Appendix (Antimicrobial Stewardship in Inpatients)

(Written section in the main volume: p. 113-114)
13. Basic Principles for Infections in Inpatients > (1) Diagnostic and Therapeutic Processes > (v) Optimization of choice of antibacterial agents > 1) Timing of assessment of treatment effectiveness and culture results

<Evidence for improper administration in empiric therapy>

In empiric therapy, treatments may be initiated with no accurate understanding of what bacterium has infected a patient, or even whether the patient actually has a bacterial infection.[1] In some cases, antibacterial agents are administered for clinical conditions that do not require them, or which are inappropriate for the clinical conditions. One report indicated that approximately 20% of antibacterial agents were not required for inpatients,[2] while another report indicated that 30% of antibacterial agents were inappropriate.[3] In addition, a report from Japan also indicated that nearly 40% of antibacterial agents administered to inpatients were inappropriate in some way.[4]

(Written section in the main volume: p. 116-117)
13. Basic Principles for Infections in Inpatients > (1) Diagnostic and Therapeutic Processes > (vi) Duration of antimicrobial therapy > 1) Recent trends of the duration of antimicrobial therapy for the common infections during hospitalization

Table 1. Therapy Duration and Recent Trend for Commonly Encountered Infections (Including Points to Note)

Infection	Standard therapy duration	Short-term therapy duration	Points to note	References
Hospital-acquired pneumonia, including VAP	14-15 days	7-8 days	RCT for VAP due to *Pseudomonas aeruginosa*: Failed to show non-inferiority of an 8-day therapy to a 15-day therapy. The short-term therapy may not be indicated for severe or immunosuppressed cases, or in a case due to *Staphylococcus aureus*, resistant bacteria, etc.	5,6
Uncomplicated cystitis in women	3 (3-7) days	—	3 days for co-trimoxazole and fluoroquinolones; 3-7 days for β-lactams such as amoxicillin/clavulanate; a single dose for aminoglycosides	7
Uncomplicated pyelonephritis in women	10-14 days	5-7 days	Most of the evidence supporting the short-term therapy is derived from fluoroquinolones. The susceptibility rate of *E. coli* to fluoroquinolones/co-trimoxazole has been decreasing. The efficacy of a 7-day therapy with β-lactams would be expected since there is an overlap with uncomplicated gram-negative bacteremia.	7
Febrile UTI in men	14 days	—	Prostatitis: Some experts recommend a 3- to 4-week therapy. An RCT reported that a short-term therapy for 7 days showed inferiority to a 14-day therapy.	8
CAUTI	7-14 days	5 days for non-severe cases treated with levofloxacin A 7-day course shall be considered for therapy with intravenous β-lactams or oral antibacterial agents with excellent bioavailability, even if complicated by bacteremia.	The susceptibility rate of *E. coli* to fluoroquinolones/co-trimoxazole has been decreasing. A retrospective study using propensity score matching suggested that a 7-day therapy might be comparable to a 14-day therapy, if the therapy of complicated UTI associated with bacteremia, including CA-UTI treated by only intravenous β-lactams or oral antibacterial agents with excellent bioavailability, and that otherwise a 10-day therapy would be required.	9,10

Infection	Standard therapy duration	Short-term therapy duration	Points to note	References
Cellulitis	10 days	5-6 days	In general, necrotizing fasciitis and subcutaneous abscess require surgical intervention. For severe cases, an RCT showed that there was a significantly higher incidence of relapse after 90 days in the 6-day therapy group, compared with the 12-day therapy groups.	11,12
Uncomplicated CRBSI	CNS: 5-7 days *Enterococci*, gram-negative bacteria: 7-14 days *Staphylococcus aureus*, *Candida* spp.: At least 14 days after a negative blood culture	—	Fever resolution and negative blood culture within 72 hours, catheter removal, and the absence of infective endocarditis and pyogenic thrombophlebitis are assumed for the short-term therapy. The recommended duration of therapy for *Staphylococcus aureus* is a 4-week, in principle. However, the therapy duration can potentially be shortened to 14 days if all the following criteria, as well as the above assumptions are fulfilled: absence of specific underlying conditions such as diabetes mellitus and immunodeficiency; absence of intravascular artificial devices, and no findings suggestive of disseminated lesions.	13,14
Acute cholecystitis	7-14 days	Mild to moderate: 24 hours after cholecystectomy Severe: 4-7 days after cholecystectomy	Note that therapy for 14 days or longer is recommend when complicated with bacteremia due to gram-positive bacteria, such as *Enterococci* or *Streptococcus*. A 4- to 7-day therapy is recommended for mild cases, when gallbladder necrosis or emphysematous changes are observed during surgery.	15
Acute suppurative cholangitis	4-7 days	3-5 days	Observational studies and small-scale RCTs suggested the potential non-inferiority of a short-term therapy (3-5 days) to a long-term therapy. RCTs for further evaluation are ongoing.	15-17

Infection	Standard therapy duration	Short-term therapy duration	Points to note	References
Perforative peritonitis	10-15 days	4-8 days	A short-term therapy is considered when good source control can be achieved by surgery, etc. For cases with inadequate source control, the therapy duration should be comprehensively determined based on severity, changes in hemodynamics and findings on symptoms, results from imaging assessment, etc. There are no sufficient data on whether a short-term therapy can be indicated for immunocompromised cases, severe cases, or blood culture-positive cases with blood culture positivity.	18,19
Postoperative intra-abdominal infection with adequate drainage	10-15 days	4-8 days	Short-term therapy would be considered when good source control can be achieved by surgical intervention. There are no sufficient data on whether a short-term therapy can be indicated for immunocompromised cases, severe cases, or cases with blood culture positivity.	18,19
Postoperative intra-abdominal infection with inadequate drainage	Must be considered on a case-by-case basis	Not clear	The therapy duration should be comprehensively determined further based on severity, changes in hemodynamics and findings on symptoms, results from imaging assessment, etc.	—
Uncomplicated *Staphylococcus aureus* bacteremia	28-42 days after a negative blood culture	14 days after a negative blood culture	A short-term therapy can be considered if all of the items in "Separate volume 1. (1) *Staphylococcus aureus*, Treatment 3)" are fulfilled.	20
Uncomplicated gram-negative bacteremia (*Enterobacterales*)	10-14 days	7 days	Non-inferiority of a 7-day therapy to a 14-day therapy has been reported in several RCTs and meta-analyses.	21-24
Uncomplicated gram-negative bacteremia (glucose non-fermenting bacteria [e.g., *Pseudomonas aeruginosa*, *Acinetobacter*, etc.])	11-15 days (can be extended up to 21 days)	6-11 days	A retrospective study for uncomplicated bacteremia due to *Pseudomonas aeruginosa* suggested the potential non-inferiority of a short-term therapy to a long-term therapy. An RCT is ongoing for *Pseudomonas aeruginosa* bacteremia.	25-27

(Written section in the main volume: p. 119)
13. Basic Principles for Infections in Inpatients > (1) Diagnostic and Therapeutic Processes > (vi) Duration of antimicrobial therapy > 2) Essential concepts of determining the duration of antimicrobial therapy and some pitfalls > B) Conditions for indication of short-term therapy

<Supplementary evidence for short-term therapy of gram-negative bacteremia>

For applying the 7-day short-course therapy for gram-negative bacteremia, the case should achieve hemodynamical stability and defervescence by 48 hours prior to the discontinuation of the antimicrobial therapy.[28] Moreover, there is no consensual definition for "uncomplicated" bacteremia for gram-negative bacteria, and RCTs commonly excluded cases with severe immunodeficiency, bacteremia due to multiple bacteria, abscesses, and infective endocarditis, and some RCTs excluded bacteremia cases originated from pneumonia.[21,23,24]

(Written section in the main volume: p. 123)
13. Basic Principles for Infections in Inpatients > (2) Management > (i) Principles for confronting the cases with insufficient response to antimicrobial therapy > B) The process to differentiate the causes for insufficient response to the antimicrobial therapy

<Evidence supporting the principles for confronting the cases with insufficient response to treatment >

A study investing the causes of early treatment failure in the immunocompetent cases with community-acquired pneumonia, 238 (18%) of 1383 cases failed to achieve defervescence 48-72 hours after the initiation of antimicrobial therapy.[29] Among the 238 cases, only 81 cases (6%) needed antimicrobial changes or intervention like chest drainage (early treatment failure cases). In the 81 early treatment failure cases, 54 cases (67%) experienced disease progressions, such as worsening pneumonia or sepsis, despite of the appropriate antimicrobial therapy, 18 cases (22%) complicated with empyema. Furthermore, 52 early treatment failure cases with identified causative pathogens, inappropriate therapy was the cause of treatment failure in only 16 cases (31%). Among them, treatment failures were due to atypical pneumonia like legionellosis or tuberculosis in 12 cases, and only one case was attributable to antimicrobial resistance. In another study evaluating 71 cases of pneumonia in ICUs, 44 cases (62%) were determined to show an inadequate response. The causes of inadequate response were inappropriate antimicrobial treatment (23%), infectious complications other than pneumonia such as candidemia and catheter infection (16%), bacterial pneumonia due to other microorganisms (14%), complication by pulmonary empyema (14%), non-infectious causes (15%), and unidentified causes (36%).[30] However, it should be noted that these evidences are from relatively old literature and the epidemiology of antimicrobial resistance may be different from those in the current era.

Other than pneumonia, in a study evaluated 843 females with community-acquired uncomplicated acute pyelonephritis, fever resolution could not be achieved within 72 hours after the initiation of antimicrobial therapy in 29% of the cases. These cases were significantly more frequently accompanied with renal abscess or bacteremia than the cases achieving defervescence. However, there was no significant relationship with the inappropriate selection of antimicrobial agents.[31] In another instance, in a study evaluated the cases with CRBSI due to coagulase-negative staphylococci, 16% of cases did not improve 48 hours after catheter removal, and 83% and 7% were complicated with suppurative thrombophlebitis and remote abscess formation, respectively.[32]

(Written section in the separate volume: p. 5)
1. Microorganisms of Concern for Infections in Inpatients > (1) *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus* [MRSA])

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

According to the package inserts, the maximum doses are 5 g/day for cefazolin and 6 mg/kg for daptomycin. For cefazolin, in the examples of the examination results from the Health Insurance Claims Review and Reimbursement Services in Japan, it is indicated that "cefazolin sodium hydrate [injection]" will be acceptable for the review, in principle when "intravenously administered at 2 g/dose, every 8 hours" to "severe cases that meet the current indications."

(Written section in the separate volume: p. 6)
1. Microorganisms of Concern for Infections in Inpatients > (2) Enterococci (including vancomycin-resistant enterococci [VRE]) > Microbiological characteristics and diagnosis

<Resistance level by resistance type and susceptibility to each glycopeptide>

The VanA-, VanB-, VanD-, and VanM-types have high resistance. Normally, the VanA-type shows a high resistance to vancomycin and teicoplanin, while the VanB-type shows a high resistance to vancomycin but susceptibility to teicoplanin. The VanC-type shows a low resistance to vancomycin, but susceptibility to teicoplanin.

(Written section in the separate volume: p. 6-7)
1. Microorganisms of Concern for Infections in Inpatients > (2) Enterococci (including vancomycin-resistant enterococci [VRE]) > Treatment policy

<Evidence for daptomycin>

Although a high-dose (8-12 mg/kg) use is recommended for VRE bacteremia, especially for infective endocarditis, based on concerns regarding resistance induction, etc., a careful determination on a case-by-case basis and the required procedure must be conducted when using it at medical institutions, since this is an off-label dose.[33-35] Although little data has been obtained under actual clinical settings, it is considered that the combination use of daptomycin with other antibacterial agents such as β-lactams (ampicillin, etc.), aminoglycosides, and tigecycline enhances its antibacterial activity toward VRE.[36] One report indicated that treatment of VRE bacteremia with daptomycin alone microbiologically failed frequently, especially when the minimum inhibitory concentration (MIC) of daptomycin increased to 3-4 μg/mL, compared with the group with a low MIC.[1,37] Thus, combination use with other antibacterial agents such as ampicillin is recommended, especially for infective endocarditis, etc.

Table 2. Examples of Monotherapy to Treat VRE Bloodstream Infections (Excluding Infective Endocarditis)

According to the package insert of ampicillin, "The usual adult dose of 1-4 g (potency)/day divided into one or two doses is given as ampicillin dissolved in 100 to 500 mL of transfusion fluid, via intravenous infusion over 1-2 hours. In general, a higher dose than usual is used for sepsis, infective endocarditis, and purulent meningitis. The dose can increase

or decrease, depending on age and symptoms." It is described in the example of the review information, that " 'ampicillin sodium [injection]' is acceptable for the review, in principle, when 'intravenously administered at 2 g/dose, every 4 hours' for 'bacterial meningitis'."

The package insert of daptomycin describes that the indicated type of bacterium is "methicillin-resistant *Staphylococcus aureus* (MRSA) with a susceptibility to daptomycin," and "the usual adult dose is 6 mg/kg once daily, every 24 hours, by intravenous infusion over 30 minutes or slow-bolus intravenous injection" for sepsis and infective endocarditis.

(Written section in the separate volume: p. 8)
1. Microorganisms of Concern for Infections in Inpatients > (3) *Enterobacterales* > (i) Overview

Table 2. Example of *Enterobacterales*[38]

Order	Family	Genus	Example of predominant species
Enterobacterales	*Enterobacteriaceae*	*Escherichia*	*E. coli*
		Klebsiella	*K. pneumoniae*, *K. oxytoca*, *K. aerogenes*
		Enterobacter	*E. cloacae*
		Citrobacter, Salmonella, Shigella	*C. freundii*
	Morganellaceae	*Proteus*	*P. mirabilis, P. vulgaris*
		Morganella	*M. morganii*
		Providencia	*P. rettgeri, P. stuartii*
	Yersiniaceae	*Serratia*	*S. marcescens*
		Yersinia	
	Erwiniaceae, Budviciaceae, Hafniaceae, Pectobacteriaceae		

(Written section in the separate volume: p. 9-10)
1. Microorganisms of Concern for Infections in Inpatients > (3) *Enterobacterales* > (ii) ESBL-producing *Enterobacterales* > Treatment policy

<Existing evidence for therapeutic drugs>

A randomized control trial (the MERINO study) did not demonstrate the non-inferiority of tazobactam/piperacillin to carbapenem for bloodstream infections due to ESBL-producing *E. coli* (n = 328; 86%) or *K. pneumoniae* (n = 51; 13%).[39] Thus, the use of tazobactam/piperacillin is not recommended for patients with bloodstream infections due to ESBL-producing bacteria, in general.[40] However, it was found that β-lactamase (OXA-1)-producing bacteria other than ESBL account for nearly 70% of the ESBL-producing bacteria included in the MERINO trial, having potentially affected the efficacy of tazobactam/piperacillin. A previous study in Japan have shown a far lower frequency of OXA-1-producing strains among ESBL-producing *E. coli*.[1] In addition, in the MERINO trial, subgroup analyses of urinary tract-derived bloodstream infections or subgroup analyses after excluding strains with a tazobactam/piperacillin MIC>16 μg/mL did not reveal a significant difference in efficacy (30-day fatality rate) compared to meropenem.[42] Thus, it is not necessarily required to change to carbapenems for cases of urinary tract infection that have already showed a tendency toward improvement, cases of hepatobiliary disease that received drainage, etc. However, a careful determination is required on a case-by-case basis.

A previous observational study indicated the non-inferiority of cephamycins and oxacephems to carbapenems for bloodstream infections due to ESBL-producing *E. coli*.[43] However, since the cases with hematological malignancy and neutropenia were excluded from the analysis, and therefore the use of cephamycins should be avoided in such settings. An observational multi-center study also confirmed the non-inferiority, especially for urinary tract infections due to ESBL-producing *E. coli*.[44] Currently, an RCT for cefmetazole and carbapenems for bloodstream infections due to ESBL-producing *E. coli* is ongoing.[45] Conversely, a report from Japan showed an increase of AmpC-producing bacteria to which cefmetazole was ineffective when the MIC for *E. coli* is ≥16 μg/mL.[46] For ESBL-producing bacteria other than *E. coli*, there have been limited data indicating the clinical effectiveness of cefmetazole.

Table 3. Examples of the Treatment of ESBL-producing *Enterobacterales* Infections

In the package insert, the maximum dose of levofloxacin is 500 mg/dose, once a day for both oral dosing and intravenous infusion. The package inserts for co-trimoxazole (tablets) in Japan indicate that the therapeutic dose for general infections is 4 tablets per day (2 tablets/dose, twice a day). Intravenous infusion of co-trimoxazole is indicated for *pneumocystis* pneumonia only.

(Written section in the separate volume: p. 11)
1. Microorganisms of Concern for Infections in Inpatients > (3) *Enterobacterales* > (iii) AmpC-producing *Enterobacterales* > Microbiological diagnosis

< Method to differentiate plasmid-mediated AmpC-producing strain from and ESBL-producing strain>

A report in Japan indicated that the highest differential diagnostic potential was obtained when setting the screening criteria for plasmid-mediated AmpC production as MIC ≥16 μg/mL for cefmetazole and ≥4 μg/mL for flomoxef.[46] Thus, half or more of plasmid-mediated AmpC-producing strains may be overlooked when non-susceptibility to cefmetazole (≥32 μg/mL) is set as the criteria.

<Confirmation test for plasmid-mediated AmpC>

Confirmation tests include phenotyping and genetic tests. A phenotyping test presumes the presence of plasmid-mediated AmpC, based on hydrolysis of cephamycins or recovery of susceptibility to 3rd generation cephalosporins in the presence of an AmpC inhibitor (boronic acid, cloxacillin, etc.). On the other hand, it is also possible to confirm the presence of the plasmid-mediated AmpC gene via genetic tests such as PCR.

(Written section in the separate volume: p. 11-12)
1. Microorganisms of Concern for Infections in Inpatients > (3) *Enterobacterales* > (iii) AmpC-producing *Enterobacterales* > Treatment policy

<SDD>

Susceptible dose dependent (SDD) means a susceptible category where the clinical efficacy of an antimicrobial agent cannot be obtained by the usual dosage and administration, but can be expected when the dose and frequency are increased.[47]

<Pros and cons for the use of cefepime for chromosome-mediated AmpC-producing *Enterobacterales* for which the MIC of cefepime is in the SDD range (4-8 μg/mL)>

In an observational study in Taiwan comparing cefepime and carbapenems for the treatment of *Enterobacter cloacae* bacteremia,[48] it was reported that treatment with cefepime resulted in death in all cases with ESBL-producing strains (10/10 cases), while no deaths in cases with non-ESBL-producing strains (0/6 cases), when the MIC of cefepime was in the SDD range. Citing this data, The Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections by the Infectious Diseases Society of America (IDSA) [40] proposes to avoid the use of cefepime when the MIC is in the SDD range. In contrast, there was also a report indicating non-inferiority of the prognosis was not inferior, compared with carbapenems, even in the SDD range, when a high-dose/an extended infusion regimen was used.[49] In addition, when the MIC is in the SDD range, the frequency of ESBL-producing strains differs depending on geographic region, and few ESBL-producing strains are found in some regions.[50] Currently, the use of cefepime should be considered after excluding the potential for ESBL production by conducting at least a confirmation assay, when the MIC of cefepime is in the SDD range. In cases where a confirmation assay cannot be conducted, the use of cefepime must be considered carefully.

(Written section in the separate volume: p. 13)
Table 4. Treatment Examples for AmpC-producing *Enterobacterales* Infections

Table 3. Treatment Examples for AmpC-producing *Enterobacterales* Infections (Including Points to Note)[40]

Name of antibacterial agent	Recommended dose	Species with a relatively high risk of excessive production of AmpC (*E. cloacae*, *K. aerogenes*, *C. freundii*, etc.)	Species with a relatively low or unknown risk of excessive production of AmpC (*S. marcescens*, *M. morganii*, *P. rettgeri*, *H. alvei*, etc.)	Points to note
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 ¶[49,51]	○	○	When the MIC is in the SDD range (4-8 μg/mL), a phenotyping or a genetic test shall be conducted to confirm non-ESBL-producing strain. When ESBL production is confirmed, the use of cefepime shall be avoided.[48] Although there is no conclusion as to whether cefepime can be used when the MIC of the isolate is in the SDD range but not producing ESBL, it shall be administered at maximum dose (2 g every 8 hours) and with extended infusion regimen (administration over 3 hours per dose), when it is used.[49] Also, an extended infusion regimen shall be considered for severe cases. A maximum of 4 g/day is specified in the package insert

Name of antibacterial agent	Recommended dose	Species with a relatively high risk of excessive production of AmpC (*E. cloacae*, *K. aerogenes*, *C. freundii*, etc.)	Species with a relatively low or unknown risk of excessive production of AmpC (*S. marcescens*, *M. morganii*, *P. rettgeri*, *H. alvei*, etc.)	Points to note
Tazobactam/ piperacillin	Intravenous infusion, 4.5 g/dose, every 6 hours ¶[52]	▲	▲	Although there is no clinical rationale for an extended infusion, a meta-analysis in a clinical study of gram-negative rod infections (however, *P. aeruginosa* infection was the most common) which compared extended and usual infusion suggested the potential improvement of clinical prognosis by extended infusion.[53] Therefore, an extended infusion regimen where administration is conducted over 4 hours per dose should be considered. In the package insert, the recommended dose differs between diseases: a dose of 4.5 g/dose, every 6 hours is the dosage and administration for febrile neutropenia, while for pneumonia, the dose can be increased to 4.5 g/dose, every 6 hours, according to the symptoms and pathological conditions.
Meropenem	Intravenous infusion, 1 g/dose, every 8 hours	○	○	Previously, this was considered as the first line. However, it is preferable to develop a treatment strategy that preserves carbapenems in the current situation, where carbapenem-resistant gram-negative rods have become dominant in clinical practice. Therefore, the use should strictly be avoided if treatment with any other drug is available. An extended infusion regimen where administration is conducted over 3 hours per dose shall be considered for severe cases.
Levofloxacin	Intravenous infusion/oral administration, 500 (−750) mg/dose, every 24 hours ¶[54,55] Infusion duration: 500 mg over 1 hour and 750 mg over at least 90 minutes are indicated in the package insert by the FDA.	○	○	Due to the high oral bioavailability, switching to oral administration can be considered when conditions are stable.[40] Attention should be paid to convulsion development and QT prolongation in patients with serious heart disorders, or tendon ruptures in geriatrics. A maximum of 500 mg/dose, once a day is indicated in the package insert in Japan.

Name of antibacterial agent	Recommended dose	Species with a relatively high risk of excessive production of AmpC (*E. cloacae*, *K. aerogenes*, *C. freundii*, etc.)	Species with a relatively low or unknown risk of excessive production of AmpC (*S. marcescens*, *M. morganii*, *P. rettgeri*, *H. alvei*, etc.)	Points to note
Co-trimoxazole	Cystitis: <Oral dose> 2 tablets/dose (160 mg/dose as trimethoprim [80 mg tablets]), twice a day Other infections: <Oral dose> 2-4 tablets/dose (4-6 mg/kg/dose as trimethoprim [80 mg tablets]), twice a day ¶[55] <Intravenous infusion> 2-4 ampules (4-6 mg/kg/dose as trimethoprim [80 mg/ampule]), every 12 hours ¶	○	○	2 ampules (160 mg/dose as trimethoprim [80 mg/ampule]), every 12 hours is possible for cystitis. Due to the high oral bioavailability, switching to oral administration can be considered when conditions are stable.[40] Attention should be paid to the development of rash, impaired liver, and function and hematological disorder. In addition, attention should be paid to acute kidney injury and electrolyte abnormalities. No high dose of 12-15 ampules, as recommended for *pneumocystis* pneumonia and *S. maltpophilia* infection, is required. Thus, the incidence of adverse reactions can be decreased. An intravenous infusion of co-trimoxazole is administered after mixing 1 ampule (trimethoprim 80 mg) with 125 mL (or 75 mL when the transfusion fluid volume is restricted) of 5% glucose or physiological saline. The package inserts for co-trimoxazole (oral) in Japan indicate that the therapeutic dose for general infections is 4 tablets per day (2 tablets/dose, twice a day). Intravenous infusion is indicated for *Pneumocystis* pneumonia only.

Name of antibacterial agent	Recommended dose	Species with a relatively high risk of excessive production of AmpC (*E. cloacae*, *K. aerogenes*, *C. freundii*, etc.)	Species with a relatively low or unknown risk of excessive production of AmpC (*S. marcescens*, *M. morganii*, *P. rettgeri*, *H. alvei*, etc.)	Points to note
Amikacin	Cystitis: 15 mg/kg/dose Single intravenous infusion Other infections: intravenous infusion at an initial dose of 20 mg/kg, followed by TDM (peak/MIC: 8-10, trough concentration: <5 μg/mL)[40] See the Clinical Practice Guidelines for Therapeutic Drug Monitoring of Antimicrobial Agents 2022.[56]	○	○	Since there is limited clinical experience on aminoglycosides for non-UTI, with a potential for a worsened prognosis and an increased risk of kidney injury, at least, its monotherapy shall be avoided.[57] Among aminoglycosides, amikacin maintains susceptibility with the highest frequency.[58] However, tobramycin or gentamicin is available in a similar manner, if susceptibility is preserved. In the Clinical Practice Guidelines for Therapeutic Drug Monitoring of Antimicrobial Agents, the target trough concentration is <4 μg/mL for a 1-day single dose of AMK.[56] However, the target trough concentration was set at <5 μg/mL, according to the treatment guidelines by the IDSA.[40]

(Written section in the separate volume: p. 15-17)
1. Microorganisms of Concern for Infections in Inpatients > (3) *Enterobacterales* >
(iv) Carbapenem-resistant *Enterobacterales*

<Risk factors for CRE acquisition>

The risk factors for CRE acquisition (including both colonization and infection) include a history of overseas travel (especially, a history of local medical or antibacterial exposure), a history of broad-spectrum antibacterial agents (especially broad-spectrum β-lactams, including carbapenems and fluoroquinolones within the past 3 months), a history of extensive medical exposure (long-term hospitalization or institutionalization, use of medical devices such as a urinary tract or intravascular catheter, etc., a history of invasive procedures such as surgery and ventilator management), decreased ADL, and abundant comorbidities.[59,60] Especially in Japan, the frequency of carbapenemase-producing *Enterobacterales* (CPE) is low among CRE, and the IMP-type MBL accounts for 85% to 90% of CPE. Thus, a history of overseas travel is an important factor for CPE other than the IMP-type.

<Evidence for combination therapy for CRE infection>

Both in the Guidance for Treatment by the IDSA[40] and the European Society of Clinical Microbiology and the Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant gram-negative bacilli (endorsed by the European Society of Intensive Care Medicine), [61] combination therapies are not endorsed if susceptibility to novel β-lactams (including ceftazidime-avibactam, meropenem-vaborbactam, and cefiderocol, which were approved in 2015 onwards overseas, as well as relebactam/imipenem/cilastatin, which are available in Japan as of July 17, 2023) is confirmed and CRE is treated with these new drugs. However, the activity of any antibacterial agents alone, excluding cefiderocol, cannot be expected for the IMP-type MBL-producing CPE that is frequent in Japan. Thus, there is still debatable on the use of combination therapies. The ESCMID guidelines[61] conditionally recommend the treatment of severe cases of CRE infection for which these new drugs are not available with at least two conventional active antibacterial agents. On the other hand, monotherapy is recommended as a good practice statement for mild infection.

An observational study suggested a potential improvement of prognosis by including meropenem in a combination regimen, when the MIC of meropenem was ≤8 μg/mL,[62] especially for severe cases.[63] In a sub-analysis of only CRE bacteremia from two randomized controlled studies for carbapenem-resistant gram-negative rod infection, which compared combination therapy with colistin and meropenem and monotherapy with colistin,[64,65] it was indicated that mortality was numerically decreased by combination therapy in both of the studies, although there was no statistically significant difference, due to the small number of cases. However, it should be noted that the KPC-type of CPE infection accounts for the majority of CRE infections, which was the target in studies comparing combination therapy and monotherapy. Thus, unfortunately, there have been no studies for MBL-producing CPE infection, including the IMP-type, which is most common in Japan, comparing combination therapy and monotherapy.[66]

For novel β-lactams approved in 2014 onward overseas, monotherapies are recommended by the guidelines, since sufficient activity is expected for each monotherapy when susceptibility is confirmed as mentioned above. In fact, a meta-analysis for ceftazidime-avibactam, which has the highest use experience, indicated that there was no difference in the prognosis of CRE infection between monotherapy and combination therapy.[67,68] However, it should also be noted that the KPC-type CPE or non-CP-CRE

infection accounts for the majority of CRE infections. Unfortunately, the drugs with favorable activity as a monotherapy for MBL-producing CPE infection, including the IMP-type are limited to cefiderocol, among novel β-lactams. There have been no data for the question as to whether cefiderocol should be used as a monotherapy or combination therapy for CRE infection, including MBL-producing bacteria. However, in a phase 3 study of severe infection due to carbapenem-resistant gram-negative bacteria, comparing the conventional drugs and cefiderocol, the treatment was conducted by monotherapy (despite the fact that combination therapy was allowed) in 85% of cases in the cefiderocol group,[69] while the treatment was conducted by cefiderocol alone in 13/16 cases (81%), even for MBL-producing strains only.[70]

<Mechanism of carbapenem-resistance in non-CP-CRE>

Carbapenem-resistance can be developed through additive and synergistic resistance mechanisms, including the production of broad-spectrum β-lactamases such as AmpC and ESBL, as well as reduced outer membrane permeability to β-lactams, even when carbapenemases are not produced. At least 80% of CREs detected in Japan are due to these mechanisms, as mentioned above.

(Written section in the separate volume: p. 17)
Table 6. Treatment Examples for Carbapenem-resistant *Enterobacterales* Infections

Table 4. Treatment Examples for Carbapenem-resistant *Enterobacterales* Infections (Including Points to Note)[40]

Name of antibacterial agent	Recommended dose (for patients with normal hepatic and renal functions)	Activity *in vitro*		Points to note
		Non-CP-CRE	CPE (assuming the IMP-type)	
Levofloxacin	See the section on AmpC-producing *Enterobacterales*	○	○	If susceptibility is confirmed, the efficacy can be expected in a manner similar to carbapenem-susceptible *Enterobacterales* infection. Due to high oral bioavailability, switching to oral administration can be considered.[40] A maximum of 500 mg/dose, once a day is indicated in the package insert in Japan.
Co-trimoxazole	See the section on AmpC-producing *Enterobacterales*	○	○	If susceptibility is confirmed, the efficacy can be expected in a manner similar to carbapenem-susceptible *Enterobacterales* infection. Due to high oral bioavailability, switching to oral administration can be considered.[40] The package inserts for co-trimoxazole (oral) in Japan indicate that the therapeutic dose for general infections is 4 tablets per day (2 tablets/dose, twice a day). Intravenous infusion is indicated for *Pneumocystis* pneumonia only.
Amikacin	See the section on AmpC-producing *Enterobacterales*	○	○	Since there is limited clinical experience on aminoglycosides for non-UTI, with a potential for a worsened prognosis and an increased risk of kidney injury, at least, its monotherapy shall be avoided.[57] Among aminoglycosides, amikacin maintains susceptibility with the highest frequency.[71] Tobramycin and gentamicin can also be used if susceptibility is confirmed.

Name of antibacterial agent	Recommended dose (for patients with normal hepatic and renal functions)	Activity *in vitro*		Points to note
		Non-CP-CRE	CPE (assuming the IMP-type)	
Colistin	Intravenous infusion at a loading dose of 9 M units (equivalent to 300 mg), followed by 4.5 M units (equivalent to 150 mg)/dose, every 12 hours ¶ In the package insert in Japan, intravenous infusion at 1.25-2.5 mg/kg/dose over 30 minutes, twice a day is indicated.	○	○	This drug disappeared from the market in the 1980s due to major adverse events of renal toxicity and neurotoxicity. However, due to the appearance of multidrug-resistant gram-negative rod infection in the 2000s, to which only colistin has a preferable activity, it was re-approved as a last resort in 2015. Colistin shows an unstable blood concentration with a high risk of renal toxicity, compared with the same polypeptide, polymyxin B.[72] In addition, polypeptides show poor distribution in the lungs, and the combination use of inhalation therapy is preferable for respiratory tract infection, even when systemic administration is conducted.[73] However, only intravenous administration is available in Japan. Although there is no description in the package insert, a high-loading dose (300 mg) is recommended for the initial dose in the international guidelines, due to the unstable blood concentration.[73] Colistin should not be selected when there is a safer option.
Fosfomycin	Recommended dose overseas: intravenous infusion, 4 g/dose, every 6 hours, or 6 g/dose, every 8 hours ¶	○	○	Since there have been limited data for CRE infection, with a high risk for the development of resistance, its monotherapy should be avoided for non-UTI.[74] Although the maximum dose is 2-4 g in the package insert in Japan, this dose has not been evaluated in clinical studies for the treatment of CRE infection. However, attention should be paid to heart failure due to the sodium load, especially at high doses.[75] In the US, the oral products of fosfomycin are the option for the treatment of cystitis due to drug-resistant gram-negative rods. However, there is a difference in oral products between Japan (fosfomycin calcium) and the US (fosfomycin trometamol). Since the product used in Japan has low oral bioavailability and low distribution into the urinary tract, with poor clinical experience, this is not a therapeutic option for drug-resistant gram-negative rod infection.

Name of antibacterial agent	Recommended dose (for patients with normal hepatic and renal functions)	Activity *in vitro*		Points to note
		Non-CP-CRE	CPE (assuming the IMP-type)	
Tigecycline	Initial single-dose intravenous infusion at 100-200 mg, followed by 50-100 mg/dose, every 12 hours¶[76] Dose in the package insert: Single-dose intravenous infusion at 100 mg, followed by 50 mg/dose, every 12 hours, over 30-60 minutes[77]	○	○	Tigecycline is distributed into tissues immediately after administration, leading to an unstable blood concentration, with poor distribution into the urinary tract. Thus, it is not a therapeutic option for bloodstream infection or UTI (at least as a monotherapy).[40] A high dose of 100 mg/dose, every 12 hours is preferable for CRE infection (especially, pneumonia).[78]
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 ¶[65,79] (An extended infusion regimen where administration is conducted over 3 hours per dose shall be considered.) In the package insert, the above dose is indicated for purulent meningitis only.	▲	×	Most CREs, which are notified due to resistance to both imipenem and cefmetazole despite susceptibility to meropenem, based on the Infectious Diseases Control Law, are non-CP-CREs and maintain susceptibility to meropenem. If there is susceptibility to meropenem despite a lack of susceptibility to imipenem, an extended infusion regimen of meropenem (over 3 hours per dose) is a therapeutic option.[40] At least, its monotherapy should be avoided for CPE infection, even when there is susceptibility to meropenem.
Relebactam/ imipenem/ cilastatin	Intravenous infusion, 1.25 g/dose, every 6 hours (over 30 minutes per dose)	○	×	For non-CP-CRE infection, the susceptibility to relebactam/imipenem/cilastatin is frequently maintained.[80,81] However, since there is only limited clinical experience, this should not be selected when there is an option to select non-β-lactams for which there is more clinical experience. Due to limited stability at room temperature, an extended infusion regimen has not been established.

Name of antibacterial agent	Recommended dose (for patients with normal hepatic and renal functions)	Activity *in vitro*		Points to note
		Non-CP-CRE	CPE (assuming the IMP-type)	
Aztreonam	Intravenous infusion, 2 g/dose, every 8 hours (over 3 hours per dose) ¶[82] A maximum of 4 g/day is indicated in the package insert.	×	▲	Aztreonam has an *in vivo* activity toward MBL, including the IMP-type. However, most CPEs co-produce other broad-spectrum β-lactamases, including ESBL together with carbapenemases. Thus, aztreonam is hydrolyzed, resulting in the frequent development of resistance. Theoretically, the combination use of relebactam/imipenem/cilastatin with aztreonam can avoid the hydrolysis of aztreonam by inhibiting broad-spectrum β-lactamases including ESBL, allowing it to exhibit its activity toward MBL. In addition, there are reports of the *in vitro* inhibitory effect of combination therapy on MBL, with a focus on the NDM-type MBL.[83,84] However, there has been no clinical experience thus far. (The Guidance on Treatment by the IDSA recommends combination use with ceftazidime-avibactam in an extended infusion regimen over 3 hours, which is not available in Japan at the moment.) In the package insert of aztreonam, the maximum dose is 2-4 g/day. However, this dose has not been evaluated for MBL-producing bacterial infection.
Cefiderocol	Intravenous infusion, 2 g/dose, every 8 hours (over 3 hours per dose)	○	○	Only this antibacterial agent has an activity toward MBL as a monotherapy, and to preserve its activity for MBL, its use for other CPE and non-CP-CRE infections needs to be avoided.
Ceftadizime-Avibacatam	Intravenous infusion 2.5 g/dose, every 8 hours (over 3 hours per dose)	○	×	Combination use with aztreonam can avoid the hydrolysis of aztreonam by inhibiting broad-spectrum β-lactamases including ESBL (co-produced by CPE), allowing it to exhibit its activity toward MBL.

* For the use of tigecycline and colistin, the guideline for the proper use of each drug is published by the Japanese Society of Chemotherapy.[85,86]

(Written section in the separate volume: p. 21-22)
1. Microorganisms of Concern for Infections in Inpatients > (4) *Pseudomonas aeruginosa*

<Difference between drug-resistant *Pseudomonas aeruginosa*, as defined by the Infectious Diseases Control Law and world standard MDRP>

The cutoff value of the MIC for being judged as drug-resistant *Pseudomonas aeruginosa*, as defined by the Infectious Diseases Control Law, is based on the criteria used up to 2011 by the Clinical and Laboratory Standards Institute (CLSI), but differs from the current criteria.[87]

<Mechanism of β-lactam-resistance in *Pseudomonas aeruginosa* and epidemiology in Japan>

If *Pseudomonas aeruginosa* reveals carbapenem-resistance, one of the following mechanisms will be involved: 1) acquisition and production of carbapenemases, 2) decreased permeability due to deficiency/mutation of the outer membrane protein OprD, or 3) extracellular effusion from the cytoplasm due to excessive production/mutation of multidrug efflux pumps. The most common carbapenemase is the IMP-type,[88] and there have been additional reports on the VIM-[89] and GES-types.[90] However, carbapenemase-producing strains account for only 10% of carbapenem-resistant strains, as described in the main text.

<Evidence for novel β-lactams for drug-resistant *Pseudomonas aeruginosa* infection>

Highly resistant *Pseudomonas aeruginosa*, such as difficult-to-treat resistance *P. aeruginosa* (DTR-PA) were rarely included in the target population by phase 3 studies. This is due to difficulties in setting a comparator. In observational studies for post-market drug-resistant *Pseudomonas aeruginosa,* comparing the group mainly treated with colistin and aminoglycosides, and the group treated with tazobactam/ceftolozane (sample size for the tazobactam/ceftolozane group: approximately 82-100 cases), the tazobactam/ceftolozane group showed a higher clinical cure rate and lower incidence of kidney injury in both studies.[91,92] Whereas relebactam/imipenem/cilastatin continues to be highly positioned for the treatment of infection due to KPC-producing bacteria in the US, there is still limited treatment experience for drug-resistant *P. aeruginosa*, worldwide.[93] Accordingly, there have been no accumulated data on clinical efficacy comparing it with the conventional drugs (especially colistin and aminoglycosides), resistance development during treatment course, etc.

Table 5. Classification and Definition of Drug-resistant *Pseudomonas aeruginosa*

Classification	Definition
Difficult-to-treat resistant *Pseudomonas aeruginosa*: DTR-PA	*Pseudomonas aeruginosa* that is non-susceptible to all conventional β-lactams and fluoroquinolones
World standard multidrug-resistant *Pseudomonas aeruginosa*: MDRP[94]	Bacteria with non-susceptible antibacterial agents in ≥3 categories of the following eight categories: 1) combinations of anti-pseudomonal penicillins and β-lactamase inhibitors, 2) anti-pseudomonal cephalosporins, 3) anti-pseudomonal carbapenems, 4) monobactams (aztreonam), 5) anti-pseudomonal fluoroquinolones, 6) aminoglycosides, 7) fosfomycins (fosfomycin), and 8) polypeptides
Extensively drug-resistant *Pseudomonas aerugionsa*: XDR-PA	Bacteria with remaining susceptibility to all drugs in ≤2 categories of the above eight categories
Drug-resistant *Pseudomonas aeruginosa* defined by the Infectious Diseases Control Law	Bacteria that meet all of the following three criteria: MIC of imipenem ≥16 μg/mL, MIC of amikacin ≥32 μg/mL, and MIC of ciprofloxacin ≥4 μg/mL.

(Written section in the separate volume: p. 23)
Table 8. Treatment Examples for Carbapenem-resistant *Pseudomonas aeruginosa* Infections

Table 6. Treatment Examples for Carbapenem-resistant *Pseudomonas aeruginosa* Infections (Including Points to Note)[40]

Antibacterial agent class	Name of antibacterial agent	Recommended dose	Points to note
Conventional β-lactams	Ceftazidime	Intravenous infusion, 2 g/dose, every 8 hours ¶[95] Consider the 3-hour extended infusion for severe cases. A maximum of 4 g/day is indicated in the package insert. In the examples of the examination results from the Health Insurance Claims Review and Reimbursement Services in Japan, it is described that "'ceftazidime hydrate [injection]' is acceptable for the review, in principle, when 'intravenously administered at 2 g per dose, every 8 hours' for 'febrile neutropenia'."	When susceptibility to conventional β-lactams (i.e., tazobactam/piperacillin, ceftazidime, cefepime, and aztreonam) or fluoroquinolones is confirmed, these drugs, which have a narrower spectrum than carbapenems shall be selected on a high priority basis. Even in the cases with carbapenem resistance, if susceptibility to β-lactams is confirmed, a high-dose and an extended-infusion p regimen of these drugs can be used for treatment. However, treatment with novel β-lactams shall also be considered for severe cases and cases with inadequate control of the infection foci. Although the maximum dose of aztreonam is 4 g/day in the package insert, this dose has not been evaluated in clinical studies for the treatment of *Pseudomonas aeruginosa* infection.
	Cefepime	Intravenous infusion, 1-2 g/dose, every 8 hours ¶[51] Consider the 3-hour extended infusion for severe cases. A maximum of 4 g/day is indicated in the package insert.	
	Piperacillin	Intravenous infusion, 4 g/dose, every 6 hours Consider the 4-hour extended infusion for severe cases.[96] Package insert: 4 g (potency)/dose, 4 times a day, for refractory or severe cases	
	Tazobactam/ piperacillin	Intravenous infusion, 4.5 g/dose, every 6 hours ¶ Consider the 4-hour extended infusion for severe cases.[95,96] In the package insert, the recommended dose differs between diseases: a dose of 4.5 g/dose, every 6 hours is recommended for febrile neutropenia and severe pneumonia	
	Aztreonam	Intravenous infusion, 2 g/dose, every 8 hours ¶[97,98] A maximum of 4 g/day is indicated in the package insert. Consider the 3-hour extended infusion for severe cases.[82,99]	

Antibacterial agent class	Name of antibacterial agent	Recommended dose	Points to note
Fluoroquinolones	Levofloxacin	See the section on AmpC-producing *Enterobacterales*	Considering the development of drug resistance is less frequent in ciprofloxacin compared with levofloxacin[100] and the narrower activity toward gram-positive cocci, the use of ciprofloxacin should be prioritized for the infection due to *Pseudomonas aeruginosa* alone Although the maximum dose of ciprofloxacin, as an intravenous infusion and oral administration is 600-800 mg/day according to the package insert, the evaluation of this dose is extremely limited in clinical studies for the treatment of *Pseudomonas aeruginosa* infection.
	Ciprofloxacin	Cystitis: 400 mg/dose, every 12 hours by intravenous infusion over 1 hour, or orally at 500 mg/dose, every 12 hours ¶[55] Other infections: Intravenous infusion over 1 hour, 400 mg/dose, every 8 hours, or orally at 500-750 mg/dose, every 12 hours ¶[55] Package insert in Japan Intravenous infusion over 1 hour at 400 mg/dose, every 12 hours A dose increase is allowed every 8 hours, depending on the patient's condition. In the package insert, the indications of ciprofloxacin [injection] for adults are limited to sepsis, secondary infection due to trauma/thermal burn, operative wound, etc., pneumonia, peritonitis, cholecystitis, cholangitis, and anthrax. However, in the examples of the examination results from the Health Insurance Claims Review and Reimbursement Services in Japan, it is indicated that "ciprofloxacin [injection]" is acceptable for the review when prescribed for "secondary infection due to pyothorax/lung abscess/pulmonary suppuration/chronic respiratory disease," "pyrexia of unknown origin with reduced neutrophils," or "intrauterine infection." In the package insert, the dosage and administration of ciprofloxacin tablets is oral administration at 100-200 mg/dose, every 8-12 hours (dose increase/reduction is permitted, as appropriate).	
Novel β-lactams	Tazobactam/ ceftolozane	Cystitis: Intravenous infusion, 1.5 g/dose, every 8 hours (over 1 hour per dose) Other infections: Intravenous infusion, 1.5-3 g/dose, every 8 hours (over 1 hour per dose)	Based on the PK/PD theory, a high dose is recommended, especially for respiratory tract infection.[101]
	Relebactam/ imipenem/ cilastatin	Intravenous infusion, 1.25 g/dose, every 6 hours (over 30 minutes per dose)	Due to limited stability at room temperature, an extended infusion regimen has not been established.

Antibacterial agent class	Name of antibacterial agent	Recommended dose	Points to note
Aminoglycosides	Amikacin	See the section on AmpC-producing *Enterobacterales*	Since there is limited clinical experience on aminoglycosides for non-UTI, with a potential for a worsened prognosis and an increased risk of kidney injury, at least, its monotherapy shall be avoided.[57] Among aminoglycosides, amikacin maintains susceptibility with the highest frequency.[102] On the other hand, tobramycin has the highest anti-*Pseudomonas aeruginosa* activity.[103] Accordingly, tobramycin shall be assigned a high priority if susceptibility is confirmed.
	Tobramycin	Cystitis: Single-dose intravenous infusion, 5 mg/kg/dose Other infections: intravenous infusion at an initial dose of 7 mg/kg, followed by dose modification to achieve a peak/MIC of 8-10 and a trough concentration of <1 μg/mL.[40] See the Clinical Practice Guidelines for Therapeutic Drug Monitoring of Antimicrobial Agents 2022.[56]	
	Gentamicin	Cystitis: Single-dose intravenous infusion, 5 mg/kg/dose Other infections: intravenous infusion at an initial dose of 7 mg/kg, followed by dose modification to achieve a peak/MIC of 8-10 and a trough concentration of <1 μg/mL.[40] See the Clinical Practice Guidelines for Therapeutic Drug Monitoring of Antimicrobial Agents 2022.[56]	
Polypeptides	Colistin	See the section on CRE.	For precautions concerning adverse events and doses of colistin, see the section on CRE.

Table 7. Efficacy of Each Therapeutic Agent for MDRP and DTR-PA

Antibacterial agent	MDRP	DTR-PA
Ceftazidime	▲	×
Cefepime	▲	×
Tazobactam/piperacillin	▲	×
Aztreonam	▲	×
Levofloxacin	▲	×
Ciprofloxacin	▲	×
Tazobactam/ceftolozane	○	○
Relebactam/imipenem/cilastatin	○	○
Amikacin	▲	○
Tobramycin	▲	○
Gentamicin	▲	○
Colistin	○	○

(Written section in the separate volume: p. 25-26)
1. Microorganisms of Concern for Infections in Inpatients > (5) Other Gram-negative rods (glucose non-fermenting Gram-negative rods other than *P. aeruginosa*) > (i) *Acinetobacter* spp. (mainly *Acinetobacter baumannii*)

<Issues and mechanism of action for drug resistance in *Acinetobacter* spp.>

A. baumannii has abundant endogenous drug-resistance mechanisms, as well as the ability to acquire exogenous drug-resistance mechanisms. Therefore, its drug resistance is becoming an issue worldwide.[104] The most major issue is carbapenem-resistance. The World Health Organization categorizes carbapenem-resistant *Acinetobacter baumannii* (CRAB) as the most emergent "critical" bacterium among the drug-resistant bacteria, requiring urgent research and the development of novel antibacterial agents.[105] In a report estimating worldwide drug-resistant bacteria-related deaths in 2019, *Acinetobacter baumannii* is included in the top 6 bacteria with related deaths, with an estimated number of related deaths of approximately 420,000.[106]

CRAB has been distributed worldwide, the most problematic is the wide distribution in the Southeast Asia, the South Asia, the South America, and the Eastern Europe including Russia.[106-108] CRAB has been also the growing concerns in the Europe and the North America. In the clinical isolates of *A. baumannii*, the susceptibility rates to meropenem were 55.7% in the Europe and 88.8% in the North America in 1997-2000, however, in 2013-2016, which worsened to 13.7% and 54.5%, respectively.[107]

β-lactamases, especially oxacillinases (OXAs) are predominantly involved in carbapenem resistance, and OXA-23, -40/24, -51, and -58 are known to be predominant.[109-111] Among these, OXA-51 is normally located on chromosomes and expressed after the acquisition of an insertion sequence with promoter activity. In contrast, OXA-23, -40/24, and -58[40] are acquired and transmitted through plasmid. Metallo-β-lactamases (MBL) are also involved.[112] MBL can be disseminated across species,[113] and this is one of the dissemination mechanisms of carbapenem resistance. Mutations of penicillin-binding protein (PBP) 2, the reduction of porins in outer membrane, and the upregulation of drug-efflux pump may also attribute to carbapenem resistance in some cases.[112]

In Japan, the proportions of CRAB and multidrug resistant Acinetobacter (MDRA) have remained lower than those in other countries.[114] According to the data in 2021 by the Japan Nosocomial Infections Surveillance (JANIS), the non-susceptible rate to meropenem in detected *Acinetobacter* spp. was 1.7%, while the percentage of medical institutions isolating MDRA was 0.8%.[115] In Japan, it was reported that the acquired carbapenemases contained in CRAB were in the following order, from the highest: OXA-23, IMP, and OXA-51.[115]

<Considerations regarding microbiological testing>

The "multidrug-resistance" of *Acinetobacter* species in the Japanese Infectious Diseases Control Law is defined when the isolate is resistance to all the following three categories of antimicrobials: broad-spectrum beta-lactams (carbapenems), aminoglycosides, and fluoroquinolones. In detail, the isolates are determined as "multidrug-resistant" if the MIC values of the isolates satisfy all the following: ≥16 μg/mL for imipenem-cilastatin, ≥32 μg/mL for Amikacin, and ≥4 μg/mL for ciprofloxacin.[116] It should be noted that these cutoff values of MIC to determine drug resistance are based on the former CLSI standards used up to 2011, but differ from the current criteria (CLSI M100-S32).[87,117] Moreover, the criteria of MDRA in the JANIS are also different and defined when the MIC values of the isolates satisfy all the following: ≥16 μg/mL for imipenem-cilastatin, ≥32 μg/mL for Amikacin, and ≥4 μg/mL for ciprofloxacin or ≥8 μg/mL for levofloxacin (Japan Nosocomial

Infections Surveillance, Ministry of Health, Labor and Welfare: Determination criteria for drug-resistant bacteria [ver. 3.2]).[118]

<Existing evidence for therapeutic drugs>

Tetracyclines, colistin

Although tetracycline derivatives are relatively well tolerated, when the tetracycline derivatives are used for the treatment of severe *Acinetobacter* infections, there is a concern about their poor serum concentration due to the rapid tissue penetration and large distribution volumes.[119] Observation studies of tigecycline reported its inferior clinical response to other regimens.[120,121] Moreover, in a meta-analysis comparing the efficacy of tigecycline and other regimens for treating pneumonia cases due to MDRA, there reported no significant differences among both groups concerning the clinical efficacy and mortality, whereas, in the microbiological efficacy, tigecycline was significantly inferior to other regimens.[122] Furthermore, the CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) have not defined the breakpoint of susceptibility to tigecycline for *Acinetobacter* spp.[87,123] Therefore, the guidance for treatment by the IDSA indicates that minocycline is more preferable.[40] Colistin has concerns of a high incidence of kidney injury and a narrow therapeutic window, and these concerns are particularly problematic among the elderies.[124-126] Thus, a careful follow-up for renal function is required, especially in elderies.[126]

Combination therapy

Most randomized controlled trials (RCTs) have failed to show the superiority of combination therapy to monotherapy.[64,65,127-130] For example, there was no superiority of combination therapy with colistin and meropenem in two RCTs.[65] In addition, an RCT showing superiority was conducted unblinded, and the sample size was as relatively small as 39.[131] Moreover, although combination therapy with colistin (a polypeptide) is commonly used,[132] there is a great concern regarding adverse reactions, as mentioned above, and the optimal combination of antimicrobials for *Acinetobacter* infections remains unclear.

Unapproved drugs in Japan

Regarding unapproved drugs in Japan, cefiderocol[133-135] and eravacycline[136] are considered promising. However, there are insufficient clinical data regarding these drugs, and the accumulation of data is recquired.[137,138] In a phase 3 study of cefiderocol for carbapenem-resistant gram-negative bacteria infection, comparing it with other therapeutic drugs, it was reported that cases due to *Acinetobacter* spp. showed a higher 28-day mortality.[69] The guidelines by the ESCMID do not recommend its use due to the limited clinical data, although this is conditional.[61]

(Written section in the separate volume: p. 27)

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

In the Japanese domestic attached document of meropenem, the doses of 2 g q8h is only adapted for bacterial meningitis. In the Japanese domestic attached document, the daily maximum dose of cefepime is 4 g Regarding sulbactam-ampicillin, the IDSA guidance recommends the daily dose of 18-27 g,[40] while the daily maximum dose of the Japanese domestic attached document is 12 g. Moreover, the approved use of sulbactam-ampicillin in the Japanese domestic attached document doesn't include infections caused by *Acinetobacter* spp. In the examples of the examination results from the Health Insurance Claims Review & Reimbursement services in Japan, it is documented that "in principle, it passes the

examination when the injection form of sulbactam-ampicillin is intravenously administered for brain abscess in the dosage of 3 to 4.5 g q6h."

Note that the guidance for treatment by the IDSA recommends a dose of minocycline of 200 mg, every 12 hours,[40] which exceeds the maximum dose of 200 mg/day in the Japanese attached document.

In the Japanese attached document, the usage and dosage of tigecycline is described as follows; "in general, for adults, tigecycline is intravenously administered at the dosage of 100 mg as a drip infusion over 30 to 60 minutes for the first dose, followed by the dosages of 50 mg as a drip infusion over 30 to 60 minutes, every 12 hours."[86]

(Written section in the separate volume: p. 28-29)
1. Microorganisms of Concern for Infections in Inpatients > (5) Other Gram-negative rods (glucose non-fermenting Gram-negative rods other than *P. aeruginosa*) >
(ii) *Stenotrophomonas maltophilia*

<Considerations regarding microbiological testing>

The interpretation of the results of antimicrobial susceptibility tests of *S. maltophilia* needs cautions because it is reported that the lack of reproducibility of the antimicrobial susceptibility test for levofloxacin and ceftazidime when using disk methods, E-test and frequently used antimicrobial susceptibility testing.[144,145] In addition, it should be noted that drugs other than co-trimoxazole have insufficient data supporting the relationship between antimicrobial susceptibility results and their treatment outcomes.[40,146]

Moreover, it should be noted that *Stenotrophomonas maltophilia* is not detectable by some multiplex nuclear acid detecting assays, especially the equipment using the multiplex-PCR methods or microarray methods which were recently reimbursed by the national health insurance. For example, the Verigene gram-negative blood culture nucleic acid test and the FILMARRAY™ BCID Panel don't target *S. maltophilia*, whereas the BioFire® BCID2® Panel targets *S. maltophilia*.

<Mechanism of drug resistance>

S. maltophilia has two endogenous β-lactamases, known as L1 and L2.[139] L1 is a metallo-β-lactamase that can cleave broad-spectrum carbapenems (except for aztreonam), whereas L2 is a class A β-lactamase that can cleave broad-spectrum cephalosporins and aztreonam. For aminoglycosides, there are several mechanisms of drug resistance, including drug efflux pumps.[139] For fluoroquinolones, there are several mechanisms of drug resistance, such as the overexpression or mutation of drug efflux pumps and the overexpression of Smqnr, which protects DNA gyrase and topoisomerase IV, the targets of the fluoroquinolones.[140,141] For co-trimoxazole which is considered as the first-line, it is known that drug resistance is also developed by the overexpression of drug efflux pumps or the acquisition of resistance genes, *sul* and *dfrA*, in a class I integron via plasmid.[142,143]

<Existing evidence for therapeutic drugs>

Although no randomized controlled trials have been conducted, co-trimoxazole are broadly used as the first-line, due to endogenous drug resistance mechanisms for a variety of antimicrobials and abundant use experience on co-trimoxazole.[40,146] Although there is a concern regarding increased resistance to co-trimoxazole, an international study conducted at 259 participating sites from 1997 to 2016 reported that the susceptibility rate was 97.2% from 2001 to 2004, and 95.7% from 2013 to 2016, showing no significant worsening.[107] On the

other hand, there are concerns regarding adverse reactions of treatment with co-trimoxazole, such as kidney injury, liver injury, infusion volume overload in intravenous preparation, hyperkalemia, myelosuppression, and skin rash.[2,139] Other than co-trimoxazole, observational studies indicated clinical data showing the non-inferiority of fluoroquinolones, including levofloxacin,[147-149] and tetracyclines such as minocycline and tigecycline[150-152] to co-trimoxazole, if susceptible.

Among the non-approved drugs in Japan, cefiderocol,[135,153] eravacycline,[150,154] and combination therapy of ceftazidime/avibactam with aztreonam[150,155-157] are considered promising. However, there has been no sufficient accumulation of clinical data. Thus, co-trimoxazole remains the current first-line for *S. maltophilia* infections.[40]

(Written section in the separate volume: p. 31-32)
1. Microorganisms of Concern for Infections in Inpatients > (6) *Clostridioides difficile* > Treatment policy

Table 8. Treatment Examples for CDI[158-160]

Drug	Dose	Points to note
Non-severe/non-fulminant case (first time)		
Fidaxomicin	Oral administration, 200 mg/dose, every 12 hours, for 10 days	First-line in the guidelines in Europe and the US. There is no difference in the cure rate with vancomycin. However, the recurrence rate is lower than vancomycin. Thus, this is recommended for cases with a high risk of recurrence in the Japanese guidelines. Its reimbursement price (8,024 yen/day as of March 2023) is higher than that of vancomycin (910 yen/500 mg).
Vancomycin	Oral administration, 125 mg/dose, every 6 hours, for 10 days	This is an option for cases with a low risk of recurrence, since there is no difference in cure rate from fidaxomicin.
Metronidazole	Oral administration, 500 mg/dose, every 8 hours, for 10 days	Although this is considered for mild cases with no risk of recurrence, the guidelines in Europe and the US consider it to be a regimen when the two drugs above are not available.
Non-severe/non-fulminant case (first recurrence)		
Fidaxomicin	Oral administration, 200 mg/dose, every 12 hours, for 10 days	
Vancomycin	Oral administration, 125 mg/dose, every 6 hours, for 10 days	
Vancomycin	Pulse/taper dose therapy	This is described in the guidelines in Europe and the US. There is difficulty completing the treatment. One of the regimens is shown below (oral dose). 125 mg/dose, 4 times a day, for 10-14 days → 125 mg/dose, twice a day, for 1 week → 125 mg/dose, once a day, for 1 week → 125 mg/dose, once every 2-3 days, for 2-8 weeks
Non-severe/non-fulminant case (second recurrence, refractory cases)		
Fidaxomicin	Oral administration, 200 mg/dose, every 12 hours, for 10 days	
Vancomycin	Pulse/taper dose therapy	
Severe case		
Vancomycin	Oral administration, 125 mg/dose, every 6 hours	
Fidaxomicin	Oral administration, 200 mg/dose, every 12 hours, for 10 days	

Drug	Dose	Points to note
Fulminant case		
Vancomycin + metronidazole	Oral administration, 500 mg/dose, every 6 hours + intravenous infusion, 500 mg/dose, every 8 hours (intravenous infusion over at least 20 minutes), for 10-14 days	The guidelines in the US describe the rectal administration of vancomycin for ileus. The guidelines by the ESCMID do not recommend additional intravenous metronidazole. Thus, this regimen is controversial as an option.
Fidaxomicin	Oral administration, 200 mg/dose, every 12 hours, for 10 days	Described in the guidelines by the ESCMID.

<Treatment of CDI in the case when discontinuation of antibacterial agents is difficult>

Although there is little data, the following examples are proposed.[161]

Evaluate the necessity of antibacterial agents except for the treatment of CDI and except for the treatment of switch to an antibacterial agent with a low risk for CDI.

PPIs (proton pump inhibitors) shall be discontinued if possible.

Do not treat with metronidazole (treatment failure and increased 30-day mortality have been reported).

The reported drugs with a high risk for CDI include fluoroquinolones, clindamycin, broad-spectrum penicillins, 2nd generation or later cephalosporins, and carbapenems.[162]

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