascular ultrasound, passive leg raises or fluid challenges) (2). Two authors (DJP, PQE)

reviewed searches, first screening titles and abstracts followed by a full-text review of selected articles. Author consensus resolved uncertainty regarding study inclusion.

Endpoints

For included studies we first examined the overall effect of bundles on survival. We then examined in these studies whether the effect on survival of bundles stipulating a 30mL/kg fluid volume differed from the effects of bundles either stipulating a volume other than 30mL/kg fluid or that did not stipulate a volume (termed individualized volumes). The same analysis was done comparing the survival effects of bundles requiring serial lactate measurements versus bundles that did not. In studies reporting data, the effects of bundles on the proportion of patients receiving antibiotics or fluids within the stipulated time (termed timely administration), the time to the administration of these components, and/or the volume of administered fluid were also assessed.

Data extraction and quality assessment

Two authors (DJP and PQE) extracted data from studies using a standardized tool (Appendix-2) and three authors (DJP, JS, and PQE) checked data accuracy. Extracted data included the study location, type of sepsis investigated (sepsis, severe sepsis or septic shock), baseline patient characteristics (age, sex, comorbidities, illness severity, and site of infection), the outcomes examined, bundle composition and data about bundle administration including the interval from time-zero to intervention administration; the proportion of patients receiving the intervention within the stipulated time goals; the amount of the intervention administered if it was a treatment; overall bundle administration; and adverse effects potentially related to bundle

use. Fluid infusion requirements in bundles were defined as either stipulating 30mL/kg, stipulating a specific volume other than 30mL/kg, or not stipulating any specific volume (i.e. individualized volumes). Baseline characteristics in a study were considered to favor the bundle group if bundle patients were younger, had fewer comorbidities or decreased illness severity, or had a lower proportion of pulmonary or abdominal infections ($p<0.05$ considered statistically significant).

We recorded adjunctive aids in studies that may have confounded survival results including i) educational aids to improve provider recognition and care of septic patients (e.g., conferences or lectures) or ii) prioritized care aids which directly affected the management of septic patients (e.g., priority bed allocation or sepsis alert systems). Risk of bias was to be assessed for randomized trials with the Cochrane Collaboration's risk of bias assessment tool, and for observational studies with the Newcastle-Ottawa Scale (3,4). Two investigators (DJP and PQE) assessed this risk independently and settled disagreements by consensus. All components of either tool had to be graded as low risk to conclude that a study had a low risk of bias overall. For observational studies, comparability bias was based on whether the severity of illness and the presence of comorbidities were recorded and similar at baseline.

The primary outcome examined was survival assessed as the odds ratio of survival and considered in the following hierarchy: 90-day, 60-day, 30-day, 28-day, hospital, or intensive care unit. We assessed outcome bias based on whether survival was determined blindly and/or from record linkage or not, and whether ≥28-d survival and follow-up adequacy were reported.

Data synthesis and analysis

We determined effect estimates for each intervention. For binary outcomes including survival or the proportion of patients receiving an intervention, odds ratios (OR) and their 95% confidence intervals (95%CI) were calculated. For time to a test or treatment or the amount of treatment, reported median and interquartile range values were converted to mean difference and standard error (SE) values using the method of Wan *et al.* (5) We provided outcome summary estimates for the included studies using random-effects model adjusting for < 20 studies with the Hartung-Knapp method (6). Heterogeneity among studies was assessed using the Q statistic and I^2 value (7). Two-sided p-values <0.05 were considered significant. Publication bias was assessed using funnel plots and Egger's regression (p-value <0.10 considered significant) (8). All analyses were performed using R (version 3.4.4) with packages meta (version 4.9-1) and metafor (version 2.0-0) (9-11).

Role of funding source

Intra-mural funding from the National Institutes of Health (NIH) supported this work. The NIH had no role in the design of the study or the collection, analysis, and interpretation of the data.

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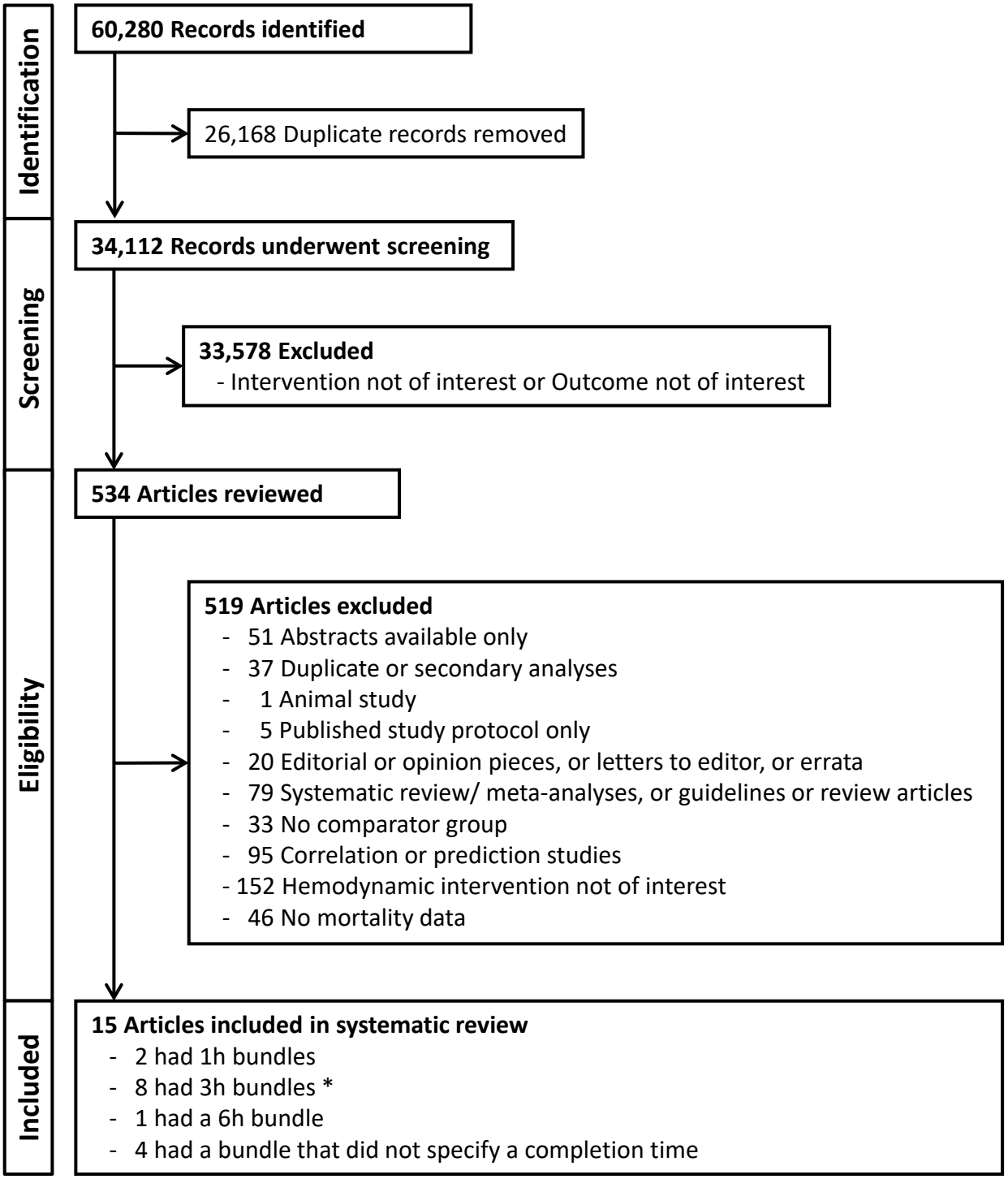
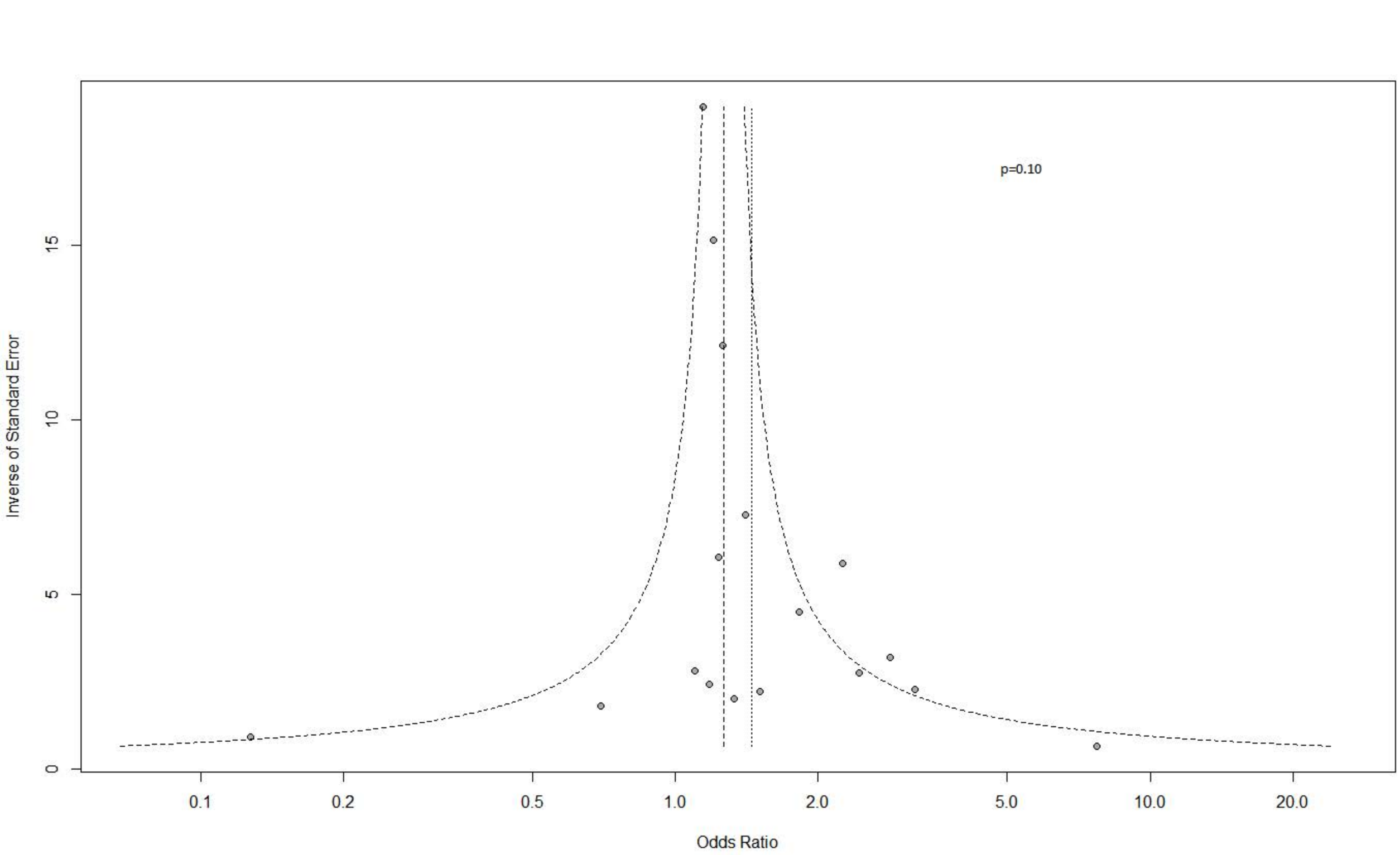
Appendix Figure 1



Key:

* One of these articles investigated three individual cohorts of patients and each cohort is treated as a separate study in the present analysis. Seventeen total studies were analyzed here.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Inverse of Standard Error
0
5
10
15
0.1
0.2
0.5
1.0
2.0
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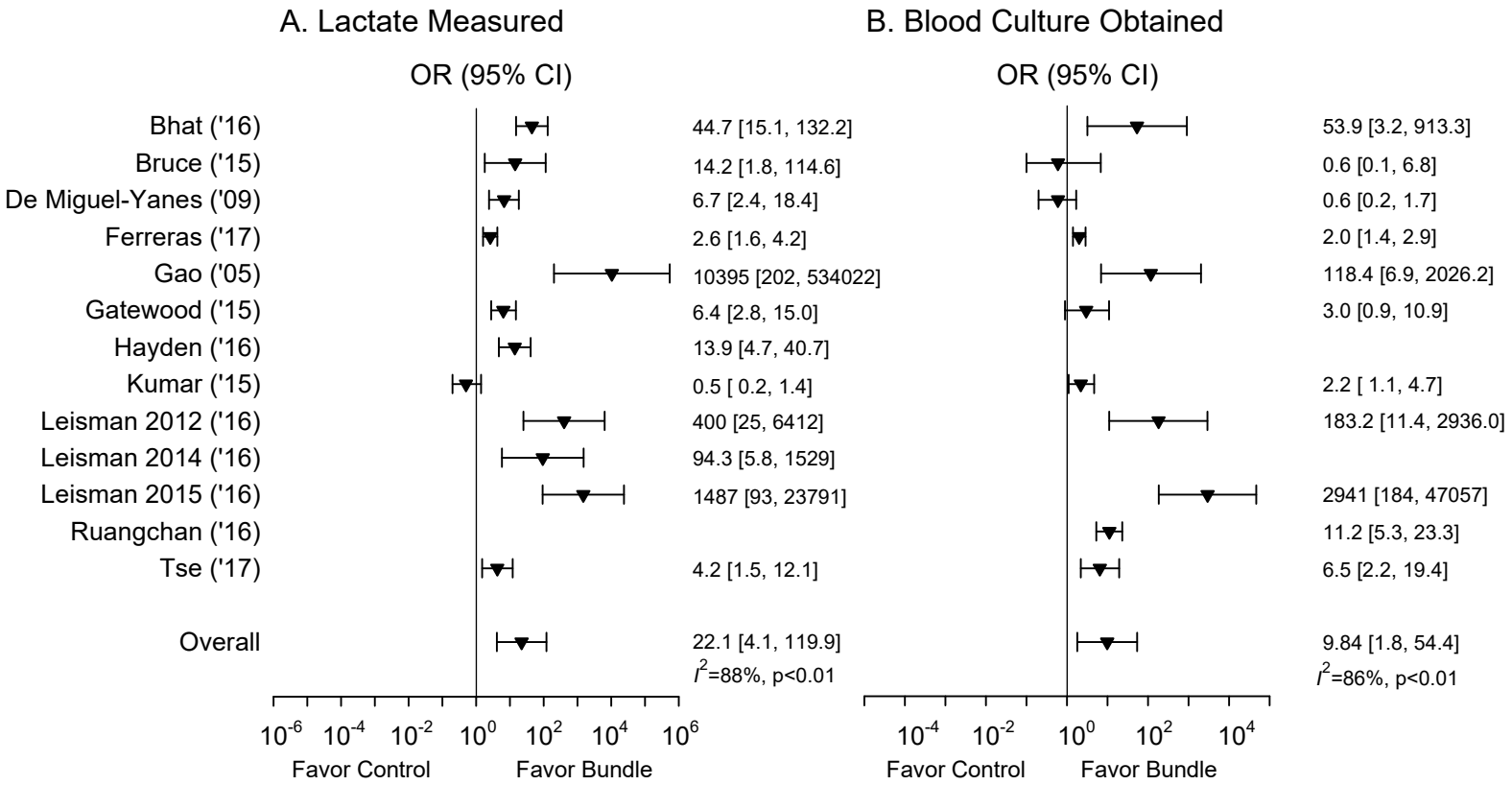
10.0
20.0
Odds Ratio

Appendix Figure 3



Appendix Table 1. CMS SEP-1 Performance Measure version 5.4

Date of first release notes	12/27/2017
Hospital IQR Program measurement period	7/1/18 (third quarter of 2018) to 12/31/18 (fourth quarter of 2018)
Received within three hours of presentation of severe sepsis: • Initial lactate level measurement • Broad spectrum or other antibiotics administered • Blood cultures drawn prior to antibiotics	Yes
AND received within six hours of presentation of severe sepsis: • Repeat lactate level measurement only if initial lactate level is elevated	Yes
AND ONLY if: Initial Hypotension present initiated within three hours of Initial Hypotension: • Resuscitation with 30 mL/kg crystalloid fluids OR Septic Shock Present initiated within three hours of septic shock presentation: • Resuscitation with 30 mL/kg crystalloid fluids	Yes
AND ONLY IF hypotension persists after fluid administration, received within six hours of presentation of septic shock: • Vasopressors	Yes
AND ONLY if hypotension persists after fluid administration or initial lactate >= 4 mmol/L, received within six hours of presentation of septic shock: • Repeat volume status and tissue perfusion assessment	Yes
Figures	Pages 8–17
Tasks	Up to 75 tasks from pages 18–31

IQR = Inpatient Quality Reporting; SEP-1 = Severe Sepsis and Septic Shock Early Management Bundle.

Appendix Table 2. Summary of whether age, co-morbidities, illness severity and site of infection were reported in both intervention and control groups and parameters with imbalances favoring the bundle group (**) in the 17 studies

Author (y)	Age	Sex	Co-morbid Illnesses	Illness Severity	Type of Illness Severity Score Reported	Site of Infection
Austrian (’17)	Yes	Yes	Yes	No	NR	Yes
Bhat (’16)	No	No	No	No	NR	No
Bruce (’15)	Yes	Yes	No	Yes**	Organ dysfunction	Yes
De Miguel-Yanes (’09)	Yes	Yes	No	Yes	APACHE	Yes
Ferreras (’17)	Yes	Yes	Yes	Yes	SOFA	Yes
Gao (’05)	Yes	Yes	No	Yes	MEWS	Yes
Gatewood (’15)	No	No	No	No	NR	No
Hayden (’16)	Yes	Yes	No	No	NR	Yes
Kumar (’15)	No	No	No	No	NR	No
Leisman 2012* (’16)	Yes	Yes	No	Yes**	Organ dysfunction	No
Leisman 2014* (’16)	Yes	Yes	Yes	Yes**	Organ dysfunction	No
Leisman 2015* (’16)	Yes	Yes	Yes	Yes**	Organ dysfunction	Yes
Liu (‘15)	Yes	Yes	Yes	Yes	LAPS2	No
Prasad (’17)	Yes	Yes	Yes	Yes	Not stated †	No
Ruangchan (’16)	Yes	Yes	Yes	Yes	SOFA	Yes
Teles (’17)	Yes	Yes	Yes	Yes	APACHE	Yes
Tse (’17)	Yes	Yes	Yes	Yes	Organ dysfunction	No

APACHE = Acute Physiology and Chronic Health Evaluation; MEWS = Modified Early Warning Score; SOFA = Sequential Organ Failure Assessment (SOFA) Score

* See text for description of these three cohorts

**Higher systolic blood pressure in one study (Bruce’15) or evidence of reduced injury for some organ at baseline in three studies (Leisman 2012, 2014 and 2015) potentially favoring the bundle groups

† Severity of illness reported as minor, moderate, major or extreme

Appendix Table 3. Summary of the outcomes reported in the 17 studies

Author (y)	Primary Endpoint	Secondary Endpoint(s)	Mortality Definition	Adjusted Mortality	Variables Examined in Multivariate Analysis
Austrian (’17)	HM	HLOS, Time to first lactate	HM	No	NR
Bhat (’16)	M	LOS	M	No	NR
Bruce (’15)	HM	Compliance, time to antibiotics	HM	Yes	Organ dysfunction, UTI, positive blood culture, vasopressors, body weight
De Miguel-Yanes (’09)	Compliance	HM	HM	Yes	Acute illness, fluid overload, HDU care
Ferreras (’17)	30d M	HM, Comp	30d M	No	NR
Gao (’05)	Compliance	HM	HM	No	NR
Gatewood (’15)	Compliance	M	M	No	NR
Hayden (’16)	Time to interventions	M	HM	No	NR
Kumar (’15)	Compliance	HM	HM	No	NR
Leisman 2012* (’16)	HM	ICU admit, VP	HM	Yes	Age, Acute Illness**
Leisman 2014* (’16)	HM	ICU admit, VP, HLOS, HC	HM	Yes	Age, Acute Illness, Co-morbidities**
Leisman 2015* (’16)	HM	ICU admit, ILOS, VP, MV, HLOS, HC	HM	Yes	Age, Acute Illness, Co-morbidities**
Liu (‘15)	HM	-	HM	Yes	Age, Sex, Acute Illness, Co-morbidities**
Prasad (’17)	HM, Compliance	-	HM	Yes	Age, Acute Illness, Co-morbidities
Ruangchan (’16)	M	ILOS, HLOS	M	Yes	Acute Illness
Teles (’17)	M	-	M	Yes	Age, Acute Illness, Co-morbidities
Tse (’17)	HM	Time to Abx	HM	Yes	Age, Acute Illness

mortality: M = mortality; HM = hospital mortality; 28d M = 28-day mortality; 30d M = 30-day mortality; NR = not reported; length of stay: LOS = length of stay; ILOS = ICU length of stay; HLOS = hospital length of stay; Compliance = compliance with bundle components; HC = hospital cost; ICU admit = ICU admission; LC = lactate clearance; MV = mechanical ventilation duration; VP = vasopressor;
* See Table 1 and text for description of these three cohorts; **Adjusted estimates of bundle effects on survival were reported

Appendix Table 4. Bundle components to be administered in bundle groups and management in the control groups of the 17 studies

Author (y)	Overall Bundle Time	Bundle Group									Control Group
		Reported time zero	Laboratory Data		Antibiotics		Fluids		Other Interventions		
			Lactate	BCx	Timing	Type	Timing	Volume	Adjunctive Aids	Other	
Austrian (’17)	NS	NR	Yes	Yes	NS	Appropriate	NS	NS	Yes	-	No sepsis alert
Bhat (’16)	1h	Sepsis diagnosis	Yes, ≤1h	Yes, ≤1h	≤1h	NS	≤1h	NS	Yes	O_2 therapy ≤1h; measure UOP ≤1h	No bundle
Bruce (’15)	3h	Sepsis diagnosis	Yes	Yes	NS	BS	≤30min	≥20ml/kg bolus	Yes	-	No bundle
De Miguel-Yanes (’09)	3h	Sepsis diagnosis	Yes	Yes	≤3h	NS	≤1h	≥20ml/kg	Yes	VP/I	No bundle
Ferreras (’17)	3h	ED arrival	Yes	Yes	≤1h	NS	NS	30mL/kg	Yes	-	No bundle
Gao (’05)	6h	Sepsis criteria met ‡	-	Yes	≤1h	NS	≤30min	500mL	No	Hb of 7–9g/dL; VP/I	Bundle uncompleted
Gatewood (’15)	3h	ED triage	Yes	Yes	≤3h	NS	≤2h	≥2L	Yes	-	No bundle
Hayden (’16)	NS	ED arrival	Yes	Yes	NS	BS	NS	30mL/kg bolus	Yes	-	No bundle
Kumar (’15)	1h	Initial nursing assessment	Yes, ≤1h	Yes, ≤1h	≤1h	NS	≤1h	NS	Yes	-	No bundle
Leisman 2012 (’16)*	3h	Sepsis criteria met §	Yes	Yes	≤3h	BS	≤30min	30mL/kg bolus	Yes	-	Bundle uncompleted
Leisman 2014 (’16)*	3h	Sepsis criteria met §	Yes	Yes	≤3h	BS	≤30min	30mL/kg bolus	Yes	-	Bundle uncompleted
Leisman 2015 (’16)*	3h	Sepsis criteria met §	Yes	Yes	≤3h	BS	≤30min	30mL/kg bolus	Yes	-	Bundle uncompleted
Liu (‘16)	3h	Initial lactate test results obtained	Yes**	NS	≤3h	NS	≤3h	30mL/kg	Yes	-	No bundle
Prasad (’17)	3h	Sepsis criteria met ‖	Yes	Yes	≤3h in ED; ≤1h inpatient	NS	NS	NS	No	VP/I	Bundle uncompleted
Ruangchan (’16)	NS	Sepsis diagnosis	-	Yes	≤1h	Empiric	≤2h	1.5 to 2L	No	-	Bundle uncompleted
Teles (’17)	3h	Sepsis diagnosis	Yes	Yes	≤1h	BS	NS	30mL/kg bolus	No	VP/I	Bundle uncompleted
Tse (’17)	NS	ED registration	Yes	Yes	≤1h	NS	NS	500-1000mL bolus, titrate up to 30mL/kg	Yes	VP/I	No bundle

* See text for description of these three cohorts; ** obtained second lactate value; ‡ All the following fulfilled: signs and symptoms of infection, documented source of infection and ≥1 organ dysfunction;§ Time of laboratory result or time of vital sign measurement causing patient to meet sepsis criteria; ‖ Time at which two SIRS critera and one sign of organ failure in the presence of known or suspected infection met

NS = not stated; BS = broad-spectrum antibiotics; O_2 = oxygen; UOP = urine output; Hb = hemoglobin; VP/I = vasopressor and/or inotrope for persistent hypotension

Appendix Table 5. Summary of data regarding antibiotic goals and administration in the control and bundle groups in each of the 17 studies

Author (y)	Antibiotic Administration						
	Goal	% of Patients Meeting Goal		Time to Antibiotics*		Reported % Culture Positive	Reported % Appropriate Antibiotics
		C	B	C	B		
Austrian (’17)	NR	NR	NR	NR	NR	NR	NR
Bhat (’16)	<1h	9	81	NR	NR	NR	NR
Bruce (’15)	Broad spectrum antibiotics	76	77	135 (40,336)	108 (20,699)	NR	NR
De Miguel-Yanes (’09)	< 3h	25	62	NR	NR	NR	NR
Ferreras (’17)	<1h	NR	NR	112 (55, 169)	89 (41, 166)	36 – 48% ‡	NR
Gao (’05)	< 6h	NR	NR	NR	NR	NR	NR
Gatewood (’15)	< 3h	50	84	NR	NR	NR	NR
Hayden (’16)	Broad spectrum antibiotics	NR	NR	139±74	81±39	54 – 77% ‡	NR
Kumar (’15)	<1h	29	52	NR	NR	NR	NR
Leisman 2012 (’16)	< 3h	68	100	87 (-10, 184)	38 (-19, 95)	NR	NR
Leisman 2014 (’16)	< 3h	75	100	66 (20, 172)	32 (1, 73)	NR	NR
Leisman 2015 (’16)	< 3h	59	100	85 (20, 208)	29 (-4, 66)	NR	NR
Liu (‘15)	< 3h	95	96	48±66	42±66	NR	NR
Prasad (’17)	< 3h in ED or < 1h as inpatient	NR	NR	NR	NR	NR	NR
Ruangchan (’16)	< 1h	40	89	NR	NR	NR	NR
Teles (’17)	< 1h	NR	NR	NR	NR	14% ‡	NR
Tse (’17)	<1h	39	73	NR	NR	88% ‡	NR

C – Control; B – Bundle group; NR – not reported;
* Reported as either mean (±SD) or median (IQR) minutes; † Variability for time to antibiotics, volume of fluid and time to fluid administration not reported;
‡ any culture positive, sensitivities to identified organism not provided

Appendix Table 6. Summary of data regarding fluid goals and infusion in the control and bundle groups in each of the 17 studies

Author (y)	Fluid Infusion						
	Goal	% of Patients Meeting Goal		Volume of fluid		Time to fluid	
		C	B	C	B	C	B
Austrian (’17)	NR	NR	NR	NR	NR	NR	NR
Bhat (’16)	≤ 1h	9	74	NR	NR	NR	NR
Bruce (’15)	≥ 20mL/kg ≤30min	58	72	NR	NR	NR	NR
De Miguel-Yanes (’09)	20mL/kg	NR	NR	NR	NR	NR	NR
Ferreras (’17)	30mL/kg	26	57	NR	NR	131 (88, 182)	92 (48, 170) ‡
Gao (’05)	500mL q30min	NR	NR	NR	NR	NR	NR
Gatewood (’15)	2L ≤2h	46	74	NR	NR	NR	NR
Hayden (’16)	30mL/kg	NR	NR	NR	NR	56±64	35±31
Kumar (’15)	≤1h	29	52	NR	NR	NR	NR
Leisman 2012 (’16)	≤30min	36	100	NR	NR	48 (-11,107)	4.5 (-32, 41)
Leisman 2014 (’16)	≤30min	36	100	NR	NR	34 (0, 73)	0 (0, 7)
Leisman 2015 (’16)	≤30min	31	100	NR	NR	42 (-20, 120)	0 (-48, 10)
Liu (‘16)	30mL/kg ≤3h	60	67	1800±1200	1900±1200	NR	NR
Prasad (’17)	Fluid bolus	NR	NR	NR	NR	NR	NR
Ruangchan (’16)	1.5 to 2L ≤2h	NR	NR	220 (160,628)	1500 (1000,2000)	NR	NR
Teles (’17)	30mL/kg	NR	NR	NR	NR	NR	NR
Tse (’17)	500-1000mL NS bolus, titrate up to 30mL/kg	NR	NR	NR	NR	NR	NR

C – Control; B – Bundle group; NR – not reported;

* Reported as either mean (±SD) or median (IQR) minutes; † Variability for time to antibiotics, volume of fluid and time to fluid administration not reported; ‡ Data verified with first author; § All the following fulfilled: signs and symptoms of infection, documented source of infection and ≥1 organ dysfunction; ‖ Time of laboratory result or vital sign measurement causing patient to meet sepsis criteria

¶ Time at which two SIRS critera and one sign of organ failure in the presence of known or suspected infection met

Appendix Table 7. Summary of data reported regarding lactate measurements, blood cultures, vasopressor administration and bundle use in patients in the control and bundle groups in each of the 17 studies

	Lactate Measurement						Blood Cultures		Vasopressor Administration				Bundle Use	
	% of patients with lactate measurement		Time to lactate measurement *		Lactate level		% of patients with blood cultures		% of patients with vasopressors		Time to vasopressors *		% of patients with all bundle components	
	C	B	C	B	C	B	C	B	C	B	C	B	C	B
Austrian ('17)	91	91	11 ±56	10±35	NR	NR	79	79	29	23	NR	NR	NR	NR
Bhat ('16)	9	81	NR	NR	NR	NR	67	100	NR	NR	NR	NR	1	67
Bruce (’15)	84	99	NR	NR	NR	NR	98	97	NR	NR	NR	NR	NR	NR
De Miguel-Yanes (’09)	12	46	NR	NR	NR	NR	85	78	NR	NR	NR	NR	NR	NR
Ferreras ('17)	69	86	NR	NR	NR	NR	50	66	NR	NR	NR	NR	NR	NR
Gao (’05)	0	100	NR	NR	NR	NR	46	100	38	100	NR	NR	0	100
Gatewood (’15)	63	92	NR	NR	NR	NR	90	96	NR	NR	NR	NR	28	71
Hayden (’16)	69	97	NR	NR	2.4±2.4	2.8±2.4	NR	NR	NR	NR	139±219	125±132	NR	NR
Kumar (’15)	18	10	NR	NR	NR	NR	33	52	NR	NR	NR	NR	4	8
Leisman 2012 (’16)	84	100	NR	NR	NR	NR	92	100	NR	NR	NR	NR	NR	NR
Leisman 2014 (’16)	94	100	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Leisman 2015 (’16)	74	100	NR	NR	NR	NR	59	100	NR	NR	NR	NR	NR	NR
Liu (‘15) †	NR	NR	114±126	114±72	2.6±0.6	2.6±0.6	NR	NR	NR	NR	NR	NR	34	45
Prasad (’17)	NR	100	NR	NR	NR	NR	NR	100	NR	100	NR	NR	28	72
Ruangchan (’16)	NR	NR	NR	NR	NR	NR	50	92	33	59	NR	NR	NR	NR
Teles (’17)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tse ('17)	39	73	NR	NR	NR	NR	29	73	NR	NR	NR	NR	NR	NR

C – Control; B – Bundle group; NR – not reported;
*reported as mean(±SD) minutes; † % of patients with second lactate 50% vs 51%

Appendix Table 8. Summary of whether educational and/or prioritized care aids were employed, the risk of bias and whether adverse events with bundle use were recorded in the 17 Studies

Authors (y)	Adjunctive Aid†	Educational Aid	Prioritized Care Aid			Risk of Bias	Adverse Events Recorded
		Lectures/ Meetings	Sepsis Alert	Expedited consult	Screening checklist	# of Elements Scored as High or Unknown Risk Out of 8 Possible	
Austrian (’17)	Yes	+	+	-	+	4	No
Bhat (’16)	Yes	-	+	-	-	5	No
Bruce (’15)	Yes	+	+	-	-	2	No
De Miguel-Yanes (’09)	Yes	+	?	?	?	2	No
Ferreras (’17)	Yes	+	+	-	+	3	No
Gao (’05)	No	-	-	-	-	4	No
Gatewood (’15)	Yes	-	+	-	+	4	No
Hayden (’16)	Yes	-	+	-	-	4	No
Kumar (’15)	Yes	+	-	-	+	4	No
Leisman 2012* (’16)	Yes	-	+	-	-	2	No
Leisman 2014*(’16)	Yes	-	+	-	-	2	No
Leisman 2015* (’16)	Yes	-	+	-	-	2	No
Liu (‘15)	Yes	+	-	-	-	3	No
Prasad (’17)	No	-	-	-	-	3	No
Ruangchan (’16)	No	-	-	-	-	4	No
Teles (’17)	No	-	-	-	-	3	No
Tse (’17)	Yes	+	-	-	+	3	No

* See text for description of these three cohorts

† Adjunctive aids included educational aids introduced to improve recognition or management of septic patients by providers (e.g. lectures or meetings) or prioritized care aids (e.g. sepsis pager/alert systems, expedited sepsis consults and sepsis checklists/ triage systems)

Appendix Table 9. Risk of bias assessment for all elements of the Newcastle-Ottawa Tool for each of the 17 observational studies

Author (y)	Selection Bias			Comparability Bias†		Outcome Bias‡		
	Intervention group represents at risk patients§	Controls from same population as intervention group	Data obtained from secure source	Analysis controlled for illness severity	Analysis controlled for co-morbidities, age, and infection site	Mortality assessed blindly or from record linkage	≥ 28d mortality reported	Adequacy follow-up ¶
Austrian ('17)	Yes	Yes	Yes	No	No	Yes	No	UK
Bhat ('16)	No	Yes	Yes	No	No	Yes	No	UK
Bruce ('15)	Yes	Yes	Yes	Yes	No	Yes	Yes	UK
De Miguel-Yanes ('09)	Yes	Yes	Yes	Yes	No	Yes	Yes	UK
Ferreras ('17)	Yes	Yes	Yes	No	No	Yes	Yes	UK
Gao ('05)	Yes	Yes	Yes	No	No	Yes	No **	UK
Gatewood ('15)	Yes	Yes	Yes	No	No	Yes	No **	UK
Hayden ('16)	Yes	Yes	Yes	No	No	Yes	No **	UK
Kumar ('15)	Yes	Yes	Yes	No	No	Yes	No **	UK
Leisman 2012* ('16)	Yes	Yes	Yes	Yes	No	Yes	No **	Yes
Leisman 2014*('16)	Yes	Yes	Yes	Yes	No	Yes	No **	Yes
Leisman 2015* ('16)	Yes	Yes	Yes	Yes	No	Yes	No **	Yes
Liu ('15)	Yes	Yes	Yes	Yes	No	Yes	Yes	UK
Prasad ('17)	Yes	Yes	Yes	Yes	No	Yes	No **	UK
Ruangchan ('16)	Yes	Yes	Yes	No	No	Yes	No **	UK
Teles ('17)	Yes	Yes	Yes	Yes	No	Yes	No **	UK
Tse ('17)	Yes	Yes	Yes	Yes	No	Yes	No	UK

UK = unknown;
* See Table 1 and text for description of these three cohorts;
† Mortality adjusted for severity of acute illness or co-morbid conditions including all of the following: age, chronic illness and site of infection;
‡ Mortality at ≥28d was considered long enough follow-up and reports had to state that follow-up was adequate;
§ Randomly selected patients or all consecutively encountered patients;
‖ Did not report adverse events;
¶ Study did not provide flow-sheet showing patients screened or reasons for exclusion after screening;
** Reported mortality less than 28-d mortality