


Optimizing Antimicrobial Use in Japan: Strategies for Dosage, Combination Therapy, De-Escalation, Oral Switching, Duration, and Guideline Adherence

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Abstract: Antimicrobial stewardship has gained momentum in Japan, prompting the adoption of various strategies to optimize antimicrobial use. Key recommendations include individualized dosing, dosing intervals, and treatment regimens tailored to the patient's condition, causative pathogens, and affected organs. Combination therapy is advised for empiric treatment of severe infections and suspected multidrug-resistant organisms. Early initiation of antimicrobial therapy followed by de-escalation may enhance clinical outcomes and reduce resistance development. Additionally, while clear criteria for intravenous-to-oral switch therapy remain undefined, its implementation could play a crucial role in optimizing antimicrobial administration. The duration of therapy should be guided by disease pathophysiology rather than isolated inflammatory markers, including C-reactive protein, with adherence to established guidelines and clinical recommendations. These strategies have been incorporated at the bedside, and optimized antibiotics use are now advanced in Japan.

Keywords: antibiotics, combination therapy, de-escalation, optimization, switch therapy

Introduction

In Japan, in the spring of 2016, the government released an action plan to combat antimicrobial resistance (AMR), clearly stating that the country is proactively tackling resistant bacterial infections, which have become a global threat as same as other Group of seven developed countries.¹ “Appropriate use of antimicrobial agents” is one of the key pillars of the antimicrobial resistance measures, and the concept is important.

In Japan, compared with the other countries in the world, including United States, national health insurance system are applied for all residents in Japan generally, most of the people access to the clinic/hospitals easily, and may get the antibiotics relative inexpensively.^{2,3} In addition, isolated biomarkers, such as C-reactive protein (CRP), have been used to evaluate the inflammation status of the patients and considered more important rather than procalcitonin, the patients status, and guideline recommendation.⁴ Therefore, use of antibiotics might be different and misunderstanding for a long time, and most of the intravenous beta lactams had been used twice a day rather than three times a day although the patients showed the normal renal functions.⁴ Furthermore, antibiotics sometimes used for more than 20 days until CRP became negative although the 14 days are regular duration for the bacteremia patients in Japan. After the action plan 2016 released, antibiotics uses were reduced about 30%; however, antimicrobial resistances, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and fluoroquinolone-resistant Enterobacterial bacteria were not reduced until 2020.²

In the United States, CDC recommended the core elements of the antimicrobial stewardship program and recommend use of the guidelines modified to adapt the situation of each antibiotics use although about 30% of all antibiotics prescribed in US acute care hospitals are also either unnecessary or suboptimal.⁵

In this issue, specific antimicrobial use recommended in the “Guidance for Practice of Antimicrobial Appropriate Use Support Program” published in 2017 and revised in 2025 will be introduced.⁶

Review

Optimization of Dosage and Administration Intervals

Optimizing the dose, administration interval, type, and treatment regimen of selected antimicrobial agents based on the results of pharmacokinetic analysis of individual patient conditions, causative organisms, affected organs, and pharmacokinetics/pharmacodynamics (PK/PD) theory including therapeutic drug monitoring (TDM) is an important role of antimicrobial stewardship (AS) because it is highly likely to lead to clinical outcomes and reduction of healthcare costs. The dosage of antimicrobial agents varies greatly depending on patient background such as age, renal function, and weight, and even in the same individual, the dosage of the same antimicrobial agent may differ, not to mention the antimicrobial agent of choice, if the causative organism is different or the affected organ is different (for example, the recommended dosage of meropenem is different for pneumonia and meningitis).⁷

Furthermore, severe infections such as infective endocarditis and osteomyelitis require higher doses and longer duration of antimicrobial therapy.⁸ Reports from the US indicate that as a result of AST interventions in hospitalized patients, conversely, increased antimicrobial use, prolonged hospital stay, and increased prescribing at discharge were observed.^{9,10} Therefore, it is important to note that optimal treatment focused on patient prognosis does not necessarily result in reduced antimicrobial use. In addition, for some antimicrobial agents, including aminoglycosides and vancomycin (VCM), individualization of dosage and administration based on TDM can improve their therapeutic efficacy and reduce the risk of adverse drug reactions. These concepts and practices are particularly important in AS and are recommended (see TDM section).^{11,12}

Although computerized prescribing assistance to physicians has been shown to improve compliance with guidelines for antimicrobial dosing and reduce adverse drug reactions, it has been previously reported that there was no difference in treatment efficacy (clinical cure, in-hospital mortality, length of hospital stay, etc) and the relationship between pharmacokinetic monitoring and dose adjustment.^{13,14} The relationship between the program and the frequency of resistant bacteria in the facility has not yet been clearly demonstrated. On the other hand, there are reports that interventions by antimicrobial stewardship team (AST) on the content and dosage of carbapenems prescribed, mainly in hematology, can reduce the incidence of resistant bacteria, and that AST intervention (Infection control team: ICT consultation) in MRSA bacteremia was significantly correlated with improved prognosis.^{15,16} Further accumulation of evidence will be needed.

Combination Therapy as Optimal Treatment

The evidence that routine combination therapy reduces the risk of adverse reactions and the number of resistant organisms is not necessarily sufficient for common bacterial infections such as pneumonia.⁶ The significance of combination therapy is only to save lives, such as for empirical treatment for severe infections including septic patients who are in poor general condition and in whom infected with multi-drug resistant bacteria. The combination therapy is not necessarily sufficient for common bacterial infections such as septicemia. However, it should always be kept in mind to avoid inappropriate long-term use of broad-spectrum antimicrobial agents such as carbapenems as monotherapy.

The Significance of Combination Therapy in the First Place is as follows:

1. When the causative microorganism is unknown, a wider range of presumptive causative microorganisms can be covered.
2. Stronger antibacterial action against the causative microorganisms (including anti-inflammatory and immunological actions).
3. It Is Expected to Be Less Likely to Cause Bacterial Resistance and to Be More Effective Than Monotherapy.

With regard to (1), inappropriate initial treatment has previously been shown to significantly reduce survival (39% vs 24%), especially in ICU patients (42% vs 18%) in an analysis of a group of septic patients in whom the causative organism was subsequently identified.¹⁷ It was also recently reported that in cholangitis-derived bacteremia,

inappropriate initial antimicrobial selection was significantly associated with poor prognosis.¹⁸ Furthermore, in severe rickettsial infections, the need for broader-spectrum antimicrobials in the initial treatment phase has been suggested.¹⁹

Regarding (2), antimicrobial agents mainly inhibiting protein synthesis: macrolides have been reported to be effective in combination in severe pneumonia,^{20,21} and clindamycin in necrotizing fasciitis and gas gangrene has been recommended as potentially useful, even if the results do not necessarily agree with those of susceptibility studies.²²

As for (3), the basic concept of multidrug combination therapy in human immunodeficiency virus (HIV) infection and tuberculosis is representative. In infections with common bacteria, it has been reported that combination therapy including broad-spectrum antimicrobial agents may improve the prognosis of patients with severe infections and prevent the emergence of resistant bacteria, especially Extended Spectrum Beta-Lactamase (ESBL)-producing bacteria.¹⁷ In the case of resistant Gram-negative rods such as *Pseudomonas aeruginosa*, there have been relatively few reports of apparent inhibition of resistance by combination therapy, but it was reported that the combination therapy group did not correlate with improved prognosis in ventilator-associated pneumonia (VAP) involving *P. aeruginosa* compared to the monotherapy group, while the appearance of multidrug-resistant *P. aeruginosa* was significantly reduced.²³

It was reported that there was no difference in the incidence of resistant bacteria between aminoglycosides combined with β -lactams and β -lactams alone,²⁴ and that the combination of aminoglycosides or quinolones in *P. aeruginosa* did not significantly improve the outcome of treatment compared with β -lactams alone.²⁵ However, combination therapy in the treatment of infective endocarditis is well known, and the use of beta-lactams in combination with gentamicin or CTRX is recommended, especially with enterococci in mind.²⁶

In principle, anti-MRSA drugs should be used alone, but the efficacy of VCM, teicoplanin (TEIC), arbekacin (ABK), and daptomycin (DAP) in combination with β -lactams has been demonstrated in vitro and in vivo for MRSA infections with mixed infections, while further studies are needed to determine their clinical usefulness.^{27,28} Rifampicin (RFP) and Trimethoprim/sulfamethoxazole (ST) combination therapy for MRSA infection should not be used as monotherapy because of its susceptibility to resistance.^{29,30} Combination therapy with VCM and RFP may be used empirically, but should be considered carefully in each case, as there is no higher level of clinical evidence than for VCM monotherapy.³¹

Early Initiation and De-Escalation of Antimicrobials as Optimal Therapy

It goes without saying that antimicrobial agents should be started as early as possible. Usually, we collect as much information as possible to estimate the causative organisms, select the most appropriate antimicrobial agent, and start empiric therapy. Recently, even in sepsis, it is no longer necessary to administer antimicrobials within one hour of the start of treatment, as it used to be, but within three hours for sepsis without shock, and it is now recommended that treatment be initiated only after a thorough investigation into the cause and that unnecessary use of broad-spectrum antimicrobial agents be corrected.³² However, in patients at risk of severe disease due to underlying disease or immunosuppressive therapy (eg, suspected sepsis due to febrile neutropenia or suspected meningococcal infection during anticomplement therapy), it may be desirable to minimize testing, such as blood cultures, and start empirical therapy as early as possible.³³

On the other hand, optimization of antimicrobial regimens, ie, discontinuation of combination therapy and de-escalation of selective agents, by elimination of bacteria in bacterial cultures and improvement of systemic conditions, may lead to more efficient treatment of causative organisms and, consequently, to reduction of unnecessary use and cost of antimicrobial agents, as well as to reduction of resistant organisms. This is an important therapeutic concept especially in the treatment of severe infectious diseases such as sepsis in ICUs. In other words, more optimal antimicrobial therapy based on the results of laboratory tests and observation of clinical conditions is a desirable approach to reduce the possibility of development of bacterial resistance due to inappropriate or excessive long-term administration of broad-spectrum antimicrobial agents, provided that the patient's disease condition continues to improve.

De-escalation, including drug discontinuation, can be considered as one of the measures, and is relatively easy in infectious diseases such as VAP and bacteremia, where the identification and disappearance of the causative organism can be clearly observed, and is particularly effective in severe cases.^{13,33,34} Furthermore, among 625 patients with infectious diseases treated with combination therapy, 54% were switched to more optimal therapy including de-escalation within 7 months by intervention of an infectious disease physician or pharmacist, resulting in cost savings of more than

\$100,000, suggesting that from a health economic point of view, de-escalation is one of the most important concepts that should be actively practiced.³⁵

In addition, in our country, aspiration pneumonia is common among the elderly, and in cases such as MRSA pneumonia, combination therapy targeting resistant bacteria has little therapeutic effect and may instead increase the mortality rate due to side effects or problems with individual patients themselves and we refrain from it.^{36,37} Especially in clinical practice in the community, where many common infections such as healthcare- and nursing-related pneumonia occur, there is a movement to recommend starting treatment with a narrow-range antimicrobial agent and using a combination of antimicrobial agents while monitoring response, or escalating to a broader-range antimicrobial agent.^{22,38}

Finally, in viral infections such as influenza and COVID-19, aggressive and as early as possible use of antiviral drugs has been shown to improve clinical symptoms and prognosis and reduce sequelae, while in bacterial infections, early de-escalation and combination therapy have been observed to reduce the appearance of resistant strains.^{39–42} While early de-escalation and combination therapy have been observed to reduce the emergence of resistant strains and reduce healthcare costs, it has also been suggested that they may not necessarily lead to improved mortality.²³ Although early administration and early de-escalation as a principle of antimicrobial therapy is one of the important elements of AS, there still seem to be issues to be explored regarding its detailed methods, application, and its benefits.

Switch Therapy to Oral Drugs as Optimal Treatment

Although the specific criteria and methods of switch therapy are still unclear, a systematic changeover from injectable drugs to oral drugs as the patient's general condition improves, taking into account the bioavailability of antimicrobial agents, is likely to reduce hospital stays, costs, side effects, and complications associated with intravenous administration, and is an important issue for further study. This is an important issue for further study.^{38,43}

Some oral drugs, such as linezolid and tedizolid, have extremely high bioavailability and are comparable to intravenous drugs with the same medication, and from a health care economic perspective associated with price and length of hospital stay, the switch to oral drugs is desirable.⁴⁴ Even a switch from the relatively inexpensive intravenous VCM to the rather pricey oral linezolid has been reported to have resulted in cost savings of nearly \$300,000 per year due to early discharge from the hospital.⁴⁵

There are also reports that the therapeutic efficacy of intravenous and oral quinolones is not necessarily superior to that of intravenous.⁴⁶ Rather, as mentioned above, excessive prescription of oral quinolones in discharge prescriptions must be discouraged.¹⁰ However, recently, it was reported that 21784 (6%) of 378041 community-acquired pneumonia patients were switched early, most frequently to fluoroquinolones.⁴⁷ Patients switched early had fewer days on IV antibiotics, shorter duration of inpatient antibiotic treatment, shorter length of stay, and lower hospitalization costs, but no significant excesses in 14-day in-hospital mortality or late ICU admission. Switched patients received the “early de-escalation” such as within hospitalized day 3. Within 3 days switch from drip infusion to oral antibiotics might improve outcomes, and a part of “early de-escalation”. Furthermore, there have been a number of reports that blood levels of voriconazole and other drugs do not always reach the predicted levels when switching from intravenous to oral medication, and clinical data are being analyzed.⁵ These data were suggested the switch therapy might have benefit and considered as a part of the AS activity. There are several ways that antimicrobial stewardship practices can be implemented in the healthcare setting.⁴⁸

The criteria for switching from intravenous to oral medication have recently been recommended as follows⁴⁹

1. Clinical symptoms are improving.
2. The patient has maintained a fever of less than 38°C for 24 hours and has stable respiratory and circulatory status.
3. Infections requiring continued treatment with intravenous antibacterial agents (eg, meningitis, febrile neutropenia, infective endocarditis, etc).
4. It can be administered orally or by nasogastric tube and is expected to be absorbed adequately.
5. Appropriate oral antimicrobial options.
6. Patients are able to continue oral antimicrobials without self-interruption (in the case of outpatients), etc.

However, there is no clear evidence for any of the above, and it was suggested that no one intervention could be identified as the safest and most effective as most of the included studies used a bundle of interventions in the review reports.⁵⁰ All interventions resulted in optimizing antibiotic use and reducing health care expenditures without compromising the clinical outcomes in that review. The future study is an important issue to be considered in terms of guideline items.^{32,42–44}

Duration of Administration and Use of Various Guidelines

The duration of antimicrobial therapy depends on the disease state. For example, in the case of pneumonia, the standard treatment period is 5 days, and 48–72 hours of fever resolution is recommended at the end of treatment.^{9,51} For bacteremia, 14 days is generally recommended, but in the case of bacteremia caused by Gram-positive bacteria, 2 weeks or longer is recommended in consideration of the risk of infective endocarditis when cholangitis is associated, while evidence has emerged that 4 to 7 days, or 7 to 10 days, is sufficient for Gram-negative bacteria after the infection nest is controlled.⁵² Bacteremia caused by MRSA or fungi is considered to be “administered 14 days after confirmation of negative blood culture” for non-complex infections.^{53,54} Thus, the duration of treatment of infectious diseases must be determined by considering the patient’s background, infected organs, and causative microorganisms.

Background factors those we should consider when we determine the antibiotics therapy period as follows⁴⁹

1. Patient’s underlying disease: especially immunodeficiency and anatomical changes/abnormalities.
2. Infectious organs.
3. Causative microorganisms and their susceptibility.
4. No local infectious complications such as abscess, abscessed thorax, pyogenic thrombus, etc (No abscess or other complication, clinical course) (If the patient is also doing well, a shorter treatment period can be considered.
5. There are not any remote infectious complications (arthritis, vertebrobasilar discitis, infective endocarditis, etc).
6. The catheter or other artificial device are not infected, and if so, it has been removed or deflated. (Consider extending the duration of treatment if the artifact is difficult to remove or if there is an undrained abscess.)
7. In cases of bloodstream infections, especially those caused by *Staphylococcus aureus* and *Candida* species, and intravascular infections including catheter-related bloodstream infections, is there evidence of negative blood culture.
8. Good response to anti-microbial therapy (generally evaluated at about 72 hours) and others

Although the description of the review methodology might be lacking and many of the referred data are single armed, retrospective studies in this review, in any case, the number of days of antimicrobial administration is recommended according to the pathophysiology of the disease, taking into consideration not inflammatory findings in individual patients such as CRP but also relapse, and should be determined according to various guidelines and guidance.^{11,22,38,49,52–54}

Conclusions

Antimicrobial doses, dosing intervals, and treatment regimens should be individualized according to the patient’s condition, causative organisms, and affected organs. Although the detailed methodology and huge cohort data might be lacking in this review, early antimicrobial therapy is extremely important, and combination therapy, de-escalation, and switch therapy within 3 days after hospitalization may be important issues to be considered in the future in Japan. The duration of antimicrobial therapy should be determined according to the disease state, not by individual inflammatory findings, including as CRP, and should be determined in accordance with the situation at the bedside in Japan, as same as guidelines and guidance of all over the world.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Ministry of Health, Labour and Welfare. The countermeasures for antimicrobial resistance action plan 2016-2020. 2016. Available from: <http://www.mhlw.go.jp/content/10900000/0000152795.pdf>. Accessed July 29, 2025.
2. Ministry of Health, Labour and Welfare. The countermeasures for antimicrobial resistance action plan 2023-2027. 2023. Available from: http://www.mhlw.go.jp/content/10900000/ap_gaiyou.pdf. Accessed July 29, 2025.
3. Kido K, Tsukamoto K. Japan's health care system faces a perfect storm. *Int J Health Plann Manage*. 2020;35(1):e210–e217. doi:10.1002/hpm.2936
4. Kubo K, Sakuraya M, Sugimoto H, et al. Benefits and harms of procalcitonin- or c-reactive protein-guided antimicrobial discontinuation in critically ill adults with sepsis: a systematic review and network meta-analysis. *Crit Care Med*. 2024;52(10):e522–e534. doi:10.1097/CCM.0000000000006366
5. Centers for Disease Control. The core elements of hospital antibiotic stewardship programs. 2024. Available from: <http://www.cdc.gov/antibiotic-use/hcp/core-elements/hospital.html>. Accessed July 29, 2025.
6. The committee of guidance for antimicrobial stewardship. Japanese society for chemotherapy guidance for implementing the antimicrobial stewardship program, revised edition for fiscal year 2024. *Jpn J Chemother*. 2025;2:95–156.
7. Cunha BC, Cunha, BA. *Antibiotic Essentials*. 17th ed. 2020. Middlesex, UK.
8. Gilbert D, Chambers H, Saag M, Pavia A, Boucher H. *Sanford Guide to Antimicrobial Therapy*. 51st ed. 2021. Sperryville, VA, USA.
9. Mehta JM, Haynes K, Wileyto EP, et al. Comparison of prior authorization and prospective audit with feedback for antimicrobial stewardship. *Infect Control Hosp Epidemiol*. 2014;35(9):1092–1099. doi:10.1086/677624
10. Vaughn VM, Gandhi T, Conlon A, Chopra V, Malani AN, Flanders SA. The association of antibiotic stewardship with fluoroquinolone prescribing in Michigan hospitals: a multi-hospital cohort study. *Clin Infect Dis*. 2019;69(8):1269–1277. doi:10.1093/cid/ciy1102
11. The Japanese society of chemotherapy and the Japan TDM society. *Guidelines Clin Prac TDM Antimicrob Agen*. 2022.
12. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant staphylococcus aureus infections: a revised consensus guideline and review by the American society of health-system pharmacists. *Infect Am J Health Syst Pharm*. 2020;77(11):835–864. doi:10.1093/ajhp/zxaa036
13. Wang HY, Lu CL, Wu MP, Huang MH, Huang YB. Effectiveness of an integrated CPOE decision-supporting system with clinical pharmacist monitoring practice. *Int J Clin Pharmacol Ther*. 2012;50(06):375–382. doi:10.5414/CP201678
14. Evans RS, Pestotnik SL, Classen DC, Burke JP. Evaluation of a computer-assisted antibiotic-dose monitor. *Ann Pharmacother*. 1999;33(10):1026–1031. doi:10.1345/aph.18391
15. Miyawaki K, Miwa Y, Seki M, Asari S, Tomono K, Kurokawa N. Correlation between the consumption of meropenem or doripenem and meropenem susceptibility of *Pseudomonas aeruginosa* in a University Hospital in Japan. *Biol Pharm Bull*. 2012;35(6):946–949. doi:10.1248/bpb.35.946
16. Isobe M, Uejima E, Seki M, et al. Methicillin-resistant Staphylococcus aureus bacteremia at a university hospital in Japan. *J Infect Chemother*. 2012;18(6):841–848. doi:10.1007/s10156-012-0423-6
17. Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Bilker WB, Lautenbach E. Impact of inadequate initial antimicrobial therapy on mortality in infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae: variability by site of infection. *Arch Intern Med*. 2005;165(12):1375–1380. doi:10.1001/archinte.165.12.1375
18. Tagashira Y, Sakamoto N, Isogai T, et al. Impact of inadequate initial antimicrobial therapy on mortality in patients with bacteraemic cholangitis: a retrospective cohort study. *Clin Microbiol Infect*. 2017;23(10):740–747. doi:10.1016/j.cmi.2017.02.027
19. Seki M, Ikari N, Yamamoto S, et al. Severe Japanese spotted fever successfully treated with fluoroquinolone. *Med*. 2006;45:1323–1326.
20. Arnold FW, Summersgill JT, Lajoie AS, et al. Community-acquired pneumonia organization (CAPO) investigators. A worldwide perspective of atypical pathogens in community-acquired pneumonia. *Am J Respir Crit Care Med*. 2007;175(10):1086–1093. doi:10.1164/rccm.200603-3500C
21. Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intens Care Med*. 2010;36(4):612–620. doi:10.1007/s00134-009-1730-y
22. The Japanese society of infectious diseases and the Japanese society of chemotherapy, JAID/JSC guide to the treatment of infectious diseases. 2023.
23. Deconinck L, Meybeck A, Patoz P, et al. Impact of combination therapy and early de-escalation on outcome of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. *Infect Dis*. 2017;49(5):396–404. doi:10.1080/23744235.2016.1277035
24. Bliziotis IA, Samonis G, Vardakas KZ, Chrysanthopoulou S, Falagas ME. Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. *Clin Infect Dis*. 2005;41(2):149–158. doi:10.1086/430912
25. Marangos MN, Nicolau DP, Quintiliani R, Nightingale CH. Influence of gentamicin dosing interval on the efficacy of penicillin-containing regimens in. *J Antimicrob Chemother*. 1997;39(4):519–522. doi:10.1093/jac/39.4.519
26. Fernandez-Hidalgo N, Almirante B, Gavaldà J, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating enterococcus faecalis infective endocarditis. *Clin Infect Dis*. 2013;56(9):1261–1268. doi:10.1093/cid/cit052
27. Hagiwara M, Wiskirchen DE, Kuti JL, Nicolau DP. In vitro pharmacodynamics of vancomycin and cefazolin alone and in combination against methicillin-resistant staphylococcus aureus. *Antimicrob Agents Chemother*. 2012;56(1):202–207. doi:10.1128/AAC.05473-11
28. Fernandez J, Abbanat D, Shang W, et al. Synergistic activity of ceftobiprole and vancomycin in a rat model of infective synergistic activity of ceftobiprole and vancomycin in a rat model of infective endocarditis caused by methicillin-resistant and glycopeptide-intermediate staphylococcus aureus. *Antimicrob Agents Chemother*. 2012;56(3):1746–1784.
29. Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. *Clin Microbiol Rev*. 2010;23(1):14–34. doi:10.1128/CMR.00034-09
30. Sato T, Ito R, Kawamura M, Fujimura S. The risk of emerging resistance to trimethoprim/sulfamethoxazole in staphylococcus aureus. *Infect Drug Resist*. 2022;15:4779–4784. doi:10.2147/IDR.S375588
31. Ma H, Chang J, Peng L, Gao Y, Zhang G, Luo Z. Adjunctive rifampin for the treatment of staphylococcus aureus bacteremia with deep infections: a meta. *PLoS One*. 2020. doi:10.1371/journal.pone.0230383
32. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for the management of Intensive. *Care Med*. 2021;47:1181–1247.

33. Matsushima A, Tasaki O, Shimizu K, et al. Preemptive antibiotic treatment based on gram staining reduced the incidence of. *J Trauma*. 2008;15(1):321–322. doi:10.1007/s00134-013-3077-7
34. Garnacho-Montero J, Gutiérrez-Pizarraya A, Escobedo-Ortega A, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med*. 2014;40(1):32–40. doi:10.1007/s00134-013-3077-7
35. Briceland LL, Nightingale CH, Quintiliani R, Cooper BW, Smith KS. Antibiotic streamlining from combination therapy to monotherapy utilizing an interdisciplinary approach. *Arch Intern Med*. 1988;148(9):2019–2022. doi:10.1001/archinte.1988.00380090091022
36. Kett DH, Cano E, Quartin AA, et al. Implementation of guidelines for the management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis*. 2011;11(3):181–189. doi:10.1016/S1473-3099(10)70314-5
37. Sakaguchi M, Shime N, Fujita N, Fujiki S, Hashimoto S. Current problems in the diagnosis and treatment of hospital-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. *J Anesth*. 2008;22(2):125–130. doi:10.1007/s00540-007-0600-4
38. Japanese Respiratory Society. *Guidelines for Adult Pneumonia*; 2024.
39. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the infectious diseases society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clinical Infect Dis*. 2019;68(6):895–902. doi:10.1093/cid/ciy874
40. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in. *N Engl J Med*. 2022;386(6):509–520. doi:10.1056/NEJMoa2116044
41. Seki M, Hashimoto K, Enami K, et al. Use of molnupiravir for COVID-19 patients in Japan. *J Clin Med Res*. 2022;4:1–4.
42. Mukae H, Yotsuyanagi H, Ohmagari N, et al. A randomized Phase 2/3 study of ensitrelvir, a novel oral SARS-CoV-2 3C-like protease inhibitor, in Japanese patients with mild-to-moderate COVID-19 or asymptomatic SARS-CoV-2 infection: results of the phase 2a part. *Antimicrob Agents Chemother*. 2022;66(10):e0069722. doi:10.1128/aac.00697-22
43. Nathwani D, Lawson W, Dryden M, et al. Implementing criteria-based early switch/early discharge programmes: a European perspective. *Clin Microbiol Infect*. 2015;21:S47–51. doi:10.1016/j.cmi.2015.03.023
44. Roger C, Roberts JA, Muller L. Clin pharmacokinetic. *Clin Pharmacokinetic*. 2018;57(5):559–575. doi:10.1007/s40262-017-0601-x
45. McCollum M, Rhew DC, Parodi S. Cost analysis of switching from i.v. vancomycin to P.O. linezolid for the management of methicillin-resistant *Staphylococcus* species. *Clin Ther*. 2003;25(12):3173–3189. doi:10.1016/S0149-2918(03)90101-9
46. Belforti RK, Lagu T, Haessler S, et al. Association between initial route of fluoroquinolone administration and outcomes in patients hospitalized for community-acquired pneumonia. *Clin Infect Dis*. 2016;63(1):1–9. doi:10.1093/cid/ciw209
47. Deshpande A, Klompas M, Guo N, et al. Intravenous to oral antibiotic switch therapy among patients hospitalized with community-acquired pneumonia. *Clin Infect Dis*. 2023;77(2):174–185. doi:10.1093/cid/ciad196
48. Bankar NJ, Ugemuge S, Ambad RS, Hawale DV, Timilsina DR. Implementation of antimicrobial stewardship in the healthcare setting. *Cureus*. 2022;14(7):e26664. doi:10.7759/cureus.26664
49. Infectious Diseases Division, Department of Infectious Disease Control, Health and Welfare Bureau. *Ministry of Health, Labour and Welfare. Guide to the Proper Use of Antimicrobial Agents*. Third ed. Tokyo: Infectious Diseases Division, Department of Infectious Disease Control, Health and Welfare Bureau, Ministry of Health, Labour and Welfare; 2023.
50. Garwan YM, Alsalloum MA, Thabit AK, Jose J, Eljaaly K. Effectiveness of antimicrobial stewardship interventions on early switch from intravenous-to-oral antimicrobials in hospitalized adults: a systematic review. *Am J Infect Control*. 2023;51(1):89–98. doi:10.1016/j.ajic.2022.05.017
51. Metlay JP, Waterer GW. treatment of community-acquired pneumonia during the coronavirus disease 2019 (COVID-19) pandemic. *Ann Intern Med*. 2020;173(4):304–305. doi:10.7326/M20-2189
52. Committee for Revision and Publication of Clinical Guidelines for Acute Cholangitis and Cholecystitis. *Guidelines for the diagnosis and treatment of acute cholangitis and cholecystitis*. 2018.
53. The Japanese society of infectious diseases and the Japanese society of chemotherapy. revised guidelines for the treatment of MRSA infections. 2024.
54. The Japanese Society of Medical Mycology. *Guidelines for diagnosis and treatment of invasive candidiasis* 2013.

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