The Dutch Working Party on Antibiotic Policy (SWAB) guideline for empirical antibacterial therapy of sepsis in adults

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Content

Summary and what's new in comparison with the previous sepsis guideline

The Dutch Working Party on Antibiotic Policy (SWAB) in collaboration with the Dutch Society of Medical Microbiology, the Netherlands Society of Internal Medicine, the Dutch Society for Intensive Care, the Dutch Society for Surgery, the Dutch Society of Hospital Pharmacists and the Dutch Society of Emergency Physicians, has updated the Dutch evidence-based guidelines on antibacterial therapy of sepsis in adults. The guidelines were completely revised in comparison to the 2010 version. The current guidelines are written for adult patients with *bacterial* sepsis according to the Sepsis-3 criteria.[1] Some causes of sepsis are not included, such as neutropenic sepsis, osteomyelitis, meningitis, mediastinitis and endocarditis. We also did not provide recommendations on patients with sepsis and intravascular prosthetic material or long-term central venous catheters.

One important revision is the distinction between low, increased and high risk of infection with Enterobacterales resistant to third generation cephalosporins (3GRC-E) to guide the choice of empirical therapy. Other new topics included empirical antibacterial therapy in patients with a reported penicillin allergy and the role of pharmacokinetic/pharmacodynamic to guide dosing in sepsis.

The guideline is based on 10 population, intervention, comparison, and outcomes (PICO) questions relevant for the Dutch clinical setting that the committee generated (**Table 1**). For each question we performed evidence summaries, which were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. Quality of evidence for clinically relevant outcomes was graded from high to very low. The committee formulated recommendations after structured discussions as strong or weak. When evidence could not be obtained, recommendations were provided on the basis of opinions and experiences (good practice statements). Based on this process, we formulated 55 recommendations on the antibacterial management of sepsis in adults (see recommendations below).

The committee would like to underscore the difficulty of providing evidence-based recommendations for patients with sepsis. In the Netherlands, the probability of the causative pathogen producing ESBL enzymes is an important variable in the choice of empirical treatment. 3GCR-E is often used as a proxy for ESBL-production. National surveillance data from 2017 showed that 6% of *Escherichia coli* and 10% of *Klebsiella pneumoniae* blood isolates were resistant to 3rd generation cephalosporins. However, Dutch research has shown that it is difficult to predict whether the causative pathogen will be a 3GRC-E in a patient with sepsis. The committee recommends to cover 3GCR-E in patients if prior (1-year) culture revealed 3GCR-E. In patients without prior (1-year) cultures showing 3GCR-E the decision to empirically cover 3GCR-E should be made on an individual patient basis taking into account multiple risk factors.

In current clinical practice the choice of empirical antibacterial treatment of sepsis differs considerably between hospitals, varying from a third generation cephalosporin, piperacillin-tazobactam, a combination of a second/third generation cephalosporin with short-term treatment with an aminoglycoside, a combination of a second or third generation cephalosporin with a fluoroquinolone to a carbapenem. The final choice is therefore dictated by the likelihood of involvement of a resistant causative pathogen, by the desire to avoid the use of third-generation cephalosporins,

fluoroquinolones and/or carbapenems from an antibiotic stewardship perspective and by risks of toxicity and other potential adverse events for the patient.

We therefore cannot provide strong recommendations on the best empirical treatment in sepsis based on the currently available literature. We found only subtle differences between strategies on clinical outcomes in studies that were also frequently not generalizable to the Dutch clinical setting. Every strategy has advantages and disadvantages depending on the mentioned perspectives (resistance epidemiology, pharmacokinetic/pharmacodynamic (PK/PD) properties, antibiotic stewardship, adverse events). Consequently, the committee provided pragmatic suggestions for empirical treatment choices in patients with sepsis based on current evidence, reported resistance rates nationally, the antibiotic stewardship perspective and risk of adverse events.

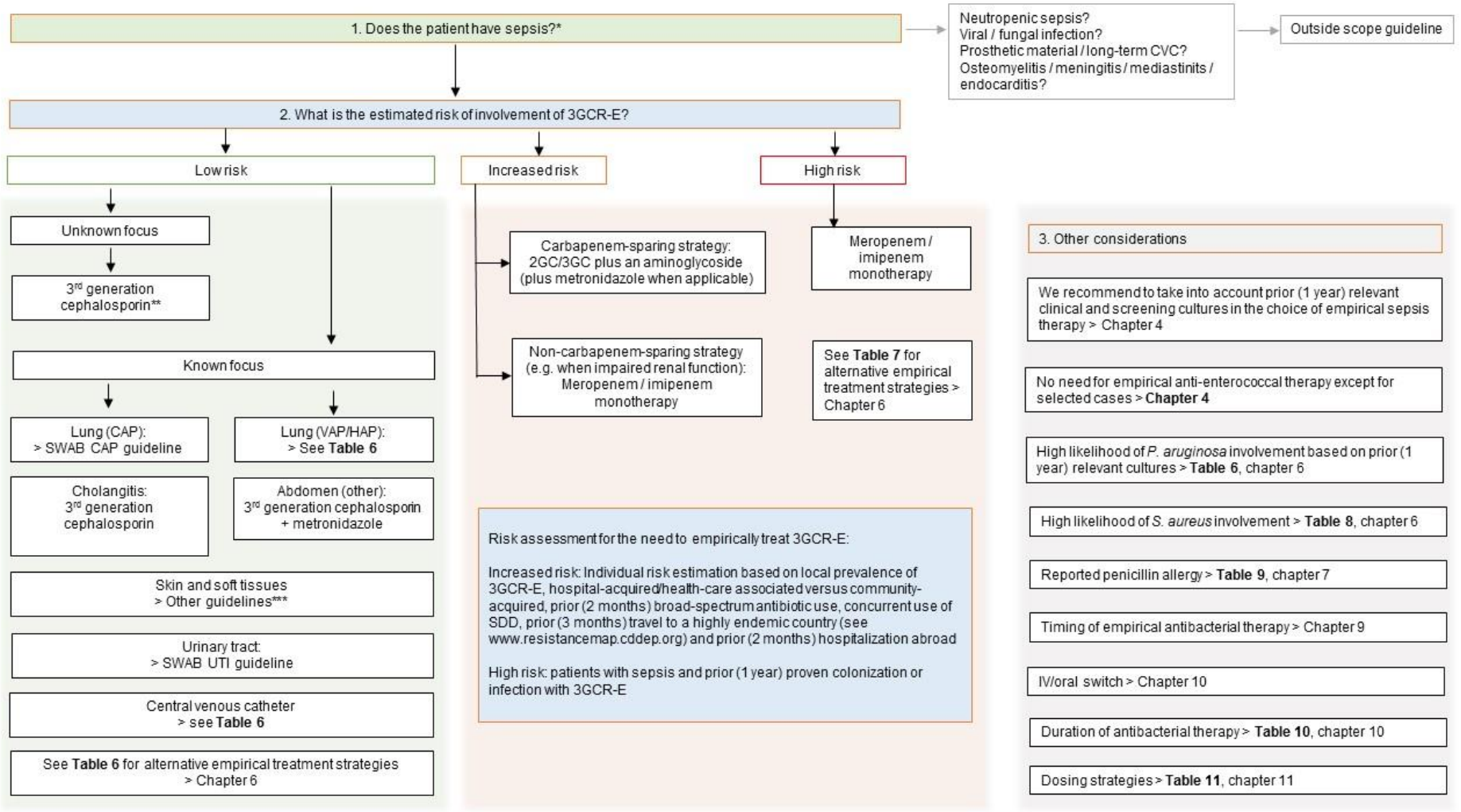
In patients with sepsis, we generally recommend using a beta-lactam antibiotic covering the most likely involved pathogens. Also, we recommend to cover pathogens in prior (1-year) relevant cultures in general. We added suggestions on empirical therapy for *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus* spp.

Similarly, we provided pragmatic suggestions for empirical therapy in patients with sepsis and a reported penicillin allergy and for the optimal timing to start empirical antibacterial treatment in a patient with sepsis. Based on new studies, we were able to generally recommend on shorter treatment durations of patients with sepsis in comparison with the previous guidelines. The committee also underscores the responsibility of clinicians to de-escalate antibacterial therapy in patients with sepsis, especially when very broad spectrum has been started. Due to toxicity concerns, we strongly recommend to stop empirical aminoglycoside treatment after two days.

Among recommendations on PK/PD considerations in patients with sepsis, the committee strongly recommends continuous or prolonged infusion of piperacillin-tazobactam and meropenem based on high quality evidence. Therapeutic drug monitoring is recommended for all patients on aminoglycoside and vancomycin treatment.

A flow chart is provided in **Figure 1** which summarizes the given recommendations on the empirical antibacterial treatment of sepsis.

Figure 1. Flow chart of guideline recommendations on empirical antibiotic treatment of sepsis



* For the diagnosis and non-antibiotic treatment of sepsis we refer to the Dutch guideline 'Sepsis fase 1'.[2] ** For this guideline 3GC includes ceftriaxone and cefotaxim and does not include the anti-pseudomonal cephalosporin ceftazidime. *** Guidelines on skin and soft tissue infections.[3,4] Abbreviations: 3GCR-E: 3rd generation cephalosporin-resistant Enterobacterales; 2GC: second generation cephalosporin; 3GC: 3rd generation cephalosporin; SDD: selective decontamination of the digestive tract.

Recommendations

I Causative bacterial pathogens in sepsis

Which patients are at risk for sepsis due to third-generation cephalosporin-resistant Enterobacterales or *P. aeruginosa* in the Netherlands? (chapter 3)

Recommendation	**Strength**	**Quality of evidence**
1. We recommend empirical therapy against 3GCR-E in patients with sepsis and prior (1 year) proven infection or colonization with 3GCR-E	Strong	Very low
2. We suggest that clinicians take into account the risk of 3GCR-E involvement in sepsis on an individual patient basis to decide if empirical antibacterial therapy against 3GCR-E is appropriate Factors to guide this decision include local prevalence of 3GCR-E, if the infection is hospital-acquired/health-care associated versus community-acquired, prior (2 months) broad-spectrum antibiotic use, concurrent use of SDD, prior (3 months) travel to a highly endemic country (see https://resistancemap.cddep.org/) and prior (2 months) hospitalization abroad	Weak	Very low
3. We recommend empirical therapy against *P. aeruginosa* in patients with sepsis and prior (1 year) infection or colonization with *P. aeruginosa*	Strong	Very low

II Empirical antibacterial therapy in sepsis

What is the importance of appropriate empirical therapy in patients with sepsis? (chapter 4)

Recommendation	**Strength**	**Quality of evidence**
4. We recommend empirical broad-spectrum antibacterial therapy for patients presenting with sepsis to cover all pathogenic bacteria that are likely to be involved	Strong	Moderate
5. We recommend to take into account prior (1 year) resistance in relevant clinical and screenings cultures in the choice of empirical sepsis therapy	Strong	Very low
6. We recommend that empirical antibacterial therapy is guided by the local distribution of pathogens associated with sepsis and their antimicrobial susceptibilities	Strong	Very low
7. We suggest empirical antibacterial therapy for patients presenting with sepsis to cover HRMO when these are likely to be involved	Weak	Very low

8. We suggest empirical antibacterial therapy covering anaerobic bacteria for patients presenting with sepsis and intra-abdominal infections of the lower intestinal tract or necrotizing soft tissue infections	Weak	Very low
9. We generally suggest against routine empirical treatment of anaerobic bacteria in patients presenting with sepsis due to aspiration pneumonia, unless empyema or a lung abscess is suspected	Weak	Very low
10. We generally recommend against routine empirical treatment of enterococci in patients presenting with sepsis	Strong	Moderate
11. We suggest that anti-enterococcal therapy could be considered in individual patients with sepsis, e.g. those who have a high likelihood of enterococcal involvement based on recent relevant cultures and those with recent complicated intra-abdominal surgery or a suspected CVC infection and substantial exposure to broad spectrum antibiotics	Weak	Very low

What is the effect of double active empirical antibacterial therapy compared to monotherapy in patients with sepsis? (chapter 5)

Recommendation	**Strength**	**Quality of evidence**
12. We recommend against routine double active empirical antibacterial therapy* for patients with sepsis or septic shock.	Strong	Moderate
13. We suggest that double active therapy is not routinely used as definite therapy for patients with sepsis due to *P. aeruginosa* infection	Weak	Very low
14. We suggest that double active therapy is not routinely used as definite therapy for patients with sepsis due to *S. aureus* infection not associated to prosthetic material	Weak	Moderate

* We defined double active antibacterial therapy as treatment with two classes of antibiotics, both targeting the known or suspected causing pathogen(s) (e.g., ceftriaxone and an aminoglycoside to target gram-negative pathogens) and with the specific purpose to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Also frequently referred to as combination antibiotic therapy. Of note, the use of two antibiotics for the increased likelihood of covering the causing agent (broadening the spectrum), or for covering multiple causing agents (e.g., aerobic and anaerobic bacteria) was not included in the definition of double active therapy.

What is the optimal choice of empirical therapy in patients with sepsis in the Netherlands? (chapter 6)

Antibacterial therapy in patients with sepsis in general

Recommendation	**Strength**	**Quality of evidence**
15. In patients with sepsis, we generally recommend using a beta-lactam antibiotic covering the most likely involved pathogens	Strong	Moderate
16. In patients with sepsis in general / with no obvious source of infection, we suggest a 3rd generation cephalosporin (3GC). Alternative empirical treatment strategies are listed in **Table 6**	Weak	Low

17. In patients with sepsis due to HAP or VAP, we suggest that there are equivalent empirical treatment strategies, listed in **Table 6**	Weak	Low
18. In patients with sepsis due to cholangitis, we suggest a 3GC. Alternative empirical treatment strategies are listed in **Table 6**	Weak	Low
19. In patients with sepsis due to intra-abdominal infection, we suggest a combination of a 3GC with metronidazole. Alternative empirical treatment strategies are listed in **Table 6**	Weak	Low
20. In patients with sepsis and a suspected CVC infection*, we recommend prompt removal of the line	Strong	GPS
21. In patients with sepsis and suspected CVC infection, we suggest empirical treatment with a 3GC** with gentamicin or high dose ciprofloxacin Alternative treatment strategies are listed in **Table 6**	Weak	GPS
22. For the empirical treatment of sepsis due to UTI, CAP and SSSI's, we refer to other guidelines[3-6]		

* Recommendations for sepsis due to suspected long-term CVC's were not included in this guideline

** 3GC may be given in high dose for more optimal PK/PD for *S. aureus* infections in accordance to EUCAST

Antibacterial therapy in patients with sepsis and increased risk of involvement of 3GCR-E

23. In patients with sepsis and high risk of involvement of 3GCR-E based on prior (1 year) infection/colonization, we recommend meropenem or imipenem as empirical antibacterial therapy. Alternative strategies are listed in **Table 7**	Strong	Moderate
24. In patients with sepsis and increased risk of involvement of 3GCR-E but no prior (1 year) infection/colonization, we suggest that a carbapenem-sparing strategy (listed in **Table 7**) is acceptable	Weak	Very low
25. We cannot provide a recommendation for or against empirical or definite treatment with piperacillin-tazobactam in patients with sepsis due to chromosomal AmpC-producing Enterobacterales (such as *Enterobacter, Serratia, Citrobacter, Providencia* and *Morganella* spp)	-	-
26. In patients with sepsis due to ESBL-producing Enterobacterales, we recommend against piperacillin-tazobactam as definite antibacterial therapy regardless of the in vitro susceptibility	Strong	Moderate

Antibacterial therapy in patients with sepsis and increased risk of involvement of Staphylococcus aureus

27. There is insufficient evidence to recommend against empirical use of other beta-lactam antibiotics than flucloxacillin or cefazolin in patients with sepsis in which *S. aureus* is a likely pathogen. Empirical sepsis treatment strategies when there is a substantial risk of *S. aureus* involvement are listed in **Table 8**	-	-
28. For definite therapy of patients with sepsis due to *S. aureus*, we refer to the Dutch guideline on *S. aureus* bacteraemia.[7]		

<u>What is the optimal empirical antibacterial therapy of sepsis in patients with a penicillin allergy? (chapter 7)</u>

Recommendation	Strength	Quality of evidence
29. In patients with sepsis and a reported penicillin allergy, we recommend to obtain information (i.e. medical history and skin test results) about the presumed allergy if possible	Strong	GPS
30. In patients with sepsis and a reported penicillin allergy but in whom the allergy is very unlikely, we suggest that penicillins can be used if needed (see **Table 9**)	Weak	Very low
31. In patients with sepsis and a reported penicillin allergy that was proven, possible or unspecified, we suggest to avoid penicillins during the primary sepsis treatment and to choose alternative beta-lactams (cephalosporins, carbapenems)	Weak	Very low
32. In patients with sepsis and an unspecified or possible immediate type penicillin allergy, we suggest to plan penicillin allergy testing and/or a controlled penicillin challenge when the patient has recovered from sepsis	Weak	Very low

III Timing and duration of antibacterial therapy in sepsis

What is the optimal timing of empirical antibacterial therapy in patients with sepsis? (chapter 8)

Recommendation	Strength	Quality of evidence
33. In patients with sepsis or septic shock, we recommend that the administration of antibacterial treatment should be initiated promptly with health care systems working to reduce that time to as short a duration as feasible	Strong	Low

What is the optimal duration of antibacterial treatment for sepsis? (chapter 9)

Recommendation	Strength	Quality of evidence
34. For treatment duration of sepsis due to CAP, UTI, SSSI and of sepsis due to *S. aureus* infection, we refer to other guidelines[3-8]		
35. We recommend source control interventions when possible to support antibacterial treatment in patients with sepsis.	Strong	Low
36. We recommend that a four-day course of antibacterial treatment is appropriate for patients with sepsis due to intra-abdominal infections following effective source control and with favourable clinical response	Strong	Moderate
37. We suggest that shorter courses of antibacterial treatment (up to three days) are appropriate in patients with sepsis and cholangitis following adequate drainage of the biliary tree	Weak	Very low
38. We recommend that an antibacterial treatment duration of 7 days is adequate for most patients with sepsis due to VAP	Strong	Moderate

39. We suggest that an antibacterial treatment duration of 7 days is adequate for most patients with sepsis due to HAP	Weak	Very low
40. We suggest that an antibacterial treatment duration of 7 days at maximum is adequate for most patients with sepsis due to suspected CVC infection with gram-negative pathogens following removal of the CVC and with favourable clinical response	Weak	Very low
41. We suggest that an antibacterial treatment duration of 0 to 7 days is adequate for most patients with sepsis due to suspected CVC infection with CNS or enterococci following removal of the CVC and with favourable clinical response	Weak	GPS
42. We suggest that an antibacterial treatment duration of 7 days is adequate for sepsis and septic shock without a clear focus in most patients with favourable clinical response	Weak	Low
43. We recommend daily assessment for the need of antibacterial therapy in patients with sepsis and to discontinue therapy when during follow-up there is lack of clinical or microbiological evidence of infection	Strong	GPS
44. We suggest that procalcitonin levels are used to support shortening the duration of antibacterial therapy in patients with sepsis if optimal duration of antibiotic therapy is unclear	Weak	Moderate
45. We recommend to consider antibiotic de-escalation (resulting in smaller spectrum antibiotics) in all patients on antibiotics for sepsis on a daily basis and based on pathogen identification, sensitivities and risk of adverse events	Strong	Very low
46. We recommend to stop empirical aminoglycoside therapy within a maximum of two days	Strong	Low
47. We recommend to switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is feasible	Strong	Very low

IV Pharmacokinetic and pharmacodynamic considerations in sepsis

In patients with sepsis, should we recommend pharmacokinetic/pharmacodynamic dosing optimization for empirical antibacterial therapy? (chapter 10)

Recommendation	**Strength**	**Quality of evidence**
48. In patients with sepsis, we suggest that dosing strategies of antibacterial therapy be optimized based on accepted pharmacokinetic / pharmacodynamic principles and specific drug properties **(Table 11)**	Weak	Low
49. In patients with sepsis we recommend prolonged or continuous* infusion of piperacillin-tazobactam and carbapenems	Strong	High

50. In patients with sepsis we suggest prolonged or continuous* infusion of other beta-lactam antibiotics than piperacillin-tazobactam and carbapenems	Weak	Low
51. In patients with sepsis, we recommend direct therapeutic drug monitoring (including either mid-dosing or both peak and through levels) during aminoglycoside treatment in patients with sepsis and septic shock	Strong	GPS
52. In patients with sepsis, we recommend therapeutic drug monitoring during vancomycin treatment in patients with sepsis and septic shock	Strong	GPS
53. In patients with sepsis, we suggest therapeutic drug monitoring when there are concerns on target attainment of other antibacterial drugs than aminoglycoside and vancomycin (e.g. extreme body weight, augmented or decreased renal clearance, hypoalbuminemia)	Weak	GPS
54. In patients with sepsis, we suggest continuous* infusion of vancomycin	Weak	GPS
55. In patients with sepsis in whom ciprofloxacin is indicated, we suggest empirical ciprofloxacin three times daily 400 mg iv	Weak	GPS

***** Continuous infusion includes one intermittent dose as a loading dose

Introduction and methodology

General introduction

Sepsis is currently defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1,9,10] Sepsis and septic shock are common reasons for intensive care unit (ICU) admission and have high mortality rates, even at long-term follow-up.[11-18] In 2004, the estimated annual number of admissions for severe sepsis in Dutch ICU's was 7700 to 9500.[19] The incidence of sepsis may have risen in recent decennia, possibly due to ageing and increasing numbers of immunocompromised patients.[12,14,20] Antibacterial therapy is an essential part of effective sepsis treatment. Inappropriate or delayed antibacterial treatment in patients with sepsis and septic shock are associated with increased morbidity and mortality.[21-26]

The Dutch Working Party on Antibiotic Policy (SWAB), initiated by the Dutch Association of Internal Medicine, the Dutch Society for Medical Microbiology and the Dutch Association of Hospital Pharmacists, coordinates activities in the Netherlands with the aim to optimize antibiotic use, to contain the development of antimicrobial resistance, and to limit the costs of antibiotic use. For this purpose, SWAB develops evidence-based guidelines on antibiotic treatment, intended for the Dutch situation. SWAB also yearly reports on the use of antibiotics and on trends in antimicrobial resistance in The Netherlands in NethMap (available from www.swab.nl), in collaboration with the Centre for Infectious Diseases Control, National Institute for Public Health and the Environment (CIb-RIVM).[27]

The general objective of the SWAB sepsis guideline is to guide medical professionals in empirical antibacterial treatment for adults with sepsis and septic shock in hospitals in the Netherlands. The current guideline on empirical antibacterial therapy of sepsis in the Netherlands is an update of the SWAB sepsis guideline published in 2010.[28] The first step for the update included the establishment of

a guideline committee with individuals from all relevant Dutch professional medical societies involved in the care for adults with sepsis. The group included experts in the field of sepsis and methodology.

Scope and target audience

The guideline articulates the prevailing professional standard in sepsis and contains general recommendations for the antibacterial treatment of hospitalized adults. Sepsis is a complex syndrome that can originate from multiple sites of infection. Patients with sepsis comprise a very heterogeneous population and in the individual patient there are always nuances and uncertainties in the ultimate diagnosis of sepsis. It is therefore possible that these recommendations are not applicable in an individual patient case. The applicability of the guideline in clinical practice is the responsibility of the treating physician. There may be facts or circumstances when non-adherence to the guideline is desirable in the interest of good patient care.

We aimed to provide an overview of the quality of available evidence and give evidence-based recommendations for empirical treatment of sepsis in adults (≥18 years old). We restricted the guideline to the most important causes of sepsis. Pneumonia is the most common source of sepsis in adults, followed by abdominal infections, urinary tract infections (UTI) and complicated skin and soft tissue infections (SSTI).[13,15,29-31] In addition, we included sepsis in general or of (yet) unknown origin and a separate chapter on sepsis and suspected central venous catheter infection. The definitions used in this guideline are specified in the next section.

The SWAB sepsis guideline cannot be applied to children with sepsis nor to patients with sepsis due to viral or fungal infections. For these infections we refer to the SWAB guideline on fungal infections[32] and guidelines on treating specific viral infections, like Influenza.[33] Other populations that are excluded from the guideline are patients with neutropenic fever or sepsis and patients with sepsis due to central venous catheters for long term venous access (e.g. port-a-cath, Broviac). This guideline doesn't include recommendations on the *diagnosis* of sepsis; treatment of sepsis other than antibacterial treatment, including interventions on source control; monitoring of sepsis; and care after recovery of sepsis. For recommendations on these topics, we refer to the general Dutch sepsis guideline of which this SWAB guideline is a component, initiated by the NIV, and of which the concept of the first phase was recently distributed.[2]

The guideline committee defined the scope of the guideline and key questions to be answered. The definite list of key questions was based on key questions in the previous version of the guideline and priorities for clinical practice. **Table 1** shows the final key questions. Questions covering interventions were structured into the PICO format (Population; Intervention; Control; Outcomes, see appendix). Guideline committee members were assigned to one or more key questions.

Table 1. Key questions SWAB guideline for empirical antibacterial therapy of sepsis in adults

I	**Causative bacterial pathogens in sepsis**
1	Which bacteria are most frequently isolated from patients with sepsis in the Netherlands?

2	What are the resistance patterns of the most frequently isolated bacteria in patients with sepsis in the Netherlands?
3	Which patients are at risk for sepsis due to third-generation cephalosporin-resistant Enterobacterales (3GCR-E) or *P. aeruginosa* in the Netherlands?
II	**Empirical antibacterial therapy of sepsis**
4	What is the importance of appropriate empirical therapy in patients with sepsis?
5	What is the effect of double active empirical antibacterial therapy compared to monotherapy in patients with sepsis?
6	What is the optimal choice of empirical therapy in patients with sepsis in the Netherlands?
7	What is the optimal empirical antibacterial therapy of sepsis in patients with a penicillin allergy?
III	**Timing and duration of antibacterial therapy in sepsis**
8	What is the optimal timing of empirical antibacterial therapy in patients with sepsis?
9	What is the optimal duration of antibacterial treatment for sepsis?
IV	**Pharmacokinetic and pharmacodynamic considerations in sepsis**
10	In patients with sepsis, should we recommend pharmacokinetic/pharmacodynamic dosing optimization for empirical antibacterial therapy?

Methodology

The guideline was written according to the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument.[34] In line with the AGREE instrument, the Guideline committee followed a guideline development process comparable to that of the Infectious Diseases Society of America (IDSA), which includes a systematic method of grading both the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong).[35]

Search strategy

In January 2017 the Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock 2016 were published.[36] In addition, several other international guidelines relevant to the treatment of sepsis have been published recently, including the 2017 IDSA guideline on hospital-acquired infections (HAP) and ventilator-associated infections (VAP) and the 2017 Surgical Infection Society (SIS) guideline on intra-abdominal infections.[37,38] To prevent duplication of efforts we assessed the quality of these guidelines using the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument.[34] The overall quality of the guidelines was high. We therefore used the literature included in these guidelines for similar key questions and updated the literature since the search done by the

guidelines if necessary. We subsequently assessed if the evidence, grading of the evidence and recommendations were applicable to the Dutch situation and patients with sepsis. If not, we independently graded the evidence and developed recommendations as described below.

Several SWAB or other Dutch guidelines relevant for the treatment of sepsis have been published in recent years, including the Dutch Society of Medical Microbiology (NVMM) concept guideline on *S. aureus* bacteraemia (2019),[7] the SWAB guidelines on management of community-acquired pneumonia (CAP, 2016),[6,39] invasive fungal infections (2017)[32] and for antimicrobial stewardship (2016).[40] The SWAB guideline on management of complicated urinary tract infections (2013) is currently being updated.[5] The SWAB guideline on bacterial central nervous system infections (2012)[8] is older but still adequate as judged by the SWAB executive board. The same holds true for the Dutch evidence-based guideline on necrotizing soft tissue infections (2015) and the Dutch society of Dermatology and Venereal Disease (NVDV) guideline on cellulitis and erysipelas (2013).[3,4] Providing different recommendations to established Dutch guidelines is not preferable as many will be updated before the next update of the SWAB sepsis guideline. Therefore, relevant findings and recommendations in the mentioned Dutch guidelines are summarized and referred to. Relevant new evidence was mentioned only when it would change practice to patients with sepsis.

For questions not covered by the mentioned guidelines, we performed a search for systematic reviews and included studies from relevant systematic reviews in PubMed, Embase and the Cochrane library. When no systematic reviews were available we performed a search for randomized controlled trials (RCT) in the same databases. Searches were either updated since the search in 2009 of the previous SWAB sepsis guideline when applicable, or performed without a date limit. Two guideline members and a clinical librarian set up the searches for systematic reviews and randomized controlled trials. The search strategy included synonyms for sepsis, the relevant study design and other appropriate components of the population and intervention within the PICO question.

Studies were included on the basis of study design (RCT or systematic review), patient population, appropriate intervention and control based on the key question. Studies were included when at least 50% of the patients were non-neutropenic adults with sepsis, bacteraemia or severe/complicated infection (as defined by the study conductors) or when outcomes were reported separately for these patients. We restricted to studies that included clinically relevant outcomes.[41] In addition we included studies reporting on the development of antibacterial drug resistance. We therefore included the following outcome measures as defined by the conductors of individual studies:

1. Mortality: short-term mortality, long-term mortality (critically important outcome measure)
2. Morbidity: failure-free days, clinical cure, treatment failure, recurrence of infection, length of ICU/hospital stay (important outcome measure)
3. Adverse consequences of therapy: superinfections with or without resistant micro-organisms (important outcome measure); other adverse events; colonisation with resistant micro-organisms

We did not include non-clinical, surrogate or economic outcome measures. Studies only reported in languages other than English and Dutch were excluded.

For evidence on drug resistance in the Netherlands, the guideline committee used surveillance data from 2017 in the NethMap annual report 2018.[27] Reports of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guided the interpretation of susceptibility test results.[42]

Quality assessment of literature and formulation of recommendations

One guideline member performed quality assessment of the literature for individual key questions, which was subsequently verified by other guideline members. The quality of evidence per outcome variable was graded according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, adopted by SWAB. Quality of evidence is determined by several factors, the most important of these being study design (**Figure 2**).[43] The remaining factors (e.g. risk of bias) can downgrade or upgrade the quality of evidence based on design. For example, an observational study with a serious risk of bias is considered to have a very low quality of evidence. Also, if the number of patients with sepsis in a study was not reported or very likely to be low, we downgraded based on indirectness. The quality of evidence is indicated with a hyphen (-) when no evidence was obtained from the literature. For readability purposes, we summarized quality of evidence for all clinically relevant outcomes in the conclusions tables.

In the final step of the process recommendations were made. The strength of recommendations was graded as Strong or Weak, taking the quality of evidence, patients' values, resources and costs, and the balance between benefits, harms and burdens into account (**Figure 2**).[44] The SWAB Stewardship Guideline committee and for example the WHO are of the opinion that a low quality of evidence does not necessarily lead to a weak recommendation.[35,45] For example, little evidence supports sepsis removing the CVC in patients with sepsis and a suspected CVC infection, but the guideline committee nevertheless strongly recommends to do it if possible. Likewise, strong evidence for a certain intervention can sometimes nevertheless result in a weak recommendation. The reasons for the guideline committee to give strong or weak recommendations are discussed for each recommendation in the section "Other considerations", where applicable divided into patients' values, resources and costs, and the balance between benefits, harms and burdens. Notably, since cost is a variable that is highly subjective to the setting and time of research, it was difficult to translate the effects of the included studies to the current healthcare environment in the Netherlands.

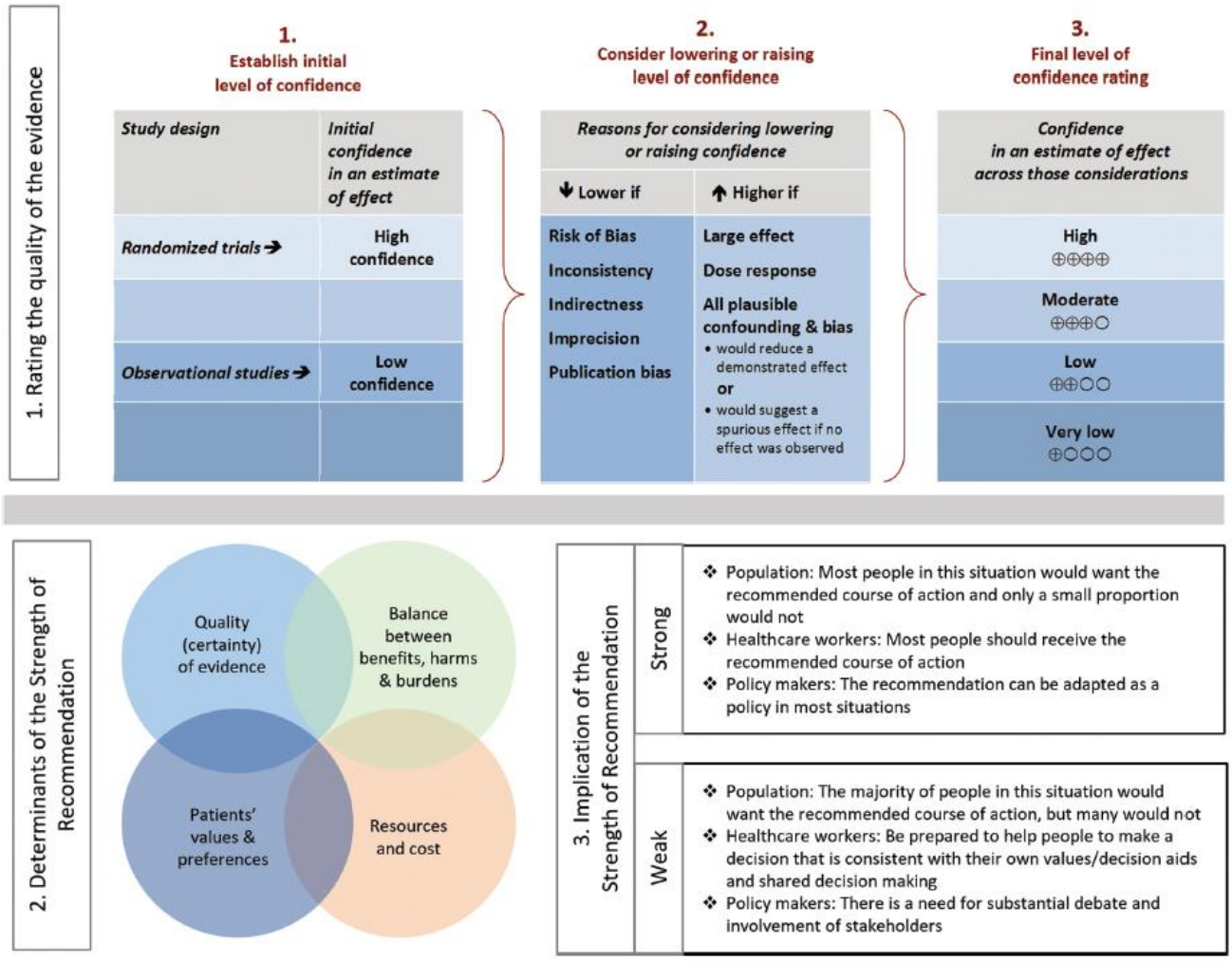


Figure 2 Overview of GRADE methodology. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[2,3]

When evidence could not be obtained, assigned guideline group members for the key question proposed recommendations on the basis of opinions and experiences. These good practice statements (GPS) were not graded using the GRADE approach and were developed according to criteria in **Table 2**.[46]

Table 2. Criteria for the development of good practice statements (GPS)[46]

A question applicable to any recommendation (but often violated in good practice statements)
1. Is the statement clear and actionable?
Questions particular to good practice statements
2. Is the message really necessary in regard to actual health care practice?
3. After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences.
4. Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy (opportunity cost is large)?

5. Is there a well-documented clear and explicit rationale connecting the indirect evidence?
The answers to all questions 2 - 5 should be yes to proceed with a good practice statement.

Details on the literature search and evidence summaries were published in the appendix. Drafted recommendations per key question were presented to the complete guideline working group and consensus reached by discussion and voting. Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts delegated from the professional societies, including the NIV, NVMM, NVZA, NVIC, NVvH and NVSHA. We summarized the recommendations in one figure. The draft guideline was subsequently submitted to the members of relevant professional societies for external review. The guideline working group will adjust the guideline according to comments in the external review through group discussion. The final version will be presented for formal approval to the SWAB executive board, consisting of mandated representatives of the professional societies.

Implementation and dissemination of the guideline

The formal publication of the guideline will be announced to all relevant professional societies and presented at relevant national conferences. The recommendations in the guideline are available online at https://swabid.nl.

Conflicts of interest policy and funding

The SWAB employs strict guidelines with regard to potential conflicts of interests, as described in the SWAB Format for Guideline Development (www.swab.nl). For the development of this guideline, the SWAB was funded by the Dutch National Institute for Public Health and the Environment (CIb-RIVM). See **Table 3** for disclosures of the members of the Guideline committee.

Update

SWAB intends to revise their guidelines every 5 years. The potential need for earlier revisions will be determined by the SWAB board at annual intervals, based on current literature. If necessary, the guideline committee will be reconvened to discuss potential changes. Therefore, in 2025 or earlier if necessary, the guideline will be re-evaluated.

Table 3. Conflicts of interest of members of the SWAB sepsis guideline committee

Member	Potential conflict of interest
E Sieswerda	None
H.I. Bax	None
J.J. Hoogerwerf	None
M.G.J. de Boer	Chair Stichting Werkgroep Antibioticabeleid; Chair COIG Infectieziekten en Immuniteit, NIV
M. Boermeester	Institutional payment for consultancy / advisory board for Johnson&Johnson, Bard, Acelity, Gore; Institutional grants Johnson&Johnson, Mylan, Bard, Acelity, LifeCell/Allergan, New Compliance
Marc Bonten	Consultant for Janssen Vaccines, (paid to UMCU); Research funding Janssen Vaccines, Immunexpress, Vedanta, (paid to UMCU); Research funding Innovative Medicines Initiative, (paid to UMCU)
D. Dekker	None
R. Gerth van Wijk	Board member EAACI (European Academy of Allergy and Clinical Imunology); President UEMS Section and Board of Allergology; Member of several national and international guideline committees
N. P. Juffermans	Research funding ZonMW, Sanquin, Horizon2020, CSL Behring (not related to the current guideline)
M. Kuindersma	None
P.D. van der Linden	Treasurer Stichting Werkgroep Antibioticabeleid
D. C. Melles	None
P. Pickkers	Consultancy board memberships (not related to the current guideline). Chair SepsisNet Nederland Foundation (unpaid)
J. A. Schouten	Member Wetenschappelijke Adviesraad (paid); Radboud Center Infectious Diseases ESGAP (ESCMID) secretary; SWAB member; Unrestricted educational Grant MSD
J.R. Rebel	Curriculum-, en implementatiecommissie NVSHA; Visitatiecommissie NVSHA; Member of local sepsis guideline committee
A. R. H. van Zanten	Head of ICU & Research, Ziekenhuis Gelderse Valei, Ede; Chair SKMS guideline Sepsis; Research grants Adrenoss, Nutricia, Beacon, Cardinal Health; Lectures (paid) not related to antibacterial therapy of Abbott, Baxter, BBraun, Fresenius-Kabi, Lyric, Nutricia, Nestle; The SKMS Sepsis guideline has been developed parallel to the SWAB sepsis guideline.
J. M. Prins	Editor in chief digital guideline antimicrobial therapy “SWAB ID”, (paid to AMC); Member Wetenschappelijke Adviesraad Zorginstituut Nederland, CG (paid); Member Board Stichting de Merel (non-profit, paid to AMC)
W. J. Wiersinga	Research funding from NWO, ZonMW and Horizon2020 (not related to the current guideline)

Definitions and abbreviations

Table 4. Definitions and abbreviations

Sepsis and infection	
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection[10]. For the diagnosis and non-antibiotic treatment of sepsis we refer to the Dutch guideline 'Sepsis fase 1'.[2]
Septic shock	A subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone[9]. Clinically defined as sepsis with persisting hypotension requiring vasopressors to maintain the mean arterial pressure ≥65 mmHg, and with a serum lactate >2 mmol/L.
Bacteraemia	Also called bloodstream infection, the presence of bacteria in the blood as demonstrated by culture.
Central line-related bloodstream infection (CLABSI)	CLABSI is defined as bacteraemia / candidemia in a patient with an intravascular catheter in situ with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infection (i.e. fever, chills, and/or hypotension), and no apparent source for the bloodstream infection except the catheter. Bloodstream infections are considered to be associated with a central line if the line was in use during the 48-hour period before the development of the bloodstream infection.[47,48]
Highly Resistant Microorganisms (HRMO)	Enterobacterales, except *Enterobacter cloacae*, were considered HRMO if they were resistant to cefotaxime/ceftriaxone and/or ceftazidime as indicator agents for the production of Extended-spectrum beta-lactamase (ESBL), or resistant to both fluoroquinolones and aminoglycosides. *E. cloacae* was considered an HRMO if resistant to both fluoroquinolones and aminoglycosides. *P. aeruginosa* was considered an HRMO if resistant to ≥3 antibacterial therapy groups among fluoroquinolones, aminoglycosides, carbapenems, ceftazidime and piperacillin-tazobactam. Acinetobacter spp. were considered HRMO when resistant to imipenem or meropenem or resistance to both fluoroquinolones and aminoglycosides.**
Hospital-acquired pneumonia (HAP)	Pneumonia not present at the time of hospital admission and occurring 48 hours or more after admission[37]
Ventilator-associated pneumonia (VAP)	Pneumonia occurring two days or more after start invasive mechanical ventilation[37]
Place of acquisition	
Community-acquired	Occurrence of infection outside of hospital or within two days of admission, except for patients hospitalized in the past 30-90 days, residing in nursing homes, receiving haemodialysis or having long-term intravascular devices.
ICU-acquired	Acquired during stay in the ICU (two days or more)

Nosocomial	Acquired during hospital stay (two days or more after admission) or acquired within 30-90 days after hospital discharge, on haemodialysis, residing in a nursing home or having long-term intravascular devices
Therapy	
Antibiotic de-escalation	Changing treatment to narrow-spectrum antibiotic or stop antibiotics as soon as culture results are available.[40]***
Broad-spectrum therapy	Use of one or more antibacterial agents with the specific intent of broadening range of potential pathogens covered during empirical therapy
Definite therapy	Therapy targeted to a specific pathogen after microbiologic identification
Double active therapy	Antibacterial treatment with two classes of antibiotics, both targeting the known or suspected causing pathogen(s) (e.g., ceftriaxone and an aminoglycoside to target gram-negative pathogens) and with the specific purpose to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Also frequently referred to as combination antibiotic therapy. Of note, the use of two antibiotics for the increased likelihood of covering the causing agent (broadening the spectrum), or for covering multiple causing agents (e.g., aerobic and anaerobic bacteria) was not included in the definition of double active therapy.
Empirical therapy	Initial therapy started in the absence of definitive microbiologic pathogen identification
2nd generation cephalosporin (2GC)	Antibacterial treatment class. In this guideline 2GC is equivalent to intravenous cefuroxime
3rd generation cephalosporin (3GC)	Antibacterial treatment class. In this guideline 3GC includes (intravenous) ceftriaxone and cefotaxime and does not include the anti-pseudomonal cephalosporin ceftazidime
3GCR-E	Enterobacterales resistant to 3GC
PK/PD	Pharmacokinetic/pharmacodynamic
SDD	Selective decontamination of the digestive tract

*Sepsis criteria are derived from the 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[1,9,10] In these new sepsis definition the presence of organ dysfunction is central and a requirement; until then organ dysfunction identified "severe" sepsis, a term that was abandoned in the Sepsis-3 definition.

**HRMO definitions are, In line with Nethmap, as defined by of the Working Group on Infection Prevention (WIP, www.rivm.nl/Onderwerpen/W/Werkgroep_Infectie_Preventie_WIP).

***Definition of antibiotic de-escalation in accordance with consensus guideline European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2019: 1. Replacing broad-spectrum antimicrobials with agents of a narrower spectrum or a lower ecological impact. or: 2. Stopping components of an antimicrobial combination.

Key questions

I Causative bacterial pathogens in sepsis

Introduction

Chapter 1 summarizes the epidemiology of bacterial pathogens involved in sepsis in the Netherlands, and their resistance patterns. Chapter 2 identifies risk factors for Enterobacterales resistant to 3rd generation cephalosporins or Pseudomonas.

1. Which bacteria are most frequently isolated from patients with sepsis in the Netherlands?

Evidence summary

Reported pathogens in Dutch sepsis studies

In recent years a number of prospective studies reporting on the bacterial aetiology of sepsis in the Netherlands have been published.[49-51] The PHANTASi trial was an open label RCT comparing the effect of early administration of antibiotics in the ambulance to usual care in patients with sepsis (n=2672 patients; primary results are discussed in chapter 7).[49] Most patients had severe sepsis (57%), a minority septic shock (3.9%) and 9.5% of patients were admitted to the ICU. The most frequent suspected primary sources of sepsis were pulmonary (55%), urinary tract (22%), abdominal (6.6%) and skin or soft tissue (5.5%) infections. The remaining patients had infections at other sites (6.5%) or no infection (1.5%). In patients in which cultures were taken gram-positive pathogens were identified in 21% (staphylococci 9.1%, streptococci 7.7%), gram-negative pathogens in 30% (*E. coli* 21%, other 9.6%), and fungal pathogens in 3.4% of cases.

The Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project prospectively included almost 7000 intensive care unit (ICU) patients between 2011 and 2014.[50,51] In a sub-cohort of 2579 patient with sepsis, the most frequent suspected primary sources of sepsis were pulmonary (50%), abdominal (16%), bloodstream (8.9%), urinary tract (6.3%), and skin or soft tissue (4.6%) infections.[31] In a report of 1060 patients of the MARS project with definite or probable infection and sepsis, gram-positive pathogens were identified in 48%, gram-negative pathogens in 58% and fungal pathogens in 11% of cases.[52] In some sepsis episodes multiple causative pathogens were isolated. The number of patients with community-acquired versus healthcare-associated sepsis was not yet reported.

A retrospective cohort study from the Netherlands reported causes of sepsis in all patients in 2012 hospitalized in two university hospitals with a diagnosis of sepsis.[53] Among 252 patients, 60% had severe sepsis or septic shock. The most common sources of sepsis were urinary tract infections (UTI; 30%) and respiratory tract infections (17%). In patients with severe sepsis or septic shock, source of sepsis was predominantly intra-abdominal and the respiratory tract. *E. coli* was the most commonly isolated pathogen. These data are in line with two earlier Dutch retrospective cohort studies in which the aetiology of sepsis was described.[54,55]

Nethmap surveillance data from blood cultures

NethMap reported 23,816 blood isolates from unselected hospital departments from hospitalized patients in 2017.[27] The majority (87%) of the blood isolates were derived from patients in the general ward, while 13% came from ICU patients. The most frequently isolated micro-organisms from blood were: coagulase-negative staphylococci (CNS) (34%), *E. coli* (23%), *S. aureus* (10%), *Klebsiella pneumonia (4%)* and *Enterococcus faecalis/faecium* (5%). Of importance, NethMap doesn't report other clinical characteristics, including the site of infection, the proportion that was community-acquired or nosocomial, the clinical significance and whether the patient suffered from sepsis. Also, it is unknown what the number of negative blood cultures was.

Reported pathogens in sepsis due to HAP and VAP

In the MARS project, pathogens involved in sepsis due to HAP/VAP were *S. aureus* (17%), Enterobacterales (15%), *P. aeruginosa* (10%) and *H. influenzae* (5%) [personal communication MJMB]. International data show somewhat different distributions of pathogens for sepsis due to HAP and VAP compared to the Netherlands. The IDSA guideline on HAP and VAP performed a meta-analysis of worldwide studies since 2000 on prevalence of pathogens of HAP and VAP.[37] For HAP, they reported a higher prevalence of non-glucose-fermenting gram-negative bacilli (19% of isolates, with *Pseudomonas* species accounting for 13% and *Acinetobacter* species accounting for 4%). For VAP the IDSA guideline reported worldwide prevalence data of VAP pathogens: *S. aureus* (20%–30%), *P. aeruginosa* (10%–20%), enteric gram-negative bacilli (20%–40%), and *Acinetobacter baumannii* (5%–10%). In contrast, NethMap reported 1% *Acinetobacter* species in sputum in ICU patients, suggesting that HAP/VAP due to *A. baumannii* is below 1%.[27]

Reported pathogens in sepsis due to intra-abdominal infection

A large European study summarized causative pathogens of community-acquired and hospital-associated complicated intra-abdominal infections (13% with sepsis).[56] Overall, cultured pathogens were *E. coli* (approximately 41%), enteric anaerobes (approximately 13%, mainly *Bacteroides* spp), other Enterobacterales (approximately 13%), *Enterococcus* species (16%) and streptococci (6.6%). *Enterococcus* spp were cultured in 12% of community-acquired infections and 24% of hospital-associated infections. *K. pneumoniae* and *P. aeruginosa* were more common in hospital-acquired than in community-acquired infections. The Surgical Infection Society (SIS) guideline reported that anaerobic micro-organisms are more prevalent for sources of infection in the distal gastrointestinal tract compared to the proximal gastrointestinal tract.[38] A retrospective study from the Netherlands reported only one bacteraemia with anaerobic bacteria among a total 80 patients with acute cholangitis of which 46% had a positive blood culture.[57]

Reported pathogens in sepsis due to suspected CVC infection

A search in the ISIS-AR database identified 506 CLABSI in 2017 (see appendix for search strategy).[58] Of these, CNS (56%) were the most common causative pathogen, followed by *S. aureus* (18%), gram-negative bacteria (fermenting and non-fermenting) (13.6%) and *Enterococcus* spp (6.4%).

Another surveillance database (PREZIES) reported CLABSI in the Netherlands from 2012 to 2016.[59] The report showed CNS (67%) as the most commonly isolated causative pathogens, followed by gram-negative bacteria (fermenters and non-fermenters. 8.9%), *S. aureus* (6.7%), *Enterococcus faecium* (5.4%) and *Candida albicans* (4.7%).

Internationally, a recent US study on CLABSI in oncology patients reported the following pathogens: gram-negative bacteria (23.9%), CNS (16.9%), *Enterococcus* spp (16.9%), *Candida* spp (16.1%) and S. *aureus* (12.4%).[60] A large surveillance study on nosocomial bloodstream infections reported pathogens of more than 70,000 CLABSI.[61] The most common pathogens were CNS (31.3%), gram negative bacteria (26.8), S. *aureus* (20.2%), and Candida species (9.0%).

Conclusions

Conclusion	Quality of evidence
A Dutch prospective study showed that in patients with sepsis and ICU admission gram-positive pathogens were isolated in 48% and gram-negative pathogens in 58% of patients	Moderate [31]
A Dutch randomized trial showed that in patients with community-onset sepsis gram-negative pathogens (mostly *E. coli*) were cultured in 30% and gram-positive pathogens in 21% of patients	Moderate[49]
Dutch surveillance data from 2017 showed that the most frequently isolated micro-organisms from blood cultures were coagulase-negative staphylococci (CNS), *E*. *coli* and *S. aureus*	Moderate[27]
A Dutch prospective study and pooled international data showed that the most frequently isolated micro-organisms in patients with sepsis due to HAP or VAP and ICU admission were *S. aureus*, Enterobacterales and *P. aeruginosa*	Moderate[37]
In contrast to pooled international data, Dutch surveillance data showed that *A. baumannii* is not frequently isolated in respiratory culture of hospitalized patients	Moderate[27]
A European study showed that the most frequently isolated micro-organisms in patient with sepsis due to intra-abdominal infections were *E. coli*, enteric anaerobes, other Enterobacterales, Enterococcus species and streptococci	Very low[56]
Two Dutch surveillance databases showed that most frequently isolated micro-organisms in patients with CLABSI were CNS, gram-negative bacteria (fermenters and non-fermenters), *S. aureus*, *Enterococcus* spp and *Candida albicans*	Moderate[58,59]

2. What are the resistance patterns of the most frequently isolated bacteria in patients with sepsis in the Netherlands?

Evidence summary

Percentages of antibacterial drug resistance of the most frequent pathogens in blood cultures of patients in unselected departments in the Netherlands in 2017 are shown in **Table 5**.[27] It should be noted that resistance rates in NethMap are based on the first isolate per species per patient per year. Emergence of resistance within bacteria in individual patients, especially those patients that stay

longer in the hospital and those with recurrent infections, might therefore be higher than reported here.

In 2017, *S. aureus* was cultured in 10% of positive blood cultures.[27] Of these, 1% was resistant to oxacillin, which was unchanged compared to prevalence reported in the previous SWAB sepsis guideline 2010 based on Nethmap data from 2007.[28] Clindamycin resistance in *S. aureus* blood isolates increased from 2% in 2007 to 9% in 2017 (including inducible resistance).

Amoxicillin-clavulanic acid resistance in *E. coli* (from 6 to 37%) and *K. pneumoniae* (from 5 to 17%) increased substantially between 2007 and 2017. This is probably partly due to a new antimicrobial susceptibility testing panel for Gram-negative bacteria that was introduced for the Vitek-2 automated system in 2016, which is the automated system used by most laboratories in the Netherlands.[62] In this new panel resistance to amoxicillin-clavulanic acid is tested according to EUCAST guidelines, while previous testing was based on the guidelines from Clinical and Laboratory Standards Institute (CLSI). The change in guideline use resulted in higher MIC values for amoxicillin-clavulanic acid.

Resistance to cephalosporins, ciprofloxacin and gentamicin in Enterobacterales also mostly increased between 2007 and 2017 Nethmap reports. The previous SWAB sepsis guideline reported that in 2008 4 and 2% of *E. coli* isolates from blood were resistant to 2nd and 3rd generation cephalosporins.[28] In 2017, 12 and 6% of *E.coli* blood isolates were resistant to 2nd and 3rd generation cephalosporins, respectively.[27] Ciprofloxacin resistance in *E. coli* isolates from blood increased from 9% to 14% between 2008 and 2017.[27,28] Gentamicin resistance was 3% in *E. coli* blood isolates in 2008 and 4% in 2017.[27,28] Nethmap reported that 8% of *E. coli* blood isolates was a HRMO in 2017, defined as resistant to 3rd generation cephalosporins and/or resistant to both ciprofloxacin and aminoglycosides. Of all first clinical *E. coli* isolates of patients hospitalized in general wards and ICU, between 5% and 6% harboured ESBL. An additional search in ISIS-AR data showed that 67% of ESBL-producing *E. coli* blood isolates were also resistant to ciprofloxacin. Gentamicin resistance co-occurred within 21% of ESBL-producing *E. coli* blood isolates.

The previous SWAB sepsis guideline reported that in 2008 6% of *K. pneumoniae* isolates from blood were resistant to 2nd and 3rd generation cephalosporins.[28] In 2017, 14 and 10% of *K. pneumoniae* blood isolates were resistant to 2nd and 3rd generation cephalosporins respectively.[27] Ciprofloxacin resistance in *K. pneumoniae* isolates from blood increased from 2% to 14% between 2008 and 2017.[27,28] Gentamicin resistance was 3% in *K. pneumoniae* blood isolates in 2008 and 5% in 2017.[27,28] Nethmap reported that 11% of *K. pneumoniae* blood isolates was a HRMO in 2017. Of all first clinical *K. pneumoniae* isolates of patients hospitalized in general wards and ICU, approximately 9% harboured ESBL. An additional search in ISIS-AR data showed that 70% of ESBL-producing *K. pneumoniae* blood isolates were resistant to ciprofloxacin. Gentamicin resistance co-occurred within 38% of ESBL-producing *K. pneumoniae* blood isolates.

Nethmap 2018 reported that prevalences of carbapenem resistance in *E. coli* and *K. pneumoniae* have been low and stable between 2012 and 2017. Among all *E. coli* and *K. pneumoniae* isolates with available meropenem or imipenem MIC in 2017, 0.03% and 0.42% of isolates respectively had meropenem and/or imipenem resistance.

A Dutch study confirmed that between 2008 and 2012, the rate of ESBL-producing *E. coli* and *K. pneumoniae* in blood culture increased over time.[63] Among blood isolates from ICU, the rate of ESBL-producing *K. pneumonia* was stable.

For *P. aeruginosa* no large increases in resistance have been observed. In 2008 3% of *P. aeruginosa* isolates from blood were resistant to ceftazidime, while piperacillin-tazobactam resistance was found in 2% of isolates and meropenem resistance in 3%. In 2017, these rates were 2, 5 and 1% respectively. Reported tobramycin and ciprofloxacin resistance was 2 and 8%. In 2017, these rates were 1 and 9% respectively.

One study within the MARS project (2011 – 2014) reported data on resistance within a subset of ICU patients with non-pneumonia derived sepsis.[64] Colonization or infection with resistant bacteria was based on clinical and surveillance samples obtained in the period ranging from 2 days before until 2 days after ICU admission for sepsis. Percentages of resistance of specific drug-resistant bacteria in 648 patients were 10% for 3rd generation cephalosporins, 8% for ciprofloxacin, 6% for gentamicin, 2% for piperacillin-tazobactam, and 0.5% for meropenem. Resistance patterns from the PHANTASi trial were not yet reported at the time of writing.

Table 5. Percentage of growth and resistance of most frequent pathogens in blood cultures of patients in unselected departments in the Netherlands in 2017

	In blood culture	Amoxicillin-clavulanic acid	Cefuroxime	Ceftriaxone	Gentamicin	Ciprofloxacin	Piperacillin-tazobactam	Amoxi-clav + gentamicin	Amoxi-clav + ciprofloxacin	Cefuroxime + gentamicin	Cefuroxime + ciprofloxacin	Ceftriaxone + gentamicin	Ceftriaxone + ciprofloxacin
E. coli	23%	37%	12%	6%	4%	14%	5%	3%	9%	2%	6%	1%	4%
K. pneumoniae	4%	17%	14%	10%	5%	14%	7%	4%	9%	4%	9%	4%	7%
P. mirabilis	1%	8%	1%	1%	5%	11%	1%	2%	2%	0%	0%	0%	0%
E. cloacae	1%				3%	5%							
Other Enterobacterales	5%												
K. oxytoca	1%	9%	NA	3%	0%	1%	7%	0%	1%	0%	1%	0%	1%
S. marcescens	1%				1%	5%							
M. morganii	0%				4%	9%							
E. aerogenes	0%				0%	2%							
C. freundii	0%				6%	7%							
C. koseri	0%	3%	NA	0%	0%	2%	0%	0%	0%	0%	0%	0%	0%
P. aeruginosa	2%				2%	9%	5%						
S. aureus	10%	1%		1%	0%	6%	1%						
Other Gram-positives	12%												

Conclusions

Conclusion	Quality of evidence
A Dutch prospective study showed the following resistance patterns to causative bacteria in patients with sepsis admitted to the ICU (excluding pneumonia): 3rd generation cephalosporins 10%, ciprofloxacin 8%, gentamicin 6%, piperacillin-tazobactam 2%, and meropenem 0.5%	Moderate[64]
Dutch surveillance data from 2017 showed that risk of MRSA bacteraemia has been stable over 10 years and low at 1% of all *S. aureus* bacteraemias in the Netherlands	Moderate[27]
Dutch surveillance data showed that rate of ESBL in blood cultures is increasing annually. In 2017, 6% of *E. coli* and 10% of *K. pneumoniae* blood isolates were resistant to 3rd generation cephalosporins	Moderate[27,63]
Dutch surveillance data from 2017 showed that prevalence of carbapenem resistance in all *E. coli* and *K. pneumoniae* isolates was stable over 5 years and low at 0.03% and 0.42%	Moderate[27]
Dutch surveillance data on antimicrobial resistance of specific pathogens for empirical sepsis therapies are reported in **Table 5**	Moderate[27]

3. Which patients are at risk for sepsis due to third-generation cephalosporin-resistant Enterobacterales (3GCR-E) or *P. aeruginosa* in the Netherlands?

Evidence summary

Predictors for sepsis due to third-generation cephalosporin-resistant Enterobacterales (3GCR-E)

There were no systematic reviews that specifically summarized predictors for sepsis due to Enterobacterales resistant to 3rd generation cephalosporins (3GCR-E) or HRMO.

One systematic review summarized colonization and risk of subsequent bacteraemia with ESBL-producing Enterobacterales in patients with solid and haematological malignancies.[65] The analysis included ten studies, of which three European (Germany and Spain), and the majority of patients had haematological malignancies. Patients colonized in surveillance cultures (mostly at admission) were 13 times more likely to develop a bacteraemia with an ESBL-producing Enterobacterales compared to patients not colonized.

The previous version of the SWAB sepsis guideline suggested to start empirical therapy covering HRMO in patients with known colonization with HRMO and those treated with 3rd generation cephalosporins or fluoroquinolones in the prior 30 days.[28] These recommendations were externally validated by Rottier et al. in a Dutch retrospective study within a tertiary hospital and a regional hospital.[66] The study included 9442 episodes in which blood cultures were drawn and iv antibacterial therapy was started. The authors defined positive predictive values (PPV) of the SWAB sepsis guideline recommendations to predict bacteraemia and any culture-positive infection with 3GCR-E. PPVs of prior (90 days and 1 year) colonization with 3GCR-E were 7.4% and 6.1% for predicting bacteraemia and 34.4% and 28.2% for predicting any culture-positive infection with 3GCR-E. PPVs of prior (30 days) treatment with cephalosporins or fluoroquinolones were 1.3% for predicting bacteraemia and 6.9% for predicting any culture-positive infection with 3GCR-E. PPVs of both risk factors combined were 1.8% for bacteraemia and 9.7% for any culture-positive infection.

Another study from the same research group reported on an internally validated prediction tool for *community-onset* and *hospital-onset* bacteraemia with 3GCR-E in patients suspected of serious gram-negative infections, among eight hospitals in the Netherlands from 2008 - 2010.[67] In this case-control study, cases included all consecutive patients with 3GCR-E bacteraemia, while controls had other infectious episodes and were matched on hospital, time and place of onset (community vs hospital). The final risk prediction model for c*ommunity-onset* 3GCR-E bacteraemia included prior (1 year) identification of 3GCR-E, suspected urinary source of bacteraemia, being immunocompromised, any prior (2 months) use of antibiotics and older age (all associated with higher risk of bacteraemia with 3GCR-E). The model also included the lower respiratory tract as suspected source of bacteraemia as a factor that decreased the risk of bacteraemia with 3GCR-E. A cut-off score proposed by the authors for daily practice had 54.3% sensitivity and 87.3% specificity. For *hospital-onset* bacteraemia with 3GCR-E, the final risk prediction model included renal disease, prior (1 year) identification of 3GCR-E, any solid malignancy, signs of hypoperfusion, prior (1 month) surgical procedure, a central venous catheter, prior (2 months) use of cephalosporins, longer length of stay (associated with a higher risk of bacteraemia with 3GCR-E) and lower respiratory tract as suspected source of bacteraemia (associated with a decreased risk of bacteraemia with 3GCR-E). The proposed cut-off score for daily practice had

81.5% sensitivity and 73.5% specificity. Both prediction tools are currently being validated in other hospitals worldwide with similar prevalences of 3GCR-E.[68]

One observational study outside the Netherlands externally validated a prediction tool for infection with ESBL-producing Enterobacterales on admission.[69] In this study from the US, a prediction tool was used that was developed in a previous Italian study from Tumbarello in 2011 to predict positive clinical cultures with ESBL-producing Enterobacterales <48h of admission.[70] This original prediction model was developed within a retrospective case-control study of patients from one hospital and externally validated in a retrospective case-control study of patients from two other hospitals. The model included prior (3 months) antibiotic therapy with beta-lactams and/or fluoroquinolones, prior (12 months) hospitalization, transfer from another healthcare facility, Charlson Comorbidity Score of ≥4, recent (30 day) history of urinary catheterization, age ≥70 years. The US study that validated the Italian model was a retrospective case-control study in a single hospital. Cases had a positive culture with ESBL-producing Enterobacterales in clinical samples <48h of hospitalization and clinical signs of infection. The number of sepsis patients and general prevalence of ESBL-producing Enterobacterales was not reported. Most clinical cultures were urine (76%) or blood (15%). The Italian model performed well in the US cohort, but Charlson Comorbidity Score ≥4 and age ≥70 were not significantly associated with cases. The proposed cut-off score within the Italian study had a sensitivity of 95% and specificity of 47% in the US study.

Predictors for sepsis due to *P. aeruginosa*

There were no systematic reviews that specifically summarized predictors for sepsis due to *P. aeruginosa*. One systematic review summarized predictors of community-onset *P. aeruginosa* bacteraemia.[71] Two included retrospective observational studies defined predictors in multivariate analysis and in comparison to *E. coli* or other gram-negative bacteria bacteraemia. Predictors were healthcare-associated infection, the presence of a urinary device or a central venous catheter, age>90, neutropenia, presentation of septic shock and recent antibiotic use.

Conclusions

Conclusion	**Quality of evidence**
Pooled data in haematology/oncology patients showed that colonization (mostly on admission) with ESBL-producing Enterobacterales was associated with an increased risk of bacteraemia with ESBL-producing Enterobacterales	Very low[65]
In an observational study of hospitalized patients in the Netherlands with suspected serious infection, prior (1 year) colonization with Enterobacterales resistant to 3rd generation cephalosporins (3GCR-E) had a PPV of 6.1% for bacteraemia and 28.2% for any culture-positive infection with 3GCR-E	Very low[66]
In an observational study of hospitalized patients in the Netherlands with suspected serious infection with gram-negative bacteria, combining prior (90 days) colonization with 3GCR-E and/or prior (30 days) treatment with cephalosporins or fluoroquinolones had a PPV of 1.8% for bacteraemia and 9.7% for any culture-positive infection with 3GCR-E	Very low[66]

In an observational study of hospitalized patients in the Netherlands with suspected serious infection with gram-negative bacteria, an internally validated risk prediction model* had 54.3% sensitivity and 87.3% specificity for predicting *community-onset* bacteraemia with 3GCR-E * including prior (1 year) identification of 3GCR-E, suspected urinary source of bacteraemia, being immunocompromised, any prior (2 months) use of antibiotics, older age and the lower respiratory tract as suspected source of bacteraemia	Very low[67]
In an observational study of hospitalized patients in the Netherlands with suspected serious infection with gram-negative bacteria, an internally validated risk prediction model* had 81.5% sensitivity and 73.5% specificity for predicting *hospital-onset* bacteraemia with 3GCR-E * including renal disease, prior (1 year) identification of 3GCR-E, any solid malignancy, signs of hypoperfusion, prior (1 month) surgical procedure, a central venous catheter, prior (2 months) use of cephalosporins, longer length of stay and the lower respiratory tract as suspected source of bacteraemia	Very low[67]
In an observational study of hospitalized patients in the US with community-onset infections, an externally validated risk prediction model* had 95% sensitivity and 47% specificity for predicting involvement of ESBL-producing bacteria * including prior (3 months) antibiotic therapy with beta-lactams and/or fluoroquinolones, prior (12 months) hospitalization, transfer from another healthcare facility, Charlson Comorbidity Score of ≥4, recent (30 day) history of urinary catheterization and age ≥70 years	Very low[69]
In two observational studies of patients with community-onset gram-negative bacteraemia, predictors for *P. aeruginosa* were healthcare-associated infection, the presence of a urinary device or a central venous catheter, age>90, neutropenia, presentation of septic shock and recent antibiotic use	Very low[71]

Other considerations

The optimal choice of empirical therapy for sepsis includes a risk assessment on the involvement of 3GCR-E or *P. aeruginosa* as the causative pathogen in order to start the appropriate empirical therapy (chapter 6) and to limit use of broad-spectrum antibacterial therapy as much as possible.

High quality studies with externally validated prediction tools in patients with sepsis and septic shock are currently not available. Incidence of sepsis due to 3GCR-E may differ significantly in other countries compared to the Netherlands and hamper the generalizability of many international studies for this guideline. The retrospective validation of the previous SWAB sepsis guideline recommendations showed low PPVs when using both prior colonization and cephalosporin/fluoroquinolone use in predicting serious infection with 3GCR-E. However, prior 1 year and 3 months colonization appropriately predicted culture-positive infection with these bacteria in 28% and 34% of patients. It should be noted that the underlying study population were patients in whom a blood culture was drawn and iv antibiotics were started. This was reflected in the relatively low number of positive blood cultures (18% any bacteria, 8% Enterobacterales). The question remains how the predictors would perform in patients fulfilling sepsis or septic shock criteria and therefore a higher likelihood of bacteraemia.[72] The same applies to the other study of Rottier et al. on the new proposed prediction tool.[67] In addition, a considerable amount of Dutch patients with bacteraemia due to 3GCR-E were excluded from both studies. The excluded patients developed bacteraemia after or during treatment for another infection and may therefore have had a higher risk of bacteraemia with 3GCR-E.

Other reported risk prediction models for ESBL-producing Enterobacterales bacteraemia have not yet been externally validated.[73-76] Without external validation it is difficult to estimate the performance of these models in the Dutch situation. Also, several large epidemiological studies assessed single predictors of antimicrobial resistance in serious infections. MacFadden et al. recently showed that in patients with gram-negative bacteraemia, a prior (1 year) clinical culture with a gram-negative bacteria resistant to the drug of interest had high specificity and positive predictive value for resistance and should be a reason to choose another antibiotic.[77] A meta-analysis and retrospective cohort study also found high positive predictive values of previous ESBL-producing Enterobacterales (ESBL-E) colonization on the occurrence of subsequent infection due to ESBL-E and VAP due to ESBL-E respectively.[78,79]

Based on currently available evidence, it is challenging to provide general recommendations on the risk factors that should be used for the decision to start empirical therapy in sepsis directed to HRMO. Findings are also conflicting and this is most likely due to the multifactorial nature of the risk of HRMO. For example, use of 3rd generation cephalosporins or fluoroquinolones in the previous 30 days as suggested by the previous SWAB sepsis guideline hardly improved appropriate therapy rates and was associated with unnecessary use of carbapenem.[66] In contrast, any use of antibiotics in the prior two months (community-onset) and use of cephalosporins in the prior two months (hospital-onset) were items in the Dutch prediction models on 3GCR-E bacteraemia.[67] Also, in other studies previous antibiotics were to some extent related to HRMO infection or colonization.[80-82] However, patients in the intensive care unit (ICU) who receive selective decontamination of the digestive tract (SDD, including a four days 3rd generation cephalosporin treatment and frequent surveillance cultures) and as a result have negative surveillance cultures, have a lower risk of bacteraemia due to HRMO.[83] This further underscores the complexity of developing validated and clinically useful prediction scores to help select which septic patient should get empirical therapy aimed against 3GCR-E in the Netherlands.

The international SSC guideline does not provide specific recommendations on the decision to start empirical treatment against HRMO in patients with sepsis. The SWAB guideline committee decided that some guidance in choices would be preferable. We concluded that prior (1 year) infection or colonization is the strongest and most common risk factor predicting subsequent infection with 3GCR-E.[65,67,78,79]

Until high quality and externally validated prediction rules are available, the committee agreed that clinicians should take several other factors into account on an individual patient basis to decide if empirical antibacterial therapy against 3GCR-E patients with sepsis is appropriate. These include local prevalence of 3GCR-E,[84] whether the sepsis is hospital-acquired,[67,69,85] and to a lesser extent healthcare-associated, versus community-acquired, whether the patient had prior (2 months) treatment with antibiotics and whether or not the patient receives SDD.[67,69,83] Finally, the committee regarded the high rate of HRMO colonization in travellers and refugees from highly endemic countries such as the Indian subcontinent as another risk factor to consider in the choice of empirical treatment in patients with sepsis. As many travellers will not be colonized anymore after several months, we suggested to include three months prior travel in the individual risk assessment, especially when the patient travelled in a highly endemic country. Prevalence of HRMO per country is available online at https://resistancemap.cddep.org/. The committee felt that risk of 3GCR-E involvement is especially high in patients with sepsis who were recently hospitalized abroad for >24 hours. There is no strong

evidence to support this statement, but it is in accordance to national infection prevention guidelines on which patients to screen for HRMO.[86] We therefore included this as a separate suggestion. Finally, it is essential to realise the limitations of using risk factors for the decision to treat for 3GCR-E, to weigh potential risk factors against the associated risk of overtreatment and to ensure antibiotic de-escalation if possible (chapter 10).

With regards to the risk of sepsis due to *P. aeruginosa*, we found no Dutch or externally validated studies on prediction rules for sepsis or severe infections due to *P. aeruginosa*. Based on 2017 Nethmap data, the a priori risk of a bloodstream infection with *P. aeruginosa* in the Netherlands seems relatively low: in 2% of positive blood cultures in hospitalized patients *P. aeruginosa* was identified (chapter 2). Identified risk factors for *P. aeruginosa* are healthcare-associated infection, presence of a urinary device or a central venous catheter, extreme old age, neutropenia, presentation with septic shock and recent antibiotic use. However, the quality of this evidence is very low and no prediction tools have been designed (nor validated) in this setting. A large French prospective ICU study showed that almost all *P. aeruginosa* isolates of clinical infection were similar to isolates found in prior screening cultures.[87] Most clinical infections were VAP, followed by surgical site infections and bacteraemia, but numbers were low. Described risk factors therefore overlap risk factors for sepsis due to 3GCR-E to a large extent. Also, for the Dutch clinical setting, empirical therapy for 3GCR-E is generally effective for *P. aeruginosa* infections. Until high quality studies are available, the committee suggests to empirically cover *P. aeruginosa* in patients with sepsis when prior (1-year) cultures showed *P. aeruginosa* (chapter 4). In addition, we suggest to cover *P. aeruginosa* in patients with sepsis due to HAP/VAP or suspected infected CVC infection (chapter 6a). The guideline committee does not make a recommendation for or against the empirical coverage of *P. aeruginosa* in patients with sepsis of unknown origin or with a source other than HAP/VAP or suspected infected CVC infection when no prior cultures are available but the above-mentioned risk factors are present. This will depend on individual patient characteristics and local epidemiology. For recommendations on antibacterial therapy in sepsis due to 3GCR-E or *P. aeruginosa*, we refer to chapter 6.

Recommendations

Recommendation	**Strength**	**Quality of evidence**
1. We recommend empirical therapy against 3GCR-E in patients with sepsis and prior (1 year) proven infection or colonization with 3GCR-E	Strong	Very low
2. We suggest that clinicians take into account the risk of 3GCR-E involvement in sepsis on an individual patient basis to decide if empirical antibacterial therapy against 3GCR-E is appropriate Factors to guide this decision include local prevalence of 3GCR-E, if the infection is hospital-acquired/health-care associated versus community-acquired, prior (2 months) broad-spectrum antibiotic use, concurrent use of SDD, prior (3 months) travel to a highly endemic country (see https://resistancemap.cddep.org/) and prior (2 months) hospitalization abroad	Weak	Very low

3. We recommend empirical therapy against *P. aeruginosa* in patients with sepsis and prior (1 year) infection or colonization with *P. aeruginosa*	Strong	Very low

II Empirical antibacterial therapy of sepsis

Introduction

The choice of empirical antibacterial treatment in sepsis depends on several factors. General factors to consider are the site of infection, the bacteria that are potentially involved and the pharmacokinetics of antibacterial agents. Other important factors are: previous culture results, whether the infection is community acquired or healthcare associated, the degree to which a patient is immunocompromised, other comorbidities and the presence of foreign material in the body. In addition, it is essential to consider the local epidemiology and resistance patterns of pathogens commonly involved in sepsis (chapter I). In chapter 4 to 7 we summarized the evidence on empirical antibacterial therapy in patients with sepsis in general with a focus on the Netherlands. We included the following topics: importance of appropriate empirical therapy (chapter 4), empirical monotherapy versus double active therapy (chapter 5), and empirical therapy for sepsis due to the most common causes of infection when there is no suspicion of involvement of Enterobacterales resistant to 3rd generation cephalosporins (3GCR-E, chapter 6a). In that chapter we also summarized evidence and provided recommendations on empirical antibacterial therapy of sepsis and potential involvement of specific micro-organisms: patients at risk of sepsis due to 3GCR-E (chapter 6b) and patients with sepsis and risk of involvement of *S. aureus* (chapter 6c). In chapter 7, we summarized evidence on empirical therapy in patients with sepsis and a reported penicillin allergy.

4. What is the importance of appropriate empirical therapy in patients with sepsis?

Evidence summary

Appropriate empirical therapy in sepsis in general

Paul et al. performed a meta-analysis on the effect of appropriate empirical antibiotic therapy on 30-day, all-cause mortality in adults with sepsis and microbiologically documented infection including 70 prospective studies.[26] Appropriate antibacterial therapy was defined as treatment matching in vitro susceptibility of the cultured pathogen. Inappropriate therapy was associated with increased mortality in most analyses. Among studies adjusting for comorbidity and sepsis severity, inappropriate therapy was associated with higher mortality (OR 1.60; 95% CI 1.37 to 1.86; 26 studies). Included studies had low risk of bias, but there was considerable heterogeneity and some suggestion of publication bias.

Marquet et al. performed a meta-analysis of appropriate empirical antibacterial therapy in patients with severe infections (defined as pneumonia, bacteraemia, sepsis, severe sepsis, or septic shock) on mortality, length of stay and costs.[88] A total of 27 high quality observational studies were included. The meta-analysis showed that appropriate in-hospital empirical antibacterial therapy was associated with reduced 30-day mortality (RR 0.71, 95% CI 0.62 - 0.82). Similar effect was found in the studies reporting in-hospital mortality (RR 0.67, 95% CI 0.56 - 0.80), but with high heterogeneity. Sensitivity analysis showed that data were robust. Inappropriate antibacterial therapy was also associated with increased costs and length of stay in some studies.

In line, another systematic review summarized the effect of inappropriate empirical therapy on mortality in 39 studies on nosocomial infections with gram-negative bacteria.[89] Sites of infection were

respiratory, intra-abdominal, bloodstream, and urinary tract, and the majority studied patients with bacteraemia. Appropriate therapy was related to susceptibility and timeliness (administration of therapy <24 to 72 hours) in 68% of studies and to susceptibility only in 20% of studies. Overall mortality was lower when receiving appropriate antibacterial therapy (OR 0.38, 95% CI 0.30-0.47), but with significant heterogeneity (65%). Similar effect estimates were found for 14-day, 30-day mortality, as well as for many subgroup analyses on overall mortality, including infections caused by *Acinetobacter* spp. and *Pseudomonas* spp. and serious gram-negative infections.

Appropriate empirical therapy in sepsis due to HRMO

The impact of appropriate empirical therapy on severe infections due to HRMO has been assessed in observational studies only. A meta-analysis on empirical therapy for bacteraemia with ESBL-producing Enterobacterales showed a decreased risk of death with appropriate therapy (RR 0.44, 95%CI 0.44 – 0.88).[90] The number of patients with sepsis was not reported and the analyses were not adjusted for confounders. The previously described systematic review of 191 observational studies in >70,000, mainly bacteraemic patients found that inappropriate empirical therapy was associated with higher mortality.[84] A meta-analysis assessing mortality in bacteraemia due to ESBL-producing Enterobacterales compared to non-ESBL-producing Enterobacterales also assessed the effect of inadequate empirical therapy on mortality.[91] Overall, mortality in ESBL-producing Enterobacterales bacteraemia was increased. The odds ratio decreased when adjusted for inadequate empirical therapy.

Appropriate empirical therapy in sepsis due to anaerobic bacteria

We found no systematic reviews or RCTs assessing the effect of appropriate empirical therapy in sepsis due to anaerobic bacteria in general. Also, there are no randomized studies available on the effect of anti-anaerobic treatment in patients with sepsis due to suspected aspiration pneumonia. The 2017 Surgical Infection Society (SIS) guideline on intra-abdominal infections performed a systematic literature search on appropriate empirical therapy in intra-abdominal infections.[38] Five studies showed that appropriate empirical therapy covering anaerobic bacteria reduced treatment failure and death in mostly complicated intra-abdominal infections. The Dutch evidence-based guideline on necrotizing soft tissue infections did not systematically search for evidence on anaerobic coverage in empirical treatment.[3]

Appropriate empirical therapy in sepsis due to enterococci

In the previous SWAB sepsis guideline in 2010, evidence on the effect of empirical coverage of enterococci in patients with intra-abdominal sepsis was summarized.[28] Eleven RCTs in patients with complicated intra-abdominal infections showed that empirical regimens with antibiotic coverage of enterococci was not associated with a better clinical outcome than regimens without coverage of enterococci, although APACHE scores were generally low. Since then two more RCTs showed a similar outcome, i.e. no difference in outcomes between a regimen with antibiotic coverage of enterococci (tigecycline) compared to a regimen without coverage of enterococci (ceftriaxone and metronidazole).[92,93] Most patients had APACHE scores < 10. The SWAB guideline on urinary tract infections (UTI) did not systematically summarize the need to cover enterococci.[5] We found no RCTs or systematic reviews comparing anti-enterococcal therapy in patients with sepsis and a suspected CVC infection.

Conclusions

Conclusion	Quality of evidence
Pooled data showed a large beneficial effect of appropriate empirical antibacterial therapy on 30-day mortality, in-hospital mortality and cost in patients with severe infections	Moderate to very low[26,88]
Pooled data showed that appropriate empirical antibacterial therapy reduces all-cause mortality in patients with gram-negative infections, including the subgroups with infection due to *Acinetobacter* spp. or *Pseudomonas* spp.	Very low[89]
Pooled observational data showed a beneficial effect of appropriate empirical antibacterial therapy reduces 30-day mortality in patients with bacteraemia with ESBL-producing Enterobacterales	Very low[90]
Pooled data showed that empirical anti-anaerobic therapy reduces treatment failure and mortality in patients with intra-abdominal infections	Very low[38]
We found no RCTs or systematic reviews on the effect of anti-anaerobic therapy in other causes of sepsis when anaerobic bacteria might be involved	-
Multiple RCTs showed that empirical anti-enterococcal therapy did not change treatment outcomes compared to no anti-enterococcal empirical therapy in patients with complicated intra-abdominal infections	Moderate[28,92,93]
We found no RCTs or systematic reviews on the effect of anti-enterococcal therapy in other causes of sepsis when *Enterococcus* spp. might be involved	-

Other considerations

The importance of appropriate empirical antibacterial therapy in patients with sepsis has been supported by systematic reviews of observational studies only. The effect has been found rather consistent and includes reduced mortality, costs and length of hospital stay. However, published studies show large heterogeneity and there is a high risk of bias due to confounding. Heterogeneity could relate to many factors, including type of infection, source control interventions, diagnostic criteria, involved bacteria, efficacy of antibacterial treatment and immune status. Methodological causes of heterogeneity could be different study designs, risks of bias, choice of statistical model and adjustment for confounding factors.

Overall, the committee believes that the large and consistent benefits of appropriate empirical therapy in serious infections are convincing. In those patients appropriate empirical therapy generally outweighs potential harms of broader-spectrum empirical therapy, especially when resources and logistics are optimized to stop or de-escalate in an early stage when feasible. Initial empirical therapy in sepsis therefore needs to be broad enough to cover potentially involved pathogenic bacteria. This recommendation is in line with the SSC guideline which states that all likely pathogens should be covered.[36]

As discussed, predicting which empirical therapy in sepsis is appropriate is complex and depends on numerous factors, including local and national antimicrobial resistance data.[40] The question that frequently arises is which threshold of antibiotic resistance should guide the decision to broaden the empirical antibiotic treatment. There are no studies that have validated acceptable resistance

prevalence cut-offs for antibacterial therapy for the empirical treatment of sepsis. Several studies have aimed to predict the likelihood of bacteraemia in general or involvement of resistant pathogens in patients with suspected infections, but cut-offs for acceptable likelihoods are generally not provided (see also chapter 2).[67,73,74,80,94] [67,73,74,80,94] In addition, no formal resistance cut-offs for appropriate empirical therapy specifically for sepsis have been defined. The annual NethMap report on surveillance data of antibiotic resistance in the Netherlands generally use <10% resistance prevalence as a cut-off for appropriateness of an antibiotic agent as empirical therapy. However, as discussed in the first chapters, NethMap data cannot be directly extrapolated to patients with sepsis. In addition, it does not take into account that in the empirical treatment setting when the causative pathogen is yet unknown, the a priori chance of resistance is lower than the resistance prevalence of single pathogens reported in national surveillance programs.[66] However, as discussed in chapter 3, prior (1 year) infection or colonization with a resistant gram-negative pathogen seems predictive and specific for subsequent infections with gram-negative pathogens that have similar resistance.[65,67,77-79] This has also been found for other pathogens such as MRSA.[95,96] The committee therefore settled to recommend to take into account prior (1 year) relevant clinical and screenings cultures in the choice of empirical sepsis therapy in general. We cannot recommend on a cut-off for resistance prevalence in the choice of empirical antibacterial therapy. Importantly, local resistance rates of potentially involved pathogens and their resistance is one of the key factors that should be taken into account in the choice of empirical therapy of sepsis in general.

Studies in patients with sepsis due to HRMO are very scarce. As a result, the published meta-analyses on the importance of appropriate empirical therapy in sepsis due to HRMO are often based on very low quality data according to GRADE and are mainly based on patients with bacteraemia. In contrast to the findings of the summarized meta-analyses, a Dutch retrospective study found no effect of inappropriate therapy within 24 hour of onset in ESBL bacteraemia on 30-day mortality in 232 patients.[97] Overall, in 42% of included patients the urinary tract was the source of the ESBL bacteraemia. Separate data for 75 patients with severe sepsis or septic shock showed a trend towards increased mortality rate of inappropriate therapy within 24 hour in univariate analysis, but not in multivariate analysis. Other reports have also suggested that inappropriate therapy is not associated with increased mortality in patients with ESBL-bacteraemia with an urinary source.[98,99] With only very limited data at hand, the committee suggests that until larger and prospective studies show otherwise, initial appropriate empirical therapy is of similar importance in patients with sepsis due to HRMO as in patients with sepsis in general.

With regards to appropriate empirical therapy of anaerobic bacterial pathogens in patients with sepsis there is lack of studies, probably in part due to difficulties in culturing anaerobic bacteria. For intra-abdominal infections, a limited number of studies showed improved outcomes when anaerobic coverage is included in the empirical treatment.[38] In line with the SIS guideline and The Dutch evidence-based guideline on necrotizing soft tissue infections we therefore suggest anaerobic coverage in patients with sepsis and likely involvement of anaerobic pathogens.[3,38] Sources of anaerobic infection include intra-abdominal infections, especially when related to the distal gastro-intestinal tract and necrotizing soft tissue infections. For cholangitis, the guideline committee follows the SIS guideline on intra-abdominal infections suggesting that anti-anaerobic therapy is generally not necessary.[38,57] An exception are patients in whom a biliary-enteric anastomosis is present, in whom empirical therapy with coverage of anaerobic bacteria can be considered. The need of anaerobic coverage in aspiration

pneumonia remains controversial. The recent IDSA guideline on CAP summarized the evidence for empirical treatment of anaerobic bacteria in patients with aspiration pneumonia.[100] Very low quality evidence in hospitalized patients showed that anaerobic bacteria are not a frequent cause of aspiration pneumonia. In addition, no studies were available on the added value of anaerobic treatment in aspiration pneumonia. The IDSA guideline on CAP committee therefore suggests not to cover anaerobic bacteria in aspiration pneumonia unless a long abscess or empyema is suspected. The SWAB sepsis guideline committee agreed to follow this suggestion for HAP and VAP, as most data comes from hospitalized patients.

Regarding the coverage of enterococci in the empirical therapy of sepsis, most trial data are from patients with complicated intra-abdominal infections. Overall, empirical treatment strategies that compared the inclusion or exclusion of anti-enterococcal treatment in these patients showed no difference in clinical outcomes.[38] It should be noted however that most of these studies included patients with community-acquired intra-abdominal infections who underwent source control, were not severely immunocompromised and did not have severe sepsis. There is no clear evidence to support or refute empirical anti-enterococcal treatment in hospital-acquired intra-abdominal infections, patients that have no adequate source control, the severely immunocompromised and patients with severe sepsis.[38] For enterococcal bacteraemia, retrospective data showed that appropriate antibacterial therapy (defined as treatment with in vitro activity for at least 6 days) independently reduced mortality (OR 0.33, 95% CI: 0.14 to 0.79).[101] Another single-centre study found any appropriate antibiotic as well as more days of iv amoxicillin as factors reducing mortality in enterococcal bacteraemia.[102] However, a Danish population-wide study and a Japanese cohort study did not find an association between initial appropriate empirical therapy for enterococci and 30-day mortality.[103,104] In the majority of cases in the Danish population-wide study, the infection was hospital-acquired. The SIS guideline recommends to consider anti-enterococcal empirical therapy in high-risk patients with community-acquired intra-abdominal infections and those with hospital-acquired intra-abdominal infections, taking into account recent abdominal surgery, substantial recent exposure to broad spectrum antibiotics and signs of sepsis and septic shock.[38] The SWAB guideline on UTI states that it is debatable if enterococci should be covered in the empirical therapy of UTI and provides separate recommendations with and without covering *E. faecalis*. Based on the limited data available, the committee suggests not to cover enterococci in empirical therapy in patients with sepsis in general and most patients with community-acquired intra-abdominal infections. We suggest that anti-enterococcal therapy could be considered in individual patients with sepsis, e.g. those who have a high likelihood of enterococcal involvement based on recent relevant cultures and those with recent complicated intra-abdominal surgery or a suspected CVC infection and substantial exposure to broad spectrum antibiotics.

Recommendations

Recommendation	**Strength**	**Quality of evidence**
4. We recommend empirical broad-spectrum antibacterial therapy for patients presenting with sepsis to cover all pathogenic bacteria that are likely to be involved	Strong	Moderate

5. We recommend to take into account prior (1 year) resistance in relevant clinical and screenings cultures in the choice of empirical sepsis therapy	Strong	Very low
6. We recommend that empirical antibacterial therapy is guided by the local distribution of pathogens associated with sepsis and their antimicrobial susceptibilities	Strong	Very low
7. We suggest empirical antibacterial therapy for patients presenting with sepsis to cover HRMO when these are likely to be involved	Weak	Very low
8. We suggest empirical antibacterial therapy covering anaerobic bacteria for patients presenting with sepsis and intra-abdominal infections of the lower intestinal tract or necrotizing soft tissue infections	Weak	Very low
9. We generally suggest against routine empirical treatment of anaerobic bacteria in patients presenting with sepsis due to aspiration pneumonia, unless empyema or a lung abscess is suspected	Weak	Very low
10. We generally recommend against routine empirical treatment of enterococci in patients presenting with sepsis	Strong	Moderate
11. We suggest that anti-enterococcal therapy could be considered in individual patients with sepsis, e.g. those who have a high likelihood of enterococcal involvement based on recent relevant cultures and those with recent complicated intra-abdominal surgery or a suspected CVC infection and substantial exposure to broad spectrum antibiotics	Weak	Very low

5. What is the effect of double active empirical antibacterial therapy compared to monotherapy in patients with sepsis?

Double active empirical antibacterial therapy, also frequently referred to as combination antibiotic therapy, is defined as antibacterial treatment with multiple classes of antibiotics, each targeting the known or suspected causing pathogen(s) (e.g., ceftriaxone and an aminoglycoside to target gram-negative pathogens) and with the specific purpose to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Since the previous SWAB sepsis guideline 2010, two meta-analysis examined the effect of double active empirical antibiotic therapy compared to empirical monotherapy in patients with sepsis,[105] severe sepsis or septic shock.[106] The Cochrane systematic review of Paul et al. included 69 trials that compared treatment with a combination of a beta-lactam antibiotic and aminoglycoside to beta-lactam antibiotic monotherapy in patients with sepsis.[105] Overall mortality in all studies reporting on mortality was 10% (range 0 – 26%). In 23 trials the same beta-lactam was used in the monotherapy and double active therapy group, and the meta-analysis showed no difference in all-cause 30-day mortality (RR 0.97, 95% CI 0.73 to 1.30; 13 studies) and clinical failure in the first 30 days (RR 1.11, 95% CI 0.95 to 1.29; 20 studies). In 43 trials a broader spectrum beta-lactam was used in the monotherapy group, and there was non-significantly reduced all-cause 30-day mortality with monotherapy (RR 0.85, 95% CI 0.71 to 1.01) and a lower risk of clinical failure in the first 30 days (RR 0.75, 95% CI 0.67 to 0.84). Subgroup analysis of patients with sepsis due to gram-negative bacteria

showed similar results, although the subgroup of patients with *P. aeruginosa* infection was too small to draw a conclusion. There was no difference in the rate of emergence of resistance. There was a substantial lower risk of nephrotoxicity in the monotherapy group in general (RR 0.30, 95% CI 0.23 to 0.39), but only five trials reported a once daily dosing schedule. In these trials, the RR for nephrotoxicity was 0.17 (95% CI 0.06 – 0.53) in the monotherapy group compared to the double active therapy group that received once daily dosing aminoglycosides.

The second meta-analysis on 13 RCTs restricted the analysis of double active therapy versus monotherapy to adult ICU patients with severe sepsis or septic shock.[106] SOFA scores were not available, but >80% of included patients had APACHE II scores >20. Overall mortality was 22% (6 – 33%). RCTs compared beta-lactam monotherapy to a double active therapy of a beta-lactam with an aminoglycoside (7 RCTs) or quinolone (3 RCTs) or one of both (1 RCT). Four RCTs used the same beta-lactam in both groups. There was no difference in mortality at longest follow-up (RR 1.11, 95% CI 0.95 to 1.29; 11 studies, 2266 patients) or other relevant clinical outcomes such as nephrotoxicity. It was not possible to perform the (pre-specified) subgroup analysis based on SOFA score or for patients with shock versus patients without shock. In addition, no subgroup analysis was performed for studies with the same beta-lactam in both groups or for patients with *P. aeruginosa* infections. The investigators performed a trial sequential analysis showing that it is unlikely (<5%) that there would be a true relative mortality difference between mono- and double active therapy of 20% or more.

One of the included RCTs in the meta-analysis mentioned here directly above had the best external validity for this guideline as it included patients with severe sepsis and used the same treatment in both arms.[107] It compared meropenem monotherapy to meropenem and moxifloxacin double active therapy in patients who met criteria of severe sepsis or septic shock in Germany between 2007 and 2010. Patients with recent carbapenem or quinolone treatment and those known to be colonized with MRSA or VRE were excluded. Of the 600 patients randomized, 551 were included in the intention-to-treat analysis. Mean SOFA and APACHE II score were 9.5 and 21.6. Overall 28-day mortality was 22.9% at day 28. Sites of infection were pulmonary (41%), intra-abdominal (38%), urogenital (12%) and SSTI (10%), and 50% had nosocomial sepsis. In 35% of the patients sepsis was microbiologically confirmed and included gram-positive bacteria in 53%, gram-negative bacteria in 49% and fungi (mainly *Candida* spp.) in 29%. *Pseudomonas* spp. was cultured in 38 patients (7% of those with microbiologically confirmed sepsis) in any material. The study showed no difference in mean SOFA score of double active therapy compared to monotherapy in the first 14 days after inclusion (primary endpoint). In line, there was no difference in 28-day mortality or 90-day mortality between both groups. Emergence of bacteria resistant to meropenem at day 21 occurred significantly more often in the monotherapy group (n=9, 5.4%) compared to the double active therapy group (n=1, 1.3%). There was no difference in overall number of adverse events or serious adverse events. Outcomes within the subgroup of patients with *P. aeruginosa* infection were not reported.

The previous SWAB sepsis guideline described the meta-analysis of Safdar et al., which found a lower mortality rate in patients treated with double active therapy in *P. aeruginosa* bacteraemia.[108] The study had considerable limitations, such as the inclusion of treatment arms with aminoglycoside monotherapy. A more recent meta-analysis focussed on beta-lactam monotherapy versus beta-lactam plus aminoglycoside or fluoroquinolone in *P. aeruginosa* infections.[109] It included 19 studies (11 retrospective cohort studies, 8 RCTs) showing no additional effect of double active therapy on

mortality, including after stratification for empirical or definite double active therapy. A subgroup analysis for patients with severe infections or bacteraemia showed no benefit of *definite* double active therapy on mortality in patients with severe infections (RR 0.96, 95% CI 0.75–1.24, heterogeneity not reported) or bacteraemia (RR 0.95, 95% CI 0.67–1.34). The subgroup analysis could not be performed for the effect of *empirical* double active therapy on mortality. There was a significant benefit of empirical double active therapy on clinical cure in all patients (RR 1.23, 95% CI 1.05–1.43), but this benefit disappeared when looking at RCTs separately. The authors reported many reasons for risk of bias and concluded that no solid conclusions could be drawn regarding the comparative effectiveness of double active versus monotherapy in *P. aeruginosa* infections. Similar findings were reported in another meta-analysis reporting on mortality using appropriate empirical double active therapy versus appropriate empirical monotherapy in *P. aeruginosa* bacteraemia.[110]

The Dutch guideline on *S. aureus* bacteraemia summarized evidence on double active therapy for this indication.[7] Very low quality evidence showed no additional effect of adding aminoglycosides to anti-staphylococcal penicillins versus anti-staphylococcal penicillin monotherapy on recurrence of bacteraemia and mortality. Adding aminoglycosides to anti-staphylococcal penicillins increased the risk of adverse events. A recent RCT on adjunctive rifampicin to anti-staphylococcal treatment (mostly flucloxacillin or vancomycin) in patients with *S. aureus* bacteraemia and median SOFA score of 2 did not show a benefit on the composite outcome of 12-week treatment failure, disease recurrence or death (HR 0.96, 95% CI 0.68 – 1.35).[111] There was a small, statistically significant reduction in disease recurrences in patients treated with rifampicin in a post-hoc analysis (1 versus 4%), but the clinical significance was unsure. Patients treated with rifampin more often suffered from adverse events and drug interactions (HR 1.78, 95% CI 1.20–2.65), but from a similar number of grade 3-4 adverse events (HR 1.12, 95% CI 0.88–1.43).

Regarding pneumonia-derived sepsis, a Cochrane systematic review on the treatment of VAP could not demonstrate a beneficial effect of combination antibacterial therapy compared to monotherapy.[112] Overall mortality in the four included RCTs was 20%. Antibiotic therapies evaluated in these patients with VAP included ceftazidime/amikacin versus meropenem, ceftazidime plus linezolid versus ceftobiprole, cefepime plus amikacin or levofloxacin versus cefepime and meropenem plus ciprofloxacin versus meropenem. There was no additional effect of double active antibiotic therapy compared to monotherapy for the treatment of VAP on mortality (4 RCTs, 2 of which used the same beta-lactam in both groups). Another meta-analysis within the IDSA guideline on HAP and VAP (see next chapter for more details) also could not demonstrate a beneficial effect of double active antibiotic therapy compared to monotherapy for the treatment of VAP with regards to mortality, clinical response, adverse events or acquired resistance.[37] We did not find appropriate meta-analyses on double active therapy specifically in patients with sepsis and an intra-abdominal focus.

Conclusions

Conclusion	**Quality of evidence**
Pooled data showed no additional effect of beta-lactam + aminoglycoside double active therapy compared to the same or a different beta-lactam given	Moderate to low[105]

as monotherapy in patients with sepsis on all-cause mortality and clinical failure	
Pooled data showed an increased risk of clinical failure and nephrotoxicity for beta-lactam + aminoglycoside double active therapy compared to a different beta-lactam given as monotherapy in patients with sepsis	Very low[105]
Pooled data showed no additional effect of empirical double active therapy compared to empirical monotherapy on all-cause mortality, secondary infections and emergence of resistance in patients with sepsis and septic shock	Moderate to very low[106]
One randomized trial in patients with severe sepsis and septic shock showed no additional effect of double active therapy of meropenem with moxifloxacin compared to meropenem monotherapy on 28-day mortality, 90-day mortality, and adverse events at the end of study Emergence of resistance at day 21 occurred less often in the double active therapy group compared to the monotherapy group	Moderate to low[107]
One randomized trial in patients with *S. aureus* bacteraemia showed no additional effect of adjunctive rifampicin to anti-staphylococcal treatment (mostly flucloxacillin or vancomycin) on 12-week treatment failure, disease recurrence or death	Moderate[111]
One randomized trial in patients with *S. aureus* bacteraemia showed an increase in side effects of adjunctive rifampicin to anti-staphylococcal treatment (mostly flucloxacillin or vancomycin), but no difference in serious adverse events	High to moderate[111]
Pooled data in patients with severe *P. aeruginosa* infections showed that there is insufficient data to draw conclusions on the effect of empirical double active therapy of a beta-lactam plus aminoglycoside or fluoroquinolone compared to beta-lactam monotherapy on mortality and clinical cure	Very low[105,109,110]
Pooled data in patients with severe *P. aeruginosa* infections showed no additional effect of definite double active therapy of a beta-lactam plus aminoglycoside or fluoroquinolone compared to beta-lactam monotherapy on mortality	Very low[109,110]
Pooled data in patients with VAP showed no additional effect of double active antibacterial therapy compared to monotherapy on all-cause mortality	Low[37,112]

Other considerations

There has been a lively and ongoing debate about double active therapy including aminoglycosides in patients with septic shock. The SSC guideline recommends to consider double active therapy in patients with severe sepsis and septic shock based on a weak recommendation and moderate quality evidence. This recommendation was largely based on two studies from Kumar et al. from 2010 with important limitations.[113,114] The first was a large retrospective study that indicated that there was a substantial survival benefit in patients with septic shock treated with double active antibacterial therapy.[114] The second study was a systematic review on the effects of double active therapy in severe sepsis and septic shock.[113] A total of 50 studies, including RCTs, prospective and retrospective observational studies, were included and showed there was no overall benefit of double active therapy (OR 0.86; 95% confidence interval, 0.71 - 1.03) with large heterogeneity. Stratification of studies with high (>25%) mortality in the monotherapy group showed a beneficial effect of double active therapy

(OR 0.54; 95% CI, 0.45 - 0.66). A subgroup analysis of critically ill patients and patients with septic shock also showed better outcomes with double active therapy (OR 0.51; 95% CI, 0.36 - 0.72). However, the committee finds it questionable if studies within this subgroup were comparable and relevant to the current guideline. All studies in the mentioned subgroup were observational (7 prospective, 5 retrospective) and mostly very small. We assessed the seven included prospective studies. Three studies included only patients with CAP or pneumococcal bacteraemia,[115-117] in another study the majority of patients in the monotherapy group were treated with aminoglycoside monotherapy for *Pseudomonas* bacteraemia,[118] and in one study mainly cephalosporin or aminoglycoside monotherapy was administered for Enterobacter species.[119] The only large study on this subject which included over 2000 patients did not find any additional beneficial effect of double active therapy in gram-negative bacteraemia.[120] The authors of the meta-analysis found no signs of publication bias, but other biases were not assessed.[113] Of note, the SSC guideline graded the data from Kumar et al. as moderate quality evidence based on observational studies with a strong association.[36] In contrast, we graded the same evidence as very low quality evidence based on observational studies with serious risk of bias, imprecision and serious indirectness (data not shown).

A Dutch study of Ong et al. studied the effect of a short-course of adjunctive gentamicin on the occurrence of renal failure, mortality and shock in 648 patients with severe sepsis and septic shock admitted to two university hospital ICUs.[64] Hospital A had a local antibiotic guideline recommending short-term combination treatment of a 3rd generation cephalosporin with an aminoglycoside, while in hospital B monotherapy with a 3rd generation cephalosporin was standard of care. Combination therapy with gentamicin (median dose 4.9 mg/kg, median duration of treatment 2 days) resulted in more renal failure at day 14 after the start of treatment compared to monotherapy (multivariate regression analysis: OR 1.39; 95% CI 1.00 - 1.94). There was no significant different duration of shock (OR 1.34; 95% CI, 0.96–1.86) and 14-day mortality (OR 1.41; 95% CI, 0.94–2.12). Pre-defined sensitivity analyses underlined the robustness of these results Confounding by indication did not seem to play a major role as almost all patients with sepsis in hospital A received aminoglycosides irrespective of for example renal function [personal communication JP and MJMB]. In both treatment groups and in both ICUs 4 to 5% of patients received inappropriate empirical treatment based on in vitro antibiotic resistance of isolated pathogens. Empirical carbapenem use was higher in the group not receiving gentamicin (15%, versus 4% in the gentamicin group). Among the patients receiving gentamicin, 9% of isolated pathogens was only susceptible to gentamicin.

With the newer meta-analyses of Paul et al., Sjovall et al., Vardakas et al., the landmark RCT of Brunkhorst et al. and the described Dutch observational study of Ong et al., the guideline committee concludes that the current evidence shows no benefits of empirical double active therapy in patients with sepsis or septic shock on all-cause mortality.[64,105-107,109] This conclusion is in line with a recent position statement of the IDSA.[121] In addition, available data in sepsis patients suggest that aminoglycoside treatment in addition to a beta-lactam might lead to lower clinical cure rates and higher rates of nephrotoxicity when compared to monotherapy (mostly a beta-lactam with broader antibacterial spectrum).[64,105] Studies in other patient populations are in line with these findings. A meta-analysis of RCTs comparing therapy of a beta-lactam with an aminoglycoside to beta-lactam monotherapy in patients with any infection showed increased risk of nephrotoxicity without any beneficial effect regarding mortality, clinical efficacy or development of resistance.[122] Another argument of using double active therapy has been with the goal to decrease the risk of antibiotic

resistance development. The trial of Brunkhorst et al. showed a higher rate of resistance in the monotherapy group of meropenem,[107] but this effect could not be confirmed in a meta-analysis of RCTs reporting on emergence of antimicrobial resistance.[123]

It should be mentioned that many of the older studies included in the described meta-analyses on double active therapy with aminoglycosides administered aminoglycosides for the complete treatment course and in multiple daily dosing schedules, making it difficult to generalize the outcomes to the current daily practice of once daily dosing and short course aminoglycoside treatment. Other limitations of the available literature are that most studies only had short follow-up and did not report on patient relevant outcomes of nephrotoxicity.[106] A systematic review in non-sepsis patients summarized the toxicity of a single dose of aminoglycoside therapy among 36 studies (RCTs and observational).[124] Among 24107 patients that received a single dose of aminoglycoside (mainly as preoperative prophylaxis), 2520 developed acute kidney injury, which was usually mild and reversible. A meta-analysis was not possible due to large heterogeneity. In contrast, the study of Ong et al. showed clinically relevant negative outcomes already after a median aminoglycoside treatment duration of two days in patients with sepsis.[64]

Based on summarized data the committee recommends against the use of double active therapy in patients with sepsis, provided that the chosen single antibacterial agent is active against the most likely pathogens involved. In contrast to the SSC guideline, we also recommend against double active therapy in patients with severe sepsis and septic shock. It should be noted that we do not recommend against the use of multiple antibacterial agents when the goal is to broaden the empirical treatment spectrum.

For sepsis due to *P. aeruginosa*, there is insufficient data from RCTs and systematic reviews to draw conclusions on benefits and risks of empirical double active therapy. The described meta-analyses showed no benefit of empirical double active therapy for *P. aeruginosa* infections in general, but numbers were too small to perform a subgroup analysis for patients with sepsis or severe infections.[105,109,110] A recent retrospective observational study of patients with septic shock and documented monomicrobial bacteraemia suggested a beneficial effect on mortality of double active empirical therapy compared to monotherapy in a subgroup of 61 patients with *P. aeruginosa* infections.[125] It was not reported with which double active empirical regimens the patients with *P. aeruginosa* were treated. Also, there was risk of confounding by indication in the analysis. Within the overall population of this study there was no beneficial effect of double active therapy compared to monotherapy when a beta-lactam was used in both groups. Other more recent observational studies of double active therapy in *P. aeruginosa* bacteraemia showed no additional effect on mortality compared to monotherapy.[126-129] One of these studies found a beneficial effect on mortality of double active therapy in the subgroup of patients treated with ciprofloxacin-based double active therapy, but not in the subgroup treated with tobramycin-based double active therapy.[128] Limited evidence showed no additional effect on mortality in patients with severe *P. aeruginosa* infections treated with definite double active therapy. The committee concluded that although there is lack of good quality data, the current evidence summary argues against the use of double active therapy as empirical and definite antibacterial treatment for *P. aeruginosa* sepsis.

For sepsis due to *S. aureus* there is limited data suggesting that adding aminoglycosides to anti-staphylococcal treatment has no benefits but may cause harm. Moderate quality evidence also doesn't

support the addition of rifampicin in patients with sepsis. In addition, in a large retrospective study in 964 patients, 53% of patients was treated with double active therapy and 59% of those with adjunctive rifampicin. Double active therapy did not affect mortality, except for the subgroup of patients with implanted foreign bodies or devices, which are outside the scope of this guideline.[130]

Recommendations

Recommendation	Strength	Quality of evidence
12. We recommend against routine double active empirical antibacterial therapy* for patients with sepsis or septic shock.	Strong	Moderate
13. We suggest that double active therapy is not routinely used as definite therapy for patients with sepsis due to *P. aeruginosa* infection	Weak	Very low
14. We suggest that double active therapy is not routinely used as definite therapy for patients with sepsis due to *S. aureus* infection not associated to prosthetic material	Weak	Moderate

* We defined double active antibacterial therapy as treatment with two classes of antibiotics, both targeting the known or suspected causing pathogen(s) (e.g., ceftriaxone and an aminoglycoside to target gram-negative pathogens) and with the specific purpose to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Also frequently referred to as combination antibiotic therapy. Of note, the use of two antibiotics for the increased likelihood of covering the causing agent (broadening the spectrum), or for covering multiple causing agents (e.g., aerobic and anaerobic bacteria) was not included in the definition of double active therapy.

6. What is the optimal choice of empirical therapy in patients with sepsis in the Netherlands?

6a. Antibacterial therapy in patients with sepsis in general

Evidence summary

Antibacterial therapy in patients with sepsis with unknown focus

We found no RCTs that specifically focus on empirical or definite antibacterial treatment of adults with sepsis when there is no identified focus.

Antibacterial therapy in patients with sepsis due to HAP / VAP

The IDSA guideline on HAP and VAP performed a systematic review of 29 RCTs on the antibacterial treatment of VAP.[37] The number of patients with sepsis was not reported, but mortality was high (average 21%, range 0 – 80%). There were no significant differences in mortality, clinical response, acquired drug resistance, or adverse events for patients treated with a cephalosporin compared to a non-cephalosporin or an antipseudomonal penicillin compared to a non-antipseudomonal penicillin. Patients treated with a carbapenem had lower mortality rates compared to patients treated with a non-carbapenem (RR 0.78; 95% CI, 0.65–0.95). Antibacterial treatments in the non-carbapenem group were a fluoroquinolone, ceftazidime, ceftazidime + an aminoglycoside, aztreonam, piperacillin-tazobactam or tigecycline.[37] The meta-analysis comparing treatment with an aminoglycoside-

containing regimen to a aminoglycoside-free regimen showed lower clinical response rates in patients treated with a aminoglycoside-containing regimen (RR 0.82; 95% CI, 0.71–0.95). The meta-analysis comparing treatment with a quinolone-containing regimen to a quinolone-free regimen showed lower rate of adverse events in patients treated with a quinolone-containing regimen (RR 0.88; 95% CI, 0.78–0.99) compared to a carbapenem-based regimen or another beta-lactam-based regimen. The previously discussed systematic review by Arthur et al.[112] showed higher clinical cure in the carbapenem group compared to tigecycline,[131] levofloxacin,[132] or piperacillin-tazobactam.[133]

The IDSA guideline additionally performed a systematic review on empirical treatment of HAP.[37] A meta-analysis was only possible on four RCTs comparing a carbapenem versus piperacillin-tazobactam. APACHE II scores were <15, 13, 13 and 23 and overall mortality rates were 2, 9, 14 and 38%. The meta-analysis showed comparable mortality in both treatment groups (RR 0.94; 95% CI, 0.66–1.34).

Antibacterial therapy in patients with sepsis due to intra-abdominal infection

Several systematic reviews have been executed to analyse outcomes of different antibacterial treatment regimens in patients with complicated intra-abdominal infections.[134-138] In addition, the previously mentioned guideline of the SIS summarized evidence on the efficacy and safety of beta-lactams in intra-abdominal infection.[38] For most of the included studies, the number of patients with sepsis was not reported. Carbapenems were assessed in most (>30) RCTs, followed by a cephalosporin plus metronidazole (21 RCTs) and piperacillin-tazobactam (14 RCTs). Overall, there were minimal differences and no consistent differences in efficacy to comparator treatments in all these trials. One systematic review reported a benefit of metronidazole-based therapy compared to carbapenem treatment on mortality (OR 0.61; 95% CI: 0.37–1.00) and clinical success (OR 1.63; 95% CI: 1.08–2.45) at the end of treatment, although the total number of events was very low.[136] Another systematic review comparing clindamycin/aminoglycoside treatment to a broad-spectrum beta-lactam (with or without beta-lactamase inhibitor) showed increased clinical cure in favour of beta-lactam treatment (OR 0.66; 95% CI: 0.54–0.81).[134] Overall there was no different rate of adverse events in both treatment groups. However, the 18 trials reporting nephrotoxicity showed a substantially increased risk of nephrotoxicity in the clindamycin/aminoglycoside treated patients (OR 3.7; 95% CI: 2.09–6.57) and a decreased risk of diarrhoea (OR 0.68, 95% CI: 0.46–1.00) compared to beta-lactam treatment. Two systematic reviews compared moxifloxacin to alternative treatments in patients with complicated intra-abdominal infections.[137,139] Overall mortality was 3.8% and average APACHE II scores 7 (range 2 – 13). Overall the studies found no differences in clinical cure and mortality between groups. The intention-to-treat analysis within the subgroup of patients with secondary peritonitis showed a non-significant trend towards lower clinical cure than the alternative treatment group (risk difference:- 3.96%; 95% CI:- 8.54% to 0.61%).[139] Adverse events occurred more frequently in the moxifloxacin group. Finally, an older systematic review comparing ciprofloxacin and metronidazole with beta-lactam-based treatments in patients with intra-abdominal infections found that ciprofloxacin-based treatment was associated with higher clinical cure rates than beta-lactam-based treatment (OR 1.69, 95% CI 1.20–2.39).[138] Average APACHE II score was reported in two studies and above 9.

Removal of central venous catheter (CVC) and antibacterial therapy in patients with sepsis and suspected CVC infection

We did not find RCTs or systematic reviews that addressed the question if CVC removal alone is sufficient in patients with sepsis and suspected CVC infection. We also did not find RCTs or systematic reviews comparing antibacterial therapy choices in patients with sepsis and a suspected CVC infection.

Antibacterial therapy in patients with sepsis in general

One meta-analysis compared treatment with beta-lactam/beta-lactamase inhibitors (BL/BIs) versus carbapenems in patients with sepsis due to several causes.[140] Patients were adults or children and had sepsis due to abdominal or pelvic infections (11 RCTs), febrile neutropenia (8) or pneumonia (7). Overall mortality in all studies combined was 5% (0 to 14%). The general analysis and several subgroup analyses showed no difference of effect on mortality, clinical failure at the end of treatment or development of resistance. For adverse events overall there was no difference between the study groups, but adverse events requiring discontinuation of the study drug occurred more often in the BL/BI group (1.36, 95% CI 1.03–1.79, 15 trials, 5304 patients). There was a higher risk of diarrhoea in the BL/BI group (RR 1.46, 95% CI 1.25–1.70, 21 trials, 6579 patients). In contrast, *Clostridium difficile*-associated diarrhoea (CDAD) occurred more frequently in the carbapenem group (RR 0.29, 95% CI 0.10–0.87, 6 trials, 2002 patients). Seizures occurred significantly more frequently in the carbapenem group when treated with imipenem (RR 0.21, 95% CI 0.05–0.93, 4 trials, 822 patients).

Conclusions

Conclusion	**Quality of evidence**
1. There are no trials or systematic reviews in patients with sepsis with unknown focus available to conclude on the comparative effect of different antibiotic classes	-
2. Pooled data showed no additional effect of treatment with a cephalosporin compared to non-cephalosporin regimens on mortality, clinical cure, acquired resistance and adverse events in patients with sepsis due to VAP	Moderate to low[37]
3. Pooled data showed no additional effect of treatment with anti-pseudomonal penicillin compared to non-anti-pseudomonal regimens on mortality, clinical cure and adverse events in patients with sepsis due to VAP	Moderate to low[37]
4. Pooled data showed decreased mortality of treatment with a carbapenem compared to non-carbapenem regimens in patients with sepsis due to VAP. There was no additional effect on clinical cure, acquired resistance and adverse events	Moderate to low[37]
5. Pooled data showed no additional effect on mortality of treatment with a aminoglycoside-containing regimen compared to non-aminoglycoside regimens in patients with sepsis due to VAP. There were lower rates of clinical response in the aminoglycoside-based regimens and no additional effect on adverse events	Low to moderate[37]
6. Pooled data showed no additional effect on mortality, clinical cure, acquired resistance of treatment with a quinolone-containing regimen compared to non-quinolone regimens in patients with sepsis due to VAP. There was a decreased risk of adverse events with a quinolone-containing regimen	Low to moderate[37]

7. Pooled data showed no additional effect of treatment with a carbapenem compared to treatment with piperacillin-tazobactam on mortality in patients with sepsis due to HAP	Low[37]
8. Trial data showed similar effect of treatment with a cephalosporin + metronidazole, piperacillin-tazobactam or a carbapenem on clinical efficacy and safety in patients with sepsis due to intra-abdominal infection	Low[38]
9. Pooled data showed lower mortality of treatment with metronidazole plus a cephalosporin or quinolone compared to treatment with a carbapenem in patients with sepsis due to intra-abdominal infection. There was no additional effect on clinical success and adverse events	Low[136]
10. Pooled data showed increased clinical cure, a large decreased risk of nephrotoxicity and an increased risk of diarrhoea of empirical treatment with broad-spectrum beta-lactam (with or without beta-lactamase inhibitor) versus clindamycin plus aminoglycoside in patients with sepsis due to intra-abdominal infection. There was no additional effect on mortality and other adverse events	Very low to low[134]
11. Trial data showed a similar effect of monotherapy with carbapenems, tigecycline, piperacillin-tazobactam and ceftolozane-tazobactam on clinical cure in patients with sepsis due to nosocomial intra-abdominal infections	Low[135]
12. Pooled data showed increased clinical cure of treatment with ciprofloxacin plus metronidazole versus alternative treatments in patients with sepsis due to intra-abdominal infections. There was no additional effect on mortality and adverse events	Moderate to low[138]
13. Pooled data showed higher rates of adverse events of treatment with moxifloxacin versus beta-lactam based treatments in patients with sepsis due to intra-abdominal infections. There was no additional effect on clinical cure and mortality.	Low[137,139]
14. There are no RCTs or systematic reviews comparing the effect of removal of the CVC to alternative strategies in patients with sepsis and suspected CVC infection	-
15. There are no RCTs or systematic reviews comparing antibiotic strategies in patients with sepsis and suspected bacterial CVC infection	-
16. Pooled data in patients with sepsis due to several causes showed increased risk of diarrhoea, but decreased risk of *Clostridium difficile* associated diarrhoea and seizures of empirical treatment with BL/BIs compared to carbapenem treatment. There was no additional effect on 30-day mortality, clinical cure, adverse events in general and development of resistance	Low to moderate[140]

Other considerations

Providing evidence-based conclusions on empirical antibacterial therapy in sepsis is challenging. Studies differ in their patient populations (severity of infection, source of infection, comorbidities, availability of culture results, local antimicrobial resistance and MIC of involved bacteria), interventions (dosing, additional antibacterial therapy, source control, timing of treatment) and outcomes (timing, definition, outcome assessment). In particular, antimicrobial resistance is much lower in the Netherlands compared to other countries and the number of Dutch patients in included trials is limited.

Another important consideration is that most trials and meta-analyses were not powered for conclusions on the occurrence of adverse events including nephrotoxicity and the development of antimicrobial resistance.

Most trials in patients with severe infections used cephalosporins, carbapenems, piperacillin-tazobactam and some fluoroquinolones, but outcomes in general did not consistently suggest that one of these classes of antibiotics is considerably more effective than others in patients with sepsis. Within the summarized evidence based on trials and meta-analyses, aminoglycoside-based regimens for sepsis due to HAP or VAP were associated with lower rates of clinical response.[37] For sepsis due to intra-abdominal infections aminoglycoside monotherapy for the aerobic gram-negative pathogens was less effective than beta-lactam treatment.[134,141] The SSC guideline does not provide detailed recommendations on the choice of empirical therapy in patients with sepsis, but they do state that in the majority of patients with sepsis a broad-spectrum beta-lactam is most appropriate.[36]

It is difficult to draw conclusions on aminoglycoside efficacy and toxicity for patients with sepsis. Almost all trials available combined aminoglycosides with other antibiotics and were therefore summarized and discussed in the chapter on double active therapy with aminoglycosides (chapter 5). It was obvious from the described Dutch study by Ong et al that including aminoglycosides in the empirical treatment of sepsis is carbapenem-sparing, but conversely leads to a significant number of patients who are essentially treated with aminoglycoside monotherapy due to resistance to the beta-lactam agent.[64] Aminoglycoside monotherapy is generally not considered appropriate empirical therapy for sepsis not originating from the urinary tract, although also on this topic there is lack of data.[142]

The committee concluded that based on the current data about efficacy and safety of beta-lactams, the experience with beta-lactams and the large number of trials using a beta-lactam, beta-lactams are most appropriate as empirical and definite therapy in the majority of patients with sepsis.

Based on the available literature, fluoroquinolones are acceptable alternatives when the risk of fluoroquinolone resistance is considered low. However, clinicians should be aware that use of fluoroquinolones has significant disadvantages regarding toxicity and development of resistance.[143-146] In the discussions on aminoglycoside-based treatment, several committee members had concerns about aminoglycoside efficacy and adverse events, especially in patients with pre-existing impaired renal function. In contrast, aminoglycoside-based treatment is current practice for empirical sepsis treatment in many hospitals as a carbapenem-sparing strategy. The committee settled that current (lack of) evidence supports *short-term* (i.e. maximum of two days) aminoglycoside treatment added to a beta-lactam agent in patients with sepsis with the only purpose of increasing the empirical antibacterial spectrum of activity until susceptibility results are available. This strategy is therefore mainly applicable to gram-negative bacteria such as 3GCR-E or *P. aeruginosa* (chapter 6b).

There is no clear evidence-based guidance on how to define appropriate empirical therapy (chapter 4) and it is difficult to predict a priori risk of the involved pathogen in patients with sepsis (chapter 3). Early detection of the pathogen combined with direct guidance from the clinical microbiology laboratory on choice of therapy could therefore be an important strategy to reduce inappropriate empirical therapy and unnecessary broad-spectrum antibiotics in patients with sepsis.[147] Potential

interventions supporting this goal are improving the appropriate collection of clinical specimens, decreasing time from collection of specimens to arrival in the microbiology lab, implementing rapid pathogen identification and antimicrobial susceptibility testing techniques.[148,149] However, studies on efficacy of antimicrobial stewardship interventions in patients with sepsis are lacking.[150,151] Although diagnosis of sepsis is no part of this guideline, the committee believes that optimizing early identification of the involved pathogen is an important tool to improve early appropriate empirical therapy and decrease unnecessarily broad-spectrum antibiotics in patients with sepsis. We therefore suggest that local antimicrobial stewardship programs incorporate improvement of early diagnosis and reporting of pathogens and susceptibility in patients with sepsis.

In current clinical practice the choice of empirical antibacterial treatment of sepsis differs considerably between hospitals, e.g., a third generation cephalosporin, piperacillin-tazobactam, a combination of a second/third generation cephalosporin with short-term aminoglycoside treatment, a combination of a second or third generation cephalosporin with a fluoroquinolone, or a carbapenem. The final choice is therefore dictated by the likelihood of involvement of a resistant causative pathogen, by the desire to avoid the use of third-generation cephalosporins, fluoroquinolones and/or carbapenems from an antibiotic stewardship perspective and by risks of toxicity and other potential adverse events for the patient.

We therefore cannot provide strong recommendations on the best empirical treatment in sepsis based on the currently available literature. We found only subtle differences between strategies in clinical outcomes in studies that were frequently not generalizable to the Dutch clinical setting. Consequently, the committee provided pragmatic suggestions for empirical treatment choices in patients with sepsis based on current evidence, reported national resistance rates, the antibiotic stewardship perspective, PK/PD considerations and risk of adverse events. Multiple options are more or less equivalent as long as the empirical treatment is appropriate in covering the most likely pathogens. All strategies have advantages and disadvantages depending on the three main perspectives (likelihood of optimally targeting the right pathogen, antimicrobial stewardship, risk of adverse events). For recommendations on empirical therapy of patients with sepsis, we used the following considerations. First, we defined the most important pathogens that should be treated in patients with specific clinical syndromes, using the data described in chapter 1 and including pharmacodynamics/pharmacokinetic considerations (PK/PD, chapter 10). We subsequently defined which empirical treatment options would be appropriate based on the national resistance data in blood culture pathogens, described in chapter 2 and the risk of involvement of 3GC-E, as described in chapter 3. We then defined alternative treatments with larger disadvantages based on resistance, PK/PD, antimicrobial stewardship, toxicity or other reasons. As an example, based on these considerations the committee considered amoxicillin-clavulanic acid plus an aminoglycoside less appropriate empirical therapy for sepsis, based on the combination of high resistance rates of Enterobacterales for amoxicillin-clavulanic acid, concerns about efficacy and toxicity on aminoglycosides and PK/PD considerations of both amoxicillin-clavulanic acid and aminoglycosides.

Hospitals could consider alternative empirical treatment options guided by local resistance rates or when patients do not (yet) qualify for sepsis according to the sepsis-3 criteria.[1] Although this guideline is intended for patients with sepsis, in reality the recommendations are frequently used for any patient in which blood cultures are taken and iv antibiotic therapy is considered. We would like to underscore

that those patients are formally outside the scope of this guideline. For those patients, higher chances of resistance might be accepted as our evidence summery on the need of appropriateness of empirical therapy (chapter 4) was only focussed on patients with sepsis.

In the current chapter 6a, recommendations are listed for sepsis patients at low risk of 3GCR-E (i.e. no previous infection or colonization with 3GCR-E and a low estimated risk of 3GCR-E involvement. See chapter 3, recommendations 1 and 2). Alternative treatment strategies are provided including in patients with increased likelihood of involvement of *P. aeruginosa* (chapter 3, recommendation 3) or enterococci (chapter 4, recommendation 11). In chapter 6b, empirical treatment recommendations are provided for patients with sepsis at increased or high risk of involvement of 3GCR-E. In chapter 6c, we provided additional recommendations on empirical therapy in patients with sepsis at increased risk of *S. aureus* involvement. Recommendations are summarized in **Figure 1** (Summary).

For definite treatment, we also refer to chapter 9 on duration of therapy in sepsis. Finally, it should be noted that for empirical sepsis therapy PK/PD considerations apply (chapter 10).

Sepsis in general

For sepsis in general or no obvious source of infection and low estimated risk of 3GCR-E or *P. aeruginosa* involvement, the committee agreed that the antibacterial spectrum should include *S. aureus, E. coli* and haemolytic streptococci. The committee prefers a 3rd generation cephalosporin. Alternative empirical choices are listed in **Table 6**.

Sepsis due to CAP

For empirical treatment of sepsis due to CAP, we refer to the 2016 SWAB guideline on CAP.[39]

Sepsis due to HAP and VAP

For sepsis due to HAP and VAP the antibacterial spectrum should include *S. aureus*, Enterobacterales, *P. aeruginosa* and *H. influenzae*. It should be noted that in the Netherlands the prevalence of VAP is thought to be lower compared to other countries due to the frequent use of SDD in Dutch ICU patients. In addition, in most patients with VAP the most likely pathogen and its resistance are known because of the frequent surveillance cultures of the respiratory tract in patients on SDD. The number of patients that need empirical therapy due to VAP will therefore be low. For sepsis due to HAP or VAP in patients with unknown surveillance cultures or those not on SDD, we recommend a 2nd or 3rd generation cephalosporin plus high dose ciprofloxacin or piperacillin-tazobactam as empirical treatment. Alternative empirical treatment options are listed in **Table 6**. As discussed in chapter 4, we generally suggest against routine empirical treatment of anaerobic bacteria in patients with sepsis due to aspiration pneumonia, unless empyema or a lung abscess is suspected.

Sepsis due to UTI

For empirical treatment of sepsis due to UTI, we refer to the SWAB guideline on complicated UTI.[5] The 2013 guideline is currently being updated.

Sepsis due to cholangitis

For sepsis due to cholangitis, empirical treatment should have activity primarily against *E. coli* and to a lesser extent other Enterobacterales. Anaerobic coverage is suggested for patients with cholangitis

and biliary-enteric anastomosis (see chapter 4). The guideline committee therefore recommends a 3rd generation cephalosporin and the addition of metronidazole for patients with biliary-enteric anastomosis. Alternative treatments are listed in **Table 6**.

Sepsis due to intra-abdominal infections

For sepsis due to other intra-abdominal infections empirical treatment should have activity against *E. coli*, streptococci, anaerobes including *Bacteroides* spp and other Enterobacterales. The committee therefore recommends a 3rd generation cephalosporin plus metronidazole. Alternative treatments are listed in **Table 6**.

Sepsis due to skin and soft tissue infection

For empirical treatment of sepsis due to skin and soft tissue infection we refer to the NVDV guideline on cellulitis and erysipelas (2013) and the Dutch evidence-based guideline on necrotizing soft tissue infections.[3,4]

Sepsis due to suspected CVC infection

For sepsis due to suspected CVC infection there is lack of high quality data. The previous SWAB sepsis guideline did not provide general recommendations on catheter removal or empirical therapy for patients with sepsis and suspected CVC infection.[28] The IDSA and SSC guidelines provided strong recommendations on the prompt removal of the line in the settings of sepsis, hemodynamic instability, endocarditis or evidence of metastatic infection, persistent bacteraemia after 72 hours of antibacterial therapy or infections due to *S. aureus, P. aeruginosa*, fungi or mycobacteria.[36,152] There is no high quality data to support this recommendations, but the committee agreed on the assumption that retaining a CVC in patients with suspected CVC infection under the mentioned circumstances is likely similar to absence of source control with potential increased risk of adverse outcomes. We therefore recommend prompt CVC removal in patients with suspected CVC infection and sepsis or septic shock.

Chapter 1 showed that in the Netherlands the most common pathogens of CLABSI are CNS, which rarely cause complicated infection in patients without prosthetic valves or other intravascular prosthetic material. In the setting of uncomplicated CLABSI with CNS and removal of the central line, antibiotic treatment is therefore commonly withheld in The Netherlands. The committee agreed that empirical therapy should cover *S. aureus* and gram-negative bacteria including *P. aeruginosa* in patients with sepsis and suspected CVC infection. We suggest several equivalent treatment options in **Table 6**.

In contrast to pooled international data, Dutch surveillance data showed that Enterococci occur in less than 6 % as causative pathogens of suspected CVC infections. Based on chapter 4 and in line with the IDSA guideline we agreed to suggest against empirical treatment of enterococci, unless there is a very high suspicion of involvement in individual cases based on recent cultures. The same holds true for the empirical coverage of CNS for CVC associated sepsis. An evidence summary on the question whether patients with intravascular prosthetic material and sepsis due to suspected CVC infection should receive empirical treatment covering Enterococci and CNS in order to prevent secondary intravascular prosthetic material infection was outside the scope of this guideline. However, the committee agreed that a vancomycin-based treatment could be considered in those patients and is suggested as an alternative in **Table 6**.

It should be noted that treatment of infected long-term catheters such as Hickman, Port-a-cath, Broviac and dialysis catheters are not covered in this guideline. Regarding the need for empirical use of an echinocandin in patients with CVC associated sepsis, the committee refers to the SWAB guidelines for the Management of Invasive Fungal Infections.[32]

Recommendations

Recommendation	**Strength**	**Quality of evidence**
15. In patients with sepsis, we generally recommend using a beta-lactam antibiotic covering the most likely involved pathogens	Strong	Moderate
16. In patients with sepsis in general / with no obvious source of infection, we suggest a 3rd generation cephalosporin (3GC). Alternative empirical treatment strategies are listed in **Table 6**	Weak	Low
17. In patients with sepsis due to HAP or VAP, we suggest that there are equivalent empirical treatment strategies, listed in **Table 6**	Weak	Low
18. In patients with sepsis due to cholangitis, we suggest a 3GC. Alternative empirical treatment strategies are listed in **Table 6**	Weak	Low
19. In patients with sepsis due to intra-abdominal infection, we suggest a combination of a 3GC with metronidazole. Alternative empirical treatment strategies are listed in **Table 6**	Weak	Low
20. In patients with sepsis and a suspected CVC infection*, we recommend prompt removal of the line	Strong	GPS
21. In patients with sepsis and suspected CVC infection, we suggest empirical treatment with a 3GC** with gentamicin or high dose ciprofloxacin Alternative treatment strategies are listed in **Table 6**	Weak	GPS
22. For the empirical treatment of sepsis due to UTI, CAP and SSSI's, we refer to other guidelines[3-6]		

* Recommendations for sepsis due to suspected long-term CVC's were not included in this guideline

** 3GC may be given in high dose for more optimal PK/PD for *S. aureus* infections in accordance to EUCAST

Table 6. Alternative empirical treatment strategies in sepsis and low estimated risk of involvement of 3GCR-E

Source	Choice	Empirical treatment strategy	Advantages	Disadvantages	Note
Unknown	1st	3GC	Relatively small spectrum Low risk of adverse events Only beta-lactam component of therapy	Potentially suboptimal *S. aureus* PK/PD	High dose 3GC optional when there is a higher likelihood of *S. aureus* involvement
	Alternative	Piperacillin-tazobactam	Spectrum includes *E. faecalis* anaerobic bacteria and *P. aeruginosa* Only beta-lactam component of therapy	Broader antibacterial spectrum compared to 1st choice Prolonged or continuous infusion strongly recommended	Optional when there is a higher likelihood of anaerobic, *P. aeruginosa* or enterococcal involvement
	Alternative	2GC plus high dose ciprofloxacin or an aminoglycoside	Spectrum includes *P. aeruginosa* Potentially better *S. aureus* PK/PD of beta-lactam component	Potentially less optimal Enterobacterales PK/PD of beta-lactam component Potentially higher risk of adverse events compared to 1st choice TDM and max 2 day treatment for aminoglycoside	Optional when there is a higher likelihood of *S. aureus* infection or *P. aeruginosa* involvement
HAP or VAP	1st	3GC plus high dose ciprofloxacin	Spectrum includes *P. aeruginosa*. Potentially better Enterobacterales PK/PD of beta-lactam component (compared to 2GC)	No anaerobic coverage. Potentially less optimal *S. aureus* PK/PD of beta-lactam component (compared to 2GC)	
	1st	Piperacillin-tazobactam	Spectrum includes *P. aeruginosa* and anaerobic bacteria Only beta-lactam component of therapy	Broader antibacterial spectrum	
	1st	2GC plus high dose ciprofloxacin	Spectrum includes *P. aeruginosa*. Potentially better *S. aureus* PK/PD of beta-lactam component (compared to 3GC)	No anaerobic coverage. Potentially less optimal Enterobacterales PK/PD of beta-lactam component (compared to 3GC)	

Cholangitis	1st	3GC	Relatively small spectrum Low risk of adverse events Only beta-lactam component of therapy	No anaerobic or enterococcal coverage.	Addition of metronidazole in patients with sepsis due to cholangitis who have biliary-enteric anastomosis
	Alternative	Piperacillin-tazobactam	Spectrum includes *E. faecalis*, anaerobic bacteria and *P. aeruginosa*	Broader antibacterial spectrum Prolonged or continuous infusion strongly recommended	Optional when there is a higher likelihood of anaerobic, enterococcal or *P. aeruginosa* involvement <u>Alternative treatment</u> option to 3GC plus metronidazole in patients with sepsis due to cholangitis who have biliary-enteric anastomosis
	Alternative	2GC/3GC plus high dose ciprofloxacin or an aminoglycoside	Spectrum includes *P. aeruginosa*	No anaerobic coverage Potentially higher risk of adverse events TDM and max 2 day treatment for aminoglycoside	Optional when there is a higher likelihood of *P. aeruginosa* involvement Addition of metronidazole in patients with sepsis due to cholangitis who have biliary-enteric anastomosis
Intra-abdominal infection	1st	3GC plus metronidazole	Relatively small spectrum Low risk of adverse events Only beta-lactam component of therapy		
	Alternative	Piperacillin-tazobactam	Spectrum includes *E. faecalis* and *P. aeruginosa*	Broader antibacterial spectrum Prolonged or continuous infusion strongly recommended	Optional when there is a higher likelihood of *P. aeruginosa* or enterococcal involvement
CVC infection Multiple equivalent treatment options	1st	High dose 3GC plus high dose ciprofloxacin or an aminoglycoside	Spectrum includes *P. aeruginosa* Potentially better *S. aureus* PK/PD (compared to regular 3GC dose)	Risk of adverse events TDM and max 2 day treatment for aminoglycoside	
	1st	Piperacillin-tazobactam	Spectrum includes *E. faecalis* and *P. aeruginosa*	Prolonged or continuous infusion strongly recommended	

	1st	2GC plus high dose ciprofloxacin or an aminoglycoside	Spectrum includes *P. aeruginosa* Potentially better *S. aureus* PK/PD of beta-lactam component (compared to regular 3GC dose)	Potentially less optimal Enterobacterales PK/PD of beta-lactam component (compared to 3GC) Risk of adverse events TDM and max 2 day treatment for aminoglycoside	
	Alternative	Flucloxacillin plus high dose ciprofloxacin or aminoglycoside	Optimal *S. aureus* therapy	No beta-lactam treatment of gram-negative pathogens Higher risk of adverse events TDM and max 2 day treatment for aminoglycoside	Optional, especially when there is a high likelihood of *S. aureus* involvement
	Alternative	Vancomycin plus gram-negative antibacterial treatment	Spectrum includes coagulase-negative Staphylococci, Enterococci	Potentially less optimal *S. aureus* treatment	Optional when there is a high likelihood of enterococcal involvement or when the patient has intravascular prosthetic material at risk of secondary infection with low virulent gram-positive pathogens

6b. Antibacterial therapy in patients with sepsis and increased risk of involvement of 3GCR-E

Evidence summary

A meta-analysis of 21 observational studies by Vardakas et al. compared all-cause mortality of carbapenem treatment versus alternative antibiotics in patients with community-acquired and healthcare-associated bacteraemia with ESBL-producing Enterobacterales.[90] Alternative antibiotics were beta-lactam/beta-lactamase inhibitors (BL/BIs), cephalosporins (mainly cefepime, which is currently not registered in the Netherlands), fluoroquinolones and aminoglycosides. Five studies were prospectively executed, 16 retrospectively. Studies were located in Asia (9 studies), Europe (6 studies) or the US (4 studies). In total, 1584 patients were included and overall mortality was 20 percent. The meta-analysis showed no difference in all-cause mortality between carbapenems and BL/BLIs for both empirical (RR 0.91, 95% CI 0.66–1.25) and definitive (RR 0.52, 95% CI 0.23–1.13) treatment of ESBL-positive bacteraemia. Carbapenems were associated with lower mortality than cefepime for empirical (RR 0.51, 95% CI 0.32–0.82) and definitive (RR 0.34, 95% CI 0.22–0.52) treatment. Patients treated with carbapenems had lower mortality compared to those treated with fluoroquinolones as empirical treatment (RR 0.34, 0.19–0.62), but not as definitive treatment (RR 0.63, 95% CI 0.34–1.15). A subgroup analysis for aminoglycoside-based treatment was not reported.

Another systematic review compared carbapenems to alternative antibiotics for the treatment of bloodstream infections caused by Enterobacterales with intrinsic, chromosomally encoded AmpC beta-lactamase (*Enterobacter, Serratia, Citrobacter, Providencia, Morganella* spp).[153] Eleven observational studies that assessed all-cause mortality of empirical and/or definite therapy were included. Alternative antibiotics were BL/BIs (piperacillin-tazobactam or ticarcillin-clavulanate), cefepime and fluoroquinolones. The meta-analysis showed no significant difference in mortality between BL/BLIs versus carbapenems for empirical therapy (OR 0.48; 95% CI 0.14–1.60) or definitive therapy (OR 0.87, 95% CI 0.32–2.36) and between cefepime versus carbapenems as empirical therapy (0.60; 95% CI 0.17–2.20) or as definitive therapy (OR 0.61; 95% CI 0.27–1.38). Patients treated with fluoroquinolones as definite treatment had lower odds of dying, probably reflecting the clinical stability that allowed for the only oral therapy option.

One randomized open-label trial compared ertapenem to cefepime and piperacillin-tazobactam for the treatment of febrile urinary tract infections due to ESBL-producing *E. coli*.[154] Almost one-third of patients had septic shock. Clinical success was defined as resolution of fever and symptoms of UTI present at entry with no development of new symptoms. Assignment to cefepime was stopped prematurely due to high failure rates (67% clinical failure in 6 patients). Piperacillin-tazobactam (n=33) and ertapenem (n=33) were equally effective (94% clinical cure). In both groups two patients (6%) had died at day 28.

A systematic review of observational studies summarized mortality of empirical treatment with a BL/BI versus carbapenems in patients with bacteraemia due to ESBL-producing Enterobacterales.[155] Types of BL/BI included in the studies were not reported. Similar to Vardakas et al.,[90] the authors found no significant difference in mortality between treatment arms for empirical and definite treatment.

The MERINO trial was an international, open-label, randomized controlled, non-inferiority trial comparing definitive therapy with piperacillin-tazobactam to meropenem in patients with bloodstream infections caused by ceftriaxone-resistant, piperacillin-tazobactam and meropenem sensitive *E. coli* and *K. pneumoniae*.[156] Bacteraemia originated from the urinary tract in 60% of patients, 86% of isolates was *E. coli* and 44% of infections was community-acquired. In 43% of patients a qSofa score ≥2 was recorded. Phenotypic ESBL production was found in 86% of isolates, while AmpC genes were found in 10.2% of isolates. The trial was stopped prematurely as it became very unlikely that continuation of the trial would show non-inferiority of piperacillin-tazobactam. In 378 evaluable patients 30-day all-cause mortality was 12.3% in patients treated with piperacillin-tazobactam and 3.7% in patients treated with meropenem (absolute risk difference 8.6%, 1-sided 97.5% CI - ∞ to 14.5, number needed to harm: 12). Results were consistent in the per-protocol analysis, among pre-specified subgroup analyses and in sensitivity analyses. There was no subgroup in which non-inferiority was shown, including in the subgroup with UTI as the source of bacteraemia and the lowest mortality. There were no significant differences between treatment arms on secondary outcomes including time to clinical and microbiologic resolution of infection, clinical success day 4, microbiologic resolution of infection and secondary infection with resistant MO or CDI. However, all showed a trend favouring meropenem. There was no sign of increased risk of developing infections with resistant microorganisms in the meropenem group, although numbers were small. Almost all deaths were not directly related to the primary infection.

A meta-analysis of Chen et al compared the effect of ceftazidime-avibactam or ceftolozane-tazobactam to alternative treatment strategies for complicated intra-abdominal infections (cIAI) or complicated urinary tract infections (cUTI) with ceftazidime-resistant gram-negative bacteria or ESBL-positive Enterobacterales.[157] Nine high quality RCTs assessing several clinical outcomes in patients with cIAI (5), cUTI (3) or both (1) were included. Overall mortality was 1.1%. There was no difference in clinical treatment success between BL/BI treatment and comparator treatment in the overall analysis (OR 1.07, 95%CI 0.80 – 1.44, 2934 patients). A subgroup analysis comparing BL/BI to meropenem showed no difference in clinical treatment success (OR 0.91, 95% CI: 0.65 – 1.26). Another subgroup analysis in patients with cUTI showed higher chance of clinical treatment success of BL/BI in patients treated for cUTI (OR 2.14, 95% CI 1.06 – 4.31. Two trials with levofloxacin and imipenem as alternative treatments). Patients treated with BL/BI had no significantly different mortality rate (OR 1.14, 95%CI 0.90 – 1.44) or rate of adverse events (OR 1.07, 95%CI 0.94 – 1.44) compared to alternative treatments, including for subgroups of patients with cIAI and cUTI. Three RCTs within the meta-analysis reported on ceftolozane-tazobactam efficacy in patients with ESBL-positive Enterobacterales infection at baseline in cIAI (2 RCTs, comparing to meropenem) and cUTI (1 RCT, comparing to levofloxacin). Clinical cure was higher in patients treated with ceftolozane-tazobactam (OR 2.89, 95% CI 1.18 – 7.09, 172 patients), although this significant difference was only based on the trial in cUTI comparing to levofloxacin. Popejoy et al. confirmed this finding separately based on pooled data on ESBL infections in two of the three trials.[158-160]

We found no RCTs on the effect of empirical aminoglycosides-based therapy in patients with sepsis or severe infections with 3GCR-E.

Except for the mentioned RCT in the systematic review of Chen et al.,[157] there are no RCTs on the effect of fluoroquinolones monotherapy in patients with sepsis or severe infections with 3GCR-E. Similarly, no RCTs were found on the effect of definite therapy with trimethoprim/sulfamethoxazole of such severe infections.

Conclusions

Conclusion	**Quality of evidence**
Pooled observational data in patients with bacteraemia due to ESBL-producing Enterobacterales show decreased mortality of empirical and definite treatment with carbapenems compared to cefepime	Very low[90]
Pooled observational data in patients with bacteraemia due to ESBL-producing Enterobacterales showed no additional effect on mortality of empirical and definite treatment with carbapenems compared to BL/BI	Very low[90,155]
One RCT in patients with bacteraemia with ESBL-producing *E. coli* and *K. pneumoniae* showed a large decrease in 30-day all-cause mortality of definite treatment with meropenem compared to piperacillin-tazobactam The same RCT showed no additional effect on adverse events and secondary infections with resistant microorganisms or *C. difficile*	High[156] Low[156]
Pooled observational data in patients with bacteraemia due to ESBL-producing Enterobacterales showed decreased mortality of empirical treatment with carbapenems compared to fluoroquinolones and no additional effect of definite treatment with carbapenems compared to fluoroquinolones	Very low[90]
There was insufficient data in patients with sepsis due to 3GCR-E to conclude on the effect of empirical treatment with aminoglycoside-based therapy	-
Pooled observational data in patients with bacteraemia due to chromosomally-encoded AmpC-producing Enterobacterales (such as *Enterobacter, Serratia, Citrobacter, Providencia* and *Morganella* species) showed no additional effect on mortality of empirical and definite treatment of carbapenems compared to BL/BI	Very low[161]
Pooled data from RCTs in patients with complicated intra-abdominal and urinary tract infections in general showed no additional effect on clinical cure, mortality and adverse events of newer BL/BI compared to alternative treatments (mainly meropenem)	Low[157]
Pooled data from RCTs in patients with complicated intra-abdominal and urinary tract infections due to ESBL-producing Enterobacterales showed increased clinical cure of ceftolozane-tazobactam compared to alternative treatments (mainly levofloxacin)	Low[157]

Other considerations

Providing evidence-based recommendations for empirical treatment of sepsis caused by Enterobacterales resistant to 3rd generation cephalosporins (3GCR-E) is complex. There is a lack of RCTs focussing on sepsis due to HRMO only and available studies are heterogeneous and have considerable limitations. Definitions and resistance testing of HRMO often differ between studies, in addition to the already mentioned limitations in chapter 3. Apart from mortality other outcomes are hardly assessed.

Carbapenems are not hydrolysed by ESBL and AmpC enzymes and are therefore generally considered an appropriate choice for the treatment of severe infections with gram-negative bacteria producing these enzymes. This is reflected by the available observational studies that compare alternative treatments to carbapenems in patients with sepsis or bacteraemia due to 3GCR-E.[90,153,155] However, the increasing use of carbapenems has been associated with increasing rates of carbapenem-resistance worldwide and the wish to use carbapenem-sparing treatments for antimicrobial stewardship purposes.[162]

The efficacy of beta-lactam/beta-lactamase inhibitors (BL/BIs) has been of specific interest in clinical practice, due to in vitro susceptibility of some 3GCR-E to these agents.[163] Three meta-analyses of observational studies showed no suggestion that the older BL/BIs (mostly piperacillin-tazobactam) are inferior compared to carbapenems for the treatment of bloodstream infections caused by bacteria producing ESBL[90,155] or with chromosomal AmpC (such as *Enterobacter, Serratia, Citrobacter, Providencia* and *Morganella* spp).[153,164] Also, the large European retrospective INCREMENT study compared BL/BI to carbapenem treatment in patients with bloodstream infections with ESBL-producing Enterobacterales that had in vitro sensitivity to the BL/BI (according to CLSI).[165] The authors found no difference in 14-day clinical cure and 30-day mortality between BL/BI and carbapenem treatment in their multivariate analysis. A similar post-hoc analysis of patients with ESBL-producing *E. coli* bacteraemia from six prospective cohorts showed comparable 30-day mortality after empirical and definite therapy with BL/BI (piperacillin-tazobactam or amoxicillin-clavulanic acid) compared to carbapenems.[99] A case-control study of patients with bacteraemia due to *Enterobacter*, *Serratia*, or *Citrobacter* species also found no differences in mortality and persistence of bacteraemia between BL/BI and meropenem or cefepime treatment.[166] Importantly, there were differences in source and severity of infection, in vitro susceptibilities and dosing strategies between the observational studies.[163,167] In addition, some individual studies within the meta-analyses suggested increased mortality in patients with ESBL bacteraemia and treatment with BL/BI compared to carbapenems.[168-170]

Concerns about increased mortality in severe infections with 3GCR-E treated with a BL/BI versus carbapenems have now been confirmed for *E. coli* and *K. pneumoniae* by the MERINO trial.[156] Although questions remain, the committee found the evidence on the difference in mortality convincing enough to currently recommend against the use of BL/BI and specifically piperacillin-tazobactam for the treatment of sepsis in patients at risk of or with proven involvement of 3GCR *E. coli* and *K. pneumoniae*. This also counts for definite therapy of patients who have recovered clinically. As 86% of isolates produced ESBL, it is very likely that the MERINO trial findings are generalizable to other ESBL-producing Enterobacterales. Future trials should assess if specific subgroups of patients can be safely treated with piperacillin-tazobactam. Suggested subgroups in the literature that could be treated with piperacillin-tazobactam are patients with urinary source of infection,[154] less severe infections, those infected with isolates with low MICs, Enterobacterales with certain types of ESBL-genes, *E. coli* (versus *Klebsiella spp*), or isolates that only produce chromosomally-encoded AmpC.[161,163]

The MERINO trial did not support the suggestion that piperacillin-tazobactam use is safe in patients with 3GCR-E bacteraemia and a urinary tract origin. In the primary analysis, the authors found no association of mortality with piperacillin-tazobactam MIC (although numbers per MIC were low) or *E. coli* vs *K. pneumoniae* infection. However, a post-hoc analysis of trial data included piperacillin-

tazobactam MICs by broth microdilution (BMD) in the analyses.[171] It showed that with BMD 17.8% of these bacteria would have been categorized as resistant to piperacillin-tazobactam according to EUCAST criteria (breakpoint at MIC 8 mg/L) while 6.4% would be resistant according to the Clinical and Laboratory Standards Institute from the US (CLSI, who have set the breakpoint at an MIC of 16 mg/L). The microbiological modified intention to treat analysis of the MERINO trial data showed increased mortality in patients with isolates with piperacillin-tazobactam BMD MICs > 16 mg/L (adjusted OR 2; 95% CI 1.3 – 3.4). An important limitation of the MERINO trial is that drugs were administered in intermittent dosing intervals. Prolonged infusion of beta-lactams, especially of piperacillin-tazobactam could have influenced efficacy (see also chapter 10).

There are conflicting opinions in the literature whether piperacillin-tazobactam is a treatment option for severe infections caused by Enterobacterales with chromosomally-producing AmpC.[161] There are concerns that strains become resistant to piperacillin-tazobactam during therapy as is shown in vitro and clinically with 3rd generation cephalosporins for *Enterobacter* bacteraemia.[172] However, piperacillin-tazobactam is only a weak inducer of chromosomal AmpC compared to amoxicillin-clavulanic acid and 3rd generation cephalosporins. There is only one study suggesting in vitro induction of high-level AmpC production and there is no guidance by EUCAST on this topic. Observational studies have concluded that piperacillin-tazobactam may be a treatment option in comparison to carbapenems, but no randomized trials are available.[153]

For the newer BL/BI's ceftazidime-avibactam and ceftolozane-tazobactam, the mentioned meta-analysis of Chen et al. showed that there might be place for these treatments in intra-abdominal and urinary tract infections caused by ESBL-producing Enterobacterales. However, sepsis patients were hardly included. In addition, because of the activity of the newer BL/BIs against carbapenemase-producing Enterobacterales (CPE), the general opinion of the committee was to reserve these agents to the treatment of infections with CPE. Emergence of resistance to these agents has been reported.[173,174]

Fluoroquinolones were less effective than carbapenems as empirical therapy in observational studies on ESBL-producing Enterobacterales bacteraemia, while equally effective as definitive therapy.[90] This difference probably reflects again the importance of in vitro susceptibility of the strain. The previously mentioned retrospective, European INCREMENT study on bacteraemia with ESBL-producing Enterobacterales also compared outcomes of patients treated with aminoglycosides or fluoroquinolones to patients treated with carbapenems.[175] Although numbers were very low, there were no differences between treatments with regard to mortality, clinical failure and length of stay. In ESBL-producing Enterobacterales, the prevalence of resistance to fluoroquinolones and aminoglycosides have been found to be high in some publications.[176] Nethmap data presented in chapter 2 showed that in the Netherlands approximately two third and one third of ESBL-producing *E. coli* isolates in blood culture are fluoroquinolone and aminoglycoside resistant, respectively.

The previously discussed study of Ong et al. showed that a strategy preferring carbapenem over aminoglycosides-based treatment in empirical treatment of 3GCR-E sepsis in the Dutch university ICU setting led to an increase of carbapenem use of 9%.[64] A carbapenem-based strategy in 3GCR-E sepsis would therefore likely further increase carbapenem use in the Netherlands, which is unwanted from an antibiotic stewardship perspective. It should be noted that that an aminoglycoside-based regimen

may be a potentially less effective and more toxic strategy compared to carbapenem treatment in patients with sepsis (chapter 6a). Also, approximately 1/3rd of ESBL-E in the Netherlands is resistant to aminoglycosides (chapter 2). In conclusion, depending on the perspective, both strategies have important limitations. In summary and as discussed in chapter 6a, the committee has concerns on aminoglycoside efficacy and safety, but does support the use of short-term (max. two days), empirical therapy including aminoglycosides as a carbapenem-sparing strategy.

Only very old reports and one recent observational studies have shown efficacy of definite therapy trimethoprim/sulfamethoxazole in serious gram-negative infections, including due to ESBL and chromosomal AmpC-producing Enterobacterales. No randomized trials are available.

Regarding empirical therapy in patients with sepsis the committee settled that in those patients with a high risk of 3GCR-E involvement based on prior infection or colonization (chapter 3, recommendation 1), we suggest to treat with a carbapenem. This recommendation especially counts for those patients with previous colonisation with ESBL-producing Enterobacterales that had co-resistance to fluoroquinolones and aminoglycosides (versus other causes of 3GCR). Alternative treatment strategies are listed in **Table 7**. We settled that from an antibiotic stewardship perspective a carbapenem-sparing empirical treatment strategy for sepsis is reasonable in patients at increased risk of 3GCR-E involvement, but no known prior (1 year) infection/colonization with 3GCR-E (chapter 3, recommendation 2) . Potential empirical treatment strategies are listed in **Table 7**.

For definite therapy of patients with sepsis due to ESBL-producing Enterobacterales, the committee recommends against the use of piperacillin-tazobactam, based on the current evidence from the MERINO trial. The committee considers a carbapenem or ciprofloxacin as appropriate *definite* therapy in case of proven susceptibility. Although there is lack of evidence, we agreed that trimethoprim/sulfamethoxazole is an appropriate alternative as *definite* therapy in case of proven susceptibility after clinical improvement. After discussion, the committee settled that no recommendation can be given for or against empirical and definite piperacillin-tazobactam therapy in sepsis due to chromosomal AmpC-producing Enterobacterales. For recommendations on antimicrobial de-escalation, see chapter 10.

Recommendations

Recommendation	**Strength**	**Quality of evidence**
23. In patients with sepsis and high risk of involvement of 3GCR-E based on prior (1 year) infection/colonization, we recommend meropenem or imipenem as empirical antibacterial therapy. Alternative strategies are listed in **Table 7**	Strong	Moderate
24. In patients with sepsis and increased risk of involvement of 3GCR-E but no prior (1 year) infection/colonization, we suggest that a carbapenem-sparing strategy (listed in **Table 7**) is acceptable	Weak	Very low
25. We cannot provide a recommendation for or against empirical or definite treatment with piperacillin-tazobactam in patients with sepsis due	-	-

to chromosomal AmpC-producing Enterobacterales (such as *Enterobacter, Serratia, Citrobacter, Providencia* and *Morganella* spp)		
26. In patients with sepsis due to ESBL-producing Enterobacterales, we recommend against piperacillin-tazobactam as definite antibacterial therapy regardless of the in vitro susceptibility	Strong	Moderate

Table 7. Alternative empirical treatment strategies in sepsis and increased or high estimated risk of involvement of 3GCR-E

Estimated risk of involvement of 3GCR-E	Choice	Empirical treatment strategy	Advantages	Disadvantages	Note
Increased risk	1st	2GC/3GC plus an aminoglycoside (plus metronidazole when applicable)	Carbapenem-sparing Fluoroquinolone-sparing	Potentially higher risk of adverse events compared to other choices TDM and max 2 day treatment for aminoglycoside Approximately 1/3rd of ESBL-producing Enterobacterales is resistant to aminoglycosides	Equivalent treatment option when there is no known renal insufficiency
	1st	Meropenem or imipenem	Only beta-lactam component of sepsis therapy Potentially lower toxicity profile, especially in case of renal insufficiency	Very broad-spectrum	Equivalent treatment option
	Alternative	2GC/3GC plus high dose ciprofloxacin (plus metronidazole when applicable)	Carbapenem-sparing Aminoglycoside-sparing	Approximately 2/3rd of ESBL-producing Enterobacterales is ciprofloxacin-resistant Risk of adverse events	Optional when local ciprofloxacin resistance allows its empirical use
High risk	1st	Meropenem or imipenem	Only beta-lactam component of sepsis therapy Potentially lower toxicity profile, especially in case of renal insufficiency	Very broad-spectrum	Preferred treatment option, especially when there was previous resistance to aminoglycosides or ciprofloxacin or risk of toxicity (e.g. known renal insufficiency)
	Alternative	2GC/3GC plus an aminoglycoside (plus metronidazole when applicable)	Carbapenem-sparing, Fluoroquinolone-sparing	Potentially higher risk of adverse events compared to other choices TDM and max 2 day treatment for aminoglycoside Approximately 1/3rd of ESBL-producing Enterobacterales is resistant to aminoglycosides	Optional when local resistance epidemiology allows, when there is no sepsis (yet) and/or when the previously cultured 3GCR-E was susceptible

	Alternative	2GC/3GC plus high dose ciprofloxacin (plus metronidazole when applicable)	Carbapenem-sparing Aminoglycoside-sparing	Nationally, approximately 2/3rd of ESBL-producing Enterobacterales is ciprofloxacin-resistant	Optional when local ciprofloxacin resistance allows its use and/or when previously cultured 3GCR-E was susceptible
	Alternative	Piperacillin-tazobactam	Carbapenem-sparing Fluoroquinolone-sparing Aminoglycoside-sparing	Likely inferior in ESBL-producing 3GCR-E sepsis	Only optional when the previously cultured 3GCR-E did not produce ESBL and was susceptible to piperacillin-tazobactam

6c. Antibacterial therapy in patients with sepsis and increased risk of involvement of Staphylococcus aureus

Evidence summary

We found no systematic reviews comparing the effect of empirical broad-spectrum beta-lactams or aminoglycoside treatment to empirical beta-lactam treatment specifically aimed at methicillin-susceptible *S. aureus* (penicillinase-resistant penicillins and first generation cephalosporins) in patients with sepsis that later turns out to be due to methicillin-susceptible *S. aureus*.

Conclusions

Conclusion	Quality of evidence
There are no RCTs or systematic reviews comparing empirical broad-spectrum beta-lactams to empirical treatment specifically aimed at methicillin-susceptible *S. aureus* (penicillinase-resistant penicillins and first generation cephalosporins) in patients with sepsis that later turns out to be due to methicillin-susceptible *S. aureus*	-

Other considerations

There is no high quality evidence available to provide guidance on the choice of empirical therapy in patients with sepsis in which *S. aureus* is likely to be involved. In these patients broader spectrum empirical therapy with optimal activity against *S aureus* is needed while awaiting culture results for definite therapy. Some studies suggest that second or 3rd generation cephalosporins or beta-lactam beta-lactamase inhibitors with or without aminoglycosides as empirical therapy are inferior compared to antistaphylococcal penicillins or cefazolin,[177,178] while other studies support empirical therapy with some of the other beta-lactams.[179] Also for definite therapy with ceftriaxone for *S. aureus* bacteraemia, only a handful retrospective studies with conflicting results are available.[178,180-184]

The committee ultimately settled that until more high quality data is available, empirical treatment options in patients with sepsis in which *S. aureus* is likely to be involved include all beta-lactams that show in vitro susceptibility to *S. aureus*. Based on PK/PD principles and in line with EUCAST recommendations, we suggest high dosing of ceftriaxone (two times daily 2 grams in normal renal function) or cefotaxim (three times daily 2 grams in normal renal function) in patients with sepsis and substantial risk of *S. aureus* involvement.[185] Alternative treatment strategies are listed in **Table 8**. The committee settled that the clinician should decide on an individual patient basis which strategy is most appropriate.

For definite therapy of *S. aureus* sepsis, we follow the NVMM guideline on *S. aureus* bacteraemia which recommends flucloxacillin in patients with *S. aureus* bacteraemia with cefazolin as an alternative when flucloxacillin is (relatively) contraindicated.[7]

Recommendations

Recommendation	Strength	Quality of evidence
27. There is insufficient evidence to recommend against empirical use of other beta-lactam antibiotics than flucloxacillin or cefazolin in patients with sepsis in which *S. aureus* is a likely pathogen. Empirical sepsis treatment strategies when there is a substantial risk of *S. aureus* involvement are listed in **Table 8**	-	-
28. For definite therapy of patients with sepsis due to *S. aureus*, we refer to the Dutch guideline on *S. aureus* bacteraemia.[7]		

Table 8. Alternative empirical treatment strategies in sepsis and suspected *S. aureus* involvement

Empirical treatment strategy	Advantages	Disadvantages	Note
3GC high dose	Potentially better *S. aureus* PK/PD compared to standard dose 3GC	Clinicians may not be used to higher dosing	In accordance with EUCAST recommendation
Flucloxacillin-based therapy	Optimal *S. aureus* therapy	Combined with ciprofloxacin or aminoglycoside: no beta-lactam treatment for gram-negative pathogens; aminoglycoside: higher risk of adverse events, TDM needed. Combined with additional beta-lactams: potentially high fluid loads	
3GC standard dose	No difference in 3GCR-E dosing compared to regular empirical sepsis therapy	Potentially suboptimal *S. aureus* PK/PD	Not in accordance with EUCAST
Cefuroxime-based therapy	Potentially better *S. aureus* PK/PD compared to 3GC standard dose	Potentially less optimal Enterobacterales PK/PD compared to 3GC	
Piperacillin-tazobactam		Broad-spectrum	
Meropenem or imipenem		Very broad-spectrum	Primarily reserved for patients at high risk of 3GCR-E
Vancomycin-based therapy		Potentially inferior treatment of *S. aureus* (compared to flucloxacillin) TDM needed	Optional when beta-lactams are contra-indicated

7. What is the optimal empirical antibacterial therapy of sepsis in patients with a penicillin allergy?

Introduction

In the setting of a patient presenting with sepsis, a concurrent immediate type allergic reaction (also known as 'type I' or 'IgE-mediated' allergic reaction') potentially results in a worse treatment outcome. This is because the symptoms of an immediate type allergic reaction – in particular anaphylactic shock - evoked by exposure to an antibiotic, would superimpose on the hemodynamic consequences of sepsis and could impair oxygenation by airway obstruction.[186] Though encountered rarely, this scenario is feared by clinicians treating patients with sepsis.

A label for an allergic reaction to beta-lactam antibiotics (mainly penicillin) is registered as frequent as in one in every ten patients.[187,188] However, a drug allergy label is often incorrect.[189,190] The presumed allergy is frequently self-reported and the label in the patient file frequently lacks discrimination between immunologically mediated drug reactions and intolerance, toxicity, or even symptoms of disease. In the event of a reported possible antibiotic allergy, an antibiotic or an entire class of antibiotics may be undeservedly avoided. As a result, the optimal, i.e. the most effective, narrow spectrum, least toxic, antibacterial therapy may not be administered.

Hence, In the setting of the patient presenting with sepsis, prudent decision-making concerning allergy and antibacterial therapy is warranted. Optimal and timely empirical antibacterial therapy positively influences patient outcome, whereas severe immunologically mediated adverse events, i.e. an immediate type allergic reaction, may do the opposite. The choice for a particular empirical antibacterial regimen is the result of clinical risk assessment and an absolute guarantee for the absence of an immediate type allergic - or other - drug reaction to the administered antibacterial therapy can never be given.[191,192] In this chapter, we aimed to summarize evidence on optimal empirical therapy in patients with sepsis and a reported penicillin allergy. In the nearby future, a SWAB guideline on beta-lactam allergy will be developed. We refer to this guideline as soon as it is published.

Evidence summary

No studies with a randomized design nor systematic reviews could be included.

Conclusions

Conclusion	Quality of evidence
There are no RCTs or systematic reviews comparing the effect of beta-lactams to alternative treatments in patients with sepsis and reported penicillin allergy	-

Other Considerations

In patients with sepsis, treatment avoiding any beta-lactam upon reported penicillin allergy is frequently chosen. However, accumulating data from observational cohort studies indicates that this negatively affects treatment outcome.[193,194] This may be either caused by less effective therapy or

increased toxicity by the antibiotic that replaced the beta-lactam antibiotic.[195] Since allergy tests cannot be used at this time, the committee agreed that a practical probability guided approach provides a rational alternative.

Standard approach to the patient reporting penicillin allergy

Medical history taking is key in determining the likelihood of the presence of a reported drug allergy. The collected data should contain information about the antibiotic involved, the timing of the presumed allergic reaction, the type of symptoms, the outcome of allergy tests if performed, the severity and the information about later re-exposure or exposure to other antibiotics.[190,192] As many as ten percent of hospitalized patients have their patient file marked with a label penicillin allergy. One of the reasons is that the difference between side effects, symptoms of the disease at that time, and immunologically mediated adverse events are - at least semantically - not appreciated. This causes an over-reporting of 'allergy', which is shown by studies in which negative skin tests were observed in vast majority (roughly 85-95%) of people who reported penicillin allergy.[190,191,196] Hence, in a patient that is not critically ill, adequate history taking is the first step to assess the a priori risk for the presence of penicillin allergy.

Several studies indicated that immediate type allergy to penicillins, and in particular to amoxicillin, gradually wanes over time.[197,198] Blanca et al. showed that in patients with an IgE-mediated skin test proven allergic reaction to penicillin, the reaction is no longer present in 50% of patients after 5 years and in 80% of patients after 10 years.[199] The committee therefore agreed that the time that elapsed since the presumed allergic reaction is therefore relevant in the approach to a patient with a reported allergy. The longer ago the event took place, the smaller the risk that an immediate type allergic reaction will occur after re-exposure.

Literature shows that skin tests can be used to determine the presence of an immediate type allergy to penicillin.[197,198,200] Several studies that explored the bedside use of these tests point to the feasibility of their use and efficacy with regard to optimization of antibacterial therapy.[196,201] However, at the moment of initiating empirical treatment of sepsis, the time for bedside testing is lacking for obvious reasons. In addition, test characteristics in the immediate post-acute sepsis phase in which most patients will still suffer from immunosuppression or immune anergy are ill defined.[202] Therefore, the application of these tests will not be further discussed here.

Cross-reactivity: penicillins and cephalosporins

Within the different classes of beta-lactam antibiotics allergic cross reactions may occur. Cross reactions within beta-lactam antibiotics, e.g. between penicillins and cephalosporins, can be caused by an immunological, IgE mediated reaction directed against the conserved parts of the beta-lactam structure or against the R1 side chain. Before 1980 cephalosporin preparations were often contaminated with ordinary penicillin moieties. After administration, this resulted in the formation of Penicilloyl Poly-L-lysine (PPL) as degradation product of ordinary penicillins. This immunogenic molecule is estimated to account for up to approximately 75% of the immediate type allergic reactions caused by ordinary penicillins.[203] Importantly, PPL is not formed as a degradation product of cephalosporins and carbapenems. In a review of studies published after 1980, the incidence of cross reactivity was estimated to be only 1.9% (8/417) in patients who had a positive penicillin skin test.[204] Moreover, anaphylactic shock did not occur in >50% of the cases that were regarded to have

experienced a cross-allergic immediate type reaction. Instead, more mild reactions, e.g. only urticarial rash, predominated. Hence, the risk of a more severe allergic cross reaction is more likely to be <1%.

Because the major determinant, PPL, is not involved in cross-reactions with cephalosporins, resemblance of the side chain (R1) may be of particular immunological importance. It is known which side chains of penicillins correspond to certain side chains of cephalosporins.[192] By selecting a cephalosporin for sepsis therapy that does not have an identical side chain compared to the original penicillin that caused the presumed allergic reaction, the risk of a cross allergic reaction can be further reduced. All intravenous cephalosporins that are used in the Netherlands do not have an identical side chain compared to the penicillins.[192,205]

Cross-reactivity: penicillins and carbapenems

Less data is available about cross-allergy between penicillins and carbapenems. Several older studies indicated that cross-allergy rates may be as high as 10-25%. However, a systematic review in 2014 reported cross-allergic reactions in only 0.3% of patients (n=295) with a previous positive skin test to penicillin.[206] With regard to other adverse events (e.g. toxicity) a higher frequency of overlap was observed. In a study with n=211 patients with documented positive skin tests for penicillin underwent skin testing with carbapenems and a subsequent graded challenge. None (0%) of the subjects developed an immediate type reaction.[207] Based on these data, the guideline committee agreed that carbapenems can be administered to patient with a penicillin allergy label with extremely limited risk of an immediate type, cross-allergic reaction.

A probability guided approach to the patient with sepsis and reported allergy to penicillins

Based on the described literature, the committee agreed on the following practical probability guided approach (**Table 9**). A brief medical history about the allergy should be performed if allowed by the patients' condition. When the patients' medical history reveals that the previous reaction can be easily recognized as not immune mediated (i.e. not allergic), penicillins, cephalosporins and carbapenems may all be administered with an extremely limited, i.e. baseline risk, of an immediate type allergic reaction. When the medical history shows a severe delayed type reactions e.g. Stevens-Johnson syndrome (SJS), toxic epidermic necrolysis (TEN), tubulointerstitial nephritis (TIN) on a beta-lactam antibiotic, this beta-lactam class should be avoided.

If the medical history reveals that the time of the possible immediate type reaction to a penicillin was over 10 years ago, and if only a few mild to moderate symptoms compatible with an immediate type reaction occurred, or in the situation that no information can be obtained about a registered allergy label in a patient with sepsis, the a priori probability of the presence of a true immediate type allergy is estimated to be 5-10%, or even lower when a this reaction occurred >10 years ago.[190,198,199] Then, the probability of a severe allergic cross-reaction to cephalosporins or carbapenems is extremely low (<0.1%).[204] The committee therefore suggests against a challenge with a penicillin during sepsis and suggests that a cephalosporin or carbapenem can be used in these patients with sepsis. When the patient has recovered from sepsis, we recommend skin testing to confirm or rule out allergy to beta-lactams and/or controlled challenge with a beta-lactam to enable optimization of antibacterial therapy in future infections.

If the possible immediate type reaction occurred <10 years ago and/or if the reaction was severe (i.e. anaphylactic shock, airway obstruction etc.), the risk of re-occurrence of a severe immediate type reaction is generally considered higher than in all other groups. Therefore, the committee recommends against re-exposure to a penicillin during sepsis in this population. Because the probability of a severe allergic cross-reaction to cephalosporins or carbapenems is still very low (<1%), we suggest that a cephalosporin or carbapenem can be used in these patients with sepsis. If a cephalosporin has been administered safely during previous hospitalizations, but after the moment of the reaction to the penicillin, cephalosporins should be considered safe for treatment of the sepsis. Also in these patients skin testing and/or controlled challenge with a beta-lactam may be considered to confirm or rule out allergy to beta-lactams when the patient has recovered from sepsis.

In case of a reported cephalosporin or carbapenem allergy label, the committee suggest to temporarily avoid the beta-lactam class and consult an expert for definite antibiotic therapy. If administration of beta-lactam antibiotics is not regarded safe, the committee suggests to use an antibiotic with equivalent antibacterial spectrum, e.g. a fluoroquinolone or an aminoglycoside in combination with a glycopeptide.

Table 9. Empirical antibacterial therapy of sepsis in patients with a penicillin allergy label.

Available allergy label data for penicillins (e.g. amoxicillin, amoxicillin-clavulanic acid, flucloxacillin, penicillin G)	**Administration of a penicillin during sepsis**	**Administration of a cephalosporin or carbapenem during sepsis**
Immediate type or delayed type* reaction very unlikely	Yes	Yes
Possible immediate type reaction occurred >10 years ago AND symptoms were mild to moderate	No**	Yes
Possible immediate type reaction occurred <10 years ago AND/OR reaction was severe (i.e. anaphylactic shock, airway oedema etc.)	No**	Yes***
Allergy testing previously confirmed immediate type penicillin allergy	No	Yes***
Information about the allergy label is not available	No**	Yes

***:** In case of delayed type reactions e.g. Stevens-Johnson syndrome (SJS), toxic epidermic necrolysis (TEN), tubulointerstitial nephritis (TIN), on a beta-lactam antibiotic, avoid the respective penicillin and choose alternative treatment or consult expert

**: After the patient has recovered from sepsis, skin testing and/or controlled challenge with a beta-lactam may be considered to confirm or rule out allergy to beta-lactams

***: Risk of a severe immediate type cross allergic reaction is still estimated to be <1%; Exposure may be avoided until skin-tests or controlled challenge is possible.

Recommendations

Recommendation	Strength	Quality of evidence
29. In patients with sepsis and a reported penicillin allergy, we recommend to obtain information (i.e. medical history and skin test results) about the presumed allergy if possible	Strong	GPS
30. In patients with sepsis and a reported penicillin allergy but in whom the allergy is very unlikely, we suggest that penicillins can be used if needed (see **Table 9**)	Weak	Very low
31. In patients with sepsis and a reported penicillin allergy that was proven, possible or unspecified, we suggest to avoid penicillins during the primary sepsis treatment and to choose alternative beta-lactams (cephalosporins, carbapenems)	Weak	Very low
32. In patients with sepsis and an unspecified or possible immediate type penicillin allergy, we suggest to plan penicillin allergy testing and/or a controlled penicillin challenge when the patient has recovered from sepsis	Weak	Very low

III Timing and duration of antibacterial therapy in sepsis

Introduction

In the previous edition of the SWAB sepsis guidelines, it was recommended to start antibacterial therapy in adult patient with severe sepsis and septic shock as soon as possible, preferably within the first hour of presentation. This recommendation is in line with the recommendations of the SSC guidelines**,** including the recently updated hour-1 sepsis bundle stressing the importance of the first golden hour and stating that antibacterial therapy should be started *immediately* for patients presenting with sepsis or septic shock.[36,208] However, the importance of this one hour time frame is currently being debated. In fact, the Infectious Diseases Society of America (IDSA) recently stated that IDSA didn't support the SSC recommendation on antibiotic timing in sepsis, particularly the formulation of this fixed 1 hour time period within which antibiotics should be administered.[121] In chapter 9 we summarized the available evidence on the topic.

Duration of antibacterial therapy in patients with sepsis and/or bacteraemia has historically been based on expert opinion. In studies determining treatment duration practices for patients with bacteraemia, patients were generally treated for 7 to 14 days, but with wide variation.[209-211] Longer duration of antibacterial treatment is associated with development of antimicrobial resistance and with adverse events, such as bacterial superinfections, *Clostridium difficile* infection and death.[212-217] Several studies have critically assessed if shorter duration of antibacterial treatment is as effective and safe as longer duration in patients with sepsis. In chapter 10 we summarized evidence on the treatment duration of sepsis in general or of unknown origin and of sepsis due to VAP/HAP, intra-abdominal infection and SSTI. In addition, we summarized evidence on PCT-guided treatment duration and de-escalation in patients with sepsis.

8. What is the optimal timing of empirical antibacterial therapy in patients with sepsis?

Evidence summary

Sterling et al. performed a systematic review and meta-analysis regarding the impact of timing of antibiotic administration on outcome in severe sepsis and septic shock patients.[218] The review included 11 observational studies. A total of 16.178 patients were evaluable for the effect of antibiotic administration within 3 hours after triage at the emergency department (ED). Patients who received antibiotics more than 3 hours after ED triage had similar mortality rates compared to patients who received antibiotics within 3 hours after ED triage (OR 1.16, 95% CI 0.92 to 1.46). A total of 11.017 patients were evaluable for the effect of antibiotic administration within 1 hour after recognition of severe sepsis/septic shock. Patients who received antibiotics more than 1 hour after severe sepsis/shock recognition had similar mortality rates compared to patients who received antibiotics within 1 hour of recognition (OR 1.46, 95% CI 0.89 to 2.40), but with heterogeneity between studies. A sensitivity analysis including 7074 patients showed no significantly increased mortality for each additional hour delay in antibiotic administration from recognition of severe sepsis and septic shock.

After publication of the 2015 meta-analysis, one multicentre, open label, randomized trial was published.[49] The previously described PHANTASi trial by Alam et al. assessed the impact of prehospital antibiotic administration in 2698 patients with sepsis, including severe sepsis (58%) and septic shock (4%). This Dutch multi-centre study compared the effects of early administration of antibiotics in the ambulance with standard of care. The 28-day mortality was similar in the intervention and standard of care group (RR 0.95 CI 0.74 – 1.24), regardless of the severity of sepsis. There were no differences in ICU admissions, length of hospital stay and/or 90 day mortality, but readmission was less likely in the intervention group (7 versus 10%, p<0.001). Reasons for re-admission were left unexplained in the manuscript. Median time to antibiotic administration after ED arrival in the standard of care group showed a non-significant decrease after training of the ED staff (93 minutes (IQR 39-140) before versus 70 minutes (IQR 36-128) after training, respectively, p 0.14).

Two key observational studies have been published after the 2015 meta-analysis.[219,220] Seymour et al. retrospectively reviewed the influence of time to treatment of 49.331 patients with sepsis and septic shock.[219] They showed that a more rapid completion of the 3-hour bundle of sepsis care was associated with a lower risk-adjusted in-hospital mortality. Also, longer time to antibiotic initiation was associated with an increased in-hospital mortality risk (OR 1.04 for each hour delay, 95% CI 1.02 – 1.05). However, this effect was only seen in those patients with septic shock who received vasopressors. The other retrospective observational study by Liu et al. in 35.000 sepsis patients showed that the adjusted OR for mortality based on each hour delay between antibiotic administration and ED registration was 1.09 (95% CI 1.05 – 1.13).[220] Mortality increased with 0.3% for sepsis (95% CI 0.01 – 0.6), 0.4% for severe sepsis (95% CI 0.1 – 0.8) and 1.8% for septic shock (95% CI 0.8 – 3) for each hour delay.

Conclusions

Conclusion	**Quality of evidence**
Pooled data in patients with sepsis showed no additional effect of antibiotic administration within 3 hours of ED triage or within 1 hour of severe sepsis/septic shock recognition on mortality	Very low[218]

One randomized trial in patients with sepsis showed no additional effect of pre-hospital antibiotic administration compared to usual care on 28-day mortality	Low[49]
Two large observational studies in patients with sepsis showed that longer time to antibiotic administration was associated with increased mortality in patients with septic shock.	Low[219,220]
Two large observational studies in patients with sepsis showed conflicting effects of longer time to antibiotic administration for patients with sepsis and severe sepsis (excluding patients with septic shock)	Very low[219,220]

Other considerations

The recommendation on timing of antibiotic therapy in patients with sepsis in the previous SWAB sepsis guideline was mainly based on the results of the landmark study by Kumar et al. in 2006 showing that each hour delay in antibiotic therapy resulted in an average decrease in survival of 7.6%.[24] Since then, other retrospective observational studies underlined Kumar's findings forming the basis for the recently updated recommendations of the SSC guidelines.[208,219-221] The one more recent meta-analysis, which included the aforementioned observational studies, however did not show a significant mortality benefit of administering antibiotics within 3 hours of ER triage or within 1 hour of shock recognition in sepsis.[218] In line, the one randomized trial on this topic could not demonstrate an effect of faster (prehospital) antibiotic administration for sepsis on outcome in a Dutch setting.[49] This study however only included only a small number of patients with septic shock.

There are several limitations related to the observational character of most of these studies that are important to consider when using the results to formulate recommendations on antibiotic timing in sepsis. First of all, time zero is open to multiple interpretations and difficult to define as the exact onset of infection is generally unknown. Studies use different definitions of time zero including time of presentation to the ED, onset of hypotension or time of initiation of the sepsis bundle. Moreover, the question is which endpoints are to be chosen, e.g. time to administration of the first antibiotic, of all antibiotics or of antibiotics that are actually active *in vitro.* In any case, the exact time between the onset of infection and antibiotic administration is variable, at least to some extent and therefore the biological plausibility that each additional hour delay of antibiotic administration has such a huge impact on survival could be argued.[222] Second, in most studies the appropriateness of the antibiotic regimens is not taken into account. Although there is also considerable heterogeneity in definitions of this parameter, information on whether the micro-organism cultured is susceptible to the empirical broad spectrum antibiotic regimen chosen, is of importance when interpreting the impact of timing of antibiotic administration in sepsis. It is of importance however to note that in a considerable part of sepsis patients, no causative pathogen is identified and thus appropriateness of antibiotic regimens cannot be assessed. Third, when considering the importance of rapid antibiotic administration, the proportion of patients in which antibiotics were unjustified because of the absence of infection should be taken into account. In this context, a recent Dutch study showed that only 57% of all patients admitted to the ICU for presumed sepsis, were actually considered as having either probable or definite infection meaning that a fair proportion of patients did not have an actual infection and received unnecessary antibiotics.[31] It is well known that antibiotic use has potential harmful consequences such as infection with *Clostridium difficile,* side effects, allergies and the emergence of drug resistance. A fourth drawback of observational studies is confounding by indication.[223] On the one hand, delay in antibiotic administration in patients with presumed sepsis could imply difficulties in the

diagnostic process as well as to the choice of empirical antibiotic regimen due to multi-drug resistance in a complex patient. On the other hand, more rapid antibiotic administration could also be related to disease severity as it is reasonable to assume that critically ill patients receive antibiotics at the earliest possible, but perhaps at the cost of appropriateness as not enough time has been spent on reviewing the medical and microbiological histories of the patient including valuable information on potential drug-resistance and former allergic reactions.

Taken all of this into account, it seems reasonable to state that in the critically ill patients with septic shock, there is little margin for error and therefore to administer antibiotics as soon as possible. This is supported by the results of Seymour et al. and Liu et al. showing that the impact of antibiotic delay was most pronounced in the patients with septic shock.[219,220] On the other hand, in patients with less severe disease, rapid antibiotic administration should be weighed against the negative impact of potentially unjustified antibiotic use when the patient turns out not to suffer from sepsis.[121,222,223] In patients with less-severe disease there is often more time for gathering appropriate diagnostic information and – in some cases – even prevent the administration of broad-spectrum antibiotics.

The SWAB sepsis guidelines committee therefore agreed to follow the view point of the IDSA arguing against defining a fixed time point within which antibiotics should be administered under all circumstances in patients with sepsis and septic shock. In line with the results published by Alam et al. on the impact of ED staff training on time to antibiotic administration and with the recent IDSA position statement, the committee encourages the efforts to improve the process of antibiotic administration once the decision is made by the physician to start antibiotic therapy in patients with presumed sepsis.[49,121]

Recommendations

Recommendation	Strength	Quality of evidence
33. In patients with sepsis or septic shock, we recommend that the administration of antibacterial treatment should be initiated promptly with health care systems working to reduce that time to as short a duration as feasible	Strong	Low

9. What is the optimal duration of antibacterial treatment for sepsis?

Evidence summary

Antibacterial treatment duration in patients with sepsis

We found no RCTs on the optimal treatment duration in adults with sepsis of unknown origin, sepsis due to cholangitis or sepsis due to suspected infected CVC. Several studies addressed optimal treatment duration in patients with gram-negative bacteraemia, VAP/HAP as well as patients with severe abdominal infections.

One randomized multicentre open-label non-inferiority trial performed in Israel and Italy compared 7 to 14 days of antibiotic therapy in 604 patients with gram-negative bacteraemia.[224] The source of

infection was the urinary tract in 68%, intra-abdominal in 12% and primary bacteraemia in 8% of patients. Gram-negative bacteria identified were Enterobacterales (90%, the majority being *E. coli*) and non-fermenters (9%, the majority being *P. aeruginosa*). Median SOFA score was 2 (IQR 1-3). Patients treated for 7 days had a similar outcome at 90 days, defined as a composite of mortality, clinical failure, re-admission or extended hospitalization, when compared to patients treated for 14 days with antibiotics (absolute risk difference: -3.9%, 95% CI, -11.9 % to 4.0%). There were no differences in adverse events. Results of a similar large multicentre trial are expected in 2022 (ClinicalTrials.gov Identifier: NCT03005145).[225]

Several meta-analysis studied short- versus long-duration of antibiotic regimens for VAP and HAP in critically ill adults.[37,226,227] One of these was performed by the IDSA HAP/VAP guideline committee which included additional information from the conductors of the individual RCTs.[37] The majority of studies included patients with sepsis, septic shock or severe illness, but data on sepsis patients were not available separately. These meta-analysis showed that a fixed period of 7 to 8 days of antibiotic treatment duration did not result in differences in 28-day mortality, clinical cure or incidence of recurrent pneumonia when compared to a longer, 10 to 15 day antibiotic treatment duration. For the subgroup of patients with VAP due to non-fermenting gram-negative bacilli, the meta-analysis showed no difference between treatment duration groups in mortality, clinical cure and recurrences.

In 2015 a trial from the US on the appropriate duration of antibacterial therapy of intra-abdominal infections was published.[228] The study compared a fixed duration of four days of antibiotics to antibiotics until two days after resolution of symptoms with a maximum duration of 10 days in patients with complicated intra-abdominal infection and adequate source control. Mean APACHE II score was 10, although this score was not reflected in the overall low study mortality of 1%. There was no difference between patients treated for four days and patients treated until two days after resolution of symptoms (5-10 days) in the composite outcome of surgical-site infection, recurrent intra-abdominal infection and 30-day mortality. There were no differences in the occurrence of adverse events. Findings were consistent in two post-hoc analyses that focused on the subset of patients in this cohort with sepsis and those with a high risk of treatment failure.[229,230]

The DURAPOP trial was a French multicentre, randomized, controlled unblinded study comparing an antibacterial therapy duration of 8 days with 15 days following source control of postoperative intra-abdominal infections (PIAI) in critically ill patients.[231] Of 236 patients included in the analysis, 62% had a SAPS score >40, indicating severe infection, and 16% had secondary bacteraemia. Antibiotic treatment choices, including de-escalation, were decided by the treating physician and in accordance to national guidelines. The primary outcome was the number of antibiotic-free days, which was higher in the shorter duration group than in the longer duration group (15 vs 12 days, respectively; $P < 0.0001$). There was no difference between groups in 45-day mortality or other secondary outcomes at day 45 (ICU stay, hospital stay, emergence of multidrug-resistance (MDR) and reoperation rate). Pre-specified subgroup analysis suggested that in patients with *Pseudomonas* infection the risk of emergence of and treated with longer treatment duration more frequently developed MDR compared to those treated with a shorter duration.

For duration of treatment in patients with sepsis due to CAP, UTI, SSSI and CNS infection and of sepsis due to S. aureus infection, we refer to other guidelines.[3-8]

Procalcitonin (PCT)-guided antibiotic treatment duration

The SWAB guideline on antimicrobial stewardship recommends to consider PCT-guided antibiotic treatment discontinuation in the ICU setting.[34] Several RCTs, including a large trial in Dutch ICU's, demonstrated that PCT-guided antibiotic treatment can result in shorter antibiotic treatment duration without an increase in length of hospital stay or mortality.[40,232] An individual patient data meta-analysis of 4482 critically-ill patients included in 11 trials compared PCT-guided antibiotic treatment to standard of care in patients with severe infection.[233] Around 50% of included patients had a pulmonary focus and almost 20% an intra-abdominal focus of sepsis. More than 70% of patients met sepsis-3 criteria and studies were mostly European. Study protocols were similar and recommended discontinuation of antibiotics if PCT decreased below 0.5 mg/L or more than 80% from peak level. Mortality was lower in patients in the PCT-guided group compared to controls (21.1% versus 23.7%; adjusted OR 0.89, 95% CI 0.80 – 0.99). Sepsis severity or focus did not change the effect on mortality. Patients with PCT-guided treatment had a significantly shorter antibiotic treatment duration than controls (adjusted coefficient -1.19 days, 95% CI -1.73 to – 0.66). A second regular meta-analysis showed similar findings of PCT-based discontinuation of antibiotics in critically ill patients.[234] Another individual patient data meta-analysis from 523 patients in 13 trials compared PCT-guided antibiotic treatment to standard of care in ICU patients with bacteraemia.[235] In line with the previous meta-analysis, PCT-guided antibiotic treatment duration resulted in shorter treatment duration compared to controls (–2.86 days; 95% CI: –4.88 to –0.84) with similar mortality rates in both groups (16.6% versus 20.0%). A final meta-analysis found similar effects of PCT-guided discontinuation of treatment on mortality in critically ill patients, but not in the subgroup of patients with sepsis.[236] Also, this meta-analysis showed that the improved mortality of the PCT-based strategy was mainly seen in studies that had lower protocol adherence or used algorithms of PCT combined with CRP.

De-escalation

Several meta-analyses have summarized evidence on the effect of antibiotic de-escalation (ADE) in patients with sepsis or severe infections.[237-240] The most recent meta-analyses showed decreased mortality in patients with ADE compared the control group.[237-239] However, these reports included observational studies in their analyses. Also, one meta-analysis clearly showed that patients with clinical improvement and other parameters associated with lower risk of treatment failure had a significantly higher likelihood of receiving ADE in the included studies, indicative of confounding by indication.[238] A subgroup analysis of patients with bacteraemia or severe sepsis found a non-significant lower mortality rate in the ADE group (adjusted OR 0.71; 95% CI 0.47 – 1.05).[237] On the other hand, a subgroup analysis restricted to the RCTs showed an almost significantly higher mortality rate in the ADE group (OR 1.72; 95% CI 0.97 – 3.07), although there was risk of bias and one RCT was on patients with CAP.[237] A French multicentre, non-blinded trial by Leone et al compared ADE to continuation of empirical therapy among 116 ICU patients with severe sepsis.[241] The study showed that ADE can be associated with longer duration of ICU stay (primary outcome, mean difference 3.4; 95% CI −1.7 to 8.5) as well as an increase in superinfections. ADE did not affect 90-day mortality.

We found no studies that focussed on ADE in patients with sepsis in which no causative agent could be identified.

Conclusions

Conclusion	Quality of evidence
One randomized trial in patients with Enterobacterales bacteraemia showed no additional effect of 14 days of treatment duration compared to 7 days of treatment duration on a composite outcome of 90-day mortality, clinical failure, re-admission or extended hospitalization	High[224]
Pooled data in patients with VAP showed no additional effect of a 10-15 days treatment duration compared to a fixed, shorter antibiotic treatment duration (7-8 days) on 28-day mortality, clinical cure and recurrent pneumonia	Moderate[37]
There are no trials or systematic reviews in patients with sepsis and HAP comparing shorter treatment duration to regular or longer treatment duration	-
One randomized trial in patients with complicated intra-abdominal infections and adequate source control showed no additional effect of a treatment duration until two days after resolution of symptoms (5-10 days) compared to a fixed four day treatment duration on a composite outcome of surgical-site infection, recurrent intra-abdominal infection and 30-day mortality	Moderate[228-230]
One randomized trial in ICU patients with severe post-operative intra-abdominal infections and adequate source control showed that a treatment duration of 8 days led to more antibiotic-free days compared to a duration of 15 days, with no additional effect on 45-day mortality, length of stay, emergence of MDR and reoperation rate	High to moderate[231]
There are no trials or systematic reviews in patients with sepsis and cholangitis comparing shorter treatment duration to regular or longer treatment duration	-
There are no trials or systematic reviews in patients with sepsis and suspected CVC infection comparing shorter treatment duration to regular or longer treatment duration	-
Pooled data in critically ill patients with sepsis showed lower or similar mortality rates and lower antibiotic treatment duration with procalcitonin-guided antibiotic treatment duration compared to standard care	Moderate[233-236]
Pooled, adjusted observational data in patients with sepsis showed that antibiotic de-escalation was not associated with higher mortality rates compared to standard care	Very low[237-239]
Pooled RCT data in patients with sepsis showed a non-significant increased mortality rate with antibiotic de-escalation compared to standard care	Low[237]
One RCT in patients with severe sepsis showed an increased length of ICU stay and more superinfections with antibiotic de-escalation compared to continuation of empirical therapy. The data showed no effect on mortality.	Moderate[241]
There are no trials or systematic reviews in patients with sepsis and negative cultures comparing antibiotic de-escalation to continuation of empirical therapy	-

Other considerations

Although there is some evidence available on antibacterial treatment duration, aggregation of evidence for sepsis is complicated by heterogeneity on causes of sepsis, comorbidities, variety in choice, route and efficacy of antibiotics, causative micro-organisms and other factors such as source control.[242]

On the other hand, several meta-analyses,[37,226,227] an RCT[224] as well as a large propensity-adjusted observational study[243] consistently showed that shorter duration of treatment is as effective and safe as the traditional, longer duration of treatment, in patient with sepsis. Similar results have been found in patients with mild to moderate-severe CAP,[6] acute cholecystitis excluding sepsis,[244] pyelonephritis,[245] uncomplicated cellulitis,[246] non-perforated appendicitis,[247] and bacteraemia.[248] In line, indirect evidence from the studies on PCT-guided discontinuation of antibacterial treatment in patients with sepsis in the ICU setting also suggests that shorter antibacterial treatment duration is safe without a detrimental effect on mortality.[40,232,233,249] These data, together with the potential adverse effects of antibiotic overuse, strengthen the committee to support the SSC recommendation of shorter durations of antibiotic therapy in most patients with sepsis.

Specifically, we agreed that the evidence supports a duration of 7 days in most patients with sepsis due to gram-negative bacteraemia or VAP, and a duration of 4 days in most patients with sepsis due to intra-abdominal infections who have had adequate source control. There is lack of evidence on optimal antibiotic treatment duration for sepsis due to HAP.[37] In line with the IDSA guideline on HAP and VAP, the SWAB sepsis committee felt that it is reasonable to extrapolate evidence from trials with patients with VAP. We therefore agreed on a weak recommendation for a treatment duration of 7 days for most patients with sepsis due to HAP. The previous SWAB sepsis guideline recommended shorter treatment duration of 1-3 days in patients with sepsis due to cholangitis or cholecystitis following adequate source control.[28] This was supported by a Dutch observational study and has been daily practice in many Dutch hospitals.[57] Although there is lack of high quality evidence, the committee is not aware of high clinical failure rates. We therefore still suggest to treat for 1-3 days following adequate source control in patients with sepsis due to cholangitis. For sepsis due to suspected CVC infection there is no high quality evidence available on treatment duration. The committee extrapolated from the RCT of Yahav et al. that for most patients with sepsis due to CVC infection with Enterobacterales and following removal of the CVC and with favourable clinical response a treatment duration of maximum 7 days is likely sufficient. We suggest this is also the case for sepsis due to non-fermenters. For enterococci and CNS there is no available evidence but as discussed in chapter 6a, empirical treatment is often withheld and removal of the CVC might be sufficient. The committee therefore settled to suggest 0 to 7 days for sepsis due to suspected CVC infection with CNS or enterococci. For sepsis in general or of (yet) unknown focus, we agreed that for most patients with a favourable clinical response, a treatment duration of 7 days will be sufficient - or can even be shortened - although there is only indirect evidence to support this statement.[224] The committee also agreed that the available evidence indirectly supports that source control is a fundamental component of sepsis treatment.

Longer treatment durations are generally indicated in patients with abscesses that cannot be drained (insufficient source control), in men with urinary tract infections and potential involvement of the prostate and in patients with SSSI.[3,4,250] Longer, individualized courses may also be considered in patients who are severely immunocompromised and patients with sepsis who have a slow clinical response. Of note however, slow clinical response should also lead to additional work-up of a new or persistent focus of infection rather than to unsubstantiated prolongation of antibiotics. Longer treatment duration is recommended in some infections due to specific micro-organisms, such as in *S. aureus* CAP or bacteraemia.[6-8] Other infections outside the scope of this guideline that generally need

longer antibiotic treatment are bone/joint infections, mediastinitis, pleural empyema and endovascular infections.

The SWAB guideline on antimicrobial stewardship recommends to consider PCT-guided antibiotic treatment discontinuation in the ICU setting.[40] More recent studies provide further support for the use of PCT-guided treatment duration in critically-ill patients with sepsis as it decreases antibiotic treatment duration with improved or similar survival compared to standard care.[233-236] A cost-effectiveness analysis suggested that the additional costs of this strategy during hospitalization are minimal (i.e. €65), although the cost-effectiveness on the long-term was unclear.[251,252] Questions remain however on the usefulness of a PCT-guided antibiotic management strategy in non-ICU sepsis patients as well as patients in which a short course of antibiotics is already indicated, such as those with sepsis due to an intra-abdominal infection. Also, with increasing antibiotic stewardship efforts one could wonder if the positive effects of a PCT-guided antibiotic management strategy on total antibiotic consumption will wane over time. And finally, PCT-testing will not be available in all hospitals in the Netherlands. In line with the SWAB guideline on antimicrobial stewardship,[40] we therefore gave a weak recommendation to use PCT levels to support shortening the duration of antibacterial therapy in patients with sepsis if the optimal duration of antibiotic therapy is unclear.

There are conflicting findings on the efficacy and safety of antibiotic de-escalation (ADE). Overall, there is lack of high quality evidence on clinical outcomes of ADE. It is unknown if ADE is an acceptable strategy in patients with sepsis in which no causative pathogen can be identified. Similarly, the effect of ADE on the development of antibiotic resistance is only assessed retrospectively.[253] Definitions of ADE differed among studies, further complicating the interpretation.[238] Here we focused on ADE as a strategy to change from broad to a smaller spectrum antibiotics, either by changing or stopping (one of) the antibiotics.

The committee agreed with the SSC good practice statements recommending daily assessment for ADE in patients with sepsis based on the potential harm associated with prolonged, unnecessary antibiotics.[36] The SWAB antimicrobial stewardship guideline provided a strong recommendation to de-escalate antibiotic therapy as soon as culture results become available based on very low quality evidence.[40] It should be noted that this guideline did not focus on patients with sepsis. An European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) consensus statement recommends to perform ADE in critically ill patients within 24 hours of definite culture results and in vitro susceptibility based on low quality evidence.[254]

Within the SWAB sepsis guideline committee there was consensus that ADE is appropriate in many clinical situations. Taken together, and in line with other relevant guidelines,[3629,40] the committee recommends to consider ADE in all patients who are on sepsis treatment, especially when culture results become available, in patients beyond 48 hours of treatment and in patients treated with antibiotics with high risk of adverse events of the empirical therapy, such as aminoglycosides. We also suggest this would include patients in whom only limited or indirect cultures show no causative pathogen. In contrast, with current conflicting evidence, including the negative outcomes of ADE in one trial on ICU length of stay,[241] the committee felt it is defendable not to perform ADE in individual patients. Example situations include a remaining duration of therapy of only one or a few days or the impossibility to switch from iv to oral antibiotic treatment.

Based on evidence summarized in chapters 5, 6a and 6b on aminoglycoside toxicity, the committee agreed that duration of empirical aminoglycoside therapy for sepsis should normally not exceed two days. We therefore recommend ADE in patients on empirical aminoglycoside therapy preferably within a maximum of two days.

It should be noted that we did not perform an additional evidence summary on iv/oral switch in patients with sepsis as this was done in the SWAB antimicrobial stewardship guideline.[40] Only very low quality data was available and we were not aware of newer trials or meta-analyses that would change the conclusions and level of evidence of the antimicrobial stewardship guideline. The SWAB sepsis guideline committee decided to support the recommendation of the SWAB antimicrobial stewardship guideline to switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is adequate.

Also in line with the SWAB antimicrobial stewardship guideline, we recommend that empirical antibacterial therapy should be discontinued in patients who initially appeared to have sepsis, but subsequently have limited clinical and microbiological evidence of infection.[40] We underscore that for early diagnosis and fast de-escalation options appropriate cultures before start of the antibacterial treatment are crucial. In addition the committee believes that a high turn-around time of tests in the microbiology laboratory, timely reporting of susceptibility results and linkage of test results to antimicrobial stewardship interventions should be improved where possible in order to maximize efforts to give the most appropriate antibiotic treatment for patients with sepsis as soon as possible.[148]

Recommendations

Recommendation	**Strength**	**Quality of evidence**
34. For treatment duration of sepsis due to CAP, UTI, SSSI and of sepsis due to *S. aureus* infection, we refer to other guidelines[3-8]		
35. We recommend source control interventions when possible to support antibacterial treatment in patients with sepsis.	Strong	Low
36. We recommend that a four-day course of antibacterial treatment is appropriate for patients with sepsis due to intra-abdominal infections following effective source control and with favourable clinical response	Strong	Moderate
37. We suggest that shorter courses of antibacterial treatment (up to three days) are appropriate in patients with sepsis and cholangitis following adequate drainage of the biliary tree	Weak	Very low
38. We recommend that an antibacterial treatment duration of 7 days is adequate for most patients with sepsis due to VAP	Strong	Moderate
39. We suggest that an antibacterial treatment duration of 7 days is adequate for most patients with sepsis due to HAP	Weak	Very low
40. We suggest that an antibacterial treatment duration of 7 days at maximum is adequate for most patients with sepsis due to suspected CVC	Weak	Very low

infection with gram-negative pathogens following removal of the CVC and with favourable clinical response		
41. We suggest that an antibacterial treatment duration of 0 to 7 days is adequate for most patients with sepsis due to suspected CVC infection with CNS or enterococci following removal of the CVC and with favourable clinical response	Weak	GPS
42. We suggest that an antibacterial treatment duration of 7 days is adequate for sepsis and septic shock without a clear focus in most patients with favourable clinical response	Weak	Low
43. We recommend daily assessment for the need of antibacterial therapy in patients with sepsis and to discontinue therapy when during follow-up there is lack of clinical or microbiological evidence of infection	Strong	GPS
44. We suggest that procalcitonin levels are used to support shortening the duration of antibacterial therapy in patients with sepsis if optimal duration of antibiotic therapy is unclear	Weak	Moderate
45. We recommend to consider antibiotic de-escalation (resulting in smaller spectrum antibiotics) in all patients on antibiotics for sepsis on a daily basis and based on pathogen identification, sensitivities and risk of adverse events	Strong	Very low
46. We recommend to stop empirical aminoglycoside therapy within a maximum of two days	Strong	Low
47. We recommend to switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is feasible	Strong	Very low

Table 10. Suggested antibacterial therapy duration in patients with sepsis

Focus of sepsis	**Suggested antibacterial treatment duration**
Intra-abdominal infections, following effective source control and with favourable clinical response	Four days[228-231]
Cholangitis, following adequate drainage of the biliary tree	Up to three days[57]
VAP	Seven days[37]
HAP	Seven days
CVC infection with gram-negative pathogen, following removal of the CVC and with favourable clinical response	Up to seven days[224]
CVC infection with CNS or enterococci, following removal of the CVC and with favourable clinical response	Zero to seven days
No clear focus	Seven days[224]

IV Pharmacokinetic and pharmacodynamic considerations in sepsis

Introduction

Pharmacokinetics (PK) describe the time course of drug concentration in body fluids after administration of a drug. This time course of drug concentration is dependent on the absorption, distribution and elimination of the drug. Pharmacodynamics (PD) describe the relationship between drug concentration in body fluids and its pharmacologic effect, i.e. antibacterial effects in the case of antibacterial drugs. In vitro and in vivo studies indicate that certain antibacterial drug exposures over time (i.e. PK) in relation to antibacterial effects of the drug (i.e. PD) are associated with clinical efficacy of the drug.[255-257] These so-called PK/PD indices can differ among antibiotic classes. For beta-lactams, clinical efficacy correlates with the percentage of time that the concentration of non-protein bound or free fraction (%fT) of the drug in serum is higher than the minimally inhibitory concentration (MIC) of the micro-organism (PK/PD index: %fT>MIC).[258] Aminoglycosides have traditionally been considered as concentration-dependent antibiotics with Cmax/MIC as the PK/PD index related to clinical efficacy.[259] However, several reports suggest that aminoglycoside efficacy is related to both time and concentration.[260-263] The PK/PD index that best describes this relation is the ratio of the area under the concentration-time curve (AUC) and the MIC, i.e. AUC/MIC ratio. The PK/PD index in most other antibiotics is also described by AUC/MIC ratio.[261]

As discussed in earlier chapters, appropriate antibacterial treatment is associated with improved survival of sepsis. However, many pathophysiological changes typical for sepsis patients can alter pharmacokinetic properties of antibiotics and can lead to inadequate antibiotic concentrations when using standard antibiotic dosing schedules.[261,264-268] These pathophysiologic changes include kidney dysfunction, augmented renal clearing (that is the enhanced renal function sometimes seen in critically ill patients), hypoalbuminemia and increased third space due to fluid therapy.[36,261] Drug concentrations of hydrophilic antibacterial agents (such as beta-lactams, aminoglycosides and vancomycin) are generally more sensitive to pharmacokinetic changes in patients with sepsis than lipophilic antibacterial agents (such as fluoroquinolones). In addition, patients with sepsis may generally be at higher risk to be infected with bacteria with higher MICs in comparison to other patients.[261]

For beta-lactams, increasing %fT>MIC can be achieved by increasing beta-lactam total dose, by increasing the number of daily doses or by providing extended or continuous infusion. For aminoglycosides, Cmax/MIC can be adjusted by the height of the dose. For vancomycin, optimal fAUC/MIC could be reached with a loading dose and continuous infusion. The concentrations of ciprofloxacin, as a lipophilic agent, are less influenced by PK changes in sepsis, but improved target attainment for bacteria with higher MICs could be achieved by increasing the dosing frequency. Obesity potentially alters PK-parameters as well.[269,270] Especially hydrophilic antibacterial agents, including beta-lactams and vancomycin, may alter pharmacokinetics in critically ill, obese patients.[271]

In this chapter we summarized evidence on clinical effects of pharmacokinetic/pharmacodynamic dosing optimization of empirical antibacterial therapy in patients with sepsis on the following questions:

- In patients with sepsis, should antibiotic dosing be based on PK/PD principles?
- Is extended or continuous infusion of B-lactam antibiotics superior to intermittent therapy in patients with sepsis?

- What is the optimal empirical dose of aminoglycosides in patients with sepsis?
- Is continuous infusion of glycopeptide antibiotics superior to intermittent therapy in patients with sepsis?
- What is the optimal empirical dose of ciprofloxacin in patients with sepsis?
- Should we optimize doses in patients with obesity and sepsis?

10. In patients with sepsis, should we recommend pharmacokinetic / pharmacodynamic dosing optimization for empirical antibacterial therapy?

Evidence summary

PK/PD-based dosing

Falagas et al. performed a systematic review on the relation between MIC and outcome of infections with susceptible gram-negative bacteria.[272] Of the 13 observational studies included, 4 studies reported on patients with bacteraemia only (all on beta-lactams) and 5 studies included patients with nosocomial infections including bacteraemia (three on beta-lactams, two on tigecycline). Patients infected with Enterobacterales with high MICs had higher all-cause mortality than patients infected with strains with lower MICs (RR 2.03; 95% CI: 1.05 – 3.92). There was no effect of MIC values on treatment failures (RR 1.18; 95% CI: 0.71 – 1.97). Among patients infected with non-fermentative gram-negative bacteria, higher MICs were associated with higher all-cause mortality (RR, 2.39; 95% CI, 1.19 – 4.81) and clinical failure (RR, 5.54; 95% CI, 2.72 to 11.27).

Jacob et al. performed a meta-analysis on vancomycin MIC and clinical outcomes in patients with MRSA infections. A subgroup analysis showed increased risk of clinical failure (RR 1.37; 95% CI: 1.09 – 1.73) and mortality (RR 1.46; 95% CI: 1.06 – 2.01) for MIC ≥1 mg/L compared to lower MICs in patients with MRSA bacteraemia.[273]

The IDSA guideline on HAP/VAP performed a systematic review of the value of PK/PD-optimized dosing on clinical outcomes, with a focus on patients with HAP and VAP.[37] PK/PD-optimized dosing decreased mortality (12% vs 24%; RR, 0.49; 95% CI, 0.34 - 0.72) and ICU length of stay (mean difference, −2.48 days; 95% CI, −3.09 to −1.87 days). PK/PD-optimized dosing showed a benefit on clinical cure (81% vs 64%; RR, 1.40; 95% CI, 1.16–1.69).

Prolonged infusion of beta-lactams - general

A recent high-quality meta-analysis of 22 RCTs compared the effect on overall mortality, clinical cure, adverse events and emergence of resistance of prolonged (continuous or ≥3 hour) to short-term (≤60 minutes) infusion of antipseudomonal beta-lactams in patients with sepsis.[274] Definitions and causes of sepsis differed between studies, but 11 studies included severely ill patients (APACHE II ≥ 20). Most studies excluded patients with impaired renal function. Included beta-lactams were carbapenems (imipenem and meropenem, 9 studies), penicillins (mostly piperacillin-tazobactam, 9 studies) and cephalosporins (ceftazidime, cefepime, cefoperazone, 8 studies). All-cause mortality data was available for 1597 patients and showed that extended or continuous infusion of beta-lactams is associated with lower mortality compared to short-term infusion (17 RCTs, RR 0.70, 95% CI 0.56 – 0.87). Subgroup analyses showed that the lower mortality rate was robust within most subgroups. For clinical cure, there was no significant difference between prolonged and short-term beta-lactam

infusion (11 RCTs, intention-to-treat analysis: RR 1.06, 95% CI 0.96 – 1.17). There was no difference in reported adverse events (7 RCTs, RR 0.88, 95% CI 0.71 – 1.09), nor in reported development of resistance (2 RCTs, RR 0.60, 95% CI 0.15 – 2.38) between both groups.

Another meta-analysis of 13 RCTs on continuous versus intermittent beta-lactam infusion in critically ill patients with predominantly respiratory infections could not demonstrate a benefit of continuous infusion on mortality (6 RCTs, RR 0.85, 95% CI 0.64 – 1.12).[275] However, continuous beta-lactam infusion resulted in a significant beneficial effect on clinical cure when compared to intermittent infusion (6 RCTs, RR 1.19, 95% CI 1.02 – 1.41). Possible explanations for the different finding with Vardakas et al. were the inclusion of one additional study on ceftriaxone,[276] one study with less than 10 patients per group which was excluded from Vardakas et al.[277] and the inclusion in the analysis of zero events in both groups of another trial.[278]

An individual patient data meta-analysis of 3 high quality RCT's compared continuous infusion to intermittent infusion (within 30 minutes) of beta-lactam antibiotics in critically ill patients with severe sepsis.[279] All three studies were also included in the meta-analysis of Vardakas and Lee.[274,275] Two-third of patients received piperacillin-tazobactam and almost one-third meropenem. The total daily doses were identical in both treatment arms. Robust, intention-to-treat analyses showed decreased 30-day mortality with more than 25% (RR 0.73, 96%CI 0.55 – 0.98) in favour of the continuous infusion group. In line, continuous beta-lactam infusion was associated with a non-significant increased probability of clinical cure of 32% (RR 1.32, 95% CI 0.97 – 1.80) compared to intermittent infusion, although there was heterogeneity between the studies regarding this outcome.

Specific beta-lactam classes

Subgroup analysis in the meta-analysis of Vardakas and another meta-analysis in severely ill patients on prolonged infusion of piperacillin-tazobactam confirmed lower mortality rates in the prolonged infusion group compared to intermittent dosing.[274,280] Subgroup analysis in the meta-analysis of Vardakas on prolonged infusion of antipseudomonal cephalosporins showed no difference in mortality rate between the prolonged and short-term infusion group (RR 0.83, 95% CI 0.40 – 1.74, 28% heterogeneity). There was a low total number of events (n=40).[274] Subgroup analysis in the meta-analysis of Vardakas on prolonged infusion of carbapenems showed a lower mortality rate in the prolonged infusion group (RR 0.67, 95% CI 0.49 – 0.91). One small, pilot randomized trial in patients with sepsis showed no effect on clinical response parameters of continuous infusion versus intermittent infusion of ceftriaxone.[276] We found no other systematic reviews or randomized controlled trials on clinical effects of prolonged infusion of other relevant beta-lactam antibiotics in patients with sepsis.

Optimal dose of aminoglycosides

There were no systematic reviews comparing doses of aminoglycosides in patients with sepsis. One RCT compared 25 mg/kg to 15 mg/kg amikacin in patients with severe sepsis or septic shock presenting in the emergency department.[281] There was no difference in incidence of nephrotoxicity. The number of events was, however, very low.

Several systematic reviews of randomized trials showed that once daily dosing is associated with lower nephrotoxicity rates compared to multiple dosing, with similar or slightly improved clinical efficacy.[282-285]

Vancomycin continuous dosing

A systematic review and meta-analysis of two RCTs and nine observational studies summarized evidence on continuous versus intermittent infusion of vancomycin.[286] Eight studies were in the ICU setting and 6 studies included patients with MRSA infections. Five studies reported SAPS II scores (range: 13 – 50).[287] Seven studies reported vancomycin doses (including loading doses) and the authors showed no difference in all-cause mortality of continuous versus intermittent infusion (RR 1.15, 95% CI 0.85 – 1.54); nor in treatment failure (no meta-analysis done) between treatment groups. There was a lower incidence of nephrotoxicity in patients treated with continuous infusion compared to those treated with intermittent infusion of vancomycin (RR 0.61, 95% CI 0.47 – 0.80).

Optimal dose of ciprofloxacin

There were no systematic reviews or randomized controlled trials comparing doses of ciprofloxacin in patients with sepsis. We did not systematically summarize PK/PD dosing optimization for other fluoroquinolones.

Obesity

There were no systematic reviews nor randomized studies comparing the effect of PK/PD based dosing to standard dosing of antibacterial agents in obese patients with sepsis. Only PK-parameters were evaluated in critically ill obese patients.

Conclusions

Conclusion	**Quality of evidence**
Pooled data in patients with severe infections showed that higher MICs were associated with increased mortality	Low[272,273]
Pooled data in patients with sepsis due to HAP and VAP showed that PK/PD based dosing (using TDM or extended infusion) was associated with decreased mortality, increased clinical cure and decreased ICU length of stay compared to dosing based on manufacturer's information	Very low[37]
Pooled RCT data in patients with sepsis showed that extended or continuous infusion of beta-lactams in general was associated with decreased all-cause mortality, increased clinical cure and no effect on adverse events and development of resistance compared to intermittent infusion	Low to high[274,279]
Pooled RCT data in patients with sepsis showed that extended or continuous infusion of piperacillin-tazobactam was associated with decreased all-cause mortality compared to intermittent infusion	Moderate[274,280]
One small RCT in patients with sepsis showed that continuous infusion of ceftriaxone was not associated with improved clinical cure	Very low[276]
Pooled RCT data in patients with sepsis showed that extended or continuous infusion of ceftazidime or cefepime is not significantly associated with decreased all-cause mortality compared to intermittent infusion	Low[274]

Pooled RCT data in patients with sepsis showed that extended or continuous infusion of carbapenems is associated with decreased all-cause mortality compared to intermittent infusion	Moderate[274]
One RCT in patients with sepsis and septic shock showed that amikacin 25 mg/kg was not associated with increased risk of nephrotoxicity compared to 15 mg/kg	Low[281]
Pooled observational data in critically ill patients showed lower nephrotoxicity and similar mortality rates in continuous vancomycin infusion compared to intermittent infusion of vancomycin	Very low[286]
We found no RCTs or systematic reviews in patients with sepsis comparing the effect of PK/PD-based ciprofloxacin dosing with standard dosing on clinical outcomes	-
We found no RCTs or systematic reviews in obese patients with sepsis comparing the effect of PK/PD-based dosing with standard dosing on clinical outcomes	-

Other considerations

As mentioned before summarizing evidence of antibacterial treatment in sepsis is challenging. Additional challenges in summarizing evidence on PK/PD-based dosing in sepsis are potential differences in PK/PD targets between antibiotics of the same class (for example, higher %fT>MIC needed for cephalosporins compared to meropenem),[261] differences in pharmacokinetic dosing interventions (for example, extended or continuous beta-lactam infusion), different pharmacokinetic characteristics between patients and within individual patients over time (for example, due to age, obesity, changes in volume of distribution of the drug, changes in renal function), different or unknown MICs of the causal bacteria and differences in reliability of MIC testing.

The committee agreed with the SSC guideline recommendation to adjust dosing based on PK/PD principles and drug properties in patients with sepsis and septic shock.[36] Evidence supports pharmacokinetically optimized dosing strategies in patients with sepsis and septic shock, but this approach is currently difficult to achieve due to lack of rapid therapeutic drug monitoring options (TDM) for many antibacterial drugs. The high-quality evidence of the effect of prolonged infusion in beta-lactams supports PK/PD-based dosing, but there is low quality or lack of evidence of the effect of PK/PD-based dosing in general, and specifically of aminoglycosides, vancomycin and ciprofloxacin and in obese patients on clinical outcomes. We felt that the available evidence as well as the many studies reporting that PK/PD targets are not reached in sepsis or critically ill patients in general supports a recommendation of PK/PD-based dosing.[36,261,288-290] Since EUCAST recommendations on breakpoints are generally accepted and based on PK/PD principles, we generally followed the EUCAST dosing recommendations on doses in specific pathogens.[42]

TDM is not yet available in the Netherlands on a large scale for antibacterial drugs other than aminoglycosides and vancomycin, including for beta-lactams. Due to lack of TDM possibilities for many antibacterial drugs in the Netherlands, we cannot currently give a strong recommendation on TDM for antibacterial therapy except for aminoglycosides and vancomycin. However, we do suggest to consider TDM in patients with sepsis and septic shock when there are concerns on target attainment of other antibacterial drugs than aminoglycoside and vancomycin and when TDM is possible.

Based on the evidence of clinical outcomes of prolonged infusion of beta-lactams in patients with sepsis, the committee agreed to recommend this strategy for carbapenems and piperacillin-tazobactam and to suggest it for other beta-lactams. There are practical disadvantages of continuous infusion of beta-lactam. As an example, venous access is often required in addition to iv infusion therapy systems. When using continuous infusion, a loading dose should be given in order to achieve early effective serum concentrations. Some beta-lactams have stability issues (e.g. amoxicillin and clavulanic acid), precluding 24 hour infusion preparations. For these beta-lactam agents extended intermittent infusion would be appropriate.

Formulating recommendations on aminoglycoside dosing is complicated due to the wide range of aminoglycoside concentrations found in patients with sepsis after low or high doses of aminoglycosides.[291-293] This wide range results in a percentage of patients with subtherapeutic concentrations (based on PK/PD models) and a percentage of patients with overexposure to the drug. Overexposure to amikacin was associated with increased mortality in the observational study of Allou et al in severe sepsis and septic shock patients.[291] On the other hand, the authors showed that patients reaching the PK/PD target had reduced mortality compared to those not reaching the target.[281] PK/PD models confirm difficulties of target attainment in aminoglycoside treatment, especially in infections with bacteria with higher MICs.[262] Recently, EUCAST changed aminoglycoside breakpoints based on PK/PD-based modelling after a general consultation round.[294] EUCAST concluded that for serious infections targets for efficacy cannot be reached and consequently do not provide breakpoints for patients with systemic infections anymore. In those infections, EUCAST suggests that aminoglycosides should be used in combination with other active therapy and provide aminoglycoside MIC's to distinguish between bacteria with and without acquired resistance mechanisms. [42] Based on the same principles, EUCAST now advices against gentamicin for *P. aeruginosa* infections. Uncertainty of target attainment and risk of toxicity are therefore a major disadvantage of aminoglycoside treatment of patients with sepsis.

Two observational studies reported that active pharmacokinetic dosing (including information on trough levels) was associated with increased clinical efficacy and decreased toxicity compared to standard dosing.[295,296] Taking in mind the wide variation of aminoglycoside concentrations in patients with sepsis, the committee recommends to implement individualized pharmacokinetic dosing, including direct therapeutic drug monitoring of aminoglycosides in patients with sepsis, in order to reduce subtherapeutic concentrations and overexposure to aminoglycosides. We suggest that either mid-dosing or both peak and through concentrations are measured and that dosing is adjusted according to the guidance of the clinical pharmacist. In the Netherlands, gentamicin and tobramycin doses of 5 mg/kg are recommended in adults with infections in general by the NVZA.[297] Doses of 6 mg/kg (tobramycin) or 6-7 mg/kg (gentamicin) are suggested for ICU patients or patients with sepsis.[297] EUCAST now suggests gentamicin and tobramycin doses of 6-7 mg/kg.[42] The SWAB guideline committee did not reach consensus on the question if one should use higher initial aminoglycoside dosing in patients with sepsis and septic shock because of lack of clinical data on toxicity in patients treated with higher initial doses. Although the committee is concerned about the efficacy and toxicity of aminoglycosides based on available clinical evidence and the suggestions based on PK/PD models by EUCAST, we felt that at this point there is insufficient evidence to recommend against aminoglycosides in patients with sepsis in general or against the specific use of empirical gentamicin

in patients with a higher likelihood of involvement of *P. aeruginosa*. In the coming years a large Dutch randomized controlled trial will assess the efficacy and safety of empirical aminoglycoside therapy in patients with sepsis.

Regarding vancomycin, there is lack of high quality studies on optimal dosing of vancomycin.[298] Very low quality evidence suggests that continuous infusion could decrease the risk of nephrotoxicity in patients with severe MRSA infections. There is no evidence on effect on other clinical outcomes. Also, the clinical consequences of nephrotoxicity haven't been studied. Use of TDM in general in vancomycin is associated with improved clinical efficacy and reduced renal toxicity as was shown in mainly observational studies in non-sepsis patient population.[299] One systematic review concluded that continuous infusion of vancomycin may be cheaper and TDM easier to perform than intermittent infusion.[300] In the Netherlands, most patients treated with vancomycin are treated for infection with coagulase negative staphylococci (CNS) or *E. faecium* which are less virulent than MRSA. Some patients with *S. aureus* infections and contra-indications for beta-lactams may be treated with vancomycin. Current practice in the Netherlands varies, with some hospitals providing continuous infusion, while many provide intermittent dosing.[300] A practical advantage of continuous infusion is that drug concentration can be measured any time after reaching steady state. Practical disadvantages for continuous infusion could be the need for extra venous access and the incompatibility with other medication. The SWAB guideline committee therefore agreed to suggest continuous infusion of vancomycin in patients with sepsis. Since vancomycin TDM is widely available, we recommend performing early TDM in patients with sepsis, i.e. 24 hour after the start.

For ciprofloxacin, several PK/PD studies have been published using clinical data of patients with moderate to severe infections, septic shock and/or of critically ill patients. Although the studies used different PK/PD targets, they show no concerns about ciprofloxacin target attainment of regular dosing (two times 400 mg iv per 24h) when bacteria with MICs <0.125 mg/L are involved.[301-304] In contrast, these and other studies showed it is difficult or impossible to reach the PK/PD target when bacteria with MICs ≥0.5 mg/L are involved.[301-306] Higher dosing (three times 400 mg iv per 24h) was only moderately effective to increase target attainment when bacteria with MICs between 0.125 and 0.5 mg/L were involved. In a study of Enterobacterales bacteraemia three times daily ciprofloxacin dosing increased percentage target attainment (defined as fAUC/MIC>250) for bacteria with MICs of 0.125 and 0.25 mg/L from approximately 70 to 95% and 10 to 40% respectively.[304] Three times daily dosing in a Dutch study of critically ill patients increased percentage target attainment (defined as fAUC/MIC>125) for bacteria with MICs of 0.25 and 0.5 mg/L from approximately 95 to 100 and 40 to 70% respectively.[303] Ciprofloxacin is generally well tolerated.[307] Ciprofloxacin in higher doses (three times daily 400 mg iv) is also reported to be safe in small studies.[307,308] EUCAST epidemiological cut-offs (ECOFF) for most Enterobacterales are 0.125 mg/L and clinical breakpoints 0.25 mg/L.[42] Higher ECOFFs are reported for *Pseudomonas* species (0.5 mg/L), *Acinetobacter* species (1 mg/L) and *Staphylococcus* species (1 mg/L). Clinical breakpoints of these three species are therefore based on high dose ciprofloxacin therapy (three times daily 400 mg iv) by EUCAST. In general, ciprofloxacin monotherapy is not recommend as monotherapy for *S. aureus* infections.

Overall, the available evidence indicates that ciprofloxacin efficacy is mainly dependent of MIC of the involved bacteria. The committee would like to emphasize that the available evidence shows suboptimal target attainment of ciprofloxacin treatment when bacteria with MIC 0.5 mg/L or higher

are involved, even with higher dosing of ciprofloxacin. In patients with sepsis and risk of involvement of bacteria with MIC 0.5 mg/L or higher, we therefore suggest against ciprofloxacin monotherapy as the first therapy of choice. If local epidemiology is such that most Enterobacterales show MICs of 0.125 to 0.25 mg/L, the available evidence supports three times daily dosing. In line with EUCAST recommendations, we support a three times daily dosing schedule for *Pseudomonas*, *Acinetobacter* spp. and *S. aureus* infections, but prefer other antibiotic classes for initial therapy of patients with sepsis due to these bacteria.[42]

Some observational studies in critically ill obese patients evaluating PK parameters are available.[309-315] One case-control study evaluated the differences in ceftazidime, piperacillin-tazobactam and meropenem concentration between obese and non-obese patients. No major differences were observed. The study showed that sepsis had a greater impact on differences in PK-parameters than obesity itself.[312] This finding is consistent with an observational study in obese ICU patients defining steady state meropenem concentrations.[311] It showed that although steady state volume of distribution was increased, the standard dosing regimen achieved an adequate probability of target attainment. Another prospective, observational study found that obese ICU patients were at risk of overdosing.[313] However, the evidence for the validity of a piperacillin toxicity cut-off value is poor. Two studies showed that underdosing of meropenem and piperacillin in obese critically ill patients may result from augmented renal function during sepsis in obese patients, especially during intermittent dosing.[309,310]

One systematic review summarized a limited number of studies on pharmacokinetic parameters of aminoglycosides in critically ill, obese patients.[315] Very limited data showed that dose adjustment and TDM of aminoglycosides based on PK/PD principles may improve target attainment in critically ill, obese patients. One retrospective study showed that obese ICU patients treated with continuous vancomycin required lower maintenance dosing than non-obese patients.[314]

The committee concluded that overall the limited evidence on beta-lactam pharmacokinetics in obese patients with sepsis suggests that sepsis characteristics influence PK/PD parameters more than obesity. Current data do not support a different approach of beta-lactam dosing in obese patients with sepsis compared to non-obese patients. For aminoglycosides and vancomycin, the committee concluded that the limited evidence supports dose adjustment in obese patients with sepsis. Similar to non-obese patients, evidence supports TDM of aminoglycosides and vancomycin in obese patients with sepsis.

Recommendations

Recommendation	**Strength**	**Quality of evidence**
48. In patients with sepsis, we suggest that dosing strategies of antibacterial therapy be optimized based on accepted pharmacokinetic / pharmacodynamic principles and specific drug properties **(Table 11)**	Weak	Low
49. In patients with sepsis we recommend prolonged or continuous* infusion of piperacillin-tazobactam and carbapenems	Strong	High

50. In patients with sepsis we suggest prolonged or continuous* infusion of other beta-lactam antibiotics than piperacillin-tazobactam and carbapenems	Weak	Low
51. In patients with sepsis, we recommend direct therapeutic drug monitoring (including either mid-dosing or both peak and through levels) during aminoglycoside treatment in patients with sepsis and septic shock	Strong	GPS
52. In patients with sepsis, we recommend therapeutic drug monitoring during vancomycin treatment in patients with sepsis and septic shock	Strong	GPS
53. In patients with sepsis, we suggest therapeutic drug monitoring when there are concerns on target attainment of other antibacterial drugs than aminoglycoside and vancomycin (e.g. extreme body weight, augmented or decreased renal clearance, hypoalbuminemia)	Weak	GPS
54. In patients with sepsis, we suggest continuous* infusion of vancomycin	Weak	GPS
55. In patients with sepsis in whom ciprofloxacin is indicated, we suggest empirical ciprofloxacin three times daily 400 mg iv	Weak	GPS

***** Continuous infusion includes one intermittent dose as a loading dose

Table 11. Recommended iv doses of empirical antibacterial treatment for sepsis

Antibacterial agent	Intermittent dosing (<60 min infusion)	Prolonged dosing (3-5 hour infusion)	Continuous infusion + loading dose	Remarks
Benzylpenicillin	6x 1 million IU	6x 1 million IU	6 million IU + 1 million IU loading dose	Higher doses optional up to 24 million IU per 24h*
Amoxicillin	6x 1000 mg	6x 1000 mg	6000 mg + 1000 mg loading dose	Higher doses optional up to 12000 mg per 24h*
Flucloxacillin	6x 1000 mg	6x 1000 mg	6000 mg + 1000 mg loading dose	Higher doses optional up to 12000 mg per 24h*
Amoxicillin-clavulanic acid	4x 1200 mg	4x 1200 mg	N.a.	
Piperacillin-tazobactam	4x 4500 mg	4x 4500 mg	18000 mg + 4500 mg loading dose	3x 4500 mg when *Pseudomonas* is not involved*
Cefazolin	3x 1000 mg	3x 1000 mg	3000 mg + 1000 mg loading dose	Higher doses optional up to 6000 mg per 24h*
Cefuroxime	3x 1500 mg	3x 1500 mg	4500 mg + 1500 mg loading dose	
Ceftriaxone	1x2000 mg	1x 2000 mg	2000 mg + 2000 mg loading dose	2x 2000 mg when *S. aureus* is involved*
Ceftazidime	3x 2000 mg	3x 2000 mg (3 hour infusion)	6000 mg + 2000 mg loading dose	3x 1000 mg or 3000 mg per 24h + 1000 mg loading dose optional when *Pseudomonas* is not involved
Imipenem	4x 1000 mg	4x 1000 mg	4000 mg + 1000 mg loading dose	4x 500 mg optional when *Pseudomonas* is not involved
Meropenem	3x 1000 mg	3x 1000 mg (3 hour infusion)	3000 mg + 1000 mg loading dose	Higher doses optional up to 6000 mg per 24h*
Ciprofloxacin	3x 400 mg	N.a	N.a.	2x 400 mg when *Pseudomonas* is not involved*
Gentamicin	1x 5 mg/kg**	N.a.	N.a.	1x 6-7 mg/kg may be indicated in sepsis due to Enterobacterales * Adjusted for adjusted body weight** Immediate TDM recommended*** Should be given in combination with other antibacterial therapy, generally a beta-lactam agent. Gentamicin may be a suboptimal choice for *P. aeruginosa* based on PK/PD models****
Tobramycin	1x 5 mg/kg**	N.a.	N.a.	1x 6-7 mg/kg may be indicated in sepsis due to Enterobacterales or *Pseudomonas** Adjusted for adjusted body weight** Immediate TDM recommended***

				Should be given in combination with other antibacterial therapy, generally a beta-lactam agent.****
Vancomycin	2-3x 15-20 mg/kg + 25-30 mg/kg loading dose	N.a.	30-40 mg/kg + 15-20 mg/kg loading dose	Adjusted for adjusted body weight** TDM recommended***
Metronidazole	3x 500 mg	N.a.	N.a.	
Trimethoprim-sulfamethoxazole	2x 960 mg	N.a.	N.a.	Higher doses optional*

* See also EUCAST dosing table (http://www.eucast.org/) for guidance on which pathogens may require higher dosing and other relevant guidelines for infections that require other dosages. In case of higher 24h doses a higher loading dose is indicated (i.e. one intermittent dose)

** Adjusted for adjusted body weight (ideal body weight + 0,4*(true body weight – ideal body weight. Ideal body weight: man: 50 kg + 0,9 * (cm > 150 cm); woman: 45 kg + 0,9 * (cm > 150 cm). See https://tdm-monografie.org/

*** See https://tdm-monografie.org/

**** Since 2020 EUCAST doesn't provide formal breakpoints for aminoglycosides in systemic infection (excluding UTI) with Enterobacterales, *Pseudomonas*, *Acinetobacter* and *Staphylococcus* species anymore. EUCAST recommends that in systemic infections with these species, the aminoglycoside must be supported by other active therapy. In addition, there are no breakpoints for gentamicin in any infection with *Pseudomonas* species anymore. See EUCAST clinical breakpoints table and http://www.eucast.org/guidance_documents/.

Acknowledgements

The Guidelines Committee would like to thank all individuals and societies who contributed to the development of these guidelines.

Appendix

Literature searches

1. Which bacteria are most frequently isolated from patients with sepsis in the Netherlands?

For chapter 1a we searched for epidemiological studies on bacterial aetiology of sepsis and resistance patterns. We focussed on studies from the Netherlands. We also used NethMap 2017 data and the PREZIES database.[27] NethMap is an annual report, published by the SWAB in collaboration with the National Institute for Public Health and the Environment of the Netherlands (RIVM). It contains data from ongoing surveillance of antibacterial agents and resistance among common human pathogens.

In addition, we requested information on pathogens causing central venous catheter infections from the Dutch national AMR surveillance system (Infectious Diseases Surveillance Information System for Antimicrobial Resistance or ISIS-AR).[58] For this search, all 2017 cultures categorized as catheter tip or blood were selected. Blood cultures (BC) taken from lines (documented as BC taken from a line) were excluded. Central venous catheter infection was identified when a peripheral blood culture and a tip culture were both positive within a maximum of one day difference (before or after) in the date of taking the sample into process, growing the same microorganism. If a patient had more than one "set" meeting this definition, only the first positive set was evaluated.

2. What are the resistance patterns of the most frequently isolated bacteria in patients with sepsis in the Netherlands?

For chapter 1b we used studies from the Netherlands found for chapter 1a and NethMap 2017 data.[27] In addition, we requested additional resistance data from the Dutch national AMR surveillance system (Infectious Diseases Surveillance Information System for Antimicrobial Resistance or ISIS-AR).[58]

3. Which patients are at risk for sepsis due to third-generation cephalosporin-resistant Enterobacterales (3GCR-E) or *P. aeruginosa* in the Netherlands?

For chapter 2, we restricted the evidence summary to systematic reviews, externally validated prediction rules and Dutch cohort studies on risk factors for sepsis or severe infections with Enterobacterales resistant to third-generation cephalosporins (3GCR-E) or with *P. aeruginosa*. We also included studies on HRMO (gram-negatives) in general and a large systematic review that assessed risk factors for inappropriate empirical therapy.

We focussed our search on evidence on risk factors for sepsis due the HRMO that are most frequently encountered in the Netherlands: Enterobacterales resistant to 3rd generation cephalosporins or shown to harbour ESBL or AmpC genes. Sepsis due to these microorganisms would not be appropriately treated with current general empirical therapy recommendations.[28] We did not systematically search for risk factors for sepsis due to other HRMOs , i.e. Enterobacterales resistant to both fluoroquinolones and aminoglycosides, *P. aeruginosa* resistant to ≥3 antibacterial therapy groups (among fluoroquinolones, aminoglycosides, carbapenems, ceftazidime and piperacillin-tazobactam) and *Acinetobacter spp. r*esistant to imipenem or meropenem or resistant to both fluoroquinolones and aminoglycosides. Due to the low prevalence of sepsis due carbapenemase-producing gram-negative bacteria, penicillin-resistant *S. pneumoniae* and *N. meningitidis*, MRSA or VRE in the Netherlands we did not include studies on risk factors for sepsis due to these bacteria.[27,316]

4. What is the importance of appropriate empirical therapy in patients with sepsis?

For this key question we used the literature and grading presented in the SSC 2016 guideline, IDSA guideline on HAP/VAP and SIS guideline on intra-abdominal infections.[36-38] In addition, we referred to the SWAB guideline on management of complicated urinary tract infections and the Dutch evidence-based guideline on necrotizing soft tissue infections (2015).[3,5] An additional search for relevant studies on the topic led to five systematic reviews and two RCTs.[84,88-93]

5. What is the effect of double active empirical antibiotic therapy compared to monotherapy in patients with sepsis?

For this key question we used the literature and grading presented in the SSC 2016 guideline, IDSA guideline on HAP/VAP.[36,37] In addition, we referred to the Dutch guideline on *S. aureus* bacteraemia.[7] An additional search for relevant studies on the topic led to three systematic reviews and one RCT.[106,110-112]

6. What is the optimal choice of empirical therapy in patients with sepsis in The Netherlands

For this key question we used the literature and grading presented in the SSC 2016 guideline, IDSA guideline on HAP/VAP and SIS guideline on intra-abdominal infections.[36-38] An additional search for studies published since the searches of these guidelines led to 12 systematic reviews and two RCTs.[90,112,134-138,140,153-158] Due to the low prevalence of sepsis due to MRSA in the Netherlands we did not include studies on empirical treatment of sepsis and risk of involvement of MRSA. We did not summarize evidence on treatment of necrotizing pancreatitis and sepsis due to diabetic foot infection.

We additionally performed a search of all relevant studies published from June 2008 until October 2018 in MEDLINE and PubMed databases, for the following question:

- What is the optimal empirical therapy for a suspected central catheter infection?

All abstracts were screened for relevance. The specific search strategies are described in **Table A**. These results were added to the literature presented in the IDSA Guideline 2009 for catheter related infections.

Table A. Search strategy empirical therapy in sepsis due to suspected infected CVC

Search no.	Query	results	relevant
1	"Catheter-Related Infections/diagnosis"[Mesh] AND "Terminology as Topic"[Mesh] AND (Dutch[lang] OR English[lang])	3	1
2	"catheter related bloodstream infection defining [TIAB]"	10	1
3	((("Catheter-Related Infections/epidemiology"[Mesh]) OR "Catheter-Related Infections/microbiology"[Mesh]) AND "Cross Infection/microbiology"[Mesh]) AND "Bacteremia/microbiology"[Mesh]	111	10
4	(("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh]) AND "Clinical Trials as Topic"[Mesh]	18	0
5	(("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh]) AND "Randomized Controlled Trial"[pt]	29	1
6	(("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh]) AND "empiric"[TIAB]	25	1
7	((((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh])))) AND "Teicoplanin"[Mesh]	7	0
8	((((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh])))) AND ("Prostheses and Implants"[Mesh])	8	0
9	((((("Catheter-Related Infections"[Mesh]) AND "Anti-Bacterial Agents/therapeutic use"[Mesh])))) AND "Prosthesis-Related Infections"[Mesh]	8	0
10	(("Catheter-Related Infections"[Mesh])) AND "Prosthesis-Related Infections"[Mesh]	47	1
11	"Catheter-Related Infections"[Mesh]) AND "Candidemia"[Mesh]	89	1
12	"Anti-Bacterial Agents/therapeutic use"[Mesh]) AND "tunneled catheter"	16	0
13	"Anti-Bacterial Agents/therapeutic use"[Mesh] AND "Hickman"[TIAB]	65	0
14	"Coagulase-Negative Staphylococci [tiab] and/or enterococci [tiab] and joint infections [tiab]"	120	1

For chapter 6b we focussed on evidence for treatment efficacy for sepsis due the HRMO that are most frequently encountered in the Netherlands: Enterobacterales resistant to 3rd generation cephalosporins or have shown to harbour ESBL or AmpC genes (3GCR-E). Sepsis due to these microorganisms would not be appropriately treated with current general empirical therapy recommendations.[28] We did not systematically search for risk factors for sepsis due to other HRMOs. In addition, we did not systematically summarize antibacterial agents that are currently not easily

available in the Netherlands, such as ampicillin/sulbactam, cefoxitin, cefepime, cefoperazone/sulbactam and doripenem.

For chapter 6c we performed a literature search on the efficacy and safety of empirical treatment with 3rd generation cephalosporins in patients with sepsis due to *S. aureus* infections. For definite treatment of sepsis due to *S. aureus* we refer to the NVMM guideline on *S. aureus* bacteraemia.

7. What is the optimal empirical antibacterial therapy of sepsis in patients with a penicillin allergy?

For chapter 5, we included systematic reviews and randomized trials on the following specific question: what is the optimal empirical antibacterial therapy of sepsis in patients with a penicillin allergy? We focused our search on the use or avoidance of beta-lactams because for sepsis treatment.

PICO
P: patients presenting with sepsis and reporting a penicillin allergy
I: patients treated with antibiotics including a beta-lactam* antibiotic
C: patients treated with antibiotics not including a beta-lactam*
O: mortality (30-day)/ no. of immediate type reactions to the antibiotic / toxicity or intolerability

Because we could not include any RCTs or systematic reviews, we performed an adjusted search for studies that would contribute to a pragmatic approach to reported allergy in the patient with sepsis.

8. What is the optimal timing of empirical antibacterial therapy in patients with sepsis?

For this key question, we used the literature as presented in the SSC 2016 guidelines, chapter on antibacterial therapy.[36] An additional search for studies published since the SSC guidelines led to one RCT. In addition, we included two large landmark observational studies to our evidence summary.

9. What is the optimal duration of antibacterial treatment for sepsis?

For this key question, we used the literature presented in the SSC 2016 guideline, IDSA guideline on HAP/VAP 2016 and SWAB guideline on antimicrobial stewardship 2016.[36,37,40] An additional search for studies published since the SSC search for this question led to new meta-analyses on PCT-guided antibiotic treatment duration.[233-235] Also, a consensus statement on antimicrobial de-escalation in critically ill patients from the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) was used for relevant literature on de-escalation in patients with sepsis.[254]

10. In patients with sepsis, should we recommend pharmacokinetic / pharmacodynamic dosing optimization for empirical antibacterial therapy?

For this key question we used the literature and grading presented in the SSC 2016 guideline and IDSA guideline on HAP/VAP.[36,37] An additional search for studies published since the SSC search for this question led to three new systematic reviews on beta-lactams,[74,274,280] and a clinical practice guideline and systematic review on vancomycin.[286,298]

In addition to the included meta-analyses, many other meta-analyses have been published comparing extended or continuous beta-lactam infusion to intermittent infusion in different ways, generally showing either reduced mortality in the prolonged infusion group or no difference between extended and intermittent infusion.[277,317-324] Not all meta-analyses were restricted to patients with sepsis. Also, some meta-analyses included observational studies, while the meta-analyses including RCTs only were published in 2011 and 2013, thereby missing at least 7 RCTs on the subject. These meta-analysis were therefore not summarized.

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