Manual of Antimicrobial Stewardship
3rd Edition, Separate Volume

Microorganisms of Concern for Infections in Inpatients

Division of Infectious Disease Prevention and Control,
Department of Infectious Disease Prevention and Control,
Public Health Bureau, Ministry of Health, Labour and Welfare

TABLE OF CONTENTS

1. Microorganisms of Concern for Infections in Inpatients

(1) *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus* [MRSA])

Overview of epidemiology and clinical characteristics

Staphylococci are a type of bacterium normally present in the skin and mucous membranes. They are present in the nasal cavity of healthy individuals at a ratio of approximately 30%. These bacteria are known to cause a wide range of clinical conditions from simple skin infections such as folliculitis to serious life-threatening infections such as osteomyelitis, pneumonia, and infective endocarditis, as well as clinical conditions related to toxin production including toxic-shock syndrome. It is also a frequently identified causative microorganism for death associated with bacterial infections.[1]

It should be noted that, unlike *S. aureus*, if Coagulase-negative staphylococci (CNS) with relatively weak pathogenicity is detected from blood culture, it is often necessary to assess whether it is a true infection or contamination. However, among CNS, *Staphylococcus lugdunensis* is known to behave as *S. aureus* clinically. Thus, if this bacterium is detected in blood culture, it shall be handled in the same manner as *S. aureus*.[2]

Five points are described below, focusing on the clinically significant condition of "*S. aureus* bacteremia."

Microbiological diagnosis

1) If microorganisms are detected in blood culture, it should be considered "genuine."

The possibility of contamination is approximately 1% to 1.5% when *S. aureus* is detected in blood culture.[3,4] *S. aureus* bacteremia is associated with various clinical conditions including infective endocarditis and is a disease with high mortality.[5] Thus, if *S. aureus* is detected in blood culture, it should not be immediately considered as contamination even if it is detected in only one bottle, and it should be treated as genuine *S. aureus* bacteremia until the possibility is denied.

Treatment

2) Consultation with an infectious disease specialist is recommended.

Previous studies have shown that consultation with an infectious disease specialist not only improves the quality of treatment (e.g., early control of the focus of infection, blood culture re-examination, cardiac ultrasound, proper selection and duration of antibacterial administration) in patients with *S. aureus* bacteremia but also decreases patient mortality and leads to early hospital discharge.[5]

3) Assessment and treatment of *S. aureus* bacteremia should be performed as a "set."

When *S. aureus* bacteremia is identified, it is necessary to determine whether the condition is "complicated" or "uncomplicated" bacteremia. This is a very important evaluation because therapy duration will change accordingly, and the following set of evaluations should always be performed. The patient is considered to have "uncomplicated" bacteremia when all of the following conditions a through e are met:

a. Exclusion of infective endocarditis
   Echocardiography is considered essential for all patients. Transesophageal echocardiography (TEE) is particularly necessary for patients considered to be at high

risk for infective endocarditis (patients with embolic symptoms, pacemaker implantation, history of infective endocarditis, post-prosthetic valve surgery, and intravenous drug users).[6]

b. No foreign materials in the body
Check for artificial valves, pacemakers/implantable defibrillators, prostheses, etc.

c. Negative repeated blood cultures within 2 to 4 days
When providing treatment for *S. aureus* bacteremia, negative blood cultures should be always confirmed. From the perspective of determination of therapy duration, the blood culture process should be repeated within 2 to 4 days of collection of the first positive sample.

d. Resolution of fever within 72 hours after the initiation of appropriate antibacterial therapy

e. No metastatic foci (secondary sites of infection that have spread hematogenously)
Common metastatic foci include those in the heart valves, bones and joints, intervertebral discs, epidural space, and intra-abdominal organs (liver, kidneys, spleen, etc.).[7] Drainage and removal should be proactively considered for sites deemed to be the focus of infection. Continued placement of an infected catheter increases the risk of recurrence.[7]

4) The duration of antimicrobial therapy should be at least 2 to 4 weeks and should be administered intravenously.

Due to the high recurrence rate and the nature of the disease, *S. aureus* bacteremia, once diagnosed, requires the following treatment: “at least a 2-week infusion” in uncomplicated bacteremia and “at least a 4-week infusion” in complicated bacteremia.[8] At the time of diagnosis of bacteremia, if there is any intravascular foreign material that can be removed, such as an intravenous catheter, it should be removed as much as possible.

5) When selecting initial antibacterial agents, the possibility of MRSA should be considered.

For a period when *S. aureus* is detected from a blood culture and when the antimicrobial susceptibility is still unknown, initial treatment should be with anti-MRSA drugs (such as vancomycin), considering the possibility that the organism is MRSA. On the other hand, there is also an idea to use cefazolin to cover MSSA in addition to anti-MRSA drugs during this period.[7,9] At present, no conclusion has been reached regarding which approach is better.

Table 1. Anti-*Staphylococcus aureus* Agents Used to Treat *Staphylococcus aureus* Bacteremia

Drug name	Target	Dose in patients with normal renal function	Characteristic adverse reactions
Cefazolin[7, 10]	MSSA	Intravenous infusion, 2 g/dose, every 8 hours¶	—
Vancomycin[11]	MRSA	Intravenous infusion Initial dose of 25–30 mg/kg Maintenance dose of 20 mg/kg, every 12 hours Adjustment of the dose by TDM Target AUC of 400–600 μg·h/mL For the dose of 1 g, ensure that the infusion time is 1 hour or longer* For the dose of 1 g or more, extend the administration time by approximately 30 minutes or more per 500 mg as a guide*	Renal impairment Vancomycin hypersensitivity DRESS Red man syndrome*
Daptomycin[12,13]	MRSA	Intravenous infusion, 6–10 mg/kg/dose, every 24 hours¶ Over 30 minutes**	Rhabdomyolysis (monitor CK levels regularly) Eosinophilic pneumonia

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

* Pay attention to the administration time because red man syndrome (development of erythema and, in rare cases, development of hypotension and angioedema as well) may develop due to histamine release after the rapid intravenous infusion of vancomycin.

** Should not be administered for pneumonia as it binds to the pulmonary surfactant and becomes inactivated.

¶ As the table includes doses overseas, see page 6 of the Appendix for doses in the package insert in Japan and examples of medical information provision by the Medical Fee Payment Fund.

(2) Enterococci (including vancomycin-resistant enterococci [VRE])

Epidemiology and clinical characteristics

Enterococci associated with human infection include *Enterococcus faecalis*, *Enterococcus faecium*, *Enterococcus gallinarum,* and *Enterococcus casseliflavus*. The most frequently isolated strain from clinical specimens is *E. faecalis* followed by *E. faecium*. Enterococci are indigenous bacteria in the gastrointestinal tract, causing healthcare-associated infections, particularly in critically ill patients and immunosuppressed patients. Infection caused by vancomycin-resistant enterococci (VRE) is categorized as a Category V Infectious Disease based on the Infectious Diseases Control Law and is one of the infectious diseases requiring reporting of all cases.[14] The number of reports of VRE infections in Japan was less than 100 annually from 2011 to 2019, but tended to increase to 136 and 124 in 2020 and 2021, respectively.[15] Most VRE are *E. faecium*. Enterococci including VRE are important causative microorganisms of healthcare-associated urinary tract infection (UTI), especially CAUTI, and may cause CRBSI, infective endocarditis, intra-abdominal infections, skin and soft tissue infections, SSI, etc.[16] There is also a report that the case fatality rate of VRE bacteremia was 1.8 times higher than that of vancomycin-susceptible enterococci.[17]

Patients in hospitals acquire VRE infections via the environment, healthcare professionals, devices, etc., in hospitals, and then carry them in the gastrointestinal tract. Some patients develop the disease. Known risk factors for acquiring VRE infections include a history of antibacterial exposure (especially 3rd-generation cephalosporins and vancomycin), length of hospital stay, critically ill patients, use of invasive devices, ICU admission, long-term care facility stay, and exposure to a carrier of VRE or a contaminated environment.[16] The frequency of detection of enterococci is higher in many foreign countries than in Japan, and detection is occasionally observed in patients with a history of medical exposure overseas.[18]

Microbiological characteristics and diagnosis

In VRE, the binding affinity of glycopeptide antimicrobials to the terminal of the peptidoglycan precursor of the cell wall is reduced, leading to resistance. In the reporting criteria under the Infectious Diseases Control Law, VRE is defined as vancomycin MIC of 16 μg/mL or higher against isolated enterococcal strains.[14] The degree of resistance and the antimicrobial susceptibility to each glycopeptides vary depending on the resistant types (see page 6 of the Appendix).[19]

Treatment policy

Consultation with an infectious disease specialist is recommended for the treatment of VRE infections. Identification of the focus of infection, confirmation of susceptibility to the major antibacterial agents (ampicillin and teicoplanin), and a history of allergy are particularly important before treating VRE infections. Particular attention should be paid to infective endocarditis and meningitis because these conditions require treatment including combination therapy with antibacterial agents. Cure with antibacterial agents alone is difficult for infections such as abscess, as well as CRBSI and other infections. In some cases, surgical drainage or catheter removal may be required. Ampicillin is an important drug in the treatment of ampicillin-susceptible VRE infections. Among patients who self-reported a history of penicillin allergy, fewer patients actually had allergies for which penicillin cannot be used.[20] Assessment shall also be performed by an infectious disease specialist, allergy specialist, and pharmacist as necessary.

Examples of monotherapy for VRE bloodstream infections (excluding infective endocarditis) are tabulated.

E. faecalis and VanC-type VRE are often susceptible to ampicillin. Moreover, VanB -type and VanC-type VREs are usually susceptible to teicoplanin. Daptomycin or linezolid is the cornerstone of antibacterial therapy in the treatment of VRE infections other than these.[2,16]

Although daptomycin is not indicated for the treatment of VRE infections in the package insert, it shows bactericidal activity and is recommended in various guidelines, thereby being used for the treatment of VRE infections[2,19,21] (see page 6 of the Appendix). Linezolid is indicated for *E. faecium* infection in the package insert, but it cannot be easily selected as a first-line drug from the viewpoints of bacteriostatic activity, serious and frequent adverse reactions, resistance induction, and high treatment failure rate compared with other drugs.[19,22] The use of this drug for bacteremia and infective endocarditis should be considered only when other drugs are ineffective or cannot be used due to drug resistance, adverse reactions, etc.

Table 2. Examples of Monotherapy to Treat VRE Bloodstream Infections (Excluding Infective Endocarditis)[2,16,19]

Susceptibility pattern	Example:	Drugs as well as dosage and administration in the case of normal renal function (example)	Important adverse reactions
1. Ampicillin susceptible	*E. faecalis*, VanC-type (*E. gallinarum*, *E. casseliflavus)*	Intravenous infusion of ampicillin 2 g/dose, every 4–6 hours¶	—
2. Ampicillin resistant and teicoplanin susceptible	VanB type *E. faecium*	Intravenous infusion of teicoplanin¶ Require dose setting for each body weight as well as the loading dose	Renal impairment, hypersensitivity to teicoplanin, eighth cranial nerve disorders, cytopenia, etc.
3. Ampicillin resistant and teicoplanin resistant	VanA-type *E. faecium*	Intravenous infusion of daptomycin 8–12 mg/kg/dose, every 24 hours¶ Over 30 minutes	As myotoxicity may be observed, monitor CK levels regularly. As eosinophilic pneumonitis may develop, pay attention to the development of respiratory symptoms, hypoxemia, and abnormal chest X-ray findings.
		Intravenous infusion of linezolid (alternative agent to daptomycin) 600 mg/dose, every 12 hours Over 30 minutes to 2 hours	Cytopenia, neuropathy (including optic nerve disorder), lactic acidosis, etc., may develop.

¶ As the table includes doses overseas, see pages 6–7 of the Appendix for indications and doses in the package insert in Japan.

(3) *Enterobacterales*

(i) Overview

Overview of epidemiology and clinical characteristics

Enterobacterales are also responsible for community acquired infections in the gastrointestinal tract (*Salmonella* spp., *Shigella* spp., diarrheagenic *Escherichia coli*), but often become causative microorganisms for infections outside the gastrointestinal tract and can cause both community-acquired infections and nosocomial (healthcare-associated) infections in all organs. *E. coli* is particularly important as a causative microorganism of community-acquired UTI, etc. As antimicrobial-resistant *Enterobacterales* may also contribute to hospital outbreaks, infection control becomes important as well.[2]

Microbiological characteristics

Recently, as a result of phylogenetic analysis and classification using genome sequence data, the term *Enterobacterales* was proposed for use. This term is a higher level (order) and synonymous with *Enterobacteriaceae* used thus far.[23] *Enterobacterales*, which fermentatively degrade glucose, are facultative anaerobic gram-negative bacilli that are negative in oxidase test, and include many bacteria responsible for infections in humans.[24] Representative pathogens in terms of frequency, etc. for infections in inpatients are listed in the Appendix (see page 7 of the Appendix). Those pathogens have many antibacterial-resistance mechanisms. In particular, β-lactams resistance by β-lactamase production (such as penicillinase, ESBL, carbapenemase, AmpC production), quinolone resistance, etc., are known to pose an issue.

Treatment policy

In principle, treatment should be provided according to antimicrobial susceptibility. If treatment is initiated empirically, antibiogram included in the PDF format of feedback information of Japan Nosocomial Infections Surveillance (JANIS) for each medical institution shall be referred to (it can also be prepared by the feedback information of Japan Surveillance for Infection Prevention and Healthcare Epidemiology [J-SIPHE]). The details of treatment for ESBL-producing *Enterobacterales*, AmpC-producing *Enterobacterales*, and carbapenem-resistant *Enterobacterales* (CRE) are described in each section.

(ii) ESBL-producing *Enterobacterales*

Epidemiology and clinical characteristics

ESBL is an enzyme that can typically degrade penicillins, 1st- to 3rd-generation cephalosporins, and monobactams, but cannot degrade cephamycins and carbapenems. ESBL is inhibited by β-lactamase inhibitors such as clavulanic acid.[25] Previously, *Klebsiella pneumoniae* producing TEM-type and SHV-type ESBL was predominant; however, since the 2000s, CTX-M-type ESBL-producing *E. coli* has become predominant.[26] According to the data of JANIS in 2021, the percentages of *E. coli*, *K. pneumoniae*, and *Proteus mirabilis* resistance to cefotaxime in inpatients at medical institutions nationwide were 26.8%, 11.7%, and 19.6%, respectively. Many cefotaxime-resistant bacteria are considered to be ESBL-producing *Enterobacterales* (hereinafter referred to as ESBL-producing bacteria).[27] In addition, for outpatient samples, 17.7% of *E. coli* are resistant to cefotaxime,[28] and the spread of ESBL-producing *E. coli* to the community has come to an issue. The most common clinical presentation is UTI. Intra-abdominal infections such as hepatobiliary infections as well as sepsis attributed to them may also occur. Although less frequent, they can also be causative microorganisms of pneumonia and skin and soft tissue infections. Known infection risk factors include the use of antibacterial agents in the past year, a history of long-term care facility stay, a history of hospitalization, a history of ICU stay, a history of indwelling medical devices, and a history of overseas travel (particularly in South Asia and Southeast Asia),[29-31] but there are some unknown factors that pose an infection risk in the community.

Microbiological diagnosis

Confirmation of ESBL production is recommended. The bacterial species for which the criteria for such confirmation have been established are *E. coli, Klebsiella oxytoca*, *K. pneumoniae*, and *P. mirabilis*,[32] but ESBL production has also been found in other species such as many gram-negative bacilli including *Enterobacterales*. It is necessary to pay attention to bacteria of the *Enterobacterales* group, which are susceptible to carbapenems and cephamycins but resistant to 3rd-generation cephalosporins (cefotaxime, cefpodoxime, ceftazidime, etc.). The above 4 bacterial species shall be diagnosed by confirmation tests using ESBL inhibitors.[33]

Treatment policy

When ESBL-producing bacteria are detected in non-sterile specimens such as sputum or drain tips, it does not necessarily mean that they are causing an infection, but rather that they are being colonized (asymptomatic carriage). Patients with asymptomatic bacteriuria who have no special patient background (pregnant women, patients prior to urological invasive procedure, patients within 1 month after a kidney transplant) are usually not eligible for treatment.[34] In cases of infections caused by ESBL-producing bacteria, carbapenems are recommended especially for severe cases and in immunocompromised patients. On the other hand, as the use of carbapenems may increase the risk of carrying carbapenem-resistant bacteria,[35] the use of alternative therapy to carbapenem should be considered in a situation when available. Details such as existing evidence for therapeutic drugs are provided separately (see page 8 of the Appendix). As for oral drugs, ESBL-producing bacteria often show resistance to fluoroquinolones in particular, and these drugs should only be used if susceptibility is confirmed. Although some studies have suggested the efficacy of oral carbapenem/penem antibacterial agents to treat UTI,[36, 37] they are not yet sufficient as assessments of the efficacy of these agents against ESBL-producing bacteria. Furthermore, as these agents are treated as off-label use in some cases in Japan, their active use is not recommended at present.

Table 3. Examples of Treatment of ESBL-producing *Enterobacterales* Infections[38-41]

Bloodstream infections	
<Severe cases, immunocompromised cases, CRBSI, etc.> Intravenous infusion of meropenem, 1 g/dose, every 8 hours **<Non-severe UTI, biliary disease with sufficient drainage, etc.>** Intravenous infusion of cefmetazole, 1 g/dose, every 8 hours	
Non-bloodstream infections	
Uncomplicated cystitis	Sulfamethoxazole/trimethoprim (Co-trimoxazole) 2 tablets (160 mg as trimethoprim [80 mg/tablet])/dose, oral, twice daily Clavulanate/amoxicillin (250 mg) 1 tablet/dose + amoxicillin (250 mg) 1 tablet/dose, oral, three times a day[42]
Pyelonephritis/ complicated UTI	**< Cases capable of oral intake >** Levofloxacin 500–750 mg/dose, oral, once daily¶[43] Co-trimoxazole 2–4 tablets/dose (4–6 mg/kg/dose as trimethoprim [80 mg/tablet]), oral, twice daily¶[44] **< Cases unable to take orally >** Intravenous infusion of levofloxacin, 500–750 mg/dose, every 24 hours¶[43] Infusion duration: 1 hour for the dose of 500 mg In the FDA package insert, 90 minutes for the dose of 750 mg Intravenous infusion of cefmetazole, 1 g/dose, every 8 hours
Other infections (pneumonia, intra-abdominal infection, etc.)	**<Severe cases, immunocompromised cases, etc.>** Intravenous infusion of meropenem, 1 g/dose, every 8 hours **<Non-severe cases, cases with sufficient drainage performed, etc.>** Intravenous infusion of cefmetazole, 1 g/dose, every 6–8 hours Intravenous infusion of levofloxacin, 500–750 mg/dose, every 24 hours¶[43] Infusion duration: 1 hour for the dose of 500 mg In the FDA package insert, 90 minutes for the dose of 750 mg **<Non-severe cases/ cases capable of oral intake with sufficient drainage performed>** Levofloxacin 500–750 mg/dose, oral, once daily¶[43] Co-trimoxazole 2–4 tablets/dose (4–6 mg/kg/dose as trimethoprim [80 mg/tablet]), oral, twice daily¶[44]

A. Doses are shown for patients with normal renal function. Adjustment is required in accordance with renal function. Aminoglycosides may be an option in patients with normal renal function (see the section on AmpC-producing *Enterobacterales*).

B. As they may be resistant to levofloxacin, co-trimoxazole, clavulanate/amoxicillin, and amoxicillin, these drugs should always be used after confirmation of susceptibility. Co-trimoxazole can also be administered via intravenous infusion (see the section on AmpC-producing *Enterobacterales*).

C. Flomoxef can be used instead of cefmetazole, but there is less data on dosage and administration for the treatment of ESBL-producing bacteria in humans than there is for cefmetazole.[39] When using flomoxef, it is recommended to administer it through intravenous infusion at a dose of 1 g every 6 hours based on simulation data.[38]

D. Therapy duration will be determined according to the primary disease and its clinical course.

¶ As the table includes doses overseas, see page 8 of the Appendix for indications and doses in the package insert in Japan.

(iii) AmpC-producing *Enterobacterales*

Overview of epidemiology and clinical characteristics

Representative *Enterobacterales* that encode the AmpC β-lactamase on chromosomes include *Enterobacter cloacae*, *Klebsiella aerogenes*, *Citrobacter freundii*, *Serratia marcescens*, *Morganella morganii*, *Providencia rettgeri*, and *Hafnia alvei*.

The greatest feature of chromosomal AmpC-producing *Enterobacterales* (hereafter referred to as chromosomal AmpC-producing *Enterobacterales*) infection is that, even if they are susceptible to 3rd-generation and lower-generation cephalosporins before treatment, they may become resistant to these agents during treatment, which may consequently lead to treatment failure. In clinical studies, the rate of resistance development during treatment is approximately 20% at most,[45] and development of resistance (i.e., microbiological failure) does not necessarily mean clinical failure.[46] Furthermore, the risk for development of resistance to 3rd-generation cephalosporins varies among the species of chromosomal AmpC-producing *Enterobacterales*, with the highest risk for *E. cloacae*, *K. aerogenes*, and *C. freundii*,[47] whereas, for other species, it is not yet well understood whether the risk is relatively low or what the actual risk is.

Moreover, even in species such as *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis*, which do not encode the AmpC β-lactamase producing gene on chromosomes, or *E. coli*, which encode the AmpC β-lactamase on the chromosome, but it is rarely clinical problematic, the AmpC gene derived from chromosomal AmpC-producing *Enterobacterales* may be acquired through mobile genetic elements such as a plasmid. These plasmid-mediated AmpC-producing *Enterobacterales* are, in principle, usually not susceptible to 3rd-generation and lower-generation cephalosporins.

Microbiological diagnosis

In bacterial strains that produce plasmid-mediated AmpC such as *E. coli*, *K. pneumoniae, K. oxytoca*, *P. mirabilis*, it is necessary to distinguish them from ESBL-producing strain if they show not susceptible to 3rd-generation cephalosporins. ESBL-producing strains are highly susceptible to cephamycins and oxacephems, whereas plasmid-mediated AmpC-producing strains show resistance to these in many cases. Confirmation tests by phenotypic testing and/or genetic testing shall be performed for screen positive strains (see page 9 of the Appendix).

Treatment policy

In the case where chromosomal AmpC-producing *Enterobacterales* show susceptibility to 3rd-generation cephalosporins, there is a concern about the development of resistance during treatment if *E. cloacae*, *K. aerogenes*, and *C. freundii* that have a high risk of aforementioned AmpC overproduction are the causative microorganisms. The use of 3rd-generation cephalosporins for treatment of infection with these species is not recommended except in the case of mild UTIs such as cystitis because existing observational studies focus only on resistance development, and a very limited number of studies have evaluated the clinical prognosis.

On the other hand, if other strains such as *S. marcescens, M. morganii*, *P. rettgeri*, or *H. alvei* are causative microorganisms, in principle, antibacterial agents can be selected according to their susceptibility.[41] However, even for these species, when the bacterial burden is high and when it is difficult to control the focus of infection by surgical intervention, such as drainage, the use of 3rd-generation cephalosporins should be carefully considered even if they are susceptible to these agents.

Cefepime, which is a 4th-generation cephalosporin, exhibits stable activities even against AmpC-overproducing strains. Observational studies have reported its treatment results to be comparable with those of carbapenems for chromosomal AmpC-producing bacterial infections.[48] However, if cefepime MIC is not in the susceptibility range (≤2 μg/mL) for chromosomal AmpC-producing strain, they may be ESBL-producing strain. If they are determined to be ESBL-producing strain in confirmation tests, cefepime shall not be an option (see pages 9 of the Appendix).

Tazobactam/piperacillin was found to have similar outcomes in patients with bacteremia caused by chromosomal AmpC-producing *Enterobacterales* in a randomized controlled trial (RCT) when compared with meropenem.[49] However, owing to the few cases enrolled in the study (72 patients in both groups combined), a definitive conclusion was not reached. Further large-scale RCTs are therefore awaited. Some observational studies have reported increased mortality by using tazobactam/piperacillin compared with that using carbapenems in bacteremia caused by chromosomal AmpC-producing *Enterobacterales*.[50,51] Therefore, the use of tazobactam/piperacillin should be considered with caution, especially in severe infections.

As non-β-lactams are not affected by AmpC β-lactamase, co-trimoxazole and fluoroquinolones can be effective options to treat systemic infections, moreover, aminoglycosides can be used to treat UTIs, provided that susceptibility is confirmed even if they are chromosomal AmpC-producing bacterial infections. Co-trimoxazole and fluoroquinolones, in particular, have high oral bioavailability as well, and can therefore also be used when aiming at early switching to oral antibacterial agents.[52] In any situation, it is recommended to consult an infectious disease specialist or an in-hospital AST if it is difficult to make a judgment.

Table 4. Treatment Examples for AmpC-producing *Enterobacterales* Infections[41]

Name of antibacterial agent	Recommended dose	Bacterial strains A**	Bacterial strains B**
Ceftriaxone	Intravenous infusion, 1–2 g/dose, every 12–24 hours	×	▲
Cefepime (MIC ≤2 μg/mL)	Intravenous infusion, 1–2 g/dose, every 8 hours¶[53,54]	○	○
Tazobactam/ piperacillin	Intravenous infusion, 4.5 g/dose, every 6 hours¶[49]	▲	▲
Meropenem	Intravenous infusion, 1 g/dose, every 8 hours	○	○
Levofloxacin	Intravenous infusion, 500–750 mg/dose, every 24 hours, oral¶[44,55] Infusion duration: 1 hour for the dose of 500 mg In the FDA package insert, 90 minutes for the dose of 750 mg	○	○
Co-trimoxazole	Cystitis (oral dose): 2 tablets/dose (160 mg/dose as trimethoprim [80 mg/tablet]), twice daily Other infections: <Oral dose> 2–4 tablets/dose (4–6 mg/kg/dose as trimethoprim [80 mg/tablet]), twice daily¶[44] <Intravenous infusion> 2–4 ampules (4–6 mg/kg/dose as trimethoprim [80 mg/ampule]), every 12 hours¶	○	○
Amikacin	Cystitis: 15 mg/kg/dose, single intravenous infusion Other infections: Intravenous infusion, initial dose of 20 mg/kg, followed by TDM (peak/MIC 8–10, trough value <5 μg/mL)[41]	○	○

* See pages 10–13 of the Appendix for details including points to consider.

** Bacterial strains A: Strains with a relatively high risk for AmpC overproduction (*E. cloacae, K. aerogenes, C. freundii*, etc.); Bacterial strains B: Strains with a relatively low risk or unknown risk of AmpC overproduction (*S. marcescens, M. morganii, P. rettgeri, H. alvei*, etc.)

¶ As the table includes doses overseas, see pages 10–13 of the Appendix for indications and doses in the package insert in Japan.

Table 5. Examples of Recommended Therapeutic Drugs Against AmpC-producing *Enterobacterales* Infections (See Above and Pages 10–13 of the Appendix for Details)

Recommended drugs (confirm susceptibility to each drug; for cefepime, MIC ≤2 μg/mL)	**Bacterial strains with relatively high risk of AmpC overproduction (*E. cloacae, K. aerogenes, C. freundii*, etc.)**	**Bacterial strains with relatively low risk or unknown risk of AmpC overproduction (*S. marcescens, M. morganii, P. rettgeri, H. alvei*, etc.)**
First-line agents	Cefepime, co-trimoxazole, levofloxacin, amikacin (UTI)	Cefepime, co-trimoxazole, levofloxacin, amikacin (UTI)
If the strain is not sensitive to first-line agents	Meropenem	Meropenem
Alternative therapeutic drugs	Tazobactam/piperacillin	Ceftriaxone, tazobactam/piperacillin

(iv) Carbapenem-resistant *Enterobacterales*

Overview of epidemiology and clinical characteristics

Carbapenem-resistant *Enterobacterales* (CRE) infection is classified into Category V of infectious diseases requiring all cases to be reported.[56] Approximately 16% to 17% of CRE isolated in Japan are carbapenemase-producing *Enterobacterales* (CPE), and the remaining 80% or more are non-carbapenemase-producing *Enterobacterales* (non-CP-CRE). There are several enzyme types of carbapenemase, and the most frequently isolated type in Japan is the IMP-type, classified as a metallo-β-lactamase (MBL), which accounts for 85% to 90% of CPE.[57] On the other hand, common types overseas are the NDM-type, VIM-type, KPC-type, OXA-48-like, etc.[57] See page 14 of the Appendix for risk factors for the acquisition of CRE (including both colonization and infection).

Among CRE infections, UTI is the most frequent infection, followed by bacteremia and respiratory tract infections.[27,57] Mortality from CRE infections in Japan is approximately 15% to 20%, which tends to be lower than that in other countries.[58,59]

Microbiological diagnosis

Discussions have remained inconclusive about whether treatment should be changed by identifying CPE and non-CP-CRE based on the presence or absence of carbapenemase production in CRE infections, and whether the prognosis varies.[60]

Moreover, it is not known what prognosis will be obtained when carbapenems are used to treat infections caused by CPE that are susceptible to carbapenems, e.g., the IMP-6-producing strain,[61] which is frequently isolated mainly in western Japan and is susceptible to imipenem.[60] It is suggested that there is a risk of resistance development during treatment that can lead to failure.[62] Therefore, it is desirable to assess the presence or absence of carbapenemase production wherever possible even for carbapenem-susceptible strains, and meropenem MIC ≥ 0.25 μg/mL is recommended as the screening criterion for CPE.[63] Confirmation tests shall be performed using the modified carbapenem inactivation method (mCIM) or the Carba NP test for strains that meet the screening criteria.[32] For those strains that are determined to be carbapenemase-positive by these tests, the mCIM and EDTA-modified carbapenem inactivation method (eCIM) shall be used in combination to determine whether they produce MBL or not, or specific enzyme types shall be determined using immunochromatography or genetic testing (polymerase chain reaction [PCR], microarray) (Figure 1).

Treatment policy

1) General remarks

The most common reason why CRE infections are difficult to treat is that they show extensive resistance to conventional β-lactams, including carbapenem. Therefore, since 2015 in the United States (US), several novel β-lactams, including ceftazidime-avibactam, meropenem-vaborbactam, relebactam/imipenem/cilastatin, and cefiderocol, have been developed and introduced in the market, all of which have activity against the most common CPE in the US.

On the other hand, if the susceptibility to non-β-lactams such as levofloxacin and co-trimoxazole is confirmed, such agents can be used for treatment, similarly to infections caused by carbapenem-susceptible *Enterobacterales*. In patients with *Enterobacterales* bacteremia[55] or ESBL/AmpC-producing *Enterobacterales* bacteremia,[52] it has been already shown that, especially in mild cases, the prognosis does not deteriorate despite oral stepdown therapy with fluoroquinolones or co-trimoxazole, which have high oral availability compared with continuation of treatment with intravenous antibacterial agents.

It is problematic when the case with an isolate are resistant to levofloxacin or co-trimoxazole. In such cases, there is no choice but to use non-β-lactams that lack a balance between efficacy and side effects such as colistin, tigecycline, aminoglycosides, and intravenous fosfomycin (hereinafter the 4 classes of antibacterial agents below are referred to as conventional drugs) for which clinical efficacy has not been established, and which have a high frequency of adverse events.

No conclusion has been reached regarding the efficacy of combination therapy to treat CRE infections when novel β-lactams cannot be used (see pages 14–15 of the Appendix for details).[64] There are limited data showing which antibacterial agent combinations are superior even when providing combination therapy, and there are no data comparing combination therapy and monotherapy, especially focusing on MBL-producing CPE infections (or non-CP-CRE infections), which are common in Japan (see pages 14–15 of the Appendix for details).[65] CRE infections in Japan are mostly treated using monotherapy,[58] and although the number of cases is limited, a decrease in the mortality rate by combination therapy has not been confirmed.

In summary, for CRE bacteremia in Japan, there is no reasonable reason that monotherapy with an antibacterial agent, such as fluoroquinolones or ST combination, cannot be considered as oral stepdown therapy for mild cases of UTIs or non-UTIs, or even in severe cases after stabilization of the condition by intravenous antibacterial therapy. On the other hand, when novel β-lactams cannot be used in patients with non-UTIs or for severe cases for which there is no choice but to use fluoroquinolones, co-trimoxazole, or conventional drugs, combination therapy is suggested rather than monotherapy because the clinical efficacy has not been sufficiently established.[66] However, once the general condition becomes stable, switching to monotherapy should be considered in consideration of the risk of adverse events.

2) Therapeutic strategy in treating CPE infections in Japan (Figure 1)

Guidelines for the Treatment of Infections Caused by Multidrug-Resistant Gram-Negative Bacilli[66] issued by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections[41] issued by the Infectious Diseases Society of America (IDSA) both recommend the combination therapy of ceftazidime-avibactam and aztreonam or monotherapy with cefiderocol for the treatment of MBL-producing CPE infections including the IMP-type (neither ceftazidime-avibactam nor cefiderocol is available as of July 17, 2023). Cefiderocol is the only conventional β-lactam antibacterial agent that enables single-drug treatment of MBL-producing CPE infections including the IMP- and NDM-types, and its use for CPE infections other than for MBL-producing CPE and for non-CP-CRE infections should be avoided as much as possible to preserve its activity in treating MBL-producing CPE.

When comparing the IMP-type carbapenemase producing[67] strain (the main CPE in Japan) and the KPC-type carbapenemase producing[68] strain (the main CPE in the US) from the viewpoint of antibacterial susceptibility, the biggest difference is that the IMP-type is more likely to remain susceptible to non-β-lactams, specifically the co-trimoxazole, fluoroquinolones, and aminoglycosides. Therefore, treatment options include fluoroquinolones and co-trimoxazole to treat non-UTIs, and aminoglycosides in addition to these to treat urinary tract infections.[58,69] They are also the most frequently selected options in the actual therapeutic experience.[67]

3) Treatment strategy for non-CP-CRE infections

See page 15 of the Appendix for the mechanism of carbapenem resistance in non-CP-CRE. As is the case with CPE infections, non-β-lactams can be used to treat non-CP-CRE infections as long as their susceptibility is confirmed. In addition, as a difference from CPE infections, a high dose and extended-infusion meropenem can be a treatment option for non-CP-CRE infections with isolates non-susceptible to imipenem but susceptible to meropenem (particularly in mild cases and for UTIs).[41] Furthermore, the new drug relebactam/imipenem/cilastatin[70,71] (and ceftazidime/avibactam, cefiderocol[72]) available in Japan as of July 17, 2023, has been reported to remain active in non-CP-CRE infections. Therefore, it may be a potential treatment option only if no other antibacterial agents are available.

Table 6. Treatment Examples for Carbapenem-resistant *Enterobacterales* Infections[41]

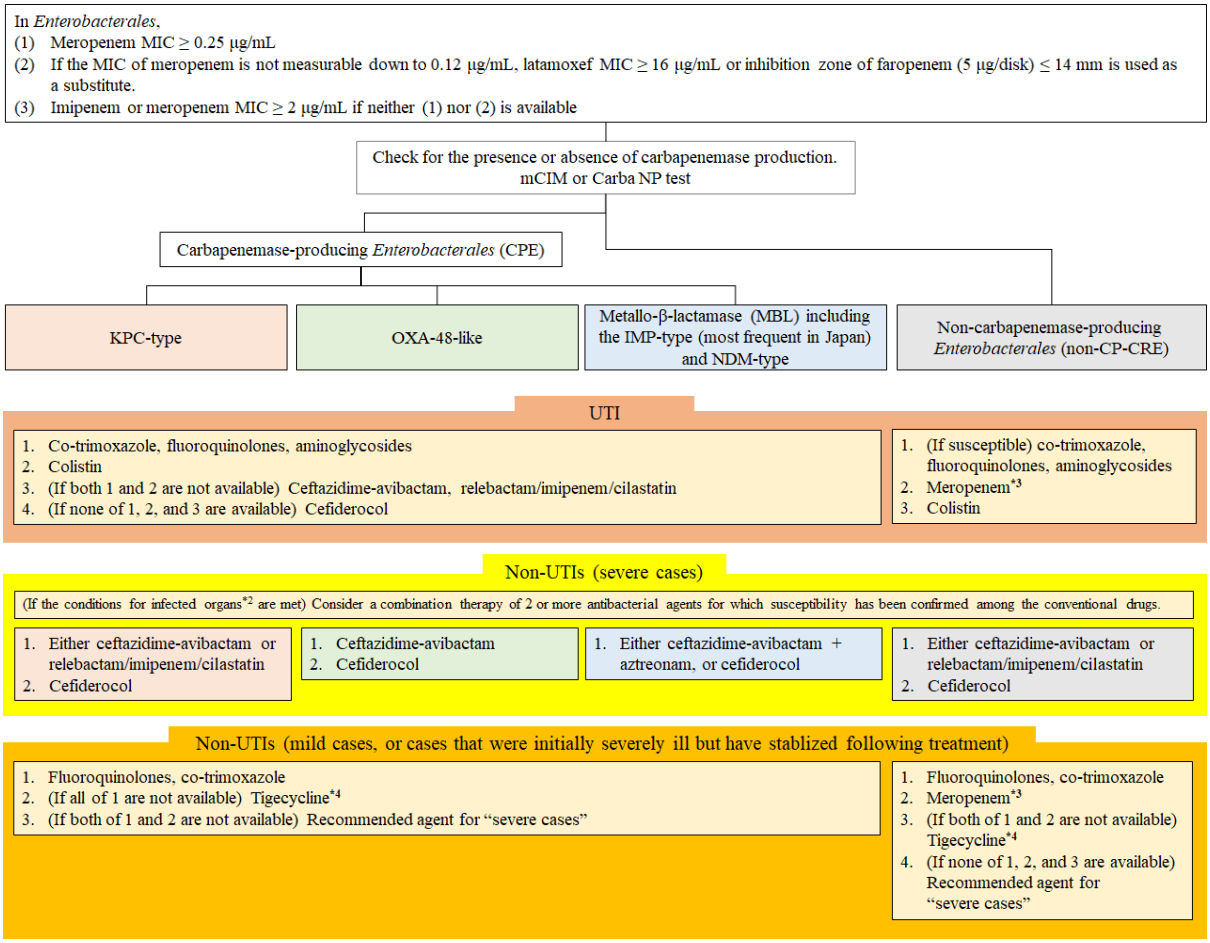
Name of antibacterial agent	Recommended dose (for patients with normal hepatic and renal functions)	Activity *in vitro*	
		Non-CP-CRE	CPE (assuming the IMP type)
Levofloxacin	See the section on AmpC-producing *Enterobacterales*	○	○
Co-trimoxazole	See the section on AmpC-producing *Enterobacterales*	○	○
Amikacin	See the section on AmpC-producing *Enterobacterales*	○	○
Colistin**	Intravenous infusion: Initial loading dose of 9 M units (equivalent to 300 mg), followed by 4.5 M units/dose (equivalent to 150 mg) Every 12 hours,[73] intravenous infusion over 30 minutes or longer¶	○	○
Tigecycline**	Intravenous infusion: Initial single dose of 100–200 mg, followed by 50–100 mg/dose, every 12 hours¶[74] For 30 to 60 minutes[75]	○	○
Meropenem (if it is resistant to imipenem/ cilastatin but sensitive to meropenem)	Cystitis: Intravenous infusion, 1 g/dose, every 8 hours (over 30 minutes per dose) Other infections: Intravenous infusion, 2 g/dose, every 8 hours¶[76,77] (consider the 3-hour extended infusion)	▲	×
Relebactam/ imipenem/ cilastatin	Intravenous infusion, 1.25 g/dose, every 6 hours (over 30 minutes per dose)	○	×

* See pages 16–19 of the Appendix for details including points to note and the balance between clinical efficacy and safety.

** For the use of tigecycline and colistin, the guideline for the proper use of each drug is published by the Japanese Society of Chemotherapy.[78,79]

¶ As the table includes doses overseas, see pages 16–19 of the Appendix for indications and doses in the package insert in Japan.

Flowchart of CRE Diagnosis and Targeted Therapy*1



*1: This table assumes, in principle, that antimicrobial susceptibility tests have been conducted and that antimicrobial susceptibility to antibacterial agents listed in the table has been confirmed.

*2: Criteria for infected organs when conventional drugs are used in combination therapy for severe cases.

	Infected organs				
	Urinary tract	Lungs	Intra-abdominal	Blood flow	Skin and soft tissues
Fluoroquinolones	○	○	○	○	○
Co-trimoxazole	○	○	○	○	○
Aminoglycosides*5	○	×	▲	▲	▲
Tigecycline	▲	▲	○	▲	○
Fosfomycin (intravenous)	▲	×	×	×	×
Colistin*5	○	×	▲	▲	▲
Meropenem*6 (MIC≤8μg/mL)	○	○	○	○	○

Antibacterial agents × cannot be one of the concomitant drugs for relevant organs.
Priority should be given to the antibacterial agents ○ over ▲. It is desirable to avoid monotherapy with the antibacterial agents ▲ for relevant organs.

*3: If the isolate is resistant to imipenem and susceptible to meropenem, higher dose (2 g every 8 hours) and extend infusion (3 hours per dose) meropenem can be a treatment option, expecially in UTI and mild cases.

*4: Double-dose administration (100 mg/dose, every 12 hours) should be considered, especially when used as monotherapy for pneumonia.

*5: Combination therapy with aminoglycosides and colistin should be avoided, because of the increased risk of renal impairment.

*6: Even if the strain is not susceptible to meropenem, high dose and extended infusion meropenem can be considered as candidate for combination therapy in the case of MIC of meropenem ≤8 μg/mL.

Figure 1. Flowchart of CRE Diagnosis and Targeted Therapy

A case that meets all the following 3 criteria may be classified as a “non-severe case.” A case that does not meet 1 or more criteria may be classified as a “severe case.”

Table 7. Criteria for Classifying the Cases of UTIs as Severe or Non-severe[80-84]

☐ **Hemodynamically stable**
<Examples> • Blood pressure can be maintained by initial fluid resuscitation without the use of vasopressors. • Neither tachycardia (≥130 beats per minute [bpm]) nor tachypnea (≥25 bpm) is observed. • Oxygen equivalent of the fraction of inspired oxygen (FiO_2) ≥40% is not required to maintain an oxygen saturation (SpO_2) of ≥93% (≥89% in patients with known chronic obstructive pulmonary disease [COPD]). • Systolic blood pressure is ≥90 mmHg (or ≥ [ordinary systolic blood pressure − 40 mmHg]). • Anuria for ≥18 hours is not observed, or urine output is ≥0.5 mL/kg/h. • There is no cyanosed skin/lips/tongue, pale skin, or macular rash. • There is no “skin rash that does not fade by compression.”
☐ **Non-immunocompromised (or immunocompromised, but general condition is stable)**
<Examples> • Neutropenia (<500 /μL) • Confirmed acquired immunodeficiency syndrome (AIDS) (CD4 <200 mm^3 or the presence of any indicator of AIDS) • Steroid use (at least at a dose equivalent to 20 mg of prednisolone per day for ≥2 weeks) • Anticancer treatment within 6 months • Immunosuppressive or biological drug therapy within 1 month (tumor necrosis factor [TNF] inhibitors, anti-interleukin [IL]-6 receptor antibodies, T-cell selective co-stimulation modulators, anti-CD20 antibodies, methotrexate, etc.) • Hematopoietic stem cell transplant within 1 year • Solid-organ transplant • Congenital immunodeficiency
☐ **Successful in source control**
<Examples> • Removal of infected artificial materials/catheters/devices, drainage of accumulated infectious fluid, release of obstruction of the infected urinary/biliary tract, etc.

Specific examples of non-UTIs (severe cases)

●Case 1: A man in his 50s who had Stage IIIa rectal cancer and underwent proctectomy for radical cure after preoperative chemotherapy. He developed secondary peritonitis due to postoperative anastomotic leak, leading to septic shock. IMP-type CPE was isolated from a blood culture and a culture of fluid (ascites) at the time of peritoneal drain insertion.

●Case 2: A woman in her 60s who developed septic shock and acute kidney injury due to acute obstructive suppurative cholangitis caused by a common bile duct stone. non-CP-CRE was isolated from a blood culture and a culture of bile taken at the time of emergency biliary drainage.

●Case 3: A man in his 70s with a history of COPD. During overseas travel, he developed community-acquired pneumonia and was managed with mechanical ventilation in the ICU of a Turkish hospital. After tracheostomy, he was transported to Japan for medical care. After arriving, he developed pneumonia again and required oxygen supply, PaO_2/FiO_2 ratio deteriorated to 180. OXA-48-like CPE was isolated from a sputum culture.

●Case 4: A woman in her 60s on chemotherapy for acute myeloid leukemia. She developed neutropenic fever and neutropenic enterocolitis. IMP-type CPE was isolated from a blood culture.

●Case 5: A man in his 50s with uncontrolled diabetes mellitus and a history of frequent travel to India. He developed necrotizing fasciitis caused by infection at the site of diabetic gangrene of the foot, leading to septic shock. NDM-type CPE was isolated from the wound and a blood culture.

Specific examples of non-UTIs (non-severe cases)

●Case 1: A man in his 70s with Parkinson's disease. He had a history of multiple episodes of aspiration pneumonia. He was admitted to the hospital due to fever and was diagnosed with aspiration pneumonia. Although CRP increased, his vital signs were stable. SpO_2 was 97% with oxygen administration at 1 L/min via a cannula. Non-CP-CRE was detected in sputum.

●Case 2: A woman in her 70s being treated with oral prednisolone 5 mg for rheumatoid arthritis. She had suffered from pain in the right lower leg since the previous day and had visited the emergency room. She had redness and was diagnosed with cellulitis. There was an effusion from the site that was partially erosive. She was hemodynamically stable and admitted to a general ward.
Her blood culture was negative. However, Gram staining of the effusion from the wound showed positive results for white blood cells and *Enterobacterales*-like Gram-negative rods, and IMP-type CPE was isolated from the effusion culture.

Specific examples of non-UTIs (cases where the patient's condition was severe initially but stabilized after initiation of treatment)

●Case 1: A woman in her 90s with old cerebral infarction and vascular dementia. She was admitted to a hospital, with diagnoses of cellulitis, subcutaneous abscess, and osteomyelitis around/in a sacral pressure ulcer. Non-CP-CRE was detected in a pus culture, but she had a negative blood culture. She was in a state of septic shock on admission. Relebactam/imipenem/cilastatin treatment and intensive care were initiated, and vital signs returned to normal during the first week.

●Case 2: A man in his 60s who lived in Taiwan and was on oral medication for diabetes mellitus during a visit to Japan for sightseeing. In his hotel, he had fever and difficulty moving and had to be transported to the hospital in an ambulance. On hospital admission, he was in a state of septic shock, requiring fluid therapy and vasopressor treatment. He had a 10-cm liver abscess and underwent emergency drainage. KPC-type carbapenemase producing *K. pneumoniae* was isolated from a blood culture obtained on admission, and liver abscess drainage was performed. The drain that was placed provided sufficient drainage, and his general condition improved 2 weeks later.

(4) *Pseudomonas aeruginosa*

Overview of epidemiology and clinical characteristics

Drug-resistant *P. aeruginosa* infection is a notifiable Category V Infectious Disease to be monitored under sentinel surveillance in Japan.[85] It should be noted that the definition of drug-resistant *P. aeruginosa* in the Infectious Diseases Control Law differs from that of multidrug-resistant *P. aeruginosa* (MDRP) in global standards (see pages 20–21 of the Appendix for details).

In the previous definitions of antimicrobial-resistant bacteria, no weight was assigned to each antibacterial agent, and those with a preferable balance between efficacy and toxicity (e.g., β-lactams, fluoroquinolones) and those without it (e.g., aminoglycosides, polymyxins) were handled in a similar manner, which was a weak point when the definitions were applied to clinical practice. Given this fact, the concept of difficult-to-treat resistant *P. aeruginosa* (DTR-PA) has been newly and recently proposed.[86] DTR-PA is defined as *P. aeruginosa* non-susceptible to all β-lactams and fluoroquinolones. In other words, among conventional drugs, only aminoglycosides and polymyxins have activity against DTR-PA infections. This clinically relevant concept of DTR-PA has been widely adopted in overseas guidance and in the guidelines for the treatment of resistant bacteria.[41,66]

Microbiological diagnosis

In Japan, carbapenemase-producing strains account for only <10% of carbapenem-resistant (or meropenem-resistant, to be more precise) *P. aeruginosa*,[87] with the most frequent carbapenemase being the IMP type (see pages 20–21 of the Appendix for details). For IMP-type carbapenemase, which is highly resistant to meropenem,[88] there is little need to worry about carbapenemase-producing strains with susceptibility to carbapenem as is the case for CPE, and that can be screened for carbapenem (meropenem) resistance in principle.

Screen-positive strains shall be confirmed using the mCIM or Carba NP test,[32] or using CIM Tris.[89] For those strains that are determined to be carbapenemase-positive by these tests, specific enzyme types shall be determined using immunochromatography or genetic testing (PCR, microarray).

Treatment policy

Unless otherwise specified, the following descriptions are based on the assumption that the strain does not produce carbapenemase. In the case of MDRP infection, a β-lactam with confirmed susceptibility can be selected when it maintains susceptibility to any conventional β-lactam (even if it has resistance to carbapenems).[41] A novel β-lactam, which is described below, can be another treatment option for patients with MDRP infections who have an uncontrolled focus of infection or in whom the condition is severe.

It is more difficult to choose a treatment for DTR-PA infections. In this case, the clinical efficacy of conventional drugs have not been established except for in the case of UTIs, and antibacterial treatment options only include aminoglycosides and colistin, which have a high frequency of adverse events. Since 2014, all novel β-lactams approved overseas can reduce the frequency of kidney injuries without worsening clinical prognosis in resistant Gram-negative rod infections, mainly in CRE infections, compared with conventional aminoglycoside- or colistin-based treatment.[90] Of these antibacterial agents, the following 2 agents are available in Japan as of September 14, 2023: tazobactam/ceftolozane and relebactam/imipenem/cilastatin.

Observational studies have already shown that tazobactam/ceftolozane treatment against resistant *P. aeruginosa* achieves a higher clinical cure rate with a lower frequency of kidney injuries, compared with conventional colistin- or aminoglycoside-based treatment.[91]

For relebactam/imipenem/cilastatin, clinical experience in *P. aeruginosa* infection is still limited; however, a sub-analysis of a phase 3 study suggested that it could reduce the frequency of kidney injuries without lowering the treatment-response rate in patients infected with *P. aeruginosa* that is non-susceptible to imipenem, compared with the combination of colistin and imipenem/cilastatin (see pages 20–21 of the Appendix for details).[92] Both agents remain active against non-carbapenemase producing carbapenem-resistant strains, and data from the US have confirmed susceptibility to these agents in approximately 50% to 70% of cases of DTR-PA.[93] Although there is no clinical study comparing tazobactam/ceftolozane and relebactam/imipenem/cilastatin in treating *P. aeruginosa* infections, tazobactam/ceftolozane is more likely to be used because there is abundant clinical experience and because susceptibility can be measured using a commercially available instrument (as of February 25, 2023). However, tazobactam/ceftolozane use has been reported to lead to the appearance of resistant strains in up to 20% of cases during and after use.[94] As the frequency of cross-resistance between tazobactam/ceftolozane and relebactam/imipenem/cilastatin is relatively low,[95] tazobactam-/ceftolozane-resistant strains may remain susceptible to relebactam/imipenem/cilastatin. Regarding the use of these novel agents, there is no evidence that combination therapy is superior to monotherapy;[91,96] thus, combination therapy is not recommended. In the future, ceftazidime-avibactam[97,98] and cefiderocol[99,100] could be available as treatment options for DTR-PA infections as well as tazobactam/ceftolozane and relebactam/imipenem/cilastatin. Unlike other novel β-lactamase inhibitors, however, cefiderocol has not been shown to improve treatment outcomes in comparison with conventional drugs.[99] As described in the section on CRE, it is the only β-lactam that can be used alone to treat MBL-producing CPE infections. Therefore, the use of cefiderocol should be avoided as much as possible when other agents are available.

On the other hand, cefiderocol as well as non-β-lactam fluoroquinolones and aminoglycosides can be a treatment option when the strain is identified as a carbapenemase-producing one, because many such strains in Japan are IMP-type MBL-producing strains.[101]

Table 8. Treatment Examples for Carbapenem-resistant *P. aeruginosa* Infections[41]

Antibacterial agent class	Name of the antimicrobial agent	Recommended dose
Conventional β-lactams	Ceftazidime	Intravenous infusion, 2 g/dose, every 8 hours ¶[102]
	Cefepime	Intravenous infusion, 1–2 g/dose, every 8 hours ¶[103] Consider the 3-hour extended infusion for severe cases.[103]
	Piperacillin	Intravenous infusion, 4 g/dose, every 6 hours Consider the 4-hour extended infusion for severe cases.[104]
	Tazobactam/ piperacillin	Intravenous infusion, 4.5 g/dose, every 6 hours ¶ Consider the 4-hour extended infusion for severe cases.[104,105]
	Aztreonam	Intravenous infusion, 2 g/dose, every 8 hours [106] ¶ Consider the 3-hour extended infusion for severe cases.[107,108]
Fluoroquinolones	Levofloxacin	See the section on AmpC-producing *Enterobacterales*
	Ciprofloxacin	Cystitis: Intravenous infusion over 1 hour, 400 mg/dose, every 12 hours or oral administration, 500 mg/dose, every 12 hours ¶[44,55] Other infections: Intravenous infusion over 1 hour, 400 mg/dose, every 8 hours or oral administration, 500–750 mg/dose, every 12 hours ¶[44,55]
Novel β-lactams	Tazobactam/ ceftolozane	Cystitis: Intravenous infusion, 1.5 g/dose, every 8 hours Other infections: Intravenous infusion, 1.5–3 g/dose, every 8 hours (over 1 hour per dose)
	Relebactam/ imipenem/ cilastatin	Intravenous infusion, 1.25 g/dose, every 6 hours (over 30 minutes per dose)
Aminoglycosides	Amikacin	See the section on AmpC-producing *Enterobacterales*
	Tobramycin[11,41]	Cystitis: Single intravenous infusion, 5 mg/kg/dose Other infections: Intravenous infusion at an initial dose of 7 mg/kg followed by dose adjustment to achieve a peak/MIC of 8–10 and a trough of <1 μg/mL.
	Gentamicin[11,41]	Cystitis: Single intravenous infusion, 5 mg/kg/dose Other infections: Intravenous infusion at an initial dose of 7 mg/kg followed by dose adjustment to achieve a peak/MIC of 8–10 and a trough of <1 μg/mL.
Polymyxins	Colistin	See the section on CRE.

¶ As the table includes doses overseas, see Table 6 on pages 22–24 of the Appendix for indications and doses in the package insert in Japan.

Table 9. Examples of Recommended Therapeutic Agents Against Carbapenem-resistant *P. aeruginosa* (See Above and Table 7 on Page 24 of the Appendix for Details)

Recommended drugs (check susceptibility to each drug)	
First-line agents	Ceftazidime, cefepime, piperacillin, tazobactam/piperacillin, levofloxacin, ciprofloxacin, amikacin-tobramycin-gentamicin (for UTIs)
If the strain is not sensitive to first-line agents	Tazobactam/ceftolozane, relebactam/imipenem/cilastatin
Alternative therapeutic drugs	Aztreonam, colistin

(5) Other Gram-negative rods (glucose non-fermenting Gram-negative rods other than *P. aeruginosa*)

(i) *Acinetobacter* spp.

Overview of epidemiology and clinical characteristics

Acinetobacter spp. are small and typically glucose non-fermenting Gram-negative rods that are widely distributed in environments such as soil and natural water.[109] They can survive for a long time in nosocomial environments, and therefore, can cause long-term outbreaks in hospitals. Among *Acinetobacter* spp., *A. baumannii* is the most prevalent human pathogen.[109] *A. baumannii* can cause hospital-acquired pneumonia, sepsis, wound infections, etc. Among them, hospital-acquired pneumonia, particularly ventilator-associated pneumonia (VAP), is clinically problematic.[109,110] Typical risk factors for *Acinetobacter* infections include advanced age, severe underlying disease, immunodeficiency, traumatic injury, burn, and surgical treatment. Additional risk factors include insertion of intrabody devices, mechanical ventilation use, long-term hospitalization, and exposure to antibacterial agents.[111] It is also known to cause community acquired infections (mainly pneumonia) in warm and humid regions including Australia, Oceania, China, Taiwan, and Thailand,[112] but the number of such cases is limited in Japan.[113]

A. baumannii has abundant endogenous antimicrobial-resistance mechanisms as well as an ability to acquire exogenous antimicrobial-resistance mechanisms (see page 25 of the Appendix for details). Therefore, its antimicrobial-resistance is becoming problematic worldwide.[109] The most major issue is carbapenem-resistance. The World Health Organization categorizes carbapenem-resistant *A. baumannii* (CRAB) as the most emergent "critical" bacterium among the antimicrobial-resistant bacteria, requiring urgent research and the development of novel antibacterial agents.[114] In recent years, it has been reported that multidrug-resistant *Acinetobacter* spp. (MDRA) were brought into medical institutions in Japan via persons who had experienced medical exposure overseas, and some of these cases led to nosocomial outbreaks.[18,115,116] Therefore, these species should also be recognized as drug resistant bacteria that are likely to be carried over from overseas.[117]

Microbiological diagnosis

In Japan, the infection caused by multi-drug *Acinetobacter* species is defined as one of the Category V infectious diseases in the Infectious Diseases Control Law and the mandatory reporting disease. [118] The definition of "antimicrobial resistance" for reporting the case is resistance to the following 3 classes of agents: broad-spectrum β-lactams (carbapenems in standards), aminoglycosides, and fluoroquinolones (see page 25 of the Appendix for details).[118] Reporting of carriers is not mandatory.

Treatment policy

Acinetobacter spp. are the cause of invasive infections inducing hospital-acquired pneumonia, mainly VAP.[109,110] They can also cause CRBSIs and bacteremia with a focus unknown.[119] Although treatment is indicated if any of them are detected in a blood culture, they often colonize respiratory or wound specimens.[120] Therefore, it shall be assessed whether they are actually the cause of invasive infection when isolated from a clinical specimen.[2] When the infections involve the artificial devices, the source control is essential, for example, removal of the intrabody artificial devices in the device infections or removal of intravascular catheter in CRBSI.

When the strain remains susceptible to antibacterial agents, β-lactams are the first-line treatment.[2,110] Among them, carbapenems are considered the most reliable and are regarded as the first-line treatment for severe infections.[110,121]

Sulbactam, a β-lactamase inhibitor, is effective[122] and can be a treatment option when the strain is susceptible to this agent.[41,121,123] It is available as a combination with ampicillin in Japan. Carbapenem-resistant strains may be susceptible to sulbactam because the mechanisms of resistance to these agents differ.[123] Sulbactam/ampicillin is cited as a first-line treatment against CRAB in the IDSA guidance on treatment.[41] However, it is a matter of concern that the optimal dosage and administration method are unknown. The daily dose of sulbactam/ampicillin recommended by the IDSA is 18 to 27 g (6 to 9 g of sulbactam), which is much higher than that shown in the package insert in Japan (a maximum daily dose of 12 g).[41] Therefore, caution is required during clinical use.

Additionally, a multicenter retrospective observational study demonstrated that the therapeutic effect of a 4th-generation cephalosporin (cefepime) on bacteremia caused by *Acinetobacter* spp. was comparable to that of carbapenems.[124] Therefore, this agent can be a treatment option for susceptible strains.

In addition to sulbactam described above, tigecycline, minocycline, and colistin, which are tetracyclines (glycylcyclines), can be treatment options against carbapenem-resistant *Acinetobacter* spp.,[125,126] but there are clinical concerns. According to the IDSA guidance, combination therapies with two or more susceptible antibiotics is recommended for moderate to severe *Acinetobacter* infections, whereas single agent therapy can be used for mild infections.[41]

However, many RCTs have failed to demonstrate the superiority of combination therapy over monotherapy.[76,127-131] Colistin-based (polymyxin-based) combination therapy is often used,[132] but there is a great concern about adverse reactions, and the appropriate combination is not clear. Thus, consultation with an infectious disease specialist in or outside a hospital should be considered for the treatment of moderate or severe CRAB infections. See page 26 of the Appendix for details such as existing evidence for therapeutic agents.

Table 10. Key Options and Points to Note for Antibacterial Treatment Against *Acinetobacter* spp.[41]

Drug name	Dose	Dosing interval	Points to note
Meropenem	1–2 g¶	Intravenous infusion, every 8 hours	• In the package insert, administration at a dose of 2 g three times a day is indicated for purulent meningitis only. • The concomitant use of valproic acid is contraindicated.
Cefepime	2 g¶[53]	Intravenous infusion, every 8–12 hours	• Up to 4 g/day in the package insert • Particularly in patients with renal impairment, overdose may cause neuropsychiatric symptoms such as disturbed consciousness and convulsions.
Sulbactam/ ampicillin	3 g (sulbactam: 1 g)¶[133-136]	Intravenous infusion, every 6 hours	• The IDSA guidance on treatment states that the daily dose is 18–27 g, whereas the package insert states that the dosage is up to 12 g/day.
Minocycline	100 mg¶	Intravenous infusion, every 12 hours	• Combination therapy shall be considered particularly for moderate cases, severe cases, and poor responders. • The dose may be increased to 200 mg only for the first dose. • Administration to children aged ≤8 years shall be avoided because dental pigmentation may occur. • Vascular pain is likely to occur, but it can be managed by prolonging the duration of infusion in many cases. • The IDSA guidance on treatment recommends administration at a dose of 200 mg every 12 hours, which exceeds the maximum dose stated in the package insert.
Tigecycline	See the section on CRE.	—	—
Colistin	See the section on CRE.	—	—

¶ As the table includes doses overseas, see pages 26–27 of the Appendix for indications and doses in the package insert in Japan.

Table 11. Examples of Recommended Therapeutic Agents Against *Acinetobacter* spp. (See the Text of This Document and Pages 26–27 of the Appendix for Details)

Recommended drugs (check susceptibility to each drug)	Mild cases	Moderate/severe cases
First-line agents	Cefepime, sulbactam/ampicillin, minocycline	Meropenem or cefepime + minocycline or colistin or tigecycline (combination therapy with at least 2 agents to which the strain has susceptibility)
Alternative therapeutic drugs	Colistin, tigecycline	—

(ii) *Stenotrophomonas maltophilia*

Overview of epidemiology and clinical characteristics

S. maltophilia is a glucose non-fermenting Gram-negative rod.[137,138] It can survive in nutritionally poor aquatic environments inside and outside hospitals and adhere to plastic, leading to biofilm formation.[137] Therefore, it is detected on artificial materials used in clinical practice such as venous cannulas as well as in in-hospital environments such as dialysates, tap water, and sinks.[137]

Infections caused by *S. maltophilia* are commonly associated with bacteremia (including CRBSIs) and respiratory infections.[138,139] Particularly in patients with hematologic malignancies, rapidly progressing hemorrhagic pneumonia is known to be a pathological condition with a high mortality.[140,141] *S. maltophilia* infection has also been reported to cause a wide range of other infections including endophthalmitis, endocarditis, meningitis, skin/soft tissue infections, and implant-related infections.[137]

Risk factors for *S. maltophilia* infection include malignant tumors (mainly hematologic malignancies, particularly hematopoietic stem cell transplant recipients), underlying diseases (cystic fibrosis, human immunodeficiency virus infection, etc.), use of intravenous drugs, accidental injury, surgery, long-term hospitalization, use of intravenous/urethral catheters, ICU stay, mechanical ventilation use, and immunosuppressive therapy.[137]

Microbiological diagnosis

In Japan, no mandatory reporting is required in cases with *S. maltophilia* colonization or infection. For the antimicrobial susceptibility tests available in Japan, the Clinical and Laboratory Standards Institute (CLSI) has established criteria for assessing MICs for the co-trimoxazole, levofloxacin, minocycline, and ceftazidime,[32] whereas the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has established criteria for assessing MICs only for the co-trimoxazole (see pages 27–28 of the Appendix for details).[142]

Treatment policy

S. maltophilia mainly causes CRBSI and pneumonia in patients with the aforementioned risk factors.[139] When *S. maltophilia* is isolated from blood cultures, antimicrobial therapy should invariably be administered. However, this organism is often associated with colonization in respiratory tract, especially among the patients with long-term ICU stay, those with intense antimicrobial therapy with carbapenems and those with tracheostomy. Therefore, when *S. maltophilia* is isolated from respiratory sample, a careful assessment for whether the isolate is related with invasive infections before the administration of antimicrobials.[139] The focus of infection shall be controlled through appropriate interventions, such as removal of the catheter in the case of CRBSI.[132,143]

Although there are no RCTs on antimicrobial agents against *S. maltophilia*, co-trimoxazole is regarded as the first-line treatment and is widely used because there is abundant usage experience and because this bacterium has endogenous mechanisms of resistance to several agents (see pages 27–28 of the Appendix for details).[41,144] However, adverse reactions such as kidney injury, liver injury, volume load in intravenous preparation, hyperkalemia, myelosuppression, and skin rash have been raised as concerns during treatment with co-trimoxazole.[145,146]

According to the IDSA guidance, monotherapy with co-trimoxazole, minocycline, tigecycline, or levofloxacin may be adopted for mild cases, among which, co-trimoxazole and minocycline are the most favorable.[41] Regarding fluoroquinolones and tetracyclines, on the other hand, there are concerns of acquiring resistance during treatment for

fluoroquinolones[146,147] and achieving the poor serum concentration of tetracycline derivatives because of their rapid tissue distribution.[126] It is, therefore, recommended that co-trimoxazole and minocycline should be used for moderate or severe cases, or that minocycline, tigecycline, or levofloxacin (minocycline is the most preferable) should be added for poor responders to initial monotherapy with co-trimoxazole. However, there is no sufficient data demonstrating the superiority of the combination therapy.[148] Ceftazidime, which has endogenous β-lactamase activity, should not be used for treatment regardless of severity.[41] The CLSI and EUCAST have not established break points for the determination of the susceptibility of *S. maltophilia* to colistin and tigecycline[149] (a break point is a reference value used to predict the therapeutic effect of an antibacterial agent based on the results from the antibacterial susceptibility test).[142]

Table 12. Key Options of Antibacterial Treatment Against *S. maltophilia*[41]

Drug name	Administration method
Co-trimoxazole (infusion)	See the section on AmpC-producing *Enterobacterales*
Levofloxacin	See the section on AmpC-producing *Enterobacterales*¶
Minocycline	See the section on *Acinetobacter* spp.
Tigecycline	See the section on CRE¶

Table 13. Examples of Recommended Therapeutic Agents Against *S. maltophilia* (See the Text of This Document and Pages 27–28 of the Appendix for Details)

Recommended drugs (check susceptibility to each drug)	Mild cases	Moderate/severe cases
First-line agents	Co-trimoxazole, minocycline	Co-trimoxazole + minocycline
Alternative therapeutic drugs	Tigecycline, levofloxacin	Co-trimoxazole + tigecycline or levofloxacin

(6) *Clostridioides difficile*

Overview of epidemiology and clinical characteristics

C. difficile is an obligate anaerobic, spore-forming Gram-positive rod that causes *C. difficile* infections (CDIs), which can lead to hospital-acquired diarrhea and other diseases. In addition to diarrhea, *C. difficile* is known to cause ileus and toxic megacolon in severe cases. In addition, *C. difficile* is known to form spores that are resistant to heat, radiation, desiccation, high-pressure treatment, drugs, making it an important organism for hospital infection control. It is known that toxins A and B produced by *C. difficile* are involved in the pathogenesis of CDI and that *C. difficile* that does not produce toxin A/B does not cause CDIs.

It has also been reported in the US that *C. difficile* is the most frequently found bacteria in hospitals.[150] A systematic review and meta-analysis published in 2020 reported that the frequency of hospital acquired CDIs was 8.3 events/10,000 patient-days.[151] A multicenter prospective study in Japan reported it to be 7.4 events/10,000 patient-days. This frequency is similar to that in Europe and the US, which means CDI is a significant infectious disease in Japan as well.[152] Given that approximately 95% of patients with CDIs have received services such as outpatient care and hospitalization at medical institutions or nursing facilities, CDI can be perceived as a healthcare associated infectious disease.[153]

CDIs should be suspected when diarrhea occurs at least 3 times within 24 hours (Bristol Stool Scale score ≥5: soft semisolid stools, indeterminate-form mushy stools, liquid stools without solids) or when the frequency of bowel movement is higher than usual.[154]

According to the Japanese guidelines (*Clostridioides difficile* Infection Treatment Guideline 2022), it is not necessary to adhere to the frequency of bowel movement in the elderly or other individuals who have no independent bowel movement.[155] When a new case of diarrhea is identified in a hospital, a test shall be considered first. A patient may not have diarrhea but may have ileus and/or toxic megacolon, although such an occurrence is uncommon. If an inpatient develops these symptoms, then CDI should be suspected. As exposure to antibacterial agents within the past 3 months has been reported to be a risk factor,[156] CDIs shall be included in differential diagnoses when a past history of exposure to antibacterial agents is confirmed even in outpatients with diarrhea. It is also known that even a single dose of antibacterial treatment can cause CDIs.[157]

Other reported risk factors include age, use of gastric secretion inhibitors (including proton pump inhibitors [PPIs] and H2 receptor antagonists), and recent hospitalization, all of which are common risk factors in hospitalized patients.[158]

Microbiological diagnosis

A kit to detect toxin and glutamate dehydrogenase (GDH) antigen simultaneously, as well as nucleic acid amplification test (NAAT) and stool culture test are available in Japan. A positive result for GDH antigen suggests the presence of *C. difficile*. Although the available algorithms differ among institutions, it has been proposed that a kit to detect toxin and GDH simultaneously should be primarily used, and that NAAT or stool culture should be conducted if the test results are negative for the toxin and positive for GDH.[155,159]

Patients with no diarrhea, ileus, or toxic megacolon shall not be tested. It has been pointed out that the excessive implementation of NAAT particularly yields false-positive results, leading to excessive treatment.[160]

A test shall not be repeated (however, retesting may be considered if the possibility remains 1 week later). Post-treatment testing is not recommended, and therefore it is recommended that patients not be asked to undergo post-treatment testing, such as at the time of hospital transfer.

CDI is an infectious disease characterized by recurrence. Recurrent CDI is defined as a CDI that recurs within 8 weeks after the previous onset.[155,159,161] Approximately 30% of patients experience recurrence even after appropriate treatment, with recurrence after the first infection occurring in 10% to 20% of cases and recurrence after the first recurrence (second recurrence) occurring in 40% to 65% of cases.[162-165] The following risk factors have been listed:[155] advanced age (≥65 years), use of antibacterial agents, serious underlying disease, history of CDI, use of PPIs, healthcare-associated CDI (history of hospitalization within 3 months prior to onset).

Treatment policy

Any antibacterial agent being used shall be discontinued first, if possible.

There is no difference in the cure rate between fidaxomicin and vancomycin, but the recurrence rate is lower with fidaxomicin.[166] Given the great difference in costs, however, treatment needs to be selected based on whether or not it is recurrent and how severe it is.[166,167] The Japanese guideline defines cases with at least 2 events of recurrence as refractory cases (cases where diarrhea does not improve after the completion of standard treatment are also defined as refractory cases).[155]

Table 14. Examples of Criteria for Assessing CDI Severity[155,159,161]

Guideline	Severe	Fulminant
IDSA/The Society for Healthcare Epidemiology of America	WBC count >15,000 cells/mL or serum Cre ≥1.5 mg/dL	Decreased blood pressure, shock, ileus, or toxic megacolon
European Society of Clinical Microbiology and Infectious Diseases	WBC >15,000 cells/mL or serum Cre increased by >50% compared with that at baseline, or body temperature >38.5°C	Decreased blood pressure, shock, increased lactate levels, ileus, toxic megacolon, gastrointestinal perforation
The Japanese Association for Infectious Diseases	No clear criteria	

Table 15. Examples of CDI Treatment[155,159,161]

Drugs	Dose (oral administration unless otherwise specified)	Dosing interval	Therapy duration
Non-severe/non-fulminant cases (first time)			
Fidaxomicin	200 mg	Every 12 hours	10 days
Vancomycin	125 mg	Every 6 hours	10 days
Metronidazole	500 mg	Every 8 hours	10 days
Non-severe/non-fulminant cases (first recurrence)			
Fidaxomicin	Same as the first time		
Vancomycin	Same as the first time		
Vancomycin	Pulsed and tapered therapy (see pages 29–30 of the Appendix)		
Non-severe/non-fulminant cases (second recurrence, refractory cases)			
Fidaxomicin	Same as the first time		
Vancomycin	Pulse/taper therapy (see pages 29–30 of the Appendix)		
Severe cases			
Vancomycin	Same as the first time		
Fidaxomicin	Same as the first time		
Fulminant cases			
Vancomycin + metronidazole	Oral administration at a dose of 500 mg every 6 hours + intravenous infusion at a dose of 500 mg every 8 hours (intravenous infusion over 20 minutes) 10–14 days		
Fidaxomicin	Same as the first time		

*See pages 29–30 of the Appendix for details including points to consider.

For indications for total colectomy or diverting loop ileostomy as surgical treatment, consultation with an experienced surgeon or infectious disease specialist is recommended. Fecal transplantation for recurrent cases is known to be highly effective in preventing recurrence, but it is not covered by health insurance in Japan. As serious adverse events have also been reported, it is advisable to consult an infectious disease specialist when considering this treatment. The active use of probiotics is not recommended because there is insufficient evidence regarding their use to prevent the onset/recurrence of CDI or as a concomitant medication for the treatment of CDI. Probiotics may cause bacteremia depending on patient characteristics, and therefore, their indications should be checked carefully before use.[168] Treatment of CDI when discontinuation of antibacterial agents is difficult is described on pages 29–30 of the Appendix.

(7) *Candida* spp.

Overview of epidemiology and clinical characteristics

Candida infections account for approximately 70% to 90% of invasive fungal infections, and the mortality in cases of invasive candidiasis with candidemia, deep-seated candidiasis, or both is as high as 40% to 60%.[169,170] The main portals of entry in invasive candidiasis are the skin, intravascular catheter, and gastrointestinal tract.[169]

The 5 major strains of *Candida* spp. are *Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis,* and *Candida krusei*. The resistance of *C. glabrata* and *C. krusei* to azole, the natural resistance of *C. parapsilosis* to candins, and CRBSIs due to biofilm formation currently pose problems.[169,171,172]

Candida auris, which was first detected in an ear canal specimen in 2009 in Japan, has been found worldwide thereafter, and its resistance not only to azole but also to polyene has become a problem.[173]

Risk factors for invasive candidiasis include the use of broad-spectrum antibacterial agents, central venous catheterization, total parenteral nutrition, post-abdominal surgery state, high APACHEII score, malignant tumors, neutropenia, chemotherapy, post-transplantation state, acute kidney injury, hemodialysis, diabetes mellitus, long-term hospitalization, ICU stay, immature baby, and low birth weight.[171,172]

Microbiological diagnosis

Blood β-D-glucan measurement (sensitivity 65%–85%, specificity 75%–85%) can be used for screening,[174,175] and blood culture (sensitivity approximately 50%, specificity unknown) can be used for a definite diagnosis.[169] For β-D-glucan measurement, there are several kits currently available in Japan, but it should be noted that each of them has a different cutoff value. It should also be noted that the negative predictive value in this measurement is high, whereas it shows false-positive results in individuals being treated with antibacterial agents or albumin.[176] It should be noted that blood cultures require 2-3 days to become positive and have a low positive rate.[169,171,172]

As of February 2023, whole blood PCR (T2 *Candida* panel), which is not covered by health insurance in Japan, is used in the US and other regions, and it has a sensitivity and specificity of 91% and 94%, respectively.[169,171,172] The *Candida* score is a screening test to predict invasive candidiasis, and invasive candidiasis is predicted when patients score ≥3 of 5 points for the following 4 items: (1) total parenteral nutrition (1 point), (2) surgery (1 point), (3) multifocal colonization (1 points), and (4) severe sepsis (2 points) (sensitivity 81%, specificity 74%).[177]

Treatment policy

Treatment is largely divided into treatment with antifungal agents and control of the infection focus (removal of intravascular catheter/artificial material, surgical drainage, or debridement), and the former is further divided by purposes as follows:[171]

(1) Prophylactic treatment: Administered to asymptomatic patients with persistent neutropenia after hematopoietic stem cell transplant or organ transplant
(2) Empiric treatment: For symptomatic patients who have stayed in the ICU for ≥96 hours, are receiving treatment with broad spectrum antibacterial agents, and have a history of total parenteral nutrition, gastrointestinal surgery, or sepsis
(3) Preemptive treatment: Conducted for patients who have been confirmed to be positive for β-D-glucan or to have multifocal colonization, as well as to meet the conditions listed in the column on empirical treatment
(4) Targeted treatment: For patients in whom culture was detected at a sterile site

For invasive candidiasis, echinocandins (micafungin, caspofungin) or polyenes (amphotericin B, liposomal amphotericin B) exhibiting bactericidal action are the first-line treatment.[171,178,179] Generally, echinocandins associated with relatively few adverse reactions and low resistance are selected. Against *C. parapsilosis*, azoles or echinocandins shall be selected based on the results from the antimicrobial susceptibility test. Against *C. glabrata* and *C. krusei*, echinocandins shall be selected.[179] In a meta-analysis comparing the effects of echinocandins, polyenes, and azoles in invasive candidiasis, echinocandins had the highest treatment success rate, but there was no significant difference in the survival rate.[180] The classification (Table 16) and dose (Table 17) of antifungal agents are shown below.

In the event of candidemia, fundoscopy to assess endophthalmitis early (within 7 days), and echocardiography to rule out infective endocarditis (preferably within 24 hours) shall be performed.[178,179]

If resolution of candidemia, stable general condition, and sufficient susceptibility are confirmed after 5 to 7 days of treatment, switching from echinocandins/polyenes to narrower-spectrum agents, i.e., azoles, shall be considered.[178,179]

The typical duration of therapy with antifungal agents is as follows: until 14 days after negative conversion of blood culture, which shall be obtained every day (or every other day) until negative conversion is confirmed, and resolution of the symptoms of candidemia without metastatic focus of infection or neutropenia; until at least 6 weeks after surgery for *Candida* infective endocarditis (longer if surgery is not possible); until successful control of infection focus and resolution of symptoms of intra-abdominal candidiasis; for at least 4 to 6 weeks for candidal endophthalmitis; and for 14 days for *Candida* complicated UTIs.[178,179]

Consultation with an infectious disease department is an independent improvement factor for the 30-day prognosis of candidemia; therefore, consultation with an infectious disease specialist shall be actively considered at institutions where possible.[181]

Table 16. Classification of Antifungal Agents

	Echinocandins	Polyene macrolides	Azoles
Main agents	Micafungin Caspofungin	Amphotericin B Liposome formulation of the above	Fluconazole
Action	Bactericidal	Bactericidal	Bacteriostatic
Mechanism	Inhibition of cell wall synthesis	Disruption of cell membrane	Inhibition of cell membrane synthesis
Points to note	Difficult to penetrate the eye, urinary tract, and central nervous system Infusion only	Liver/renal injury Electrolyte abnormality Fever	Liver injury Frequent drug interaction Teratogenicity

Table 17. Dose of Antifungal Agents

Drug name	Initial dose	Maintenance dose (daily)	Notes
Micafungin	–	Intravenous infusion at 100 mg/dose Every 24 hours Over 1 hour	An increase in dose up to 150 mg/dose shall be considered for severe cases.
Caspofungin	70 mg/dose on Day 1 Every 24 hours Intravenous infusion over approximately 1 hour	Intravenous infusion at 50 mg/dose Every 24 hours Over approximately 1 hour	The dose shall be decreased to 35 mg/day for individuals with liver disorders (Child-Pugh score: 7–9).
Liposomal amphotericin B	–	Intravenous infusion at 2.5–5 mg/kg/dose Every 24 hours Over 1–2 hours	–
Fluconazole	–	Intravenous infusion at 400 mg/dose Every 24 hours	The dose shall be decreased by 50% when CCr is <50. Switching from intravenous infusion to oral administration at the same dose shall be considered if oral administration and intestinal absorption are possible.

Table 18. Examples of Recommended Therapeutic Agents for Invasive *Candida* Without Endophthalmitis[179]

Recommended drugs (check susceptibility to each drug)			
<Empiric treatment>	<Targeted treatment>		
	C. albicans	*C. glabrata, C. krusei*	*C. parapsilosis*
Micafungin, caspofungin	Fluconazole	Micafungin, caspofungin	Fluconazole, micafungin, or caspofungin shall be selected based on susceptibility.

2. References

1. GBD 2019 Antimicrobial Resistance Collaborators. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022 Dec;400(10369):2221-2248.
2. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Philadelphia: Elsevier 2019.
3. Pien BC, Sundaram P, Raoof N. et al. The clinical and prognostic importance of positive blood cultures in adults. Am J Med. 2010 Sep;123(9):819-828.
4. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E. et al. Clinical management of Staphylococcus aureus bacteraemia. Lancet Infect Dis 2011 Mar;11(3):208-222.
5. Bai AD, Morris AM. Management of Staphylococcus aureus bacteremia in adults. CMAJ. 2019 Sep;191(135):E967.
6. Bai AD, Agarwal A, Steinberg M. et al. Clinical predictors and clinical prediction rules to estimate initial patient risk for infective endocarditis in Staphylococcus aureus bacteraemia: a systematic review and meta-analysis. Clin Microbiol Infect. 2017 Dec;23(12):900-906.
7. Government of South Australia. Staphylococcus aureus Bacteraemia Management Clinical Guideline. Version 2.0. 2023.
8. Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia require blood cultures? JAMA 2012;308:502-511.
9. Lam JC, Stokes W. The Golden Grapes of Wrath - Staphylococcus aureus Bacteremia: A Clinical Review. Am J Med. 2023 Jan;136(1):19-26.
10. Li J, Echevarria KL, Hughes DW, Cadena JA, Bowling JE, Lewis JS, 2nd. Comparison of cefazolin versus oxacillin for treatment of complicated bacteremia caused by methicillin-susceptible Staphylococcus aureus. Antimicrob Agents Chemother. 2014 Sep;58(9):5117-5124.
11. The Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. Clinical Practice Guideline for the Therapeutic Drug Monitoring 2022 [In Japanese]. at https://www.chemotherapy.or.jp/uploads/files/guideline/tdm2022.pdf.)
12. Liu C, Bayer A, Cosgrove SE. et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011 Feb;52(3):e18-55.
13. Figueroa DA, Mangini E, Amodio-Groton M. et al. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. Clin Infect Dis 2009 Jul;49(2):177-180.
14. Ministry of Health, Labour and Welfare. Vancomycin-resistant *Enterococci* infection [In Japanese]. at https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-14-01.html.)
15. National Institute of Infectious Diseases. List of outbreak trend surveys by year (total number of cases) [In Japanese]. at https://www.niid.go.jp/niid/ja/ydata/11530-report-ja2021-30.html.)
16. Cetinkaya Y, Falk P, Mayhall CG. Vancomycin-resistant enterococci. Clin Microbiol Rev 2000;13:686-707.

17. Prematunge C, MacDougall C, Johnstone J. et al. VRE and VSE Bacteremia Outcomes in the Era of Effective VRE Therapy: A Systematic Review and Meta-analysis. Infect Control Hosp Epidemiol. 2016;37:26-35.
18. Hayakawa K, Mezaki K, Sugiki Y. et al. High rate of multidrug-resistant organism colonization among patients hospitalized overseas highlights the need for preemptive infection control. Am J Infect Control. 2016 Nov;44(11):e257-e259.
19. The Japanese Society of Chemotherapy and the Certification System Review Committee for Antimicrobial Chemotherapy Certified Physicians.Textbook for Continuing Education in the Proper Use of Antimicrobial Agents, 3rd edition 2020 [In Japanese].
20. Wurpts G, Aberer W, Dickel H. et al. Guideline on diagnostic procedures for suspected hypersensitivity to beta-lactam antibiotics: Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) in collaboration with the German Society of Allergology (AeDA), German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Austrian Society for Allergology and Immunology (OGAI), and the Paul-Ehrlich Society for Chemotherapy (PEG). Allergol Select. 2020 May;4:11-43.
21. Baddour LM, Wilson WR, Bayer AS. et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2015 Oct;132(15):1435-1486.
22. Britt NS, Potter EM, Patel N, Steed ME. Comparison of the Effectiveness and Safety of Linezolid and Daptomycin in Vancomycin-Resistant Enterococcal Bloodstream Infection: A National Cohort Study of Veterans Affairs Patients. Clin Infect Dis. 2015 Sep;61(6):871-878.
23. Adeolu M, Alnajar S, Naushad S, Gupta RS. Genome-based phylogeny and taxonomy of the 'Enterobacteriales': proposal for Enterobacterales ord. nov. divided into the families Enterobacteriaceae, Erwiniaceae fam. nov., Pectobacteriaceae fam. nov., Yersiniaceae fam. nov., Hafniaceae fam. nov., Morganellaceae fam. nov., and Budviciaceae fam. nov. Int J Syst Evol Microbiol. 2016 Dec;66(12):5575-5599.
24. Sohei Harada. Genetics and epidemiology of antibiotic-resistant Enterobaterales [In Japanese]. The Journal of the Japanese Society for Clinical Microbiology. 2021;31(4): 229-238.
25. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev. 2005 Oct;18(4):657-686.
26. Castanheira M, Simner PJ, Bradford PA. Extended-spectrum beta-lactamases: an update on their characteristics, epidemiology and detection. JAC Antimicrob Resist. 2021 Jul;3(3):dlab092.
27. JANIS Open Report. Clinical Laboratory Division Inpatient 2021. at https://janis.mhlw.go.jp/english/report/open_report/2021/3/1/ken_Open_Report_Eng_202100_clsi2012.pdf.)
28. JANIS Open Report. Clinical Laboratory Division Outpatient 2021 [In Japanese]. at https://janis.mhlw.go.jp/report/open_report/2021/3/1/ken_Open_Report_202100_Outpatient.pdf.)
29. Arcilla MS, van Hattem JM, Haverkate MR. et al. Import and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. Lancet Infect Dis. 2017 Jan;17(1):78-85.

30. Rodriguez-Bano J, Picon E, Gijon P. et al. Community-onset bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli: risk factors and prognosis. Clin Infect Dis. 2010 Jan;50(1):40-48.

31. Goodman KE, Lessler J, Cosgrove SE. et al. A Clinical Decision Tree to Predict Whether a Bacteremic Patient Is Infected With an Extended-Spectrum beta-Lactamase-Producing Organism. Clin Infect Dis. 2016 Oct;63(7):896-903.

32. CSLI M100-32nd Edition. at http://em100.edaptivedocs.net/dashboard.aspx,.)

33. The Japanese Society for Clinical Microbiology. Guidance on testing for multidrug-resistant bacteria 2021 [In Japanese]. at https://www.jscm.org/modules/guideline/index.php?content_id=15.)

34. Nicolle LE, Gupta K, Bradley SF. et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2019 May;68(10):e83-e110.

35. Armand-Lefevre L, Angebault C, Barbier F. et al. Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. Antimicrob Agents Chemother. 2013 Mar;57(3):1488-1495.

36. Ishikawa K, Uehara Y, Mori N. et al. In Vitro Activity and Clinical Efficacy of Faropenem against Third-Generation Cephalosporin-Resistant Escherichia coli and Klebsiella pneumoniae. Antimicrob Agents Chemother. 2022 Jun;66(6):e0012522.

37. Eckburg PB, Muir L, Critchley IA. et al. Oral Tebipenem Pivoxil Hydrobromide in Complicated Urinary Tract Infection. N Engl J Med. 2022 Apr;386(14):1327-1338.

38. Hamada Y, Kasai H, Suzuki-Ito M, Matsumura Y, Doi Y, Hayakawa K. Pharmacokinetic/Pharmacodynamic Analysis and Dose Optimization of Cefmetazole and Flomoxef against Extended-Spectrum beta-Lactamase-Producing Enterobacterales in Patients with Invasive Urinary Tract Infection Considering Renal Function. Antibiotics (Basel). 2022 Mar;11(4):456.

39. Hayakawa K, Matsumura Y, Uemura K. et al. Effectiveness of cefmetazole versus meropenem for invasive urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. Antimicrob Agents Chemother 2023 Oct;67(10):e0051023.

40. JAID/JSC infectious disease treatment guide/guideline development committee. JAID/JSC infectious disease treatment guide 2019 [in Japanese].Tokyo: Life Science Publishing; 2019. Print.

41. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Clin Infect Dis. 2023 Jul:ciad428.

42. Rodriguez-Bano J, Alcala JC, Cisneros JM. et al. Community infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. Arch Intern Med. 2008 Sep;168(17):1897-1902.

43. Lo CL, Lee CC, Li CW. et al. Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. J Microbiol Immunol Infect. 2017 Jun;50(3):355-61.

44. Punjabi C, Tien V, Meng L, Deresinski S, Holubar M. Oral Fluoroquinolone or Trimethoprim-sulfamethoxazole vs. ss-lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis. Open Forum Infect Dis. 2019 Aug;6(10):ofz364.

45. Tamma PD, Doi Y, Bonomo RA, Johnson JK, Simner PJ, Antibacterial Resistance Leadership G. A Primer on AmpC beta-Lactamases: Necessary Knowledge for an Increasingly Multidrug-resistant World. Clin Infect Dis. 2019 Sep;69(8):1446-1455.

46. Sho Nishimura. The AmpC story that seems to be well understood but is not (1) [in Japanese]. J-IDEO. 2017;1(3):343-350.

47. Kohlmann R, Bahr T, Gatermann SG. Species-specific mutation rates for AmpC derepression in Enterobacterales with chromosomally encoded inducible AmpC beta-lactamase. J Antimicrob Chemother. 2018 Jun;73(6):1530-1536.

48. Tamma PD, Girdwood SC, Gopaul R. et al. The use of cefepime for treating AmpC beta-lactamase-producing Enterobacteriaceae. Clin Infect Dis. 2013 Sep;57(6):781-788.

49. Stewart AG, Paterson DL, Young B. et al. Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC beta-Lactamase-Producing Enterobacter spp, Citrobacter freundii, Morganella morganii, Providencia spp, or Serratia marcescens: A Pilot Multicenter Randomized Controlled Trial (MERINO-2). Open Forum Infect Dis. 2021 Aug;8(8):ofab387.

50. Chaubey VP, Pitout JD, Dalton B, Gregson DB, Ross T, Laupland KB. Clinical and microbiological characteristics of bloodstream infections due to AmpC beta-lactamase producing Enterobacteriaceae: an active surveillance cohort in a large centralized Canadian region. BMC Infect Dis. 2014 Dec;14:647.

51. Cheng L, Nelson BC, Mehta M. et al. Piperacillin-Tazobactam versus Other Antibacterial Agents for Treatment of Bloodstream Infections Due to AmpC beta-Lactamase-Producing Enterobacteriaceae. Antimicrob Agents Chemother. 2017 May;61(6):e00276-17.

52. Meije Y, Pigrau C, Fernandez-Hidalgo N. et al. Non-intravenous carbapenem-sparing antibiotics for definitive treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBL) or AmpC beta-lactamase: A propensity score study. Int J Antimicrob Agents. 2019 Aug;54(2):189-196.

53. Maan G, Keitoku K, Kimura N. et al. Cefepime-induced neurotoxicity: systematic review. J Antimicrob Chemother 2022 Oct;77(11):2908-2921.

54. Kunz Coyne AJ, El Ghali A, Lucas K, et al. High-dose Cefepime vs Carbapenems for Bacteremia Caused by Enterobacterales With Moderate to High Risk of Clinically Significant AmpC beta-lactamase Production. Open Forum Infect Dis. 2023 Jan;10(3):ofad034.

55. Tamma PD, Conley AT, Cosgrove SE. et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med. 2019 Mar;179(3):316-323.

56. Ministry of Health, Labour and Welfare. Carbapenem-resistant *Enterobacterales* [in Japanese]. at https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-140912-1.html.)

57. National Institute of Infectious Diseases. Carbapenem-resistant *Enterobacterale*s（CRE）Infectious Agent Surveillance Report 2021 [In Japanese]. IASR Vol.44 p130-131:August 2023. at https://www.niid.go.jp/niid/ja/cre-m/cre-iasrd/12223-522d03.htmljh.)

58. Oka K, Matsumoto A, Tetsuka N. et al. Clinical characteristics and treatment outcomes of carbapenem-resistant Enterobacterales infections in Japan. J Glob Antimicrob Resist. 2022 Jun;29:247-252.

59. van Loon K, Voor In 't Holt AF, Vos MC. A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant Enterobacteriaceae. Antimicrob Agents Chemother. 2017 Dec;62(1):e01730-17.

60. Sho Nishimura. CRE and CPE topics often confused(2) [in Japanese]. J-IDEO. 2019;3(3):346-355..

61. Shigemoto N, Kuwahara R, Kayama S. et al. Emergence in Japan of an imipenem-susceptible, meropenem-resistant Klebsiella pneumoniae carrying blaIMP-6. Diagn Microbiol Infect Dis. 2012 Jan;72(1):109-112.

62. Yano H, Ogawa M, Endo S. et al. High frequency of IMP-6 among clinical isolates of metallo-beta-lactamase-producing Escherichia coli in Japan. Antimicrob Agents Chemother. 2012 Aug;56(8):4554-4555.

63. EUCAST guideline for the detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance, v2. 2017. at https://www.eucast.org/resistance_mechanisms.)

64. Sho Nishimura. Treatment of CRE (4) [in Japanese]. J-IDEO. 2020;4(4):99-105.

65. Perez F, El Chakhtoura NG, Yasmin M, Bonomo RA. Polymyxins: To Combine or Not to Combine? Antibiotics (Basel). 2019 Apr;8(2):38.

66. Paul M, Carrara E, Retamar P. et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022 Apr;28(4):521-547.

67. Hayakawa K, Nakano R, Hase R. et al. Comparison between IMP carbapenemase-producing Enterobacteriaceae and non-carbapenemase-producing Enterobacteriaceae: a multicentre prospective study of the clinical and molecular epidemiology of carbapenem-resistant Enterobacteriaceae. J Antimicrob Chemother. 2020 Mar;75(3):697-708.

68. van Duin D, Arias CA, Komarow L. et al. Molecular and clinical epidemiology of carbapenem-resistant Enterobacterales in the USA (CRACKLE-2): a prospective cohort study. Lancet Infect Dis. 2020 Jun;20(6):731-741.

69. Saito S, Hayakawa K, Tsuzuki S. et al. A Matched Case-Case-Control Study of the Impact of Clinical Outcomes and Risk Factors of Patients with IMP-Type Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae in Japan. Antimicrob Agents Chemother. 2021 Feb;65(3):e01483-20.

70. Senchyna F, Gaur RL, Sandlund J. et al. Diversity of resistance mechanisms in carbapenem-resistant Enterobacteriaceae at a health care system in Northern California, from 2013 to 2016. Diagn Microbiol Infect Dis. 2019 Mar;93(3):250-257.

71. Bonnin RA, Bernabeu S, Emeraud C. et al. In Vitro Activity of Imipenem-Relebactam, Meropenem-Vaborbactam, Ceftazidime-Avibactam and Comparators on Carbapenem-Resistant Non-Carbapenemase-Producing Enterobacterales. Antibiotics (Basel). 2023 Jan;12(1):102.

72. Tamma PD, Bergman Y, Jacobs EB. et al. Comparing the activity of novel antibiotic agents against carbapenem-resistant Enterobacterales clinical isolates. Infect Control Hosp Epidemiol. 2023 May;44(5):762-767.

73. Tsuji BT, Pogue JM, Zavascki AP, et al. International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy 2019;39:10-39.

74. Zha L, Pan L, Guo J, French N, Villanueva EV, Tefsen B. Effectiveness and Safety of High Dose Tigecycline for the Treatment of Severe Infections: A Systematic Review and Meta-Analysis. Adv Ther 2020 Mar;37(3):1049-1064.

75. De Pascale G, Lisi L, Ciotti GMP. et al. Pharmacokinetics of high-dose tigecycline in critically ill patients with severe infections. Ann Intensive Care. 2020 Jul;10(1):94.

76. Paul M, Daikos GL, Durante-Mangoni E. et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. Lancet Infect Dis. 2018 Apr;18(4):391-400.

77. Pascale R, Giannella M, Bartoletti M, Viale P, Pea F. Use of meropenem in treating carbapenem-resistant Enterobacteriaceae infections. Expert Rev Anti Infect Ther. 2019 Oct;17(10):819-827.

78. Practical guide for appropriate use of colistin: update [In Japanese]. Japanese Journal of Chemotherapy. 2015;63(3):290-329. at https://www.chemotherapy.or.jp/uploads/files/guideline/colistin_guideline_update.pdf.)

79. Guide to the proper use of tigecycline 2014 [In Japanese]. Japanese Journal of Chemotherapy. 2014;62(3):311-366.

80. Tamma PD, Han JH, Rock C. et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum beta-lactamase bacteremia. Clin Infect Dis. 2015 May;60(9):1319-1325.

81. NICE Guideline. Sepsis: recognition, diagnosis and early management. 2017. at https://www.nice.org.uk/guidance/ng51/resources/sepsis-recognition-diagnosis-and-early-management-pdf-1837508256709.)

82. Heil EL, Bork JT, Abbo LM. et al. Optimizing the Management of Uncomplicated Gram-Negative Bloodstream Infections: Consensus Guidance Using a Modified Delphi Process. Open Forum Infect Dis. 2021 Oct;8(10):ofab434.

83. Poutsiaka DD, Davidson LE, Kahn KL, Bates DW, Snydman DR, Hibberd PL. Risk factors for death after sepsis in patients immunosuppressed before the onset of sepsis. Scand J Infect Dis. 2009;41(6-7):469-479.

84. Evans L, Rhodes A, Alhazzani W. et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov;47(11):1181-1247.

85. Ministry of Health, Labour and Welfare. Drug-resistant *Pseudomonas aeruginosa* infections[In Japanese]. at https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-42-01.html.)

86. Kadri SS, Adjemian J, Lai YL. et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin Infect Dis. 2018 Nov;67(12):1803-1814.

87. Mano Y, Saga T, Ishii Y. et al. Molecular analysis of the integrons of metallo-beta-lactamase-producing Pseudomonas aeruginosa isolates collected by nationwide surveillance programs across Japan. BMC Microbiol. 2015 Feb;15:41.

88. Nakayama R, Inoue-Tsuda M, Matsui H, Ito T, Hanaki H. Classification of the metallo beta-lactamase subtype produced by the carbapenem-resistant Pseudomonas aeruginosa isolates in Japan. J Infect Chemother. 2022 Feb;28(2):170-175.

89. Uechi K, Tada T, Shimada K. et al. A Modified Carbapenem Inactivation Method, CIMTris, for Carbapenemase Production in Acinetobacter and Pseudomonas Species. J Clin Microbiol. 2017 Dec;55(12):3405-3410.

90. Sho Nishimura. Treatment of CRE (5) [in Japanese]. J-IDEO. 2020;4(5):758-771.

91. Pogue JM, Kaye KS, Veve MP. et al. Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant Pseudomonas aeruginosa. Clin Infect Dis. 2020 Jul;71(2):304-310.

92. Motsch J, Murta de Oliveira C, Stus V. et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections. Clin Infect Dis. 2020 Apr;70(9):1799-1808.

93. Karlowsky JA, Lob SH, Raddatz J. et al. In Vitro Activity of Imipenem/Relebactam and Ceftolozane/Tazobactam Against Clinical Isolates of Gram-negative Bacilli With Difficult-to-Treat Resistance and Multidrug-resistant Phenotypes-Study for Monitoring Antimicrobial Resistance Trends, United States 2015-2017. Clin Infect Dis. 2021 Jun;72(12):2112-2120.

94. Sho Nishimura. No one tells you when to use ZERBAXA [in Japanese]. J-IDEO. 2019;3 (4):582-593.

95. Karlowsky JA, Lob SH, DeRyke CA. et al. In Vitro Activity of Ceftolozane-Tazobactam, Imipenem-Relebactam, Ceftazidime-Avibactam, and Comparators against Pseudomonas aeruginosa Isolates Collected in United States Hospitals According to Results from the SMART Surveillance Program, 2018 to 2020. Antimicrob Agents Chemother. 2022 May;66(5):e0018922.

96. Hart DE, Gallagher JC, Puzniak LA, Hirsch EB, C/T Alliance to deliver Real-world Evidence (CARE). A Multicenter Evaluation of Ceftolozane/Tazobactam Treatment Outcomes in Immunocompromised Patients With Multidrug-Resistant Pseudomonas aeruginosa Infections. Open Forum Infect Dis. 2021 Mar;8(3):ofab089.

97. Corbella L, Boan J, San-Juan R. et al. Effectiveness of ceftazidime-avibactam for the treatment of infections due to Pseudomonas aeruginosa. Int J Antimicrob Agents. 2022 Feb;59(2):106517.

98. Stone GG, Newell P, Gasink LB. et al. Clinical activity of ceftazidime/avibactam against MDR Enterobacteriaceae and Pseudomonas aeruginosa: pooled data from the ceftazidime/avibactam Phase III clinical trial programme. J Antimicrob Chemother. 2018 Sep;73(9):2519-2523.

99. Bassetti M, Echols R, Matsunaga Y. et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis. 2021 Feb;21(2):226-240.

100. Satlin MJ, Simner PJ, Slover CM, Yamano Y, Nagata TD, Portsmouth S. Cefiderocol Treatment for Patients with Multidrug- and Carbapenem-Resistant Pseudomonas aeruginosa Infections in the Compassionate Use Program. Antimicrob Agents Chemother. 2023 Jul;67(7):e0019423.

101. Timsit JF, Paul M, Shields RK. et al. Cefiderocol for the Treatment of Infections Due to Metallo-B-lactamase-Producing Pathogens in the CREDIBLE-CR and APEKS-NP Phase 3 Randomized Studies. Clin Infect Dis. 2022 Sep;75(6):1081-1084.

102. Gill CM, Aktas E, Alfouzan W. et al. Elevated MICs of Susceptible Antipseudomonal Cephalosporins in Non-Carbapenemase-Producing, Carbapenem-Resistant Pseudomonas aeruginosa: Implications for Dose Optimization. Antimicrob Agents Chemother. 2021 Oct;65(11):e0120421.

103. Bauer KA, West JE, O'Brien JM, Goff DA. Extended-infusion cefepime reduces mortality in patients with Pseudomonas aeruginosa infections. Antimicrob Agents Chemother. 2013 Jul;57(7):2907-2912.

104. Lodise TP, Jr., Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis. 2007 Feb;44(3):357-363.

105. Hong LT, Downes KJ, FakhriRavari A. et al. International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: Endorsed by the American College of Clinical Pharmacy, British Society for Antimicrobial Chemotherapy, Cystic Fibrosis Foundation, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America, Society of Critical Care Medicine, and Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2023 Aug;43(8):740-777.

106. Ramsey C, MacGowan AP. A review of the pharmacokinetics and pharmacodynamics of aztreonam. J Antimicrob Chemother. 2016 Oct;71(10):2704-2712.

107. Moriyama B, Henning SA, Childs R. et al. High-dose continuous infusion beta-lactam antibiotics for the treatment of resistant Pseudomonas aeruginosa infections in immunocompromised patients. Ann Pharmacother. 2010 May;44(5):929-935.

108. Vinks AA, van Rossem RN, Mathot RA, Heijerman HG, Mouton JW. Pharmacokinetics of aztreonam in healthy subjects and patients with cystic fibrosis and evaluation of dose-exposure relationships using monte carlo simulation. Antimicrob Agents Chemother. 2007 Sep;51(9):3049-3055.

109. Peleg AY, Seifert H, Paterson DL. Acinetobacter baumannii: emergence of a successful pathogen. Clin Microbiol Rev. 2008 Jul;21(3):538-582.

110. Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and Pathophysiological Overview of Acinetobacter Infections: a Century of Challenges. Clin Microbiol Rev. 2017 Jan;30(1):409-447.

111. Karageorgopoulos DE, Falagas ME. Current control and treatment of multidrug-resistant Acinetobacter baumannii infections. Lancet Infect Dis. 2008 Dec;8(12):751-762.

112. Falagas ME, Karveli EA, Kelesidis I, Kelesidis T. Community-acquired Acinetobacter infections. Eur J Clin Microbiol Infect Dis. 2007 Dec;26(12):857-868.

113. Asai N, Sakanashi D, Suematsu H. et al. Clinical manifestations and risk factors of community-onset Acinetobacter species pneumonia in Japan; case control study in a single institute in Japan. J Infect Chemother. 2019 Aug;25(8):639-642.

114. WHO priority pathogens list for R&D of new antibiotics. 2017. at https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed.)

115. Outbreak of multi-drug resistant Acinetobacter baumannii infections in ICU associated with an index case came back from Korea. IASR Vol.31,No.7 (No.365) July 2010 p.197-198 [In Japanese].at http://idsc.nih.go.jp/iasr/31/365/dj3654.html.)

116. Tojo M, Mawatari M, Hayakawa K. et al. Multidrug-resistant Acinetobactor baumannii isolated from a traveler returned from Brunei. J Infect Chemother. 2015 Mar;21(3):212-214.

117. Guidance on measures to prevent the introduction of highly drug-resistant bacteria from abroad in healthcare institutions., DCC. 2019. at https://dcc.ncgm.go.jp/prevention/resource/resource05.pdf.)

118. Ministry of Health, Labour and Welfare. Drug-resistant *Acinetobacter* infections. at https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-05-140912-4.html.)

119. Wisplinghoff H, Edmond MB, Pfaller MA, Jones RN, Wenzel RP, Seifert H. Nosocomial bloodstream infections caused by Acinetobacter species in United States hospitals: clinical features, molecular epidemiology, and antimicrobial susceptibility. Clin Infect Dis. 2000 Sep;31(7):690-697.

120. Martin-Aspas A, Guerrero-Sanchez FM, Garcia-Colchero F, Rodriguez-Roca S, Giron-Gonzalez JA. Differential characteristics of Acinetobacter baumannii colonization and infection: risk factors, clinical picture, and mortality. Infect Drug Resist. 2018 Jun;11:861-872.

121. Fishbain J, Peleg AY. Treatment of Acinetobacter infections. Clin Infect Dis. 2010 Jul;51(1):79-84.

122. Penwell WF, Shapiro AB, Giacobbe RA. et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in Acinetobacter baumannii. Antimicrob Agents Chemother. 2015 Mar;59(3):1680-1689.

123. Isler B, Doi Y, Bonomo RA, Paterson DL. New Treatment Options against Carbapenem-Resistant Acinetobacter baumannii Infections. Antimicrob Agents Chemother. 2019 Dec;63(1):e01110-18.

124. Chang YY, Yang YS, Wu SL. et al. Comparison of Cefepime-Cefpirome and Carbapenem Therapy for Acinetobacter Bloodstream Infection in a Multicenter Study. Antimicrob Agents Chemother. 2020 May;64(6):e02392-19.

125. Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. Carbapenem-resistant Acinetobacter baumannii: in pursuit of an effective treatment. Clin Microbiol Infect. 2019 Aug;25(8):951-957.

126. Ritchie DJ, Garavaglia-Wilson A. A review of intravenous minocycline for treatment of multidrug-resistant Acinetobacter infections. Clin Infect Dis. 2014 Dec;59 Suppl 6:S374-80.

127. Durante-Mangoni E, Signoriello G, Andini R. et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. Clin Infect Dis. 2013 Aug;57(3):349-358.

128. Park HJ, Cho JH, Kim HJ, Han SH, Jeong SH, Byun MK. Colistin monotherapy versus colistin/rifampicin combination therapy in pneumonia caused by colistin-resistant Acinetobacter baumannii: A randomised controlled trial. J Glob Antimicrob Resist. 2019 Jun;17:66-71.

129. Kaye KS, Marchaim D, Thamlikitkul V, et al. Colistin Monotherapy versus Combination Therapy for Carbapenem-Resistant Organisms. NEJM Evid 2023;2.

130. Aydemir H, Akduman D, Piskin N. et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. Epidemiol Infect. 2013 Jun;141(6):1214-1222.

131. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother. 2014 Sep;58(9):5598-5601.

132. Perez F, Adachi J, Bonomo RA. Antibiotic-resistant gram-negative bacterial infections in patients with cancer. Clin Infect Dis. 2014 Nov;59 Suppl 5:S335-9.

133. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: a systematic review and network meta-analysis. J Antimicrob Chemother. 2018 Jan;73(1):22-32.

134. Chen H, Liu Q, Chen Z, Li C. Efficacy of sulbactam for the treatment of Acinetobacter baumannii complex infection: A systematic review and meta-analysis. J Infect Chemother. 2017 May;23(5):278-285.

135. Jaruratanasirikul S, Wongpoowarak W, Aeinlang N, Jullangkoon M. Pharmacodynamics modeling to optimize dosage regimens of sulbactam. Antimicrob Agents Chemother. 2013 Jul;57(7):3441-3444.

136. Jaruratanasirikul S, Wongpoowarak W, Wattanavijitkul T. et al. Population Pharmacokinetics and Pharmacodynamics Modeling To Optimize Dosage Regimens of Sulbactam in Critically Ill Patients with Severe Sepsis Caused by Acinetobacter baumannii. Antimicrob Agents Chemother. 2016 Nov;60(12):7236-7244.

137. Brooke JS. Stenotrophomonas maltophilia: an emerging global opportunistic pathogen. Clin Microbiol Rev. 2012 Jan;25(1):2-41.

138. Brooke JS. Advances in the Microbiology of Stenotrophomonas maltophilia. Clin Microbiol Rev. 2021 Jul;34(3):e0003019.

139. Safdar A, Rolston KV. Stenotrophomonas maltophilia: changing spectrum of a serious bacterial pathogen in patients with cancer. Clin Infect Dis. 2007 Dec;45(12):1602-1609.

140. Kim SH, Cha MK, Kang CI. et al. Pathogenic significance of hemorrhagic pneumonia in hematologic malignancy patients with Stenotrophomonas maltophilia bacteremia: clinical and microbiological analysis. Eur J Clin Microbiol Infect Dis. 2019 Feb;38(2):285-295.

141. Araoka H, Fujii T, Izutsu K. et al. Rapidly progressive fatal hemorrhagic pneumonia caused by Stenotrophomonas maltophilia in hematologic malignancy. Transpl Infect Dis. 2012 Aug;14(4):355-363.

142. EUCAST Clinical Breakpoints v 13.0.

143. Cairo J, Hachem R, Rangaraj G, Granwehr B, Raad I. Predictors of catheter-related gram-negative bacilli bacteraemia among cancer patients. Clin Microbiol Infect. 2011 Nov;17(11):1711-1716.

144. Mojica MF, Humphries R, Lipuma JJ. et al. Clinical challenges treating Stenotrophomonas maltophilia infections: an update. JAC Antimicrob Resist. 2022 May;4(3):dlac040.

145. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. JAMA Intern Med. 2017 Sep;177(9):1308-1315.

146. Cho SY, Kang CI, Kim J. et al. Can levofloxacin be a useful alternative to trimethoprim-sulfamethoxazole for treating Stenotrophomonas maltophilia bacteremia? Antimicrob Agents Chemother. 2014;58(1):581-3.

147. Nys C, Cherabuddi K, Venugopalan V, Klinker KP. Clinical and Microbiologic Outcomes in Patients with Monomicrobial Stenotrophomonas maltophilia Infections. Antimicrob Agents Chemother. 2019 Oct;63(11):e00788-19.

148. Shah MD, Coe KE, El Boghdadly Z. et al. Efficacy of combination therapy versus monotherapy in the treatment of Stenotrophomonas maltophilia pneumonia. J Antimicrob Chemother. 2019 Jul;74(7):2055-2059.

149. Yoshikazu Ishii. Antibiotic susceptibility testing and breakpoint ―Their problems and future prospects ― [In Japanese]. Japanese Journal of Chemotherapy. 2011;59(5):454-459.

150. Magill SS, O'Leary E, Janelle SJ. et al. Changes in Prevalence of Health Care-Associated Infections in U.S. Hospitals. N Engl J Med. 2018 Nov;379(18):1732-1744.

151. Marra AR, Perencevich EN, Nelson RE. et al. Incidence and Outcomes Associated With Clostridium difficile Infections: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Jan;3(1):e1917597.

152. Kato H, Senoh M, Honda H. et al. Clostridioides (Clostridium) difficile infection burden in Japan: A multicenter prospective study. Anaerobe. 2019Dec;60:102011.

153. Lessa FC, Mu Y, Bamberg WM. et al. Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015 Feb;372(9):825-834.

154. Kociolek LK, Gerding DN, Carrico R. et al. Strategies to prevent Clostridioides difficile infections in acute-care hospitals: 2022 Update. Infect Control Hosp Epidemiol. 2023 Apr;44(4):527-549.

155. Japanese Clinical Practice Guidelines for Management of Clostridioides (Clostridium) difficile infection 2022. Committee for development of the Japanese Clinical Practice Guidelines for Management of Clostridioides(Clostridium)difficile infection by the Japanese Society of Chemotherapy and Japanese Association for Infectious Diseases,ed. [In Japanese]. at https://www.kansensho.or.jp/uploads/files/guidelines/guideline_cdi_230125.pdf.)

156. Keessen EC, Hensgens MP, Spigaglia P. et al. Antimicrobial susceptibility profiles of human and piglet Clostridium difficile PCR-ribotype 078. Antimicrob Resist Infect Control. 2013 Apr;2:14.

157. Privitera G, Scarpellini P, Ortisi G, Nicastro G, Nicolin R, de Lalla F. Prospective study of Clostridium difficile intestinal colonization and disease following single-dose antibiotic prophylaxis in surgery. Antimicrob Agents Chemother. 1991 Jan;35(1):208-210.

158. Finn E, Andersson FL, Madin-Warburton M. Burden of Clostridioides difficile infection (CDI) - a systematic review of the epidemiology of primary and recurrent CDI. BMC Infect Dis. 2021 May;21(1):456.

159. van Prehn J, Reigadas E, Vogelzang EH. et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults. Clin Microbiol Infect. 2021 Dec;27 Suppl 2:S1-S21.

160. Polage CR, Gyorke CE, Kennedy MA. et al. Overdiagnosis of Clostridium difficile Infection in the Molecular Test Era. JAMA Intern Med. 2015 Nov;175(11):1792-1801.

161. Johnson S, Lavergne V, Skinner AM. et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021 Sep;73(5):755-757.

162. Figueroa I, Johnson S, Sambol SP, Goldstein EJ, Citron DM, Gerding DN. Relapse versus reinfection: recurrent Clostridium difficile infection following treatment with fidaxomicin or vancomycin. Clin Infect Dis. 2012 Aug;55 Suppl 2:S104-9.

163. Johnson S. Recurrent Clostridium difficile infection: causality and therapeutic approaches. Int J Antimicrob Agents. 2009 Mar;33 Suppl 1:S33-6.

164. Pepin J, Routhier S, Gagnon S, Brazeau I. Management and outcomes of a first recurrence of Clostridium difficile-associated disease in Quebec, Canada. Clin Infect Dis. 2006 Mar;42(6):758-764.

165. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol. 2002 Jul;97(7):1769-1775.

166. Okumura H, Fukushima A, Taieb V, Shoji S, English M. Fidaxomicin compared with vancomycin and metronidazole for the treatment of Clostridioides (Clostridium) difficile infection: A network meta-analysis. J Infect Chemother. 2020 Jan;26(1):43-50.

167. Tashiro S, Mihara T, Sasaki M. et al. Oral fidaxomicin versus vancomycin for the treatment of Clostridioides difficile infection: A systematic review and meta-analysis of randomized controlled trials. J Infect Chemother. 2022 Nov;28(11):1536-1545.

168. Probiotics revisited. JAMA. 2014 Nov;312(5):1796.

169. Clancy CJ, Nguyen MH. Diagnosing Invasive Candidiasis. J Clin Microbiol. 2018 Apr;56(5):e01909-17.

170. Calandra T, Roberts JA, Antonelli M, Bassetti M, Vincent JL. Diagnosis and management of invasive candidiasis in the ICU: an updated approach to an old enemy. Crit Care. 2016 May;20(1):125.

171. Bassetti M, Mikulska M, Viscoli C. Bench-to-bedside review: therapeutic management of invasive candidiasis in the intensive care unit. Crit Care. 2010;14(6):244.

172. Kullberg BJ, Arendrup MC. Invasive Candidiasis. N Engl J Med. 2015 Oct;373(15):1445-1456.

173. Jeffery-Smith A, Taori SK, Schelenz S. et al. Candida auris: a Review of the Literature. Clin Microbiol Rev. 2017 Nov;31(1):e00029-17.

174. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. beta-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis. 2011 Mar;52(6):750-770.

175. Onishi A, Sugiyama D, Kogata Y. et al. Diagnostic accuracy of serum 1,3-beta-D-glucan for pneumocystis jiroveci pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. J Clin Microbiol. 2012 Jan;50(1):7-15.

176. Koichiro Yoshida, Yoshihito Niki. Measurement of plasmaβ-D-glucan in diagnosis of invasive fungal infections [In Japanese]. J Jpn Soc Intensive Care Med. 2010;17:1-3.

177. Leon C, Ruiz-Santana S, Saavedra P. et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med. 2006 Mar;34(3):730-7.

178. The Japanese Society for Medical Mycology. Clinical Practice Guidelines for Diagnosis and Treatment of Invasive Candidiasis. [In Japanese]. Med Mycol J. 2013;54(2):147-251.

179. Pappas PG, Kauffman CA, Andes DR. et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb;62(4):e1-50.

180. Demir KK, Butler-Laporte G, Del Corpo O. et al. Comparative effectiveness of amphotericin B, azoles and echinocandins in the treatment of candidemia and invasive candidiasis: A systematic review and network meta-analysis. Mycoses. 2021 Sep;64(9):1098-1110.

181. Ishikane M, Hayakawa K, Kutsuna S, Takeshita N, Ohmagari N. The impact of infectious disease consultation in candidemia in a tertiary care hospital in Japan over 12 years. PLoS One. 2019 Apr;14(4):e0215996.

Manual of Antimicrobial Stewardship, 3rd Edition, published November 16, 2023

Published by: Division of Infectious Disease Prevention and Control, Department of Infectious Disease Prevention and Control, Public Health Bureau, Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-8916

Division of Infectious Disease Prevention and Control, Department of Infectious Disease Prevention and Control, Public Health Bureau, Ministry of Health, Labour and Welfare,
ed. Manual of Antimicrobial Stewardship. 3rd Edition. Tokyo: Division of Infectious Disease Prevention and Control, Department of Infectious Disease Prevention and Control, Public Health Bureau, Ministry of Health, Labour and Welfare; 2023