J Infect Chemother xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Guideline

The JAID/JSC guidelines for management of infectious diseases 2017 – Sepsis and catheter-related bloodstream infection

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ARTICLE INFO

Article history:
Received 10 December 2018
Received in revised form

28 October 2019
Accepted 29 November 2019
Available online xxx

1. Introduction

Sepsis is one of the most serious conditions among all infectious diseases. To establish a sepsis treatment system as the basis of bacterial infection treatment, knowledge regarding infectious disease medicine/chemotherapeutics must be collected. Due to the recent appearance of various antimicrobial-drug-resistant bacteria, it is necessary to flexibly switch strategies to treat bacterial infection. This is not exceptional in the field of sepsis. It is also necessary to manage such infection, considering the involvement of antimicrobial-drug-resistant bacteria, including MRSA(methicillin resistant *Staphylococcus aureus*) and ESBL(extended spectrum β-lactamase)-producing bacteria. Antimicrobial-drug-resistant bacteria have been routinely detected in patients not only with nosocomial but also with community-acquired infection.

Sepsis is defined as a severe condition derived from a primary infection site. On the other hand, we often encounter patients with narrow-sense blood stream infection caused by intravascularly inserted catheters in clinical practice. Although there is a dissociation as a condition to be described in the “Sepsis” section, it was included in this section for convenience. In patients with sepsis, as a rule, a primary infected focus should be investigated, and treatment must be performed in accordance with the site of infection and condition. However, in the present guidelines, antimicrobial chemotherapy as empiric therapy is described, focusing on initial treatment with antimicrobial drugs for sepsis at a time point when a primary focus is unclear or inaccurate. In the “Catheter-related bloodstream infection” section, definitive therapy after the identification of causative bacteria is concretely described.

In the JAID/JSC Guide for Management of Infectious Diseases 2011, which were published in 2012, and a revision published in 2014: the JAID/JSC Guide for Management of Infectious Diseases 2014, “sepsis” is described in the first chapter. In the year of 2017, an additional revision will be edited. In this article, the “guidelines” structure was adopted to provide additional explanations. We hope that the present guidelines will contribute to the appropriate use of antimicrobial drugs by health care professionals in clinical practice through the understanding of the descriptive background of the above guides as pocket versions and evidence. Recent guidelines have been prepared according to Minds' regulations. Essentially, it is ideal to prepare the present guidelines according to them. However, to avoid a delay in book publication and clinical application related to persistence to the system in a restricted time, the present guidelines were not always prepared according to Minds' regulations. This article was completed by publishing a draft of the present guidelines on the homepages of the Japanese Association for Infectious Diseases and Japanese Society of Chemotherapy, collecting public comments, and revising the draft in accordance with proper advice. The most important point of this project was to

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https://doi.org/10.1016/j.jiac.2019.11.011

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clarify which antimicrobial drug should be selected by physicians/pharmacists facing sepsis treatment and contribute to therapeutics in clinical practice. On the assumption that incomplete points, such as the absence of "Clinical Questions", may be complemented or revised at the next committee meeting, we hope that the present guidelines will be applied in clinical practice.

The present guidelines will be revised every few years based on the above viewpoint, future appearance or spreading of new resistant bacteria, and necessity of providing information on the development of new antimicrobial drugs.

In Japan, the "Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016" [1], which were prepared by the Japanese Society of Intensive Care Medicine and Japanese Association for Acute Medicine, were recently published. Internationally, "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016" [2] were published. In these guidelines, entire sepsis treatment is described, consisting of extremely abundant contents as a golden standard in accordance with close guideline-preparing methods. However, the contents are not specific to antimicrobial therapy, and no concrete antimicrobial drug name is mentioned. On the other hand, the contents of the present guidelines primarily consist of antimicrobial chemotherapy, especially drugs selected for empiric therapy (concerning catheter-related bloodstream infection, definitive therapy is mentioned) on the assumption that the above two guidelines may be sufficiently understood [1,2]. Briefly, the purpose of the JAID/JSC Guidelines for Management of Sepsis is to support the more accurate selection of an antimicrobial drug, which plays a role in treatment, in the presence of septic conditions requiring life-saving management such as shock and multiple organ failure.

1. Recommendation grade and evidence level of references

Recommendation grades		Evidence levels	
A	Strongly recommended	I	Randomized controlled study
B	General recommendation	II	Non-randomized controlled study
C	Comprehensive evaluation	III	Case report
		IV	Specialist's opinion

2. Definition of first- and second-choice drugs

First-choice drug	Drugs to be initially used
Second-choice drug	Drugs to be selected when a first-choice drug cannot be used due to allergy, organ disorder, or local factors

As the most important point, physicians must consider that the start of antimicrobial chemotherapy for sepsis, that is, fatal organ failure, in the early phase (within 1 h) is the sole requirement, and that source-of-infection control and intensive care control involving the airway/respiration/circulation are essential for sepsis treatment from the viewpoint of lifesaving.

3. A list of doses for neonates is shown on the last page.

4. †:The mark indicates a condition that is not covered by health insurance in Japan (including the name of an infectious disease, dose, and type of bacteria).

2. Sepsis

A) Adults

—Executive summary—

1) Definition/diagnosis

- Definition of sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection.
- As sepsis causes shock or organ failure, infectious disease treatment should be performed while managing the general condition (A: airway management, B: breath stabilization in the respiratory state, C: circulation: withdrawal from shock, stabilization of circulation)(A I).
- Sepsis had been defined as presented in Table 1, but a new definition and diagnostic criteria (Table 2, Fig. 1) were proposed in 2016.

2) Summary of treatment: Community-acquired sepsis

- If a diagnosis of sepsis is made, physicians should make maximum efforts to start antimicrobial chemotherapy, as empiric therapy, within 1 h.
- In patients with severe community-acquired sepsis (or a tentative diagnosis of community-acquired sepsis), treatment with 3rd-generation cephalosporins should be started, considering causative microorganisms such as *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* (A II).
- Carbapenems should be selected for high-risk patients regarding infection with ESBL-producing bacteria, that is, those with the following histories: i) a history of ESBL-producing bacteria detection, ii) recent antimicrobial drug administration (especially β-lactams), iii) the presence of organ disorders such as chronic respiratory disease and liver disease, iv) a history of invasive urological treatment, and v) admission to long-term care facilities (B II).
- In patients in whom infection with *S. pneumoniae* is suspected, combination therapy with VCM should be considered if infection with low β-lactam-sensitive bacteria is suspected based on the patient background (A II).

3) Summary of treatment: Nosocomial or community-acquired, healthcare-associated infection

- Assuming that causative microorganisms may include gram-negative bacilli, such as *Pseudomonas aeruginosa*, and multidrug-resistant gram-positive coccus, such as methicillin-resistant *Staphylococcus aureus* (MRSA), combination therapy with β-lactams, which exhibits *anti-P. aeruginosa* activity, and *anti*-MRSA drugs should be considered (A II).
- As the susceptibility of causative microorganisms to antimicrobial drugs differs among medical institutions, drugs should be selected by reviewing institutional antibiograms (A IV).
- In severe-status patients or those with neutropenia/immunodeficiency, such as cell-mediated immunodeficiency, the risk of infection with *Candida* is high. In such cases, combination therapy with antifungal drugs should be considered (C II).

1 Explanation

[Epidemiological background: Infected organs]

According to a study, infectious diseases affected the lungs (35%), abdomen (21%), urinary tract (13%), skin & soft tissue (7%), and others (8%), causing sepsis, whereas foci were unclear in 16% of the patients [5]. According to the Sepsis Registry Survey conducted by the Japanese Association for Acute Medicine, the most frequent organ/system was the respiratory system (436 patients, 39.5%), followed by the intraabdominal organs (268 patients, 24.3%), urinary tract (160 patients, 14.5%), and soft dermal tissue (110 patients, 10.0%) [6].

[Epidemiological background: Causative microorganisms]

Trends in microorganisms that cause sepsis depend on the patient background. The most frequent microorganism that causes adult sepsis through community-acquired infection is *Escherichia coli*, followed by *Streptococcus pneumoniae* and *Staphylococcus aureus* [7]. However, among patients with sepsis related to community-acquired

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Table 1
Definition of sepsis and diagnostic criteria for sepsis in 2001.

Infection in which some of the followings are observed or suspected
General parameters
Fever (>38.3 °C)
Hypothermia (core temperature <36 °C)
Heart rate >90 bpm or >2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 h)
Hyperglycemia (plasma glucose >140 mg/dL) in the absence of diabetes
Inflammatory parameters
Leukocytosis (>12,000/μL)
Leukopenia (<4000/μL)
Normal white blood cell count with >10% immature forms
Plasma CRP >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic parameters
Arterial hypotension (SBP <90 mmHg, MAP <70, or an SBP >40 mmHg in adults or <2 SD below normal for age)
Organ dysfunction parameters
Arterial hypoxemia (PaO_2/FIO_2 <300)
Acute oliguria (urine output: <0.5 mL/kg/hr for at least 2 h despite sufficient fluid infusion loading)
Creatinine increase >0.5 mg/dL
Coagulation abnormalities (INR>1.5 or aPTT >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/μL)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL)
Tissue perfusion parameters
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

SD: standard deviation.
CRP: C-reactive protein.
SBP: systolic blood pressure.
MAP: mean arterial pressure.
INR: international normalized ratio.
aPTT: activated partial thromboplastin.
Diagnostic criteria for sepsis in the pediatric population: signs and symptoms of inflammation plus infection with hyper-or hypothermia (rectal temperature >38.5 °C or <35 °C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses.
(Referenced from: Levy MM, Fink MP, Marshall JC et al., 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6 [3]).

Table 2
Definition of sepsis and diagnostic criteria in 2016 (Sepsis-3), In 2016, a new definition and diagnostic criteria for sepsis were proposed, as presented in 2-1 to 2-3. However, few studies have examined their usefulness.

2-1 Definition of sepsis (Sepsis-3)
Life-threatening organ dysfunction caused by a dysregulated host response to infection
2-2 Diagnosis of sepsis (Sepsis-3)
In ICU-admitted patients with a 2-point or greater increase in the SOFA score (Table 3) related to an infectious disease, or in non-ICU patients meeting ≥2 items of qSOFA, sepsis should be suspected, and organ disorder must be confirmed using the SOFA score (Fig. 1). qSOFA score -Respiratory rate: ≥22 times/min -Systolic blood pressure: ≤100 mmHg -Abnormal changes in consciousness
2-3 Diagnosis of septic shock (when all of the following criteria are met)
-After adequate initial fluid infusion -Hypotension requiring vasopressors to maintain a mean blood pressure of ≥65 mmHg -Serum lactic acid level: >2 mmol/L

Modified from the translated Reference 4: Singer M. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.

infection, causative microorganisms differ in those admitted to long-term care facilities. Concretely, as gram-negative bacilli, *Enterobacteriaceae*, such as *E. coli* and *Proteus*, and *P. aeruginosa* cause sepsis. Furthermore, the detection rate of *S. aureus* is high, as demonstrated for community-acquired infection, but MRSA accounts for 1/3 of that [8]. As the reason for this, the frequent exposure of those admitted to long-term care facilities to medical practice may result in healthcare-associated infectious diseases.

The Sepsis Registry Survey, which was conducted by the Japanese Society of Intensive Care Medicine, epidemiologically examined sepsis patients admitted to the intensive care units of medical institutions in Japan. In the study, 66 patients were registered in the field of internal medicine, 58 in the field of surgery, and 142 (including 3 with trauma) in the field of emergency medicine. According to this survey, MRSA (22.0%), *E. coli* (14.0%), *Klebsiella pneumoniae* (11.8%), methicillin-sensitive *Staphylococcus aureus*(MSSA) (9.7%), *P. aeruginosa* (9.2%), *Enterobacter* spp. (7.4%), and *S. pneumoniae* (6.0%) were frequently detected as causative microorganisms [9].

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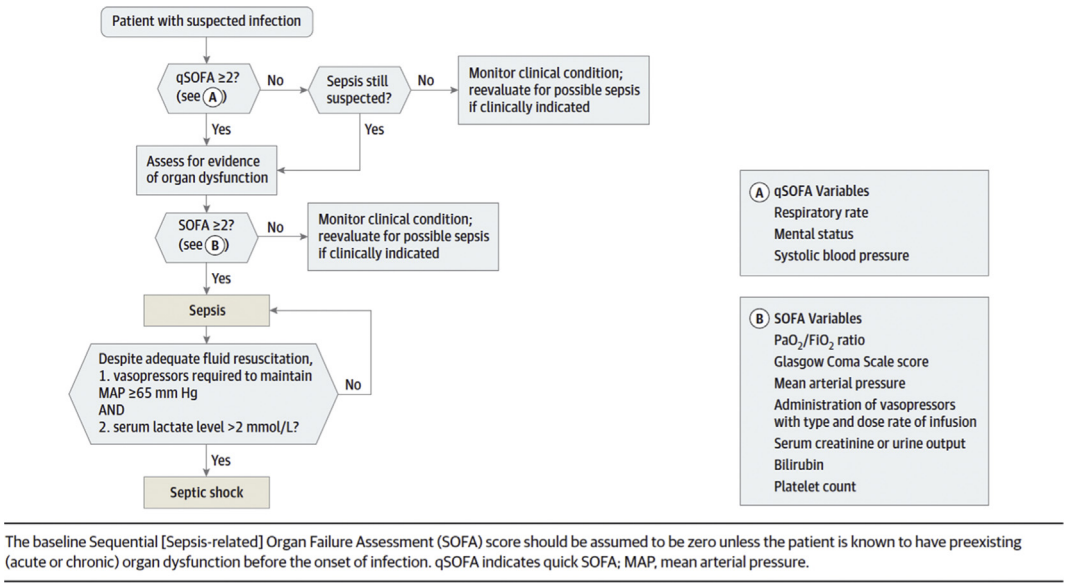

Fig. 1. Algorithm for the diagnosis of sepsis. Modified from the translated Reference 4: Singer M. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10. * The above contents were quoted from Reference [4], and modified.

Table 3
SOFA score. Sepsis-related Organ Failure Assessment → Sequential Organ Failure Assessment.

	0	1	2	3	4
PaO_2/FiO_2 [mmHg]	≥400	<400	<300	<200 +Respiratory support	<100 + Respiratory support
Platelet count [$\times 10^3/\mu L$]	≥150	<150	<100	<50	<20
T.Bil [mg/dL]	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Arterial hypotension	Mean arterial pressure ≥70 mmHg	Mean arterial pressure <70 mmHg	DOA <5γ or DOB (regardless of the dose)	DOA >5.1–15γ or AD ≤0.1γ or NAD ≤0.1γ	DOA >15γ or AD >0.1γ or NAD >0.1γ
GCS	15	13–14	10–12	6–9	<6
Serum Cr [mg/dL]	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output				<500 mL/day	<200 mL/day

PaO_2/FiO_2: Partial pressure of oxygen in arterial blood/Fraction of inspired oxygen, DOA: Dopamine, DOB: Dobutamine, AD: Adrenaline, NAD: Noradrenaline, Catecholamine: Dose administered over ≥1 h, GCS: Glasgow coma scale.
Modified from the translated Reference 4: Singer M. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10.

It is possible to predict causative microorganisms at the bacteremia level to some degree by investigating trends in the results of blood culture in medical institutions. According to an annual report published by the Clinical Laboratory Division of the Japan Nosocomial Infections Surveillance(JANIS), Ministry of Health, Labour and Welfare, which is a public surveillance system in Japan, in 2011, *S. aureus* (14.7%), *E. coli* (13.2%), *Staphylococcus epidermidis* (11.3%), coagulase-negative *Staphylococcus* (CNS)(9.5%), *K. pneumoniae* (6.0%), *Enterococcus faecalis* (3.4%), and *P. aeruginosa* (3.4%) were frequently detected on blood culture [10].

According to the Sepsis Registry Survey conducted by the Japanese Association for Acute Medicine, 314 strains were detected in blood samples from 624 patients, including 147 g-positive coccus and 140 g-negative bacillus strains. The most frequent type of bacteria was *E. coli*, accounting for 14.0%, followed by *S. aureus* (9.9%) (MSSA: 6.4%, MRSA: 3.5%), *K. pneumoniae* (8.6%), *S. pneumoniae* (4.5%), *P. aeruginosa* (3.8%), and *Bacteroides* (3.2%) [11].

Naturally, the definition of bacteremia differs from that of sepsis. The former refers to a type of infectious disease (or its suspicion) with a positive reaction on blood culture. The latter refers to severe infection regardless of positive/negative reactions on blood culture. It must be considered that the entity of bacteremia has recently changed. The purpose of this chapter is to introduce antimicrobial chemotherapy for sepsis, but we review changes in the entity of a blood-culture-positive state (bacteremia) as an assumption. Briefly, bacteremia is classified into 3 entities: 1) community-acquired bacteremia, 2) community-acquired, healthcare-associated bacteremia, and 3) nosocomial bacteremia. The different characteristics of respective types have been demonstrated. In 2002, Friedman et al. defined healthcare-associated bacteremia as a condition meeting one of the following criteria: 1) home transvenous treatment, wound treatment, enteral nutrition, or home nursing within the past 30 days, 2) hemodialysis or chemotherapy by intravenous injection within the past 30 days, 3) a history of admission to an acute care hospital for ≥2 days within the past 90 days, and 4) admission to a long-term care facility [12]. They regarded "patients with positive reactions on a culture test using blood samples collected on admission or within 48 h after admission who do not meet the definition of healthcare-associated infection" as having community-acquired bacteremia, "those with positive reactions on a culture test using blood samples collected ≥48 h after admission (however, on admission or later in patients referred from long-term care facilities)" as having nosocomial bacteremia, and "those, with positive reactions on a culture test using blood samples collected on admission or within 48 h after admission, meeting the definition of

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healthcare-associated infection" as having community-acquired, medical-care-associated hbacteremia.

As a result, it was shown that many patients with healthcare-associated bacteremia had undergone endovascular catheter insertion, with a high detection rate of *S. aureus* as a causative microorganism, and that the detection rate of MRSA, as a causative microorganism, was high even in patients with community-acquired, healthcare-associated bacteremia, being similar to that in those with nosocomial bacteremia. In summary, the distribution of causative microorganisms and resistance tendency in patients with community-acquired, healthcare-associated bacteremia are similar to those in patients with nosocomial bacteremia. As bacteremia is concomitantly present in many severe-status patients with sepsis, this must also be considered when selecting empiric therapy for sepsis.

[Precautions for the selection of treatment]

① Community-acquired sepsis

Definition: Sepsis before admission or within 48 h after admission that does not meet the definition of healthcare-associated infection.

* Healthcare-associated infection (described above): A condition meeting one of the following criteria: 1) home transvenous treatment, wound treatment, enteral nutrition, or home nursing within the past 30 days, 2) hemodialysis or chemotherapy by intravenous injection within the past 30 days, 3) a history of admission to an acute care hospital for ≥2 days within the past 90 days, and 4) admission to a long-term care facility.

In patients with community-acquired sepsis (or a tentative diagnosis of community-acquired sepsis), *E. coli*, *S. pneumoniae*, and *S. aureus* should be considered as causative microorganisms. Treatment with 3rd-generation cephalosporins should be started (A II) [11].

Even in patients with community-acquired infection, the involvement of antimicrobial-drug-resistant bacteria must be considered in accordance with the patient background. Recently, infection with extended-spectrum β-lactamase (ESBL)-producing bacteria has become a community issue. High-risk states for infection with ESBL-producing bacteria include: 1) a history of ESBL-producing bacteria detection, 2) recent antimicrobial drug administration (especially β-lactams), 3) the presence of organ disorders such as chronic respiratory disease and liver disease, 4) a history of invasive urological treatment, and 5) admission to long-term care facilities [11]. In such cases, treatment should be selected, considering infection with ESBL-producing bacteria (B II).

When infection with *S. pneumoniae* is suspected, the involvement of low β-lactam-sensitive strains should be considered in some areas/medical institutions. This is particularly important in the case of meningitis. In this case, combination therapy with VCM must be considered (A II) [12].

② Nosocomial or community-acquired, healthcare-associated infection

Definition: Nosocomial sepsis is defined as "sepsis that occurred ≥48 h after admission", and community-acquired, healthcare-associated sepsis as "healthcare-associated infection-derived sepsis that occurred before admission or within 48 h after admission".

In this case, gram-negative bacillus, especially *P. aeruginosa*, and multidrug-resistant gram-positive coccus, such as MRSA, should be initially considered as causative microorganisms. As empiric therapy, β-lactams, which exhibit *anti-P. aeruginosa* actions, should be combined with *anti*-MRSA drugs (A II). In particular, the risk of MRSA-related bacteremia is high in patients undergoing hemodialysis and those after venous catheter insertion at outpatient clinics; therefore, combination therapy with VCM should be considered (A II).

The most important point is that the tendency of microorganisms that cause infectious diseases varies among medial institutions. Concretely, the susceptibility of gram-negative bacilli, such as *P. aeruginosa*, to antimicrobial drugs markedly differs among medical institutions. Therefore, drugs should be selected by reviewing the antibiograms of the medical institution (A IV) [12].

In severe-status patients evaluated based on the SOFA score or those with neutropenia/immunodeficiency, such as cell-mediated immunodeficiency, the risk of infection with *Candida* is high. In such cases, combination therapy with antifungal drugs should also be considered. (C II) [13].

2. Empiric therapy

(1) Community-acquired infection.

First choices

- Standard recommendations
  - Drip infusion of CTRX at 2 g/session, once to twice a day
  - Drip infusion of CTX at 2 g/session, 3†times a day
  - Drip infusion of TAZ/PIPC at 4.5 g/session, 3 to 4†times a day
- High-risk group for infection with ESBL-producing bacteria

Carbapenems should be used in patients meeting one of the following criteria: 1) a history of ESBL-producing bacteria detection, 2) recent antimicrobial drug administration (especially β-lactams), 3) the presence of organ disorders such as chronic respiratory disease and liver disease, 4) a history of invasive urological treatment, and 5) admission to long-term care facilities.

- Drip infusion of MEPM at 1 g/session, 3 times a day
- Drip infusion of IPM/CS at 0.5 g/session, 4 times a day
- Drip infusion of DRPM at 0.5–1 g/session, 3 times a day
- Drip infusion of PAPM/BP at 1 g/session, twice a day
- Drip infusion of BIPM at 0.3 g/session, 4 times a day

- Areas where low β-lactam-sensitive *S. pneumoniae* has been frequently detected
  - The twice-a-day drip infusion of VCM at 1 g/session (or 15 mg/kg) should be added to one of the above regimens.

Note) Second choices

- In the presence of allergy to β-lactams,
  - Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day

Note)+ one of the following regimens:

- Drip infusion of PZFX at 1000 mg/session, twice a day
- Drip infusion of CPFX at 400 mg/session, 3 times a day
- Drip infusion of LVFX at 500 mg/session, once a day

Note) When administering glycopeptides, therapeutic drug monitoring (TDM) must always be conducted.

(2) Nosocomial or community-acquired, healthcare-associated infection.

First choices

- Among the following β-lactams, which exhibit *anti-P. aeruginosa* actions, drugs to which the susceptibility of bacteria is maintained should be selected by reviewing the antibiograms of the medical institution against non-glucose-fermenting bacteria, such as *P. aeruginosa*, and *Enterobacteriaceae*(including ESBL-producing bacteria) such as *E. coli*:
  - Drip infusion of CFPM at 1 g/session, 3 to 4 times a day
  - Drip infusion of CZOP at 1 g/session, 3 to 4 times a day
  - Drip infusion of CAZ at 1 g/session, 3 to 4 times a day
  - Drip infusion of TAZ/PIPC at 4.5 g/session, 3 to 4†times a day
  - Drip infusion of MEPM at 1 g/session, 3 times a day
  - Drip infusion of IPM/CS at 0.5 g/session, 4 times a day

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- Drip infusion of DRPM at 0.5–1 g/session, 3 times a day
- Drip infusion of BIPM at 0.3 g/session, 4 times a day

One of the above regimens + one of the following ones (when MRSA infection cannot be ruled out):

- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day[Note)]
- Drip infusion of TEIC at 400 mg/session, twice a day on Day 1 and once a day from Day 2[Note)]
- Drip infusion of ABK at 200 mg/session, once a day

In severe-status patients or those with neutropenia/immunodeficiency, such as cell-mediated immune disorder, combination therapy with one of the following regimens should be adopted, considering infection with *Candida*:

- Drip infusion of MCFG at 100 mg/session, once a day
- Drip infusion of CPFG at 70 mg/session on Day 1 (once a day) and at 50 mg/session from Day 2 (once a day)
- Drip infusion of L-AMB at 2.5–5.0 mg/kg/session, once a day

Second choices.

- In the presence of allergy to β-lactams,
  - Drip infusion of PZFX at 1000 mg/session, twice a day
  - Drip infusion of CPFX at 400 mg/session, 3 times a day
  - Drip infusion of LVFX at 500 mg/session, once a day

  One of the above regimens + one of the following ones (when MRSA infection cannot be ruled out):
  - Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day[Note)]
  - Drip infusion of TEIC at 400 mg/session, twice a day on Day 1 and once a day from Day 2[Note)]
  - Drip infusion of ABK at 200 mg/session, once a day

  In severe-status patients or those with neutropenia/immunodeficiency, such as cell-mediated immune disorder, combination therapy with one of the following regimens should be adopted, considering infection with *Candida*:
  - Drip infusion of MCFG at 100 mg/session, once a day
  - Drip infusion of CPFG at 70 mg/session on Day 1 (once a day) and at 50 mg/session from Day 2 (once a day)
  - Drip infusion of L-AMB at 2.5–5.0 mg/kg/session, once a day

  Note) When administering glycopeptides, TDM must always be conducted.

3. Definitive therapy

If the primary focus or causative bacteria are clarified, the regimen should be switched to antimicrobial drugs of which the favorable transfer to the infected organ, cost-effectiveness, and clinical efficacy were demonstrated (de-escalation). See various guidelines.

Indications for DAP include sepsis, but the type of bacteria to be targeted is limited to MRSA. If pneumonia is absent in the presence of MRSA-related sepsis, DAP may be selected. In adults, 6 mg/kg of DAP should be slowly injected through an intravenous route or intravenously dripped over 30 min every 24 h.

B) Children (after infancy, normal immune state): Community-acquired sepsis

—Executive summary—

- ■ Recently, *S. pneumoniae* and *E. coli* have been frequently detected as causative bacteria for community-acquired sepsis in infants/children aged ≥4 months in Japan. In infants aged <4 months, *Streptococcus agalactiae* has been frequently detected (A II).
- ■ In patients with serious conditions, such as shock, shock management should be initially performed as a top priority, and an adequate antimicrobial drug should be administered as early as possible after collecting samples for culture (A I).
- ■ To neonates aged <1 month, 1- to 3-month-old infants with an unfavorable general condition, and infants/children with a leukocyte count of ≤5000/μL or ≥15,000/μL, parenteral antimicrobial drugs should be administered under hospital care (A II).
- ■ For empiric therapy, CTX or CTRX should be used. In areas where infection with *S. aureus* is frequent, VCM should be added (A II).
- ■ When examining the effects of antimicrobial drugs with respect to the administration period, there was no significant difference between short (5–7 days) and long (7–21 days) periods (A II).

1. Explanation

[Characteristics and classification of the disease]

In the field of pediatrics, diagnostic criteria were published based on the entity of SIRS in 2005, which was delayed by ≥ 10 years in comparison with those for adults [14]. Only a few studies have adopted the diagnostic criteria. Therefore, in this chapter, sepsis was defined as “an infectious disease or bacteria (fungus)-related SIRS, causing serious symptoms that may influence the prognosis in the absence of treatment, with persistent or intermittent bacteria (fungus)-related bacteremia” and “a condition of which the clinical characteristics meet the definition of sepsis, although a diagnosis of bacteremia cannot be made” [15,16], as previously defined. Concerning the distribution of age, sepsis frequently develops in infants aged <1 year to 1-year-old children. Its incidence decreases with age.

Sepsis is classified into two types: primary sepsis, in which local, primary, infected foci, such as meningitis, pneumonia, and urinary tract infection, are unclear, and secondary sepsis, in which bacteria are released into blood from local, infected foci [6,7]. Secondary sepsis is described in guidelines for the management of respective infected foci, such as meningitis, pneumonia, and urinary tract infection, therefore, primary sepsis is introduced in this article.

Initial symptoms of sepsis include abnormalities in body temperature regulation (high fever, hypothermia), tachycardia, and tachypnea. Advanced sepsis causes serious symptoms such as shock, respiratory failure, consciousness disorder, and convulsion. In patients with secondary sepsis, symptoms associated with local, infected foci initially occur. However, in some patients with primary sepsis, secondary organ disorder induces local symptoms [15,16].

Occult bacteremia refers to a condition in which bacteria are detected on blood culture despite the appearance of only mild symptoms of upper airway inflammation in addition to fever and a favorable general condition, which does not meet criteria for SIRS [17,18]. However, meningitis occurs in 3–5% of untreated patients with occult bacteremia [19–21]. The incidence of sepsis depends on the arrangement of social infrastructure, involving health, welfare, and medical practice, race, and climate. In Japan, previous studies regarding community-acquired sepsis in children presented the results of treatment in a single institution alone [22–24]; its incidence remains to not be clarified. According to studies before the widespread use of *Haemophilus influenzae* type b (Hib) vaccine and heptavalent/13-valent pneumococcal conjugate vaccine (PCV7/13), occult bacteremia accounted for 3–5% of infants/children, aged 3–36 months, who were brought to hospitals with fever (39 °C or higher) [25–27]. However, studies after the widespread use of Hib vaccine and PCV7/13 indicated that the incidence of occult bacteremia had decreased to 0–3% [28–30].

[Type and frequency of causative microorganisms]

Please cite this article as: Arakawa S et al., The JAID/JSC guidelines for management of infectious diseases 2017 – Sepsis and catheter-related bloodstream infection, J Infect Chemother, https://doi.org/10.1016/j.jiac.2019.11.011

In Japan, most studies regarding causative microorganisms for community-acquired sepsis reported that the most frequent causative microorganism was *S. pneumoniae* [22–24], although they involved a single hospital.

According to a study involving 176 infants/children with septic shock who were brought to 16 emergency hospitals by ambulance in 12 European countries in 2010–2011 [31], 98 isolated strains consisted of 25 *Neisseria meningitidis* strains, 15 *E. coli* strains, 11 *S. pneumoniae* strains, 7 *S. epidermidis* strains, 6 *Pseudomonas* strains, 5 *Streptococcus pyogenes* strains, 5 *S. aureus* strains, 4 *Klebsiella* strains, and 3 *S. agalactiae* strains. With respect to age, the detection rate of *S. agalactiae* was particularly high in infants aged <4 months.

After the widespread use of Hib vaccine, the incidence of *H. influenzae*-related sepsis rapidly decreased [18,19]. That of *S. pneumoniae*-related sepsis also decreased after the widespread use of PCV7 [28–30], but a serum type that is not contained in PCV7 or 13 is involved in the etiology [32,33], and the efficacy is less marked than that for *H. influenzae*-related sepsis. A study regarding changes in causative bacteria from 1998 until 2003 [22] indicated that *H. influenzae* was not detected, and that there was a slight decrease in the detection rate of *S. pneumoniae*. There was an increase in the detection rate of *E. coli*, but urinary tract infection was present in most cases. There was a slight increase in the detection rate of *S. aureus* [34], and many studies reported community-acquired sepsis related to MRSA [35,36]. The detection rates of *N. meningitidis* and *S. pyogenes* differed among the years [34]. However, the incidence of *N. meningitidis*-related sepsis in Japan is markedly lower than in other countries, although the reason is unclear; only a few patients per year have been reported [37]. Concerning *Salmonella*, non-typhoidal *Salmonella* was detected in most cases; there were no marked changes [34]. As a rare type of causative bacteria, *Listeria monocytogenes* was reported. In Japan, the incidence of *L. monocytogenes*-related sepsis in children and adults is 0.65/1,000,000 persons, being estimated to be approximately 1/10 of that in Europe and the United States [28].

[Rule of antimicrobial therapy]

With respect to antimicrobial therapy for community-acquired sepsis, many studies have not established any control group, and no randomized, comparative study has been conducted. Even if it had been performed, no study would have adopted the double-blind method. Therefore, currently, antimicrobial drugs selected based on trends in the susceptibility of causative bacteria and antimicrobial drugs selected based on these characteristics are empirically used. When examining antibacterial activity against main bacteria isolated from children's blood samples in Japan based on the MIC value alone, PAPM [38] exhibited potent antibacterial activity against *S. pneumoniae*, PAPM [39] against *S. agalactiae*, CTRX [39] against *E. coli*, and DRPM [40] against *S. pyogenes*.

For empiric therapy, CTRX or CTX, which have a potent antibacterial activity against gram-negative bacilli, such as *S. pneumoniae*, *S. agalactiae* (especially infants aged <4 months), *S. aureus*, *S. epidermidis*, *N. meningitidis*, and *E. coli*, should be selected. In the National Institute for Health and Care Excellence (NICE) guidelines [41], it is described that parenteral antimicrobial drugs should be administered to neonates aged <1 month, 1- to 3-month-old infants with an unfavorable general condition, and infants/children with a leukocyte count of ≤5000/μL or ≥15,000/μL under hospital care. In textbooks [5,6] in Europe and the United States, including the NICE guidelines [41], it is recommended that ABPC should be combined with CTRX or CTX as empiric therapy, considering *L. monocytogenes*. However, in Japan, *L. monocytogenes* is rare [42], so the necessity of combination therapy is low. Furthermore, VCM should be added in areas where infection with MRSA is frequent among types of *S. aureus*. If neither CTRX nor CTX is available for some reason, MEPM should be selected. A study suggested that the efficacy and safety of MEPM are similar to those of CTX [43]. However, the routine use of carbapenems should be avoided.

In patients with shock or a shock-like condition, shock management should be performed as a priority, and antimicrobial drugs should be administered as early as possible (within 1 h) after collecting samples for culture [44,45]. For patients with occult bacteremia, drugs that may control *S. pneumoniae* and gram-negative bacilli, such as *E. coli*, should be selected, considering the frequency of causative bacteria. Concerning antimicrobial drug administration for occult bacteremia, a meta-analysis showed that there was no significant difference in the efficacy between oral and parenteral routes [18]. With the widespread use of Hib vaccine and PCV13, occult bacteremia has been rarely reported, and the risk of meningitis is low; therefore, for infants/children with a favorable general condition despite fever in whom occult bacteremia is suspected, there is an option to collect blood samples for culture and avoid the administration of antimicrobial drugs until the results of blood culture become clear [15].

Concerning the administration period, the completion of administration should be decided based on improvements in laboratory data and clinical findings. A meta-analysis comparing a short period (5–7 days) with a long period (7–21 days) showed that there was no significant difference in the efficacy [46].

2. Empiric therapy

First choices.

- Intravenous injection or drip infusion of CTRX at 50–100 mg/kg/session, once to twice a day (maximum: 100 mg/kg/day, 4 g/day)
- Intravenous injection or drip infusion of CTX at 50 mg/kg/session, 4 times a day (maximum: 4 g/day)

One of the above regimens + (institutions where the detection rate of MRSA is high, or cases in which MRSA cannot be ruled out)

- Drip infusion of VCM at 15 mg/kg/session, 4 times a day (maximum: 2 g/day)

Second choices.

- Drip infusion of TAZ/PIPC at 112.5 mg/kg/session, 3 times a day (maximum: 13.5 g/day)
- Drip infusion of MEPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)
- Drip infusion of DRPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)

+ (institutions where the detection rate of MRSA is high, or cases in which MRSA cannot be ruled out)

- Drip infusion of VCM at 15 mg/kg/session, 4 times a day (maximum: 2 g/day)

If allergy to β-lactams is present, the administration of AZT or CPFX should be considered instead of these drugs.

- Drip infusion of AZT at 30 mg/kg/session, 4 times a day (maximum: 4 g/day)
- Drip infusion of CPFX at 10 mg/kg/session, 3 times a day (maximum: 1.2 g/day)

When administering VCM, its blood concentration should be measured (TDM) at appropriate points so that an optimal level may be maintained.

3. Definitive therapy

If the primary focus or causative bacteria are clarified, the regimen should be switched to antimicrobial drugs which show

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the favorable transfer to the infected organ, cost-effectiveness, and clinical efficacy were demonstrated (de-escalation). See various guidelines.

Occult bacteremia.

- Intravenous injection or drip infusion of CTRX at 25–50 mg/kg/session, once to twice a day (maximum: 50 mg/kg/day, 2 g/day)
- Intravenous injection or drip infusion of CTX at 25 mg/kg/session, 3 to 4 times a day (maximum: 4 g/day)

C) Children: Nosocomial sepsis (excluding neonates)

Limitations.

- This section was described, considering a severe, rapidly progressing infectious disease in which infection is suspected, but the focus is unclear, that is, severe sepsis (corresponding to "severe sepsis [14]" defined at the International Pediatric Sepsis Consensus Conference in 2005).
- In patients in whom the focus was clarified and those with sepsis related to catheter or neutropenia, see various guidelines.

—Executive summary—

- The nosocomial-sepsis-related mortality rate in children is not low.
- Physicians must make maximum efforts to promptly conduct adequate initial management by evaluating the emergency level and severity based on the general condition.
- Empiric therapy should be started within 1 h after severe sepsis is recognized.
- Drugs for empiric therapy should be selected, considering the regional prevalence, place of onset (community/hospital), underlying disease/patient, and presence or absence of risks (for example: presence or absence of devices, neutropenia)(B IV).
- Positive control of the source of infection should be performed in the early stage (B IV).

1. Explanation

In the United States, a study examined the severe-sepsis-related mortality rate in children, and reported that the rates were 2% in children without underlying diseases and 8% in those with chronic diseases [47]. In Japan, a study of 127 children with severe sepsis admitted to pediatric intensive care units (PICUs) indicated that PICU-acquired sepsis accounted for 37% (47/127), and that hospital-acquired sepsis accounted for 28% (36/127), with 28-day mortality rates of 10.6 and 33.3%, respectively. According to the study, risk factors for mortality included concomitant blood diseases (OR: 8.97, 95%CI: 1.56–51.60) and shock (OR: 5.35, 95%CI: 1.04–27.44) [48].

To evaluate the emergency level and severity in the initial phase, "vital signs" and "appearance" are important. If children play cheerfully despite high fever, the possibility of a severe condition may be extremely low. "Cyanosis, rapid breathing, poor peripheral perfusion, petechial rash, parental concern, and clinician instinct" are clinical findings suggestive of severe childhood infection [49]. Whether the condition may become severe should be evaluated in the early stage by promptly assessing the presence or absence of airway obstruction, respiratory disorder (tachypnea, effort respiration, hypoxemia), and tissue circulatory failure (weak pulse, cold/wet/white skin, prolongation of the capillary refilling time (CRT), anuria/oliguria) [50].

Initially, it is important to evaluate whether life-threatening circumstances, such as shock and respiratory failure, are progressing through adequate severity assessment. If the condition is evaluated as severe, antimicrobial drugs must be administered earlier. Briefly, antimicrobial drug administration within 1 h after septic shock diagnosis is recommended [51,52]. As the efficacy of empiric therapy is significantly associated with an improvement in the prognosis [53], broad-spectrum antimicrobial drugs that sufficiently cover frequently detected causative bacteria should be administered.

Few randomized controlled trials (RCTs) or observational studies have examined antimicrobial therapy limited to nosocomial, non-focus-identified sepsis in children. As frequent causative bacteria for nosocomial childhood sepsis that may become severe, *S. aureus* (including MRSA), *Enterobacteriaceae* (*E. coli*, *Klebsiella*), and non-glucose-fermented bacteria (especially, *P. aeruginosa*) have been reported [54–56]. In particular, if *Enterobacteriaceae*-related sepsis is suspected, ESBL-producing bacteria must be considered [57].

For antimicrobial therapy for nosocomial sepsis, *S. aureus* and gram-negative bacteria should be extensively covered until causative bacteria become clear [58]. It is unnecessary to cover anaerobic bacteria, but it should be considered in patients in whom intrapelvic infection is suspected, those with neutropenia, and those receiving steroids [59]. *In vitro* studies demonstrated the synergistic effects of broad-spectrum penicillins and aminoglycosides against *P. aeruginosa* [60,61]; this may be considered. However, some investigators opposed it [62,63], and the risk of kidney dysfunction may be increased; therefore, combination therapy with aminoglycosides is not recommended in the present guidelines.

A monobactam, aztreonam (AZT), is available even in patients with allergy to penicillins/cephems. In the United States, a study indicated that 15% of *Enterobacteriaceae* was resistant to AZT. This drug should be selected in reference to institutional antibiograms [64]. Fluoroquinolones, such as CPFX, were reported to cause arthropathy, with an incidence of approximately 2–3%; their use is limited [65]. However, if severe sepsis related to gram-negative bacillus, for which β-lactams, including AZT, are ineffective, is suspected, the emergent use of fluoroquinolones should be considered.

Source-of-infection control, such as debridement, drainage, and device removal, is important. Early, positive intervention is significant. The usefulness of such control in patients with necrotic fasciitis [66], perforative peritonitis [67], lung abscess, or empyema [68] was demonstrated. If there is no treatment response despite the use of adequate antimicrobial drugs during the course, the necessity of source-of-infection control should be reviewed.

2. Empiric therapy

First choices.

Of the following β-lactams, which exhibit *anti-P. aeruginosa* actions, drugs to which the susceptibility is maintained should be selected based on institutional antibiograms against gram-negative bacteria (*P. aeruginosa*, *Enterobacteriaceae*):

- Intravenous injection or drip infusion of PIPC at 100 mg/kg/session, 3 times a day (maximum: 12 g/day)
- Drip infusion of TAZ/PIPC at 112.5 mg/kg/session, 3 times a day (maximum: 13.5 g/day)
- Intravenous injection or drip infusion of CAZ at 50 mg/kg/session, 3 to 4 times a day (maximum: 4 g/day†)
- Intravenous injection or drip infusion of CFPM†at 50 mg/kg/session, 3 times a day (maximum: 4 g/day)
  * High-risk group for infection with ESBL-producing bacteria (ESBL-producing bacteria-positive reactions on previous culture, institutional prevalence)
- Drip infusion of MEPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)

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- Drip infusion of DRPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)
  * When MRSA infection cannot be ruled out, in addition to the above β-lactams,
- Drip infusion of VCM at 15 mg/kg/session, 4 times a day (maximum: 2 g/day)
- Drip infusion of ABK at 4–6 mg (titer)/kg/session, once a day
  * When fungal infection cannot be ruled out, in addition to the above β-lactams,
- Drip infusion of FLCZ at 6–12 mg/kg/session, once a day (maximum: 400 mg/day)
- Drip infusion of AMPH-B at 0.25 mg/kg/session (the dose may be increased to 1.0 mg/kg at maximum), once a day
- Drip infusion of L-AMB at 2.5–5 mg/kg/session, once a day
- Drip infusion of MCFG at 3–6 mg/kg/session, once a day (maximum: 150 mg/day)

Second choices.

In the presence of allergy to β-lactams, the use of AZT or CPFX must be considered instead of them.

- Drip infusion of AZT at 30 mg/kg/session, 4 times a day (maximum: 4 g/day)
- Drip infusion of CPFX at 10 mg/kg/session, 3 times a day (maximum: 1.2 g/day)

When administering VCM, its blood concentration should be measured (TDM) at appropriate points so that an optimal level may be maintained.

3. Definitive therapy

If the primary focus or causative bacteria are clarified, the regimen should be switched to antimicrobial drugs which show the favorable transfer to the infected organ, cost-effectiveness, and clinical efficacy were demonstrated (de-escalation). See various guidelines.

D) Neonatal sepsis

—Executive summary—

- Neonatal sepsis may rapidly exacerbate in a few hours, and, if sepsis is suspected, physicians must make maximum efforts to start antimicrobial therapy as early as possible (within 1 h) after collecting samples for culture.
- In Japan, group B *Streptococcus* (GBS) is the most frequently detected in neonates with early-onset sepsis, which occurs <7 days after birth. Gram-negative bacilli, such as *E. coli*, and *S. aureus* are frequently detected in those with late-onset sepsis, which occurs ≥7 days after birth (A II).
- As empiric therapy for early-onset sepsis, combination therapy with ABPC and GM or that with ABPC and CTX is selected (A II).
- Late-onset sepsis is caused by bacteria existing under the environment of the institution in most cases. Therefore, drugs for empiric therapy should be established by preparing institutional and regional antibiograms (A II).
- As the risk of resistant bacteria or fungus proliferation may increase with the prolongation of the antimicrobial-drug administration period, administration should be promptly completed after the disappearance of bacteria in blood and improvements in symptoms/laboratory data (A II).
- If bacterial infection is ruled out, administration should be discontinued within 48 h after the start of treatment (A I).
- Education and guidance for physicians prescribing drugs regarding the adequate use of antimicrobial drugs decreased the number of resistant bacteria. Education is very important (A II).

1. Explanation

[Characteristics and classification of the disease]

Neonatal sepsis is invasive, systemic bacterial infection that occurs during the neonatal period. The WHO defined this period as <28 days after birth, but some studies defined it as ≤1 month after birth, whereas others included sepsis in low-birth-weight infants, aged even over 1 month, admitted to the NICU as neonatal sepsis.

Neonatal sepsis is classified into 4 types based on the timing of infection, but there are many duplicated neonates: (1) transplacental infection: placenta-mediated fetal infection following maternal infection with microorganisms, (2) intrauterine infection: premature rupture-related transvaginal ascending infection causes chorioamnionitis, and a fetus sucks infected amniotic fluid, leading to infection, (3) birth canal infection: infection with bacteria existing in the birth canal at the time of birth, and (4) postnatal infection: infection with bacteria acquired from the environment or family after birth [69].

With respect to the timing of onset, neonatal sepsis is classified into two types: early-onset sepsis (<7 days after birth) and late-onset sepsis (≥7 days after birth) [69,70]. However, some studies defined early-onset sepsis as occurring within 72 h after birth. Early-onset sepsis may be primarily associated with intrauterine or birth canal infection. Late-onset sepsis may be associated with birth canal or postnatal infection. Furthermore, some studies regarded the onset of sepsis in low-birth-weight infants, aged over 1 month, admitted to the NICU as its very late onset [69].

In neonates, neither cell-mediated nor humoral immunity is advanced. This is more marked in premature babies [69,70]. In premature low-birth-weight and high-risk neonates admitted to the NICU, neither respiratory/circulatory nor digestive tract functions are advanced, and various disorders may occur; therefore, to maintain their lives, endotracheal tubes, central venous catheters, and gastric tubes must be used over a long period. Furthermore, many cares, such as postural changes, aspiration, and lactation, by staff are necessary. The temperature and humidity of incubators for neonates admitted must be established as high to maintain the body temperature. However, such an environment may cause the proliferation of many microorganisms or cross infection. Therefore, the NICU is an environment in which infection may frequently occur [69,70].

Furthermore, initial symptoms of severe infection are not specific in many neonates [69,70]. If antimicrobial therapy is delayed, the condition may rapidly deteriorate; therefore, antimicrobial drugs tend to be administered before a definitive diagnosis of bacterial infection is made. Although the prophylactic administration of antimicrobial drugs after intubation or umbilical catheter insertion is ineffective [71–73], these drugs are administered in many cases. The routine administration of antimicrobial drugs leads to the invasion/proliferation of resistant bacteria or fungus in inpatients or NICU environments [74,75].

There is no specific clinical symptom of neonatal sepsis. Relatively frequent symptoms are presented below. There is no fever, and hypothermia is noted in many cases. Various symptoms, such as convulsion, a reduction in body motion, apparent death, polypnea/retractive breathing, deterioration of ventilation conditions (in respirator-wearing neonates), brady-/tachycardia, shock, unfavorable suckling, vomiting/abdominal swelling, enhancement of jaundice, and purpura, are observed. Furthermore, vague signs,

Please cite this article as: Arakawa S et al., The JAID/JSC guidelines for management of infectious diseases 2017 — Sepsis and catheter-related bloodstream infection, J Infect Chemother, https://doi.org/10.1016/j.jiac.2019.11.011

such as “not doing well”, suggest the onset of sepsis in some cases [69,70].

[Type and frequency of causative microorganisms]

The incidence of neonatal sepsis and causative bacteria depend on the social infrastructure, involving health, welfare, and medical practice, race, and climate. In Europe and the United States, *S. agalactiae* is the most frequently detected in neonates with early-onset sepsis, followed by *E. coli*, *S. aureus*, and CNS [76–79]. As relatively rare causative bacteria, *L. monocytogenes*, *S. pyogenes*, *H. influenzae*, *S. pneumoniae*, and *Enterococcus* spp. have been reported [76–79]. In neonates with late-onset sepsis, gram-negative bacilli, such as *E. coli*, *Pseudomonas* spp., *Serratia* spp., *Enterobacter* spp., and *Klebsiella* spp., additionally *S. aureus*, CNS, and *Candida* are detected. In addition, antimicrobial-drug-resistant bacteria, such as MRSA and ESBL-producing bacteria, are frequently detected, which is a characteristic [80–83].

Most of the data on neonatal sepsis in Japan is based on reports from a single institution [84–87]. According to these reports, *S. agalactiae* was the most frequently detected in neonates with early-onset sepsis, followed by *E. coli* and *Staphylococcus* spp. Late-onset sepsis was caused by gram-negative bacilli, such as *Enterobacter cloacae, K. pneumoniae,* and *P. aeruginosa*, which exist in hospital environments, MRSA, CNS, and *Candida*. Community-acquired sepsis may occur after discharge from obstetric institutions. See the section “Children tentatively diagnosed with sepsis in whom the primary focus is unclear (after infancy, normal immune state): Community-acquired sepsis”.

[Rules of antimicrobial therapy]

Neonatal sepsis may rapidly exacerbate within a few hours. If sepsis is suspected, antimicrobial therapy should be started as early as possible (within 1 h) after collecting samples for culture [69,70].

With respect to antimicrobial therapy for neonatal sepsis, almost no comparative controlled study has been conducted, and drugs are empirically selected based on trends in the susceptibility of causative bacteria and the characteristics of antimicrobial drugs. As empiric therapy for early-onset sepsis, combination therapy with penicillins (PCG, ABPC) and GM or that with ABPC and CTX is routinely selected, considering gram-negative bacilli, such as *S. agalactiae* and *E. coli*, and *L. monocytogenes* [69,70,88,89]. The NICE indicated that combination therapy with penicillins (PCG, ABPC) and GM covered 95–97% of bacteria that cause early-onset sepsis, and that combination therapy with ABPC and CTX covered 100% [89]. As GM affects the kidney and auditory sense, therapeutic drug monitoring (TDM) should be performed [90]. For neonates at a gestational age of ≥32 weeks, it is recommended that a daily dose should be administered at one time rather than at several divided doses [91,92]. CTX has a more potent antibacterial activity against gram-negative bacilli compared with GM, and its transfer to cerebrospinal fluid is favorable. TDM is not necessary, differing from GM; therefore, CTX is frequently used instead of GM [93]. A study reported that the efficacy of CTX was similar to or more marked than that of combination therapy with ABPC and GM [94]. However, the routine use of CTX should be avoided for the following reasons: CTX therapy may induce resistant bacteria [95,96]; it increases the incidence of fungal infection [97–99]; and it leads to the formation of abnormal intestinal flora [100,101]. The protein binding rate of CTRX, which is another 3rd-generation cephem, is high, and CTRX administration to neonates with hyperbilirubinemia should be avoided. As crystals can form, the simultaneous administration of CTRX and calcium-containing fluid preparations should be avoided. CTRX must be carefully administered to neonates [102].

Late-onset sepsis during admission to the NICU is related to bacteria existing in the institutional environment in many cases [103,104]. As an etiological factor, infectious diseases associated with artificial respirators or catheters inserted into blood vessels are frequent, which is a characteristic [105]. A study indicated that sepsis that can be managed by combination therapy with ABPC and GM accounted for approximately 30% in some institutions [106]; there are many types of causative bacteria against which 3rd-generation cephalosporins or carbapenems must be selected on a priority basis [107]. Drugs for empiric therapy should be established by preparing institutional and regional antibiograms [108].

Concerning the administration period, the results of a randomized, comparative study involving 7- and 14-day administration showed that there was no difference between the two groups among neonates with sepsis caused by bacteria other than *S. aureus*. However, among those with sepsis caused by *S. aureus*, the results of treatment in the 7-day group were unfavorable [109]. In another randomized, comparative study involving 10- and 14-day administration, there was no significant difference between the two groups [110]. As the risk of resistant bacteria or fungus proliferation in the normal flora may increase with the prolongation of the antimicrobial-drug administration period [74,111], administration should be promptly completed after the disappearance of bacteria in blood and improvements in symptoms/laboratory data. If bacterial infection is ruled out, administration should be discontinued within 48 h after the start of treatment [69,70].

According to a study [112], education and guidance for physicians prescribing drugs regarding the adequate use of antimicrobial drugs decreased the number of resistant bacteria, suggesting the importance of education. The arrangement of a systematic education/guidance system regarding antimicrobial drugs, drug management system to limit the use of carbapenems and *anti*-MRSA drugs, and examination system to promptly report the frequency of bacteria detection and state of resistance for effective empiric therapy is essential for the adequate use of antimicrobial drugs [108].

2. With respect to the dosage and administration for empiric therapy, see “Appendix. Doses for neonates” on the last pages.

- Early onset
  - Intravenous injection or drip infusion of ABPC + drip infusion of GM
  - Intravenous injection or drip infusion of ABPC + intravenous injection or drip infusion of CTX
    * If meningitis cannot be ruled out, ABPC + CTX therapy should be selected.
    * In institutions where infection with *S. aureus* is frequent, the drip infusion of ABPC + CTX + VCM should be performed.
- Late onset
  - Intravenous injection or drip infusion of ABPC + drip infusion of GM
  - Intravenous injection or drip infusion of ABPC + intravenous injection or drip infusion of CTX
    * In institutions where infection with *S. aureus* or CNS is frequent, the drip infusion of ABPC + CTX + VCM or MEPM + VCM should be performed.
    * In institutions where ESBL-producing bacteria or strongly resistant gram-negative bacilli are frequently isolated, the drip infusion of MEPM should be performed.
    * If fungal infection cannot be ruled out, FLCZ, AMPH-B, L-AMB, or MCFG should be added.
- In the presence of allergy to β-lactams,

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The use of AZT should be considered instead of them.

3. Definitive therapy

If the primary focus or causative bacteria are clarified, the regimen should be switched to antimicrobial drugs of which the favorable transfer to the infected organ, cost-effectiveness, and clinical efficacy were demonstrated (de-escalation). See various guidelines.

See "Appendix. Doses for neonates".

3. Catheter-related bloodstream infection

A) Adult catheter-related bloodstream infection

—Executive summary—

- A diagnosis of catheter-related bloodstream infection [113,114] is made based on the detection of the same microorganism on the culture of ≥1 set of blood collected from the peripheral vein through skin and catheter end culture (A I) [113,115] or on percutaneously and catheter-collected blood culture (A II) [113,116].
- There are peripheral and central venous catheters. In particular, central venous catheter infection is frequent, causing serious complications [114].
- As representative causative microorganisms, CNS, *S. aureus* (including MRSA), *Candida* spp., *Enterococcus* spp., and gram-negative bacilli (*E. coli*, *Enterobacter* spp., *P. aeruginosa*, *Klebsiella* spp.) have been reported (B II) [5,117].
- Antimicrobial therapy should be performed after blood culture (≥2 sets if possible)(1 set: catheter blood collection)(A II) [118]. However, a blood culture priority-related delay in antimicrobial therapy must be avoided (A II) [119,120].
- As empiric therapy, combination therapy with *anti*-MRSA drugs and broad-spectrum antimicrobial drugs is recommended (A II) [8].
- For definitive therapy, antimicrobial drugs should be selected based on causative bacteria.

1. Explanation

[Clinical symptoms]

As catheters to be inserted into blood vessels, various catheters, such as peripheral venous catheters, central venous catheters, peripheral arterial catheters, pulmonary artery catheters, and pressure-monitoring systems, are used. Bloodstream infection associated with the use of these devices is termed "catheter-related bloodstream infection (CR-BSI)". Infectious-disease-specific symptoms, such as fever, chills, and shivering, are observed, but pyretolysis is achieved by catheter removal alone in some cases. In severe-status patients, CR-BSI complicated by organ disorder related to systemic inflammatory response syndrome (SIRS) is not rare.

[Diagnosis]

To diagnose CR-BSI, blood culture is necessary. It is important to collect blood before the use of antimicrobial drugs (A I) [121]. Before blood collection, >0.5% chlorhexidine alcohol should be used to disinfect the skin at the site of collection (A II) [122,123]. If it is not available, povidone iodine should be used.

Two sets or more of blood should be collected. If possible, 1 set of blood should be collected from a catheter that may be contaminated, and 1 set from a peripheral vein [124,125].

A definitive diagnosis of CR-BSI is made based on positive reactions on percutaneously(from peripheral vein) collected blood culture (≥1 set) and catheter end culture (A I), or such reactions on percutaneously and catheter-collected blood culture (A II) [115,116].

With respect to quantitative blood culture as a criterion for CR-BSI, a definitive diagnosis of CR-BSI may be made if the number of microorganism colonies in blood collected from a catheter is ≥ 3 times greater than in blood collected from the periphery (A II) [113,115]. Concerning the differential time to positivity (DTP), a definitive diagnosis of CR-BSI may be made if a blood sample collected from a catheter becomes positive ≥2 h earlier than that collected from the periphery (A II) [113,116].

[Causative bacteria]

As causative bacteria, CNS, *S. aureus*, *Enterococcus* spp., and *Candida* spp. have been frequently detected [117,126]. According to CDC [126] and epidemiologically important pathogen surveillance/control (SCOPE) database reports [127], gram-negative bacilli accounted for 19 and 21% of CR-BSI pathogens, respectively.

Concerning all pathogens that cause CR-BSI, the issue of drug resistance has been raised. Currently, MRSA accounts for approximately 50% of all strains of *S. aureus* isolated from ICU inpatients, but the incidence of CR-BSI with MRSA has recently decreased [128]. With respect to gram-negative bacilli, the rates of 3rd-generation cephalosporin-resistant *Klebsiella* spp. and *E. coli* strains have markedly increased, and the rates of imipenem-resistant and ceftazidime-resistant *P. aeruginosa* strains have also increased [129]. Concerning *Candida* spp., attention must be paid to an increase in the rate of fluconazole-resistant strains.

[Etiological factors]

The following 4 routes may be involved in the development of catheter infection [113]: (1) dermal microorganisms at the site of insertion invade a subcutaneous catheter route, or enter along the catheter surface, forming a colony at the catheter end [114,129–131], (2) direct catheter or catheter hub contamination related to contacts with the fingers or contaminated fluid preparations or instruments [113,117,132], (3) hematogenous dissemination from other infected foci into a catheter (the incidence is unclear) [118,133], and (4) fluid contamination [134].

Considering the above etiological factors for CR-BSI, physicians must pay attention to the following points regarding the handling of endovascular catheters:

① Peripheral venous catheters should be exchanged every 3–4 days (B I) [135–137]. Concerning central venous catheters, regular exchanges are unnecessary. These catheters should be exchanged in the presence of functional failure or signs of infection (A II) [138,139].

② Neither a CVC nor PICC should be removed in the presence of fever alone. If infection related to other factors is clarified, or if the non-infectious etiology of fever is suspected, the validity of catheter removal should be clinically evaluated (A II) [140].

③ Guidewire exchanges should be conducted to exchange a non-tunnel-type catheter with functional failure if evidence on infection is absent (B I) [141,142].

④ When preserving a catheter, antimicrobial drugs should be administered through a catheter with bacterial colonization (C III). Furthermore, prophylactic antibiotic lock should be used in patients, on long-term catheter insertion, with a history of CR-BSI (several times) despite optimal, maximum aseptic techniques [143,144] (antibiotic lock is not routinely performed in Japan).

⑤ If sepsis, infectious endocarditis, or thrombophlebitis is present, if there is no response despite antimicrobial chemotherapy for ≥72 h, or if patients are infected with *S. aureus*, *P. aeruginosa*, Fungi, or *Mycobacterium*, long-term indwelling catheters should be removed (A II). If patients are infected with gram-negative bacilli, *S. aureus*, *Enterococci*,

Please cite this article as: Arakawa S et al., The JAID/JSC guidelines for management of infectious diseases 2017 — Sepsis and catheter-related bloodstream infection, J Infect Chemother, https://doi.org/10.1016/j.jiac.2019.11.011

Fungi, or *Mycobacterium*, short-term indwelling catheters should also be removed (A II) [145,146].

⑥ If a positive reaction is detected on blood culture despite after 72 h antimicrobial chemotherapy in catheter-preserved patients, catheters should be removed (B II) [145,146].

⑦ If the possibility of contamination is ruled out in the presence of microorganisms that are difficult to sterilize (*Bacillus* spp., *Micrococcus* spp., *Propionibacterium* spp.), long- and short-term indwelling catheters should be removed (B III) [147–149].

⑧ To cases in which fungemia or bacteremia persists after catheter removal (≥72 h): Antimicrobial chemotherapy for 6–8 weeks should be performed, considering infectious endocarditis, thrombophlebitis, and myelitis (A II) [150,151].

[Rules of treatment]

Antimicrobial therapy for CR-BSI should be started within 1 h after onset, considering that early administration improves the prognosis [51]. As described above, samples for blood culture should be collected before the start of antimicrobial therapy (A I) [152], but a blood culture priority-related delay in antimicrobial therapy must be avoided. When selecting antimicrobial drugs, empiric therapy should be started using drugs that have activities against all expected bacteria, and combination therapy with VCM and broad-spectrum antimicrobial drugs is recommended based on trends in pathogenic microorganisms (A II) [45,118,153]. Concerning LZD, a previous clinical trial of CR-BSI did not show any difference from VCM; currently, it is not necessary to select LZD for empiric therapy (A I) [154]. Empiric therapy covering gram-negative bacteria should be selected, considering the regional antimicrobial susceptibility of bacteria and severity of disease (A II) [154]. Furthermore, combination therapy that may cover resistant bacteria, including *P. aeruginosa*, should be performed in patients with neutropenia, sepsis, or multidrug-resistant gram-negative bacteria (A II) [45,154,155]. In severe-status patients in whom CR-BSI is suspected after catheter insertion through the inguinal region, antifungal drugs against *Candida* spp. must be added [156]. Of strains recently isolated from patients with candidemia, *Candida albicans* accounted for 45–58%, and *Candida glabrata* accounted for 12–24%; the rate of non-*albicans Candida* has increased. As *C. glabrata* is strongly resistant to FLCZ, the use of MCFG, CPFG, or L-AMB should be considered under a tentative diagnosis of candidemia (B I) [156,157]. Doses should be established based on PK/PD from the viewpoints of the efficacy, safety, and attenuation of resistant bacteria [155]. If the type of bacteria and susceptibility are clarified based on the results of blood culture, the regimen should be promptly switched to the most appropriate antimicrobial drug (de-escalation, definitive therapy).

2. Empiric therapy (With respect to the doses of β-lactams, see the notes on page 48–49)

First choices.

- Drip infusion of DAP at 6 mg/kg/session, once a day
- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day

One of the above regimens + one of the following regimens:

- Drip infusion of 4th-generation cephems
- Drip infusion of carbapenems
- Drip infusion of TAZ/PIPC

Second choices.

- Drip infusion of LZD at 600 mg/session, twice a day

+ one of the following regimens:

- Drip infusion of PZFX at 1000 mg/session, twice a day
- Drip infusion of CPFX at 400 mg/session, 3 times a day
- Drip infusion of LVFX at 500 mg/session, once a day

- For severe-status patients (shock, signs of organ disorder) or those with background factors such as immune depression and long-term antimicrobial therapy

First choices.

- Drip infusion of DAP at 6 mg/kg/session, once a day
- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day

One of the above regimens + one of the following regimens:

- Drip infusion of 4th-generation cephems
- Drip infusion of carbapenems
- Drip infusion of TAZ/PIPC

+ one of the following regimens:

- Drip infusion of MCFG at 150 mg/session, once a day
- Drip infusion of CPFG at 70 mg/session (loading dose) on Day 1 (once a day) and at 50 mg/session from Day 2 (once a day)
- Drip infusion of FLCZ at 400 mg/session, once a day, or drip infusion of L-AMB at 2.5–5 mg/kg/session, once a day (alternative drug: F-FLCZ)

Note: MCFG or CPFG should be selected as a priority in areas where non-*albicans Candida* is frequent.

Biofilm formation reduces the antifungal activities of all antifungal drugs. In particular, its influence on azoles is marked. These are primarily based on data from in vitro studies and animal experiments. For patients in whom endovascular catheter removal is impossible, L-AMB or Candins are recommended.

Second choices.

- Drip infusion of LZD at 600 mg/session, twice a day

+ one of the following regimens:

- Drip infusion of PZFX at 1000 mg/session, twice a day
- Drip infusion of CPFX at 400 mg/session, 3 times a day
- Drip infusion of LVFX at 500 mg/session, once a day

+ one of the following regimens:

- Drip infusion of MCFG at 100 mg/session, once a day
- Drip infusion of CPFG at 70 mg/session (loading dose) on Day 1 (once a day) and at 50 mg/session from Day 2 (once a day)
- Drip infusion of FLCZ at 400 mg/session, once a day
- Drip infusion of L-AMB at 2.5–5 mg/kg/session, once a day (alternative drug: F-FLCZ)

Note: Doses of β-lactams.

Drip infusion of CFPM at 1 g/session, 2 to 3 times a day
Drip infusion of CZOP at 1 g/session, 2 to 3 times a day
Drip infusion of MEPM at 1 g/session, 3 times a day
Drip infusion of DRPM at 0.5 g/session, 3 times a day
Drip infusion of IPM/CS at 0.5 g/session, 4 times a day
Drip infusion of PAPM at 1 g/session, twice a day

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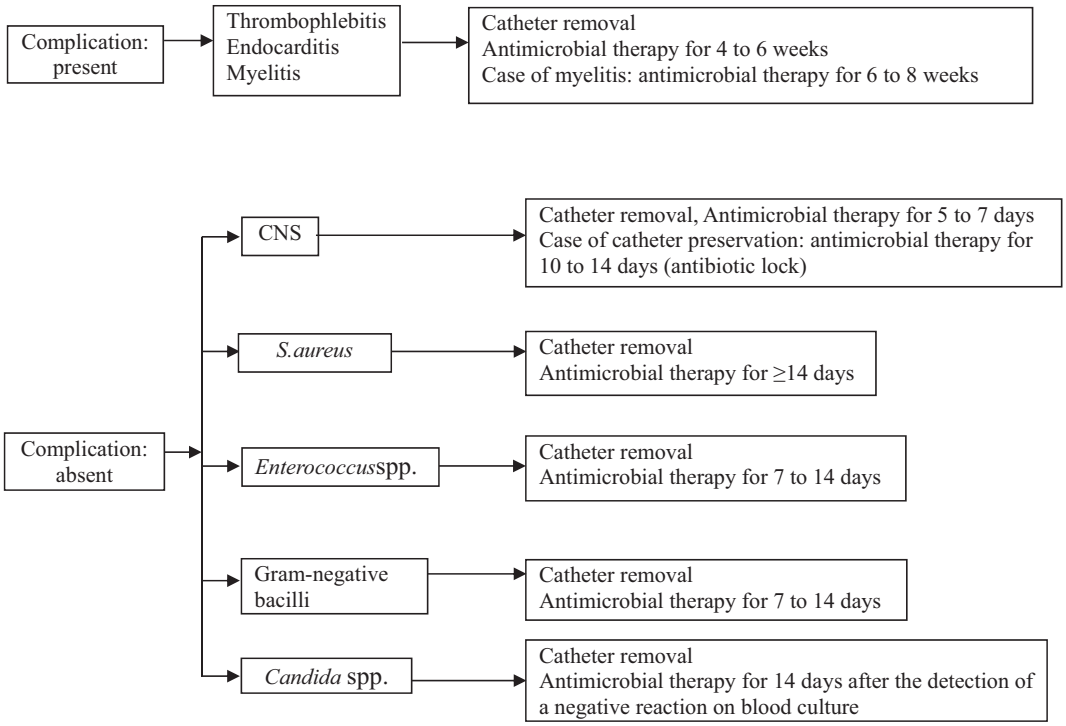

Fig. 2. Management of bloodstream infection in patients wearing a CVC or AC for a short period. Note: Complications refer to pacemaker insertion, signs of infectious endocarditis or thrombophlebitis, and immunocompromised states related to malignant tumors or other factors. A study indicated the efficacy of antibiotic lock, and it is recommended in the IDSA guidelines. However, it should be conducted, considering that the appearance of resistant bacteria may increase.

Drip infusion of BIPM at 0.3 g/session, 4 times a day
Drip infusion of TAZ/PIPC at 4.5 g/session, 3 times a day

3. Definitive therapy

Basic concept.

- Empiric therapy is switched due to its ineffectiveness in some cases, whereas it is switched to narrow-spectrum antimicrobial drugs for de-escalation despite its effectiveness in other cases. In any case, antimicrobial drugs should be selected based on the results of blood culture/drug susceptibility tests.
- In cases of endovascular indwelling catheter-associated bloodstream infection, the antimicrobial-drug administration period should be established based on the duration of catheter insertion (short or long)(See Figs. 2 and 3: Management of bloodstream infection.).

The following antimicrobial drugs against respective detected bacteria should be selected:

S. aureus:
MSSA:
First choice.

- Drip infusion of CEZ at 2 g/session, 3 times a day†

Second choice.

- Drip infusion of SBT/ABPC at 3 g/session, 4 times a day

MRSA:
First choices.

- Drip infusion of DAP at 6 mg/kg/session, once a day
- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day

Second choice.

- Drip infusion of LZD at 600 mg/session, twice a day

CNS:
MS(methicillin-sensitive)-CNS:
First choice.

- Drip infusion of CEZ at 2 g/session, 3 times a day†

Second choice.

- Drip infusion of SBT/ABPC at 3 g/session, 4 times a day

MR(methicillin-resistant)-CNS:
First choices.

- Drip infusion of DAP at 6 mg/kg/session, once a day
- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day

Second choice.

- Drip infusion of LZD at 600 mg/session, twice a day

Enterococcus faecalis/faecium:
ABPC-susceptible bacteria:
First choice.

- Drip infusion of ABPC at 2 g/session, 4 to 6 times a day

Second choice.

- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day

ABPC-resistant, VCM-susceptible bacteria:

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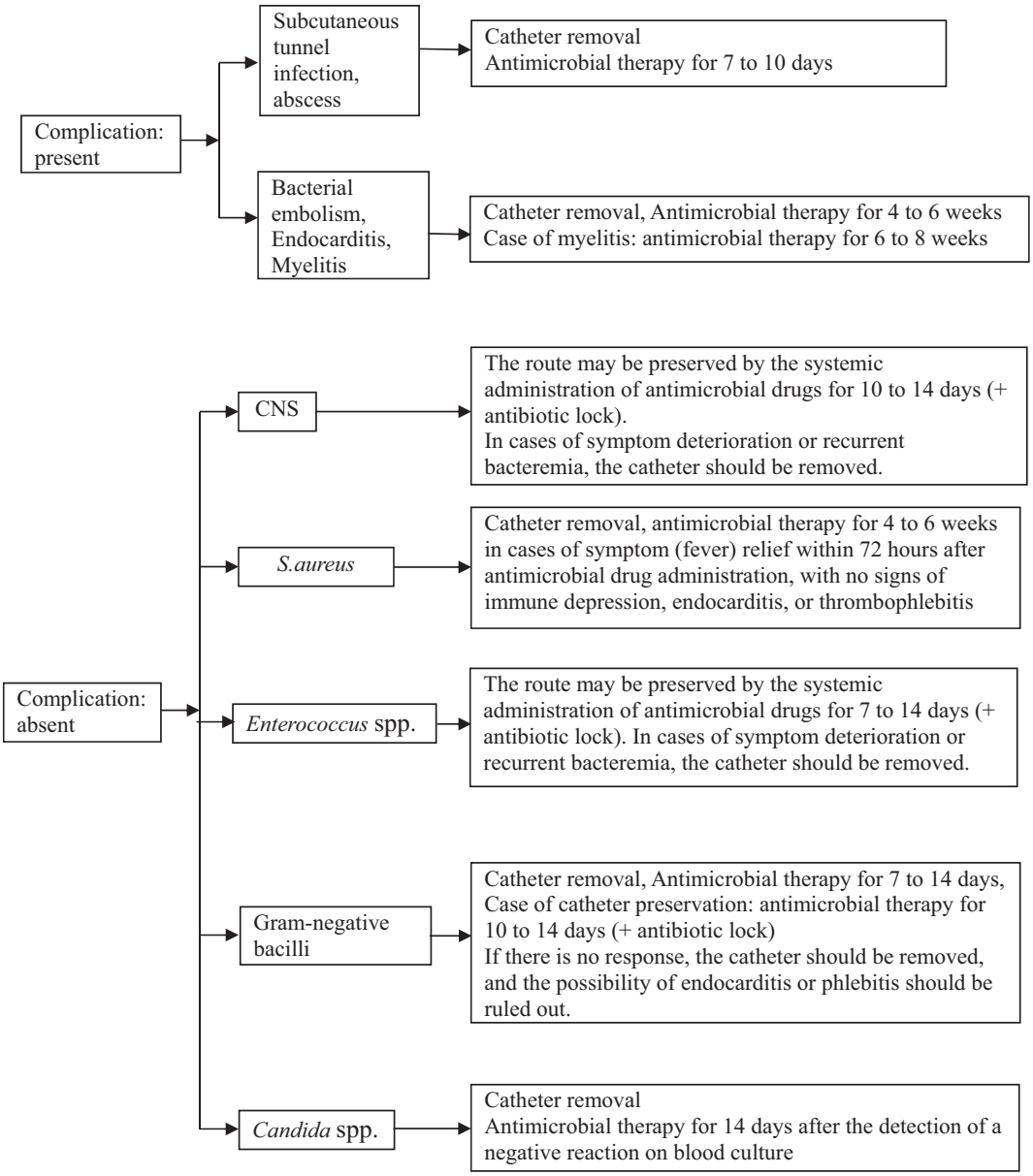

Fig. 3. Management of bloodstream infection in patients wearing a CV catheter or CV port over a long period.

- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day ± drip infusion of GM at 60 mg/session, 3 times a day

ABPC-resistant, VCM-resistant bacteria:

- Drip infusion of LZD at 600 mg/session, twice a day

E. coli, *K. pneumoniae*:
Non-ESBL-producing bacteria:
First choices.

- Drip infusion of CEZ at 2 g/session, 3 times a day†
- Drip infusion of CTM at 2 g/session, 3 times a day†
- Drip infusion of CTRX at 2 g/session, once a day

Second choices.

- Drip infusion of PZFX at 1000 mg/session, twice a day
- Drip infusion of CPFX at 400 mg/session, 3 times a day

ESBL-producing bacteria:

- Drip infusion of MEPM at 0.5–1 g/session, 3 times a day
- Drip infusion of DRPM at 0.5–1 g/session, 3 times a day

Enterobacter spp., *Serratia marcescens*:

- Drip infusion of MEPM at 0.5–1 g/session, 3 times a day
- Drip infusion of DRPM at 0.5–1 g/session, 3 times a day
- Drip infusion of CFPM at 1 g/session, 3 times a day
- Drip infusion of PZFX at 1000 mg/session, twice a day
- Drip infusion of CPFX at 400 mg/session, 3 times a day

Acinetobacter spp.:

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- Drip infusion of SBT/ABPC at 3 g/session, 3 to 4 times a day
- Drip infusion of MEPM at 0.5–1 g/session, 3 times a day + drip infusion of MINO at 100 mg/session, twice a day
- Drip infusion of DRPM at 0.5–1 g/session, 3 times a day + drip infusion of MINO at 100 mg/session, twice a day

P. aeruginosa:

- Drip infusion of CFPM at 2 g/session, 3 times a day†
- Drip infusion of CZOP at 2 g/session, 3 times a day†
- Drip infusion of MEPM at 1 g/session, 3 times a day
- Drip infusion of DRPM at 0.5 g/session, 3 times a day
- Drip infusion of TAZ/PIPC at 4.5 g/session, 3 to 4 times a day†

±

- Drip infusion of AMK at 15 mg/kg/session, once a day

Burkholderia cepacia:

- Drip infusion of MEPM at 0.5–1 g/session, 3 times a day

Fungi.
C. albicans or other types of *Candida* spp.:
First choices.

- Drip infusion of MCFG at 100 mg/session, once a day
- Drip infusion of CPFG at 70 mg/session on Day 1 (once a day) and at 50 mg/session from Day 2 (once a day)
- Drip infusion of FLCZ at 400 mg/session, once a day

Second choice.

- Drip infusion of L-AMB at 2.5–5 mg/kg/session, once a day

Rare causative microorganisms.
Corynebacterium spp.:
First choice.

- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day

Second choice.

- Drip infusion of LZD at 600 mg/session, twice a day

Chryseobacterium spp.:
First choices.

- Drip infusion of MINO at 100 mg/session, twice a day
- Drip infusion of LVFX at 500 mg/session, once a day

Second choices.

- Drip infusion of MEPM at 1 g/session, 3 times a day
- Drip infusion of DRPM at 0.5 g/session, 3 times a day
- Drip infusion of ST at 3–5 mg/kg/session, 3 times a day

Ochrobacterium spp.:
First choices.

- Drip infusion of CPFX at 400 mg/session, 3 times a day
- Drip infusion of ST at 3–5 mg/kg/session, 3 times a day

Second choices.

- Drip infusion of MEPM at 1 g/session, 3 times a day
- Drip infusion of DRPM at 0.5 g/session, 3 times a day

Bacillus spp.:
First choice.

- Drip infusion of VCM at 1 g/session (or 15 mg/kg), twice a day

Second choice.

- Drip infusion of CLDM at 600 mg/session, 3 times a day

Note: When administering glycopeptides, TDM should always be performed. To prevent the appearance of resistant bacteria, the drug susceptibility of bacteria should be confirmed as a rule, and the administration period should be reduced to a minimum necessary for disease treatment.

B) Childhood catheter-related bloodstream infection

—Executive summary—

- CNS is the most frequently detected as causative bacteria. Although there are differences among institutions, frequent causative bacteria include MRSA, *Enterococcus* spp, enteric bacteria, non-glucose-fermenting bacteria, and fungus (A II).
- As empiric therapy, combination therapy with VCM and 3rd- or 4th-generation cephems or carbapenems should be performed. Concrete drugs should be selected in reference to institutional and regional antibiograms (A II).
- If CR-BSI is suspected, catheter removal should be considered, but it is difficult to secure a new blood vessel in many children; therefore, when continuing catheter insertion unavoidably, follow-up must be carefully conducted based on culture tests (A II).
- In patients on total parenteral nutrition, those receiving long-term therapy with broad-spectrum antimicrobial drugs, those with hematological malignancy, those who underwent transplantation, and those in whom fungus was detected from various sites, fungus may be etiologically involved, and antifungal drugs should also be combined (A II).

1. Explanation

[Characteristics and classification of the disease]

As the definition, characteristics, and diagnosis of the disease are similar between children and adults, see the “Adult catheter-related bloodstream infection(CR-BSI)” section.

There are no marked differences in initial symptoms between this disease and sepsis. In children/school children, abnormalities in body temperature regulation (high fever, hypothermia), tachycardia, and polypnea are observed. If the condition is advanced, shock, respiratory failure, consciousness disorder, or convulsion may occur. In neonates and infants, abnormalities in body temperature regulation (high fever, hypothermia), a reduction in body motion, apparent death, unfavorable suckling, vomiting/abdominal swelling, and polypnea/retractive breathing are noted. In respirator-wearing neonates and infants, the deterioration of ventilation conditions brady-/tachycardia, shock, and convulsion are observed. As an initial symptom, “not doing well” alone is noted in some cases. When the route of infection is the site of skin needling or port insertion, local signs of infection, such as flare around the skin, swelling, and exudate, are observed in some cases.

According to the NHSN report (United States) on neonates (in the NICU) in 2011, the incidence of CR-BSI was 0.9–2.5 per 1000 total days of central vein insertion, and it was higher in neonates

Please cite this article as: Arakawa S et al., The JAID/JSC guidelines for management of infectious diseases 2017 – Sepsis and catheter-related bloodstream infection, J Infect Chemother, https://doi.org/10.1016/j.jiac.2019.11.011

with a lower birth weight. In children (in the PICU), its incidence was 0.9–1.8, but it was higher (2.1–2.2) in those with hematological malignancy [158]. In Japan, no large-scale survey regarding catheter-associated sepsis has been conducted.

[Type and frequency of causative microorganisms]

The causative bacteria for CR-BSI registered on the NHSN from 2009 until 2010 [159] were published, involving adults and children. CNS accounted for 20.5%, followed by *S. aureus* (12.3%) and *E. faecalis* (8.8%). As the other types of bacteria, gram-negative bacilli, especially enteric bacteria, such as *E. coli*, *Klebsiella* spp., and *Enterobacter* spp., non-glucose-fermenting bacteria, such as *Pseudomonas* spp. and *Acinetobacter* spp., and fungus were frequently detected. MRSA accounted for approximately 50% of *S. aureus* strains detected. Various resistant bacteria, such as ESBL-producing gram-negative bacilli and VCM-resistant *Enterococcus*, were detected, although their detection rates were lower than that of MRSA. Most studies involving children alone indicated CNS as the most frequent type of causative bacteria, but its detection rate ranged from 30 to 80%; it varied among the studies [160–165]. As on bacteria following CNS, similar types of bacteria have been reported, although there were differences between the NHSN results and detection rates. Furthermore, ≥2 types of bacteria were simultaneously detected in many patients. The detection rates of MRSA and MR-CNS differed among studies, but they ranged from 30 to 60% [160–165].

[Rules of antimicrobial therapy]

For empiric therapy, VCM, which has a potent antibacterial activity against CNS, which is the most frequent type of causative bacteria, MRSA, and *Enterococcus* spp., should be selected [118]. As the antibacterial activity of VCM against gram-negative bacilli is weak, combination therapy with β-lactamase inhibitor/penicillin combination drugs and 3rd- or 4th-generation cephems or carbapenems against gram-negative bacilli is recommended [118]. As the antimicrobial susceptibility of gram-negative bacilli markedly differs among areas or institutions, regional and institutional antibiograms should be prepared, and antimicrobial drugs for empiric therapy should be selected based on them. In patients on total parenteral nutrition, those receiving long-term therapy with broad-spectrum antimicrobial drugs, those with hematological malignancy, those who underwent transplantation, and those in whom fungus was detected from various sites, fungus may be etiologically involved, and antifungal drugs should also be combined [166,167].

If CR-BSI is suspected, catheter removal should be considered, as described for adults. However, it is difficult to secure a new blood vessel in many children; therefore, catheter removal must be carefully selected. Some studies involving neonates compared a group in which catheter removal was performed early after a definitive diagnosis was made with a group in which it was not conducted, and reported that the success rate of treatment was slightly lower in the latter [168–170]. When catheter removal is considered difficult, careful follow-up is necessary [13]. If clinical symptoms deteriorate or repeatedly appear, or if the disappearance of causative bacteria in blood is not achieved, a catheter must be removed. According to several studies, when preserving a catheter, a treatment procedure to lock it with antimicrobial drugs [171,172] or ethanol [173–175] while performing the systemic administration of antimicrobial drugs was effective. However, the results in small-scale populations were published, and a larger number of patients must be investigated in the future.

No study has presented evidence regarding the administration period of antimicrobial drugs for childhood CR-BSI. Currently, it is established in accordance with the treatment of adult CR-BSI. See the "Adult CR-BSI (Figs. 2 and 3).

2. Empiric therapy

First choices.

- Drip infusion of VCM at 15 mg/kg/session, 4 times a day (maximum: 2 g/day)

+ one of the following regimens:

- Intravenous injection or drip infusion of CFPM† at 50 mg/kg/session, 3 times a day (maximum: 4 g/day)
- Intravenous injection or drip infusion of CAZ at 50 mg/kg/session, 3 to 4 times a day (maximum: 4 g/day)
- Drip infusion of TAZ/PIPC at 112.5 mg/kg/session, 3 times a day (maximum: 13.5 g/day)
- Drip infusion of MEPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)
- Drip infusion of DRPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)

Second choices.

- Drip infusion of LZD at 10 mg/kg/session, 3 times a day (maximum: 600 mg/session) in children/infants aged <12 years or twice a day (maximum: 600 mg/session) in children aged ≥12 years

+ one of the following regimens:

- Intravenous injection or drip infusion of CFPM†at 50 mg/kg/session, 3 times a day (maximum: 4 g/day)
- Intravenous injection or drip infusion of CAZ at 50 mg/kg/session, 3 to 4 times a day (maximum: 4 g/day)
- Drip infusion of TAZ/PIPC at 112.5 mg/kg/session, 3 times a day (maximum: 13.5 g/day)
- Drip infusion of MEPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)
- Drip infusion of DRPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)

†In the pediatric field, CFPM is not covered by health insurance.

3. Definitive therapy

Empiric therapy is switched due to its ineffectiveness in some cases, whereas it is switched to narrow-spectrum antimicrobial drugs for de-escalation despite its effectiveness in other cases. In any case, antimicrobial drugs should be selected based on the results of blood culture/drug susceptibility tests (See regimens for adults.).

The following antimicrobial drugs should be selected against respective detected bacteria:

MSSA, MS-CNS:
First choices.

- Intravenous injection or drip infusion of CEZ at 33 mg/kg/session, 3 times a day (maximum: 5 g/day)
- Intravenous injection or drip infusion of ABPC at 50 mg/kg/session, 4 times a day (maximum: 12 g/day)

Second choice (for patients with allergy to β-lactams)

- Drip infusion of VCM at 15 mg/kg/session, 4 times a day (maximum: 2 g/day)

MRSA, MR-CNS:
First choice.

- Drip infusion of VCM at 15 mg/kg/session, 4 times a day (maximum: 2 g/day)

Second choice.

- Drip infusion of LZD at 10 mg/kg/session, 3 times a day (maximum: 600 mg/session) in children/infants aged <12 years or twice a day (maximum: 600 mg/session) in children aged ≥12 years

E. faecalis:
First choice.

- Intravenous injection or drip infusion of ABPC at 50 mg/kg/session, 4 times a day (maximum: 12 g/day)

Second choice.

- Drip infusion of VCM at 15 mg/kg/session, 4 times a day (maximum: 2 g/day)

E. faecium:
First choice.

- Drip infusion of VCM at 15 mg/kg/session, 4 times a day (maximum: 2 g/day)

Second choice.

- Drip infusion of LZD at 10 mg/kg/session, 3 times a day (maximum: 600 mg/session) in children/infants aged <12 years or twice a day (maximum: 600 mg/session) in children aged ≥12 years

Enterobacteriaceae (non-ESBL-producing):
First choices.

- Intravenous injection or drip infusion of CTX at 50 mg/kg/session, 4 times a day (maximum: 4 g/day)
- Intravenous injection or drip infusion of CTRX at 50–100 mg/kg/session, once to twice a day (maximum: 100 mg/kg/day, 4 g/day)
- Drip infusion of TAZ/PIPC at 112.5 mg/kg/session, 3 times a day (maximum: 13.5 g/day)

Second choices.

- Drip infusion of MEPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)
- Drip infusion of DRPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)

Enterobacteriaceae (ESBL-producing):

- Drip infusion of MEPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)
- Drip infusion of DRPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)

P. aeruginosa:
First choices.

- Intravenous injection or drip infusion of CAZ at 50 mg/kg/session, 3 to 4 times a day (maximum: 4 g/day)

±

- Drip infusion of TOB at 2–2.5 mg/kg/session, 3 times a day

Second choices.

- Drip infusion of TAZ/PIPC at 112.5 mg/kg/session, 3 times a day (maximum: 13.5 g/day)
- Drip infusion of MEPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)
- Drip infusion of DRPM at 40 mg/kg/session, 3 times a day (maximum: 3 g/day)

one of the above regimens ±

- Drip infusion of TOB at 2–2.5 mg/kg/session, 3 times a day

Candida spp.:

- Drip infusion of MCFG at 3–6 mg/kg/session, once a day (maximum: 150 mg/day)
- Drip infusion of CPFG at 70 mg/m^2 (loading dose) on Day 1 (once a day) and at 50–70 mg/m^2 from Day 2 (once a day)
- Drip infusion of L-AMB at 2.5–5 mg/kg/session, once a day
- Drip infusion of FLCZ at 3–12 mg/kg/session, once a day (maximum: 400 mg/day)

Self-reporting of the conflict of interest:

Soichi Arakawa received a lecture fee from Taisho Toyama Pharmaceutical Co., Ltd.

Hiroshi Sakata received a lecture fee from Meiji Seika Pharma Co., Ltd.

Toshiyuki Mayumi received research funds from Roche Diagnostics K.K. and scholarship contributions from the Japan Blood Products Organization and Pfizer Japan Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.11.011.

References

[1] Nishida O, Ogura h, Inoue S, Iba T, Imaizumi H, Egi M, et al. The Japanese clinical practice guidelines for management of spesis and spetic shock 2016 (J-SSCG 2016). J Jpn Soc Intensive Care Med 2017;24(Suppl. 2):232. J Jpn Assoc Acute Med 2017;28(Suppl):232.

[2] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–77.

[3] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250–6.

[4] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock(sepsis-3). JAMA 2016;315:801–10.

[5] Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, et al. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. Ann Emerg Med 2006;48:28–54.

[6] Fujishima S, Gando S, Saitoh D, Mayumi T, Kushimoto S, Shiraishi S, et al. A multicenter, prospective evaluation of quality of care and mortality in Japan based on the Surviving Sepsis Campaign guidelines. J Infect Chemother 2014;20:115–20.

[7] Valles J, Rello J, Ochagavia A, Garnacho J, Alcala MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest 2003;123:1615–24.

[8] Mylotte JM, Tayara A, Goodnough S. Epidemiology of bloodstream infection in nursing home residents: evaluation in a large cohort from multiple homes. Clin Infect Dis 2002;35:1484–90.

[9] The Japanese Society of Intensive Care Medicine Committee of Sepsis Registry. The Japanese guidelines for the management of sepsis. J Jpn Soc Intensive Care Med 2012. 109p. (ref. 2013), http://www.jsicm.org/SepsisJapan2012.pdf.

[10] Japan Nosocomial Infections Surveillance. JANIS. http://www.nih-janis.jp/. (ref. 2013-11-18).
[11] Takuma K, Fujishima S, Saitoh D, Shiraishi S, Ikeda H, Araki T, et al. Examination of bacteria isolated from patients with severe sepsis. J Jpn Assoc Acute Med 2013;24:283–90.
[12] Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137:791–7.
[13] The JAID/JSC Guide/Guidelines to Clinical Management of Infectious Disease Committee. The JAID/JSC guide to clinical management of infectious diseases 2014. Tokyo: Life Science Co. Ltd.; 2014. p. 1–20. Sepsis.
[14] Goldstein B, Giroir B, Randolph A. International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.
[15] Enrione MA, Powell KR. Sepsis, septic shock, and systemic inflammatory response syndorome. In: Kliegman RM, Stanton BMD, Geme JS, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011. p. 1094–9.
[16] Kaplian Sheldon L, Jesus G, Vallejo. Bacteremia and septic shock. In: Feigin RD, Cherry J, Demmler-Harrison GJ, Kaplan SL, editors. Feigin and Cherry's textbook of pediatric infectious diseases. 6th ed. Saunders; 2009. p. 837–51.
[17] Powell KR. Fever without a focus. In: Kliegman RM, Stanton BMD, Geme JS, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011. p. 1087–93.
[18] Parrati DL, Feigin RD. Fever without source and fever of unknown origin. In: Feigin RD, Stanton BMD, Geme JS, Schor NF, Behrman RE, editors. Feigin and Cherry's textbook of pediatric infectious diseases. 6th ed. Saunders; 2009. p. 851–62.
[19] Rothrock SG, Green SM, Harper MB, Clark MC, Mcllmail DP, Bachur R. Parenteral vs oral antibiotics in the prevention of serious bacterial infections in children with Streptococcus pneumoniae occult bacteremia: a meta-analysis. Acad Emerg Med 1998;5:599–606.
[20] Bachur R, Harper MB. Reevaluation of outpatients with *Streptococcus pneumoniae* bacteremia. Pediatrics 2000;105:502–9.
[21] Baraff LJ. Management of fever without source in infants and children. Ann Emerg Med 2000;36:602–14.
[22] Shimizu M, Kuroda M, Kawamura M, Yamada N, Maeba H, Goto C, et al. Study of bacteremia due to community-acquired infection in pediatric outpatients. J Jpn Pediatr Soc 2008;112:1527–33.
[23] Higashigawa M, Suzuki M, Omori Y, Ogawa M, Fujiwara T, Inoue M. Clinical investigations of 26 cases of bacteremia in infants and children. J Jpn Pediatr Soc 2009;113:1557–63.
[24] Asai H, Ishibazawa E, Igarashi K, Tsutida E, Nohara F, Kajino M, et al. A study of bacteremia in pediatric hospitalized-patients. J Jpn Pediatr Soc 2010;114:1389–93.
[25] Wright PF, Thompson J, McKee Jr KT, Vaughn WK, Sell SH, Karzon DT. Patterns of illness in the highly febrile young child: epidemiologic, clinical, and laboratory correlates. Pediatrics 1981;67:694–700.
[26] Carroll WL, Farrell MK, Singer JI, Jackson MA, Lobel JS, Lewis ED. Treatment of occult bacteremia: a prospective randomized clinical trial. Pediatrics 1983;72:608–12.
[27] Fleisher GR, Rosenberg N, Vinci R, Steinberg J, Powell K, Christy C, et al. Intramuscular versus oral antibiotic therapy for the prevention of meningitis and other bacterial sequelae in young, febrile children at risk for occult bacteremia. J Pediatr 1994;124:504–12.
[28] Alpern ER, Alessandrini EA, Bell LM, Shaw KN, McGowan KL. Occult bacteremia from a pediatric emergency department: current prevalence, time to detection, and outcome. Pediatrics 2000;106:505–11.
[29] Stoll ML, Rubin LG. Incidence of occult bacteremia among highly febrile young children in the era of thepneumococcal conjugate vaccine: a study from a Children's Hospital Emergency Department and Urgent Care Center. Arch Pediatr Adolesc Med 2004;158:671–5.
[30] Pantell RH, Newman TB, Bernzweig J, Bergman DM, Takayama JI, Segal M, et al. Management and outcomes of care of fever in early infancy. JAMA 2004;291:1203–12.
[31] Van de Voorde P, Emerson B, Gomez B, Willems J, Yildizdas D, Iglowstein I, et al. Paediatric communityacquired septic shock: results from the REPEM network study. Eur J Pediatr 2013;172:667–74.
[32] Alpern ER, Alessandrini EA, McGowan KL, Bell LM, Shaw KN. Serotype prevalence of occult pneumococcal bacteremia. Pediatrics 2001;108:E23.
[33] Doit C, Mariani-Kurkdjian P, Mahjoub-Messai F, Bidet P, Bonacorsi S, Carol A, et al. Epidemiology of pediatric community-acquired bloodstream infections in a children hospital in Paris, France, 2001 to 2008. Diagn Microbiol Infect Dis 2010;66:332–5.
[34] Herz AM, Greenhow TL, Alcantara J, Hansen J, Baxter RP, Black SB, et al. Changing epidemiology of outpatient bacteremia in 3-to 36-month-old children after the introduction of the heptavalent-conjugated pneumococcal vaccine. Pediatr Infect Dis J 2006;25:293–300.
[35] Burke RE, Halpern MS, Baron EJ, Gutierrez K. Pediatric and neonatal Staphylococcus aureus bacteremia: epidemiology, risk factors, and outcome. Infect Control Hosp Epidemiol 2009;30:636–44.
[36] Suryadevara M, Moro MR, Rosenbaum PF, Kiska D, Riddell S, Weiner LB, et al. Incidence of invasive community-onset *Staphylococcus aureus* infections in children in Central New York. J Pediatr 2010;156:152–4.
[37] Horino T, Kato T, Sato F, Sakamoto M, Nakazawa Y, Yoshida M, et al. Meningococcemia without meningitis in Japan. Intern Med 2008;47:1543–7.
[38] Sakata H. Susceptibility in parenteral antibiotics in *Streptococcus pneumoniae* isolated from children with invasive pneumococcal disease. J Jpn Assoc Infect Dis 2013;87:1–5.
[39] Sakata H, Kokubo M, Shirai M, Kajino M, Takase M, Okamoto T, et al. Antimicrobial susceptibility of *Escherichia coli* and *Streptococcus agalactiae* isolated from liquor or blood in infants. J Jpn Pediatr Soc 2005;109:22–5.
[40] Sakata H. Susceptibility and *emm* type of *Streptococcus pyogenes* isolated from children with severe infection. J Infect Chemother 2013;19:1042–6.
[41] National institute for health and care excellence. NICE clinical guideline. Feverish illness in children: Assessment and initial management in children younger than 5 years. London: the Royal College of Obstetricians and Gynaecologists; 2013.
[42] Okutani A, Okada Y, Yamamoto S, Igimi S. Nationwide survey of human *Listeria monocytogenes* infection in Japan. Epidemiol Infect 2004;132:769–72.
[43] Hsu HL, Lu CY, Tseng HY, Lee PI, Lai HP, Lin WC, et al. Empirical monotherapy with meropenem in serious bacterial infections in children. J Microbiol Immunol Infect 2001;34:275–80.
[44] Kissoon N, Orr RA, Carcillo JA. Updated American College of Critical Care Medicine–pediatric advanced life support guidelines for management of pediatric and neonatal septic shock: relevance to the emergency care clinician. Pediatr Emerg Care 2010;26:867–9.
[45] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296–327.
[46] Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Crit Care 2011;15:R267.
[47] Odetola FO, Gebremariam A, Freed GL. Patient and hospital correlates of clinical outcomes and resource utilization in severe pediatric sepsis. Pediatrics 2007;119:487–94.
[48] Shime N, Kawasaki T, Saito O, Akamine Y, Toda Y, Takeuchi M, et al. Incidence and risk factors for mortality in paediatric severe sepsis: results from the national paediatric intensive care registry in Japan. Intensive Care Med 2012;38(7):1191–7. https://doi.org/10.1007/s00134-012-2550-z. Epub 2012 Apr 18.
[49] Van den Bruel A, Haj-Hassan T, Thompson M, Buntinx F, Mant D. European Research Network on Recognising Serious Infection investigators. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. Lancet 2010;375:834–45.
[50] Aehlert Barbara, Miyasaka K. Japanese version of the Pediatric Advanced Life Support Study Guide—Basis and application of advanced life support for children (1st version). 2008. p. 190–3.
[51] Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34(6):1589–96. PMID: 16625125.
[52] Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. Antimicrob Agents Chemother 2005;49(9):3640–5. PMID: 16127033.
[53] Paul M, Kariv G, Goldberg E, Raskin M, Shaked H, Hazzan R, et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2010;65(12):2658–65. https://doi.org/10.1093/jac/dkq373. Epub 2010 Oct 14. Review. PMID: 20947620.
[54] Albano EA, Pizzo PA. Infectious complications in childhood acute leukemias. Pediatr Clin N Am 1988;35:873–901.
[55] Toltzis P, Blumer JL. Antibiotic-resistant gram-negative bacteria in the critical care setting. Pediatr Clin N Am 1995;42:687–702.
[56] Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in the pediatric intensive care units in the United States. National Nosocomial Infections Surveillance. Pediatrics 1999;103:e39.
[57] Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev 2005;18:657–86.
[58] Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730–51.
[59] Zaidi AK, Knaut AL, Mirrett S, Reller LB. Value of routine anaerobic blood cultures for pediatric patients. J Pediatr 1995;127(2):263–8.
[60] Lau WK, Young LS, Black RE, Winston DJ, Linne SR, Weinstein RJ, et al. Comparative efficacy and toxicity of amikacin/carbenicillin versus gentamicin/carbenicillin in leukopenic patients: a randomized prospective trial. Am J Med 1977;62:959–66.
[61] Shales DM, Bass SN. Combination antimicrobial therapy. Pediatr Clin N Am 1983;30:121–34.
[62] Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med 1989;87:540–6.

Please cite this article as: Arakawa S et al., The JAID/JSC guidelines for management of infectious diseases 2017 – Sepsis and catheter-related bloodstream infection, J Infect Chemother, https://doi.org/10.1016/j.jiac.2019.11.011

[63] Korvick JA, Bryan CS, Farber B, Beam Jr TR, Schenfeld L, Muder RR, et al. Prospective observational study of *Klebsiella* bacteremia in 230 patients: outcome for antibiotic combinations versus monotherapy. Antimicrob Agents Chemother 1992;36:2639–44.
[64] Sader HS, Fritsche TR, Jones RN. Potency and spectrum trends for cefepime tested against 65746 clinical bacterial isolates collected in North American medical centers: results from the SENTRY Antimicrobial Surveillance Program (1998-2003). Diagn Microbiol Infect Dis 2005;52:265–73.
[65] Gendrel D, Chalumeau M, Moulin F, Raymond J. Fluoroquinolones in paediatrics: a risk for the patient or for the community? Lancet Infect Dis 2003;3(9):537–46.
[66] Murphy JJ, Granger R, Blair GK, Miller GG, Fraser GC, Magee JF. Necrotizing fasciitis in childhood. J Pediatr Surg 1995;30:1131–4.
[67] Haecker FM, Berger D, Schumacher U, Friess D, Schweizer P. Peritonitis in childhood: aspects of pathogenesis and therapy. Pediatr Surg Int 2000;16:182–8.
[68] Wu MH, Tseng YL, Lin MY, Lai WW. Surgical treatment of pediatric lung abscess. Pediatr Surg Int 1997;12:293–5.
[69] Stoll BJ. Infections of the neonatal infant. In: Kliegman RM, Stanton BMD, Geme JS, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders Elsevier; 2011. p. 794–811.
[70] Nizet V, Klein JO. Bacterial sepsis and meningitis. In: Remington JS, Wilson C, Nizet V, Maldonado Y, editors. Infectious diseases of the fetus and newborn infant. 7th ed. Philadelphia: Elsevier; 2006. p. 222–75.
[71] Inglis GD, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous catheters. Cochrane Database Syst Rev 2005;19(4):CD005251.
[72] Inglis GD, Jardine LA, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in ventilated newborn infants. Cochrane Database Syst Rev 2007;18(3):CD004338.
[73] Inglis GD, Jardine LA, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters. Cochrane Database Syst Rev 2007;17(4):CD004697.
[74] Singh N, Patel KM, Léger MM, Short B, Sprague BM, Kalu N, et al. Risk of resistant infections with *Enterobacteriaceae* in hospitalized neonates. Pediatr Infect Dis J 2002;21:1029–33.
[75] Isaacs D. Unnatural selection: reducing antibiotic resistance in neonatal units. Arch Dis Child Fetal Neonatal Ed 2006;91:F72–4.
[76] Kuhn P, Dheu C, Bolender C, Chognot D, Keller L, Demil H, et al. Incidence and distribution of pathogens in early-onset neonatal sepsis in the era of antenatal antibiotics. Paediatr Perinat Epidemiol 2010;24:479–87.
[77] Sgro M, Shah PS, Campbell D, Tenuta A, Shivananda S, Lee SK. Early-onset neonatal sepsis: rate and organism pattern between 2003 and 2008. J Perinatol 2011;31:794–8.
[78] Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and *E. coli* disease continues. Pediatrics 2011;127:817–26.
[79] Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed 2011;96:F9–14.
[80] Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. Am J Perinatol 2013;30:131–41.
[81] Hornik CP, Fort P, Clark RH, Watt K, Benjamin Jr DK, Smith PB, et al. Early and late onset sepsis in verylow-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev 2012;88(Suppl2):S69–74.
[82] Didier C, Streicher MP, Chognot D, Campagni R, Schnebelen A, Messer J, et al. Late-onset neonatal infections: incidences and pathogens in the era of antenatal antibiotics. Eur J Pediatr 2012;171:681–7.
[83] Wynn JL, Benjamin Jr DK, Benjamin DK, Cohen-Wolkowiez M, Clark RH, Smith PB. Very late onset infections in the neonatal intensive care unit. Early Hum Dev 2012;88:217–25.
[84] Kazukawa H, Ogita J, Makino T, Ishiwada N, Otsuka H, Kurosaki T, et al. Study of neonatal sepsis in a neonatal intensive care unit -Infection with hemolytic streptococcus B or *Pseudomonas aeruginosa*-. J Pediatr Infect Dis Immunol 2007;19:3–8.
[85] Morioka I, Morikawa S, Miwa A, Minami H, Yoshii K, Kugo M, et al. Culture-proven neonatal sepsis in Japanese neonatal care units in 2006-2008. Neonatology 2012;102:75–80.
[86] Tsuji S, Kinoshita Y, Ogata H, Kitamura N, Tatsumi K, Ohashi A, et al. Neonatal sepsis in a neonatal intensive care unit : a twenty-three years retrospective study (1978-2001). Acta Neonatologica Japonica 2003;39:1–4.
[87] Yamamoto W, Yoda H, Nakajima Y, Endo D, Yashiro K, Kawakami T. Early-onset sepsis in a neonatal intensive care unit; A fifteen years retrospective study (1991-2005). J Jpn Soc Perin Neon Med 2007;43:70–4.
[88] Gilbert D, Moellering R, Eliopoulos G, Chambers H, Saag M. The Sanford guide to antimicrobial therapy 2013. 43rd ed. Antimicrobial Therapy Inc. USA; 2013.
[89] National institute for health and care excellence. NICE clinical guideline. Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment ofearly-onset neonatal infection. London: The Royal College of Obstetricians and Gynaecologists; 2012.
[90] Touw DJ, Westerman EM, Sprij AJ. Therapeutic drug monitoring of aminoglycosides in neonates. Clin Pharmacokinet 2009;48:71–88.
[91] Agarwal G, Rastogi A, Pyati S, Wilks A, Pildes RS. Comparison of once-daily versus twice-daily gentamicin dosing regimens in infants≥2500g. J Perinatol 2002;22:268–74.
[92] Hagen I, Øymar K. Pharmacological differences between once daily and twice daily gentamicin dosage in newborns with suspected sepsis. Pharm World Sci 2009;31:18–23.
[93] Jacobs RF, Kearns GL. Cefotaxime and desacetylcefotaxime in neonates and children: a review of microbiologic, pharmacokinetic, and clinical experience. Diagn Microbiol Infect Dis 1989;12:93–9.
[94] Odio CM. Cefotaxime for treatment of neonatal sepsis and meningitis. Diagn Microbiol Infect Dis 1995;22:111–7.
[95] Bryan CS, John Jr JF, Pai MS, Austin TL. Gentamicin vs cefotaxime for therapy of neonatal sepsis. Relationship to drug resistance. Am J Dis Child 1985;139:1086–9.
[96] de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policyto prevent emergence of resistant bacilli. Lancet 2000;355(9208):973–8.
[97] Manzoni P, Farina D, Leonessa M, d'Oulx EA, Galletto P, Mostert M, et al. Risk factors for progression to invasive fungal infection in preterm neonates with fungal colonization. Pediatrics 2006;118:2359–64.
[98] Benjamin Jr DK, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics 2006;117:84–92.
[99] Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin Jr DK. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. Pediatrics 2006;118:717–22.
[100] Sakata H, Yoshioka H, Fujita K. Development of the intestinal flora in very low birth weight infants compared to normal full-term newborns. Eur J Pediatr 1985;144:186–90.
[101] Gewolb IH, Schwalbe RS, Taciak VL, Harrison TS, Panigrahi P. Stool microflora in extremely low birthweight infants. Arch Dis Child Fetal Neonatal Ed 1999;80:F167–73.
[102] Monte SV, Prescott WA, Johnson KK, Kuhman L, Paladino JA. Safety of ceftriaxone sodium at extremes of age. Expert Opin Drug Saf 2008;7:515–23.
[103] Bizzarro MJ, Gallagher PG. Antibiotic-resistant organisms in the neonatal intensive care unit. Semin Perinatol 2007;31:26–32.
[104] Toltzis P. Colonization with antibiotic-resistant Gram-negative bacilli in the neonatal intensive care unit. Minerva Pediatr 2003;55:385–93.
[105] Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD neonatal research network. Pediatrics 2002;110:285–91.
[106] Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. Lancet 2005;365:1175–88.
[107] Sakata H. Antimicrobial susceptibility of Gram-negative bacillus causing late-onset neonatal bacteremia in a neonatal intensive care unit. Jpn J Chemother 2005;53:623–6.
[108] Patel SJ, Saiman L. Principles and strategies of antimicrobial stewardship in the neonatal intensive care unit. Semin Perinatol 2012;36:431–6.
[109] Chowdhary G, Dutta S, Narang A. Randomized controlled trial of 7-Day vs. 14-Day antibiotics for neonatal sepsis. J Trop Pediatr 2006;52:427–32.
[110] Gathwala G, Sindwani A, Singh J, Choudhry O, Chaudhary U. Ten days vs. 14 days antibiotic therapy in culture-proven neonatal sepsis. J Trop Pediatr 2010;56:433–5.
[111] Namblar S, Singh N. Change in epidemiology of health care-associated infection in a neonatal intensive care unit. Pediatr Infect Dis J 2002;21:839–42.
[112] Calil R, Marba ST, von Nowakonski A, Tresoldi AT. Reduction in colonization and nosocomial infection by multiresistant bacteria in a neonatal unit after institution of educational measures and restriction in the use of cephalosporins. Am J Infect Contr 2001;29:133–8.
[113] Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009;45:1–49.
[114] O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. CDC; 2011. https://www.cdc.gov/infectioncontrol/pdf/guidelines/bsi-guidelines.pdf (accessed2017-02-15.
[115] Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med 2005;142:451–66.
[116] Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med 2004;140:18–25.
[117] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–17.
[118] Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009;49:1–45.

Please cite this article as: Arakawa S et al., The JAID/JSC guidelines for management of infectious diseases 2017 – Sepsis and catheter-related bloodstream infection, J Infect Chemother, https://doi.org/10.1016/j.jiac.2019.11.011

[119] Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, et al. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. Am J Respir Crit Care Med 2009;180:861–6.

[120] Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010;38:1045–53.

[121] Bekeris LG, Tworek JA, Walsh MK, Valenstein PN. Trends in blood culture contamination: a College of American Pathologists Q-Tracks study of 356 institutions. Arch Pathol Lab Med 2005;129:1222–5.

[122] Little JR, Murray PR, Traynor PS, Spitznagel E. A randomized trial of povidone-iodine compared with iodine tincture for venipuncture site disinfection: effects on rates of blood culture contamination. Am J Med 1999;107:119–25.

[123] Mimoz O, Karim A, Mercat A, Cosseron M, Falissard B, Parker F, et al. Chlorhexidine compared with povidone-iodine as skin preparation before blood culture. A randomized, controlled trial. Ann Intern Med 1999;131:834–7.

[124] DesJardin JA, Falagas ME, Ruthazer R, Griffith J, Wawrose D, Schenkein D, et al. Clinical utility of blood cultures drawn from indwelling central venous catheters in hospitalized patients with cancer. Ann Intern Med 1999;131:641–7.

[125] Martinez JA, DesJardin JA, Aronoff M, Supran S, Nasraway SA, Snydman DR. Clinical utility of blood cultures drawn from central venous or arterial catheters in critically ill surgical patients. Crit Care Med 2002;30:7–13.

[126] A report from the NNIS system. National nosocomial infections surveillance (NNIS) system report, data summary from January 1990-may 1999, issued June 1999. Am J Infect Contr 1999;27:520–32.

[127] Gaynes R, Edwards JR. National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 2005;41:848–54.

[128] Burton DC, Edwards JR, Horan TC, Jernigan JA, Fridkin SK. Methicillin-resistant Staphylococcus aureus central line-associated bloodstream infections in US intensive care units, 1997-2007. JAMA 2009;301:727–36.

[129] Safdar N, Maki DG. The pathogenesis of catheter-related bloodstream infection with noncuffed short-term central venous catheters. Intensive Care Med 2004;30:62–7.

[130] Mermel LA, McCormick RD, Springman SR, Maki DG. The pathogenesis and epidemiology of catheterrelated infection with pulmonary artery Swan-Ganz catheters: a prospective study utilizing molecular subtyping. Am J Med 1991;91:197S–205S.

[131] Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheterrelated infection. N Engl J Med 1977;296:1305–9.

[132] Dobbins BM, Kite P, Kindon A, McMahon MJ, Wilcox MH. DNA fingerprinting analysis of coagulase negative staphylococci implicated in catheter related bloodstream infections. J Clin Pathol 2002;55:824–8.

[133] Anaissie E, Samonis G, Kontoyiannis D, Costerton J, Sabharwal U, Bodey G, et al. Role of catheter colonization and infrequent hematogenous seeding in catheter-related infections. Eur J Clin Microbiol Infect Dis 1995;14:134–7.

[134] Raad I, Hanna HA, Awad A, Alrahwan A, Bivins C, Khan A, et al. Optimal frequency of changing intravenous administration sets: is it safe to prolong use beyond 72 hours? Infect Control Hosp Epidemiol 2001;22:136–9.

[135] Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters. Arandomized controlled trial. Ann Intern Med 1991;114:845–54.

[136] Tager IB, Ginsberg MB, Ellis SE, Walsh NE, Dupont I, Simchen E, et al. An epidemiologic study of the risks associated with peripheral intravenous catheters. Am J Epidemiol 1983;118:839–51.

[137] Lai KK. Safety of prolonging peripheral cannula and i.v. tubing use from 72 hours to 96 hours. Am J InfectControl 1998;26:66–70.

[138] Eyer S, Brummitt C, Crossley K, Siegel R, Cerra F. Catheter-related sepsis: prospective, randomized study of three methods of long-term catheter maintenance. Crit Care Med 1990;18:1073–9.

[139] Uldall PR, Merchant N, Woods F, Yarworski U, Vas S. Changing subclavian haemodialysis cannulas to reduce infection. Lancet 1981;1:1373.

[140] Pettigrew RA, Lang SD, Haydock DA, Parry BR, Bremner DA, Hill GL. Catheter-related sepsis in patients on intravenous nutrition: a prospective study of quantitative catheter cultures and guidewire changes for suspected sepsis. Br J Surg 1985;72:52–5.

[141] Cobb DK, High KP, Sawyer RG, Sable CA, Adams RB, Lindley DA, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. N Engl J Med 1992;327:1062–8.

[142] Beathard GA. Management of bacteremia associated with tunneled-cuffed hemodialysis catheters. J Am Soc Nephrol 1999;10:1045–9.

[143] Dogra GK, Herson H, Hutchison B, Irish AB, Herth CH, Golledge C, et al. Prevention of tunneled hemodialysis catheter-related infections using catheter-restricted filling with gentamicin and citrate: a randomized controlled study. J Am Soc Nephrol 2002;13:2133–9.

[144] Allon M. Prophylaxis against dialysis catheter-related bacteremia with a novel antimicrobial lock solution. Clin Infect Dis 2003;36:1539–44.

[145] Fowler Jr VG, Justice A, Moore C, Benjamin Jr DK, Woods CW, Campbell S, et al. Risk factors for hematogenous complications of intravascular catheter-associated Staphylococcus aureus bacteremia. Clin Infect Dis 2005;40:695–703.

[146] Fowler Jr VG, Miro JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. JAMA 2005;293:3012–21.

[147] Cotton DJ, Gill VJ, Marshall DJ, Gress J, Thaler M, Pizzo PA. Clinical features and therapeutic interventions in 17 cases of Bacillus bacteremia in an immunosuppressed patient population. J Clin Microbiol 1987;25:672–4.

[148] Peces R, Gago E, Tejada F, Laures AS, Alvarez-Grande J. Relapsing bacteraemia due to Micrococcus luteus in a haemodialysis patient with a Perm-Cath catheter. Nephrol Dial Transplant 1997;12:2428–9.

[149] Blue SR, Singh VR, Saubolle MA. Bacillus licheniformis bacteremia: five cases associated with indwelling central venous catheters. Clin Infect Dis 1995;20:629–33.

[150] Fowler Jr VG, Olsen MK, Corey GR, Woods CW, Cabell CH, Reller LB, et al. Clinical identifiers of complicated Staphylococcus aureus bacteremia. Arch Intern Med 2003;163:2066–72.

[151] Chang FY, MacDonald BB, Peacock Jr JE, Musher DM, Triplett P, Mylotte JM, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltim) 2003;82:322–32.

[152] Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. J Infect Dis 1993;168:400–7.

[153] The Japanese Society of Intensive Care Medicine Committee of Sepsis Registry. JSICM sepsis 1st Registry. 2007 (October-December 2007).

[154] Blot SI, Depuydt P, Annemans L, Benoit D, Hoste E, De Waele JJ, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis 2005;41:1591–8.

[155] Wilcox MH, Tack KJ, Bouza E, Herr DL, Ruf BR, Ijzerman MM, et al. Complicated skin and skin-structure infections and catheter-related bloodstream infections: noninferiority of linezolid in a phase 3 study. Clin Infect Dis 2009;48:203–12.

[156] Yamaguchi H, Nishiyama Y, Uchida K, Takahashi C, Kawashima C, Hayashi M, et al. Nationwide survey of antifungal drug susceptibility of clinical fungal isolates in Japan for the Japan antifungal surveillance program (JASP), 2005. J Jpn Soc Clin microbiol 2009;19:128–41.

[157] Spellberg BJ, Filler SG, Edwards Jr JE. Current treatment strategies for disseminated candidiasis. Clin Infect Dis 2006;42:244–51.

[158] Dudeck MA, Horan TC, Peterson KD, Allen-Bridson K, Morrell GC, Anttila A, et al. National Healthcare Safety Network (NHSN) report, data summary for 2011,device-associated module. http://www.cdc.gov/nhsn/PDFs/dataStat/NHSN-Report-2011-Data-Summary.pdf.

[159] Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2009—2010. Infect Control Hosp Epidemiol 2013;34:1–14.

[160] Newman N, Issa A, Greenberg D, Kapelushnik J, Cohen Z, Leibovitz E. Central venous catheter-associated bloodstream infections. Pediatr Blood Cancer 2012;59:410–4.

[161] Dueñas L, Bran de Casares A, Rosenthal VD, Jesús Machuca L. Device-associated infections rates in pediatrics and neonatal intensive care units in El Salvador: findings of the INICC. J Infect Dev Ctries 2011;5:445–51.

[162] Advani S, Reich NG, Sengupta A, Gosey L, Milstone AM. Central line-associated bloodstream infection in hospitalized children with peripherally inserted central venous catheters: extending risk analyses outside the intensive care unit. Clin Infect Dis 2011;52:1108–15.

[163] Simon A, Bode U, Beutel K. Diagnosis and treatment of catheter-related infections in pediatric oncology: an update. Clin Microbiol Infect 2006;12:606–20.

[164] Hocevar SN, Edwards JR, Horan TC, Morrell GC, Iwamoto M, Lessa FC. Device-associated infections among neonatal intensive care unit patients: incidence and associated pathogens reported to the National Healthcare Safety Network, 2006-2008. Infect Control Hosp Epidemiol 2012;33:1200–6.

[165] L'Hériteau F, Lacavé L, Leboucher B, Decousser JW, De Chillaz C, Astagneau P, et al. NEOCAT, surveillance network of catheter-related bloodstream infections in neonates: 2010 data. Arch Pediatr 2012;19:984–9.

[166] Lorente L, Jimenez A, Santana M, Iribarren JL, Jiménez JJ, Martín MM, et al. Microorganisms responsible for intravasculacatheter-related bloodstream infection according to the catheter site. Crit Care Med 2007;35:2424–7.

[167] Raad I, Hanna H, Boktour M, Girgawy E, Danawi H, Mardani M, et al. Management of central venous catheters in patients with cancer and candidemia. Clin Infect Dis 2004;38:1119–27.

[168] Benjamin Jr DK, Miller W, Garges H, Benjamin DK, McKinney Jr RE, Cotton M, et al. Bacteremia, central catheters, and neonates: when to pull the line. Pediatrics 2001;107:1272–6.

[169] Karlowicz MG, Furigay PJ, Croitoru DP, Buescher ES. Central venous catheter removal versus in situ treatment in neonates with coagulase-negative staphylococcal bacteremia. Pediatr Infect Dis J 2002;21:22–7.

[170] Nazemi KJ, Buescher ES, Kelly Jr RE, Karlowicz MG. Central venous catheter removal versus in situ treatment in neonates with *Enterobacteriaceae* bacteremia. Pediatrics 2003;111:e269–74.

[171] Megged O, Shalit I, Yaniv I, Fisher S, Livni G, Levy I. Outcome of antibiotic lock technique for persistent central venous catheter-associated coagulase-negative *Staphylococcus* bacteremia in children. Eur J Clin Microbiol Infect Dis 2010;29:157–61.

Please cite this article as: Arakawa S et al., The JAID/JSC guidelines for management of infectious diseases 2017 – Sepsis and catheter-related bloodstream infection, J Infect Chemother, https://doi.org/10.1016/j.jiac.2019.11.011

[172] Henrickson KJ, Axtell RA, Hoover SM, Kuhn SM, Pritchett J, Kehl SC, et al. Prevention of central venous catheter-related infections and thrombotic events in immunocompromised children by the use of vancomycin/ciprofloxacin/heparin solution, 2000 flush solution: a randomized, multicenter, double-blind trial. J Clin Oncol 2000;18:1269–78.
[173] Valentine KM. Ethanol lock therapy for catheter-associated blood stream infections in a pediatric intensive care unit. Pediatr Crit Care Med 2011;12:e292–6.
[174] Wolf J, Shenep JL, Clifford V, Curtis N, Flynn PM. Ethanol lock therapy in pediatric hematology and oncology. Pediatr Blood Cancer 2013;60:18–25.
[175] Pieroni KP, Nespor C, Ng M, Garcia M, Hurwitz M, Berquist WE, et al. Evaluation of ethanol lock therapy in pediatric patients on long-term parenteral nutrition. Nutr Clin Pract 2013;28:226–31.

Please cite this article as: Arakawa S et al., The JAID/JSC guidelines for management of infectious diseases 2017 – Sepsis and catheter-related bloodstream infection, J Infect Chemother, https://doi.org/10.1016/j.jiac.2019.11.011