Supplementary Information for

Assessing Appropriateness of Antibiotic Therapy: A Scoping Review of Definitions and Their Clinical Implication

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List of abbreviations

AAT	appropriate antibiotic therapy
AMS	antimicrobial stewardship
CDI	*Clostridioides difficile* infection
CNS	central nervous system
ED	emergency department
ESBL	extended-spectrum beta-lactamase
ICU	intensive care unit
i.v.	intravenous
IQR	interquartile range
KPC	*Klebsiella pneumoniae* carbapenemase
LOS	length of stay
MDR	multi drug resistance
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
RCT	randomized controlled trial
spp.	species pluralis
A. baumannii	*Acinetobacter baumannii*
A. calcoaceticus	*Acinetobacter calcoaceticus*
A. nosocomialis	*Acinetobacter nosocomialis*
C. difficile	*Clostridioides difficile*
E. aerogenes	*Enterobacter aerogenes*
E. cloacae	*Enterobacter cloacae*
E. coli	*Escherichia coli*
E. faecalis	*Enterococcus faecalis*
E. faecium	*Enterococcus faecium*
E. meningoseptica	*Elizabethkingia meningoseptica*
K. oxytoca	*Klebsiella oxytoca*
K. pneumoniae	*Klebsiella pneumoniae*
L. monocytogenes	*Listeria monocytogenes*
L. pneumophila	*Legionella pneumophila*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
P. aeruginosa	*Pseudomonas aeruginosa*
P. mirabilis	*Proteus mirabilis*
S. agalactiae	*Streptococcus agalactiae*
S. aureus	*Staphylococcus aureus*
S. maltophilia	*Stenotrophomonas maltophilia*
S. pneumoniae	*Streptococcus pneumoniae*
S. saprophyticus	*Staphylococcus saprophyticus*
VRE	Vancomycin-resistant *enterococci*

S Table 1: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	p. 1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	p. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	p. 3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	p. 3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	p. 4
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	p. 4
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	p. 4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Suppl. p. 9-10
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	p. 4
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	p. 4
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	p. 4-5, Suppl. p. 7-8
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	not applicable
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	p. 5
RESULTS			

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	p. 6
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Suppl. p. 12-55
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	not applicable
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Suppl. p. 12-55
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	p. 5-13
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	p. 13-14
Limitations	20	Discuss the limitations of the scoping review process.	p. 18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	p. 18
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	p. 19

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

S Section 1: Detailed Study Methodology

In order to gain a comprehensive overview of studies and identify existing research gaps, a systematic literature search was conducted. We targeted studies evaluating the effect of AAT on patient outcomes in adult patients with confirmed or suspected bacterial infections treated in the inpatient setting. Studies published after 2011 were included as we did not expect earlier publications to incorporate AMS recommendations on defining AAT.

Search Strategy

We conducted the literature search on November 24, 2021 in PubMed, Web of Science and Cochrane Library. Search terms combining antibiotic therapy, appropriate or adequate and outcome measures were used (full search terms provided in supplements p. 9. Originally, search terms were developed to identify studies evaluating the impact of antibiotic stewardship programs on AAT as well. However, this group of studies is not included in the current analysis and will be presented elsewhere, as we focus here on research associating risk factors with clinical outcomes. Search results were managed with EndNote.

Eligibility Criteria

Screening procedures were performed by one of the authors (LN) and questions were discussed with a second author (PB). Discrepancies were sorted and reason for exclusion was noted. No blinding to study authors or location was done. Retrospective and prospective observational studies with control groups were included, but not reviews, case reports or conference contributions. Inclusion was limited to studies available in English language. Exclusion criteria were: studies evaluating prophylactic antibiotic use, studies conducted in dental care or outpatient settings, nursing homes and long-term care facilities, pediatric cohorts, cohorts with over 10% percent of patients infected with a non-bacterial pathogen, cohorts focusing on COVID-19 or HIV only. Publications had to evaluate the impact of appropriate or adequate antibiotic therapy on patient outcomes and/or emergence of antibiotic resistance. When multiple publications presented data from the same study or database and analyzed time periods were overlapping, we chose to include the study presenting a larger cohort of patients and/or the more recent publication only.

Data Extraction

The data was extracted by two of the authors (LN and AH), and questions were discussed with a third author (PB). Extracted variables included study inclusion criteria, the definition(s) of AAT applied and all available outcomes of interest. Variables were extracted into a REDCap database.

Definition of AAT

Recent literature suggesting QIs for AAT was used to create a predefined list of potential aspects used in definitions of AAT. Each study definition of AAT was checked for the following aspects: in-vitro susceptibility, timely initiation of therapy, dosing, route of administration, aminoglycoside restriction, duration of therapy, guideline-based choice of therapy, expert assessment, diagnostic procedures (such as taking blood cultures), adequate documentation of therapy in patient notes, antibiotic de-escalation, switch to oral therapy when feasible and process-related measures (such as bedside consultation). When other aspects were used, these were additionally extracted. The detailed steps used to determine the appropriateness of treatment based on these aspects were investigated. When a study used a comprehensive definition for AAT (for overall treatment) but reported outcomes in relation to empirical and definite therapy separately, we counted the definition towards both empirical and definite AAT individually. Otherwise, it was considered a definition for the entire treatment course. Definitions of AAT that had no related outcome were excluded from data analysis, while outcomes without an associated definition were considered to pertain to an "unclear" definition.

To investigate factors that influenced how AAT was defined, we grouped AAT definitions as follows: studies defining appropriateness by susceptibility only, by susceptibility and one other aspect (with a subcategory of susceptibility and timely initiation of therapy), by susceptibility and at least two other aspects and studies defining AAT non-susceptibility centered (such as guideline-based definitions). In this context, susceptibility referred to therapy based on individual in-vitro susceptibility testing. We also studied the development of the AAT definition, and the limitations and/or strengths mentioned by study authors regarding their own definitions. We compared relevant characteristics of studies including type of infection setting after grouping similar AAT definitions to identify any pattern in the use of definitions.

Outcomes related to AAT

All patient outcomes reported in relation to AAT were included. Details on the direction of association (AAT or IAT associated with favorable outcome), type of analysis (univariable or multivariable), and whether a significant effect ($p < 0.05$) was found, were extracted. Results of multivariable analysis were extracted whenever available; when not, univariable analysis was used. An association was referred to as independent when AAT was significantly and favorably associated with the outcome after adjustment for other risk factors in a multivariable analysis, e.g. AAT being significantly associated with lower mortality or shorter LOS. Outcomes based on the entire study cohort were preferred over subgroup-based outcomes. All-cause mortality was classified as early mortality (2 to 15 days), late mortality (21 to 30 days) or long-term mortality (>30 days to 1-year mortality). Overall mortality

without mention of a time period was grouped along with in-hospital mortality. Clinical failure was summarized along with clinical success after harmonizing the direction of association (details provided in supplements p. 11).

Potential risk factors

We also evaluated which potential risk factors other than AAT were considered for their effect on outcomes of interest. Covariates related to disease severity, comorbidities, immunosuppression and infection with a resistant pathogen were specifically checked to see whether they were considered as a risk factor in the study (as univariable analysis). All independent risk factors found significant upon multivariable analysis were broadly classified into categories of disease severity, comorbidities, immunosuppression, infection with a resistant pathogen, age, treatment, past treatment, pathogen, focus of infection, site of acquisition, institutional factors, sex, and microbiological factors.

Other definitions

Sepsis, septic shock, febrile neutropenia and bacteremia (including bacteremia due to specific foci, such as bacteremic urinary tract infection) were summarized as bloodstream infection (BSI). A subgroup of severe BSI including sepsis and septic shock was formed. With regard to acquisition, studies were classified as enrolling healthcare-acquired infection (HCAI, including both hospital-acquired and healthcare-associated infection), community-acquired infection (CAI, infections acquired outside the hospital as well as studies combining CAI and healthcare-associated infection) or unrestricted. Studies targeting patients with malignancy, undergoing stem cell transplantation or solid organ transplant recipients were grouped together as “immunosuppressed and cancer patients”.

S Section 2: Search Terms used in PubMed, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL)

PubMed:

("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents" [Pharmacological Action] OR Anti-infective agents [MeSH] OR Antibiotic* [tiab] OR Antiinfective* [tiab] OR "Anti infective*" [tiab] OR Antimicrobial* [tiab] OR "Anti microbial*" [tiab] OR Antibacterial* [tiab] OR "Anti bacterial*" [tiab]) AND (Stewardship [tiab] OR Policy [tiab] OR Policies [tiab] OR guideline*[tiab] OR inappropriat*[tiab] OR inadequat*[tiab] OR appropriat*[tiab] OR adequate*[tiab]) AND ((mortalit*[tiab] OR death[tiab] OR dead[tiab] OR alive[tiab] OR surviv*[tiab] OR "length of stay"[tiab] OR (("hospital stay"[tiab] OR hospitalization[tiab]) AND (length[tiab] OR period[tiab])) OR "length of hospitalisation"[tiab] OR "duration of hospitalization"[tiab] OR LOS[tiab] OR "Morbidity"[Mesh:NoExp] OR morbidit*[tiab] OR "Drug Resistance"[Mesh] OR resistan*[tiab])) AND ("2011/01/01"[Date - Publication] : "2021/11/24"[Date - Publication]) AND ("observational study"[tiab] OR "retrospective study"[tiab] OR "prospective study"[tiab] OR "trial"[tiab] OR "cohort"[tiab] OR "intervention* study"[tiab] OR "case-control study"[tiab] OR "case control study"[tiab] OR "cross sectional study"[tiab] OR "cross-sectional study"[tiab] OR "prospective analysis"[tiab] OR "retrospective analysis"[tiab] OR "study investigation"[tiab] OR "study investigati"[tiab] OR research[tiab] OR intervention*[tiab]) NOT "review"[Title] NOT "Malaria*"[tiab] NOT "HIV"[tiab] NOT (Review[Publication Type]) NOT (systematic review[Publication Type]) NOT ("dental" [tiab])) NOT ("dentist*" [tiab])) NOT ("antifung*" [Title])) NOT ("neonat*" [Title])) NOT ("infant*" [Title])) NOT children[Title])) NOT pediatric[Title])) NOT paediatric[Title])) NOT ("ambulatory" [Title])) NOT ("primary care" [Title])) NOT ("outpatient*" [Title])) NOT ("general practitioner*" [Title])) NOT ("prophyla*" [Title]) NOT ("COVID" [Title]) NOT (Case reports[pt]) NOT (editorial[pt]) NOT (News[pt]) AND (humans[Filter]))

Web of Science:

TS=("Anti bacterial" OR "anti infective" OR antibiotic OR antiinfective OR antimicrobial OR "anti microbial" OR antibacterial) AND TS=(stewardship OR (polic* NEAR/3 antibiotic) OR (polic* NEAR/3 antimicrobial) OR (guideline* NEAR/3 antibiotic) OR (guideline* NEAR/3 antimicrobial) OR inappropriat* OR inadequat* OR appropriat* OR adequat*) AND TS=("mortalit*" OR "death" OR "dead" OR "alive" OR "survi*" OR "length of stay" OR "length of hospitalisation" OR "duration of hospitalization" OR "LOS" OR "morbidit*" OR "resistan*") AND TS= ("observational study" OR "retrospective NEAR/3 study" OR "prospective NEAR/3 study" OR "trial" OR "cohort" OR "intervention* NEAR/5 study" OR "case-control* study" OR "case control* NEAR/3 study" OR "prospective NEAR/5 analys*s" OR "retrospective NEAR/5 analys*s" OR "research NEAR/5 investigati*" OR "study NEAR/5 investigati*" OR research OR cross-sectional NEAR/3 study OR "cross sectional" NEAR/3 study) NOT TS=("malaria*" OR "HIV" OR "dental" OR "dentist*") NOT TI=("neonat*" OR "pediatric*" OR "ambulatory" OR "primary care" OR "outpatient*" OR "general practitioner*" OR "prophyla*" OR "COVID" OR "review") NOT DT==("REVIEW" OR "RETRACTION" OR "REPRINT" OR "CORRECTION" OR "MEETING ABSTRACT" OR "LETTER" OR "BOOK CHAPTER" OR "EDITORIAL MATERIAL" OR "PROCEEDINGS PAPER") NOT TS=("veterinary" OR "animal" OR "agriculture")

Cochrane Central Register of Controlled Trials (CENTRAL):

#1	("Anti bacterial" OR "anti infective" OR antibiotic OR antiinfective OR antimicrobial OR "anti microbial" OR antibacterial):ti,ab,kw
#2	("mortalit*" OR "death" OR "dead" OR "alive" OR "survi*" OR "length of stay" OR "length of hospitalisation" OR "duration of hospitalization" OR "LOS" OR "morbidit*" OR "resistan*"):ti,ab,kw
#3	(stewardship OR (polic* NEAR antibiotic) OR (polic* NEAR antimicrobial) OR (guideline* NEAR antibiotic) OR (guideline* NEAR antimicrobial) OR inappropriat* OR inadequat* OR appropriat* OR adequat*):ti,ab,kw
#4	("observational study" OR (retrospective NEAR study) OR (prospective NEAR study) OR "trial" OR "cohort" OR (intervention* NEAR study) OR "case-control*study" OR ("case control" NEAR study) OR (prospective NEAR analys*s) OR (retrospective NEAR analys*s) OR (research NEAR investigati*) OR (study NEAR investigati*) OR "research" OR (cross-sectional NEAR study) OR ("cross sectional" NEAR study)):ti,ab,kw
#5	#1 AND #2 AND #3 AND #4
#6	("neonat*" OR "pediatric*" OR "ambulatory" OR "primary care" OR "outpatient*" OR "general practicioner*" OR "prophylax*" OR "COVID" OR "review" OR "veterinary" OR "animal" OR "agriculture"):ti
#7	("malaria*" OR "HIV" OR "dental" OR "dentist*"):ti,ab,kw
#8	#5 NOT (#6 OR #7) with Cochrane Library publication date Between Jan 2011 and Nov 2021

S Section 2: Grouping of study outcomes: clinical failure, clinical success and adverse events

Outcomes grouped together as “clinical failure”:

- Readmission or death within 30 days
- Recurrence of urinary tract infection
- Poor prognosis
- Progression from tracheobronchitis to pneumonia
- Slowly resolving pneumonia
- Unfavorable outcomes

Outcomes grouped together as “clinical success”:

- Resolution of pneumonia on day 28
- Time until defervescence and time until normalization of peripheral leucocyte count (composite)
- Resolution of secondary peritonitis
- Clinical response within 72 hours (decline of fever, leukocytosis and C-reactive protein, improvement of hypoxemia and shock)
- Extubation or discharge alive
- Discharge alive after more than 48h without transition to hospice or palliative care

Outcomes grouped as “adverse events”:

- Infectious complications
- Mechanical ventilation
- Surgical complications by day 30
- Relaparotomy or percutaneous drainage by day 30

S Table 2: Overview of characteristics of included studies

First Author	Year	Study design[a]	Country	Mention of AAT in study objectives	Pathogen	Infectious Focus	Phase(s) of antibiotic treatment studied	Outcome
De Rosa [1]	2011	retrospective cohort study	Italy	yes	ESBL-producing *E. coli*, *K. pneumoniae* or *P. mirabilis*	bacteremia	empiric	all-cause 21-day mortality
Fayad [2]	2011	retrospective cohort study	France	no	unrestricted	infective endocarditis	unclear	all-cause in-hospital mortality
Fernández-Hidalgo [3]	2011	prospective cohort study	Spain	yes	unrestricted	left-sided infective endocarditis	overall	- all-cause in-hospital mortality - adverse events (acute kidney injury)
Johnson [4]	2011	retrospective cohort study	United States	no	gram-negative bacteria	severe sepsis	empiric	all-cause in-hospital mortality
Joo [5]	2011	retrospective cohort study	South Korea	yes	*P. aeruginosa*	bacteremia	empiric	all-cause 30-day/1 month mortality
Lin [6]	2011	retrospective case cohort based on case control study	Taiwan	no	unrestricted	bacteremia	empiric	all-cause 28-day mortality
Micek [7]	2011	retrospective cohort study	United States	yes	unrestricted	healthcare-associated pneumonia	empiric	all-cause in-hospital mortality
Montravers [8]	2011	prospective cohort study	France	no	unrestricted	unrestricted	empiric	all-cause ICU mortality
Plataki [9]	2011	retrospective / secondary analysis of prospective data	United States	no	unrestricted	septic shock	empiric	adverse events (acute kidney injury)
Reisfeld [10]	2011	retrospective cohort study	Israel	yes	gram-negative bacteria	bacteremia	- empiric - definite	all-cause 30-day/1 month mortality
Rello [11]	2011	prospective cohort study	Belgium, France, Germany,	no	unrestricted	hospital-acquired pneumonia, ventilator-	empiric	- all-cause mortality - ICU length of stay

			Greece, Italy, Ireland, Portugal, Spain, Turkey			associated pneumonia		- duration of mechanical ventilation
Schechner [12]	2011	prospective cohort study	Israel	yes	*P. aeruginosa*	bacteremia	empiric	all-cause in-hospital mortality
Schreiber [13]	2011	retrospective cohort study	United States	no	*S. aureus*	pneumonia	empiric	all-cause in-hospital mortality
Seligman [14]	2011	prospective cohort study	Brazil	no	unrestricted	ventilator-associated pneumonia	empiric	all-cause 28-day mortality
Shorr [15]	2011	retrospective cohort study	United States	yes	gram-negative bacteria	severe sepsis	empiric	in-hospital length of stay
Suppli [16]	2011	retrospective / secondary analysis of prospective data	Denmark	yes	*E. faecalis*, *E. faecium*	bloodstream infection	overall	all-cause 30-day/1 month mortality
Tumbarello [17]	2011	retrospective cohort study	Italy	no	*P. aeruginosa*	bloodstream infection	empiric	all-cause 21-day mortality
Wang [18]	2011	retrospective cohort study	Taiwan	no	ESBL-producing *E. coli* or *K. pneumoniae*	bacteremia	- empiric - definite	all-cause 14-day mortality
Zarkotou [19]	2011	prospective cohort study	Greece	yes	KPC-producing *K. pneumoniae*	bloodstream infection	- empiric - definite	infection-related in-hopital mortality
Aguilar-Duran [20]	2012	prospective cohort study	Spain	no	gram-negative bacilli, *Enterococcus* spp, *Staphylococcus* spp, betahemolytic *Streptococcus* spp.	bacteremic urinary tract infection	empiric	all-cause 30-day/1 month mortality
Ariza [21]	2012	retrospective cohort study	Spain	yes	unrestricted	spontaneous bacterial peritonitis	empiric	all-cause 30-day/1 month mortality
Bouza [22]	2012	prospective cohort study	Spain	no	unrestricted	ventilator-associated pneumonia	empiric	all-cause in-hospital mortality

Castillo [23]	2012	retrospective case cohort based on case control study	Colombia	no	*S. aureus*	bacteremia	empiric	all-cause 30-day/1 month mortality
Chidiac [24]	2012	prospective cohort study	France	no	*L. pneumophila*	Legionnaires' disease	- empiric - definite	all-cause 30-day/1 month mortality
Chuang [25]	2012	prospective cohort study	Taiwan	yes	*A. baumannii*	bacteremia	unclear	microbiological failure
de Gouvêa [26]	2012	retrospective cohort study	Brazil	no	*A. baumannii*	unrestricted	empiric	- infection-related mortality - all-cause 30-day/1 month mortality
Gözel [27]	2012	prospective cohort study	Turkey	no	gram-negative bacteria	bloodstream infection	empiric	- all-cause 14-day mortality - all-cause 30-day/1 month mortality
Halilovic [28]	2012	retrospective cohort study	United States	no	unrestricted	cellulitis, cutaneous abscess	empiric	clinical failure (repeat incision and drainage, change in antimicrobial therapy or extension of antimicrobial duration due to inadequate response)
Hernández-Torres [29]	2012	prospective cohort study	Spain	yes	multidrug and carbapenem-resistant *A. baumannii*	unrestricted	- empiric - definite	all-cause in-hospital mortality
Horino [30]	2012	retrospective cohort study	Japan	no	*P. aeruginosa*	bacteremia	empiric	all-cause 30-day/1 month mortality
Huang [31]	2012	retrospective cohort study	Taiwan	no	*A. baumannii*	bacteremia	empiric	all-cause 30-day/1 month mortality
Jung [32]	2012	retrospective cohort study	South Korea	no	*K. pneumoniae*	bloodstream infection	- empiric - definite	all-cause 30-day/1 month mortality
Kim [33]	2012	retrospective cohort study	South Korea	yes	*A. baumannii*	bloodstream infection	definite	all-cause 14-day mortality

Lee [34]	2012	retrospective cohort study	Taiwan	no	ESBL-producing *E. coli* or *K. pneumoniae*	bacteremia	empiric	infection-related in-hopital mortality
Lye [35]	2012	retrospective cohort study	Singapore	no	Enterobacteriaceae, *P. aeruginosa*, *A. baumannii*	septic bacteremia	- empiric - definite	- all-cause 30-day/1 month mortality - post-infection hospital length of stay
Micek [36]	2012	retrospective cohort study	United States	no	gram-negative bacteria	severe sepsis or septic shock	empiric	in-hospital length of stay
O'Neal [37]	2012	retrospective cohort study	United States	no	*Enterobacter* spp.	bacteremia	empiric	- all-cause in-hospital mortality - clinical failure (non-resolving infection signs, ongoing fluid resuscitation or persistent Enterobacter bacteremia within 72 h, inotropic support > 72 h)
Park [38]	2012	retrospective cohort study	South Korea	no	*P. aeruginosa*	bacteremic pneumonia	empiric	- all-cause 7-day mortality - all-cause 14-day mortality - all-cause 28-day mortality
Qureshi [39]	2012	retrospective case cohort based on case control study	United States	no	*E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. cloacae*, *E. aerogenes*	bacteremia	empiric	all-cause 28-day mortality
Sancho [40]	2012	prospective cohort study	Spain	no	unrestricted	bloodstream infection	empiric	infection-related in-hopital mortality
Silveira [41]	2012	retrospective cohort study	Brazil	yes	unrestricted	community-acquired pneumonia	empiric	all-cause 30-day/1 month mortality

Tabah [42]	2012	prospective cohort study	Belgium, Netherlands, Germany, Poland, Romania, Hungary, Turkey, Greece, Serbia, Croatia, Italy, Austria, Spain, Portugal, France, Switzerland, Canada, Brazil, Morocco, Tunisia, United Arab Emirates, China, Australia, Japan	no	unrestricted	bloodstream infection	unclear	all-cause 28-day mortality
Tumbarello [43]	2012	retrospective case cohort based on case control study	Italy	no	*P. mirabilis*	bloodstream infection	empiric	all-cause 21-day mortality
Wu [44]	2012	prospective cohort study	Taiwan	no	ESBL-producing *E. coli*	bloodstream infection	empiric	all-cause 30-day/1 month mortality
Zervos [45]	2012	retrospective cohort study	United States	yes	unrestricted	complicated skin and soft tissue infection	empiric	- all-cause in-hospital mortality - in-hospital length of stay - clinical failure (readmission or death by day 30)

Adrie [46]	2013	retrospective / secondary analysis of prospective data	France	yes	unrestricted	community-acquired pneumonia	empiric	all-cause 60-day/2 month mortality
Bowers [47]	2013	retrospective cohort study	USA, Singapore	no	*P. aeruginosa*	bacteremia	empiric	all-cause 30-day/1 month mortality
Capone [48]	2013	prospective cohort study	Italy	no	Ertapenem-resistant *K. pneumoniae*	unrestricted	unclear	all-cause in-hospital mortality
Cardoso [49]	2013	prospective cohort study	Portugal	yes	unrestricted	unrestricted	empiric	all-cause in-hospital mortality
Ferreira [50]	2013	retrospective cohort study	Portugal	no	unrestricted	infective endocarditis	overall	all-cause in-hospital mortality
Gasch [51, 52]	2013	prospective cohort study	Spain	no	MRSA	bacteremia	empiric	- all-cause 2-day mortality - all-cause 30-day/1 month mortality
Heintz [53]	2013	retrospective cohort study	United States	no	VRE	urinary tract infection	- empiric - definite	clinical failure (extended antibiotic therapy within 30 days, positive follow-up blood culture within 7 days of completing treatment, 30-day infection-related readmission or 30-day all-cause mortality)
Horcajada [54]	2013	prospective cohort study	Spain	yes	*Enterobacteriaceae*, *P. aeruginosa*, non-fermenting gram-negative bacilli, *Enterococcus* spp., *S. saprophyticus*	bacteremic urinary tract infection	empiric	all-cause 30-day/1 month mortality
Kang [55]	2013	retrospective cohort study	South Korea	yes	unrestricted	bacteremic biliary tract infection	- empiric - definite, no definition	all-cause 30-day/1 month mortality
Kang [56]	2013	retrospective cohort study	South Korea	no	ESBL-producing *E. coli*	bacteremia	empiric	- all-cause 30-day/1 month mortality

								- clinical failure (no improvement, deterioration of clinical parameters or death by day 3)
Kuo [57]	2013	retrospective cohort study	Taiwan	yes	*A. nosocomialis*	bacteremia	empiric	all-cause 14-day mortality
Lee [58]	2013	retrospective cohort study	Taiwan	yes	unrestricted	bacteremia	empiric	all-cause 28-day mortality
Lee [59]	2013	unclear/unknown	Taiwan	no	*A. baumannii*, *A. nosocomialis*	bacteremic hospital-acquired pneumonia	empiric	all-cause 14-day mortality
Metan [60]	2013	retrospective cohort study	Turkey	no	gram-negative bacteria	bacteremia	empiric	all-cause 7-day mortality
Navarro-San Francisco [61]	2013	prospective cohort study	Spain	no	carbapenemase-producing Enterobacteriaceae	bloodstream infection	other	all-cause 30-day/1 month mortality
Palmer [62]	2013	prospective cohort study	United States	no	gram-negative bacteria	bacteremia	empiric	all-cause in-hospital mortality
Park [63]	2013	retrospective cohort study	South Korea	yes	*P. aeruginosa*, *A. baumannii*	bacteremia	- empiric - definite, no definition	all-cause 14-day mortality
Peña [64]	2013	retrospective cohort study	Spain	no	*P. aeruginosa*	ventilator-associated lower respiratory tract infection	- empiric - definite	- all-cause 7-day mortality - all-cause in-hospital mortality
Phua [65]	2013	prospective cohort study	Singapore	no	unrestricted	severe sepsis	empiric	all-cause in-hospital mortality
Retamar [66]	2013	prospective cohort study	Spain	no	unrestricted	bloodstream infection	empiric	- all-cause 14-day mortality - all-cause 30-day/1 month mortality
Ruiz-Giardin [67]	2013	retrospective cohort study	Spain	yes	unrestricted	bacteremia	empiric	all-cause mortality
Shorr [68]	2013	retrospective cohort study	United States	no	unrestricted	non-nosocomial pneumonia	empiric	all-cause hospital readmission

Tumbarello [69]	2013	retrospective / secondary analysis of prospective data	Italy	yes	*P. aeruginosa*	hospital-acquired pneumonia, healthcare-associated pneumonia	empiric	- all-cause ICU mortality - duration of mechanical ventilation
Vallés [70]	2013	retrospective / secondary analysis of prospective data	Spain	no	unrestricted	bacteremia	empiric	all-cause ICU mortality
Willmann [71]	2013	retrospective cohort study	Germany	no	*P. aeruginosa*	bloodstream infection	- empiric - definite	- all-cause in-hospital mortality - in-hospital length of stay
Yang [72]	2013	retrospective cohort study	Taiwan	yes	unrestricted	bacteremia	empiric	all-cause in-hospital mortality
Yang [73]	2013	retrospective cohort study	Taiwan	no	*A. baumannii*, *A. nosocomialis*	bloodstream infection	empiric	all-cause 14-day mortality
Zheng [74]	2013	retrospective cohort study	China	no	*A. baumannii*	nosocomial pneumonia	empiric	all-cause 28-day mortality
Anderson [75]	2014	retrospective cohort study	United States	yes	unrestricted	bloodstream infection	empiric	- all-cause in-hospital mortality - ICU admission - in-hospital length of stay - post-infection hospital length of stay - all-cause hospital readmission
Bloos [76]	2014	prospective cohort study	Germany	yes	unrestricted	severe sepsis or septic shock	empiric	all-cause 28-day mortality
Chusri [77]	2014	retrospective cohort study	Thailand	no	*A. calcoaceticus-baumannii* complex	unrestricted	empiric	all-cause 30-day/1 month mortality
Corrêa [78]	2014	secondary data from an RCT	Brazil	no	unrestricted	ventilator-associated pneumonia	empiric	all-cause 28-day mortality

De Bus [79]	2014	retrospective cohort study	Belgium	no	unrestricted	hospital-acquired pneumonia	empiric	- all-cause ICU mortality - ICU length of stay
Esparcia [80]	2014	retrospective cohort study	Spain	yes	unrestricted	urinary tract infection	empiric	all-cause in-hospital mortality
Falcone [81]	2014	prospective cohort study	Italy	no	ESBL-producing Enterobacteriaceae	bloodstream infection	empiric	all-cause 21-day mortality
Fayad [82]	2014	retrospective cohort study	France	no	unrestricted	infective endocarditis	other	all-cause in-hospital mortality
Garnacho-Montero [83]	2014	prospective cohort study	Spain	no	unrestricted	severe sepsis or septic shock	empiric	all-cause in-hospital mortality
Girometti [84]	2014	retrospective cohort study	Italy	yes	*K. pneumoniae*	bloodstream infection	empiric	all-cause 30-day/1 month mortality
Gonçalves-Pereira [85]	2014	prospective cohort study	Portugal	no	unrestricted	unrestricted	empiric	all-cause in-hospital mortality
Hsu [86]	2014	retrospective cohort study	Taiwan	no	*S. aureus*	bacteremia	empiric	all-cause in-hospital mortality
Jeong [87]	2014	retrospective / secondary analysis of prospective data	South Korea	no	unrestricted	community-acquired severe pneumonia, healthcare-associated severe pneumonia	empiric	all-cause in-hospital mortality
Kim [88]	2014	retrospective cohort study	South Korea	yes	*P. aeruginosa*	bacteremia	- empiric - definite	all-cause 14-day mortality
Lee [89]	2014	retrospective cohort study	Taiwan	no	*A. baumannii* complex	bacteremia	empiric	infection-related 30-day/1 month mortality
Lipsky [90]	2014	prospective cohort study	United States	yes	unrestricted	complicated skin and soft tissue infection	empiric	in-hospital length of stay
Membrilla-Fernández [91]	2014	prospective cohort study	Spain	yes	unrestricted	secondary peritonitis	empiric	- all-cause mortality - clinical failure (no complete resolution of all symptoms of infection)

Nygård [92]	2014	prospective cohort study	Norway	no	unrestricted	severe sepsis	2 definitions for empiric	all-cause in-hospital mortality
Park [93]	2014	prospective cohort study	South Korea	no	unrestricted	severe sepsis or septic shock	empiric, no definition	all-cause 28-day mortality
Pelegrín [94]	2014	retrospective / secondary analysis of prospective data	Spain	no	*L. monocytogenes*	meningoencephalitis	empiric	all-cause in-hospital mortality
Shorr [95]	2014	retrospective cohort study	United States	yes	*Acinetobacter* spp.	sepsis	empiric	all-cause in-hospital mortality
Spoorenberg [96]	2014	retrospective cohort study	Netherlands	yes	unrestricted	complicated urinary tract infection	overall	in-hospital length of stay
Vallés [97]	2014	prospective cohort study	Spain	no	unrestricted	severe community-acquired pneumonia, severe healthcare-associated pneumonia	empiric	all-cause ICU mortality
Van Aken [98]	2014	retrospective case cohort based on case control study	Sweden	no	*E. coli*	bacteremia	empiric	- all-cause 14-day mortality - post-infection hospital length of stay
Vilella [99]	2014	retrospective cohort study	United States	yes	unrestricted	sepsis	empiric	- all-cause in-hospital mortality - ICU length of stay
Yokota [100]	2014	retrospective cohort study	Brazil	yes	unrestricted	severe sepsis or septic shock	empiric	all-cause in-hospital mortality
Zeng [101]	2014	retrospective cohort study	China	no	gram-negative bacteria	severe sepsis or septic shock	definite	all-cause 30-day/1 month mortality
Zilberberg [102]	2014	retrospective cohort study	United States	yes	gram-negative bacteria	severe sepsis or septic shock	empiric	all-cause in-hospital mortality
Al-Dorzi [103]	2015	retrospective cohort study	Saudi Arabia	yes	*Acinetobacter* spp.	bacteremia	empiric	- all-cause in-hospital mortality - all-cause ICU mortality

								- in-hospital length of stay - ICU length of stay - duration of mechanical ventilation
Allou [104]	2015	prospective cohort study	France	no	unrestricted	postoperative pneumonia	empiric	all-cause in-hospital mortality
Andria [105]	2015	retrospective cohort study	Israel	no	gram-negative aerobic bacteria	bacteremia	empiric	- all-cause 14-day mortality - all-cause 1-year mortality
Bass [106]	2015	retrospective cohort study	United States	yes	carbapenem-resistant gram-negative bacteria	septic bloodstream infection	unclear	all-cause 30-day/1 month mortality
Bastug [107]	2015	retrospective cohort study	Turkey	no	unrestricted	sterile site infection, bloodstream infection, urinary tract infection	empiric	all-cause 30-day/1 month mortality
Beuving [108]	2015	Secondary data from an RCT	Netherlands	yes	gram-positive cocci, facultative aerobic gram-negative rods	bloodstream infection	unclear	- all-cause 30-day in-hospital mortality - in-hospital length of stay
Boel [109]	2015	retrospective cohort study	Denmark	yes	unrestricted	bacteremia	empiric	- all-cause 30-day/1 month mortality - all-cause hospital readmission - acute hospital readmission - infection-related hospital readmission
Brigmon [110]	2015	retrospective cohort study	United States	no	aerobic gram-negative bacteria	bloodstream infection	empiric	in-hospital length of stay

Coccolini [111]	2015	retrospective / secondary analysis of prospective data	multinational	no	unrestricted	intraabdominal infection secondary to acute cholecystitis	empiric	- all-cause mortality - ICU admission
Denis [112]	2015	retrospective case cohort based on case control study	France	no	*E. coli*	bacteremia	empiric	all-cause 21-day mortality
Dimopoulos [113]	2015	retrospective / secondary analysis of prospective data	Greece	no	unrestricted	bloodstream infection	empiric	all-cause 28-day mortality
Inchai [114]	2015	retrospective cohort study	Thailand	no	unrestricted	ventilator-associated pneumonia	empiric	all-cause 30-day/1 month mortality
Katsiari [115]	2015	prospective cohort study	Greece	no	carbapenemase-producing *K. pneumoniae*	unrestricted	empiric	infection-related 14-day mortality
Lee [116]	2015	retrospective cohort study	Taiwan	no	MRSA	bacteremia	empiric	infection-related 30-day/1 month mortality
Martin-Loeches [117]	2015	prospective cohort study	Spain	no	unrestricted	ICU-acquired pneumonia	empiric	all-cause ICU mortality
Martin-Loeches [118]	2015	prospective cohort study	Spain, France, Portugal, Brazil, Argentina, Ecuador, Bolivia, Colombia	no	unrestricted	ventilator-associated lower respiratory tract infection	empiric	- all-cause ICU mortality - clinical failure (progression from tracheobronchitis to pneumonia)
Oliveira [119]	2015	retrospective case cohort based on case control study	Brazil	no	Enterobacteriaceae	unrestricted	empiric	- all-cause in-hospital mortality
Park [120]	2015	retrospective cohort study	South Korea	yes	coagulase-negative staphylococci	bacteremia	empiric	- all-cause 30-day/1 month mortality - infection-related 30-day/1 month mortality

Rabello [121]	2015	retrospective / secondary analysis of prospective data	Brazil	no	unrestricted	community-acquired pneumonia, healthcare-associated pneumonia	empiric	all-cause in-hospital mortality
Ratzinger [122]	2015	prospective cohort study	Austria	yes	unrestricted	sepsis	empiric	all-cause in-hospital mortality
Shindo [123]	2015	prospective cohort study	Japan	yes	unrestricted	community-acquired pneumonia, healthcare-associated pneumonia	empiric	- all-cause 30-day/1 month mortality - all-cause in-hospital mortality
Su [124]	2015	retrospective cohort study	Taiwan	no	cefepime-resistant *P. aeruginosa*	bacteremia	empiric	- all-cause 30-day/1 month mortality - all-cause 15-day mortality
Suberviola Cañas [125]	2015	prospective cohort study	Spain	yes	unrestricted	septic shock	unclear	all-cause in-hospital mortality
Sumida [126]	2015	retrospective case cohort based on case control study	Japan	no	*S. maltophilia*, *P. aeruginosa*	bacteremia	unclear	all-cause 30-day/1 month mortality
Torres [127]	2015	prospective cohort study	Spain	no	unrestricted	community-acquired pneumonia	empiric	all-cause 30-day in-hospital mortality
Tumbarello [128]	2015	retrospective cohort study	Italy	no	KPC-producing *K. pneumoniae*	unrestricted	empiric	all-cause 14-day mortality
Wu [129]	2015	retrospective cohort study	China	no	unrestricted	bloodstream infection	empiric	all-cause 28-day mortality
Abraham [130]	2016	retrospective cohort study	United States	yes	unrestricted	bacteremia	empiric	- all-cause in-hospital mortality - in-hospital length of stay - ICU length of stay

								- duration of mechanical ventilation
Ali [131]	2016	retrospective cohort study	Qatar	no	unrestricted	ventilator-associated pneumonia	empiric	all-cause 30-day/1 month mortality
Cheng [132]	2016	retrospective cohort study	Taiwan	no	ESBL-producing *E. coli* or *K. pneumoniae*	bacteremic pneumonia	- empiric - definite	all-cause 30-day/1 month mortality
Chin [133]	2016	retrospective cohort study	Canada	yes	unrestricted	ventilator-associated pneumonia	empiric	- all-cause in-hospital mortality - all-cause ICU mortality - ICU length of stay - duration of mechanical ventilation
Coccolini [134]	2016	retrospective / secondary analysis of prospective data	multinational	no	unrestricted	intraabdominal infection secondary to acute appendicitis	empiric, no definition	- all-cause 30-day/1 month mortality - ICU admission
Cuervo [135]	2016	prospective cohort study	Spain	no	MRSA	bacteremia	empiric	- all-cause 2-day mortality - all-cause 30-day/1 month mortality
De Rosa [136]	2016	retrospective cohort study	Italy	no	*S. aureus*	bloodstream infection	definite	all-cause 21-day mortality
Fitzpatrick [137]	2016	prospective cohort study	United Kingdom	yes	*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Morganella* spp., *Citrobacter* spp., *Proteus* spp., *Pseudomonas* spp.	bacteremia	empiric	- all-cause 7-day mortality - all-cause 30-day/1 month mortality
Freire [138]	2016	retrospective cohort study	Brazil	no	extensively drug resistant *A.*	bacteremia	unclear	all-cause 30-day/1 month mortality

					baumannii-calcoaceticus complex			
Garnacho-Montero [139]	2016	prospective cohort study	Spain	no	*A. baumannii*	unrestricted	empiric	all-cause 30-day/1 month mortality
Gonzalez [140]	2016	retrospective cohort study	France	no	unrestricted	septic shock	empiric	all-cause ICU mortality
Guilbart [141]	2016	prospective cohort study	France	no	unrestricted	complicated intra-abdominal infection	2 definitions for empiric	- all-cause in-hospital mortality - ICU admission - in-hospital length of stay - ICU length of stay - adverse events (infectious complications)
Guillamet [142]	2016	retrospective cohort study	United States	no	unrestricted	bacteremic pneumonia	empiric	all-cause in-hospital mortality
Herkel [143]	2016	prospective cohort study	Czech Republic	yes	unrestricted	pneumonia	empiric	all-cause 30-day/1 month mortality
Li [144]	2016	retrospective cohort study	China	no	unrestricted	pneumonia	empiric	clinical failure (slowly resolving pneumonia)
Li [145]	2016	retrospective cohort study	China	no	unrestricted	meningitis, ventriculitis	empiric	all-cause in-hospital mortality
Maeda [146]	2016	Secondary data from quasi-experimental study	Japan	no	unrestricted	bloodstream infection	definite	all-cause in-hospital mortality
Oshima [147]	2016	retrospective cohort study	Japan	yes	unrestricted	severe sepsis or septic shock	empiric	all-cause ICU mortality
Palacios-Baena [148]	2016	retrospective cohort study	Spain	no	carbapenemase-producing Enterobacteriaceae	Unrestricted	- empiric - definite	all-cause 30-day/1 month mortality
Ruangchan [149]	2016	retrospective cohort study	Thailand	no	unrestricted	severe sepsis or septic shock	empiric	all-cause mortality
Savage [150]	2016	retrospective / secondary analysis	Canada	yes	unrestricted	bloodstream infection	empiric	all-cause in-hospital mortality

		of retrospective data						
Stoma [151]	2016	prospective cohort study	Belarus	no	unrestricted	bloodstream infection	empiric	all-cause 30-day/1 month mortality
Trecarichi [152]	2016	prospective cohort study	Italy	no	*K. pneumoniae*	bloodstream infection	empiric	all-cause 21-day mortality
Vallés [153]	2016	retrospective cohort study	Spain	no	unrestricted	severe community-acquired pneumonia	empiric	all-cause ICU mortality
Worapratya [154]	2016	prospective cohort study	Thailand	yes	unrestricted	septic shock	empiric	all-cause in-hospital mortality
Yilmaz [155]	2016	prospective cohort study	Turkey	no	*S. aureus*	bacteremia	empiric	all-cause 28-day in-hospital mortality
Yoon [156]	2016	prospective cohort study	South Korea	yes	MRSA	healthcare-associated bacteremia	empiric	- all-cause in-hospital mortality - infection-related in-hopital mortality
Zarco-Márquez [157]	2016	retrospective cohort study	Mexico	no	*S. pneumoniae*	unrestricted	empiric	all-cause 30-day/1 month mortality
Zilberberg [158]	2016	retrospective cohort study	United States	yes	*A. baumannii*	pneumonia, sepsis	empiric	all-cause in-hospital mortality
Ahn [159]	2017	retrospective cohort study	South Korea	no	unrestricted	community-acquired pneumonia, healthcare-associated pneumonia	empiric	all-cause 28-day mortality
Babich [160]	2017	prospective cohort study	Israel	yes	unrestricted	catheter-associated urinary tract infection	empiric	all-cause 30-day/1 month mortality
Battle [161]	2017	retrospective cohort study	United States	yes	aerobic gram-negative bacteria	bloodstream infection	empiric	in-hospital length of stay
Bosch-Nicolau [162]	2017	retrospective cohort study	Spain	yes	unrestricted	pyelonephritis, septic urinary tract infection	- empiric - definite, no definition	- all-cause mortality - in-hospital length of stay
Costa-de-Oliveira [163]	2017	retrospective cohort study	Portugal	no	unrestricted	bloodstream infection	empiric	- all-cause mortality

								- in-hospital length of stay
Deconinck [164]	2017	retrospective cohort study	France	yes	*P. aeruginosa*	ventilator-associated pneumonia	empiric	all-cause ICU mortality
González-Del Castillo [165]	2017	retrospective cohort study	Spain	yes	unrestricted	unrestricted	empiric	- all-cause 30-day/1 month mortality - in-hospital length of stay - all-cause hospital readmission
Goto [166]	2017	retrospective cohort study	United States	no	*S. aureus*	bacteremia	definite	all-cause 30-day/1 month mortality
Gutiérrez-Gutiérrez [167]	2017	retrospective cohort study	multinational	yes	carbapenemase-producing Enterobacteriaceae	bloodstream infection	unclear	all-cause 30-day/1 month mortality
Jokinen [168]	2017	retrospective cohort study	Finland	no	*S. aureus*	bacteremia	empiric	all-cause 28-day mortality
Joo [169]	2017	retrospective cohort study	South Korea	yes	ESBL-producing *E. coli* or *K. pneumoniae*	bacteremia	empiric	all-cause 30-day/1 month mortality
Lachhab [170]	2017	prospective cohort study	Morocco	no	unrestricted	bacteremia	unclear, no definition	all-cause ICU mortality
Li [171]	2017	retrospective cohort study	China	no	*K. pneumoniae*	bloodstream infection	- empiric - definite	all-cause 30-day/1 month mortality
Micozzi [172]	2017	retrospective cohort study	Italy	no	Carbapenem-resistant *K. pneumoniae*	unrestricted	- empiric - definite	all-cause 30-day/1 month mortality
Póvoa [173]	2017	prospective cohort study	Spain	yes	unrestricted	ventilator-associated pneumonia	empiric	all-cause ICU mortality
Palacios-Baena [174]	2017	retrospective cohort study	Spain, Germany, Italy, Greece, Israel,	yes	ESBL-producing Enterobacteriaceae	bloodstream infection	- empiric - definite	all-cause 30-day/1 month mortality

			Turkey, South Africa, Canada, United States, Argentina, Taiwan					
Papadimitriou-Olivgeris [175]	2017	retrospective case cohort based on case control study	Greece	no	carbapenemase-producing *K. pneumoniae*	bacteremia	empiric	all-cause 30-day/1 month mortality
Pouwels [176]	2017	retrospective cohort study	United Kingdom	yes	Enterobacteriaceae	bacteremia	empiric	all-cause ICU mortality
Rello [177]	2017	retrospective cohort study	multinational	no	unrestricted	community-acquired pneumonia	unclear	all-cause ICU mortality
Royo-Cebrecos [178]	2017	prospective cohort study	Spain	no	unrestricted	bacteremic cholangitis	empiric	all-cause 30-day/1 month mortality
Tagashira [179]	2017	retrospective cohort study	Japan	yes	unrestricted	bacteremic cholangitis	empiric	all-cause 30-day/1 month mortality
Thaden [180]	2017	prospective cohort study	United States	no	*S. aureus*, gram-negative bacteria	bloodstream infection	unclear	all-cause in-hospital mortality
Tuon [181]	2017	retrospective cohort study	Brazil	no	carbapenem-resistant Enterobacteriaceae	Ventilator-associated pneumonia	- empiric - definite	all-cause 30-day/1 month mortality
Wang [182]	2017	retrospective cohort study	China	no	*A. baumannii*	bacteremia	empiric	all-cause 30-day/1 month mortality
Zhang [183]	2017	retrospective cohort study	China	no	Enterococci	bloodstream infection	empiric	- all-cause 7-day mortality - all-cause 30-day/1 month mortality
Zilberberg [184]	2017	retrospective cohort study	United States	yes	Enterobacteriaceae	urinary tract infection, pneumonia, sepsis	empiric	- all-cause in-hospital mortality - in-hospital length of stay
Abdulsalam [185]	2018	prospective cohort study	India	no	*S. aureus*	bacteremia	empiric	all-cause 30-day/1 month mortality

Bassetti [186]	2018	retrospective cohort study	Italy	no	*S. aureus*	bacteremia	empiric	- all-cause 7-day mortality - all-cause 30-day/1 month mortality
Bouiller [187]	2018	prospective cohort study	France	no	MSSA	Bacteremia	- empiric - definite - overall	all-cause 30-day/1 month mortality
Chen [188]	2018	retrospective case cohort based on case control study	Taiwan	no	*A. baumannii*	bloodstream infection	empiric	all-cause 14-day mortality
Claeys [189]	2018	retrospective cohort study	United States	yes	gram-negative bacteria	lower respiratory tract infection	- empiric - definite	- all-cause 30-day/1 month mortality - all-cause in-hospital mortality - in-hospital length of stay - ICU length of stay - infection-related hospital readmission
Dewi [190]	2018	retrospective cohort study	Indonesia	yes	unrestricted	sepsis or septic shock	unclear	all-cause mortality
Fouks [191]	2018	retrospective cohort study	Israel	yes	unrestricted	surgical site infection	empiric	in-hospital length of stay
Garcia-Vidal [192]	2018	prospective cohort study	Spain	no	unrestricted	bloodstream infection	empiric	all-cause 30-day/1 month mortality
Garrouste-Orgeas [193]	2018	retrospective / secondary analysis of prospective data	France	no	*S. pneumoniae*	invasive pneumococcal infection	empiric	all-cause 28-day mortality
Holmes [194]	2018	prospective cohort study	Australia	no	*S. aureus*	bacteremia	empiric	clinical failure (all-cause mortality, persistent bacteraemia at 7 days or recurrent bacteraemia within 30 days)
Islas-Muñoz [195]	2018	prospective cohort study	Mexico	no	unrestricted	bloodstream infection	empiric	all-cause 30-day/1 month mortality

Kethireddy [196]	2018	retrospective nested cohort study	Canada, USA, Saudi Arabia	no	unrestricted	septic shock	empiric	all-cause in-hospital mortality
Lee [197]	2018	retrospective cohort study	Taiwan	no	*Acinetobacter* spp.	catheter-related bloodstream infection	empiric	all-cause 30-day/1 month mortality
Li [198]	2018	retrospective cohort study	China	no	unrestricted	ventilator-associated pneumonia	empiric	all-cause 28-day mortality
Papadopoulos [199]	2018	prospective cohort study	Greece	no	unrestricted	aspiration pneumonia	empiric	clinical failure (no clinical response within 72h of treatment)
Saliba [200]	2018	prospective cohort study	Spain	no	unrestricted	vascular catheter-related bloodstream infections	empiric	all-cause 30-day/1 month mortality
Seas [201]	2018	prospective cohort study	Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru, Venezuela	yes	*S. aureus*	bacteremia	definite	all-cause 30-day/1 month mortality
Sommer [202]	2018	retrospective / secondary analysis of prospective data	France	yes	*P. aeruginosa*	ventilator-associated pneumonia	empiric	clinical failure (no extubation or in-hospital mortality)
Tang [203]	2018	retrospective cohort study	China	no	unrestricted	bloodstream infection	empiric	all-cause 30-day/1 month mortality
Tschudin-Sutter [204]	2018	retrospective cohort study	Switzerland	no	*P. aeruginosa*	bloodstream infection	empiric	- all-cause in-hospital mortality - infection-related in-hospital mortality
Xu [205]	2018	retrospective cohort study	China	no	unrestricted	pneumonia	empiric	- all-cause 30-day/1 month mortality - all-cause 90-day/3 month mortality

Yamaga [206]	2018	retrospective cohort study	Japan	yes	unrestricted	bloodstream infection	empiric	- all-cause 28-day mortality - all-cause in-hospital mortality - all-cause 60-day/2 month mortality - all-cause ICU mortality
Battle [207]	2019	retrospective cohort study	United States	yes	gram-negative bacteria	bloodstream infection	empiric	all-cause 14-day mortality
Benítez-Sala [208]	2019	prospective cohort study	Spain	yes	unrestricted	unrestricted	empiric, no definition	all-cause mortality
Ben-Chetrit [209]	2019	retrospective cohort study	Israel	no	*E. coli*, *K. pneumoniae*	febrile neutropenia	empiric	all-cause 14-day mortality
Ben-Zvi [210]	2019	Secondary data from quasi-experimental study	Israel	no	*S. aureus*	bacteremia	empiric	all-cause 30-day/1 month mortality
Brescini [211]	2019	retrospective cohort study	Italy	no	KPC-producing *K. pneumoniae*	bloodstream infection	- empiric - definite	all-cause 30-day/1 month mortality
Callejas-Díaz [212]	2019	retrospective cohort study	Spain	no	*P. aeruginosa*	bacteremia	- empiric - definite	- all-cause mortality - attributable mortality
Castaño [213]	2019	prospective cohort study	Colombia	yes	unrestricted	severe sepsis or septic shock	empiric	- all-cause in-hospital mortality - in-hospital length of stay - ICU length of stay - ICU admission - mechanical ventilation - adverse events (renal replacement therapy)
Chusri [214]	2019	retrospective cohort study	Thailand	no	*A. baumannii*	bacteremia	empiric	all-cause 30-day/1 month mortality

Delle Rose [215]	2019	prospective cohort study	Italy	no	gram-negative bacteria	bloodstream infection	empiric	- all-cause in-hospital mortality - all-cause 14-day mortality
Eliakim-Raz [216]	2019	retrospective cohort study	Bulgaria, Greece, Hungary, Israel, Italy, Romania, Spain, Turkey	yes	unrestricted	complicated urinary tract infection	empiric	- all-cause 30-day/1 month mortality - clinical failure (continuous symptoms by day 5-7 of AAT, new infection-related symptoms or urine culture growing original pathogen within 30 days, 30-day mortality)
Gómez Belda [217]	2019	prospective cohort study	Spain	yes	unrestricted	bacteremic urinary tract infection	empiric	all-cause 30-day/1 month mortality
Huang [218]	2019	retrospective cohort study	Taiwan	no	*E. meningoseptica*, carbapenem-resistant *A. baumannii-calcoaceticus* complex, *P. aeruginosa* or *S. maltophilia*	bloodstream infection	definite	all-cause 28-day mortality
Jeon [219]	2019	retrospective cohort study	South Korea	no	unrestricted	sepsis	empiric	all-cause in-hospital mortality
Kim [220]	2019	retrospective cohort study	South Korea	yes	ESBL-producing Enterobacteriales	pyelonephritis	empiric	- in-hospital length of stay - clinical failure (symptoms not resolved within 7 days or recurrence during antibiotic treatment, negative

								urine culture within 7 days) - adverse events (composite variable)
Lat [221]	2019	prospective cohort study	United States	no	unrestricted	pneumonia	empiric	all-cause in-hospital mortality
Lim [222]	2019	retrospective cohort study	Australia	yes	ESBL-producing Enterobacteriaceae, AmpC-producing Enterobacteriaceae	bacteremia	- empiric - definite	all-cause 30-day/1 month mortality
Maruyama [223]	2019	prospective cohort study	Japan	no	unrestricted	pneumonia	empiric	all-cause 30-day/1 month mortality
Morvan [224]	2019	retrospective / secondary analysis of prospective data	France	yes	*Enterococcus* spp.	intraabdominal infection	empiric	- all-cause 30-day/1 month mortality - adverse events (infectious complications) - adverse events (relaparotomy or percutaneous drainage) - adverse events (surgical complications)
Park [225]	2019	retrospective cohort study	South Korea	no	Carbapenemase-producing Enterobacteriaceae	bloodstream infection	empiric	all-cause 30-day/1 month mortality
Ramos-Rincón [226]	2019	retrospective cohort study	Spain	no	unrestricted	bloodstream infection	empiric	all-cause in-hospital mortality
Rodriguez-Gómez [227]	2019	retrospective cohort study	Spain	yes	*K. pneumoniae*	urinary tract infection	empiric	- all-cause 30-day/1 month mortality - clinical failure (persistence or recurrence of symptoms, death

								within 21 days without clinical response)
Schuttevaer [228]	2019	retrospective cohort study	Netherlands	yes	unrestricted	bloodstream infection	empiric	all-cause 30-day/1 month mortality
Shi [229]	2019	retrospective cohort study	China	no	*P. aeruginosa*	bloodstream infection	- empiric - definite	all-cause 30-day/1 month mortality
Tacconelli [230]	2019	prospective cohort study	Italy	yes	ESBL-producing Enterobacteriaceae	unrestricted	empiric	- all-cause in-hospital mortality - in-hospital length of stay
Wang [231]	2019	retrospective cohort study	China	no	carbapenem-resistant Enterobacteriaceae	bloodstream infection	definite	all-cause in-hospital mortality
Wiggers [232]	2019	retrospective cohort study	Canada	yes	unrestricted	bacteremic urinary tract infection	empiric	- all-cause 30-day/1 month mortality - time to clinical success
Al-Sunaidar [233]	2020	retrospective cohort study	Malaysia	yes	unrestricted	sepsis	empiric	- all-cause ICU mortality - ICU length of stay
Augustin [234]	2020	retrospective cohort study	France	yes	unrestricted	post-operative peritonitis	empiric	all-cause in-hospital mortality
Babich [235]	2020	retrospective cohort study	Australia, Germany, Greece, France, Israel, Slovenia, Spain, Sweden, United Kingdom	no	*P. aeruginosa*	bacteremia	empiric	all-cause 30-day/1 month mortality
Benetazzo [236]	2020	retrospective cohort study	France	no	ESBL-producing Enterobacteriaceae	bloodstream infection	empiric	all-cause 30-day/1 month mortality

Chen [237]	2020	retrospective cohort study	Taiwan	no	unrestricted	bacteremia	empiric	all-cause 30-day/1 month mortality
Chen [238]	2020	retrospective cohort study	Taiwan	yes	*E. coli*, *K. pneumoniae*	bloodstream infection	empiric	all-cause in-hospital mortality
Dubler [239]	2020	retrospective cohort study	Germany	no	*E. faecium*	bloodstream infection	empiric	- all-cause 30-day/1 month mortality - clinical failure (death or persistent stay in the ICU)
Falcone [240]	2020	retrospective cohort study	Italy	yes	KPC-producing *K. pneumoniae*	bloodstream infection	unclear	all-cause 30-day/1 month mortality
Ingram [241]	2020	retrospective cohort study	Australia	no	unrestricted	infective endocarditis	other	clinical failure (unplanned cardiac surgery, embolic event, relapse of positive blood culture or death within 6 months)
Kang [242]	2020	retrospective cohort study	Taiwan	yes	*A. baumannii*	bacteremic pneumonia	empiric	all-cause 14-day mortality
Kawasuji [243]	2020	retrospective cohort study	Japan	no	MRSA	bacteremia	empiric	all-cause in-hospital mortality
Kim [244]	2020	retrospective cohort study	South Korea	yes	unrestricted	community-acquired pneumonia, healthcare-associated pneumonia	empiric	- all-cause 30-day/1 month mortality - in-hospital length of stay - ICU length of stay
Lambregts, Wijnakker [245]	2020	retrospective cohort study	Netherlands	yes	unrestricted	bloodstream infection	empiric	- all-cause 14-day mortality - all-cause 30-day/1 month mortality - in-hospital length of stay
Lee [246]	2020	retrospective cohort study	Taiwan	no	unrestricted	bacteremia	empiric	all-cause 30-day/1 month mortality

Lee [247]	2020	retrospective cohort study	Taiwan	yes	*S. aureus*, streptococci	bacteremia	empiric	all-cause 28-day mortality
Malbasa [248]	2020	retrospective case cohort based on case control study	Serbia	no	multidrug-resistant *Acinetobacter* spp.	bacteremia	empiric	all-cause 30-day/1 month mortality
Martinez-Nadal [249]	2020	retrospective / secondary analysis of prospective data	Spain	yes	unrestricted	bacteremia in high-risk febrile neutropenia	empiric	all-cause 30-day/1 month mortality
Mitsuboshi [250]	2020	retrospective cohort study	Japan	no	ESBL-producing *E. coli*, *K. pneumoniae*, *P. mirabilis*	bacteremia	- empiric - definite	all-cause 30-day/1 month mortality
Montero [251]	2020	retrospective cohort study	Spain	no	*P. aeruginosa*	bacteremia	- empiric - definite, no definition	- all-cause 14-day mortality - all-cause 30-day/1 month mortality
Mora-Guzmán [252]	2020	prospective cohort study	Spain	no	carbapenemase-producing Enterobacteriaceae	abdominal surgical site infection	- empiric - definite	all-cause 30-day/1 month mortality
Papadimitriou-Olivgeris [253]	2020	retrospective cohort study	Greece	no	gram-positive cocci	bloodstream infection	empiric	all-cause 14-day mortality
Rhee [254]	2020	retrospective cohort study	United States	yes	unrestricted	sepsis	empiric	- all-cause in-hospital mortality - adverse events (acute kidney injury) - C. difficile infection rate
Righolt [255]	2020	retrospective cohort study	Canada	yes	unrestricted	complicated urinary tract infection, complicated intra-abdominal infection	empiric	- all-cause 30-day/1 month mortality - in-hospital length of stay of at least 21 days - ICU length of stay - ICU admission - all-cause hospital readmission

Rivera-Espinar [256]	2020	retrospective cohort study	Spain	no	*K. pneumoniae*	ventilator-associated pneumonia	- empiric - definite	all-cause 30-day/1 month mortality
Santos [257]	2020	retrospective cohort study	Portugal	no	unrestricted	sepsis and septic shock	empiric	all-cause in-hospital mortality
Seo [258]	2020	retrospective cohort study	South Korea	no	carbapenem-resistant *E. coli* or *K. pneumoniae*	bacteremia	- empiric - definite	all-cause 14-day mortality
Seok [259]	2020	prospective cohort study	South Korea	yes	unrestricted	sepsis	empiric	- all-cause 7-day mortality - all-cause 14-day mortality - all-cause 28-day mortality
Wagner [260]	2020	retrospective cohort study	United States	no	unrestricted	unrestricted	empiric	clinical failure (30-day readmission, adverse drug reaction before discharge alive, C. difficile infection within 30 days after discharge)
Wang [261]	2020	retrospective cohort study	Taiwan	no	*A. baumannii*	bacteremia	empiric	all-cause 14-day mortality
Wiener-Well [262]	2020	retrospective cohort study	Israel	yes	unrestricted	bacteremia	- 2 definitions for empiric - unclear, no definition	- all-cause in-hospital mortality - in-hospital length of stay - clinical failure (prolonged time to defervescence or normalization of peripheral leucocyte count)
Xiao, Zhu [263]	2020	retrospective cohort study	China	no	*K. pneumoniae*	bloodstream infection	- empiric - definite	all-cause 28-day mortality
Zhao [264]	2020	retrospective cohort study	China	no	*P. aeruginosa*	bloodstream infection	- empiric	all-cause 30-day/1 month mortality

							- definite, no definition	
Aliyu [265]	2021	retrospective cohort study	United States	yes	unrestricted	septic bloodstream infection	empiric	- all-cause in-hospital mortality or discharge to hospice - in-hospital length of stay - ICU length of stay - ICU admission
Amipara [266]	2021	retrospective cohort study	United States	no	gram-negative bacteria	bloodstream infection	empiric	all-cause 28-day mortality
Cetin [267]	2021	retrospective cohort study	Turkey	no	gram-negative bacteria	bloodstream infection	empiric	all-cause 28-day mortality
Chang [268]	2021	prospective cohort study	South Korea	no	unrestricted	hospital-acquired pneumonia, ventilator-associated pneumonia	- empiric - definite	- all-cause 28-day mortality - all-cause 60-day/2 month mortality - all-cause ICU mortality - clinical failure (no complete patient recovery and stoppage of antibiotics for pneumonia on day 28)
D'Onofrio [269]	2021	prospective cohort study	Belgium	no	unrestricted	sepsis	empiric	- all-cause in-hospital mortality - in-hospital length of stay - ICU length of stay - ICU admission
Gómez-Zorrilla [270]	2021	prospective cohort study	Spain	no	Enterobacterales*, P. aeruginosa*, non-fermenting gram-	bacteremic urinary tract infection	empiric	- all-cause 30-day/1 month mortality

					negative bacteria, *S. saprophyticus*, *S. agalactiae*, *Enterococcus* spp.			- in-hospital length of stay - clinical failure (symptoms of infection not completely resolved at discharge)
Jovanovic [271]	2021	prospective cohort study	Serbia	yes	unrestricted	ventilator-associated pneumonia	empiric	- all-cause in-hospital mortality - infection-related in-hospital mortality - ICU length of stay - clinical failure (pneumonia-related sepsis) - microbiological failure
Kadri [272]	2021	retrospective cohort study	United States	yes	unrestricted	bloodstream infection	empiric	all-cause in-hospital mortality or discharge to hospice
Kohler [273]	2021	retrospective case cohort based on case control study	Switzerland	no	Enterobacterales	unrestricted	empiric	clinical failure (microbiological relapse, graft failure or death within 90 days)
Liu [274]	2021	retrospective cohort study	Taiwan	yes	Carbapenem-resistant *K. pneumoniae*	bacteremia	- empiric - definite	all-cause 30-day/1 month mortality
Man [275]	2021	retrospective cohort study	Hong Kong	yes	*K. pneumoniae*	bacteremia	empiric	- all-cause 90-day/3 month mortality - all-cause in-hospital mortality - all-cause ICU mortality - in-hospital length of stay

								- duration of mechanical ventilation
Meng [276]	2021	retrospective cohort study	China	no	*A. baumannii* complex	bloodstream infection	- empiric - definite	all-cause 28-day mortality
Moschou [277]	2021	prospective cohort study	Greece	no	unrestricted	bloodstream infection	empiric	all-cause 30-day/1 month mortality
Puzniak [278]	2021	retrospective cohort study	United States	yes	unrestricted	unrestricted	empiric	- all-cause in-hospital mortality - in-hospital length of stay - ICU length of stay
Quillici [279]	2021	retrospective cohort study	Brazil	yes	gram-negative bacteria	bloodstream infection	empiric	all-cause ICU mortality
Rodríguez [280]	2021	retrospective cohort study	Spain	no	*K. pneumoniae*	bacteremia	- empiric - definite	all-cause 14-day mortality
Shen [281]	2021	retrospective cohort study	China	no	carbapenem-resistant *K. pneumoniae*	bloodstream infection	- empiric - definite	all-cause 28-day mortality
Shorr [282]	2021	retrospective cohort study	United States	no	*S. pneumoniae*	community-acquired pneumonia	empiric	all-cause in-hospital mortality
Sun, Zhao [283]	2021	retrospective cohort study	China	no	*Aeromonas* spp.	bacteremia	empiric	clinical failure (discharge due to continuously deteriorating conditions or death)
Teelucksingh [284]	2021	retrospective cohort study	United States	yes	*P. aeruginosa*	bacteremia	empiric	clinical failure (in-hospital death, transition to hospice/palliative care)
Thy [285]	2021	retrospective cohort study	France	no	unrestricted	necrotizing skin and soft tissue infection	empiric	emergence of multidrug-resistant organisms
Yiang [286]	2021	retrospective cohort study	Taiwan	no	unrestricted	Suspected septic community-acquired or healthcare-	empiric	all-cause ICU mortality

						associated pneumonia		
Zhang [287]	2021	unclear/unknown	China	no	*E. coli*	bloodstream infection	empiric	all-cause in-hospital mortality
Zhu, Chen [288]	2021	retrospective cohort study	China	yes	*E. coli*	urinary tract infection	empiric	- all-cause 30-day/1 month mortality - in-hospital length of stay - clinical failure (recurrence of urinary tract infection) - duration of antibiotic treatment
Zilberberg [289]	2021	retrospective cohort study	United States	yes	Enterobacteriaceae, *P. aeruginosa*, A. *baumannii*, *E. faecium*, *E. faecalis*	urinary tract infection	empiric	- all-cause in-hospital mortality - in-hospital length of stay

a. Refers to the study design/data source used for our systematic review.

S Table 3: Overview of appropriate antibiotic therapy (AAT) definitions by study and respective aspects of AAT evaluated

First Author	Year	Treatment phase	Susceptibility	Timely start of therapy	Dosing	Route of administration	Duration	Guideline-based therapy	Restriction of aminoglycoside therapy	Other	Other aspects of appropriateness evaluated in the study	Total number of indicators
De Rosa [1]	2011	empiric	X	X								2
Fayad [2]	2011	unclear	X				X	X				3
Fernández-Hidalgo [3]	2011	overall	X		X	X		X		X	general rules for choice of empiric antibiotic	5
Johnson [4]	2011	empiric	X	X			X					3
Joo [5]	2011	empiric	X	X	X	X						4
Lin [6]	2011	empiric	X									1
Micek [7]	2011	empiric	X	X								2
Montravers [8]	2011	empiric	X	X								2
Plataki [9]	2011	empiric	X									1
Reisfeld [10]	2011	empiric	X		X							2
		definite	X		X							2
Rello [11]	2011	empiric	X									1
Schechner [12]	2011	empiric	X	X								2
Schreiber [13]	2011	empiric	X	X								2
Seligman [14]	2011	empiric	X									1

Shorr [15]	2011	empiric	X	X								2
Suppli [16]	2011	overall	X	X	X		X			X	no contraindactions/relevant interactions	5
Tumbarello [17]	2011	empiric	X									1
Wang [18]	2011	empiric	X									1
		definite	X									1
Zarkotou [19]	2011	empiric	X	X								2
		definite	X				X					2
Aguilar-Duran [20]	2012	empiric	X									1
Ariza [21]	2012	empiric	X									1
Bouza [22]	2012	empiric	X	X								2
Castillo [23]	2012	empiric	X	X	X	X	X					5
Chidiac [24]	2012	empiric								X	specific antibiotics that were considered (in)appropriate for the entire study cohort	1
		definite								X	specific antibiotics that were considered (in)appropriate for the entire study cohort	1
Chuang [25]	2012	unclear	X						X	X	- monotherapy with specific antibiotics other than aminoglycosides considered inappropriate - specific antibiotics considered (in)appropriate in specific resistance pattern	4
de Gouvêa [26]	2012	empiric	X	X						X	specific antibiotics considered (in)appropriate in specific resistance pattern	3
Gözel [27]	2012	empiric	X	X								2
Halilovic [28]	2012	empiric	X	X								2
Hernández-Torres [29]	2012	empiric	X		X							2
		definite	X		X		X					3
Horino [30]	2012	empiric	X									1
Huang [31]	2012	empiric	X	X					X			3
Jung [32]	2012	empiric	X							X	specific antibiotics considered (in)appropriate in specific resistance pattern	2

		definite	X							X	specific antibiotics considered (in)appropriate in specific resistance pattern	2
Kim [33]	2012	definite	X	X	X	X						4
Lee [34]	2012	empiric	X									1
Lye [35]	2012	empiric	X		X							2
		definite	X		X							2
Micek [36]	2012	empiric	X	X			X					3
O'Neal [37]	2012	empiric	X	X						X	specific antibiotics considered (in)appropriate in specific resistance pattern	3
Park [38]	2012	empiric	X	X		X						3
Qureshi [39]	2012	empiric	X									1
Sancho [40]	2012	empiric	X									1
Silveira [41]	2012	empiric						X				1
Tabah [42]	2012	unclear	X							X	- rules for appropriateness when susceptibility testing was not performed/reported - rules regarding combination therapy	3
Tumbarello [43]	2012	empiric	X	X				X				3
Wu [44]	2012	empiric	X	X								2
Zervos [45]	2012	empiric	X	X						X	rules for appropriateness when susceptibility testing was not performed/reported	3
Adrie [46]	2013	empiric	X									1
Bowers [47]	2013	empiric	X	X								2
Capone [48]	2013	unclear	X				X					2
Cardoso [49]	2013	empiric	X		X	X						3
Ferreira [50]	2013	overall					X	X				2
Gasch [51, 52]	2013	empiric	X						X			2
Heintz [53]	2013	empiric	X									1
		definite			X		X	X				3
Horcajada [54]	2013	empiric	X	X								2
Kang [55]	2013	empiric	X	X	X	X						4
Kang [56]	2013	empiric	X		X	X						3
Kuo [57]	2013	empiric	X	X	X	X						4

Lee [58]	2013	empiric	X									1
Lee [59]	2013	empiric	X	X	X	X			X			5
Metan [60]	2013	empiric	X		X	X				X	specific antibiotics considered (in)appropriate in specific resistance pattern	4
Navarro-San Francisco [61]	2013	other	X									1
Palmer [62]	2013	empiric	X									1
Park [63]	2013	empiric	X						X			2
Peña [64]	2013	empiric	X						X	X	monotherapy with specific antibiotics other than aminoglycosides considered inappropriate	3
		definite	X						X	X	monotherapy with specific antibiotics other than aminoglycosides considered inappropriate	3
Phua [65]	2013	empiric	X									1
Retamar [66]	2013	empiric	X	X	X							3
Ruiz-Giardin [67]	2013	empiric	X		X	X						3
Shorr [68]	2013	empiric	X	X								2
Tumbarello [69]	2013	empiric	X									1
Vallés [70]	2013	empiric	X	X								2
Willmann [71]	2013	empiric	X						X			2
		definite	X						X			2
Yang [72]	2013	empiric	X		X	X						3
Yang [73]	2013	empiric	X	X	X	X			X			5
Zheng [74]	2013	empiric	X	X								2
Anderson [75]	2014	empiric	X	X								2
Bloos [76]	2014	empiric								X	therapy considered inappropriate when antibiotics were changed/escalated	1
Chusri [77]	2014	empiric	X									1
Corrêa [78]	2014	empiric	X									1
De Bus [79]	2014	empiric	X									1
Esparcia [80]	2014	empiric	X									1
Falcone [81]	2014	empiric	X									1
Fayad [82]	2014	other	X				X	X				3

Garnacho-Montero [83]	2014	empiric	X	X	X							3
Girometti [84]	2014	empiric	X							X	specific antibiotics considered (in)appropriate in specific resistance pattern	2
Gonçalves-Pereira [85]	2014	empiric	X	X								2
Hsu [86]	2014	empiric	X	X								2
Jeong [87]	2014	empiric	X									1
Kim [88]	2014	empiric	X		X				X			3
		definite	X		X				X			3
Lee [89]	2014	empiric	X	X					X			3
Lipsky [90]	2014	empiric	X	X						X	rules for appropriateness when susceptibility testing was not performed/reported	3
Membrilla-Fernández [91]	2014	empiric	X									1
Nygård [92]	2014	empiric						X				1
Pelegrín [94]	2014	empiric				X				X	specific antibiotics that were considered (in)appropriate for the entire study cohort	2
Shorr [95]	2014	empiric	X	X			X					3
Spoorenberg [96]	2014	overall						X		X	- Diagnostic requirements - De-escalation of antibiotics - Switch to oral therapy	4
Vallés [97]	2014	empiric	X	X								2
Van Aken [98]	2014	empiric	X	X	X							3
Vilella [99]	2014	empiric	X									1
Yokota [100]	2014	empiric	X									1
Zeng [101]	2014	definite	X									1
Zilberberg [102]	2014	empiric	X	X			X					3
Al-Dorzi [103]	2015	empiric	X									1
Allou [104]	2015	empiric	X									1
Andria [105]	2015	empiric	X	X								2
Bass [106]	2015	unclear	X		X					X	consideration of pharmacokinetic parameters	3

Bastug [107]	2015	empiric	X	X								2
Beuving [108]	2015	unclear	X							X	unneccessarily broad therapy considered inappropriate	2
Boel [109]	2015	empiric	X									1
Brigmon [110]	2015	empiric	X		X	X						3
Coccolini [111]	2015	empiric								X	therapy considered appropriate based on clinical success	1
Denis [112]	2015	empiric	X	X	X							3
Dimopoulos [113]	2015	empiric	X									1
Inchai [114]	2015	empiric	X									1
Katsiari [115]	2015	empiric	X									1
Lee [116]	2015	empiric	X	X						X	monotherapy with specific antibiotics other than aminoglycosides considered inappropriate	3
Martin-Loeches [117]	2015	empiric	X									1
Martin-Loeches [118]	2015	empiric	X									1
Oliveira [119]	2015	empiric	X	X	X							3
Park [120]	2015	empiric	X	X								2
Rabello [121]	2015	empiric	X									1
Ratzinger [122]	2015	empiric	X									1
Shindo [123]	2015	empiric	X									1
Su [124]	2015	empiric	X		X		X					3
Suberviola Cañas [125]	2015	unclear	X									1
Sumida [126]	2015	unclear	X									1
Torres [127]	2015	empiric	X					X				2
Tumbarello [128]	2015	empiric	X									1
Wu [129]	2015	empiric	X	X	X	X						4
Abraham [130]	2016	empiric	X	X	X	X						4
Ali [131]	2016	empiric	X	X								2
Cheng [132]	2016	empiric	X									1

		definite	X									1
Chin [133]	2016	empiric	X							X	rules for appropriateness when susceptibility testing was not performed/reported	2
Cuervo [135]	2016	empiric	X						X			2
De Rosa [136]	2016	definite								X	specific antibiotics that were considered (in)appropriate for the entire study cohort	1
Fitzpatrick [137]	2016	empiric	X	X		X						3
Freire [138]	2016	unclear	X				X					2
Garnacho-Montero [139]	2016	empiric	X									1
Gonzalez [140]	2016	empiric	X									1
Guilbart [141]	2016	empiric	X									1
Guillamet [142]	2016	empiric	X									1
Herkel [143]	2016	empiric	X									1
Li [144]	2016	empiric	X									1
Li [145]	2016	empiric	X									1
Maeda [146]	2016	definite	X							X	therapy considered appropriate based on clinical success	2
Oshima [147]	2016	empiric	X									1
Palacios-Baena [148]	2016	empiric	X									1
		definite	X									1
Ruangchan [149]	2016	empiric	X									1
Savage [150]	2016	empiric	X									1
Stoma [151]	2016	empiric	X	X	X							3
Trecarichi [152]	2016	empiric	X									1
Vallés [153]	2016	empiric	X									1
Worapratya [154]	2016	empiric	X									1
Yilmaz [155]	2016	empiric								X	specific antibiotics that were considered (in)appropriate for the entire study cohort	1
Yoon [156]	2016	empiric	X	X	X	X						4
Zarco-Márquez [157]	2016	empiric	X	X			X					3

Zilberberg [158]	2016	empiric	X	X								2
Ahn [159]	2017	empiric	X									1
Babich [160]	2017	empiric	X	X								2
Battle [161]	2017	empiric	X		X	X						3
Bosch-Nicolau [162]	2017	empiric	X									1
Costa-de-Oliveira [163]	2017	empiric	X									1
Deconinck [164]	2017	empiric	X									1
González-Del Castillo [165]	2017	empiric								X	therapy considered inappropriate when antibiotics were changed/escalated	1
Goto [166]	2017	definite				X				X	specific antibiotics that were considered (in)appropriate for the entire study cohort	2
Gutiérrez-Gutiérrez [167]	2017	unclear	X	X								2
Jokinen [168]	2017	empiric	X									1
Joo [169]	2017	empiric	X	X	X	X						4
Li [171]	2017	empiric	X		X	X						3
	2017	definite	X		X	X						3
Micozzi [172]	2017	empiric	X									1
		definite	X									1
Póvoa [173]	2017	empiric	X									1
Palacios-Baena [174]	2017	empiric	X	X								2
		definite	X	X								2
Papadimitriou-Olivgeris [175]	2017	empiric	X	X	X							3
Pouwels [176]	2017	empiric	X	X								2
Rello [177]	2017	unclear						X				1
Royo-Cebrecos [178]	2017	empiric	X									1
Tagashira [179]	2017	empiric	X							X	specific antibiotics considered (in)appropriate in specific resistance pattern	2

Thaden [180]	2017	unclear	X									1
Tuon [181]	2017	empiric	X		X							2
		definite	X		X							2
Wang [182]	2017	empiric	X	X								2
Zhang [183]	2017	empiric	X		X							2
Zilberberg [184]	2017	empiric	X	X								2
Abdulsalam [185]	2018	empiric	X									1
Bassetti [186]	2018	empiric	X		X							2
Bouiller [187]	2018	general	X									1
		empiric	X									1
		definite	X									1
Chen [188]	2018	empiric	X	X	X	X						4
Claeys [189]	2018	empiric	X		X			X				3
		definite	X		X			X				3
Dewi [190]	2018	unclear			X			X		X	general rules for choice of empiric antibiotic	3
Fouks [191]	2018	empiric	X									1
Garcia-Vidal [192]	2018	empiric	X	X	X	X						4
Garrouste-Orgeas [193]	2018	empiric	X	X								2
Holmes [194]	2018	empiric	X									1
Islas-Muñoz [195]	2018	empiric	X	X			X					3
Kethireddy [196]	2018	empiric	X							X	rules for appropriateness when susceptibility testing was not performed/reported	2
Lee [197]	2018	empiric	X	X	X	X	X		X			6
Li [198]	2018	empiric	X									1
Papadopoulos [199]	2018	empiric	X									1
Saliba [200]	2018	empiric	X									1
Seas [201]	2018	definite				X				X	specific antibiotics that were considered (in)appropriate for the entire study cohort	2
Sommer [202]	2018	empiric	X	X								2
Tang [203]	2018	empiric	X									1

Tschudin-Sutter [204]	2018	empiric	X									1
Xu [205]	2018	empiric	X							X	therapy considered appropriate based on clinical success	2
Yamaga [206]	2018	empiric	X	X								2
Battle [207]	2019	empiric	X		X	X						3
Ben-Chetrit [209]	2019	empiric	X							X	specific antibiotics considered (in)appropriate in specific resistance pattern	2
Ben-Zvi [210]	2019	empiric								X	specific antibiotics that were considered (in)appropriate for the entire study cohort	1
Brescini [211]	2019	empiric	X									1
	2019	definite	X	X								2
Callejas-Díaz [212]	2019	empiric	X	X					X			3
	2019	definite	X						X			2
Castaño [213]	2019	empiric	X									1
Chusri [214]	2019	empiric	X									1
Delle Rose [215]	2019	empiric	X		X	X			X			4
Eliakim-Raz [216]	2019	empiric	X									1
Gómez Belda [217]	2019	empiric	X									1
Huang [218]	2019	definite	X				X					2
Jeon [219]	2019	empiric	X									1
Kim [220]	2019	empiric	X									1
Lat [221]	2019	empiric	X									1
Lim [222]	2019	empiric	X							X	specific antibiotics that were considered (in)appropriate for the entire study cohort	2
	2019	definite	X							X	specific antibiotics that were considered (in)appropriate for the entire study cohort	2
Maruyama [223]	2019	empiric	X									1
Morvan [224]	2019	empiric	X							X	rules for appropriateness when susceptibility testing was not performed/reported	2
Park [225]	2019	empiric	X									1

Ramos-Rincón [226]	2019	empiric	X									1
Rodriguez-Gómez [227]	2019	empiric	X							X	specific antibiotics that were considered (in)appropriate for the entire study cohort	2
Schuttevaer [228]	2019	empiric	X		X	X						3
Shi [229]	2019	empiric	X						X			2
	2019	definite	X						X			2
Tacconelli [230]	2019	empiric	X									1
Wang [231]	2019	definite	X									1
Wiggers [232]	2019	empiric	X	X								2
Al-Sunaidar [233]	2020	empiric	X	X	X			X		X	- De-escalation of antibiotics - general rules for choice of empiric antibiotic	6
Augustin [234]	2020	empiric	X									1
Babich [235]	2020	empiric	X	X								2
Benetazzo [236]	2020	empiric	X	X								2
Chen [237]	2020	empiric	X	X								2
Chen [238]	2020	empiric	X									1
Dubler [239]	2020	empiric	X			X						2
Falcone [240]	2020	unclear	X									2
Ingram [241]	2020	other			X	X	X	X				4
Kang [242]	2020	empiric	X	X	X	X			X			5
Kawasuji [243]	2020	empiric	X									1
Kim [244]	2020	empiric	X					X				2
Lambregts, Wijnakker [245]	2020	empiric	X	X								2
Lee [246]	2020	empiric	X		X	X						3
Lee [247]	2020	empiric	X	X	X	X		X				5
Malbasa [248]	2020	empiric	X	X								2
Martinez-Nadal [249]	2020	empiric	X									1
Mitsuboshi [250]	2020	empiric	X									1
		definite	X									1

Montero [251]	2020	empiric	X	X								2
Mora-Guzmán [252]	2020	empiric	X				X					2
		definite	X				X					2
Papadimitriou-Olivgeris [253]	2020	empiric	X	X	X							3
Rhee [254]	2020	empiric	X									1
Righolt [255]	2020	empiric	X									1
Rivera-Espinar [256]	2020	empiric	X							X	therapy considered appropriate based on clinical success	2
		definite	X									1
Santos [257]	2020	empiric	X									1
Seo [258]	2020	empiric	X				X					2
		definite	X				X					2
Seok [259]	2020	empiric	X							X	- Expert opinion - therapy considered appropriate based on clinical success	3
Wagner [260]	2020	empiric						X				1
Wang [261]	2020	empiric	X	X	X	X			X			5
Wiener-Well [262]	2020	empiric	X									1
Xiao, Zhu [263]	2020	empiric	X									1
		definite	X									1
Zhao [264]	2020	empiric	X	X								2
Aliyu [265]	2021	empiric	X									1
Amipara [266]	2021	empiric	X		X	X						3
Cetin [267]	2021	empiric	X									1
Chang [268]	2021	empiric	X									1
		definite	X									1
D'Onofrio [269]	2021	empiric						X				1
Gómez-Zorrilla [270]	2021	empiric	X									1
Jovanovic [271]	2021	empiric	X	X	X							3

Kadri [272]	2021	empiric	X									1
Kohler [273]	2021	empiric	X	X						X	specific antibiotics considered (in)appropriate in specific resistance pattern	3
Liu [274]	2021	empiric	X									1
	2021	definite	X									1
Man [275]	2021	empiric	X	X								2
Meng [276]	2021	empiric	X	X	X	X						4
	2021	definite	X	X	X	X						4
Moschou [277]	2021	empiric	X									1
Puzniak [278]	2021	empiric	X	X								2
Quillici [279]	2021	empiric	X	X								2
Rodríguez [280]	2021	empiric	X							X	rules regarding combination therapy	2
	2021	definite	X							X	rules regarding combination therapy	2
Shen [281]	2021	empiric	X	X								2
	2021	definite	X									1
Shorr [282]	2021	empiric	X							X	specific antibiotics that were considered (in)appropriate for the entire study cohort	2
Sun, Zhao [283]	2021	empiric	X									1
Teelucksingh [284]	2021	empiric	X	X						X	specific antibiotics that were considered (in)appropriate for the entire study cohort	3
Thy [285]	2021	empiric	X									1
Yiang [286]	2021	empiric	X									1
Zhang [287]	2021	empiric	X							X	therapy considered appropriate based on clinical success	2
Zhu, Chen [288]	2021	empiric	X									1
Zilberberg [289]	2021	empiric	X	X								2

S Table 4: Definitions of the terms "empiric" and "definite" therapy reported in the studies

While 89/258 (34.50%) of studies providing a definition of empiric AAT defined what "empiric" referred to in their respective study context, this was true for 26/41 (63.41%) studies investigating definite AAT. 118/258 (45.74%) studies defined a timeframe that was considered to be empiric, 11/41 (26.83%) a timeframe for definite therapy.

Category	Treatment Phase	Aspects used in respective definitions		Number of studies (%)
Definition	Empiric	Antibiotic regimen prescribed before availability of culture and/or in vitro susceptibility test results		47 (52.81%)
		Antibiotic regimen started within specific time after microbiological culture collection		21 (23.60%)
		First antibiotic regimen prescribed/antibiotics administered during first day(s)		14 (15.73%)
		Antibiotic regimen started within specific time after infection onset		14 (15.73%)
		Other		4 (4.49%)
	Definite	Antibiotic regimen started/changed to after pathogen identification and/or availability of susceptibility testing		23 (88.46%)
		Other		4 (15.38%)
Timing	Empiric	Timeframe	<24 hours	3 (2.54%)
			24 hours/same day	63 (53.39%)
			48 hours	41 (34.75%)
			72 hours	9 (7.63%)
			5 days	2 (1.69%)
		Timepoint	After microbiological culture collection	55 (46.61%)
			After infection onset/diagnosis	40 (33.90%)
			Hospital/ICU admission	9 (7.63%)
			Unspecific/Other	14 (11.86%)
	Definite	Timeframe	24 hours	3 (27.27%)
			48 – 72 hours	3 (27.27%)
			4 – 5 days	3 (27.27%)
			7 days	2 (18.18%)
		Timepoint	After microbiological culture collection	6 (54.55%)
			After pathogen identification/susceptibility testing	4 (36.36%)
			Unspecific	1 (9.09%)

S Table 5: Overview of aspects included in study definitions of appropriate antibiotic therapy (AAT) for unclear and other treatment phase

Aspect	Number of definitions	definitions with details on evaluation
Total number of definitions of unclear AAT	14	
Susceptibility	12 (85.71%)	8 (66.67%)
Timing	1 (7.14%)	1 (100.00%)
Dosing	2 (14.29%)	1 (50.00%)
Route of administration	-	-
Aminoglycoside restriction	1 (7.14%)	1 (100.00%)
Duration	3 (21.43%)	3 (100.00%)
Guideline-based choice of antibiotic agent	2 (14.29%)	1 (50.00%)
Other	5 (35.71%)	5 (100.00%)
Total number of definitions of other AAT	3	
Susceptibility	2 (66.67%)	1 (50.00%)
Timing	-	-
Dosing	1 (33.33%)	1 (100.00%)
Route of administration	1 (33.33%)	1 (100.00%)
Aminoglycoside restriction	-	-
Duration	2 (66.67%)	2 (100.00%)
Guideline-based choice of antibiotic agent	2 (66.67%)	2 (100.00%)
Other	-	-

S Table 6: Detailed methods for evaluation of appropriate antibiotic therapy (AAT) aspects in study definitions of empiric therapy (n=258)

Aspect	Subaspects	Number of definitions	Number of definitions with details on evaluation
Total number of definitions of empiric AAT		258 (100.00%)	
Susceptibility		245 (94.96%)	151 (61.63%)
	Clinical breakpoints		
	Clinical and Laboratory Standards Institute		109 (72.19%)
	European Committee on Antimicrobial Susceptibility Testing		26 (17.22%)
	French Society for Microbiology		12 (7.95%)
	Mixed		4 (2.65%)
Timing		92 (35.66%)	91 (98.91%)
	Reference point for timely initiation		
	Microbiological culture collection		47 (51.65%)
	Symptom onset / diagnosis of infection		28 (30.77%)
	Hospital admission / ED presentation		7 (7.69%)
	Specific timeframe without reference point		5 (5.49%)
	Other / Mixed		4 (4.40%)
	Time until antibiotic had to be started		
	Within 6h		3 (3.27%)
	Within 12h		1 (1.10%)
	Within 24h / same day		50 (54.95%)
	Within 48h		29 (31.87%)
	Within 72h		6 (6.59%)
	Other		1 (1.10%)
Dosing		49 (18.99%)	21 (42.86%)
	Assessment of dosing*		
	Appropriate for endorgan function		8 (38.10%)
	According to guideline		7 (33.33%)
	Adaption to renal function when required		6 (28.57%)
	Appropriate dosing interval		4 (19.05%)
	Other		3 (14.29%)
Route of Administration		34 (13.18%)	14 (41.18%)
	Assessment of route of administration*		
	Only i.v. therapy considered appropriate		7 (50.00%)
	According to guideline		3 (21.43%)
	Only i.v. therapy considered appropriate with exceptions for antibiotics with good bioavailability		3 (21.43%)
	Other		1 (7.14%)
Aminoglycoside restriction		16 (6.20%)	16 (100.00%)
	Assessment of aminoglycoside use*		
	Use of aminoglycosides as monotherapy was not considered adequate		12 (75.00%)
	Any aminoglycoside use considered inappropriate		2 (12.50%)
	Other aspects		3 (18.75%)
Duration		11 (4.26%)	10 (90.91%)
	Minimum duration of therapy required		
	24 hours		6 (60.00%)
	48 hours		1 (10.00%)
	72 hours		3 (30.00%)
		11 (4.26%)	11 (100.00%)

Guideline-based choice of antibiotic agent	Applied guideline Local guideline Non-local guideline Local or non-local guideline		 5 (45.45%) 4 (36.36%) 2 (18.18%)
Other[a]		33 (12.79%)	33 (100.00%)
	Specific antibiotics considered (in)appropriate in specific resistance pattern		8 (24.24%)
	Rules for appropriateness when susceptibility testing was not performed/reported		5 (15.15%)
	Specific antibiotics considered appropriate for the entire study cohort		5 (15.15%)
	Therapy considered appropriate based on clinical success		5 (15.15%)
	Specific antibiotics considered inappropriate for the entire study cohort		3 (9.09%)
	Other		8 (24.24%)

a. One study may use multiple aspects of assessment.

S Table 7: Detailed methods for evaluation of appropriate antibiotic therapy (AAT) aspects in study definitions of definite therapy (n=41)

Aspect	Subaspects	Number of definitions	Number of definitions with details on evaluation
Total number of definitions of definite AAT		41 (100%)	
Susceptibility		36 (87.81%)	31 (86.11%)
	Clinical breakpoints		
	Clinical and Laboratory Standards Institute		20 (64.52%)
	European Committee on Antimicrobial Susceptibility Testing		7 (22.58%)
	Mixed		4 (12.90%)
Timing		4 (9.76%)	4 (100.00%)
	Reference point for timely initiation		
	Microbiological culture collection		1 (25.00%)
	Symptom onset / diagnosis of infection		1 (25.00%)
	Other / Mixed		2 (50.00%)
	Time until antibiotic has to be started		
	Within 24h		2 (50.00%)
	Within 96h		1 (25.00%)
	Within 120h		1 (25.00%)
Dosing		10 (24.39%)	7 (70.00%)
	Assessment of dosing*		
	Appropriate for endorgan function		1 (14.29%)
	According to guideline		4 (57.14%)
	Adaption to renal function when required		2 (28.57%)
	Appropriate dosing interval		1 (14.29%)
	Other		1 (14.29%)
Route of Administration		5 (12.20%)	2 (40.00%)
	Assessment of route of administration*		
	Only i.v. therapy considered appropriate		2 (100.00%)
Aminoglycoside restriction		5 (12.20%)	5 (100.00%)
	Use of aminoglycosides as monotherapy was not considered adequate		5 (100.00%)
Duration		6 (14.63%)	6 (100.00%)
	Assessment of duration of therapy		
	Minimum duration of therapy required		5 (83.33%)
	According to local guideline		1 (16.67%)
Guideline-based choice of antibiotic agent		2 (4.88%)	2 (100.00%)
	Applied guideline		
	Local guideline		1 (50.00%)
	Local or non-local guideline		1 (50.00%)
Other[a]		9 (21.95%)	9 (100.00%)
	Specific antibiotics considered appropriate for the entire study cohort		4 (44.44%)
	Therapy considered appropriate based on clinical success		1 (11.11%)
	Specific antibiotics considered inappropriate for the entire study cohort		1 (11.11%)
	Other		3 (33.33%)

a. One study may use multiple aspects of assessment.

S Table 8: Assessment of appropriate antibiotic therapy (AAT) in patients without pathogen identification among studies including such patients and providing information on AAT assessment

Of 62 studies including patients without pathogen identification, 61 studies included both microbiologically confirmed and non-confirmed infections, while 1 study included culture-negative infections only. 55/62 studies (88.71%) studies provided the number of isolated pathogens, with a mean percentage (IQR) of isolated pathogens of 62.9% (45;78.8). Assessment of AAT in studies without pathogen identification is presented in the table below.

Assessment of appropriateness	**n**	**%**
No assessment of appropriateness	24	50.00
Study definition of AAT applies to both culture-negative and culture-positive patients	11	22.92
Guideline-based assessment of appropriateness	7	14.58
Expert assessment	3	6.25
Treatment considered appropriate for all culture-negative patients	3	6.25
Other	3	6.25

S Table 9: Assessment of AMS objectives and individual appropriate antibiotic therapy (AAT) aspects for their effect on patient outcomes

115/284 (40.49%) studies providing definition of AAT assessed the effect of AMS objectives and/or individual aspects of their respective AAT definition on outcomes.

Aspects of AMS assessed in the corresponding studies	**n**	**%**
Combination therapy	52	44.07
Source control	29	25.22
Time to AAT	28	24.35
Timely administration of antibiotics	19	16.52
Duration of antibiotic therapy	16	13.91
De-escalation or streamlining	9	7.83
Appropriate diagnostics	8	6.97
Infectious disease consultation	7	6.09
Change of empiric therapy	6	5.22
Dosing	5	4.35
Process-related aspects	4	3.48
Susceptibility	3	2.61
Guideline-based therapy	3	2.61
Intravenous to oral switch	2	1.74
Use of specific antibiotics	2	1.74
AMS intervention	2	1.74
Route of administration	2	1.74
Documentation related to antibiotic therapy	1	0.87
Other	7	6.09

S Table 10: Sources and other ways of determining study definitions of appropriate antibiotic therapy (AAT)

77/288 (26.74%) studies specified how the AAT definition was developed

Development of the AAT definition was based on	n	%
Adoption of definition from previous study	68	87.01
Guideline	12	14.47
Consensus procedure	2	2.63
Expert opinion	2	2.63

S Table 11: Mentioned strengths and limitations of appropriate antibiotic therapy (AAT) definitions among studies providing critical assessment of their respective study definitions

15/288 (5.21%) studies commented on the strengths of their definition, 61/288 (21.18%) commented on limitations

Strengths mentioned	**n**	**%**
Definition in accordance with previous publication(s)	5	33.33
Definition of AAT very comprehensive	3	20.00
Definition clear and/or precise	2	13.33
Study results support that the definition of AAT is well chosen	2	13.33
Other	3	20.00
Limitations mentioned	**n**	**%**
Aspects that were not evaluated as part of the definition	48	78.69
Dosing (including therapeutic drug monitoring and dosing interval)	16	26.23
Timing	7	11.48
Pharmacodynamics and pharmacokinetics (including tissue penetration and interactions)	6	9.84
Route of administration	4	6.56
Duration	3	4.92
Indication of antibiotic treatment	2	3.28
Aminoglycoside restriction	2	3.28
Other	4	6.56
Generally, more aspects of AAT should have been evaluated	4	6.56
In vitro sensitivity does not equal in vivo effectiveness or treatment of choice	8	13.11
Breakpoint-related limitations	7	11.48
Breakpoints used in the study not up-to-date	4	6.56
Breakpoints vary between agencies	3	4.92
Appropriateness of empirical or definite therapy was not evaluated	3	4.92
Lack of standard definition of AAT to base the study definition upon	3	4.92
Susceptibility-based definition does not sanction overtreatment or promotes unnecessary use of broad-spectrum antibiotics	3	4.92
Tigecycline was considered appropriate in BSI	2	3.28
Different definitions for culture-positive and culture-negative patients	2	3.28
Patients without positive cultures were not evaluated for appropriateness	2	3.28
Other	21	34.43

S Table 12: Study characteristics and definitions of appropriate antibiotic therapy (AAT) grouped according to use of susceptibility and other aspects for empiric therapy (n=258)

	Grouping of AAT-definition					
	susceptibility only	Susceptibility + 1 other aspect	Susceptibility + timing	Susceptibility + ≥ 2 other aspects	Non-susceptibility-centered	All definitions of empirical AAT
Study characteristic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	105 (40.70%)	76 (29.46%)	46 (17.83%)	64 (24.81%)	13 (5.04%)	258 (100.00%)
Year of publication						
2011 – 2014	28 (26.67%)	28 (36.84%)	20 (43.48%)	28 (43.75%)	5 (38.46%)	89 (34.50%)
2015 – 2018	56 (53.33%)	28 (36.84%)	14 (30.43%)	24 (37.50%)	5 (38.46%)	113 (43.80%)
2019 – 2021	21 (20.00%)	20 (26.32%)	12 (26.09%)	12 (18.75%)	3 (23.08%)	56 (21.71%)
Geographical Distribution						
Europe	49 (46.67%)	30 (39.47%)	17 (36.96%)	19 (29.69%)	8 (61.54%)	106 (41.09%)
Asia	37 (35.24%)	26 (34.21%)	14 (30.43%)	26 (40.62%)	2 (15.38%)	91 (35.27%)
North America	12 (11.43%)	13 (17.11%)	11 (23.91%)	16 (25.00%)	1 (7.69%)	42 (16.28%)
South America	5 (4.76%)	2 (2.63%)	1 (2.17%)	3 (4.69%)	1 (7.69%)	11 (4.26%)
Oceania	1 (0.95%)	1 (1.32%)	-	-	-	2 (0.78%)
Intercontinental	1 (0.95%)	4 (5.26%)	3 (6.52%)	-	1 (7.69%)	6 (2.33%)
Hospital type						
Secondary Care	3 (2.86%)	2 (2.63%)	1 (2.17%)	4 (6.25%)	-	9 (3.59%)
Tertiary Care	78 (74.29%)	47 (61.84%)	27 (58.70%)	45 (70.31%)	10 (76.92%)	180 (69.77%)
Mixed	7 (6.67%)	11 (14.47%)	9 (19.57%)	7 (10.94%)	1 (7.69%)	26 (10.08%)
Unclear	17 (16.19%)	16 (21.05%)	9 (19.57%)	8 (12.50%)	2 (15.38%)	43 (16.67%)
Study department						
Hospital wide	55 (52.38%)	51 (67.11%)	28 (60.87%)	48 (75.00%)	5 (38.46%)	159 (61.63%)
ICU	33 (31.43%)	18 (23.68%)	13 (28.26%)	11 (17.19%)	1 (7.69%)	63 (24.42%)
Emergency department	6 (5.71%)	2 (2.63%)	1 (2.17%)	4 (6.25%)	2 (15.38%)	14 (5.43%)
Mixed	11 (10.48%)	5 (6.58%)	4 (8.70%)	-	4 (30.77%)	20 (7.75%)
Unclear	-	-	-	1 (1.56%)	1 (7.69%)	2 (0.78%)
Target pathogens						
P. aeruginosa	5 (4.76%)	8 (10.53%)	6 (13.04%)	7 (10.94%)	-	20 (7.75%)
K. pneumoniae	7 (6.67%)	8 (10.53%)	3 (6.52%)	2 (3.12%)	-	17 (6.59%)
S. aureus	5 (4.76%)	5 (6.58%)	2 (4.35%)	3 (4.69%)	2 (15.38%)	15 (5.81%)
A. baumannii	2 (1.90%)	4 (5.26%)	3 (6.52%)	6 (9.38%)	-	12 (4.65%)
E. coli	1 (0.95%)	2 (2.63%)	1 (2.17%)	3 (4.69%)	-	6 (2.33%)

S. pneumoniae	-	2 (2.63%)	1 (2.17%)	1 (1.56%)	-	3 (1.16%)
Mixed	19 (18.10%)	23 (30.26%)	13 (28.26%)	22 (34.38%)	-	64 (24.81%)
Other	-	1 (1.32%)	-	2 (3.12%)	2 (15.38%)	5 (1.94%)
Unrestricted by pathogen	66 (62.86%)	23 (30.26%)	17 (36.96%)	18 (28.12%)	9 (69.23%)	116 (44.96%)
Resistance mechanism of target pathogens						
Carbapenem-resistance	7 (6.67%)	6 (7.89%)	2 (4.35%)	1 (1.56%)	-	14 (5.43%)
ESBL-production	7 (6.67%)	5 (6.58%)	4 (8.70%)	2 (3.12%)	-	14 (5.43%)
MRSA	1 (0.95%)	2 (2.63%)	-	2 (3.12%)	-	5 (1.94%)
VRE	1 (0.95%)	-	-	-	-	1 (0.39%)
Unspecified	-	1 (1.32%)	1 (2.17%)	1 (1.56%)	-	2 (0.78%)
Unrestricted by resistance	89 (84.76%)	62 (81.58%)	139 (84.78%)	58 (90.62%)	13 (100.00%)	222 (86.05%)
Target type of infection						
Bloodstream infection	59 (56.19%)	47 (61.84%)	28 (60.87%)	54 (84.38%)	6 (46.15%)	166 (64.34%)
Respiratory infection	24 (22.86%)	15 (19.74%)	8 (17.39%)	3 (4.69%)	2 (15.38%)	44 (17.05%)
Urinary tract infection	7 (6.67%)	3 (3.95%)	2 (4.35%)	-	-	10 (3.88%)
Abdominal infection	4 (3.81%)	2 (2.63%)	-	-	2 (15.38%)	8 (3.10%)
Central nervous system	1 (0.95%)	-	-	-	1 (7.69%)	2 (0.78%)
Skin and soft tissue	1 (0.95%)	1 (1.32%)	1 (2.17%)	2 (3.12%)	-	4 (1.55%)
Mixed / Other	3 (2.86%)	4 (5.26%)	4 (8.70%)	-	-	7 (2.71%)
Unrestricted by type of infection	6 (5.71%)	4 (5.26%)	3 (6.52%)	5 (7.81%)	2 (15.38%)	17 (6.59%)
Target site of acquisition						
Healthcare-setting	24 (22.86%)	15 (19.74%)	8 (17.39%)	11 (17.19%)	-	50 (19.38%)
Community acquired	17 (16.19%)	11 (14.47%)	7 (15.22%)	10 (15.62%)	7 (53.85%)	45 (17.44%)
Unrestricted by acquisition	64 (60.95%)	50 (65.79%)	31 (67.39%)	43 (67.19%)	6 (46.15%)	163 (63.18%)
Immunosuppressed and cancer patients	8 (7.62%)	6 (7.89%)	3 (6.52%)	7 (10.94%)	-	21 (8.14%)
Appropriateness in study objectives						
AAT mentioned in study objectives	35 (33.33%)	31 (40.79%)	21 (45.65%)	25 (39.06%)	4 (30.77%)	95 (36.82%)
Impact of AAT on outcomes in study objectives	27 (25.71%)	25 (32.89%)	16 (34.78%)	22 (34.38%)	3 (23.08%)	77 (29.84%)
Source of definition specified in the paper	23 (21.90%)	20 (26.32%)	12 (26.09%)	21 (32.81%)	2 (15.38%)	66 (25.58%)
Reflection of quality/limitations of the definition in the paper	18 (17.14%)	18 (24.32%)	11 (23.91%)	16 (25.00%)	2 (15.38%)	54 (21.09%)

S Table 13: Study characteristics and definitions of appropriate antibiotic therapy (AAT) grouped according to use of susceptibility and other aspects for definite therapy (n=41)

	Grouping of AAT-definition					
	susceptibility only	Susceptibility + 1 other aspect	Susceptibility + timing	Susceptibility + ≥ 2 other aspects	Non-susceptibility-centered	All definitions of definite AAT
Study characteristic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	13 (31.71%)	16 (39.02%)	2 (4.88%)	7 (17.07%)	5 (12.20%)	41 (100.00%)
Year of publication						
2011 – 2014	2 (15.38%)	5 (31.25%)	-	4 (57.14%)	2 (40.00%)	13 (31.71%)
2015 – 2018	5 (38.46%)	8 (50.00%)	2 (100.00%)	2 (28.57%)	3 (60.00%)	18 (43.90%)
2019 – 2021	6 (46.15%)	3 (18.75%)	-	1 (14.29%)	-	10 (24.39%)
Geographical Distribution						
Europe	4 (30.77%)	6 (37.50%)	1 (50.00%)	2 (28.57%)	2 (40.00%)	14 (34.15%)
Asia	9 (69.23%)	7 (43.75%)	-	4 (57.14%)	-	20 (48.78%)
North America	-	-	-	1 (14.29%)	2 (40.00%)	3 (7.32%)
South America	-	1 (6.25%)	-	-	1 (20.00%)	2 (4.88%)
Oceania	-	1 (6.25%)	-	-	-	1 (2.44%)
Intercontinental	-	1 (6.25%)	1 (50.00%)	-	-	1 (2.44%)
Hospital type						
Secondary Care	1 (7.69%)	1 (6.25%)	-	-	-	2 (4.88%)
Tertiary Care	10 (76.92%)	14 (87.50%)	2 (100.00%)	5 (71.43%)	1 (20.00%)	30 (73.17%)
Mixed	1 (7.69%)	1 (6.25%)	-	1 (14.29%)	-	3 (7.32%)
Unclear	1 (7.69%)	-	-	1 (14.29%)	4 (80.00%)	6 (14.63%)
Study department						
Hospital wide	10 (76.92%)	15 (93.75%)	2 (100.00%)	5 (71.43%)	5 (100.00%)	35 (85.37%)
ICU	2 (15.38%)	-	-	2 (28.57%)	-	4 (9.76%)
Mixed	1 (7.69%)	1 (6.25%)	-	-	-	2 (4.88%)
Target pathogens						
P. aeruginosa	-	3 (18.75%)	-	2 (28.57%)	-	5 (12.50%)
K. pneumoniae	5 (38.46%)	4 (25.00%)	1 (50.00%)	1 (14.29%)	-	10 (24.39%)
S. aureus	1 (7.69%)	-	-	-	3 (60.00%)	4 (9.76%)
A. baumannii	-	-	-	3 (42.86%)	-	3 (7.32%)
Mixed	6 (46.15%)	8 (50.00%)	1 (50.00%)	1 (14.29%)	1 (20.00%)	16 (39.02%)
Other	-	-	-	-	1 (20.00%)	1 (2.44%)
Unrestricted by pathogen	1 (7.69%)	1 (6.25%)	-	-	-	2 (4.88%)

Resistance mechanism of target pathogens						
Carbapenem-resistance	5 (38.46%)	6 (37.50%)	1 (50.00%)	1 (14.29%)	-	12 (29.27%)
ESBL-production	3 (23.08%)	2 (12.50%)	1 (50.00%)	-	-	5 (12.20%)
VRE	-	-	-	-	1 (20.00%)	1 (2.44%)
Unrestricted by resistance	5 (38.46%)	8 (50.00%)	-	6 (85.71%)	4 (80.00%)	23 (56.10%)
Target type of infection						
Bloodstream infection	9 (69.23%)	14 (87.50%)	2 (100.00%)	4 (57.14%)	3 (60.00%)	30 (73.17%)
Respiratory infection	2 (15.38%)	1 (6.25%)	-	2 (28.57%)	1 (20.00%)	6 (14.63%)
Urinary tract infection	-	-	-	-	1 (20.00%)	1 (2.44%)
Abdominal infection	-	1 (6.25%)	-	-	-	1 (2.44%)
Mixed / Other	1 (7.69%)	-	-	-	-	1 (2.44%)
Unrestricted by type of infection	1 (7.69%)	-	-	1 (14.29%)	-	2 (4.88%)
Target site of acquisition						
Healthcare-setting	2 (15.38%)	3 (18.75%)	-	3 (42.86%)	-	8 (19.51%)
Community acquired	-	1 (6.25%)	-	-	1 (20.00%)	2 (4.88%)
Unrestricted by acquisition	11 (84.62%)	12 (75.00%)	2 (100.00%)	4 (57.14%)	4 (80.00%)	31 (75.61%)
Immunosuppressed and cancer patients	2 (15.38%)	-	-	-	-	2 (4.88%)
Appropriateness in study objectives						
AAT mentioned in study objectives	1 (7.69%)	4 (25.00%)	1 (50.00%)	4 (57.14%)	1 (20.00%)	10 (24.39%)
Impact of AAT on outcomes in study objectives	-	4 (25.00%)	1 (50.00%)	3 (42.86%)	-	7 (17.07%)
Source of definition specified in the paper	1 (7.69%)	4 (25.00%)	-	1 (14.29%)	2 (40.00%)	8 (19.51%)
Reflection of quality/limitations of the definition in the paper	1 (7.69%)	5 (31.25%)	1 (50.00%)	3 (42.86%)	1 (20.00%)	10 (24.39%)

S Table 14: Study characteristics and definitions of appropriate antibiotic therapy (AAT) grouped according to use of individual aspects for empiric therapy (n=258)

	Aspect of AAT								
	susceptibility	Timely start of therapy	dosing	Route of administration	duration	Guideline.based	Aminoglycoside restriction	other	Overall definition
Study characteristic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	n = 245	n = 92	n =49	n = 34	n =11	n = 12	n =16	n =32	n = 258
Year of publication									
2011 – 2014	84 (34.29%)	41 (44.57%)	18 (36.73%)	13 (38.24%)	5 (45.45%)	3 (25.00%)	9 (56.25%)	11 (34.38%)	89 (34.50%)
2015 – 2018	108 (44.08%)	30 (32.61%)	22 (44.90%)	14 (41.18%)	4 (36.35%)	3 (25.00%)	5 (31.25%)	13 (40.62%)	113 (43.80%)
2019 – 2021	53 (21.63%)	21 (22.83%)	9 (18.37%)	7 (20.59%)	2 (18.18%)	6 (50.00%)	2 (12.50%)	8 (25.00%)	56 (21.71%)
Geographical Distribution									
Europe	98 (40.00%)	30 (32.61%)	16 (32.65%)	9 (26.47%)	1 (9.09%)	5 (41.67%)	6 (37.50%)	13 (40.62%)	106 (41.09%)
Asia	89 (36.33%)	33 (35.87%)	24 (48.98%)	19 (55.88%)	3 (27.27%)	4 (33.33%)	10 (62.50%)	9 (28.12%)	91 (35.27%)
North America	41 (16.73%)	22 (23.91%)	6 (12.24%)	5 (14.71%)	6 (54.55%)	2 (16.67%)	-	6 (18.75%)	42 (16.28%)
South America	10 (4.08%)	4 (4.35%)	3 (6.12%)	1 (2.94%)	1 (9.09%)	1 (8.33%)	-	1 (3.12%)	11 (4.26%)
Oceania	2 (0.82%)	-	-	-	-	-	-	1 (3.12%)	2 (0.78%)
Intercontinental	5 (2.04%)	3 (3.26%)	-	-	-	-	-	2 (6.25%)	6 (2.33%)
Hospital type									
Secondary Care	9 (3.67%)	2 (2.17%)	4 (8.16%)	3 (8.82%)	-	-	-	1 (3.12%)	9 (3.59%)
Tertiary Care	170 (69.39%)	60 (65.22%)	34 (69.39%)	22 (64.71%)	10 (90.91%)	10 (83.33%)	9 (56.25%)	22 (68.75%)	180 (69.77%)
Mixed	25 (10.20%)	15 (16.30%)	5 (10.20%)	4 (11.76%)	-	-	2 (12.50%)	2 (6.25%)	26 (10.08%)
Unclear	41 (16.73%)	15 (16.30%)	6 (12.24%)	5 (14.71%)	1 (9.09%)	2 (16.67%)	5 (31.25%)	7 (21.88%)	43 (16.67%)
Study department									
Hospital wide	154 (62.86%)	62 (67.39%)	37 (75.51%)	28 (82.35%)	7 (63.64%)	3 (25.00%)	15 (93.75%)	22 (68.75%)	159 (61.63%)
ICU	62 (25.31%)	23 (25.00%)	8 (16.33%)	2 (5.88%)	2 (18.18%)	3 (25.00%)	1 (6.25%)	6 (18.75%)	63 (24.42%)
Emergency department	12 (4.90%)	2 (2.17%)	3 (6.12%)	3 (8.82%)	-	3 (25.00%)	-	2 (6.25%)	14 (5.43%)

Mixed	16 (6.53%)	4 (4.35%)	-	-	1 (9.09%)	3 (25.00%)	-	1 (3.12%)	20 (7.75%)
Unclear	1 (0.41%)	1 (1.09%)	1 (2.04%)	1 (2.94%)	1 (9.09%)	-	-	1 (3.12%)	2 (0.78%)
Target pathogens									
P. aeruginosa	20 (8.16%)	10 (10.87%)	3 (6.12%)	2 (5.88%)	1 (9.09%)	-	5 (31.25%)	2 (6.25%)	20 (7.75%)
K. pneumoniae	17 (6.94%)	4 (4.35%)	2 (4.08%)	1 (2.94%)	-	-	-	5 (15.62%)	17 (6.59%)
S. aureus	12 (5.31%)	5 (5.43%)	3 (6.12%)	2 (5.88%)	1 (9.09%)	-	2 (12.50%)	3 (9.38%)	15 (5.81%)
A. baumannii	12 (4.90%)	9 (9.78%)	5 (10.20%)	4 (11.76%)	-	-	3 (18.75%)	1 (3.12%)	12 (4.65%)
E. coli	6 (2.45%)	3 (3.26%)	3 (6.12%)	1 (2.94%)	-	-	-	1 (3.12%)	6 (2.33%)
S. pneumoniae	3 (1.22%)	2 (2.17%)	-	-	1 (9.09%)	-	-	1 (3.12%)	3 (1.16%)
Mixed	64 (26.12%)	28 (30.43%)	18 (36.73%)	12 (35.29%)	7 (63.64%)	2 (16.67%)	6 (37.50%)	6 (18.75%)	64 (24.81%)
Other	3 (1.22%)	2 (2.17%)	-	3 (8.82%)	-	1 (8.33%)	-	2 (6.25%)	5 (1.94%)
Unrestricted by pathogen	107 (43.67%)	29 (31.52%)	14 (28.57%)	9 (26.47%)	1 (9.09%)	9 (75.00%)	-	11 (34.38%)	116 (44.96%)
Resistance mechanism of target pathogens						-			
Carbapenem-resistance	14 (5.71%)	3 (3.26%)	3 (6.12%)	-	2 (18.18%)	-	-	-	14 (5.43%)
ESBL-production	14 (5.71%)	5 (5.43%)	2 (4.08%)	2 (5.88%)	-	-	-	1 (3.12%)	14 (5.43%)
MRSA	5 (2.04%)	2 (2.17%)	1 (2.04%)	1 (2.94%)	-	-	2 (12.50%)	1 (3.12%)	5 (1.94%)
VRE	1 (0.41%)	-	-	-	-	-	-	-	1 (0.39%)
Unspecified	2 (0.82%)	1 (1.09%)	1 (2.04%)	-	1 (9.09%	-	-	-	2 (0.78%
Unrestricted by resistance	209 (85.31%)	81 (88.04%)	42 (85.71%)	31 (91.18%)	8 (72.73%))	12 (100.00%)	14 (87.50%)	30 (93.75%)	222 (86.05%)
Target type of infection									
Bloodstream infection	160 (65.31%)	67 (72.83%)	43 (87.76%)	32 (94.12%)	9 (81.82%)	6 (50.00%)	15 (93.75%)	17 (53.12%)	166 (64.34%)
Respiratory infection	42 (17.14%)	9 (9.78%)	3 (6.12%)	-	-	4 (33.33%)	1 (6.25%)	6 (18.75%)	44 (17.05%)
Urinary tract infection	10 (4.08%)	2 (2.17%)	-	-	-	-	-	1 (3.12%)	10 (3.88%)
Abdominal infection	6 (2.45%)	-	-	-	1 (9.09%)	1 (8.33%)	-	2 (6.25%)	8 (3.10%)
Central nervous system	1 (0.41%)	-	-	1 (2.94%)	-	-	-	1 (3.12%)	2 (0.78%)
Skin and soft tissue	4 (1.63%)	3 (3.26%)	-	-	-	-	-	2 (6.25%)	4 (1.55%)
Mixed / Other	7 (2.86%)	4 (4.35%)	-	-	-	-	-	-	7 (2.71%)
Unrestricted by type of infection	15 (6.12%)	7 (7.61%)	3 (6.12%)	1 (2.94%)	1 (9.09%)	1 (8.33%)	-	3 (9.38%)	17 (6.59%)
Target site of acquisition									
Healthcare acquired	50 (20.41%)	15 (16.30%)	14 (28.57%)	7 (20.59%)	3 (27.27%)	-	4 (25.00%)	4 (12.50%)	50 (19.38%)
Community acquired	38 (15.51%)	13 (14.12%)	7 (14.29%)	6 (17.65%)	1 (9.09%)	7 (58.33%)	-	7 (21.88%)	45 (17.44%)

Unrestricted by acquisition	157 (64.08%)	64 (69.57%)	28 (57.14%)	21 (61.76%)	7 (63.64%)	5 (41.67%)	12 (75.00%)	21 (65.62%)	163 (63.18%)
Immunosuppressed and cancer patients	21 (8.57%)	9 (9.78%)	3 (6.12%)	3 (8.82%)	2 (18.18%)	-	-	5 (15.62%)	21 (8.14%)
Appropriateness in study objectives									
AAT mentioned in study objectives	91 (37.14%)	37 (40.22%)	20 (40.82%)	15 (44.12%)	2 (18.18%)	6 (50.00%)	3 (18.75%)	13 (40.62%)	95 (36.82%)
Impact of AAT on outcomes in study objectives	74 (30.20%)	31 (33.70%)	17 (34.69%)	14 (41.18%)	2 (18.18%)	3 (25.00%)	3 (18.75%)	11 (34.38%)	77 (29.84%)
Source of definition specified in the paper	64 (26.12%)	25 (27.17%)	17 (34.69%)	14 (41.18%)	2 (18.18%)	6 (50.00%)	1 (6.25%)	8 (25.00%)	66 (25.58%)
Reflection of quality/limitations of the definition in the paper	52 (21.40%)	23 (25.56%)	9 (18.37%)	4 (11.76%)	2 (18.18%)	2 (16.67%)	5 (31.25%)	9 (28.12%)	54 (21.09%)

S Table 15: Study characteristics and definitions of appropriate antibiotic therapy (AAT) grouped according to use of individual aspects for definite therapy (n=41)

	Aspect of AAT								
	susceptibility	Timely start of therapy	dosing	Route of administration	duration	Guideline.based	Aminoglycoside restriction	other	Overall definition
Study characteristic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	n = 36	n = 4	n = 10	n = 5	n = 6	n = 2	n = 5	n = 9	n = 41
Year of publication									
2011 – 2014	11 (30.56%)	1 (25.00%)	6 (60.00%)	1 (20.00%)	3 (50.00%)	1 (50.00%)	3 (60.00%)	3 (33.33%)	13 (31.71%)
2015 – 2018	15 (41.67%)	2 (50.00%)	3 (30.00%)	3 (60.00%)	1 (16.67%)	1 (50.00%)	2 (40.00%)	5 (55.56%)	18 (43.90%)
2019 – 2021	10 (27.78%)	1 (25.00%)	1 (10.00%)	1 (20.00%)	2 (33.33%)	-	-	1 (11.11%)	10 (24.39%)
Geographical Distribution									
Europe	12 (33.33%)	1 (25.00%)	1 (10.00%)	-	3 (50.00%)	-	3 (60.00%)	4 (44.44%)	14 (34.15%)
Asia	20 (55.56%)	2 (50.00%)	6 (60.00%)	3 (60.00%)	2 (33.33%)	-	2 (40.00%)	2 (22.22%)	20 (48.78%)
North America	1 (2.78%)	-	2 (20.00%)	1 (20.00%)	1 (16.67%)	2 (100.00)	-	1 (11.11%)	3 (7.32%)
South America	1 (2.78%)	-	1 (10.00%)	1 (20.00%)	-	-	-	1 (11.11%)	2 (4.88%)
Oceania	1 (2.78%)	-	-	-	-	-	-	1 (11.11%)	1 (2.44%)
Intercontinental	1 (2.78%)	1 (25.00%)	-	-	-	-	-	-	1 (2.44%)
Hospital type									
Secondary Care	2 (5.56%)	-	1 (10.00%)	-	-	-	-	-	2 (4.88%)
Tertiary Care	29 (80.56%)	3 (75.00%)	7 (70.00%)	2 (40.00%)	6 (100.00%)	1 (50.00%)	4 (80.00%)	5 (55.56%)	30 (73.17%)
Mixed	3 (8.33%)	1 (25.00%)	1 (10.00%)	1 (20.00%)	-	-	1 (20.00%)	-	3 (7.32%)
Unclear	2 (5.56%)	-	1 (10.00%)	2 (40.00%)	-	1 (50.00%)	-	4 (44.44%)	6 (14.63%)
Study department									
Hospital wide	30 (83.33%)	3 (75.00%)	8 (80.00%)	4 (80.00%)	5 (83.33%)	1 (50.00%)	5 (100.00%)	9 (100.00%)	35 (85.37%)
ICU	4 (11.11%)	1 (25.00%)	2 (20.00%)	1 (20.00%)	-	1 (50.00%)	-	-	4 (9.76%)
Mixed	2 (5.56%)	-	-	-	1 (16.67%)	-	-	-	2 (4.88%)

Target pathogens									
P. aeruginosa	5 (13.89%)	-	1 (10.00%)	-	-	-	5 (100.00%)	1 (11.11%)	5 (12.50%)
S. aureus	1 (2.78%)	-	-	2 (40.00%)	-	-	-	3 (33.33%)	10 (24.39%)
K. pneumoniae	10 (27.78%)	1 (25.00%)	1 (10.00%)	1 (20.00%)	1 (16.67%)	-	-	2 (22.22%)	4 (9.76%)
A. baumannii	3 (8.33%)	2 (50.00%)	3 (30.00%)	2 (40.00%)	1 (16.67%)	-	-	-	3 (7.32%)
Mixed	15 (41.67%)	1 (25.00%)	5 (50.00%)	-	4 (66.67%)	2 (100.00%)	-	1 (11.11%)	16 (39.02%)
Other	-	-	-	-	-	-	-	1 (11.11%)	1 (2.44%)
Unrestricted by pathogen	2 (5.56%)	-	-	-	-	-	-	1 (11.11%)	2 (4.88%)
Resistance mechanism of target pathogens									
Carbapenem-resistance	12 (33.33%)	1 (25.00%)	2 (20.00%)	-	5 (83.33%)	-	-	-	12 (29.27%)
ESBL-production	5 (3.89%)	1 (25.00%)	-	-	-	-	-	1 (11.11%)	5 (12.20%)
VRE	-	-	1 (10.00%)	-	1 (16.67%)	1 (50.00%)	-	-	1 (2.44%)
Unrestricted by resistance	19 (52.78%)	2 (50.00%)	7 (70.00%)	5 (100.00%)	-	1 (50.00%)	5 (100.00%)	8 (88.89%)	23 (56.10%)
Target type of infection									
Bloodstream infection	27 (75.00%)	4 (100.00%)	6 (60.00%)	5 (100.00%)	3 (50.00%)	-	4 (80.00%)	7 (77.78%)	30 (73.17%)
Respiratory infection	5 (13.89%)	-	2 (20.00%)	-	-	1 (50.00%)	1 (20.00%)	2 (22.22%)	6 (14.63%)
Urinary tract infection	-	-	1 (10.00%)	-	1 (16.67%)	1 (50.00%)	-	-	1 (2.44%)
Abdominal infection	1 (2.78%)	-	-	-	1 (16.67%)	-	-	-	1 (2.44%)
Mixed / Other	1 (2.78%)	-	-	-	-	-	-	-	1 (2.44%)
Unrestricted by type of infection	2 (5.56%)	-	1 (10.00%)	-	1 (16.67%)	-	-	-	2 (4.88%)
Target site of acquisition									
Healthcare-setting	8 (22.22%)	1 (25.00%)	4 (40.00%)	1 (20.00%)	2 (33.33%)	-	1 (20.00%)	1 (11.11%)	8 (19.51%)
Community acquired	1 (2.78%)	-	-	-	-	-	-	2 (22.22%)	2 (4.88%)
Unrestricted by acquisition	27 (75.00%)	3 (75.00%)	6 (60.00%)	4 (80.00%)	4 (66.67%)	2 (100.00%)	4 (80.00%)	6 (66.67%)	31 (75.61%)
Immunosuppressed and cancer patients	2 (5.56%)	-	-	-	-	-	-	-	2 (4.88%)
Appropriateness in study objectives									
AAT mentioned in study objectives	9 (25.00%)	2 (50.00%)	5 (50.00%)	2 (40.00%)	2 (33.33%)	1 (50.00%)	1 (20.00%)	2 (22.22%)	10 (24.39%)
	7 (19.44%)	2 (50.00%)	4 (40.00%)	1 (20.00%)	2 (33.33%)	1 (50.00%)	1 (20.00%)	1 (11.11%)	7 (17.07%)

Impact of AAT on outcomes in study objectives									
Source of definition specified in the paper	6 (16.67%)	1 (25.00%)	2 (20.00%)	2 (40.00%)	4 (66.67%)	1 (50.00%)	-	2 (22.22%)	8 (19.51%)
Reflection of quality/limitations of the definition in the paper	9 (25.00%)	2 (50.00%)	6 (60.00%)	1 (20.00%)	2 (33.33%)	2 (100.00%)	2 (40.00%)	-	10 (24.39%)

S Table 16: Overview of outcome measures and effect of empiric appropriate antibiotic therapy (AAT) on patient outcomes in univariate and multivariate analyses reported by the studies

	Total number of outcomes	**Number of outcomes tested in multivariable analysis**	**Significant effect based on multivariable analysis**		**No significant effect based on multivariable analysis**
			appropriate therapy favored	inappropriate therapy favored	
	n	n (%)	n (%)	n (%)	n (%)
Outcomes	**390**	**199 (51.03%)**	**125 (62.81%)**	**1 (0.50%)**	**73 (36.68%)**
All-Cause Mortality[a]	268	147 (54.85%)	102 (69.39%)	1 (0.68%)	44 (29.93%)
Early	35	22 (62.86%)	15 (68.18%)	1 (4.55%)	6 (27.27%)
Late	118	65 (55.08%)	40 (61.54%)	-	25 (38.46%)
Long-term	14	9 (64.29%)	9 (100.00%)	-	-
In-hospital	71	38 (53.52%)	27 (71.05%)	-	11 (28.95%)
ICU	22	11 (50.00%)	9 (81.82%)	-	2 (18.18%)
Unknown	8	2 (25.00%)	2 (100.00%)	-	-
Attributable Mortality	12	6 (50.00%)	4 (66.67%)	-	2 (33.33%)
Length of hospital stay	34	15 (44.12%)	10 (66.67%)	-	5 (33.33%)
Clinical failure	25	14 (56.00%)	7 (50.00%)	-	7 (50.00%)
ICU length of stay	16	4 (25.00%)	1 (25.00%)	-	3 (75.00%)
Hospital readmission	9	6 (66.67%)	-		6 (100.00%)
ICU admission	8	2 (25.00%)	-	-	2 (100.00%)
Adverse events	7	2 (28.57%)	-	-	2 (100.00%)
CDI rate	1	1 (100.00%)	-	-	1 (100.00%)
Microbiological failure	1	1 (100.00%)	1 (100.00%)	-	-
Time to clinical success	1	1 (100.00%)	-	-	1 (100.00%)
Duration of antibiotic therapy	1	-	-	-	-
Emergence of MDR	1	-	-	-	-

a. All-cause mortality was classified as: early mortality (2 - 15 days), late mortality (21 - 30 days), long-term mortality (over 30 days, including 60-day - 1-year mortality).

S Table 17: Overview of outcome measures and effect of definite appropriate antibiotic therapy (AAT) on patient outcomes in univariate and multivariate analyses reported by the studies

	Total number of outcomes	**Number of outcomes tested in multivariable analysis**	**Significant effect based on multivariable analysis**		**No significant effect based on multivariable analysis**
			appropriate therapy favored	inappropriate therapy favored	
	n	n (%)	n (%)	n (%)	n (%)
Outcomes	**53**	**26 (49.06%)**	**21 (80.77%)**	**-**	**5 (19.23%)**
All-Cause Mortality[a]	46	22 (47.83%)	18 (81.82%)	-	4 (18.18%)
Early	8	4 (50.00%)	4 (100.00%)	-	-
Late	29	13 (44.83%)	10 (76.92%)	-	3 (23.08%)
Long-term	2	-	-	-	-
In-hospital	7	5 (71.43%)	4 (80.00%)	-	1 (20.00%)
Attributable Mortality	2	2 (100.00%)	2 (100.00%)	-	-
Length of hospital stay	3	1 (33.33%)	1 (100.00%)	-	-
Clinical failure	2	1 (50.00%)	-	-	1 (100.00%)

a. All-cause mortality was classified as: early mortality (2 - 15 days), late mortality (21 - 30 days), long-term mortality (over 30 days, including 60-day - 1-year mortality).

S Table 18: Study characteristics and the measured effect of empiric appropriate antibiotic therapy (AAT) on all-cause mortality in the multivariable analyses reported by the studies

	Effect of AAT on all-cause mortality		
	Significant effect found[a]	**Significant effect not found**	
	n (%)	n (%)	p-value
	102 (69.86%)	44 (30.14%)	
Study characteristic			
Year of publication			
2011 – 2014	36 (78.26%)	10 (21.74%)	0.142
2015 – 2018	47 (70.15%)	20 (29.85%)	
2019 – 2021	19 (57.86%)	14 (42.42%)	
Geographical Distribution			
Europe	46 (70.77%)	19 (29.23%)	
Asia	37 (68.52%)	17 (31.48%)	0.920
North America	15 (75.00%)	5 (25.00%)	
South America	3 (60.00%)	2 (40.00%)	
Intercontinental	1 (50.00%)	1 (50.00%)	
Hospital type			
Secondary Care	3 (60.00%)	2 (40.00%)	
Tertiary Care	68 (70.83%)	28 (29.17%)	0.309
Mixed	11 (55.00%)	9 (45.00%)	
Unclear	20 (80.00%)	5 (20.00%)	
Study department			
Hospital wide	63 (67.74%)	30 (32.36%)	
ICU	26 (78.79%)	7 (21.21%)	0.274
Emergency department	4 (44.44%)	5 (55.56%)	
Mixed	8 (80.00%)	2 (20.00%)	
Unclear	1 (100.00%)	-	
Target pathogens			
P. aeruginosa	5 (83.33%)	1 (16.67%)	
E. coli	2 (66.67%)	1 (33.33%)	
S. aureus	5 (62.50%)	3 (37.50%)	
K. pneumoniae	6 (85.71%)	1 (14.29%)	0.476
A. baumannii	8 (88.89%)	1 (11.11%)	
S. pneumoniae	2 (100.00%)	-	
Mixed	22 (56.41%)	17 (43.59%)	
Other	2 (66.67%)	1 (33.33%)	
Unrestricted by pathogen	50 (72.46%)	19 (27.54%)	
Resistance mechanism of target pathogens			
Carbapenem-resistance	4 (100.00%)	-	
ESBL-production	1 (25.00%)	3 (75.00%)	0.132
MRSA	3 (60.00%)	2 (40.00%)	
Unspecified	3 (100.00%)	-	
Unrestricted by resistance	91 (70.00%)	39 (30.00%)	
Target type of infection			
Bloodstream infection	69 (68.32%)	32 (31.68%)	
Respiratory infection	14 (77.78%)	4 (22.22%)	0.456
Urinary tract infection	1 (25.00%)	3 (75.00%)	
Abdominal infection	3 (75.00%)	1 (25.00%)	

Central nervous system infection	1 (100.00%)	-	
Mixed / Other	5 (71.43%)	2 (28.57%)	
Unrestricted by type of infection	9 (81.82%)	2 (18.18%)	
Target site of acquisition			
Healthcare-setting	22 (73.33%)	8 (26.67%)	0.883
Community acquired	19 (70.37%)	8 (29.63%)	
Unrestricted by acquisition	61 (68.54%)	28 (31.46%)	
Immunosuppressed and cancer patients			
Yes	8 (57.14%)	6 (42.86%)	0.275
No	94 (71.21%)	38 (28.79%)	
AAT mentioned in study objectives			
Yes	38 (65.52%)	20 (34.48%)	0.353
No	64 (72.73%)	24 (27.27%)	
Impact of AAT on outcomes in study objectives			0.103
Yes	32 (61.54%)	20 (38.46%)	
No	70 (74.47%)	24 (25.53%)	
Source of definition specified in the paper			
Yes	26 (65.00%)	14 (35.00%)	0.431
No	76 (71.70%)	30 (28.30%)	
Reflection of quality/limitations of the definition in the paper			0.014
Yes	18 (52.94%)	16 (47.06%)	
No	84 (75.00%)	28 (25.00%)	
Definition of appropriateness			
Based on susceptibility only	35 (71.43%)	14 (28.57%)	
Susceptibility + 1 aspect	32 (66.67%)	16 (33.33%)	0.948
Susceptibility + ≥ 2 aspects	30 (71.43%)	12 (28.57%)	
Non-susceptibility-centered	4 (66.67%)	2 (33.33%)	
Aspects considered			
Susceptibility	97 (69.78%)	42 (30.22%)	0.871
Timely initiation	38 (67.86%)	18 (32.14%)	0.709
Dosing	27 (71.05%)	11 (28.95%)	0.827
Route of Administration	15 (60.00%)	10 (40.00%)	0.248
Duration of Treatment	8 (100.00%)	-	0.055
Guideline-based choice	6 (75.00%)	2 (25.00%)	0.735
Aminoglycoside restriction	10 (90.91%)	1 (9.09%)	0.111
Other	9 (60.00%)	6 (40.00%)	0.390

a. Excluding data from one study in which IAT was found to significantly reduce mortality.

S Table 19: Covariates considered as potential risk factors for unfavorable outcome among studies reporting multivariable analysis

Outcome	Covariate Category	Number of analyses (%) considering the covariate[a]
All-cause mortality (n = 179)	Disease severity	149/157 (94.91%)
	Scoring system	117 (78.52%)
	Critical disease	101 (67.79%)
	Specific organ failure	50 (33.56%)
	Laboratory values indicating severe disease	32 (21.48%)
	Vital parameters indicating severe disease	32 (21.48%)
	Other	16 (10.74%)
	Comorbidities	138/152 (90.79%)
	Scoring system	77 (55.80%)
	Severe underlying disease	77 (55.80%)
	Poor functional status	21 (15.22%)
	Specific comorbid condition	99 (71.74%)
	Other	19 (13.77%)
	Infection with resistant pathogen	78/135 (57.78%)
	Immunosuppression	85/146 (58.22%)
	Compound measure	25 (29.41%)
	Immunosuppressive medication	56 (65.88%)
	Neutropenia and neutropenic sepsis	44 (51.76%)
	Immunodeficiency disorder (conatal/acquired)	10 (11.76%)
	Other	1 (1.18%)
Length of stay (n = 17)	Disease severity	12/16 (75.00%)
	Scoring system	5 (41.67%)
	Critical disease	3 (25.00%)
	Vital parameters indicating severe disease	3 (25.00%)
	Other	4 (33.33%)
	Comorbidities	14/16 (87.50%)
	Scoring system	3 (21.43%)
	Severe underlying disease	4 (28.57%)
	Poor functional status	4 (28.57%)
	Specific comorbid condition	8 (57.14%)
	Other	6 (42.86%)
	Infection with resistant pathogen	4/15 (26.67%)
	Immunosuppression	5/14 (35.71%)
	Compound measure	4 (80.00%)
	Immunosuppressive medication	2 (40.00%)
	Neutropenia and neutropenic sepsis	2 (40.00%)
Clinical failure (n = 8)	Disease severity	6/8 (75.00%)
	Scoring system	3 (50.00%)
	Critical disease	2 (33.33%)
	Lab values indicating severe disease	1 (16.67%)
	Vital parameters indicating severe disease	1 (16.67%)
	Other	2 (33.33%)
	Comorbidities	6/8 (75.00%)
	Scoring system	1 (16.67%)
	Severe underlying disease	2 (33.33%)
	Poor functional status	1 (16.67%)
	Specific comorbid condition	5 (83.33%)

	Infection with resistant pathogen	6/7 (85.71%)
	Immunosuppression	4/6 (66.67%)
	Compound measure	3 (75.00%)
	Neutropenia and neutropenic sepsis	1 (25.00%)

a. Total number of studies varies based on how often a category was found to be non-applicable, e.g. infection with resistant pathogen in a cohort including resistant infections only. Additionally, some studies did not detail the aspects considered for analysis and if the covariates were considered was therefore deemed unknown.

S Table 20: Relationship between the considered risk factors for mortality and the measured effect of appropriate antibiotic therapy (AAT) on all-cause mortality in multivariable analysis reported in the studies[a]

		Effect of AAT on all-cause mortality		
		Significant effect found[b]	**Significant effect not found**	
		n (%)	n (%)	p-value
Overall treatment		130 (72.63%)	49 (27.37%)	
Risk factors for mortality considered[c]				
Severity of disease	Yes	113 (75.84%)	36 (24.16%)	0.016
	No	3 (37.50%)	5 (62.50%)	
Comorbidities	Yes	100 (72.46%)	38 (27.54%)	0.283
	No	12 (85.71%)	2 (14.29%)	
Immunosuppression	Yes	67 (78.82%)	18 (21.18%)	0.115
	No	41 (67.21%)	20 (32.79%)	
Infection with resistant pathogen	Yes	57 (73.08%)	21 (26.92%)	0.586
	No	44 (77.19%)	13 (22.81%)	
Independent risk factors for mortality among all studies with multivariable analysis[c, d]				
Severity of disease	Yes	110 (78.57%)	30 (21.43%)	0.163
	No	20 (66.67%)	10 (33.33%)	
Comorbidities	Yes	56 (70.89%)	23 (29.11%)	0.110
	No	74 (81.32%)	17 (18.68%)	
Immunosuppression	Yes	17 (80.95%)	4 (19.05%)	0.605
	No	113 (75.84%)	36 (24.16%)	
Infection with resistant pathogen	Yes	17 (70.83%)	7 (29.17%)	0.482
	No	113 (77.40%)	33 (22.60%)	
Independent risk factors for mortality among studies considering the respective aspects upon univariable analysis[c, d]				
Severity of disease	Yes	103 (79.84%)	26 (20.16%)	0.240
	No	10 (66.67%)	5 (33.33%)	
Comorbidities	Yes	52 (72.22%)	20 (27.78%)	0.221
	No	48 (81.36%)	11 (18.64%)	
Immunosuppression	Yes	15 (78.95%)	4 (21.05%)	0.723
	No	52 (82.54%)	11 (17.46%)	
Infection with resistant pathogen	Yes	16 (72.73%)	6 (27.27%)	0.965
	No	41 (73.21%)	15 (26.79%)	
Empiric treatment		102 (69.86%)	44 (30.14%)	
Risk factors for mortality considered[c]				
Severity of disease	Yes	85 (72.65%)	32 (27.35%)	0.035
	No	3 (37.50%)	5 (62.50%)	
Comorbidities	Yes	75 (68.81%)	34 (31.19%)	0.369
	No	9 (81.82%)	2 (18.18%)	
Immunosuppression	Yes	50 (76.92%)	15 (23.08%)	0.082
	No	31 62.00%)	19 (38.00%)	
Infection with resistant pathogen	Yes	44 (69.84%)	19 (30.16%)	0.581
	No	38 (74.51%)	13 (25.49%)	
Independent risk factors for mortality among all studies with multivariable analysis[c, d]				
Severity of disease	Yes	84 (75.68%)	27 (24.32%)	0.339
	No	18 (66.67%)	9 (33.33%)	

Comorbidities	Yes No	44 (67.69%) 58 (79.45%)	21 (32.31%) 15 (20.55%)	0.116
Immunosuppression	Yes No	14 (77.78%) 88 (73.33%)	4 (22.22%) 32 (26.67%)	0.689
Infection with resistant pathogen	Yes No	12 (66.67%) 90 (75.00%)	6 (33.33%) 30 (25.00%)	0.453
Independent risk factors for mortality among studies considering the respective aspects upon univariable analysis[c, d]				
Severity of disease	Yes No	77 (77.00%) 8 (66.67%)	23 (23.00%) 4 (33.33%)	0.429
Comorbidities	Yes No	40 (68.97%) 35 (79.55%)	18 (31.03%) 9 (20.45%)	0.230
Immunosuppression	Yes No	12 (75.00%) 38 (82.61%)	4 (25.00%) 8 (17.39%)	0.507
Infection with resistant pathogen	Yes No	11 (68.75%) 33 (70.21%)	5 (31.25%) 14 (29.79%)	0.912

a. Studies in which consideration of the specific risk factor were unknown or not applicable were excluded.

b. Excluding data from one study in which IAT was found to significantly reduce mortality.

c. 6 studies investigated both the effect of empiric and definite therapy within the same analysis, therefore contributing twice.

d. 7 studies did not provide data on factors found significant upon multivariable analysis other than AAT.

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