STICHTING WERKGROEP ANTIBIOTICABELEID

SWAB guidelines for

Antibacterial therapy of adult patients with Sepsis

Dutch Working Party on Antibiotic Policy (SWAB)

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Table of contents

Chapter 1 Introduction
General introduction
Scope of the guideline
Definitions
Key questions

Chapter 2 Aetiology and resistance patterns of microorganisms causing sepsis

Chapter 3 Combination therapy versus monotherapy for sepsis

Chapter 4 Selection of antimicrobial drugs for empirical therapy of sepsis

Chapter 5 Selection of antibacterial drugs for therapy in documented *S. aureus* sepsis

Chapter 6 Dosage of antibacterial drugs for therapy of sepsis

Chapter 7 Duration of antibacterial drugs for therapy of sepsis

Chapter 8 Switching intravenous to oral antibacterial therapy for sepsis

Chapter 9 Timing of starting antibacterial therapy for sepsis and sampling for blood cultures

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Chapter 1
Introduction

General introduction

The Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibioticabeleid, SWAB) was founded in 1996 as an initiative of the Dutch Society for Infectious Diseases (VIZ), the Dutch Society for Microbiology (NVMM), and the Dutch Association of Hospital Pharmacists (NVZA). SWAB develops national guidelines for the use of antibiotics in hospitalised patients in order to optimise the quality of prescribing, thus, contributing to the containment of antimicrobial drug costs and resistance.

The first SWAB guideline on sepsis was published in 1999. An update was considered timely to comply with the revised procedures of SWAB guideline development. This update was developed according to the Evidence Based Guideline Development method (EBRO) (1). The AGREE criteria (www.agreecollaboration.org) provided a structured framework both for the development and the assessment of the draft guideline. A systematic search of the literature was performed according to eight key questions concerning the antibiotic treatment of adult patients with sepsis. The databases from Pubmed and the Cochrane Library were used as main resources. In the separate literature searches, no time limit was chosen and the included studies go as far back as 1976. Conclusions were drawn, completed with the specific level of evidence, according to the grading system adopted by SWAB (Table 1). Subsequently, specific recommendations were formulated. Each key question will be answered in a separate chapter.

Scope of the guideline

This guideline concerns antimicrobial therapy in all adult patients with sepsis. The performed literature searches included studies on adult patients only. Therefore, this guideline can not indiscriminately be applied to children with sepsis.
In addition, this guideline does not cover the following:

- Other treatment components of sepsis such as volume resuscitation, inotropics, corticosteroids and activated protein C
- Antibiotic therapy of sepsis associated with indwelling intravascular devices which are not removed (tunnelled catheter or port-a-cath) and which need a different approach. A recent international guideline is available (2).
- Diagnostic measurements, such as the use of biomarkers

For this update, the structure of the original guideline was predominantly followed. A reasonable distinction was made between patients on the basis of immunological status (neutropenic versus non-neutropenic) and the setting in which sepsis was acquired (community-acquired, nosocomial acquired). This guideline focuses on empirical antimicrobial therapy for sepsis with no obvious site of infection at the time of presentation as well as sepsis with a probable/suspected site of infection. In case of sepsis and community-acquired pneumonia (CAP), urosepsis and sepsis and candidemia and sepsis and meningitis (draft), we refer to existing SWAB guidelines (www.swab.nl/guidelines).

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This national guideline is a framework for the target users who are members of antibiotic committees of hospitals and who should adapt the recommendations according to local susceptibility patterns and formulary strategies.

Definitions

Sepsis

There has been a lot of debate on the appropriate definition of sepsis since its original formulation in 1992 (3). However, no generally accepted alternative definition has been acknowledged. In this guideline, the preparatory committee agreed to adopt the following definition of sepsis:

Sepsis is considered present if an infection is suspected or proven and two or more of the following criteria are met: tachycardia (>90/min), tachypnea (>20/min), fever (>38.3°C) or temperature <35.6°C, leucocytosis (>12x10^9/l) or leucopenia (<4x10^9/l), >10% immature (band) forms. Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Septic shock is diagnosed when hypotension persists despite adequate fluid resuscitation or when perfusion abnormalities occur. This guideline focuses on bacterial and fungal infections associated with sepsis.

Other relevant definitions

Bloodstream infection (bacteraemia)

The presence of bacteria in the blood as demonstrated by culture.

Neutropenia

Neutropenia is defined as an absolute neutrophil count of <0.5 x 10^9/l (500 cells/mm^3) or a count of <1.0 x10^9/l (1000 cells/mm^3) with a predicted decrease to <0.5 x 10^9/l (500 cells/ mm^3) (4).

Febrile neutropenia

Fever, defined as a single oral temperature of ≥38,3º Celsius (101º F) or a temperature of ≥ 38.0º Celsius (100,5º F) for ≥1 hour (4).

Community-acquired

In the past, community-acquired infections were defined as the occurrence of infection outside of the hospital or within two days of admission. However, the quality of health-care systems has improved and nowadays more patients receive home care. Two prospective studies showed that the micro-organisms involved in community-acquired bloodstream infections in patients hospitalised in the prior 30-90 days, residing in nursing homes, receiving haemodialysis or having long-term intravascular devices (including haemodialysis) differ from the micro-organisms involved in patients with “true” community-acquired infections. The aetiology resembles the aetiology of nosocomial bloodstream infections (5, 6).

Therefore in this guideline, **community-acquired** is defined as the occurrence of infection outside of the hospital or within two days of admission, except for patients hospitalised in the

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past 30-90 days, residing in nursing homes, receiving haemodialysis or having long-term intravascular devices.

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 (≠ home for the elderly) or having long-term intravascular devices (5, 7-10).

ICU-acquired

Acquired during stay in the ICU (two days or more) (11).

Ventilator-associated pneumonia (VAP)

Onset of pneumonia after two days or more of mechanical ventilation (12-16).

Prior use of antibiotics

In the literature, many different definitions of prior use of antibiotics are being used (15-36). It is difficult to define beyond which time point the prior use of antibiotics will not affect the type of pathogens involved. One study on the association between antibiotic resistance and prescribing showed that trimethoprim resistance in bacteria isolated from urine samples was significantly associated with prior trimethoprim use. The association was strongest for patients recently exposed to trimethoprim (within eight to fifteen days prior to the date of the urine sampling), but lasted up to six months before the date of urine culture. There was no association between trimethoprim resistance and exposure more than six months previously (37). A recent Dutch study on colonisation and resistance dynamics of Gram-negative bacteria in the intestinal and oropharyngeal flora of hospitalised patients showed that the increased oropharyngeal colonisation rates during hospital stay were still present in the three months following hospital discharge. The percentage of intestinal drug-resistant *Escherichia coli* in ICU patients increased during hospitalisation and did not decrease in the three months after hospital discharge (38). Another Dutch colonisation study showed that the slight increase in the prevalence of resistant faecal *E. coli* strains at hospital discharge slowly decreased during the months after discharge, reaching the admission resistance level at six months (39).

There is insufficient evidence for an exact time frame defining **prior use of antibiotics** as a risk factor for infection with resistant micro-organisms. It seems reasonable to take into account previous use of antibiotics within three to six months prior to presentation.

Empirical antibacterial therapy

Therapy that is started before the pathogen and its susceptibility pattern are known. The choice of antibacterial therapy is largely based on local surveillance data on aetiology and antimicrobial resistance.

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Key questions

1a. What are the most common micro-organisms involved in community-acquired and nosococomial bloodstream infections with no obvious initial site of infection in the Netherlands?

1b. What are the most common micro-organisms involved in specific community-acquired and nosocomial infections associated with sepsis in the Netherlands?

1c. What is the susceptibility for relevant antibiotics of the micro-organisms most frequently isolated from blood in the Netherlands?

2. Is there evidence that combination antibacterial therapy is superior to monotherapy in adult patients with sepsis?

3a. What are the most important considerations in choosing the optimal empirical antibacterial therapy in adult patients with sepsis and no obvious site of infection in the Netherlands?

3b. What is the optimal selection of empirical antibacterial therapy in adult patients with sepsis and suspected site of infection in the Netherlands?

3c. Is there evidence that patients with intra-abdominal sepsis require empirical antibacterial therapy with activity against enterococci?

4. What is the optimal selection of antibacterial therapy in adult patients with sepsis and documented methicillin susceptible *S. aureus* bacteraemia?

5. What principles should be taken into account when dosing antibacterial agents in adult patients with sepsis?

6a. What is the optimal duration of therapy in adult patients with sepsis?

6b. Does sepsis caused by specific pathogens require a longer duration of antibacterial therapy?

7. Under what circumstances and when can intravenous therapy be switched to oral therapy in adult patients with sepsis?

8. Is there evidence for optimal timing to start antibacterial therapy in adult patients with sepsis?

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Chapter 2
Aetiology and resistance patterns

Key question 1a. What are the most common micro-organisms involved in community-acquired and nosocomial bloodstream infections with no obvious initial site of infection in the Netherlands?

Since the syndrome of sepsis is caused by the effects of microorganisms or their toxic products in the bloodstream, knowledge on the spectrum of the most common micro-organisms involved in bloodstream infections is needed to guide the selection of empirical antibiotics for sepsis. It is important to consider that not all patients with bloodstream infections have sepsis, and that patients with sepsis can have negative blood cultures (40). Moreover, although the initial site of infection can be unclear at the time of presentation, in most cases the site will become apparent during the course of the infection. As it is impossible to exclusively study the aetiology of those bloodstream infections in which no initial site of infection was apparent, studies on bloodstream infections of any site of origin were evaluated.

Large studies on the aetiology of bloodstream infections in the Netherlands are scarce (8, 41-45). NethMap 2009 was used as the main source both for bloodstream isolates and their resistance patterns (46). NethMap is an updated 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. Hospital departments as well as outpatient clinics were the sources of the isolates (from blood, urine, respiratory tract, pus and wounds) from areas covering 30% of the Dutch population. Only the first isolate of each species from a patient was included.

NethMap 2009 lists 3872 blood isolates from unselected hospital departments from patients suffering from both community-acquired and nosocomial infections. The site of infection is not specified. The most frequently isolated micro-organisms were: coagulase-negative staphylococci (CNS) (30%), *Escherichia coli* (23%), , *Staphylococcus aureus* (12%), *Streptococcus pneumoniae* (9%), *Klebsiella species* (6%) *and Enterococcus species* (6%) (Table 2). The clinical significance of the CNS blood isolates was not stated and is therefore not clear. True CNS bacteraemia is often associated with the presence of indwelling central venous catheters. In general, the mainstay of treatment of these (usually low-grade) infections is catheter removal without the administration of antibiotics. The treatment of CNS bloodstream infections in patients with long-term tunnelled central venous catheters and devices (port-a-caths) is beyond the scope of this guideline (see Chapter 1, page 5). The prevalence of *Pseudomonas spp* among these 3872 blood isolates was 3% only. In other studies, this percentage was quite variable, between 0-14% (8, 41, 44, 45).

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In NethMap, it was not specified which proportion was community-acquired or nosocomial. There are few data on polymicrobial sepsis in the Netherlands; 13% and 23 % is being reported in two studies (8, 45). Most Dutch studies were conducted in patients with nosocomial bloodstream infections (42-45). Only one study made a distinction between community-acquired and nosocomial blood stream infections (8). In addition, blood isolates from other European studies and the US were evaluated in order to study the aetiology of community-acquired and nosocomial bloodstream infections separately. Overall, the most frequently involved micro-organisms in community-acquired bloodstream infections were *E. coli* (14-42%), *S. pneumoniae* (3-33%) and *S. aureus* (7-21%) (8, 40, 47-53). The prevalence of *Pseudomonas spp* was low (0-5%). These studies were conducted in other European countries and the US. In studies reporting nosocomial bloodstream infections, CNS (6-60%), *S. aureus* (11-26%), *E. coli* (0-42%), *Enterococcus spp* (2-13%) and in some studies *Klebsiella spp* (0-13%) were most commonly involved. In general, the proportion of *Pseudomonas spp* was higher than in community-acquired bloodstream infections (0-21%) (8, 42-45, 48, 49, 52, 54-61). These studies were conducted in the Netherlands, in other European countries and in the US.

The prevalence of micro-organisms involved in bloodstream infections in patients with neutropenia and fever is reported in several Dutch studies, mainly antibiotic trials (62-66). The most common micro-organisms in these studies were: α- haemolytic streptococci (18-40%), CNS (23-27%) and Enterobacteriaceae (9-26%) (predominantly *E. coli*). In one trial, *Enterococcus spp* was more prominent (18%) (62). The overall percentage of *Pseudomonas spp* was low (2-7%). Other trials conducted in Europe and the US report similar findings. The prevalence of *Enterococcus spp* was variable (0-9%) (67-76). Most studies on patients with neutropenia and fever include blood cultures taken during consecutive episodes of fever. Thus, in addition to the use of antibiotic prophylaxis, the prevalence and distribution of the pathogens depend on the antibiotics for empirical therapy given at the start of the first episode of fever. For instance, the use of cefpirome in the study by Timmers et al. might explain the relatively high percentage of enterococci in blood cultures of their patient population with neutropenia and fever (62). The nature of involved pathogens also depends on the spectrum of the drug used for oral antibiotic prophylaxis and on whether the infection was acquired at home or in the hospital. The above mentioned trials did not specify the setting of acquisition of the infection.

Conclusions

*	It is impossible to exclusively study the aetiology of bloodstream infections in which no site of infection eventually became apparent.
*	The most frequently isolated micro-organisms involved in non-neutropenic bloodstream infections in the Netherlands are CNS (30%), *E. coli* (23%), *S. aureus* (12%), *S. pneumoniae* (9%), *Klebsiella spp* (6%) *and Enterococcus spp* (6%). In this database, no distinction is made between community-acquired and nosocomial infections. NethMap, 2009

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Level 1	In Europe and the US, the most frequently isolated micro-organisms in community-acquired non-neutropenic bloodstream infections are *E. coli* (14-42%), *S. pneumoniae* (3-33%) and *S. aureus* (7-21%). A2 Michel; Pedersen; Luzarro; Crowe; Valles; Weinstein[8, 47-49, 51, 52] B Degoricija; Crane; Baine[40, 50, 53]
Level 1	In Europe and the US, CNS (6-60%), *S. aureus* (11-26%), *E. coli* (0-42%), *Enterococcus spp* (2-13%) and in some studies *Klebsiella spp* (0-10%) are most commonly isolated in non-neutropenic nosocomial bloodstream infections. A2 Michel; Gastmeier; Vincent; Unal; Luzarro; Fluit; Crowe; Weinstein; Gordon[8, 48, 49, 52, 54-57, 61] B Mintjes-de Groot; Hopmans; Ibelings; Kieft; Lazarus; Suljagic; Renaud[42-45, 58-60]
Level 2	In patients with neutropenia and bloodstream infection in the Netherlands, α- haemolytic streptococci (18-40%), CNS (23-27%) and Enterobacteriaceae (9-26%) (predominantly *E. coli*) are most frequently isolated. Studies do not distinguish between community-acquired and nosocomial infections. B Timmers; Dompeling; De Pauw; Erjavec; Cornelissen[62-66]

***** It is impossible to grade the data from NethMap with a specific level of evidence. However, the committee considers these surveillance data to be most appropriate as NethMap analyses the largest updated Dutch database, covering 30% of the Dutch population.

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Key question 1b. What are the most common micro-organisms involved in specific community-acquired and nosocomial infections associated with sepsis in the Netherlands?

The preparatory committee considers five major infection sites of sepsis: lungs (1), urinary tract (2), abdomen including the biliary tract (3), skin and skin structure (4) and central nervous system (5). In order to make recommendations on the selection of antimicrobial therapy of sepsis from one of the aforementioned sites, it is necessary to consider the most common pathogens in both community-acquired and nosocomial infections.

1. Sepsis and pneumonia

This section has been completed in 2010. For the latest review of the literature on community acquired pneumonia (CAP), we refer to the revised SWAB guideline on CAP. It was decided not to include CAP in this guideline.

In patients with hospital-acquired pneumonia (HAP), including patients with ventilator-associated pneumonia (VAP), the most commonly involved pathogens depend on the duration of hospitalisation and ventilation (16, 77-85). Therefore, many studies on the aetiology of HAP and VAP make a distinction between early and late onset of pneumonia. The problem with comparing studies on the aetiology of HAP and VAP is that most studies included patients with VAP only and that many different definitions of early and late VAP were used. In patients with HAP, most studies used a cut-off point of hospital admission of five days (or more) to distinguish early from late onset HAP (19, 80, 84). In VAP studies, definitions of early and late onset were more variable, but the most common definition of early onset VAP is the occurrence within the first four days of mechanical ventilation (12, 14, 80, 81, 84-94). The difference in definitions of early and late VAP might explain the variation in aetiology. Early onset HAP/VAP was mainly caused by *S. pneumoniae* (12-32%), *S. aureus* (9-20%) and *H. influenzae* (26-31%) (83, 84, 86). Late onset HAP/VAP was more often caused by Enterobacteriaceae (6-26%) and non-fermentative Gram-negative bacteria (19-80%) including *P. aeruginosa* (12-64%) (80, 82-84, 86, 94, 95) (Table 3). These findings were recently confirmed in a report from the large Dutch surveillance network PREZIES. Early and late VAP were defined as ≤ and > five days of mechanical ventilation, respectively (81). However, other studies have shown that in patients with early onset HAP/VAP, the presence of non-fermentative Gram-negative bacteria and Enterobaceriaceae was not negligible, ranging from 11-45% and 4-25% respectively in different studies (80, 82, 83, 96, 97).

Several factors that explain these differences can be considered. First, several cohort studies showed that previous antibacterial therapy is associated with an increased risk of potentially resistant bacteria such as *P. aeruginosa* (16, 98) and multiresistant *Acinetobacter baumannii* (17), suggesting that the previous antibiotic therapy influences the nature of pathogens in patients with early VAP (15, 21, 22, 79, 99). Moreover, it is possible that patients classified as having early VAP in some studies, had a considerable duration of prior hospitalisation before ventilation. This would also influence the type of pathogens involved (12, 78). Two

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observational US studies on the aetiology of nursing-home acquired pneumonia also showed a considerable percentage of *P. aeruginosa* (8-52%) and of Enterobacteriaceae (12-18%) (100, 101). In both studies, the proportion of *S. aureus* was approximately 10% while only in one study, *S. pneumoniae* and *H. influenzae* were isolated in 28 and 19%, respectively (100).

2. Urosepsis

The SWAB guideline for antibacterial therapy of complicated urinary tract infections states that *E. coli* is the causative pathogen in 46%. Furthermore, *P. mirabilis, K. pneumoniae* and *Enterococcus spp* are frequently isolated (Table 4) (102). The guideline categorizes patients with or without urinary catheter. This was considered more relevant by the authors than distinguishing patients with community-acquired and nosocomial infections. A recent large Dutch study also identified *E. coli* as the major pathogen of community-acquired urinary tract infections (66%) (103). In this study as well as in another Dutch study in nursing home residents, enterococci were rarely cultured from urine samples (0-3%) (103, 104). In the latter study, other Enterobacteriaceae such as *P. mirabilis* (26%) and *K. pneumoniae* (14%) were often isolated in addition to *E. coli* (47%). In a large European trial in hospitalised patients with urinary tract infections, enterococci (13%) were more often isolated, suggesting this pathogen is predominantly causing nosocomial urinary tract infections (105).

3. Intra-abdominal sepsis

Data from a recent Dutch multicentre randomised clinical trial (RCT) comparing on-demand versus planned relaparotomy in patients with complicated intra-abdominal infections showed that the major pathogens involved in community-acquired and nosocomial intra-abdominal sepsis are Enterobacteriaceae (predominantly *E. coli*) (42% in community-acquired vs 47% in nosocomial infections), enterococci (18 vs 24%) and anaerobes (14 vs 15%) (106) (Table 5). Other pathogens were streptococci (9 vs 5%) and *Candida spp* (9 vs 6%). The percentage of *P. aeruginosa* was low (5% vs 3%). Seventy-seven percent of the patients had polymicrobial infections. In this study, no apparent differences in aetiology of community-acquired and nosocomial intra-abdominal sepsis was observed. Two older and smaller Dutch antibiotic trials in patients with intra-abdominal infections showed similar results, except for one study showing a higher percentage of Pseudomonas infections (9%) (107, 108). It is unclear whether these studies included patients with nosocomial or community-acquired infections. In other European countries, the most commonly isolated pathogens in community-acquired complicated intra-abdominal infections were Enterobacteriaceae (29-64%) followed by anaerobes (10-33%), enterococci (5-11%) and streptococci (7-13%).

Yeasts (*Candida spp)* (0-7%) (refs 30-31) and *Pseudomonas spp* (0-10%) were less prevalent (29-31, 109). However, estimating the prevalence of *Candida spp*. is difficult as many antibiotic trials only report the bacterial pathogens at baseline and do not mention any isolation of yeasts (29,110,111, 112,113). Antibiotic trials in the US in patients with intra-abdominal infections also showed that Enterobacteriaceae (16-50%) and anaerobes (31-62%) were the most commonly isolated pathogens followed by streptococci (6-15%), enterococci (0-6%) and

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Pseudomonas spp (2-8%), but it is unclear whether patients with community-acquired or nosocomial infections were included (110-112).

Five studies on patients with cholangitis showed that the most frequently isolated micro-organisms from bile were *E. coli* (17-39%), *Klebsiella spp* (13-17%), *Enterococcus spp* (6-41%). The percentage of anaerobes varied from 0 to 18%, usually isolated as a component of a polymicrobial culture (113-117). Bacteraemia occurs in 15-36% of the patients with cholangitis (115, 118). The micro-organisms isolated from blood usually show a similar distribution as those from bile, except for anaerobes and enterococci which are less frequently isolated from blood (0-1,5 and 0-5 % respectively) (117, 119).

4. Sepsis and skin and skin structure infections

Skin and skin structures infections (SSSI) are divided in two broad categories: uncomplicated and complicated SSSI. Uncomplicated SSSI include simple abscesses, impetiginous lesions, furuncles, cellulitis and erysipelas. The complicated category is heterogeneous, comprising infections involving deeper soft tissue or requiring significant surgical intervention (e.g. burns, infected ulcers, major abscesses) and/or infections in patients with underlying diseases complicating the response to treatment (e.g. diabetes mellitus and arterial or venous insufficiency). Superficial infections or abscesses at an anatomical site where the risk of anaerobic or Gram-negative pathogen involvement is increased (e.g. peri-rectal area) are considered complicated infections (120).
Necrotising fasciitis could be considered a complicated SSSI. However, as the FDA advises not to include such infrequently occurring infections in primary clinical trials supporting the approval of new antimicrobial agents, the conclusions from complicated SSSI studies can not be generalised to necrotising fasciitis (120). In this guideline, necrotising fasciitis is therefore considered as a distinctive category of SSSIs.

The predominant pathogens involved in uncomplicated SSSI are *S. aureus* and β-haemolytic streptococci (120-125). In most studies, it is not specified whether the infections were community-acquired or nosocomial. There are no Dutch data regarding the aetiology of complicated skin and skin structure infections. The SENTRY surveillance program, providing worldwide data on skin and skin structure infections, showed *S. aureus* (43%) and Enterobacteriaceae (25%) as most commonly isolated pathogens, followed by *Pseudomonas spp* (11%), *Enterococcus spp* (7%) and *Streptococcus spp* (5%) (126) (Table 6). The aetiology in trials on complicated skin and skin structure infections in the US was similar, except for anaerobic pathogens being more frequently isolated (15-27%) (35, 36, 127, 128). In most studies, no distinction is made between community-acquired and nosocomial infections.
In patients with necrotising fasciitis, monomicrobial (15-38%) and polymicrobial (66-85%) infections have been described (129-132). Monomicrobial infections are usually caused by group A streptococci (GAS) (34-54%) or *S. aureus* (11-20%) (130-132). Polymicrobial necrotising fasciitis is caused by a variety of micro-organisms including Enterobacteriacae (22-28%), anaerobes (9-36%), enterococci (9-17), non-fermentative Gram-negative micro-organisms (4-17%), *Streptococcus spp*. (9-14%) and *S. aureus* (4-15%) (130-132).

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5. Sepsis and meningitis

This section has been completed in 2010. For the latest review of the literature, we refer to the SWAB guideline on meningitis. The search results of this guideline have been included and updated. It was decided not to include any recommendations on the treatment of meningitis in this guideline.

Conclusions

Level 2	· In early onset HAP/VAP the predominant pathogens are *S. pneumoniae* (6-32%), *S. aureus* (11-31%) and *H. influenzae* (6-31%). A2 Weber[80] B Valles; Wood; George[83, 84, 86]
Level 1	· The presence of Enterobacteriaceae (4-25%) and non-fermentative Gram-negative bacteria (11-45%), including *P. aeruginosa* (4-42%) has also been described in patients with early HAP/VAP. A2 Weber; Sun; Ibrahim; Giantsou[80, 82, 96, 133] B Wood; Chevret[83, 97]
Level 1	· Late onset HAP/VAP is also caused by Enterobacteriaceae (6-26%) and non-fermentative Gram-negative bacteria (19-80%), including *P. aeruginosa* (12-64%). A2 Weber; Ibrahim; Giantsou; Sun[80, 82, 96, 133] B Wood; George; Moine; Kollef; Rello; Trouillet[16, 79, 82-84, 94]
Level 2	In patients with nursing home acquired pneumonia, *P. aeruginosa* (8-52%) and Enterobacteriaceae (12-18%) are frequently isolated aside from *S. pneumoniae, S. aureus* and *H. influenzae.* B Philips; Muder[100, 101]
Level 1	In patients with complicated urinary tract infections, *E. coli* (47-66%), *P mirabilis* (5-26%), *K. pneumoniae* (4-14%), *Enterococcus spp* (0-14%) are the predominant pathogens. Enterococci are predominantly cultured in nosocomial infections. Retrieved from Geerlings et al.: complicated urinary tract guidelines [102] A2 Fluit, Nys[103, 105] B Vromen[104]
Level 2	· Most community-acquired and nosocomial intra-abdominal infections in the Netherlands are polymicrobial and most frequently involve Enterobacteriaceae (39-47%) (*E. coli* in particular), enterococci (15-24%) and anaerobes (14-24%). Other less frequently isolated pathogens are yeasts (*Candida spp*) (5-9%) and streptococci (2-14%). B Hoogkamp; de Groot[107, 108] * Van Ruler[106]
Level 2	· In patients with cholangitis, the most frequently isolated micro-organisms from bile are *E. coli* (17-39%), *Klebsiella spp* (13-17%),

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Level 2	*Enterococcus spp* (6-41%) and anaerobes (0-18%). A2 England[134] B Chang; Reknitrmir; Weber; Leung; Leung; Hanau [113-117, 119] · The micro-organisms isolated from blood usually show a similar distribution as those from bile, except for anaerobes and enterococci which are less frequently isolated from blood (0-1,5 and 0-5 % respectively). B Leung; Hanau[117, 119]
Level 2 *Level 1* *Level 2* *Level 2*	· In patients with uncomplicated skin and skin structure infections, *S. aureus* and β-haemolytic streptococci are most frequently isolated. B Hook; Carratala; Peralta; Perl[122-125] D Stevens; Food and Drug Administration[120, 121] · Worldwide, in patients with complicated SSSI *S. aureus* (24-49%), Enterobacteriaceae (15-25%) and *Streptococcus spp* (5-20%) are most frequently isolated, followed by enterococci (7-9%), and *Pseudomonas spp* (6-11%) and anaerobes (0-27%). A2 Giordano; Goldstein; Gesser [35, 36, 127] B Pelak; Fritsche[126, 128] · In patients with monomicrobial necrotising fasciitis, Group A streptococci (34-54%) and *S. aureus* (11-20%) are most frequently isolated B Elliott; McHenry; Wong[130-132]. · Polymicrobial necrotising fasciitis is caused by a variety of micro-organisms including Enterobacteriacae (22-28%), anaerobes (9-36%), enterococci (9-17%), non-fermentative Gram-negative micro-organisms (4-17%), *Streptococcus spp*. (9-14%) and *S. aureus* (4-15%) B Elliott; McHenry; Wong[130-132].

* The level of evidence of this prospective study cannot be determined as the results have not been published yet

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Key question 1c. What is the susceptibility for relevant antibiotics of the micro-organisms most frequently isolated from blood in the Netherlands?

In order to recommend an optimal empirical antibacterial regimen for sepsis in the Netherlands, the susceptibility for relevant antibiotics of the micro-organisms most frequently isolated in bloodstream infections should be considered. The resistance rates for isolates from blood in 2006 (Table 7) were derived from the database containing isolates from patients hospitalised in "general hospital departments" as described in NethMap 2007 (135). NethMap 2009 was used to obtain the overall susceptibility for relevant antibiotics of bacteria isolated from blood, urine, respiratory tract, pus and wounds (together) in 2008 (Table 8) (46).

In 2008 it has been decided by the Netherlands Society of Medical Microbiology (NVMM) and the Society for Infectious Diseases (VIZ) to replace the North American CLSI guidelines for susceptibility testing by the European guidelines (EUCAST). These guidelines differ with respect to the interpretation of laboratory results for which breakpoint criteria are set. It has been shown that resistance levels increase using the EUCAST guidelines as lower levels of breakpoints for susceptibility are applied. This could partly explain the higher resistance rates found for amoxicillin and clavulanic acid and cephalosporins.

In order to determine the carrier state and resistance level of *S. aureus* in the community, NethMap 2009 also reported the results of nose swabs from 2369 healthy individuals as well as from nursing home residents of six different Dutch nursing homes in 2007 and 2008 (46). NethMap 2009 and NethMap 2010 contain prevalence data on extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* (46a, 46b). In the Surveillance of Extramural Resistance in the Netherlands (SERIN) surveillance 2009, urinary *E. coli* isolates resistant to co-amoxiclav were assessed for the presence of ESBL production. Five strains (1%) were ESBL positive. Among the E. coli isolates collected by ISIS-AR in 2009 the laboratory information system of Dutch clinical microbiological laboratories, 40 (0.2%) isolates were resistant to four classes of antibiotics and confirmed to be ESBL-positive. All isolates were susceptible to carbapenems. ESBL producing strains in Intensive Care Units were detected from 2000 on at varying percentages (0.5-5.9%) in one to eight centres.

Conclusions NethMap 2007 (blood isolates only) and 2009 (blood, urine, respiratory tract, pus and wounds) (46, 135)

*	⌂ In healthy *S. aureus* carriers, only 0.3% of the *S. aureus* isolates were methicillin resistant (MRSA) in the Netherlands. ⌂ 0.8% of the *S. aureus* carriers in nursing home residents were MRSA in the Netherlands ⌂ Methicillin resistance of *S. aureus* isolated from blood of hospitalised patients in 2007 was 1%. NethMap 2009 reported a MRSA percentage of 2% in unselected hospital departments. ⌂ Resistance percentages of *S. aureus* blood isolates to co-trimoxazole and

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	clindamycin were 2% and 3% respectively (NethMap 2007). NethMap 2009 reported 7% clindamycin resistance in unselected hospital departments. ⌂ Gentamicin resistance of *S. aureus* isolated from blood was 1%. NethMap 2009 reported 0.4-1% gentamicin resistance in unselected hospital departments.
*	⌂ The proportion of *S. pneumoniae* blood isolates resistant to amoxicillin was 0.2% and the resistance to penicillin of specimens isolated from all body sites in unselected hospital departments was 1%.
*	⌂ The resistance rate of β-haemolytic streptococci isolated from blood to amoxicillin was 0%. ⌂ Resistance of *S. agalactiae* blood isolates to erythromycin and clindamycin was 8 and 15% respectively. Erythromycin and clindamycin resistance in *S. pyogenes* blood isolates were 1 and 0% respectively (data not shown).
*	⌂ Amoxicillin resistance in *Enterococcus spp* in blood isolates was 18%. NethMap 2009 reported 2% *E. faecalis* resistance in unselected hospital departments and 10% resistance of *E. faecalis* isolates, collected in the ICU. ⌂ Resistance in *Enterococcus spp* isolated from blood to vancomycin was 1%. NethMap 2009 reported vancomycin resistance of *E. faecalis* isolates in one ICU in 2003 and in one ICU unit in 2007.
*	⌂ The resistance rate of *E. coli* isolated from blood to amoxicillin and clavulanic acid was 6%. NethMap 2009 reported 7% resistance in unselected hospital departments. In *E. coli* isolates from ICU patients this percentage increased to 25%. ⌂ Second and third generation cephalosporin resistance in *E. coli* isolated from blood was 4% and 2%. NethMap 2009 reported 3% resistance to third generation cephalosporins in unselected hospital departments. In ICU specimens, 15% *E. coli* resistance to second generation cephalosporins and 1-2 % resistance to cephalosporins of the third generation was reported. ⌂ Ciprofloxacin resistance in *E. coli* isolated from blood was 9% and NethMap 2009 reported a resistance rate of 10% in unselected hospital departments. In ICU isolates, 14% ciprofloxacin resistance was reported. In Urology Services, the resistance rate increased to 19%. ⌂ Gentamicin resistance in *E. coli* blood isolates was 3%. NethMap 2009 reported 4% resistance in unselected hospital departments and in ICU specimens a resistance of 5% was observed. ⌂ The percentage of multi-resistant *E. coli* strains in ICUs increased to 17% in 2007.
*	⌂ *P. mirabilis* resistance in blood isolates to amoxicillin and clavulanic

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	acid was 7%. NethMap 2009 reported 4% amoxicillin and clavulanic acid resistance in unselected hospital departments and 14% amoxicillin and clavulanic acid resistance was observed in ICUs. ⌂ Second and third generation cephalosporin resistance of *P. mirabilis* blood isolates was 0%. NethMap 2009 reported 3-8% resistance to second generation and < 1% resistance to third generation cephalosporins in ICUs. ⌂ Ciprofloxacin resistance rates in *P. mirabilis* isolated from blood and all body sites were 1% and 2% respectively. NethMap 2009 reported 7% ciprofloxacin resistance in ICUs. ⌂ *P. mirabilis* isolates from blood and from all body sites showed 3% and 4% resistance to gentamicin respectively.
*	⌂ *K. pneumoniae* resistance in blood isolates to amoxicillin and clavulanic acid was 5%. NethMap 2009 showed 3-6% resistance in unselected hospital departments and 24% resistance in ICU specimens ⌂ (Second and third generation) cephalosporin resistance of *K. pneumoniae* isolated from blood was 6%. NethMap 2009 showed 15% resistance to second generation cephalosporins and 5% resistance to third generation cephalosporins in isolates from all body sites in ICUs. ⌂ Ciprofloxacin resistance in *K. pneumoniae* blood isolates was 2%. NethMap 2009 reported ciprofloxacin resistance in 2-4 ICUs each year accounting for a resistance rate of 12%. 4% ciprofloxacin resistance was observed in unselected hospital departments. ⌂ Gentamicin resistance in *K. pneumoniae* blood isolates and in specimens isolated from all body sites was 3%. In ICU specimens, NethMap 2009 reported 11% resistance. ⌂ The percentage of multi-resistant *K. pneumoniae* strains was approximately 15%.
*	⌂ *E.cloacae* resistance in blood isolates to piperacillin/tazobactam was 12%. NethMap 2009 reported 10% piperacillin/tazobactam resistance in unselected hospital departments and 14% resistance in ICU isolates. ⌂ No resistance to imipenem was found in *E.cloacae* blood isolates ⌂ *E.cloacae* resistance in blood isolates and in specimens isolated from all body sites to meropenem was 0%. In unselected hospital departments, only 0.1% meropenem resistance was found. Meropenem resistance in ICUs was only found once in 2003. ⌂ The resistance rates of *E.cloacae* blood isolates to tobramycin, gentamicin and amikacin were 1%, 2% and 0% respectively. NethMap 2009 reported resistance of 4%, 3% and 0.1% respectively in unselected hospital departments and 10%, 6% and 0% respectively in ICUs. ⌂ The resistance of *E.cloacae* blood isolates to ciprofloxacin was 6% and 4% resistance was reported in unselected hospital departments. In ICU

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	isolates, 16% ciprofloxacin resistance was found. ⌂ *E.cloacae* resistance to co-trimoxazole among blood isolates was 10%. NethMap 2009 reported 4.5% resistance in unselected hospital departments and 10% in ICU isolates.
*	⌂ Resistance of *P. aeruginosa* to ceftazidime in blood isolates was 3%. NethMap 2009 reported 0-5% resistance in unselected hospital departments and 9% ceftazidime resistance in ICUs. ⌂ Resistance rates of *P. aeruginosa* blood isolates to piperacillin and piperacillin/tazobactam were 1% and 2%. NethMap 2009 reported piperacillin resistance of 3% in unselected hospital departments and of 17% in ICU isolates. ⌂ Tobramycin, gentamicin and amikacin resistance levels in *P. aeruginosa* isolated from blood were 2%, 0% and 2% respectively. NethMap 2009 showed 1%, 2-4% and 1% respectively in unselected hospital departments. In ICU isolates, 1-9%, 2-8% and < 4% was reported. ⌂ Ciprofloxacin resistance of *P. aeruginosa* in blood isolates was 8%. NethMap 2009 reported a resistance rate of 6% in unselected hospital departments and of 20% in ICU isolates. ⌂ Resistance rates of *P. aeruginosa* isolated from blood to imipenem and meropenem were 8% and 3% respectively. Less than 2 % resistance in specimens isolated from all body sites to meropenem was reported in unselected hospital departments and 4.5% in ICU isolates.
*	⌂ NethMap 2009 reported no penicillin resistance in *N. meningitidis*, but 2-4% of all CSF isolates were moderately susceptible to penicillin. Eight percent of the blood isolates were moderately susceptible to penicillin in 2008. ⌂ All strains (CSF and blood) were susceptible to ceftriaxone in 2008.
*	ESBL producing E.coli strains in the community were found in 1% in 2009 whereas ESBL producing E.coli strains in ICU's were found from 2000 on in percentages varying from 0.5-5.9% (NethMap 2010)

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Chapter 3
Combination therapy versus monotherapy

Key question 2. Is there evidence that combination antibacterial therapy is superior to monotherapy in adult patients with sepsis?

Gram-negative infections/bacteraemia – P. aeruginosa

The benefit of combination therapy over monotherapy in non-neutropenic as well as neutropenic patients with sepsis, particularly in patients with infections due to *P. aeruginosa*, is still a controversial subject. There might be several advantages of combination therapy. First, a broader antibiotic spectrum can be obtained. Second, enhanced potency (synergism) has been shown by many *in vitro* studies as well as in several animal models using Pseudomonas isolates. Various combinations of beta-lactam antibiotics, fluoroquinolones and aminoglycosides were synergistic (136-149). Third, *in vitro* studies and animal models on Pseudomonas infections, showed that combination therapy suppresses the emergence of resistant bacterial strains (137, 140, 145, 150-153). Disadvantages of combination therapy might be additional costs, enhanced drug-toxicity and possible induction of resistance by the broader spectrum and antagonism between specific combinations (154).

Many RCTs in non-neutropenic patients with sepsis compared single-agent antibacterial agents combined with aminoglycosides). Most studies showed no significant differences in efficacy (27, 28, 31, 155-170). However, these results are difficult to interpret because of heterogeneous patient populations and antibiotic regimens, often with different antibiotics in the monotherapy and combination therapy arms. Moreover, many studies are outdated, underpowered and studied antibiotics that nowadays would no longer be considered appropriate. In contrast to in vitro and animal studies, none of these trials focused exclusively on patients with Pseudomonas infections. In a recent large systematic review of RCTs comparing β-lactam monotherapy versus β-lactam-aminoglysoside combination therapy for non-neutropenic sepsis, studies were divided into a group comparing the same β-lactam and a group comparing different beta-lactam antibiotics (a beta-lactam with a broader spectrum in the mono-therapy arm) (171). Several subpopulations were defined, including patients with Gram-negative infections/bacteraemia and Pseudomonas infections.

Data on all-cause mortality in patients with Pseudomonas infections came from three trials only. Overall, in studies comparing the same beta-lactam, no significant differences were observed in all-cause mortality, clinical failure or bacteriological cure. However, in the subgroup of patients with sepsis, significantly less clinical failures were observed in the group receiving combination therapy, but this was not confirmed in the subgroup with Pseudomonas infections. In studies comparing different beta-lactams, a non-significant trend in reduced overall mortality in the monotherapy group was observed, reaching statistical significance in the subgroup with sepsis.

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As to clinical failure and bacteriological cure, significantly better outcomes were found in patients on monotherapy, but this was not confirmed in the subgroup with Gram-negative or Pseudomonas infections. No significant differences in superinfections and colonisation with resistant bacteria were found. A non-significant trend towards more adverse events with combination therapy was found, reaching statistical significance when nephrotoxicity was concerned. The authors of this systematic review conclude that the addition of an aminoglycoside to the same beta-lactam does not improve clinical efficacy. It is stated that the use of a narrower spectrum beta-lactam plus aminoglycoside instead of a single broad-spectrum beta-lactam, will result in increased failure rates and may be associated with increased mortality.

There are several considerations to be made. First, as most studies were not blinded, the results should be interpreted with caution. Second, in most studies of the meta-analysis, patients with sepsis represented a subpopulation only. Indeed, only 39% of included trials concerned patients with sepsis and/or suspected Gram-negative infections. Other trials included patients with pneumonia, intra-abdominal infections and urinary tract infections in which the proportion of patients with sepsis is unclear. Third, data on overall mortality were lacking in one third of included studies. Finally, the number of patients in relevant subpopulations was rather small.

Another meta-analysis on the effect of combination antibacterial therapy versus monotherapy on mortality in patients with Gram-negative bacteraemia showed no beneficial effect on mortality with combination therapy (172). A subgroup analysis of bacteraemia with *P. aeruginosa* showed a significant difference favouring combination therapy. This meta-analysis contained only two RCTs, the remainder being prospective and retrospective cohort studies. There was substantial heterogeneity in patient populations, including comorbidity and therapeutic regimens. Non-neutropenic as well as neutropenic patients were included. Three out of five studies on *P. aeruginosa* bacteraemia were retrospective and conducted before 1990. Four out of five studies used aminoglycoside mono-therapy, which nowadays is not considered appropriate.

Other (retrospective) observational studies comparing monotherapy to combination therapy in patients with Pseudomonas bacteraemia that are not included in the meta-analysis showed conflicting results (173-176). In two studies, initial combination therapy was associated with improved survival, but survival was similar in patients on definite monotherapy compared to definite combination therapy (173, 174). In two studies, no differences in mortality between patients with Pseudomonas bacteraemia on combination therapy and on monotherapy was observed (175, 176). A recent multicentre retrospective observational study on VAP caused by *P. aeruginosa* described a better outcome for patients treated with initial combination therapy. However, no differences in mortality and recurrence were observed when effective monotherapy was compared to effective combination therapy, suggesting that switching to monotherapy is safe and efficient once susceptibility is documented. No subanalyses were done on patients with sepsis and VAP (177).

In patients with neutropenia and fever, many RCTs comparing monotherapy with combination therapy have been performed. However, only a subpopulation of patients in those trials had

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documented infections and/or bacteraemia (64, 162, 178-191). Moreover, these studies have the same limitations as previously mentioned.

A large meta-analysis comparing monotherapy and combination therapy in neutropenic patients with fever, performed subgroup analyses in patients with documented infections, documented Gram-negative infections, Pseudomonas infections and bacteraemia (192). A group comparing the same β-lactam and a group comparing different beta-lactams in both treatment arms were distinguished. The authors found no significant difference in all-cause mortality in both groups, which was confirmed in all subgroup analyses, including bacteraemia and Pseudomonas infections. The number of patients with Pseudomonas infections however, was rather small. In the group comparing the same beta-lactams, no statistical difference in clinical failure was observed. Subgroup analyses showed no differences in clinical failure either, except for the patients with severe neutropenia (<100/mm^3) in which an advantage in patients on combination therapy was found. However, only two trials were included in this comparison. In the group comparing different beta-lactams, a significant advantage to monotherapy was seen. Subgroup analyses in patients with documented infections and with haematological malignancies confirmed these findings, although small numbers of patients were included, resulting in wide confidence intervals. No data were presented on the rate of bacteriological cure in both groups. There were no statistical significant differences in superinfections. Adverse events, including nephrotoxicity, were more frequently observed with combination therapy. The authors of this meta-analysis concluded that monotherapy can be regarded as the standard of care for the empirical treatment of febrile neutropenic patients. The addition of an aminoglycoside did not improve survival and was associated with significant morbidity mainly through aminoglycoside-associated nephrotoxicity. The question is whether the results of this meta-analysis can be extrapolated to neutropenic patients with sepsis. The mean percentage of documented infections was 57%, bacteraemia was present in 24% and subgroup analysis in those patients showed similar results. The number of patients with Pseudomonas infections included in the comparison on all cause mortality was small.

Another meta-analysis of RCTs concerning monotherapy versus combination therapy in patients with neutropenia and fever using clinical failure as an outcome reports a non-significant trend favouring monotherapy, including in the subgroup with bacteraemia (193). None of the included trials were blinded. The odds ratios of individual studies varied considerably and confidence intervals were wide.

In agreement with the results on the emergence of resistance in the study by Paul et al. (171), a recent meta-analysis of RCTs comparing β-lactam monotherapy to aminoglycoside/β-lactam combination therapy showed no difference in the emergence of resistance, including in the subgroup of patients with Pseudomonas infections (194).

Gram positive infections/bacteraemia - neutropenia

There is also an ongoing debate whether the initial empirical regimen in adult patients with sepsis and neutropenia should contain glycopeptides.

During the last decade, Gram-positive bacteria have replaced Gram-negatives as most common pathogens in febrile neutropenic cancer patients (62-66). This is most likely due to the widespread use of intravascular devices, antibacterial prophylaxis with fluoroquinolones and

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substantial mucosal damage caused by chemotherapy and radiotherapy (195, 196). Raad et al. showed that in cancer patients, intravascular devices are the cause of bloodstream infections in 56% (197). Worldwide, there is increasing resistance of Gram-positive pathogens to current β-lactam antibiotics.

In contrast to the low incidence of MRSA in the Netherlands, the reported percentages of MRSA in the US and non-Northern Europe are much higher, approximately 30 and 25% respectively (198, 199). Because of the emergence of vancomycin intermediate and heteroresistance in *S. aureus*, vancomycin is not routinely recommended in the empirical antibacterial therapy of patients with neutropenia and fever and its use is limited to specific indications in the US (4). The guidelines of the Infectious Diseases Society of America (IDSA) recommend the use of vancomycin in patients with neutropenia and fever with the following clinical characteristics (1) clinically suspected severe catheter-related infection, (2) known colonisation with penicillin- and cephalosporin-resistant pneumococci or methicillin-resistant *S. aureus* (MRSA), (3) positive blood cultures for Gram-positive bacteria before identification and susceptibility testing and (4) hypotension or other signs of cardiovascular impairment. (4). Another guideline from experts of countries of the Asia-Pacific region formulates similar recommendations (200). A Japanese guideline by Tamura et al. advocates the use of vancomycin in case of documented MRSA colonisation only (201). The German guidelines on this issue state that there is no place for empirical vancomycin therapy at all (202). A recent meta-analysis of RCTs on the value of adding anti Gram-positive therapy to the empirical antibacterial therapy in neutropenic patients with fever concluded that this strategy does not improve outcome (196). The subgroup of patients with Gram-positive infections showed similar outcome, although the number of patients was small.

Another recent meta-analysis of RCTs on the role of glycopeptides as part of the empirical regimen in patients with neutropenia and fever, showed that the addition of a glycopeptide to empirical treatment was associated with significantly less need for treatment modification in the study group as a whole, as well as in the three subgroups of patients with severe neutropenia, bacteraemia and documented infections (195). However, all cause mortality was similar, but significantly more adverse events, including nephrotoxicity, were observed in the glycopeptide group. Several comments were made on methodological quality of the RCTs. All studies were conducted before 1994 and outdated treatment regimens were used. Moreover, most studies were not blinded, which could have influenced treatment modification. In only six studies, the treatment regimens, apart from the addition/omission of a glycopeptide, were similar in both treatment arms. The authors of this meta-analysis concluded that there is no place for the routine use of glycopeptides as empirical therapy in patients with neutropenia and fever.

Conclusions

Level 1	There is no evidence from clinical studies in non-neutropenic patients with sepsis that combination therapy has superior efficacy compared to

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	monotherapy or vice versa, when the antibacterial spectrum of monotherapy is sufficiently broad, with regard to mortality, clinical failure, bacteriological cure and the emergence of resistance. A1 Paul; Bliziotis[192, 194] B Dupont; Jaspers; Sexton; Sandberg; McCormick; Kempf; Solberg; Rubinstein; Mouton; Larsen; Hoepelman; Limson; Sage; Cone; Extermann; Finer; Huizinga; Cometta [27, 28, 31, 150 , 155-160, 162, 163, 165-170]
Level 1	There is no evidence to support or refute the superior efficacy of combination therapy over monotherapy in patients with neutropenia and sepsis. A1 Paul; Furno[192, 193]
Level 1	There is no evidence that combination therapy has superior efficacy compared to monotherapy in non-neutropenic as well as neutropenic patients with Pseudomonas bacteraemia, provided that the antibacterial spectrum is sufficiently broad to treat Pseudomonas infections. A1 Paul; Paul[171, 192] B Safdar; Micek; Chamot[172-174]
Level 1	Combination antibiotic therapy with aminoglycosides is associated with more adverse events, especially nephrotoxicity. A1 Paul; Paul[171, 192]
Level 1	In patients with neutropenia and fever including the subgroup with documented infections, the empirical addition of glycopeptides against Gram-positive pathogens does not influence clinical outcome. A1 Paul; Vardakaz[195, 196]

Other considerations

Whether combination therapy is superior to monotherapy in patients with severe infections including sepsis is an ongoing debate. Despite lack of evidence, several guidelines recommend the use of combination therapy, in particular for patients with Pseudomonas infections (203, 204). Apart from the lack of evidence in clinical studies regarding superior efficacy and prevention of emergence of resistance, including in the subgroup of patients with Pseudomonas infections, there is a last argument defending combination therapy. It may decrease the risk of ineffective empirical therapy due to resistant pathogens. However, local data on aetiology and resistance patterns of the most commonly involved pathogens should guide the choice of empirical antibiotic therapy. Thus, it is important to realise that empirical antibacterial therapy in patients with sepsis and specific antibacterial therapy in case of proven Pseudomonas sepsis are two different entities.

As for empirical therapy in patients with sepsis, there is no clinical evidence that monotherapy, when the antibacterial spectrum is sufficiently broad, is inferior to combination therapy in patients with sepsis with or without neutropenia.

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In addition, combination therapy has been associated with increased nephrotoxicity. With respect to judging aminoglycoside toxicity, an important issue is the fact that all published studies compared combination therapy versus monotherapy for the complete treatment course and most studies used multiple daily dosing schedules (two or three times daily). In actual clinical practice, aminoglycosides are often added empirically for the first few days only and in a once-daily dosing schedule (41). A recent study on the safety of initial low-dose gentamicin in patients with *S. aureus* bacteraemia and native valve endocarditis, showed that adding low-dose gentamicin for the first four days of therapy, was associated with increased renal adverse events (205). The results of this study imply that short term aminoglycoside therapy is also associated with increased nephrotoxicity. Buijk et al. showed that renal impairment occurred in 14% of all ICU patients treated with a once-daily dosing regimen of 7 mg/kg gentamicin (41). In patients receiving only one dose of gentamicin, renal impairment occurred in 11%. In all surviving patients (72%), renal function completely recovered. This prospective observational study demonstrated that renal impairment does occur after a single dose of gentamicin in ICU patients, but that this impairment is reversible. For administration of more than two doses, therapeutic drug monitoring is needed to avoid accumulation and prolonged exposure leading to renal and otovestibular toxicity (see Chapter 6).

In summary, given the lack of evidence from clinical studies of superior efficacy and of the prevention of the emergence of resistance, together with a proven increase in renal toxicity, combination therapy with aminoglycosides does not seem preferable as empirical therapy in patients with sepsis with or without neutropenia. On the other hand, the addition of an aminoglycoside to a relatively narrow spectrum (mono) antibacterial regimen allows limitation of the use of broad spectrum monotherapy such as carbapenems and to prevent the emergence of resistance against these valuable antibiotics. The impact of only one or two doses of aminoglycosides on renal function is not extensively studied. Therefore, the committee could not issue a general recommendation on the use of combination therapy in adult patients with sepsis. The decision should be guided by local aetiology and resistance data. This has now become particularly relevant with the increasing frequency of ESBL producing microorganisms. When local epidemiology and resistance data justify the use of aminoglycosides to broaden the spectrum of empirical antibacterial therapy, the addition of an aminoglycoside to a beta-lactam agent with a narrower spectrum should be considered. Otherwise, the use of a (mono) beta-lactam antibiotic without an aminoglycoside is preferred.

As to the choice of monotherapy versus combination therapy in patients with proven Pseudomonas sepsis, the committee concluded that, although *in vitro* data and animal studies on Pseudomonas infections have clearly shown that combination therapy is associated with synergism and the prevention of the emergence of resistance, there is insufficient evidence from clinical studies that combination therapy is associated with increased efficacy.

As the incidence of MRSA in the Netherlands is low and the outcome of patients with fever and neutropenia is not improved by early addition of glycopeptides to the empirical antibacterial regimen (196), the preparatory committee agreed that the empirical use of

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glycopeptides is not indicated for sepsis in these patients. However, glycopeptides must be included in an initial empiric regimen for patients with severe sepsis known to be colonised with MRSA or those haematological patients who have recently received penicillins and cephalosporins prophylaxis, because these patients are at risk of bacteremia with penicillin resistant viridans streptococci.

Recommendations

1. Given the lack of evidence for superiority of the addition of an aminoglycoside to a beta-lactam agent, this combination is generally not recommended for empirical therapy in patients with sepsis.

2. The addition of an aminoglycoside to a beta-lactam is recommended in specific situations where, based on local resistance data and epidemiology (e.g.risk factors of ESBL), a broad spectrum of empirical therapy against Gram-negative pathogens is needed.

3. In the case of proven Pseudomonas bacteraemia, combination therapy is not recommended.

4. Glycopeptides should generally not be part of the empirical antibacterial regimen in patients with sepsis and neutropenia.

5. The addition of glycopeptides is recommended in patients with severe sepsis and neutropenia when specific risk factors for penicillin resistant streptococci, such as penicillin prophylaxis, are present.

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Chapter 4
Optimal selection of antibacterial drugs in therapy of sepsis

Key question 3a. What are the most important considerations in choosing the optimal empirical antibacterial therapy in adult patients with sepsis and no obvious site of infection in the Netherlands?

Apart from studies comparing monotherapy to combination therapy, no well designed trials have compared different antibacterial agents (monotherapy) in adult patients with sepsis without an obvious site of infection at presentation. Many observational studies show an association between inadequate (meaning *in vitro* ineffective) antibacterial therapy and mortality in patients with bacteraemia and/or sepsis (24, 51, 173 217, 206-215), stressing the importance of an effective initial choice. However, recent observational studies have suggested that the impact of effective empirical antibiotic therapy against *P. aeruginosa* and *E. coli/K. pneumoniae* bacteraemia on in-hospital mortality and length of stay was not as large as has previously been suggested (216, 217).

On the one hand, therapy should be broad enough to be effective against the most likely pathogens involved. On the other hand, broad-spectrum antibiotics are expensive and their wide use is associated with the emergence of resistance, compromising adequate future treatment. The broadness of spectrum should be based on knowledge of the most common local micro-organisms involved in sepsis and their susceptibility. In addition, the local incidence of *Pseudomonas spp,* extended spectrum beta-lactamase (ESBL) producing Gram-negative bacteria, MRSA and vancomycin resistant *Enterococcus spp* should be taken into account. Fourteen observational studies have been published on the risk factors for bacteraemia caused by ESBL-producing micro-organisms (207, 218-230).

The most frequent risk factors for ESBL-producing micro-organisms in those studies were nosocomial acquisition (207, 219, 220, 222, 224), prior use of antibiotic therapy (207, 218, 221-223, 225, 226, 228-231) (especially beta-lactam antibiotics in general and cephalosporins in particular) and the presence of an indwelling urinary catheter (207, 219, 221, 228). In addition, in eighteen studies on risk factors for the acquisition of other infections due to ESBL-producing micro-organisms (mostly urinary tract infections and respiratory tract infections), previous use of antibacterial therapy (especially cephalosporins and quinolones) was the most frequently mentioned risk factor (89, 231-247). Unfortunately, the definition of prior use in those studies varied from no definition (n = 11) to 30 (n = 9) , 60 (n = 2) and 90 days (n = 5) prior to presentation. However, none of those studies were conducted in the Netherlands and the prevalence of ESBL-producing micro-organisms (1.4-53%) was generally much higher than in our country. Therefore, the results may not be fully applicable to the situation in the Netherlands. Surprisingly, only one retrospective study described prior isolation of an ESBL-

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producing organism as a risk factor for the acquisition of bacteraemia due to an ESBL-producing organism (223).

One recent retrospective study analysed risk factors for acquisition of *P. aeruginosa* bacteraemia in patients with community-acquired Gram-negative bacteraemia (248). Severe immune deficiency (neutropenia, solid organ or bone marrow transplantation, recent chemotherapy, recent high dose corticosteroid therapy, azathioprine or ciclosporin use), age > 90 years, receipt of antibacterial therapy within 30 days prior to presentation and the presence of a central venous catheter or urinary catheter were associated with an increased risk of bacteraemia due to *P. aeruginosa.* Again, the prevalence of *P. aeruginosa* bacteraemia in this Israelian study (6.8%) was higher than the prevalence in the Netherlands.

Streamlining or de-escalation

Empirical broad spectrum therapy is reasonable in patients with sepsis, but *de-escalation* should be pursued systematically as soon as possible in order to prevent resistance and unnecessary costs. *De-escalation* involves the practice of administering broad-spectrum empirical antibiotic therapy together with early reassessment and subsequent narrowing or discontinuation of therapy based on clinical improvement and the results of cultures and antibacterial susceptibility tests. The term has been created in intensive care medicine (249). In other settings this strategy is called "*streamlining*". The decision to change or stop antibiotic therapy should be made at day two or three, at the time that microbiological data are available and when the clinical condition of patients has improved.

However, there still is no consensus on the criteria for changing or stopping antibiotic therapy. For example, it is not clear when a particular isolated microorganism is a coloniser and not a pathogen; when to stop antibiotic therapy solely on the basis of a negative test. The results of microbiological cultures depend on several factors such as previous antibiotic therapy, culture techniques and specific properties of the pathogen involved (249, 250). Therefore, the decision to discontinue therapy should be made based on the combination of the lack of clinical evidence of infection together with negative culture results. No prospective studies have been performed to evaluate the safety and efficacy of de-escalation in patients with sepsis. Several prospective studies evaluating the outcome of de-escalation in patients with VAP showed that de-escalation is safe and effective (251-254).

Clinical severity

Another important issue regarding the treatment of sepsis is whether the severity of sepsis should influence the choice of antibiotics. No RCTs have been performed to address this question.A recent observational multicenter study in Israel identified severity of infection at admission, as a predictor of ESBL bacteremia (231). It is clear that in patients with septic shock, ineffective antibiotic therapy is unacceptable (51, 208, 210, 211, 213, 255). Consequently, the antibiotic regimen in patients with septic shock should be active against the expected pathogens. However, there is no evidence of what resistance level for a given antibiotic is acceptable in the treatment of patients with sepsis.

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The SWAB guideline on therapy of invasive fungal infections (256) deals with the indications for empirical antifungal therapy in non-neutropenic and neutropenic patients with sepsis. The relevant recommendations have been adopted in the present guideline.

General Conclusions

Level 1	· Ineffective antibacterial therapy in patients with bacteraemia/sepsis is associated with increased mortality. A2 Ortega; Garnacho-Monero; Harbarth; Valles; Ibrahim; Leibovici[51, 207, 210, 211, 213, 215] B Trecarichi; Micek; MacArthur; Kang; Harbarth; Kuikka; Maki[24, 173, 206, 208, 209, 212, 214]
Level 2	· Ineffective empirical antibacterial therapy against *P.aeruginosa* and *E. coli/K. pneumoniae* was not associated with higher in-hospital mortality. B Osih; Thom[216, 217]
Level 2	·Prior use of antibacterial therapy is associated with an increased risk of acquiring an infection due to ESBL-producing micro-organisms. A2 Ortega; Linares[207, 241] B Yilmaz; Rodríguez-Baño; Mosqueda-Gómez; Rodríguez-Baño; Apisarnthanarak; Silva; Ena; Bellissimo-Rodriguez; Martinez; Skippen; Chayakulkeeree; Calbo; Tumbarello; Kanafani; Pena; Graffunder; Mendelson; Kang; Rodríguez-Baño; Colodner; Lin; Du; Kim; Ho; Menashe; Lautenbach(89, 218, 220-223, 225, 226, 228-230, 232-240, 242-247).
Level 2	·Nosocomial acquisition is associated with an increased risk of acquiring an infection due to ESBL-producing micro-organisms. A2 Ortega[207] B Memon; Henshke-Bar-Meir; Chayakulkeeree; Kim[219, 222, 224, 235]
Level 2	·The presence of indwelling urinary catheters is associated with an increased risk of acquiring an infection due to ESBL-producing micro-organisms. A2 Ortega[207] B Rodríguez-Baño; Ena; Henshke-Bar-Meir; Chayakulkeeree; Kanafani; Mendelson; Kang(89, 219, 221, 228, 235, 237, 242)
Level 3	· One study showed an association between prior isolation of an ESBL-producing organism and bacteraemia due to an ESBL-producing micro-organism. B Martinez[223]
Level 3	Severe immune deficiency including neutropenia is associated with an increased risk of bacteraemia due to *P. aeruginosa.* B Schechner[248]
*	No trials have been performed evaluating the safety and efficacy of de-

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	escalation in patients with sepsis.
*	There are no data to support or refute the statement that the selection of antibacterial agents should be influenced by the severity of sepsis.

* The preparatory committee agreed that no level of evidence can be assigned to these conclusions

Other considerations

The optimal spectrum and activity of antibacterial therapy in adult patients with sepsis and no obvious initial site of infection should be based on the suspected pathogens, their local resistance patterns and the setting of acquisition. Moreover, bacterial colonisation seems at least partially responsible for the occurrence of infections with the same micro-organisms and should be taken into account (257-261). Finally, when choosing the optimal antibacterial regimen for patients with sepsis, it is important to take prior use of antibiotic therapy into account. As is mentioned in the definitions section (Chapter 1), there is insufficient evidence for an exact time frame defining prior use of antibiotics as a risk factor for infection with resistant micro-organisms. It seems reasonable to take into account previous use of antibiotics within three to six months prior to presentation.

Since local differences in resistance patterns exist, each centre should collect local surveillance data on resistance and take these data into account when choosing the optimal antibacterial regimen for patients with sepsis. The optimal regimen for patients with septic shock should be active against all likely pathogens. Since there is no evidence from available literature of a superior antibacterial agent in the treatment of adult patients with sepsis with or without neutropenia and no obvious site of infection at initial presentation, the recommendations of the preparatory committee are based on available Dutch epidemiology and resistance data.

In patients with community-acquired sepsis without neutropenia and without an obvious site of infection at presentation, the committee considers a second or third generation cephalosporin to be sufficiently broad. Resistance rates of *E.coli* to amoxicillin and clavulanic acid in unselected hospital departments have increased to 19% (262), a level at which it seems not adequate for monotherapy anymore. Adding aminoglycosides is becoming an increasingly useful option, in particular for severely ill patients. This is dealt with in Chapter 2. Theoretically, first generation cephalosporins could be an effective alternative. However, as the first generation cephalosporin cefazolin is the standard for surgical prophylaxis in the Netherlands and resistance rates in Gram-negative bacteria are slightly higher than for second and third generation cephalosporins, it is not considered as a suitable alternative in patients with community-acquired sepsis.

In patients with nosocomial sepsis, there is an increased contribution of resistant Gram-negative micro-organisms, such as *P. aeruginosa* and *Enterobacter spp.* Therefore, the preparatory committee agreed to advise a regimen with increased activity against these Gram-negative micro-organisms. This can be achieved with various antibacterials. In patients with

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nosocomial sepsis without neutropenia and with no obvious initial site of infection, the preparatory committee considers piperacillin/tazobactam, a second or third generation cephalosporin in combination with either an aminoglycoside or an anti-pseudomonal fluoroquinolone as suitable regimens. Local epidemiology and resistance data should ultimately guide the choice of antibacterial therapy.

For example, in (departments of) hospitals with a high prevalence of ESBL-producing micro-organisms and in patients with risk factors for infections with ESBL-producing micro-organisms, a carbapenem with anti-pseudomonal activity should be chosen as empirical antibacterial regimen when sepsis with ESBL-producing pathogens is suspected. The level of prevalence that necessitates a change of empirical therapy is not known. Risk factors of ESBL infection should be used to target empirical therapy for patients with severe sepsis on an individual-patient basis.
Although the results of international studies on risk factors for acquisition of infections with ESBL-producing micro-organisms cannot be indiscriminately extrapolated to the Dutch situation due to differences in prevalence, the preparatory committee agreed that in patients with sepsis and prior use of cephalosporins and quinolones within the last 30 days prior to presentation, infections due to ESBL-producing micro-organisms should be considered as this association is widely described in the literature. In those cases, the empirical antibacterial regimen should be active against ESBL-producing micro-organisms as well. Surprisingly, only one study described the association between prior isolation of ESBL-producing micro-organisms and bacteraemia due to an ESBL-producing micro-organism. However, the preparatory committee agreed that in patients colonised with those micro-organisms, the antibacterial spectrum for sepsis needs to be active against ESBL-producing micro-organisms as well.

In patients with community-acquired or nosocomial sepsis and neutropenia, the preparatory committee agreed that a broad-spectrum antibacterial regimen against Gram-positive and (resistant) Gram-negative micro-organisms including *P. aeruginosa* should be chosen and that hardly no risk of resistance can be accepted. The results of the recent retrospective study by Schechner et al. confirm that neutropenia is a risk factor for *P. aeruginosa* in patients with Gram-negative bacteraemia (248). The preparatory committee could not reach consensus on the systematic addition of aminoglycosides to piperacillin/tazobactam in patients with community-acquired and nosocomial sepsis and neutropenia and considers that this decision should be based on local epidemiology and resistance data. Piperacillin/tazobactam +/- aminoglycoside or a carbapenem with anti-pseudomonal activity are considered appropriate empirical antibacterial regimens in those patients.

The need for empirical antifungal therapy

The SWAB guideline on antifungal therapy states that the indications for starting empirical antifungal therapy may be considered in selected cases with unexplained sepsis with an ICU stay of more than seven days and with a combination of the following risk factors: (1) significant colonisation with *Candida* and (2) clinical risk factors such as abdominal surgery,

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anastomotic leakage, the presence of a central venous catheter and the use of broad spectrum antibiotics (256). The considerations of that committee to select an echinocandin for empirical antifungal therapy in moderately to severely ill patients with sepsis without neutropenia can also be found in the SWAB 2008 guidelines for antifungal therapy (256).
In case of febrile neutropenia, the antifungal guideline committee states that recent randomised trials comparing pre-emptive and empirical antifungal therapy showed no clinically relevant differences in end points, including mortality. Therefore, the use of pre-emptive antifungal therapy (i.e., treatment based on the presence of specific markers such as serum galactomannan or specific radiological signs) and the refinement of diagnostic strategies are to be preferred over starting empirical antifungal therapy in these patients.
For empirical therapy in neutropenic patients, if indicated, voriconazole, caspofungin, or lipid-associated amphotericin B are recommended (256).

Recommendations

1. Based on available Dutch data on aetiology and resistance, the preparatory committee recommends for **community-acquired sepsis without neutropenia and without an obvious site of infection**, a second or third generation cephalosporin or amoxicillin and clavulanic acid + an aminoglycoside.

2. In patients with **nosocomial sepsis without neutropenia and with no obvious initial site of infection**, the preparatory committee recommends piperacillin/tazobactam, a second or third generation cephalosporin (except ceftazidime) in combination with either an aminoglycoside or an anti-pseudomonal fluoroquinolone. The ultimate choice of therapy should depend on local epidemiology and resistance data.

3. In (departments of) hospitals with a high prevalence of **ESBL-**producing Enterobacteriaceae, a carbapenem with anti-pseudomonal activity (imipenem/meropenem) should be chosen as empirical antibacterial therapy if an infection caused by ESBL-producing bacteria is suspected. As no critical prevalence level has been identified, risk factors of ESBL infection should be used to target empirical therapy on an individual-patient basis.

4. In patients with community-acquired and nosocomial sepsis and prior use of cephalosporins or quinolones within 30 days before presentation and/or colonised with ESBL-producing micro-organisms, the antibacterial regimen should also be active against ESBL-producing micro-organisms. This can be achieved by the addition of an aminoglycoside to the regimen or by the use of a carbapenem.

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5. In patients with **community-acquired and nosocomial sepsis and neutropenia**, the committee recommends piperacillin/tazobactam +/- an aminoglycoside* or a carbapenem with anti-pseudomonal activity (imipenem/meropenem) as empirical

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antibacterial regimen.

6. Glycopeptides should not be part of the initial empirical regimen in adult patients with sepsis with or without neutropenia (see Chapter 5).

7. Empirical antifungal therapy is not routinely recommended, but an echinocandin may be considered in selected cases with unexplained sepsis with long-term ICU stay, significant *Candida* colonisation, and clinical risk factors such as abdominal surgery, anastomotic leakage, the presence of a central venous catheter and the use of broad spectrum antibiotics

8. Empirical antimicrobial therapy for presumed sepsis should be discontinued based on clinical improvement together with the lack of clinical and microbiological evidence of infection

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* The addition of an aminoglycoside to piperacillin/tazobactam is optional. The ultimate choice should be guided by local epidemiology and resistance data.

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Key question 3b. What is the optimal selection of empirical antibacterial therapy in adult patients with sepsis and suspected site of infection in the Netherlands?

The optimal selection of empirical antibacterial drugs in adult patients with sepsis and a suspected site of infection should be based on the most commonly involved pathogens as well as their susceptibility patterns. Five major infection sites are distinguished. Relevant trials comparing antibacterial regimens will be discussed in this section. It is important to consider that the results of European, US and multinational trials comparing different antibacterial regimens can not be extrapolated to the Dutch situation as considerable differences in resistance patterns exist. In general, antimicrobial resistance is lower in the Netherlands and the number of Dutch patients in multinational trials was limited.

1. Sepsis and pneumonia

For the grading of the evidence for an optimal antibacterial regimen in patients with severe CAP and sepsis, we refer to the SWAB guideline on CAP. Relevant trials on antibacterial therapy for patients with HAP will be rated in this section.

Three non-comparative (263-265) and nine comparative (265-274) trials evaluated the efficacy of carbapenems in the treatment of patients with HAP. In the comparative trials, carbapenems with antipseudomonal activity were compared to piperacillin/tazobactam (3), cephalosporins +/- an aminoglycoside (3), quinolones (2) and ertapenem (1). Most trials showed comparable clinical and microbiological efficacy and no differences in the occurrence of adverse events. One trial showed clinical superiority of meropenem over the combination of ceftazidime and amikacin (266). In contrast, Fink et al showed better clinical and bacteriologic success rates of ciprofloxacin when compared to imipenem, the greatest difference being in eradication of Enterobacteriaceae (273).

In the subgroup of patients with HAP caused by *P aeruginosa*, failure to achieve bacteriological eradication and development of resistance was common in both groups, but resistance occurred in 53% of patients treated with imipenem vs 33% for ciprofloxacin. Norrby et al. showed comparable clinical and bacteriological efficacy of ceftazidime and imipenem, except for the subgroup of patients with Pseudomonas infections (274). In that group, the bacteriological response rate was higher in patients treated with ceftazidime, which could partially be explained by a lower resistance rate (33 vs 55% for ceftazidime and imipenem respectively). Two other studies confirmed that treatment with imipenem was significantly associated with the development of resistance of *P. aeruginosa* (44% with imipenem vs 19% with cefepime in the study by Zanetti and al. and 21% with imipenem vs 4% with piperacillin/tazobactam in the study by Jaccard et al.) (270, 272).

A recent meta-analysis on the efficacy of carbapenems compared to other antibacterial regimens revealed lower mortality rates associated with the use of carbapenems, but similar clinical and bacteriologic efficacy as well as adverse events. Furthermore, the lower mortality rate could not be confirmed by subset analysis of RCTs with high methodological quality. Several sensitivity analyses were performed comparing carbapenems to other classes of

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antibiotics (other beta-lactams alone or in combination with aminoglycosides and fluoroquinolones). Again, in the subset of patients with HAP caused by *P. aeruginosa*, carbapenems were associated with a lower treatment success and bacteriologic eradication rate, probably due to the development of resistance during the treatment (275). In all trials in which the development of resistance was compared, monotherapy was used (270-272, 274).

A meta-analysis of RCTs comparing fluoroquinolones with other antibacterial regimens (imipenem, ceftazidime) in patients with HAP, revealed equal mortality as well as clinical and bacteriological efficacy (276). However, the use of imipenem was associated with increased emergence of resistance compared to quinolones. Two studies compared the efficacy of linezolid versus vancomycin in HAP caused by gram-positive micro-organisms and showed equal efficacy (277, 278). In a retrospective analysis of the pooled results of those trials, linezolid was significantly associated with improved clinical cure and decreased mortality in all patients, in the subgroup of patients with gram-positive pneumonia and in patients with MRSA infections (34% of the patients with documented infection) (279). One of the three studies comparing piperacillin/tazobactam with ceftazidime, both combined with a glycopeptide, revealed lower mortality and improved clinical and microbiological response in patients treated with piperacillin/tazobactam in the combination (269). The second trial showed improved bacteriological eradication rates in patients on piperacillin/tazobactam, which did not result in a better clinical response or decreased mortality (280). The third study showed no difference in clinical and microbiological response (281).

The aforementioned studies on HAP/VAP are heterogeneous, making a conclusion on the optimal antibacterial regimen difficult. In order to clarify this issue, a recent meta-analysis evaluated the efficacy of different empirical antibacterial regimens and of monotherapy versus combination therapy in patients with VAP (282). No difference in mortality was seen. Pooled results showed significantly less treatment failure with meropenem compared to the combination of ceftazidime and an aminoglycoside. The meta-analysis confirmed the results of the study by Kollef et al showing less treatment failure in the subgroup of patients with gram positive infections in patients on linezolid compared to vancomycin (279). Only one trial comparing ciprofloxacin to standard antibiotic regimens (42 patients received 18 different antibacterial agents including beta-lactam (23), quinolones (12), aminoglycosides (10) and vancomycin (10); 27 patients received combination therapy) found a significant difference in superinfections favouring ciprofloxacin, discontinued at 48 hours if culture results were negative (283). Furthermore, significantly less treatment failure was seen in patients on short course ciprofloxacin. The eleven trials comparing monotherapy to combination therapy in this meta-analysis showed no significant differences in mortality, treatment failure, superinfections and adverse events (159, 162, 266, 284-291). The proportion of Pseudomonas infections was 14%, but no subgroup analysis was performed.

The emergence of multiresistant gram-negative bacteria has led to the reintroduction of colistin in clinical practice. Three comparative (292-294) and thirteen non-comparative(295-307) trials have been published on the efficacy of colistin alone or in combination with other agents with

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anti-pseudomonal activity or with rifampicin in patients with HAP caused by multiresistant *A. baumannii* and *P. aeruginosa.* In two comparative trials, imipenem was compared to colistin in patients with multiresistant *A. baumannii* and *P. aeruginosa* infections (292, 293). Both trials showed no differences in mortality, clinical cure and nephrotoxicity. The third study compared colistin with other agents with anti-pseudomonal activity in patients with infections with multiresistant *P. aeruginosa* (beta-lactam agents or quinolones) (294). A significant association between the use of colistin and clinical cure was observed without differences in microbiological cure, mortality and nephrotoxicity. The non-comparative trials evaluated the efficacy and safety of colistin in patients with infections with multiresistant *A. baumannii* and *P. aeruginosa* infections (295-307). In most studies colistin was used in combination with other agents with anti-pseudomonal activity in a proportion of the patients (295, 297, 299-304). Clinical response rates in those studies varied between 47 and 74% and all cause mortality between 27 and 56%. Nephrotoxicity ranged between 8 and 19% and in four studies 50-67% had pre-existing decreased renal function (295, 299-301). In one study, only two patients did not have pre-existent renal insufficiency and one of two patients developed renal insufficiency during colistin treatment (302). In three studies in which colistin was administered alone, a favourable response was observed in 58-77% and nephrotoxicity ranged from 9 to 30% (298, 306, 307). Two trials evaluating the efficacy and safety of colistin in combination with rifampicin in patients with multiresistant *A. baumannii* infections showed clinical cure in 76 (296) and 100% (305). In one trial, 10% nephrotoxicity was found, all of whom had previous renal failure (296). In the other trial, no nephrotoxicity was seen (305).

2. Urosepsis

Many trials have been published comparing antibacterial regimens in patients with complicated urinary tract infections (UTI), which will be the focus of this section. Six trials compared the efficacy of different fluoroquinolones in patients with complicated UTIs (308-313) and showed similar clinical and microbiological efficacy and no differences in adverse events were observed. A combined analysis of two RCTs comparing the effect of ertapenem to ceftriaxone in patients with complicated UTIs revealed no differences in clinical and microbiological efficacy and adverse events (314). Trials comparing cephalosporins to fluoroquinolones or aminoglycosides showed no differences in clinical efficacy or adverse events (315-321). One trial showed higher relapse rates in patients on cefadroxil, due to lower microbiological cure rates, but first generation cephalosporins are not routinely used as first line treatment for UTIs in general (317). The effect of piperacillin/tazobactam was compared to imipenem (322) and ofloxacin (323) in two trials. Equal clinical efficacy was concluded, but better microbiological eradication rates of piperacillin/tazobactam compared to imipenem were seen (322). Trials comparing aminoglycosides to beta-lactam antibiotics or fluoroquinolones resulted in equal clinical efficacy and adverse events (324-326).

3. Intra-abdominal sepsis

Ten (25, 33, 112, 272, 327-332) out of fourteen clinical trials (25, 29, 33, 112, 158, 272, 327-334) comparing carbapenems to a variety of other antibacterial regimens in patients with (complicated) intra-abdominal infections showed no differences in clinical outcome,

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bacteriological cure or adverse events. Carbapenems were compared to quinolones +/- metronidazole (2), piperacillin/tazobactam (3), clindamycin and an aminoglycoside (3), tigecycline (2) and cephalosporins +/- metronidazole (4). In two studies, the combination of cefepime and metronidazole was superior to imipenem (29, 333). One study showed a better clinical response in patients treated with meropenem compared to the combination of cefotaxime and metronidazole (158), while another study showed superior clinical and microbiological efficacy of imipenem compared to the combination of tobramycin and clindamycin (334). One small study showed no differences in clinical success when imipenem was compared to meropenem in patients with intra-abdominal infections (335).

Eight (26, 30, 33, 272, 327, 336-338) out of nine trials (26, 30, 33, 34, 272, 327, 336-338) comparing piperacillin/tazobactam to other antibacterial regimens showed similar clinical efficacy. In those studies, piperacillin/tazobactam was compared to clindamycin and an aminoglycoside (1), quinolones and metronidazole (1), cephalosporins and metronidazole (2), ertapenem (3) and imipenem (2). In the study by Cohn et al., the combination of ciprofloxacin and metronidazole showed higher clinical efficacy than piperacillin/tazobactam (34). However, no differences in microbiological eradication rates were seen. Since the relevance of including enterococci in the antimicrobial spectrum for patients with intra-abdominal sepsis is still a subject of debate, comparative trials on this topic will be discussed in a separate section (3c). One small study comparing ciprofloxacin and metronidazole to amoxicillin and clavulanic acid and metronidazole showed no difference in clinical efficacy (339).

Seven RCTs compared different antibiotic regimens in patients with acute biliary tract infections, four on patients with acute cholecystitis and cholangitis and three including patients with cholangitis only. Two trials used mezlocillin as one of the comparator drugs, but this drug is currently not available in the Netherlands, nor in the US. Three trials comparing fluoroquinolones to other antibiotic regimens (ceftriaxone 1, ceftazidime/ampicillin/ metronidazole 1, ampicillin/gentamicin 1) showed similar clinical efficacy and no difference in adverse events (118, 340, 341). Three trials compared the combination of ampicillin and an aminoglycoside to other antibiotic therapy (pefloxacin 1, piperacillin 1, piperacillin or cefoperazone 1) (340, 342, 343). One trial showed a better clinical cure in cholangitis patients treated with cefoperazone. This trial showed more nephrotoxicity in the patients on ampicillin/aminoglycoside but the difference was not significant (343). The other trials showed no difference in clinical efficacy and adverse events.

4. Sepsis and skin and skin structure infections

Twenty-five trials comparing antibacterial regimens in patients with (complicated) skin and skin structure infections have been published (35, 344-367), including registration trials of novel antibiotics such as next generation cephalosporins, daptomycin, linezolid, ertapenem, tigecycline and novel glycopeptides. Ten out of twelve trials comparing cephalosporins to other antibacterial classes (quinolones 6, vancomycin and cephalosporin 1, vancomcyin +/- aztreonam 1, penicillins 3, azithromycin 1) showed equal clinical and microbiological efficacy and adverse events (344, 346, 355, 358-365, 367). Two studies comparing quinolones to cephalosporins showed superior microbiological eradication with quinolones, but no

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differences in clinical efficacy and adverse events were observed (359, 362). Two (345, 347) out of three studies (345, 347, 352) comparing daptomycin to other antimicrobial agents (vancomycin 1, vancomycin or penicillinase-resistant penicillins 2) showed equal clinical efficacy at the end of treatment, but a more rapid response was observed in patients on daptomycin.
One study comparing telavancin to vancomycin or antistaphylococcal penicillins showed a better microbiological eradication rate in patients on telavancin, but there was equal clinical efficacy (348). Jauregui et al. showed equal efficacy of dalbavancin compared to linezolid, but more adverse events were reported in the group treated with linezolid (350). Breedt et al. compared tigecycline to vancomycin and aztreonam and although a superior bacteriological eradication rate was observed in patients on vancomycin and aztreonam, no differences in clinical efficacy was seen (349). Three studies comparing piperacillin/tazobactam to other antibacterial regimens (quinolones 1, ticarcillin-clavulanate 1, ertapenem 1) showed no differences in clinical cure, bacteriological cure and adverse events (35, 356, 366). One (354) of two studies (353, 354) comparing levofloxacin to ciprofloxacin in patients with uncomplicated SSSI showed a superior microbiological eradication rate with levofloxacin, but both studies showed equal clinical efficacy. Three studies comparing amoxicillin and clavulanic acid to fleroxacin in patients with uncomplicated SSSI showed comparable clincal and microbiological efficacy (368-370). Fabian et al compared imipenem to meropenem in patients with complicated SSSI and found no differences in clinical cure and adverse events (351).

5. Sepsis and meningitis

This section has been completed in the spring of 2010. For the latest review of the literature, we refer to the SWAB guideline on meningitis, in which our search has been included and updated. It has been decided not to include any recommendations on the treatment of meningitis in this guideline.

Conclusions

1. Sepsis and HAP

Level 1	· In many studies, no difference is observed in mortality, clinical and microbiological efficacy and adverse events when carbapenems are compared to beta-lactam agents alone or in combination with aminoglycosides or to quinolones in patients with HAP. A1 Siempos; Shorr[275, 276] A2 Yakovlev; Joshi[267, 269] B Schmitt; Jaccard; Zanetti; Torres; Norrby[268, 270-272, 274]
Level 1	· Meropenem is associated with less treatment failure compared to the combination of ceftazidime and an aminoglycoside. A1 Aarts[282] B Alvarez-Lerma[266]

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Level 1	· In patients with HAP caused by *P. aeruginosa*, the use of carbapenems is associated with the development of a higher resistance rate frequently resulting in lower bacteriological eradication compared to the use of other beta-lactam antibiotics and fluoroquinolones. A1 Siempos; Shorr[275, 276)}] A2 Fink[273] B Norrby ; Zanetti; Jaccard[270, 272, 274]
Level 1	Linezolid is associated with less treatment failure compared to vancomycin in the treatment of HAP caused by Gram-positive pathogens. A1 Aarts[282] B Kollef[279]
Level 2	Colistin is effective as salvage therapy in patients with HAP/VAP due to multi-resistant *A. baumannii* and *P. aeruginosa.* B Garnacho-Montero; Hachem; Kallel[292-294] C Bassetti;; Pintado; Furtado; Kallel; Kasiakou; Michalopoulos; Sobieszczyk; Linden; Markou; Ouderkirk; Levin; Mastoraki; Motaouakkil [295-307]

2. Urosepsis

Level 1	Trials comparing different fluoroquinolones in patients with complicated UTIs showed similar clinical and microbiological efficacy and adverse events. A2 Peterson; Cox; Raz[308, 310, 313] B Peng; Naber; Kromann-Andersen[309, 311, 312]
Level 2	Piperacillin/tazobactam is associated with a higher microbiological eradication rate compared to imipenem in patients with complicated urinary tract infections, although this does not result in higher clinical efficacy. A2 Naber[322]
Level 2	· Trials comparing cephalosporins to quinolones in patients with complicated urinary tract infections showed similar clinical efficacy and adverse events. B Cox; Timmerman[315, 316]
Level 2	· Trials comparing cephalosporins to aminoglycosides in patients with complicated urinary tract infections showed similar clinical efficacy and adverse events. B Penn; Cox; Madsen; Frimodt-Moller[318-321]
Level 2	Aminoglycosides have equal efficacy compared to aztreonam in patients with complicated urinary tract infections. B Mellekos; Waller[324, 325]

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3. Intra-abdominal sepsis

Level 1	· In patients with complicated intra-abdominal infections there is no difference in clinical efficacy when comparing carbapenems to fluoroquinolones +/- metronidazole. A2 Solomkin; Burnett[112, 330]
Level 2	· There is no difference in clinical efficacy and adverse events in patients with complicated intra-abdominal infections treated with carbapenems compared to piperacillin/tazobactam. B Jaccard; Niinikoski[272, 327]
Level 1	· Carbapenems have similar clinical and microbiological efficacy as tigecycline in patients with complicated intra-abdominal infections. A2 Fomin; Oliva[329, 332]
Level 2	· Studies comparing the combination of clindamycin and aminoglycosides to carbapenems in patients with intra-abdominal infections showed conflicting results as to clinical efficacy. B Solomkin; Condon; Gonzenbach[328, 331, 334]
Level 3	· One study showed superior clinical efficacy of meropenem compared to cefotaxime/metronidazole. B Kempf (158)
Level 2	· One study comparing the second generation cephalosporin cefoxitin to imipenem showed similar clinical efficacy. A2 Christou[25]
Level 2	The fourth generation cephalosporin cefepime in combination with metronidazole is superior to a carbapenem in the treatment of patients with intra-abdominal infections. A2 Barie[333] B Garbino[29]
Level 1	· Piperacillin/tazobactam is as effective as carbapenems in patients with complicated intra-abdominal infections. A2 Solomkin; Teppler[33, 338] B Jaccard; Niinikosky; Dela Pena[272, 327, 337]
Level 2	· There is no difference in clinical efficacy comparing the combination of cephalosporins and metronidazole to piperacillin/tazobactam in patients with intra-abdominal infections. B Rohrborn; Ohlin[26, 30]
Level 2	· One study showed superior clinical efficacy of the combination of ciprofloxacin and metronidazole compared to piperacillin/tazobactam. A2 Cohn[34]
Level 3	· In patients with cholangitis, one study showed a better clinical efficacy in patients treated with a third generation cephalosporin compared to ampicillin/aminoglycoside. B Muller[343]

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4. Sepsis and complicated SSSI

Level 2	· No differences in clinical efficacy have been reported comparing cephalosporins to fluoroquinolones in patients with (c)SSSI. A2 Neldner[359] B Lipsky; Powers; Gentry; Perez-Ruvacalba; Ramirez-Ronda[358, 360, 363, 364, 371]
Level 2	· Studies comparing cephalosporins to penicillins in patients with (c)SSSI showed equal clinical efficacy and adverse events. B Weigelt; Parish; Daly[355, 365, 367]
Level 2	· Azithromycin is as effective as cephalexin in patients with SSSI. A2 Kiani[361]
Level 3	· When the next generation cephalosporin ceftaroline was compared to vancomycin +/- aztreonam in patients with complicated SSSI, no differences in clinical and microbiological efficacy and adverse events were found in one study. B Talbot[346]
Level 2	· The combination of vancomycin and ceftazidime is as effective as the next generation cephalosporin ceftobiprole in patients with complicated SSSI. A2 Noel[344]
Level 2	Although daptomycin is associated with a more rapid clinical response compared to vancomycin or penicillinase-resistant penicillins in patients with complicated SSSI, clinical efficacy at the end of treatment is similar. B Davis; Krige[345, 347]
Level 2	In uncomplicated SSSI, amoxicillin and clavulanic acid and fleroxacin are comparable as to clinical and microbiological efficacy and adverse events. B Tassler; Powers; Smith[368-370]

Other considerations

1. Sepsis and pneumonia

When choosing the optimal antibacterial regimen in adult patients with sepsis due to HAP or VAP, it is important to take into account several factors such as duration of hospital stay, duration of ventilation and prior use of antibiotics, which are associated with an increased risk of infections with multi drug resistant pathogens.

The preparatory committee agreed that rather than distinguishing early and late VAP, the duration of hospitalisation and ventilation should be considered as a continuum: the longer the duration, the higher the risk of acquiring potentially multi-drug resistant pathogens. Their nature will depend on local microbiological epidemiology and resistance patterns.

Prior results of sputum cultures indicating colonisation should also be considered. The results of comparative studies do not support the choice of a specific superior antibacterial regimen in

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patients with sepsis and HAP/VAP. Although the use of meropenem has been associated with less treatment failure compared to the combination of ceftazidime and an aminoglycoside (266, 282), the preparatory committee agreed that wide spread use of carbapenems should be avoided in order to restrict the emergence of resistance to this antibiotic class. Moreover, the use of carbapenems has been associated with increased development of resistance compared to other beta-lactam antibiotics and fluoroquinolones (270, 272-276). The preparatory committee agreed on the selection of a broad-spectrum antibacterial regimen including activity against resistant Gram-negative micro-organisms such as *P. aeruginosa* and *Enterobacter spp.* The combination of amoxicillin and clavulanic acid + an aminoglycoside/ciprofloxacin or the combination of a second/third generation cephalosporin (excluding ceftazidime which has insufficient activity against Gram-positive micro-organisms) + an aminoglycoside/ciprofloxacin or piperacillin/tazobactam are considered sufficienty broad for empirical antibacterial therapy in patients with sepsis and HAP/VAP in the Netherlands.

Recommendations

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The preparatory committee recommends the combination of amoxicillin and clavulanic acid + an aminoglycoside/ciprofloxacin or the combination of a second/third generation cephalosporin (excluding ceftazidime) + an aminoglycoside/ciprofloxacin or piperacillin/tazobactam for the empirical antibacterial therapy in patients with **sepsis and HAP/VAP**.

2. Urosepsis

Since the results of clinical trials comparing antibacterial regimens in patients with complicated UTIs do not show consistent superiority of any of the investigated antibiotics, it is important to take into account the pathogens that are most frequently involved as well as their resistance patterns. The SWAB guidelines for antibacterial therapy of complicated urinary tract infections (102) recommend a second/third generation cephalosporin or the combination of amoxicillin and gentamicin. Amoxicillin and clavulanic acid is considered a second choice regimen due to higher levels of intermediate resistance. The guidelines do not distinguish community-acquired and nosocomial infections. The preparatory committee agreed that an antibacterial regimen with activity against resistant Gram-negative micro-organisms should be applied in patient with urosepsis and an indwelling urinary catheter. The combination of a second/third generation cephalosporin + an aminoglycoside/quinolone is considered as a sufficiently broad regimen in those cases.

Recommendations

1. In agreement with the SWAB guidelines for antibacterial therapy in patients with complicated urinary tract infections, the preparatory committee recommends a second/third generation cephalosporin or the combination of amoxicilin and gentamicin for the treatment of patients with **urosepsis**.

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2. The preparatory committee recommends second/third generation cephalosporins + an aminoglycoside/quinolone in patients with **urosepsis and an indwelling urinary catheter**.

3. Glycopeptides should be restricted to those septic patients with previously bacteriologically proven ***E. faecium*** urinary tract infections in which enterococci are suspected to be the causative pathogens.

3. Intra-abdominal sepsis

Several studies have shown that either piperacillin/tazobactam or carbapenems are efficacious and safe in patients with complicated intra-abdominal infections. Fourth generation cephalosporins in combination with metronidazole have been shown to be superior to monotherapy with a carbapenem (29, 333) but this is of limited relevance as fourth generation cephalosporins are not marketed anymore in the Netherlands. One study comparing clindamycin and tobramycin to imipenem showed significantly more treatment failures in patients on clindamycin/tobramycin (334), but two other studies showed no difference in efficacy comparing clindamycin plus an aminoglycoside to a carbapenem (328, 331). Moreover, more renal impairment was seen in patients treated with clindamycin + aminoglycosides in two studies (328, 331). These results imply that a carbapenem would be a better choice compared to clindamycin + aminoglycosides. However, clindamycin + aminoglycosides is nowadays not considered first line therapy in patients with complicated intra-abdominal infections. Another study that revealed superior clinical efficacy of meropenem compared to cefotaxime + metronidazole was open label and underpowered (158). One double-blind RCT showed superior efficacy of ciprofloxacin + metronidazole compared to piperacillin/tazobactam in patients with complicated intra-abdominal sepsis (34). However, ciprofloxacin + metronidazole is not considered as a suitable first-line sepsis therapy because of limited Gram-negative coverage. The relevance of enterococci in intra-abdominal sepsis, will be discussed in the next section (3c).

The preparatory committee agreed that there is no available evidence of a superior antibacterial regimen in patients with intra-abdominal sepsis. Piperacillin/tazobactam and carbapenems have been shown to be effective, but the use of carbapenems should be limited. There is no evidence that piperacillin/tazobactam is superior to amoxicillin and clavulanic acid or to a second or third generation cephalosporin plus metronidazole and available Dutch data on aetiology and resistance justify the choice of either one of those regimens in patients with community-acquired infections who have no risk factors for ESBL microorganisms. The addition of aminoglycosides should be dependent on local hospital epidemiology and resistance data.

The preparatory committee agreed that in patients with nosocomial intra-abdominal sepsis, the spectrum of activity against (resistant) Gram-negative pathogens should be extended. In those patients, amoxicillin and clavulanic acid or a second or third generation cephalosporin should

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be co-administered with an aminoglycoside. Alternatively, piperacillin/tazobactam +/- an aminoglycoside could be chosen. Again, the addition of aminoglycosides in this situation depends on local epidemiology and resistance data.

There are not many RCTs comparing different antibacterial regimens in patients with cholangitis. Moreover, some of these trials include patients with acute cholecystitis as well. Except for one study showing superior clinical efficacy of a third generation cephalosporin compared to ampicillin + tobramycin in the subgroup of patients with cholangitis, all trials showed comparable clinical efficacy and adverse events. Moreover, patients treated with ampicillin + tobramycin had (non-significantly) more nephrotoxicity. However, this study is outdated and underpowered. The preparatory committee concluded that there is no sufficient evidence of a superior regimen in patients with cholangitis. In patients with community-acquired cholangitis and sepsis, the committee considers amoxicillin and clavulanic acid +/- an aminoglycoside as most appropriate based on the most commonly involved micro-organisms. The addition of aminoglycosides depends on local resistance data. In patients with nosocomial cholangitis and sepsis, the committee agreed to select a regimen with increased activity against (resistant) Gram-negative micro-organisms.

Early (surgical) intervention is critical in controlling and eliminating the source of sepsis if sepsis is caused by perforation of the bowel, obstruction of the biliary tree or the presence of an abscess requiring drainage.

Recommendations

1. The preparatory committee recommends the combination of a second or third generation cephalosporin + metronidazole +/- an aminoglycoside* or amoxicillin and clavulanic acid +/- an aminoglycoside* for patients with **community-acquired intra-abdominal sepsis**
.
2. A second or third generation cephalosporin + metronidazole + an aminoglycoside or amoxicillin and clavulanic acid + an aminoglycoside or piperacillin/tazobactam +/- an aminoglycoside* is recommended in patients with **nosocomial intra-abdominal sepsis**.

3. The preparatory committee recommends amoxicillin + an aminoglycoside or amoxicillin and clavulanic acid +/- an aminoglycoside***** in patients with **community-acquired sepsis and cholangitis**.

4. Amoxicillin (with or without clavulanic acid) + an aminoglycoside is recommended in patients with **nosocomial sepsis and cholangitis**.

* The addition of an aminoglycoside is optional and is dependent on local hospital epidemiology and resistance data

4. Sepsis and complicated SSSI

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Because of the low prevalence of methicillin resistant *S. aureus* (MRSA) in the Netherlands, trials on complicated SSSIs studying novel antibiotics against resistant staphylococci such as linezolid, daptomycin, telavancin and others are of limited interest as empirical antibacterial therapy in sepsis and complicated SSSIs up to now. Other trials comparing older antibiotic regimens did not show any differences in clinical efficacy. Patients with necrotising fasciitis are generally not included in antibiotic trials on patients with complicated SSSI and antibiotic therapy in those patients is not properly studied. Therefore, the recommendations for sepsis and (un)complicated SSSI are mainly based on expert opinion and on Dutch epidemiology and resistance data.

The preparatory committee agreed that flucloxacillin should be used for treatment of community-acquired and nosocomial uncomplicated skin and skin structure infections and sepsis. In patients with community-acquired complicated SSSI, the preparatory committee considers a regimen with activity against Gram-positive and Gram-negative micro-organisms including anaerobic micro-organisms appropriate. In most patients with community-acquired sepsis who have no risk factors for ESBL microorganisms, amoxicillin and clavulanic acid is considered sufficiently broad. In patients with nosocomial sepsis and complicated SSSI, a regimen with increased activity against (resistant) Gram-negative micro-organisms should be chosen. Amoxicillin and clavulanic acid + an aminoglycoside or piperacillin/tazobactam are considered appropriate in those patients.

In patients with community-acquired and nosocomial sepsis and necrotising fasciitis, rapid surgical intervention is crucial. The addition of clindamycin in those patients is recommended based on the results of several studies showing GAS exotoxin suppression *in vitro* (372-376). As most cases of necrotising fasciitis are polymicrobial infections, the preparatory committee considers an antibacterial regimen with activity against Gram-positive, Gram-negative micro-organisms as well as against anaerobes essential as empirical sepsis therapy in those patients. In most patients with community-acquired sepsis who have no risk factors for ESBL microorganisms, amoxicillin and clavulanic acid + clindamycin is considered sufficiently broad. In patients with nosocomial sepsis, a regimen with increased activity against (resistant) Gram-negative micro-organisms should be selected such as amoxicillin and and clavulanic acid + an aminoglycoside + clindamycin or piperacillin/tazobactam +/- an aminoglycoside + clindamycin. The addition of an aminoglycoside is dependent on local epidemiology and resistance data.

Recommendations

1. The preparatory committee recommends flucloxacillin for the treatment of patients with sepsis and community-acquired and nosocomial **uncomplicated** skin and skin structure infections.

2. Amoxicillin and clavulanic acid is recommended in patients with sepsis and community-acquired **complicated** skin and skin structure infections.

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3. The preparatory committee recommends amoxicillin and clavulanic acid + an aminoglycoside or piperacillin/tazobactam in patients with sepsis and nosocomial **complicated** SSSI.

4. Amoxicillin and clavulanic acid + clindamycin is recommended in patients with community-acquired sepsis and necrotising fasciitis.

5. The preparatory committee recommends amoxicillin and clavulanic acid + an aminoglycoside + clindamycin or piperacillin/tazobactam +/- an aminoglycoside + clindamycin* in patients with nosocomial sepsis and necrotising fasciitis.

* The addition of an aminoglycoside is optional and dependent on local epidemiology and resistance data

5. Sepsis and meningitis

This section has been completed in the spring of 2010. For the latest review of the literature, we refer to the SWAB guideline on meningitis, in which our search has been included and updated. It has been decided not to include any recommendations on the treatment of meningitis in this guideline.

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The recommendations for antibacterial therapy in adult patients and suspected site of infection are summarised in Table 9.

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Key question 3c. Is there evidence that patients with intra-abdominal sepsis require empirical antibacterial therapy with activity against enterococci?

As the empirical coverage of enterococci in patients with intra-abdominal sepsis is still a matter of debate, grading of the available literature will be presented in this section.
There is controversy about the clinical significance of the presence of enterococci in samples of patients with (most often polymicrobial) intra-abdominal infections. In general, enterococci are considered opportunistic pathogens that rarely cause invasive disease in the absence of serious underlying conditions and/or the use of immunosuppressive therapy (24, 330, 377, 378).
Moreover, clinical significant infections with enterococci most frequently occur when patients have been treated with broad-spectrum antibacterial therapy, particularly cephalosporins or aminoglycosides (24, 377, 379, 380). It has been shown in animal models of polymicrobial intraperitoneal infections, that enterococci are relatively avirulent. However, in combination with anaerobes and other Gram-negative bacilli they cause intra-abdominal abscesses and mortality (381-384). Maki et al. showed that polymicrobial enterococcal bacteraemia had a significantly more fulminant course than monomicrobial bacteraemia (24). The pathogenic potential of enterococci seems therefore dependent on host factors (decreased defence mechanisms) as well as on microbiological characteristics of the infection (interaction between micro-organisms causing synergism).

Eleven RCTs compare antibiotic regimens with activity against enterococci with regimens that show no activity against those pathogens in patients with complicated intra-abdominal infections. In all trials, antibiotic therapy with activity against enterococci was not associated with a better clinical outcome (25, 26, 30, 33, 34, 330, 331, 333, 337, 338, 385). However, almost all studies were performed in patients with relatively low APACHE scores (mean score <10 in 6/11 studies; 5/11 studies no APACHE score stated), and five studies excluded patients with scores over 30 (33, 34, 333, 337). Moreover, most trials did not include immunocompromised patients. Therefore, it is unclear whether these results can be extrapolated to patients with intra-abdominal sepsis with or without a severely immunocompromised state. As previously mentioned, clinically relevant enterococcal infections are associated with immunocompromised conditions and mortality associated with enterococcal bacteraemia in those patients is high, 6-54% (24, 377, 378, 386-388).
Seven observational studies in patients with enterococcal bacteraemia showed that the majority of patients had a serious underlying condition and/or used previous antibiotic therapy, cephalosporins in particular (23, 24, 377-379, 388, 389). Six studies in liver transplant patients showed that a considerable percentage of infections/bacteraemias were caused by enterococci (390-395).

Conclusions

Level 1	There is no association between a favourable outcome and an antibiotic regimen including activity against enterococci in patients with

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	complicated intra-abdominal infections. A2 Solomkin; Teppler; Cohn; Christou; Barie; Burnett;Walker[25, 34, 330, 333, 338, 385, 396] B Dela Pena; Ohlin; Rohrborn; Gonzenbach[26, 30, 331, 337]
Level 2	Patients with enterococcal infections/bacteraemia most often have a serious underlying condition and/or used antibacterial therapy previously. A2 Gray[388] B Mohanty; Caballero-Granado; Michaud; Poh; Pallares; Maki [23, 24, 377-379, 389]
Level 2	In liver transplant patients with infections/bacteraemia, a considerable percentage of enterococci is isolated. A2 Singh[394] B Kawecki; Patel; Newell; McNeil; Bedini[390-393, 395]

Other considerations

Many RCTs comparing an antibacterial regimen with and without activity against enterococci in patients with severe intra-abdominal infections, show similar clinical efficacy. However, it is not clear whether this is applicable to patients with severe intra-abdominal sepsis in the Netherlands. First, most studies included patients with relatively low APACHE scores and five out of eleven studies excluded patients with severe intra-abdominal sepsis. Moreover, the percentage of enterococci involved in patients with intra-abdominal infections in those studies (4-20%, mean 11) (25, 26, 30, 33, 34, 330, 333, 337, 338) was lower than the reported prevalence in a recent observational Dutch study (21%) (106). Since enterococcal bacteraemia is mainly associated with an immunocompromised condition with a high mortality rate, it might imply that enterococcal coverage is necessary only in immunocompromised patients. However, it is not clear what percentage of the mortality is attributable to the enterococcal bacteraemia. Thus, whether enterococcal bacteraemia is a cause of mortality or a marker of severity of the underlying disease remains unclear.

The IDSA guideline on the choice of antibacterial agents for complicated intra-abdominal infections does not routinely recommend an antimicrobial regimen with activity against enterococci in patients with community-acquired intra-abdominal infections (33). A regimen with activity against those pathogens is suggested when enterococci are recovered from patients with health-care-associated (occurring after elective/emergency surgery) infections. Other experts suggest antimicrobial agents with activity against enterococci in immunocompromised patients with a high risk of enterococcal bacteraemia (e.g. liver transplant patients), patients with intra-abdominal infections and valvular heart disease or prosthetic intravascular material, patients with severe sepsis who have previously received broad spectrum antibiotics and patients with persistent infection (397, 398).

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Recommendations

The empirical antibacterial regimen for patients with **community-acquired and nosocomial intra-abdominal sepsis** does not need to be active against enterococci.

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Chapter 5
Selection of antibacterial therapy in documented *S. aureus* sepsis

Key question 4. What is the optimal selection of antibacterial drugs for therapy in adult patients with sepsis and documented methicillin susceptible S. aureus bacteraemia?

This section summarises available literature on the evidence for combination therapy as well as comparative trials on antibiotic regimens including novel antibiotics in patients with *S. aureus* sepsis. Some of those studies included a considerable number of methicillin resistant strains (MRSA) (29-64%) (399-402), which might be less relevant for the actual situation in The Netherlands where MRSA prevalence is very low (see Chapter 2, KQ 1c and Table 7-8).

There is evidence from *in vitro* and animal studies that the combination of beta-lactam antibiotics and an aminoglycoside has synergistic potential on *S.aureus* (403, 404). However, a meta-analysis on the role of aminoglycosides in combination with beta-lactam antibiotics in patients with bacterial endocarditis, failed to show any beneficial effect of this combination in terms of mortality, clinical efficacy and relapses (405). The results were similar in the subgroup of patients with *S. aureus* endocarditis (four of five included trials). More nephrotoxicity was seen in the combination therapy group, although the daily dosage of aminoglycosides was usually low (1 mg/kg q8h in two trials, 3 mg/kg qd in one trial, 80 mg q8h in one trial and 4.5 mg/kg qd in one trial). The duration of aminoglycoside therapy ranged from seven to fourteen days. The only clinical evidence supporting the use of combination therapy with an aminoglycoside and a beta-lactam antibiotic in patients with *S. aureus* bacteraemia comes from one small prospective trial comparing an anti-staphylococcal penicillin (six weeks) to an anti-staphylococcal penicillin (six weeks) and gentamicin (two weeks) in patients with *S. aureus* endocarditis (406). There was a more rapid clearance of bacteraemia in the group on combination therapy, but no differences in mortality were observed. Fowler et al. compared daptomycin to standard treatment (an anti-staphylococcal penicillin or vancomycin and gentamicin 1 mg/kg q8h for the first four days) in 236 patients with *S. aureus* (38% MRSA) bacteraemia and native valve endocarditis in a prospective RCT (400). Daptomycin was associated with a non-significant higher bacteriological failure rate, which did not result in significant differences in clinical efficacy. Standard therapy was associated with a non-significantly higher rate of adverse events that led to discontinuation of therapy. Recently, a report on the safety data from the RCT by Fowler et al. showed that either anti-staphylococcal penicillin or vancomycin in combination with initial low-dose gentamicin (1 mg/kg q8h) was associated with significanly more adverse renal events and a significantly lower creatinin clearance compared to daptomycin (205).

As to the trials comparing antibacterial regimens without aminoglycosides in patients with *S. aureus* bacteraemia, anti-staphylococcal penicillins have been shown to be superior to vancomycin against methicillin susceptible *S. aureus* (MSSA) strains (399, 407). Shorr et al. reported similar clinical and microbiological cure rates of linezolid compared to vancomycin in

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patients with *S. aureus* bacteraemia (402). Ruotsalainen et al. showed similar efficacy of an anti-staphylococcal penicillin with and without the addition of levofloxacin in patients with *S. aureus* bacteraemia (408).

Conclusions

Level 2	There is no evidence that the combination of an aminoglycoside and a beta-lactam antibiotic is superior to beta-lactam monotherapy in terms of mortality, clinical efficacy and relapse rates in patients with methicillin susceptible *S. aureus* bacteremia and endocarditis. A2 Falagas[405]
Level 3	The combination of gentamicin and an anti-staphylococcal penicillin is associated with a more rapid clearance of bacteraemia compared to monotherapy with an anti-staphylococcal penicillin. B Korzeniowski[406]
Level 1	The addition of low-dose aminoglycosides (1-3 mg/kg/day) during at least 4 days to a beta-lactam antibiotic in patients with *S. aureus* bacteraemia is associated with increased nephrotoxicity. A1 Falagas[405] B Cosgrove[205]
Level 3	Daptomycin has similar clinical efficacy compared to beta-lactam antibiotics and low dose gentamicin, despite of a higher bacteriological failure rate in patients with *S. aureus* bacteremia and native valve endoc. B Fowler[400]
Level 2	Anti-staphylococcal pencillins have been shown to be superior to vancomycin against methicillin susceptible *S. aureus* strains in the treatment of bacteraemia. B Chang; Kim[399, 407]
Level 2	Linezolid and vancomycin have similar efficacy in the treatment of patients with *S. aureus* bacteraemia. A2 Shorr[402]
Level 3	The addition of levofloxacin to anti-staphylococcal penicillins has no beneficial effect in patients with methicillin susceptible *S. aureus* bacteraemia. B Ruotsalainen[408]

Other considerations

Although data from in vitro and animal studies suggest synergistic potential of the combination of aminoglycosides and beta-lactam antibiotics in patients with methicillin susceptible *S. aureus* (MSSA) bacteraemia, its clinical relevance remains unclear. Superior clinical efficacy is not supported by available literature, but there is some evidence that the combination is associated with a more rapid clearance of the bacteraemia. It is important to limit the duration

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of bacteraemia as a longer duration is associated with the occurrence of complications (409-411). The preparatory committee considers the antistaphyloccal penicillin flucloxacillin the most appropriate antibacterial agent in patients with documented methicillin susceptible *S. aureus* (MSSA) bacteraemia. The addition of low-dose gentamicin to standard therapy is not considered appropriate because of the increased risk of nephrotoxicity and given the minimal existing data supporting its benefit.

Recommendations

1. The preparatory committee recommends flucloxacillin in patients with sepsis due to methicillin susceptible *S. aureus.*

2. The addition of initial low-dose gentamicin is not recommended in patients with sepsis due to methicillin susceptible *S. aureus*.

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Chapter 6
Dosage of antibacterial therapy

Key question 5. What principles should be taken into account when dosing antibacterial agents in adult patients with sepsis?

In the last two decades it has become apparent that pharmacokinetic (PK) and pharmacodynamic (PD) properties are major determinants of in vitro efficacy of antimicrobial agents (412). A large number of in vitro and animal studies have been conducted allowing the determination of PK/PD properties of the major antibiotic classes that need to be taken into account for optimising their efficacy (412). To answer the question of the optimal dosage of antibacterial agents in patients with sepsis, it is important to consider their different patterns of activity.

PK/PD properties of antibacterial agents are complex and the large number of studies on this issue would require a separate literature search. However, this aspect cannot be ignored when composing a guideline on the optimal antibacterial regimen in patients with sepsis, as the optimal dosage in critically ill patients is a determinant of efficacy. In this guideline, rather than an evidence based review of the literature on the optimal dosage of antibacterial agents, the most important PK/PD principles are discussed in order to justify the recommended dosages.

Three patterns of activity have been described and are important to consider when defining the optimal dosage of antibacterial agents in patients with sepsis. The first pattern of activity is characterised by *concentration-dependent* killing in which the maximum concentration [Cmax]/minimum inhibitory concentration (MIC) and /or the area under the serum concentration curve (AUC)/MIC ratios are the best PK/PD indices correlating with efficacy. The dosing of antibacterial agents exhibiting this pattern of activity is optimised via the administration of large (once daily) doses. This pattern of activity is displayed by several antibiotic classes such as aminoglycosides, fluoroquinolones and daptomycin. However, the definition of *concentration-dependent* is not absolute and there is a point beyond which increasing a drug's concentration relative to the MIC does not improve bacterial killing (413, 414). For aminoglycosides, this point appears to be at a peak/MIC ratio of 10-12 in some studies. The AUC/MIC has also shown to be important. However, it is difficult to distinguish between these two indices, as aminoglycosides are given once daily and the indices therefore highly correlated (412). Buijk et al. showed in a prospective study in 89 consecutive critically ill patients that a once-daily dosing regimen of 7 mg/kg gentamicin produced Cmax/MIC ratios >10 in the majority of patients (41). This is considered an appropriate target. Moreover, the incidence of aminoglycoside-induced nephrotoxicity is reduced by once-daily dosing (415, 416). For fluoroquinolones, some authors suggest that the best PK/PD index associated with efficacy is the Cmax/MIC ratio, which should be >10, while others suggest the AUC/MIC ratio is the best parameter, which should be >30-40 for gram positive and 100-125 for gram negative

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bacteria (412). It should be kept in mind that these values refer to unbound, that is non-protein bound, fractions of the drugs.

The second pattern of activity is characterised by *time-dependent* killing and minimal-moderate persistent effect. Higher drug concentrations are not associated with higher killing rates and optimalisation of efficacy is reached through extending the duration of exposure. The time that serum levels remain above the MIC (T>MIC) is the PK/PD index correlating with treatment efficacy. Typically, beta-lactam antibiotics exhibit this pattern of activity. It has been demonstrated that concentrations of approximately four times the MIC exert the maximum effect and that higher concentrations are not associated with increased bactericidal activity (417, 418). It has been shown that the T>MIC should be long, from 40 to 70% of the interval time between doses (412), the value depending on the micro-organism and class of beta-lactam. The value probably needs to be higher in severely ill patients. As T>MIC is the most important PK/PD index correlating with the efficacy of beta-lactam antibiotics, continuous infusion of these agents is an attractive theoretical concept. Several animal studies showed improved efficacy of continuous infusion over intermittent infusion, especially in neutropenic animals (417). A meta-analysis of RCTs comparing continuous versus intermittent infusion of different antibiotic classes in patients with various infections showed a trend towards lower clinical failure, favouring continuous infusion, but the differences were not statistically significant (419). The difference was significant in a subset of RCTs using the same total daily dose in both arms. No differences in mortality were found. Larger, well designed trials are needed to further evaluate the benefits of continuous infusion of beta-lactam agents (412, 417, 419).

The final pattern of activity is characterised by *time-dependent* killing and prolonged persistent effects. Although higher concentrations are not associated with more efficient killing, higher concentrations do produce prolonged suppression of growth of the micro-organism. The AUC/MIC ratio is the index most closely related to drug efficacy. In the experimental setting, azithromycin, tetracyclines and clindamycin and the glycylcyclines (such as tigecycline) exhibit this pattern of activity.

There is no consensus on which PK/PD index is the best parameter correlating with clinical efficacy of the glycopeptides, T > MIC, AUC/MIC and Cmax/MIC all being mentioned (412). Aside from knowledge on the major PK/PD indices determining drug efficacy, it is important to realise that pathophysiological changes in patients with sepsis occur that can affect drug distribution (416). For example, the capillary leak syndrome in these patient results in a fluid shift from the intravascular compartment to the interstitial space, increasing the volume of distribution of water-soluble drugs and lowering the serum concentration. In contrast, decreased creatinine clearance results in decreased drug clearance. Progression of sepsis is often associated with the occurrence of multi organ failure with renal and hepatic insufficiency, altering drug metabolism. Many patients will ultimately receive continuous renal replacement therapy, which also influences drug clearance (416).

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\Conclusions

*	Pharmacokinetic (PK) and pharmacodynamic (PD) properties are major determinants of in vitro efficacy of antimicrobial agents.
*	In *concentration-dependent* killing, the maximum concentration [Cmax]/minimum inhibitory concentration (MIC) and /or the area under the serum concentration curve (AUC)/MIC ratios are the best PK/PK indexes correlating with efficacy. This pattern of activity is displayed by several antibiotic classes such as aminoglycosides, fluoroquinolones and daptomycin.
*	In *time-dependent* killing with minimal-moderate persistent effect, the time that serum levels remain above the MIC (T>MIC) is the PK/PD index correlating with treatment efficacy. Typically, beta-lactam antibiotics exhibit this pattern of activity.
*	Larger, well designed trials are needed to further evaluate the benefits of continuous infusion of beta-lactam agents.
*	In *time-dependent* killing with prolonged persistent effects, the AUC/MIC ratio is the index most closely related to drug efficacy. Azithromycin, tetracyclines and clindamycin and the glycylcyclines (such as tigecycline) exhibit this pattern of activity in the experimental setting.
*	There is no consensus which PK/PD index is the best correlating with clinical efficacy of the glycopeptides, T > MIC or AUC/MIC .
*	In patients with sepsis, several factors can affect drug distribution, such as capillary leakage and alterations in kidney and liver function.

Other considerations

Dose-finding studies on antibacterial agents in sepsis are lacking and present dosing guidelines are generally based on expert opinion. As sepsis is a serious condition, experts have proposed to use the highest licensed dose (420). However, this would often lead to very high dosages, intended for difficult to reach infection sites, such as brain abscesses. For example in the Netherlands, the currently recommended dosage of cefotaxime in sepsis is 1000 mg qid (http://customid.duhs.duke.edu/NL/Main/Start.asp). However, the highest licensed dosage is 12000 mg daily (http://db.cbg-meb.nl/Bijsluiters/h27751.pdf). Authors of textbooks are remarkably reluctant to mention dosages in sepsis (421).

The preparatory committee decided to recommend an empirical single dose regimen of 7 mg/kg for gentamicin in critically ill patients. However, as the experience report by Buijk et al (41) did not include patients with organ transplants or taking other nephrotoxic drugs such as ciclosporin, vancomycin, amphotericin B, cisplatin, and high dose (>200 mg/daily) furosemide, this regimen cannot be recommended for these patient groups as there are insufficient data on reversibility of renal dysfunction.

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A dose of 5 mg/kg once daily (with dose reduction and/or a prolonged dosing interval guided by drug levels (TDM) in case of renal insufficiency) is recommended for not-critically ill patients and for those not suspected of having an infection with *Pseudomonas* or another microorganism with a high MIC (http://customid.duhs.duke.edu/NL/Main/Antibiotic.asp?AntibioticID=202).

A more sophisticated way to tackle the dosing issue would be the implementation of PK/PD models as described previously. Ideally, beta-lactam antbiotics should be dosed by continuous infusion, aiming at serum levels of at least four times the MIC of the involved micro-organism. Recently, it was demonstrated in intensive care patients that the administration of cefotaxime by continuous infusion in a dosage as low as 2000 mg per day, resulted in average serum levels of 12 mg/l whereas MICs are usually <1 mg/l (422). A recent study in critically ill patients with hypoalbuminemia showed that the unbound concentrations of the highly (95%) protein bound flucloxacillin after 2 g bolus fell below 1 mg/L 4 h after the end of the infusion, providing evidence that intermittent and continuous infusion of higher dosages (i.e. 8 to12 g/24 h) would be required(423)..
Pharmacokinetic studies show that effective serum concentrations can be reached with lower daily dosages of beta-lactam agents when using continuous infusion compared to conventional intermittent dosing (424, 425). When using continuous infusion, a loading dose should be given in order to achieve effective serum concentrations as soon as possible.

Another approach would be the use of extended infusion dosing regimens of beta-lactam agents, using at least 50-60% of the dosing interval instead of just one hour infusion (426, 427). This approach would be feasible for beta-lactam agents, of which one ore more components are probably not stable enough in solution for the application of 24h-continuous infusion (e.g. amoxicillin and clavulanic acid). A recently approved carbapenem, doripenem, is registered with a prolonged infusion time of 1 hour. Extended infusion 4h is optional (http://www.janssen-cilag.nl/content/products/janssen-cilag.nl_dut/pool_content/Doribax500mg_SPC.pdf).

Patients with sepsis have an increased V(d) and renal clearance which will require increased dosing (426). Van Zanten et al. showed that the administration of ciprofloxacin 400 mg bid would lead to inadequate AUC/MIC and C_{max} ratios in critically ill patients (428). As demonstrated by Lipman et al., ciprofloxacin at a dosage of 400 mg q8h in patients shows better pharmacokinetic profiles in patients with severe sepsis and is relatively safe (429). However, additional studies are needed to confirm these findings. The preparatory committee considers ciprofloxacin iv 400 mg tid appropriate in patients with sepsis and known colonisation with Gram-negative micro-organisms with MICs > 1 mg/l for ciprofloxacin. This generally applies to *P.aeruginosa* strains, and the tid regimen is recommended for Pseudomonas infections in the drug information leaflet (e.g**.** http://db.cbg-meb.nl/Bijsluiters/h12245.pdf). The same applies for infections in neutropenic patients. The use of 400 mg iv tid (versus bid) is optional when used as empirical antibacterial therapy in other patient categories.

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Another important aspect in defining the optimal dosage in adult patients with sepsis, is the interindividual variability in pharmacokinetic variables in those patients. Serum levels as well as AUC may vary ten to twenty-fold between patients and was demonstrated in studies on cefotaxime (422), ceftazidime (430), ciprofloxacin (428), aminoglycosides (41), vancomycin (431) and piperacillin/tazobactam (432, 433). This implies that ideally, dosing should be individualised, using therapeutic drug monitoring.

The preparatory committee considers the administration of beta-lactam agents by continuous infusion or by extended infusion-dosage regimens as valuable alternatives to conventional intermittent short (20-30 min) dosing in adult patients with sepsis. However, for each of these beta-lactam agents, the stability at room temperature should be taken into account (loss of activity, toxic degradation products) (417, 434) as well as the feasibility of such a strategy (e.g. availability of motor-operated syringes in general wards). Intermittent dosing of beta-lactam agents of low toxicity at higher dosages, according to the instructions of the manufacturer, is still considered good clinical practice.

Recently, consensus recommendations from the IDSA, the American Society of Health-System and the Society of Infectious Diseases Pharmacists were published on dosing and therapeutic monitoring of vancomycin (435). It is stated that the initial vancomycin dosages should be calculated on the basis of actual body weight, including for obese patients. Subsequent dosage adjustments should be based on actual serum concentrations. In all patients on vancomycin therapy, at least one vancomycin serum level should be determined in order to monitor efficacy. Trough serum concentrations are the most accurate method of monitoring the effectiveness of vancomycin and should be obtained just before the fourth dose. Trough vancomycin levels should be maintained above 10 mg/l to avoid the occurrence of resistance. Based on the potential to improve tissue penetration, to increase the probability of optimal target serum levels, and to improve the outcome of complicated infections (e.g. bacteraemia), trough serum concentrations of 15-20 mg/l are recommended. A loading dose of 25-30 mg/kg can be considered in order to achieve this target concentration. In most patients with a normal kidney function, subsequent dosages of 15-20 mg/kg are required to obtain the recommended trough serum concentration. When individual dosages exceed 1000 mg, the dosing period should be extended from 1 hour to 1.5-2 hours. Frequent monitoring (more than one measurement) of trough vancomycin levels are recommended in patients on prolonged vancomycin therapy (five days or more), in patients who are at risk of toxicity and in patients with an unstable kidney function. In hemodynamically stable patients, once-weekly measurement of trough vancomycin levels is sufficient. The preparatory committee agreed to adopt these recommendations.
Continuous infusion may enhance vancomycin efficacy with the standard 30 mg/kg daily dosage, thus avoiding the need to use higher total daily dosages that could increase the risk of nephrotoxicity. In the case of fully susceptible pathogens with an MIC of $\leq$ 1 mg/l, the strategy of targeting a steady-state vancomycin concentration of 15 mg/ l during continuous infusion may simultaneously enable an AUC/ MIC ratio of $\geq$360, so that both pharmacodynamic

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efficacy targets may be optimized (436). The target concentrations may vary depending on the MIC of the causative microorganisms, and 20-25 mg/l may be necessary for less susceptible organisms.

Recommendations

1. The administration of some beta-lactam agents by continuous or extended infusion (50-60% of dosing interval) is optional in adult patients with sepsis.

2. An intravenous dosage of 400 mg ciprofloxacin tid is recommended for (suspected) micro-organisms with MICs > 1mg/l such as *P. aeruginosa* and in patients with neutropenia. A tid regimen is optional as empirical start in other adult patients with sepsis.

3. The preparatory committee recommends individualization of dosing using therapeutic drug monitoring whenever possible in adult patients with sepsis. For aminoglycosides and vancomycin, therapeutic drug monitoring is recommended after 3 and 5 days respectively

4. The following agents are suitable for continuous (CI) or extended infusion (EI)
   amoxicillin and clavulanic acid iv 1200 mg qid EI (four hours)*
   flucloxacillin iv 6000 - 12000 mg daily CI
   cefuroxime iv 2250 mg daily CI or 750 tid EI
   cefotaxime iv 2000-3000 mg daily CI or 1000 mg qid EI
   ceftazidime iv 3000 mg daily CI or 1000 mg tid EI
   piperacillin/tazobactam iv 4500 mg tid EI (four to five hours)
   meropenem iv 1000 mg tid EI (3 hours)
   vancomycin iv loading dose of 500 mg followed by (15mg/kg) over 12 hours bid CI and TDM

5. The following agents are suitable for intermittent dosing
   flucloxacillin iv 1000-2000 mg 6 times daily intermittently
   amoxicillin and clavulanic acid iv 1200 mg qid intermittently
   cefuroxime iv 750 -1500 mg tid intermittently
   cefotaxime iv 1000 mg qid intermittently
   ceftazidime iv 1000 mg tid intermittently
   piperacillin/tazobactam iv 4500 mg tid intermittently
   imipenem iv 500 mg qid intermittently
   meropenem iv 1000 mg tid intermittently
   ciprofloxacin iv 400 mg bid or tid intermittently
   gentamicin iv 5-7 mg/kg once daily intermittently
   vancomycin iv loading dose of 25-30 mg/kg followed by 15-20 mg/kg bid or tid intermittently and TDM

6. In all patients on vancomycin therapy, at least one trough concentration (just before the

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fourth dosage) should be determined in order to monitor efficacy

7. Frequent measuring (more than one) of trough vancomycin concentrations is recommended in patients on prolonged therapy (five days or more), in patients with an increased risk of toxicity and in patient with an unstable kidney function.

8. The trough vancomycin concentration should be 15-20 mg/l for patients with sepsis.

* Augmentin data sheet GlaxoSmithKline NZ Limited, Auckland N Zealand

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Chapter 7
Duration of antibacterial therapy

Key question 6a. What is the optimal duration of therapy in adult patients with sepsis?

In studies on antibacterial therapy in patients with bacteraemia and/or sepsis, the treatment duration often depends on clinical and bacteriological response (28, 31, 172, 194, 437, 438). In the meta-analysis by Paul et al. comparing monotherapy and combination therapy in adult patients with sepsis, the mean duration of therapy ranged between 4 and 17.5 days. However, the optimal duration of treatment in patients with sepsis is dependent on the cause (primary and/or eventually secondary involved infection site). When the diagnosis of sepsis is rejected after three to five days of empirical therapy, stopping antibacterial drugs is mandatory.
In this section, the optimal treatment duration for each infection site associated with sepsis as well as duration of broad spectrum antibacterial therapy in patients with persisting fever and profound and prolonged neutropenia will be reviewed.

1. Sepsis and pneumonia

For the optimal duration of antibacterial therapy in patients with **CAP**, we refer to existing SWAB guidelines on CAP

A large French randomised double blind (until day eight) multicentre trial on patients with **VAP** concluded that a treatment duration of eight and fifteen days with an effective empirical regimen from day 1 had comparable clinical efficacy, except for patients with Pseudomonas infections. Although these patients had a higher infection recurrence rate, no difference in unfavourable outcome was observed. These results were confirmed by a recent retrospective study showing no differences in recurrence rates and mortality in patients treated with a shorter (three to eight days) course of antibacterial therapy for VAP caused by non-fermentative bacteria (439).

2. Urosepsis

For the discussion on the optimal duration of antibacterial therapy in patients with complicated urinary tract infections, we refer to existing SWAB guidelines (102).

3. Intra-abdominal sepsis

In most studies on antibacterial therapy in patients with severe intra-abdominal infections, treatment duration ranged from five to fifteen days, but no comparative trials have been performed (29, 33, 34, 110, 329, 337, 430, 440). One recent RCT compared three days of ertapenem versus five days or more in patients with community-acquired intra-abdominal infections. Patients with localised peritonitis requiring surgery were included. No differences in outcome were observed between the two groups. However, the number of patients in this trial was small and only patients with mild to moderate localised peritonitis were included (441).

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In patients with cholangitis, the mainstay of treatment is successful drainage of the biliary tree. A retrospective study showed no differences in complications and recurrence rates in patients treated with antibiotics for three days or less, compared to patients treated for more than five days following successful drainage (442).

4. Sepsis and skin structure infections

In studies comparing antibacterial regimens in patients with complicated SSSI, mean treatment duration ranged from six to twenty-five days, depending on the time needed for clinical response. There are no RCTs comparing different treatment durations patients with complicated SSSI.

5. Sepsis and meningitis

For the discussion on the optimal duration of antibacterial therapy in patients with meningitis, we refer to the draft SWAB guidelines.

6. Persisting fever and prolonged and profound neutropenia

The duration of broad spectrum antibacterial therapy in patients with persisting fever and prolonged and profound neutropenia without clinical or microbiological evidence of infection is still a matter of debate. It is questionable whether the risk of an incomplete therapy outweighs the risks associated with ongoing broad spectrum antibacterial therapy such as fungal superinfections and colonisation and infection with multiresistant micro-organisms. Two older prospective studies compared the outcome of different durations of antibacterial therapy in patients with persisting febrile neutropenia despite broad spectrum antibacterial therapy without clinical or microbiological evidence of infection (443, 444). In one study, significantly more acute hypotension was found in the group in which the antibacterial therapy was discontinued (444). It should be noted that in this study patients did not receive oral antimicrobial prophylaxis. More fungal infections were observed in the group on ongoing antibacterial therapy and no differences in mortality were observed. The other study showed that in the group in which antibacterial therapy was discontinued, 50% needed reinstitution of therapy after a mean of 2.4 days and 37.5% of the total group had clinical or microbiological evidence of bacterial infection (443). However, all deaths in that group were unrelated to infections and occurred within a mean of 25 days after discontinuation of therapy. In this study, almost all patients received oral antimicrobial prophylaxis and this could perhaps explain the differences in occurrence of bacteraemia after discontinuation of therapy between the two studies.

In the Netherlands, the use of antibacterial and antifungal prophylaxis in high risk patients with profound and prolonged neutropenia is generally accepted in agreement with the European conference on infections in leukaemia (ECIL) guidelines (445, 446). A recent Dutch prospective observational study was performed on the safety of early discontinuation of empirical broad spectrum antimicrobial therapy in patients with febrile neutropenia (447). Patients with haematological malignancies and treatment induced neutropenia for more than ten days were included. All patients received oral fluconazole and fluoroquinolone prophylaxis.

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Patients with febrile neutropenia were empirically treated with imipenem which was discontinued after 72 hours when no clinical or microbiological evidence of infection could be detected regardless of the presence of absence of fever. The mean duration of fever in patients with only one febrile episode was 5.5 days and the mean duration of imipenem use 4.7 days, in patients with two febrile episodes, the mean duration of fever was 9.9 days and the mean duration of total imipenem use 6.6 days and in patients with more than two febrile episodes, the mean duration of fever was 16.8 days and the mean duration of total imipenem use was 10.5 days. However, it is not specifically stated how many patients were febrile at the time of discontinuation of antimicrobial therapy. There was no increased mortality observed in the group with early discontinuation of imipenem. Sixt-seven percent of patients died from non-infectious related causes. One patient died of proven/probable aspergillosis and one patient with refractory AML died of possible invasive aspergillosis and typhlitis. The authors conclude that the discontinuation of broad spectrum antimicrobial therapy in patients with febrile neutropenia after 72 hours without clinical or microbiological evidence of infection regardless of the presence or absence of neutropenia is safe.

Conclusions

*	There are no trials comparing different treatment durations in patients with sepsis and no obvious site of infection.
Level 2	A treatment duration of eight days for VAP is noninferior compared with fifteen days. A2 Chastre[448] B Hedrick[439]
Level 3 *Level 3*	· In patients with pyelonephritis, a treatment duration shorter than ten days is associated with an increased risk of treatment failure. Retrieved from Geerlings et al.: SWAB UTI guidelines[102] · In patients with pyelonephritis treated with beta-lactam antibiotics, a treatment duration of seven days is too short. Retrieved from Geerlings et al.: SWAB UTI guidelines[102]
* *Level 3*	No comparative trials on optimal duration of treatment have been performed in patients with complicated intra-abdominal infections or patients with complicated SSSI. · In patients with acute cholangitis, a short course of antibacterial therapy (three days or less) is as effective as a longer course (more than three days) in the prevention of complications and recurrence. B Van Lent[442]
Level 3	Discontinuation of broad spectrum antimicrobial therapy after 72 hours in patients with febrile neutropenia without clinical and microbiological evidence of infection that are on continuous oral antimicrobial prophylaxis is safe B Slobbe, Joshi[443, 447]

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Other considerations

There are no trials comparing different duration of antibacterial therapy in patients with sepsis with or without neutropenia in which no site of infection has been recognised eventually. The Surviving Sepsis Campaign guidelines state that optimal duration of therapy should be guided by clinical response and a duration between seven and ten days is generally recommended (204). The preparatory committee agreed that there is no evidence to deviate from that recommendation.

Based on available literature, the preparatory committee considers a treatment duration of up to eight days appropriate for patients with sepsis and HAP/VAP.

In patients with sepsis and intra-abdominal infections or skin and skin structure infections, the duration of antibacterial therapy depends on the clinical picture which is heterogeneous. It is important to realise that surgical intervention is the mainstay of therapy in those patients. No large RCTs have been performed on the optimal duration of antibacterial therapy in those patients and the comparative trials on antibacterial therapy showed large differences in mean duration of therapy. The results of a recent trial comparing a short-course versus a longer course of ertapenem in patients with mild to moderate community-acquired intra-abdominal infections can not be extrapolated to patients with severe intra-abdominal sepsis (441).

The IDSA guideline on antibacterial therapy in patients with complicated intra-abdominal infections states that antibacterial therapy should be continued until resolution of clinical signs of infection including laboratory parameters (396). It is recommended that in case of persisting or recurrent infection after five to seven days, further diagnostic investigation should be undertaken. These recommendations are based on expert opinion.

Based on available evidence, the preparatory committee considers an antibiotic treatment duration of no more than three days appropriate for patients with sepsis and cholangitis and adequate drainage of the biliary tree.

The IDSA guideline on skin and skin structure infections does not provide standard recommendations for the optimal duration of treatment. It is stated that in case of animal bites and cellulites/abscesses, a five to ten day-course of antibacterial therapy usually is sufficient (121). In patients with neutropenia and soft tissue infections, a treatment duration of seven to ten days is recommended. In case of non-response, diagnostic interventions should be performed.

In terms of discontinuation of empirical antimicrobial therapy, given the lack of evidence from RCTs in sepsis without neutropenia the preparatory committee agreed that antimicrobial therapy should be discontinued based on clinical improvement together with the lack of clinical and microbiological evidence of infection. There is little evidence on the duration of antimicrobial therapy in patients with neutropenia and persisting fever despite 72-96 hours of broad spectrum antimicrobial therapy. The IDSA guidelines recommend to continue the initial antibiotic regimen in clinically stable patients if re-evaluation does not provide additional clinical or microbiological evidence of infection (4). However, in contrast to the ECIL guidelines, the routine administration of antibiotic prophylaxis is not recommended in these guidelines (446). According to the recent Dutch study by Slobbe et al., discontinuation of broad

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spectrum antibacterial therapy after 72 hours in patients with persisting fever and neutropenia on oral antibacterial prophylaxis is safe (447). However, further randomised studies are needed comparing the early discontinuation versus continuation of broad spectrum antimicrobial therapy in patients with ongoing febrile neutropenia.

Recommendations

1. The preparatory committee recommends a treatment duration of seven to ten days in patients with **sepsis with or without neutropenia and no obvious site of infection.**

2. In agreement with existing SWAB guidelines, the preparatory committee recommends a treatment duration of at least fourteen days in patients with **sepsis and pneumonia due to *S. aureus.***

4. In agreement with exisiting SWAB guidelines, the preparatory committee recommends a treatment duration of fourteen to twenty-one days in patients with **sepsis and pneumonia due to *L. pneumophila, M. pneumoniae or Chlamydia spp.***

5. The preparatory committee recommends after initial appropriate empirical therapy, a treatment duration of no more than eight days in patients with **sepsis and VAP.**

6. In agreement with existing SWAB guidelines, the preparatory committee recommends a treatment duration of at least ten days in patients with **urosepsis.**

7. The preparatory committee recommends a treatment duration of five to seven days in patients with **intra-abdominal sepsis**.

8. The preparatory committee recommends a short course of antibacterial therapy (up to three days) in patients with sepsis and **cholangitis** following adequate drainage of the biliary tree.

9. The preparatory committee recommends a duration of seven to ten days in general in patients with **sepsis and (complicated) SSSI.**

10. The preparatory committee agreed that broad spectrum antimicrobial therapy could be discontinued after 72 hours in a selected group of clinically stable patients with **persisting febrile neutropenia**, that show no clinical or microbiological evidence of infection whatsoever. However, in all patients oral antimicrobial prophylaxis with adequate activity against Gram-negative micro-organisms should be continued until resolution of neutropenia.

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Key question 6b. Does sepsis with a certain pathogen require a longer duration of antibacterial therapy?

1. *S. aureus*

The clinical picture of patients with *S. aureus* bacteraemia can be quite variable, ranging from **uncomplicated bacteraemia** to **complicated bacteraemia** with deep seated infections such as infective endocarditis, vertebral osteomyelitis and septic arthritis (449-452). This variability makes recommendations for the optimal duration of treatment difficult. Nine observational studies evaluating the influence of treatment duration on outcome in patients with (catheter related) *S. aureus* bacteraemia and showed conflicting results (399, 453-460). Four studies concerned patients with catheter-related *S. aureus* bacteraemia only (453, 458-460). In five other studies, various percentages (17 to 49%) were catheter-related (399, 454-457). Six studies failed to show an association between a shorter course (less than fourteen days) of therapy and recurrence or complications (399, 453-456, 458), while three studies did find an association between a shorter course of therapy and an unfavourable outcome (457, 459, 460).
The results of these studies are difficult to interpret due to the observational character. Most studies did not correct for disease severity. It is plausible that severely ill patients are more prone to recurrence, complications and death although they usually receive a longer course of antibacterial therapy. This might explain the fact that in some studies, a longer duration of therapy seemed to be associated with a worse outcome (453, 454). Moreover, there are no studies concerning *S. aureus* bacteraemia without (a proportion of) catheter-related bacteraemia. Only one RCT was conducted comparing two weeks versus four weeks of antibiotic therapy in patients with *S. aureus* bacteraemia that was not associated with endocarditis and four versus six weeks in patients with *S. aureus* bacteraemia and endocarditis (461). All patients completing the course of antibiotic therapy were bacteriologically cured and none of the patients experienced a relapse. No conclusions can be drawn on the optimal duration of therapy as only 84 patients were included of which only 38% completed the full course of antibiotic therapy.

Finally, a meta-analysis of studies on the outcome of patients with catheter-related *S. aureus* bacteraemia receiving a shorter course (fourteen days or less) of antibacterial therapy concluded that available data are flawed by bias and statistical imperfections (462). Current guidelines contain recommendations for patients with catheter-related *S. aureus* bacteraemia. In general these guidelines recommend catheter removal and a duration of four to six weeks of antibacterial therapy (2). The guidelines state that a shorter duration of therapy (minimum of fourteen days) can be considered in patients without prosthetic intravascular devices that are not diabetic or immunocompromised who have a negative transesophageal echocardiograph, who have no evidence of metastatic infection and in whom fever and bloodstream infection resolved within 72 hours of starting antibacterial therapy. Verhagen et al. performed a retrospective study on patients with *S. aureus* bacteraemia in a Dutch University Hospital, 30% being catheter related. It was shown that in five out of nine patients with relapses, the duration of treatment was shorter than ten days, leading to death in two patients. The authors recommend a treatment duration of at least ten days in patients with uncomplicated *S. aureus*

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bacteraemia and a duration ´according to the extent of infection´ in patients with complicated bacteraemia (450).
As in the IDSA guidelines and the study by Verhagen et al. a distinction in treatment duration is proposed between uncomplicated and complicated *S aureus* bacteraemia, the risk factors associated with the occurrence of complications in patients with *S aureus* bacteraemia should be considered. Fowler et al. showed in a prospective study in patients with *S aureus* bacteraemia that four variables were significantly associated with complications: a positive follow-up blood culture result, community acquisition, persistent fever at 72 hours and skin abnormalities indicating acute systemic infection (410).

Other studies showed that risk factors for complications following (catheter-related) *S. aureus* bacteraemia were increased symptom duration before the date of the first positive blood culture (409), presence of a long-term intravascular catheter or non-catheter prosthesis (409), haemodialysis (409), the presence of MRSA (409) and duration of bacteraemia (410, 411, 456, 463). The definition of persisting bacteraemia in those studies differed. Lesens et al. defined persisting bacteraemia as the presence of positive blood culture results more than 24 hours after starting effective antibacterial therapy (463), while Fowler et al defined a cut off level of more than 48-96 hours after starting effective antibacterial therapy (410). In the other two studies, persisting bacteraemia was defined as a positive blood culture result more than 72 hours after starting effective therapy (411, 456). Another recent retrospective study in cancer patients with catheter-related *S. aureus* bacteraemia showed that 40% had at least one complication and that the only risk factor associated with overall complications was renal failure at presentation (453).

Conclusions

Level 1	· Duration of bacteraemia before and following adequate treatment is an important risk factor for the occurrence of complications in patients with *S aureus* bacteraemia. A2 Fowler; Khatib[410, 411] B Johnson; Lesens[456, 463]
Level 2	· Renal failure has been associated with an increased risk for complicated *S aureus* catheter related bacteraemia. A2 Fowler[409] B Ghanem[409, 453]
Level 2	· The presence of a long-term intravascular catheter or non-catheter prosthesis and the presence of MRSA have been associated with an increased risk of complications. A2 Fowler[409]
Level 1	There is no evidence for the optimal duration of antibacterial therapy in patients with uncomplicated *S. aureus* bacteraemia. A2 Jernigan; Chang; Jensen[399, 457, 462] B Ghanem; Lentino; Kreisel; Johnson; Fatkenheuer; Zeylemaker;

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	Raad[453-456, 458-460]

Other considerations

Studies on the duration of antibacterial therapy in patients with *S. aureus* bacteraemia are difficult to interpret due to their observational character and due to different cut off levels being used defining persisting *S. aureus* bacteraemia. The preparatory committee agreed that **uncomplicated** *S. aureus* **bacteraemia** is defined as bacteraemia in patients without prosthetic intravascular devices with no evidence of metastatic complications or persisting bacteraemia. In agreement with the current IDSA guidelines, the preparatory committee agreed to use a cut off level of > 72 hours defining persisting bacteraemia. The preparatory committee agreed that there is insufficient evidence to deviate from the overall recommended duration of fourteen days after the day of the last positive blood culture for uncomplicated *S. aureus* bacteraemia. In case of **complicated** *S. aureus* **bacteraemia**, the extent of the complicating infections will determine the duration of therapy.

Recommendations

1. The preparatory committee recommends to treat uncomplicated *S. aureus* bacteraemia for fourteen days. 2. In all patients with *S. aureus* bacteraemia it is important to search for the presence of complications and the extent of the complicating infections will determine the duration of therapy, which can be up to eight weeks. 3. Persistence of positive blood culture results of more than 72 hours after starting antibacterial therapy should be considered as complicated *S. aureus* bacteraemia and treatment duration should be four to six weeks.

2. *Listeria monocytogenes*

In adult patients with *L. monocytogenes* infections, central nervous system infection and primary bacteraemia are the most common clinical syndromes (464, 465).

L. monocytogenes is an intracellular pathogen and its infection is associated with older age and an immunocompromised state (464, 466-471). No RCTs have been performed comparing different duration of treatment in patients with *Listeriosis.* However, several patients with relapses have been described which were associated with a duration of fourteen days or less (471, 472).

Conclusions

Level 3	Relapse of *Listeriosis* has been associated with an antibacterial treatment duration of fourteen days or less. C Mylonakis; McLauchlin(471, 472)

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Recommendation

Although there is no abundant literature supporting the exact duration of antibacterial treatment in patients with sepsis and *Listeriosis*, the preparatory committee recommends a duration of treatment of 21 days.

3. *Pseudomonas aeruginosa*

No RCTs have been performed comparing different treatment durations in patients with *P. aeruginosa* bacteraemia/sepsis. Moreover, no studies were conducted on the association between a shorter duration of antibacterial therapy and a worse outcome.

Conclusions

*	There is no evidence for an optimal duration of treatment in patients with *P. aeruginosa* sepsis.

10

Other considerations

As in bacteraemia caused by other micro-organisms, the duration of treatment of patients with sepsis due to *P. aeruginosa* should be dependent on the site of infection. When no site of infection is apparent, there is no evidence that therapy for sepsis due to *P. aeruginosa* should exceed the general recommended duration of seven to ten days.

Recommendation

The preparatory committee recommends a treatment duration of seven to ten days for sepsis due to *P. aeruginosa* with no apparent site of infection.

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Chapter 8
Switching intravenous to oral antibacterial therapy

Key question 7. Under what circumstances and when should intravenous therapy be switched to oral therapy?

Since in hospitalised (severely) ill patients adequate oral intake is usually difficult and intestinal absorption may be impaired, antibacterial therapy for patients with sepsis should be started intravenously. Moreover, intravenous administration quickly achieves high plasma levels. In contrast to the treatment of patients with CAP (473-476), the efficacy and safety of early switch from intravenous to oral therapy in patients with bacteraemia has not frequently been studied. Two underpowered RCTs in patients with documented bacteraemia or severe infections requiring a prolonged course of intravenous antibiotics concluded that an early switch (after three days) is safe and effective (477, 478). In both studies a course of parenteral antibacterial therapy was compared to initial parenteral therapy followed by oral ciprofloxacin, which has high bioavailability. One study included all patients with serious bacterial infections (478), while the other study included patients with proven Gram-negative bacteraemia only (477). De Marie et al. compared enteral ciprofloxacin 750 mg bid versus intravenous ciprofloxacin 400 mg bid in a randomised cross over study in five ICU patients with severe Gram-negative intra-abdominal infections who received continuous tube feeding (479). The calculated 12-h area under the serum concentration versus time curve was equivalent.

Conclusions

Level 2	Limited data support that in patients with Gram-negative bacteraemia or severe infections, an early switch (after three days) from intravenous to oral ciprofloxacin is safe and effective. B De Marie; Amodio-Groton; Paladino[(477-479)]

Other considerations

There are not many data on the safety and efficacy of an early switch from an intravenous to an oral antibacterial regimen in patients with sepsis. The decision depends on several factors including the clinical condition of the patient, the involved infection site and the bioavailability of the oral agent.

The results of the studies evaluating the safety and efficacy of an early switch from intravenous to oral antibiotics (mostly quinolones) can probably be extrapolated to other antimicrobial agents with high bioavailability, such as co-trimoxazole and clindamycin. In the US, due to the high incidence of MRSA and due to litigation issues, intravenous treatment for fourteen days (mostly as home/outpatient therapy) is considered the standard of care for *S. aureus* bacteraemia. Although evidence is lacking, switching to oral, highly bioavailable antibacterial agents after seven days is often applied in clinical practice for uncomplicated *S. aureus* bacteraemia.

Recommendations

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1. The preparatory committee recommends starting with intravenous antimicrobial therapy in adult patients with sepsis.

2. After clinical recovery and when the identity and susceptibility of the causative micro-organism has been determined, a switch to oral agents with high bioavailability can be made. For patients with uncomplicated *S. aureus* sepsis, oral, highly bioavailable antibacterial agents can be an option for the second week of treatment.

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Chapter 9
Timing of starting antibacterial therapy and sampling of blood cultures

Key question 8. Is there evidence for optimal timing to start antibacterial therapy in adult patients with sepsis?

There are no RCTs comparing the outcome of different intervals between presentation and initiation of appropriate antibacterial therapy in patients with sepsis with and without neutropenia. A recent retrospective study among 2731 adult patients with septic shock showed that administration of an effective antibacterial regimen within the first hour of documented hypotension was associated with increased survival. For every additional hour delay in initiation of effective antibacterial therapy in the first six hours after the onset of hypotension, survival dropped an average of 7.6% (255). A prospective cohort study among surgical ICU patients with severe infections showed that mortality was significantly associated with a 2.1% increase for every 30-min delay in administration of antibacterial therapy (480). Another smaller retrospective study in cancer patients with septic shock, showed a significant impact on mortality when treatment was delayed for more than two hours (481). Additionally, other retrospective studies on the impact of delayed antibacterial therapy in patients with bacterial meningitis, pneumonia and complicated skin and skin structure infections, showed similar results with increased mortality with delays in administration of antibacterial therapy ranging from four to eight hours (482-486).

Conclusions

Level 2	Postponing appropriate antibacterial therapy for more than one hour after onset of hypotension in patients with septic shock is associated with increased mortality. A2 Barie[480] B Kumar[255]

Other considerations

From the literature, it has become clear that it is important to start effective antibacterial therapy as soon as possible. Nevertheless, it is essential to have both blood cultures and cultures from suspected sites of infection taken before starting therapy in order to confirm the working diagnosis as well as to make de-escalation possible. The American Surviving Sepsis Campaign guidelines recommend starting antibacterial therapy within the first hour of recognition of **severe sepsis or septic shock** (204). Based on available literature, the preparatory committee agreed that antimicrobial therapy in patients with severe sepsis and septic shock should be started as soon as possible, preferably within the first hour of diagnosis. To optimise identification of causative organisms, the preparatory committee considers obtaining at least two sets of blood cultures and cultures from possible sites of infection mandatory before starting antimicrobial therapy. However, this should not cause significant delay in antibiotic administration. Young patients with recent (hours) onset severe sepsis/septic

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shock, including reduced conscious level and petechial or purpural rash are suspected of invasive **meningococcal disease**. This patient group should receive parenteral antibacterial therapy upon presentation.
It is not clear whether the consequences of delayed antimicrobial therapy are similar in patients with sepsis who do not meet the criteria of severe sepsis or septic shock.

Recommendations

1. Antimicrobial therapy in adult patients with **severe sepsis and septic shock** should be started as soon as possible, preferably within the first hour of presentation.

2. Before starting antimicrobial therapy, at least two sets of blood cultures and specimens for culture from suspected sites of infection should be taken. Maximal efforts should be made that this procedure does not cause significant delay in antibiotic administration.

10

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Supplement

Alternative antibiotic regimens in case of penicillin allergy

In patients with documented penicillin allergy it is important to distinguish a type I IgE mediated reaction from a type IV (T-cell) mediated rash. In patients with a non-IgE mediated penicillin rash, cephalosporins are suitable alternatives. Metronidazole should be added when anaerobes are expected. Patients with a type I IgE mediated penicillin allergy may present with urticaria, angioedema, laryngeal edema or anaphylaxis. It has been demonstrated that in patients with documented IgE mediated pencillin allergy approximately 3% also reacts to cephalosporins (487-498) and approximately 1% to carbapenems (499-501), although skin test reactivity is much higher (487, 490, 496).

Rechallenging patients with documented IgE mediated penicillin allergy may have detrimental consequences. Therefore, in patients with documented IgE mediated penicillin allergy, all beta-lactam agents should be avoided. The only exception is aztreonam (a monobactam agent) as several *in vitro* and skin testing studies showed no evidence of cross reactivity between aztreonam and penicillins (502-504). This agent has excellent Gram-negative activity and is in combination with vancomycin a suitable alternative as empirical antibacterial regimen in patients with sepsis and documented IgE mediated penicillin allergy. However, in most Dutch hospitals, aztreonam is not available anymore because its registration has been suspended. As an alternative, ciprofloxacin can be administered in combination with vancomycin. In hospitals with considerable quinolone resistance of Gram-negative micro-organisms, aminoglycosides should be added until the determination and susceptibility of the causative micro-organism are known.

Recommendations

1. Cephalosporins (+/- metronidazole*) are suitable alternatives in patients with non-IgE mediated penicillin rash
2. In case of type I IgE mediated allergic reactions to penicillins, aztreonam or ciprofloxacin +/- an aminoglycoside** in combination with vancomycin should be chosen

* when anaerobes are expected

** In hospitals with considerable quinolone resistance of Gram-negative micro-organisms

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Tables

Table 1a

Methodological quality of individual studies [(1)]

	Intervention	Aetiology, prognosis
A1	Systematic review of at least two independent A2-level studies	
A2	Randomised Controlled Trial (RCT) of sufficient methodological quality and power	Prospective cohort study with sufficient power and with adequate confounding corrections
B	Comparative Study lacking the same quality as mentioned at A2 (including patient-control and cohort studies)	Prospective cohort study lacking the same quality as mentioned at A2, retrospective cohort study or patient-control study
C	Non-comparative study	
D	Expert opinion	

Table 1b

Level of evidence of conclusions [(1)]

	Conclusions based on
1	Study of level A1 or at least two independent studies of level A2
2	One study of level A2 or at least two independent studies of level B
3	One study of level B or C
4	Expert opinion

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Table 2

Aetiology of bloodstream infections in the Netherlands in 2008[46]

	NethMap 2009 N=3872 *blood*
	%
Gram-positive bacteria	**60**
Staphylococci	
S. aureus	12
CNS	30
Streptococci	
S. pneumoniae	9
β-haemolytic streptococci	3
Enterococci	
Enterococcus spp	6
Gram-negative bacteria	**40**
Enterobacteriaceae	
E. coli	23
Klebsiella spp	6
P. mirabilis	2
E. cloacae	2
Other Enterobacteriaceae	2
Non-fermentatives	
P. aeruginosa	3
A. baumanii complex	0.3
S. maltophilia	0.3
Other Gram-negative bacteria	
H. influenzae	1
N. meningitidis	0.4
Anaerobic bacteria	*
Yeasts	*

* no data available

First isolate per clinical sample of patients in Unselected Hospital Departments in 2008, no original site of infection was specified and no distinction was made between community-acquired and nosocomial infections

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Table 3

Micro-organisms involved in Sepsis and HAP/VAP*

	Kooi [81] early HAP/ VAP *respiratory specimens*	Kooi [81] late HAP/ VAP *respiratory specimens*	Europe [86, 96, 97] early HAP/VAP *respiratory specimens*	Europe [86, 95-97] late HAP/VAP *respiratory specimens*	USA/ multinational [80, 82-84] early HAP/VAP *respiratory specimens*	USA/ multinational [80, 82-84, 94] late HAP/VAP *respiratory specimens*
	%	%	%	%	%	%
Gram-positive bacteria	**?**	**?**	**27-54**	**32-35**	**38-66**	**6-43**
Staphylococci						
S. aureus	most		9-38	17-33	11-39	4-35
CNS						
Streptococci						
S. pneumoniae	most		2-20	1-8	6-32	0-4
β-haemolytic streptococci						
α/non-haemolytic streptococci						
Enterococci						
Enterococcus spp						
Gram-negative bacteria	**?**	**?**	**39-63**	**60-65**	**30-57**	**34-92**
Enterobacteriaceae		most	0-4	5-24	7-19	6-26
E. coli						
Klebsiella spp						
Proteus spp						
Enterobacter spp						
Non-fermentatives			0-45	26-56	0-18	19-80
Pseudomonas spp		Most	0-42	25-47	0-13	12-64
Acinetobacter spp						
Moraxella spp						
Stenotrophomonas						
H.(para)influenzae	most		3-27	2-7	0-31	0-7

* No exact percentages were specified in the van der Kooi study
The total percentages of Gram positive and Gram negative micro-organisms do not always reach 100% because of various amounts of unspecified micro-organisms in different studies and because some studies only mention the most commonly involved micro-organisms

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Table 4

Micro-organisms involved in Urosepsis

	NethMap[46] CA & NC *urine samples*	other Dutch studies [103, 104] CA *urine samples*	SENTRY Europe[105] CA & NC *urine samples*
	%	%	%
Gram-positive bacteria	**22**	**0-12**	**16**
Staphylococci			
S. aureus	2		
CNS	2		
Streptococci			
S. pneumoniae			
β-haemolytic streptococcus	3		
Enterococci			
Enterococcus spp	15	0-3	13
Gram-negative Bacteria	**78**	**89-99**	**82**
Enterobacteriaceae	71	75-94	75
E. coli	46	47-66	52
Klebsiella spp	10	4-14	7
Proteus spp	9	5-26	7
Providencia		0-1	
Enterobacter spp	3	0-3	5
Other Enterobacteriaceae	3	0-3	4
Non-fermentatives		5-6	7
Pseudomonas spp	6	2-5	6
Acinetobacter spp	0.5	0-4	1

CA community-acquired ; NC nosocomial

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Table 5

Micro-organisms involved in Intra-abdominal Sepsis*

	Thesis of van Ruler[106] CA *abd. cultures*	Thesis van Ruler[106] NC *abd. cultures*	other Dutch[107, 108] CA&NC *abd. cultures*	Europe[29-31, 109] CA&NC *abd. cultures*	USA[110-112] CA&NC *abd. cultures*
	%	%	%	%	%
Gram-positive bacteria	**28**	**29**	**21-24**	**13-24**	**9-21**
Staphylococci					
S. aureus					
CNS	1	0			
Streptococci	9	5	2-14	7-13	6-15
S. pneumoniae					
β-haemolytic streptococci	1	0			
α/non-haemolytic streptococci	7	5			
Enterococci					
Enterococcus spp	18	24	15-20	5-11	0-6
Gram-negative bacteria	**47**	**50**	**46-56**	**29-68**	**18-58**
Enterobacteriaceae	42	47	39-47	29-64	16-50
E. coli	21	23			
Klebsiella spp	7	7			
Proteus spp	3	2			
Enterobacter spp	2	5			
Other Enterobacteriaceae	9	10			
Non-fermentatives					
Pseudomonas spp	5	3	3-9	0-10	2-15
Acinetobacter spp					
Stenotrophomonas					
Anaerobes	**14**	**15**	**15-24**	**10-33**	**31-26**
Bacteroides spp	3	2			
Clostridium spp	1	0			
Yeasts (*Candida spp*)	**9**	**6**	**5-7**	**0**-5**	**0****

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*The total percentages of Gram positive and Gram negative micro-organisms do not always reach 100% because of various amounts of unspecified micro-organisms in different studies and because some studies only mention the most commonly involved micro-organisms.
In some studies, apart from abdominal cultures, the results of blood cultures were included, but this concerned only a small percentage of the total amount of cultures
CA community-acquired; NC nosocomial
** No data

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Table 6

Micro-organisms involved in sepsis and complicated SSSI

	SENTRY[126] worldwide CA& NC *cultures of SSI*	USA[35, 128] CA&NC *cultures of SSI*
	%	**%**
Gram-positive bacteria	**59**	**65-68**
Staphylococci		
S. aureus	43	36-46
CNS	4	
Streptococci	4	13-20
S. pneumoniae		
β-haemolytic streptococci	4	13-20
α/non-haemolytic streptococci	1	
Enterococci		
Enterococcus spp	7	9-9
Gram-negative bacteria	**39**	**?-31***
Enterobacteriaceae	25	15-22
E. coli	9	6-7
Klebsiella spp	5	
Proteus spp	3	
Enterobacter spp	5	
Other Enterobacteriaceae	3	
Non-fermentatives	14	
Pseudomonas spp	11	?-7
Acinetobacter spp	2	
Stenotrophomonas	1	
Anaerobes	**0**	**0-20**

* Giordano et al did not specify the exact number of Pseudomonas isolates (35)
Gesser et al. only mentioned the most frequently involved pathogens: *S. aureus* (49%), Enterobacteriaceae (24%), β-haemolytic streptococci (20) and anaerobes (15%). The percentages of enterococci and *Pseudomonas spp* were not mentioned (36)
Goldstein et al. also only specified the most frequently isolated micro-organisms: *S. aureus* (24%), anaerobes (27%), β-haemolytic streptococci (9%) and *E. coli* (5%). The percentages of enterococci and *Pseudomonas spp* were not mentioned (127)
CA community-acquired; NC nosocomial

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Table 7

Resistance percentage among blood isolates of hospitalised patients in the Netherlands, NethMap 2007 (135)

	methicillin %	**amoxicillin %**	**amoxicillin and clavulanic acid %**	**cephalosporins second generation %**	**cepahalosporins third generation %**
Gram-positive					
S. aureus	1		1	1	1
S. pneumoniae		0.2		1	0
β-haem streptococci		0		0	0
Enterococcus spp		18*			
Gram-negative					
E. coli		43	6	4	2
P. mirabilis		21	7	0	0
K. pneumoniae			5	6	5
E. cloacae			97	69	31
P. aeruginosa				98	3**
N. meningitidis		0		0	0

	piperacillin %	**piperacillin/ tazobactam %**	**imipenem %**	**meropenem %**
Gram-positive				
S. aureus			1	2
S. pneumoniae			0	1
β-haem streptococci			0	0.5
Enterococcus spp			8	
Gram-negative				
E. coli	33	2	0	0
P. mirabilis	15	0	14	4
K. pneumoniae		5	0	1
E. cloacae	50	12	0	0
P. aeruginosa	1	2	8	3
N. meningitidis				

	gentamicin %	**tobramycin %**	**amikacin %**
Gram-positive			
S. aureus	1		
S. pneumoniae	100		
β-haem streptococci			

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Enterococcus spp			
Gram-negative			
E. coli	3	1	0
P. mirabilis	3		
K. pneumoniae	3		
E. cloacae	2	1	0
P. aeruginosa	0	2	2
N. meningitidis			

	vancomycin %	**ciprofloxacin %**	**co-trimoxazole %**
Gram-positive			
S. aureus	0	4	2
S. pneumoniae	0	1	3
β-haem streptococci	0		5
Enterococcus spp	1		
Gram-negative			
E. coli		9	27
P. mirabilis		1	31
K. pneumoniae		2	9
E. cloacae		6	10
P. aeruginosa		8	95
N. meningitidis			

* the high amoxicillin resistance can be explained by contribution of *E. faecium*
** this counts for ceftazidime only, for the other third generation cephalosporins there is a resistance rate of 68-76%

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Table 8

Resistance percentage of bacteria, isolated from blood, urine, respiratory tract and body fluids in adult patients with sepsis in the Netherlands against relevant antibiotics. Data are from unselected hospital departments and from the ICU (between brackets), NethMap 2009 (46)

	methicillin hospital (ICU) %	**penicillin** hospital %	**amoxicillin** hospital (ICU) **%**	**amoxicillin and clavulanic acid** hospital (ICU) %
Gram-positive				
S. aureus	2 (*)			
S. epidermidis	58 (80)			
S. pneumoniae		1		
E. faecalis			2 (10)	
Gram-negative				
E. coli			44 (52)	7 (25)
P. mirabilis			24 (37)	4 (14)
K. pneumoniae				3-6 (24)
E. cloacae				(>90)
P. aeruginosa				
N. meningitidis		0 / 2-4**		

	cephalosporins first generation hospital (ICU) %	**cephalosporins second generation** hospital (ICU) %	**cephalosporins third generation** hospital (ICU) %
Gram-positive			
S. aureus			
S. epidermidis			
S. pneumoniae			<1%¶
E. faecalis			
Gram-negative			
E. coli		(15)	3 (1-2)
P. mirabilis		(3-8)	<1(<1)
K. pneumoniae	(18)	(15)	3 (5)
E. cloacae	(>30)	(>30)	(>30)
P. aeruginosa			3 (<2)¶¶
N. meningitidis			

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	piperacillin (ICU) %	**piperacillin/ tazobactam** (ICU) **%**	**meropenem** hospital **%**
Gram-positive			
S. aureus			
S. epidermidis			53
S. pneumoniae			
E.faecalis			
Gram-negative			
E. coli	(47)	(5)	
P. mirabilis			
K. pneumoniae			
E. cloacae	(28)	10(14)	0.1(0)
P. aeruginosa	(10)		1
N. meningitidis			

	gentamicin hospital (ICU) %	**tobramycin** hospital **%**	**amikacin** hospital **%**
Gram-positive			
S. aureus	0.4-1 (0)		
S. epidermidis	21 (80)		
S. pneumoniae			
E . faecalis			
Gram-negative			
E. coli	4 (5)		
P. mirabilis	4(4)		
K. pneumoniae	3 (11)		
E. cloacae	3(6)	4(10)	0.1(0)
P. aeruginosa	6 (2-8%)	6	4
N. meningitidis			

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	vancomycin hospital **%**	**ciprofloxacin** hospital (ICU) **%**	**co-trimoxazole** hospital (ICU) **%**
Gram-positive			
S. aureus	<0.1	8(14)	
S. epidermidis	0	33(90)	30(50)
S. pneumoniae		37¶¶¶	17
E. faecalis	1(Δ)		
Gram-negative			
E. coli		10 (14)	27 (28)
P. mirabilis		2(7)	(26)
K. pneumoniae		4 (12)	(23)
E. cloacae		4(16)	4.5(10)
P. aeruginosa		6	
N. meningitidis			

* Sporadically, MRSA strains were isolated from ICUs (N=7 from 1998-2007)
** 0 % of CSF and blood isolates were penicillin resistant in 2008, but 2-4 % of the CSF isolates and 8% of the blood isolates were moderately susceptible to penicillin
¶ cefotaxime resistance rates only
¶¶ ceftazidime resistance rates only
¶¶¶ Intermediate and resistant strains were included in the analysis and it is unclear what breakpoints were used to determine the resistance rate
Δ Vancomycin resistance in ICUs was found in one unit in 2003 and in one unit in 2007

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Table 9

Empirical antibacterial therapy in patients with sepsis according to suspected site of infection*

infection site	most common pathogens	empirical therapy
Lungs community-acquired (CAP)	*S. pneumoniae, H. influenzae, M. pneumoniae, S. aureus, Legionella spp*	See SWAB guidelines on CAP
nosocomial (HAP,VAP)	*S. pneumoniae, S. aureus ,H. influenzae* with increasing duration of hospitalisation, ventilation and prior use of antibiotics also: Enterobacteriaceae, *P. aeruginosa*	• amoxicillin and clavulanic acid + gentamicin/ciprofloxacin • second/third generation cephalosporin excluding ceftazidime + gentamicin/ciprofloxacin • piperacillin/tazobactam
Urinary tract community-acquired	*E. coli, P. mirabilis, K. pneumoniae*	• second/third generation cephalosporin • amoxicillin + gentamicin
with indwelling catheter	*E. coli, P. mirabilis, K. pneumoniae Enterococci*	• second/third generation cephalosporin + gentamicin/ciprofloxacin • amoxicillin and clavulanic acid + gentamicin /ciprofloxacin • suspected *E.faecalis*: amoxicillin • suspected *E. faecium* vancomycin
Abdomen community-acquired	polymicrobial, mainly: Enterobacteriaceae, enterococci, anaerobes, *Streptococcus spp*	• second/third generation cephalosporin and metronidazole +/- gentamicin • amoxicillin and clavulanic acid +/- gentamicin
cholangitis	*E. coli, Klebsiella spp, Enterococcus spp*, anaerobes	• amoxicillin and clavulanic acid + gentamicin
nosocomial	same pathogens, more resistant Gram-negatives	• amoxicillin and clavulanic acid + gentamicin • second/third generation cephalosporin + metronidazole + gentamicin • piperacillin/tazobactam +/- gentamicin
cholangitis	same pathogens CA cholangitis, more resistant Gram-negatives	• amoxicillin and clavulanic acid + gentamicin
uncomplicated SSSI community-acquired/nosocomial	*Streptococcus spp, S. aureus*	• flucloxacillin

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complicated SSSI community-acquired	*Streptococcus spp, S. aureus,* Enterobacteriaceae	• amoxicillin and clavulanic acid
nosocomial	same pathogens, more resistant gram-negative bacteria	• amoxicillin and clavulanic acid + gentamicin • piperacillin/tazobactam
Necrotising fasciitis community-acquired	GAS, *S. aureus*	• amoxicillin and clavulanic acid + clindamycin
nosocomial	Enterobacteriacae, anaerobes, enterococci, non-fermentative Gram-negative micro-organisms, *Streptococcus spp*., *S. aureus*	• amoxicillin and clavulanic acid + gentamicin + clindamycin • piperacillin/tazobactam +/- gentamicin + clindamycin
Central Nervous System community-acquired	*N. meningitidis,S. pneumoniae* > 50 years old: also *L. monocytogenes*	See SWAB guidelines on meningitis
nosocomial	Depending on underlying conditions, mainly: *S. pneumoniae,S. aureus*	

* Alternative regimens in patients with documented penicillin allergy are discussed in the supplement on page 72

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