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Review Article

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Antimicrobial Therapy and Antimicrobial Stewardship in Sepsis

Hyeri Seok, Ji Hoon Jeon, and Dae Won Park

Division of Infectious Diseases, Korea University Medicine, Korea University Ansan Hospital, Ansan, Korea

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Corresponding Author:
Dae Won Park, MD, PhD
Division of Infectious Diseases, Korea University Ansan Hospital, Korea University Medicine, 123 Jeukgeum-ro, Danwon-gu, Ansan 15355, Korea.
Tel:+82-31-412-4270
Fax: +82-31-412-4265
E-mail: pugae1@korea.ac.kr

ORCID iDs
Hyeri Seok
https://orcid.org/0000-0002-2032-9538
Ji Hoon Jeon
https://orcid.org/0000-0002-7535-1679
Dae Won Park
https://orcid.org/0000-0002-7653-686X

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ABSTRACT

Since sepsis was first defined, sepsis management has remained challenging. To improve mortality rates for sepsis and septic shock, an accurate diagnosis and prompt administration of appropriate antibiotics are essential. The goals of antimicrobial stewardship are to achieve optimal clinical outcomes and to ensure cost-effectiveness and minimal unintended consequences, such as toxic effects and development of resistant pathogens. A combination of inadequate diagnostic criteria for sepsis and time pressure to provide broad-spectrum antimicrobial therapy remains an obstacle for antimicrobial stewardship. Efforts such as selection of appropriate empirical antibiotics and de-escalation or determination of whether or not to stop antibiotics may help to improve a patient's clinical prognosis as well as the successful implementation of antimicrobial stewardship.

Keywords: Sepsis; Septic shock; Antibiotics; Antimicrobial stewardship

INTRODUCTION

Sepsis and septic shock are diseases with a severe burden worldwide due to high mortality and prevalence [1, 2]. The major elements of sepsis treatment include proper fluid resuscitation, supportive therapy for organ dysfunction, source control, and administration of antibiotics [3, 4].

The Surviving Sepsis Campaign guidelines for sepsis treatment have recently been revised [4]. Antibiotics are frequently used in intensive care units (ICUs) with critically ill patients such as those with sepsis. A multicenter point prevalence study reported that 70% of patients in the ICU are prescribed antibiotics, indicating that the ICU is a hotspot for antibiotic use [5]. Prompt and appropriate antibiotic treatment is essential for the treatment of sepsis; however, it has been reported that antibiotics are frequently prescribed for patients with non-bacterial infection [6], which increases antibiotic selection pressure and increases multidrug-resistant organisms (MDRO) [7]. Antimicrobial resistance (AMR) has emerged as a critical issue globally [8]. Numerous initiatives counteracting AMR have been attempted, and reduced antibiotic use has been considered a priority among these initiatives [9, 10].

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One of the many strategies to reduce AMR involves the establishment of an antimicrobial stewardship program (ASP) in acute care hospitals [11]. The goal of antimicrobial stewardship is to promote appropriate use of antibiotics and to reduce antibiotic exposure [12, 13].

In this review, we discuss how to apply an ASP in the treatment of sepsis and septic shock.

OPTIMAL TIMING OF ANTIBIOTICS IN PATIENTS WITH SEPSIS

The Surviving Sepsis Campaign guidelines recommend administering empirical, broad-spectrum antibiotics within an hour of triage for patients with sepsis and septic shock [14]. This recommendation may encourage clinicians, and especially residents, to take an "administer antibiotics first and ask questions later" approach when encountering patients with a high probability of severe infection. However, the concept that an hourly delay in antibiotic administration increases mortality needs to be reconsidered, given the current worldwide increase in AMR [15]. An indiscreet and inappropriate use of antibiotics exacerbates the challenges involved with AMR. A quality enhancement program that aimed to reduce the time to the first administration of antibiotics for community-acquired pneumonia from 8 hours to 4 hours has led to a significant decrease in diagnostic accuracy [16]. However, clear evidence supporting the opinion that delayed administration of antibiotics increases mortality is limited, with most evidence based on results from retrospective analyses of data collated for other purposes. These data lack important information such as identification of infection site, appropriateness of antibiotic selection, dose of antibiotic administration, and source control. In one United States study, 18% of patients who received the management for sepsis in the emergency room (ER) were later confirmed to have no infection [17]. Furthermore, 13% of 2,579 patients who had been admitted to two ICUs in Netherlands due to a putative diagnosis of sepsis had no infection after further work-up, and 30% of patients were also confirmed to have only the potential of sepsis [18]. Rather, initial insufficient source control was found to increase 28-day mortality from 26.7% to 42.9%, regardless of the appropriateness of empirical antibiotics [19].

An analysis of 17,990 cases from the Surviving Sepsis Campaign database showed no difference in actual mortality even when the administration of antibiotics was delayed by up to 5 hours. However, mortality showed a 7.5% linear increase according to hourly delay of antibiotic administration after adjusting for the location where sepsis was suspected, geographic location, infection source, various organ failures, hypotension, and mechanical ventilation [20]. Large population-based adjustments cannot accurately reflect such complicated and subtle elements [21]. The time between time zero (when infection or organ dysfunction began) and presentation or detection of sepsis is unclear and may vary from hours to several days in most cases. Hence, a linear hourly increase in mortality risk according to a delay in antibiotic administration after presentation or the detection of sepsis may not be a reliable indicator. Kumar et al. first reported a linear increase in mortality risk according to delayed administration of antibiotics with shock patients in the ICU [22]. Delaying effective antibiotic administration for >36 hours dramatically increases the mortality risk. In practice, it is difficult to report the outcome of antibiotic susceptibility within 36 hours, and several studies have reported that patients who had been treated with inappropriate empirical antibiotics did not show differences in mortality [23-25]. Patient factors and disease-related factors have been shown as more likely to affect mortality risk [24, 25].

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Although careful judgement in antibiotic administration may increase the risk of mortality in patients with severe bacterial infection due to delayed antibiotic administration, unnecessary exposure to antibiotics including antibiotics for non-bacterial infections or prolonged antibiotic administration is also potentially harmful. A number of studies have reported the association between high mortality rates and an excessive combination of antibiotics and a longer treatment period [26-28]. Antibiotic-related adverse reactions such as *Clostridioides difficile* infections, acute renal failure, drug-induced hepatitis, bone marrow suppression, severe rash, and the acquisition of MDRO are well known. However, adverse effects on microbiome or mitochondrial toxicity are less well known.

Sepsis and septic shock should be considered separately. Timing of effective antibiotic administration is critical for patients with septic shock, whereas clear data are limited for sepsis patients without shock. Although statistical adjustments remain controversial, two retrospective studies have recently reported significant association between delayed antibiotic administration and an increase in mortality concerning patients in septic shock, whereas this association was insignificant in patients with sepsis without shock [29, 30]. Furthermore, in a randomized trial in which 2,672 suspected patients with sepsis were divided into groups where antibiotics were administered in out-of-hospital settings and in the ER, there was no difference in mortality between the two groups, although antibiotic administration in the ER group was 96 minutes (median) later than that in the out-of-hospital setting group [31]. Ninety-five percent of the patients included in that study were infected patients without sepsis or sepsis patients without shock. Therefore, it is necessary to take time to gather accurate information to determine whether antibiotics are required for patients with sepsis without shock.

A stepwise approach is needed to treat patients with possible sepsis or septic shock. Rapid and aggressive treatment should not be applied equally to all patients, but should be differentiated according to the severity of disease and an accurate diagnosis. Rapid antibiotic administration is necessary when the patients suspected of infection quickly deteriorate to shock. However, in many patients, shock or rapid aggravation may not be due to bacterial infection, and in such situations, antibiotics should be stopped immediately. Moreover, if a patient has a low probability of infection and has no shock, antibiotic administration should be carefully determined based on laboratory, radiological, and microbiological findings.

ANTIMICROBIAL DE-ESCALATION THERAPY IN PATIENTS WITH SEPSIS

Antimicrobial de-escalation (ADE) refers to replacing broad-spectrum antibiotics with narrow-spectrum antibiotics or with those having with less ecological impact, or to stop the combinatory use of antibiotics. For example, ADE could involve switching combination therapy for double coverage of specific bacteria to monotherapy, and to stop the administration of empirical antibiotics for bacteria that have not been isolated in a culture test [32]. ADE, which is a part of the ASP with a wider spectrum, should be considered with regard to antibiotic administration among various factors when treating patients with severe infection in the ICU. Prior studies reported the effects of ADE in the ICU, but most were observational studies reported by medical institutions interested in ASPs. Compared to broad-spectrum antibiotics used for empirical antimicrobial therapy, ADE is expected to have the following effects. First, ADE may help strategies to reduce MDRO (33)]. Prolonged use

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of broad-spectrum antibiotics for empirical antibiotic treatment contributes to an increase in MDRO [34, 35]. Second, ADE may reduce adverse reactions associated with the use of broad-spectrum antibiotics. Common adverse reactions include *C. difficile* infections and superimposed infection caused by MDRO or fungi. Lastly, ADE may contribute to shorten medical costs and hospital stay through reducing overall antibiotic use and expenditure [35, 36]. As cumulative dose of antibiotics is related to AMR regardless of the spectrum of antibiotics, reducing antibiotic exposure should be a priority in ASP strategy. Therefore, ADE should be reviewed based on recent studies from the ASP perspective.

In a randomized clinical trial in which patients who had undergone de-escalation of pivotal or main antibiotics were compared with patients who maintained the antibiotics, the mortality rates were not significantly different between the two groups although the broad-spectrum antibiotic use reduced in the de-escalation group [37]. However, the ICU length of stay was longer in the de-escalation group (15.2 ± 15 *vs.* 11.8 ± 12.6 days). Although ADE was shown to be associated with lower mortality in meta-analyses [38, 39], this is due to the results of observational studies and implies bias. ADE was mainly applied to patients who showed clinical improvement [32, 33]. Therefore, further studies are needed after adjustment for potential confounding variables.

ADE does not reduce the total duration of antibiotic use. In one ADE-related randomized controlled trial, the duration of antibiotic use was significantly longer in the ADE group (14.1 ± 13.4 *vs.* 9.9 ± 6.6 days) [37]. The prolonged overall antibiotic use was considered to be the possibility of superinfection in the ADE group. However, there was no significant difference between the two groups in other studies when the duration of antibiotic use was analyzed using median values and non-parametric statistics (9 *vs.* 8 days; $P = 0.11$) [32]. Other explanations for the prolonged antibiotic use have been that narrow-spectrum antibiotics would be less harmful, or have occurred through a possible miscalculation of the overall duration of antibiotic use [32]. Even if all antibiotics were discontinued early in the cohort studies, it could be mistaken to be related to ADE and shortening of the antibiotic use period when included in the ADE and analyzed [32, 40].

Although ADE has been introduced as an effective strategy for reducing AMR, no direct association has been found between ADE and the ecological impact in the ICU patients [41]. In previous ADE studies conducted with ICU patients as endpoints for MDRO acquisition, there was no significant association between ADE and MDRO acquisition [37, 42, 43]. Empirical broad-spectrum antibiotics that have less effects on AMR have been used in the short term to reduce the ecological impact. However, one recent study reported that AMR occurs early during antibiotic treatment (within the first 2 - 3 days); therefore, discontinuation or replacing broad-spectrum antibiotics with narrow-spectrum antibiotics may be less effective in ADE [44]. Furthermore, replacing one empirical broad-spectrum antibiotic with another narrow-spectrum antibiotic may be more harmful as the patient is then exposed to two antibiotics as opposed to exposure to one. When meropenem, an empirical broad-spectrum antibiotic, is replaced with levofloxacin, which is a narrow-spectrum antibiotic, for example, the accumulated ecologic impact may be greater as the patient has been exposed to two different spectrums of antibiotics within a short period. Evidences to date have been insufficient to determine the effects of ADE on AMR due to the limitations of retrospective and observational studies [41]. Further prospective studies are needed with a large number of patients.

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Of the two most critical factors concerning evidence-based ASP intervention, post-prescription review and prior authorization, the post-prescription review process, including ADE, has been shown to be more effective in reducing antibiotic use [45]. If an empirical antibiotic is appropriate, to maintain the existing antibiotics for a short term (≤5 days) may help to avoid repeated changes to the microbiome of patients through sequential use of different antibiotics.

DURATION OF ANTIBIOTIC THERAPY IN PATIENTS WITH SEPSIS

Short-term (5 - 7 days) antibiotic therapy has been shown to be effective and safe for ICU patients with community-acquired pneumonia, ventilator-associated pneumonia, urinary tract infections, complicated intra-abdominal infections, and other bacteremia [46-53]. In a prior study with sepsis patients, procalcitonin (PCT)-based antibiotic duration reduction strategy has been shown effective and safe [28, 54]. However, in a recent study involving patients with lower respiratory tract infection, PCT-based treatment did not reduce the duration of antibiotics compared to the conventional treatment [55].

Guidelines in several countries and international treatment guidelines recommend reducing the overall duration of antibiotic therapy, and short-term treatment is recommended for pneumonia, urinary tract infection, and intra-abdominal infection. However, despite such recommendations, recent studies have reported excessively prolonged antibiotic administrations, further raising the need for ASPs [56, 57].

RAPID DIAGNOSIS OF MULTI-DRUG RESISTANT ORGANISMS

The diagnosis of sepsis in critically ill patients is challenging. The primary trigger to diagnose sepsis is one or more indices among Systemic Inflammatory Response Syndrome (SIRS) criteria, namely, fever, hypothermia, leukocytosis, tachycardia, or tachypnea, which then allow possible infection sites to be found. A crucial factor in the diagnosis of infection is local signs and symptoms due to infection. As infections in different sites present different clinical symptoms, the first step to take in patients suspected to have an infection is to find the infection-related signs and symptoms. The diagnosis of infection remains difficult and more cautious and consistent approach is required in critically ill patients. The demand for new technologies that can help with diagnosis increases, for example, more precise biomarkers as well as improvement of microbiological techniques that can more quickly identify causative bacteria and susceptibility results [58].

Although confirmation of causative bacteria is necessary for ADE, approximately 40% of patients with sepsis have culture-negative results. Given that 70% of clinical decisions in patient care are based on empirical results, a quick microbiologic report is one of the key evaluation tools used in hospitals [59]. The first 3 – 6 hours after sepsis is clinically suspected are important to direct treatment and improve the prognosis; therefore, a microbiological diagnosis within 6 hours would undoubtedly be helpful for optimal treatment.

Although no direct evidence supports the use of culture testing, especially blood culture testing, there are indirect evidences that the culture test had a positive effects of improving

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the prognosis and reducing side effects and costs in ADE and oral switch from intravenous injections. Blood culture testing is considered a standard method for a microbiological diagnosis of bloodstream infection in sepsis. However, this culture-based method has a limitation in that it requires between 12 and 72 hours before obtaining false-negative or positive results from consistent antibiotic therapy.

In the identification of pathogens for sepsis, there is increasing interest in diagnosis of pathogens directly in the blood than in conventional blood culture. This method detects bacterial DNA directly from blood, and takes between 3 and 12 hours. Matrix-assisted laser desorption/ionization time of flight (MALDITOF) technology has been adopted in many microbiologic laboratories in different regions, which has significantly accelerated the diagnostic process; however, it still requires a significant length of time until detection of bacteria and the acquisition of susceptibility results [60]. New PCR-based techniques have been introduced into the market and detailed information is available within hours. Furthermore, detection of pathogen and subsequent antibiotic treatment are more rapidly available in cases such as bloodstream infection [61, 62]. However, the limitation of molecular-based diagnostic tests for bacterial pathogens is that they do not provide information on microbial susceptibility.

Although this novel method has markedly shortened the time to diagnosis and affected antibiotic use, its effect on mortality has not been validated [63]. Moreover, detection of bacteria from a specimen does not necessarily indicate pathogen in most cases. Infection and inflammation without infection must be cautiously differentiated.

IMPLEMENTATION OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM IN PATIENTS WITH SEPSIS

Implementing an ASP in a hospital requires considerable effort including a systemic ASP because only a single factor often does not lead to success. For the application of ASPs in hospitals, a multidisciplinary team approach is needed among staff members including infectious disease specialists, critical care specialists, clinical pharmacists, clinical microbiology specialists, infection control nurse practitioners, critical care nurse practitioners, and administrative employees [64, 65]. As stated in United States Centers for Disease Control and Prevention (CDC) recommendations, leadership commitment is a central component of a successful ASP [64]. The expertise of infectious disease specialists allows them to take a leadership role in implementing ASPs in hospitals. Moreover, in the ICU, integration of ICU leadership and specialized critical care are essential for successful ASPs. Clinical microbiology specialists, whose provision of adequate and critical microbiological results is essential for optimal antibiotic administration, also play an essential role. Although they do not have to be directly involved in daily patient care, clinical microbiology specialists have a clear understanding of accessibility, performance, and interpretation of microbiological diagnostic tests such as PCR-based techniques, and can optimize and question a diagnosis of infection [66]. Clinical pharmacists also comprise another essential component of the ASP as they provide expertise concerning pharmacokinetics and pharmacodynamics that are critical for adjusting doses of drugs for diverse and critically ill patients in the ICU. The participation of clinical pharmacists leads to a shorter time to targeted antibiotic therapy and a reduction in infection complications [67, 68]. Infection control and critical care nurse practitioners are underestimated in the ASP

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process and require re-evaluation of their role in ASP. Critical care nurse practitioners provide a communication hub between clinicians, pharmacy, and laboratory, and infection control nurse practitioners have key roles in the infection control and prevention [69]. Nurse-driven protocols on urinary catheter-related infection or catheter-related bloodstream infection have been associated with a reduction in antibiotic costs, early catheter removal, and a decrease in infection-related complications [70-72]. Many evidences have been reported that a multidisciplinary team approach for ASP has been successful in reducing medical costs and unnecessary antibiotic use.

The fundamental goal of the ASP is to improve outcomes and to reduce collateral damages related to antibiotics, and a multifaceted approach should be considered. However, each element should be customized according to conditions in each hospital and ICU, such as frequency of antibiotic prescription, prevalence of MDRO, and available resources. To design and execute a structured plan for improvement, obstacles that may affect staff adherence to the guidelines need to be evaluated [73].

CONCLUSION

To improve the mortality of patients with sepsis, rapid diagnosis and treatment are required as well as prompt administration of appropriate antibiotics. Surviving Sepsis Campaign guideline recommendations concerning empirical antibiotic therapy for sepsis and septic shock are in contrast to ASP objectives, which aim to use targeted antibiotics and reduce overall exposure to antibiotics. Clinicians should consider the indications of broad-spectrum antibiotic administration as well as the strategies for reducing antibiotic use. Appropriate risk assessment, implementation of the latest treatment guidelines, antibiotic de-escalation, and to stop antibiotics in patients without infection are strategies that can be applied for sepsis patients in the ICU. Despite less impact on improvement of the clinical course, a rapid diagnosis that can detect or exclude specific bacterial pathogens or resistance can be useful and, furthermore, a watchful waiting strategy is a preferable approach to ensure balanced antibiotic administration in patients without septic shock or who for those who have a low probability of infection.

ASP is necessary in the ICU, where antibiotic overuse is extensive and the issue of multidrug resistance is increasing. Implementation of ASP for the balanced use of antibiotics in critically ill patients may protect these patients by reducing the speed of antimicrobial resistance acquisition, preserving the antimicrobial activity of antibiotics, and reducing medical costs.

REFERENCES

1. Vincent JL, Marshall JC, Namendys-Silva SA, François B, Martin-Loeches I, Lipman J, Reinhart K, Antonelli M, Pickkers P, Njimi H, Jimenez E, Sakr Y; ICON investigators. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med 2014;2:380-6.
PUBMED | CROSSREF
2. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K; International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med 2016;193:259-72.
PUBMED | CROSSREF

https://doi.org/10.3947/ic.2020.52.1.19

3. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:840-51.
PUBMED | CROSSREF

4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304-77.
PUBMED | CROSSREF

5. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323-9.
PUBMED | CROSSREF

6. Luyt CE, Bréchot N, Trouillet JL, Chastre J. Antibiotic stewardship in the intensive care unit. Crit Care 2014;18:480.
PUBMED | CROSSREF

7. Timsit JF, Bassetti M, Cremer O, Daikos G, de Waele J, Kallil A, Kipnis E, Kollef M, Laupland K, Paiva JA, Rodríguez-Baño J, Ruppé É, Salluh J, Taccone FS, Weiss E, Barbier F. Rationalizing antimicrobial therapy in the ICU: a narrative review. Intensive Care Med 2019;45:172-89.
PUBMED | CROSSREF

8. Marston HD, Dixon DM, Knisely JM, Palmore TN, Fauci AS. Antimicrobial resistance. JAMA 2016;316:1193-204.
PUBMED | CROSSREF

9. Bassetti M, Poulakou G, Ruppe E, Bouza E, Van Hal SJ, Brink A. Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach. Intensive Care Med 2017;43:1464-75.
PUBMED | CROSSREF

10. De Waele JJ, Akova M, Antonelli M, Canton R, Carlet J, De Backer D, Dimopoulos G, Garnacho-Montero J, Kesecioglu J, Lipman J, Mer M, Paiva JA, Poljak M, Roberts JA, Rodriguez Bano J, Timsit JF, Zahar JR, Bassetti M. Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance. Intensive Care Med 2018;44:189-96.
PUBMED | CROSSREF

11. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol 2012;33:322-7.
PUBMED | CROSSREF

12. Dyar OJ, Huttner B, Schouten J, Pulcini C; ESGAP (ESCMID Study Group for Antimicrobial stewardshiP). What is antimicrobial stewardship? Clin Microbiol Infect 2017;23:793-8.
PUBMED | CROSSREF

13. Schuts EC, Hulscher MEJL, Mouton JWTC, Verduin CM, Stuart JW, Overdiek HWPM, van der Linden PD, Natsch S, Hertogh CMPM, Wolfs TFW, Schouten JA, Kullberg BJ, Prins JM. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:847-56.
PUBMED | CROSSREF

14. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive Care Med 2018;44:925-8.
PUBMED | CROSSREF

15. World Health Organization. Antimicrobial resistance. Available at: http://www.who.int/antimicrobial-resistance/en. Accessed 15 March 2020.

16. Welker JA, Huston M, McCue JD. Antibiotic timing and errors in diagnosing pneumonia. Arch Intern Med 2008;168:351-6.
PUBMED | CROSSREF

17. Heffner AC, Horton JM, Marchick MR, Jones AE. Etiology of illness in patients with severe sepsis admitted to the hospital from the emergency department. Clin Infect Dis 2010;50:814-20.
PUBMED | CROSSREF

18. Klein Klouwenberg PM, Cremer OL, van Vught LA, Ong DS, Frencken JF, Schultz MJ, Bonten MJ, van der Poll T. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study. Crit Care 2015;19:319.
PUBMED | CROSSREF

19. Bloos F, Thomas-Rüddel D, Rüddel H, Engel C, Schwarzkopf D, Marshall JC, Harbarth S, Simon P, Riessen R, Keh D, Dey K, Weiß M, Toussaint S, Schädler D, Weyland A, Ragaller M, Schwarzkopf K, Eiche J, Kuhnle G, Hoyer H, Hartog C, Kaisers U, Reinhart K; MEDUSA Study Group. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study. Crit Care 2014;18:R42.
PUBMED | CROSSREF

20. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, Artigas A, Schorr C, Levy MM. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749-55.
PUBMED | CROSSREF

21. Singer M. Antibiotics for sepsis: does each hour really count, or is it incestuous amplification? Am J Respir Crit Care Med 2017;196:800-2.
PUBMED | CROSSREF

22. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589-96.
PUBMED | CROSSREF

23. McGregor JC, Rich SE, Harris AD, Perencevich EN, Osih R, Lodise TP Jr, Miller RR, Furuno JP. A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. Clin Infect Dis 2007;45:329-37.
PUBMED | CROSSREF

24. Seok H, Song J, Jeon JH, Choi HK, Choi WS, Moon S, Park DW. Timing of antibiotics in septic patients: a prospective cohort study. Clin Microbiol Infect 2020. [Epub ahead of print].
PUBMED | CROSSREF

25. Fitzpatrick JM, Biswas JS, Edgeworth JD, Islam J, Jenkins N, Judge R, Lavery AJ, Melzer M, Morris-Jones S, Nsutebu EF, Peters J, Pillay DG, Pink F, Price JR, Scarborough M, Thwaites GE, Tilley R, Walker AS, Llewelyn MJ; United Kingdom Clinical Infection Research Group. Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals. Clin Microbiol Infect 2016;22:244-51.
PUBMED | CROSSREF

26. Kett DH, Cano E, Quartin AA, Mangino JE, Zervos MJ, Peyrani P, Cely CM, Ford KD, Scerpella EG, Ramirez JA; Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis 2011;11:181-9.
PUBMED | CROSSREF

27. Hranjec T, Rosenberger LH, Swenson B, Metzger R, Flohr TR, Politano AD, Riccio LM, Popovsky KA, Sawyer RG. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study. Lancet Infect Dis 2012;12:774-80.
PUBMED | CROSSREF

28. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Annane D, Reinhart K, Falsey AR, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Oliveira CF, Maravić-Stojković V, Verduri A, Beghé B, Cao B, Shehabi Y, Jensen JS, Corti C, van Oers JAH, Beishuizen A, Girbes ARJ, de Jong E, Briel M, Mueller B. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis 2018;18:95-107.
PUBMED | CROSSREF

29. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376:2235-44.
PUBMED | CROSSREF

30. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, Escobar GJ. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med 2017;196:856-63.
PUBMED | CROSSREF

31. Alam N, Oskam E, Stassen PM, Exter PV, van de Ven PM, Haak HR, Holleman F, Zanten AV, Leeuwen-Nguyen HV, Bon V, Duineveld BAM, Nannan Panday RS, Kramer MHH, Nanayakkara PWB; PHANTASi

Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med 2018;6:40-50.
PUBMED | CROSSREF

32. Tabah A, Bassetti M, Kollef MH, Zahar JR, Paiva JA, Timsit JF, Roberts JA, Schouten J, Giamarellou H, Rello J, De Waele J, Shorr AF, Leone M, Poulakou G, Depuydt P, Garnacho-Montero J. Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP). Intensive Care Med 2020;46:245-65.
PUBMED | CROSSREF
33. Mathieu C, Pastene B, Cassir N, Martin-Loeches I, Leone M. Efficacy and safety of antimicrobial de-escalation as a clinical strategy. Expert Rev Anti Infect Ther 2019;17:79-88.
PUBMED | CROSSREF
34. Wang A, Daneman N, Tan C, Brownstein JS, MacFadden DR. Evaluating the relationship between hospital antibiotic use and antibiotic resistance in common nosocomial pathogens. Infect Control Hosp Epidemiol 2017;38:1457-63.
PUBMED | CROSSREF
35. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, Huskins WC, Paterson DL, Fishman NO, Carpenter CF, Brennan PJ, Billeter M, Hooton TM; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.
PUBMED | CROSSREF
36. Pollack LA, van Santen KL, Weiner LM, Dudeck MA, Edwards JR, Srinivasan A. Antibiotic stewardship programs in U.S. acute care hospitals: findings from the 2014 national healthcare safety network annual hospital survey. Clin Infect Dis 2016;63:443-9.
PUBMED | CROSSREF
37. Leone M, Bechis C, Baumstarck K, Lefrant JY, Albanèse J, Jaber S, Lepape A, Constantin JM, Papazian L, Bruder N, Allaouchiche B, Bézulier K, Antonini F, Textoris J, Martin C; AZUREA Network Investigators. De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med 2014;40:1399-408.
PUBMED | CROSSREF
38. Tabah A, Cotta MO, Garnacho-Montero J, Schouten J, Roberts JA, Lipman J, Tacey M, Timsit JF, Leone M, Zahar JR, De Waele JJ. A systematic review of the definitions, determinants, and clinical outcomes of antimicrobial de-escalation in the intensive care unit. Clin Infect Dis 2016;62:1009-17.
PUBMED | CROSSREF
39. Paul M, Dickstein Y, Raz-Pasteur A. Antibiotic de-escalation for bloodstream infections and pneumonia: systematic review and meta-analysis. Clin Microbiol Infect 2016;22:960-7.
PUBMED | CROSSREF
40. Paskovaty A, Pastores SM, Gedrimaite Z, Kostelecky N, Riedel ER, Seo SK. Antimicrobial de-escalation in septic cancer patients: is it safe to back down? Intensive Care Med 2015;41:2022-3.
PUBMED | CROSSREF
41. De Waele JJ, Schouten J, Beovic B, Tabah A, Leone M. Antimicrobial de-escalation as part of antimicrobial stewardship in intensive care: no simple answers to simple questions-a viewpoint of experts. Intensive Care Med 2020;46:236-44.
PUBMED | CROSSREF
42. De Bus L, Denys W, Catteeuw J, Gadeyne B, Vermeulen K, Boelens J, Claeys G, De Waele JJ, Decruyenaere J, Depuydt PO. Impact of de-escalation of beta-lactam antibiotics on the emergence of antibiotic resistance in ICU patients: a retrospective observational study. Intensive Care Med 2016;42:1029-39.
PUBMED | CROSSREF
43. Gonzalez L, Cravoisy A, Barraud D, Conrad M, Nace L, Lemarié J, Bollaert PE, Gibot S. Factors influencing the implementation of antibiotic de-escalation and impact of this strategy in critically ill patients. Crit Care 2013;17:R140.
PUBMED | CROSSREF
44. Armand-Lefèvre L, Angebault C, Barbier F, Hamelet E, Defrance G, Ruppé E, Bronchard R, Lepeule R, Lucet JC, El Mniai A, Wolff M, Montravers P, Plésiat P, Andremont A. Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. Antimicrob Agents Chemother 2013;57:1488-95.
PUBMED | CROSSREF

45. Tamma PD, Avdic E, Keenan JF, Zhao Y, Anand G, Cooper J, Dezube R, Hsu S, Cosgrove SE. What is the more effective antibiotic stewardship intervention: preprescription authorization or postprescription review with feedback? Clin Infect Dis 2017;64:537-43.
PUBMED

46. De Waele JJ, Martin-Loeches I. Optimal duration of antibiotic treatment in Gram-negative infections. Curr Opin Infect Dis 2018;31:606-11.
PUBMED | CROSSREF

47. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S; PneumA Trial Group. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290:2588-98.
PUBMED | CROSSREF

48. Klompas M, Li L, Menchaca JT, Gruber S; Centers for Disease Control and Prevention Epicenters Program. Ultra-short-course antibiotics for patients with suspected ventilator-associated pneumonia but minimal and stable ventilator settings. Clin Infect Dis 2017;64:870-6.
PUBMED

49. Sandberg T, Skoog G, Hermansson AB, Kahlmeter G, Kuylenstierna N, Lannergård A, Otto G, Settergren B, Ekman GS. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet 2012;380:484-90.
PUBMED | CROSSREF

50. Chotiprasitsakul D, Han JH, Cosgrove SE, Harris AD, Lautenbach E, Conley AT, Tolomeo P, Wise J, Tamma PD; Antibacterial Resistance Leadership Group. Comparing the outcomes of adults with enterobacteriaceae bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort. Clin Infect Dis 2018;66:172-7.
PUBMED | CROSSREF

51. Montravers P, Tubach F, Lescot T, Veber B, Esposito-Farèse M, Seguin P, Paugam C, Lepape A, Meistelman C, Cousson J, Tesniere A, Plantefeve G, Blasco G, Asehnoune K, Jaber S, Lasocki S, Dupont H; DURAPOP Trial Group. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med 2018;44:300-10.
PUBMED | CROSSREF

52. Royer S, DeMerle KM, Dickson RP, Prescott HC. Shorter versus longer courses of antibiotics for infection in hospitalized patients: a systematic review and meta-analysis. J Hosp Med 2018;13:336-42.
PUBMED | CROSSREF

53. Hanretty AM, Gallagher JC. Shortened courses of antibiotics for bacterial infections: a systematic review of randomized controlled trials. Pharmacotherapy 2018;38:674-87.
PUBMED | CROSSREF

54. Lam SW, Bauer SR, Fowler R, Duggal A. Systematic review and meta-analysis of procalcitonin-guidance versus usual care for antimicrobial management in critically ill patients: focus on subgroups based on antibiotic initiation, cessation, or mixed strategies. Crit Care Med 2018;46:684-90.
PUBMED | CROSSREF

55. Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CH, Doi Y, Donnino MW, Fine J, Fine MJ, Fischer MA, Holst JM, Hou PC, Kellum JA, Khan F, Kurz MC, Lotfipour S, LoVecchio F, Peck-Palmer OM, Pike F, Prunty H, Sherwin RL, Southerland L, Terndrup T, Weissfeld LA, Yabes J, Angus DC; ProACT Investigators. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. N Engl J Med 2018;379:236-49.
PUBMED | CROSSREF

56. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, Goossens H, Laxminarayan R. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A 2018;115:E3463-70.
PUBMED | CROSSREF

57. European Centre for Disease Prevention and Control. Summary of the latest data on antibiotic consumption in the EU: 2017. Available at: https://www.ecdc.europa.eu/en/publications-data/summary-latest-data-antibiotic-consumption-eu-2017. Accessed 15 March 2020.

58. De Waele JJ, Dhaese S. Antibiotic stewardship in sepsis management: toward a balanced use of antibiotics for the severely ill patient. Expert Rev Anti Infect Ther 2019;17:89-97.
PUBMED | CROSSREF

59. Dumkow LE, Kenney RM, MacDonald NC, Carreno JJ, Malhotra MK, Davis SL. Impact of a multidisciplinary culture follow-up program of antimicrobial therapy in the emergency department. Infect Dis Ther 2014;3:45-53.
PUBMED | CROSSREF

60. Mitsuma SF, Mansour MK, Dekker JP, Kim J, Rahman MZ, Tweed-Kent A, Schuetz P. Promising new assays and technologies for the diagnosis and management of infectious diseases. Clin Infect Dis 2013;56:996-1002.
PUBMED | CROSSREF

61. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Peterson LE, Musser JM. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. J Infect 2014;69:216-25.
PUBMED | CROSSREF

62. Decousser JW, Poirel L, Nordmann P. Recent advances in biochemical and molecular diagnostics for the rapid detection of antibiotic-resistant *Enterobacteriaceae*: a focus on ß-lactam resistance. Expert Rev Mol Diagn 2017;17:327-50.
PUBMED | CROSSREF

63. Vincent JL, Brealey D, Libert N, Abidi NE, O'Dwyer M, Zacharowski K, Mikaszewska-Sokolewicz M, Schrenzel J, Simon F, Wilks M, Picard-Maureau M, Chalfin DB, Ecker DJ, Sampath R, Singer M; Rapid Diagnosis of Infections in the Critically Ill Team. Rapid diagnosis of infection in the critically ill, a multicenter study of molecular detection in bloodstream infections, pneumonia, and sterile site infections. Crit Care Med 2015;43:2283-91.
PUBMED | CROSSREF

64. Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis 2014;59(Suppl 3):S97-100.
PUBMED | CROSSREF

65. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Dellit TH, Falck-Ytter YT, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, May LS, Moran GJ, Neuhauser MM, Newland JG, Ohl CA, Samore MH, Seo SK, Trivedi KK. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of america and the society for healthcare epidemiology of america. Clin Infect Dis 2016;62:e51-77.
PUBMED | CROSSREF

66. Morency-Potvin P, Schwartz DN, Weinstein RA. Antimicrobial stewardship: how the microbiology laboratory can right the ship. Clin Microbiol Rev 2017;30:381-407.
PUBMED | CROSSREF

67. Carver PL, Lin SW, DePestel DD, Newton DW. Impact of *mec*A gene testing and intervention by infectious disease clinical pharmacists on time to optimal antimicrobial therapy for *Staphylococcus aureus* bacteremia at a University Hospital. J Clin Microbiol 2008;46:2381-3.
PUBMED | CROSSREF

68. Gentry CA, Greenfield RA, Slater LN, Wack M, Huycke MM. Outcomes of an antimicrobial control program in a teaching hospital. Am J Health Syst Pharm 2000;57:268-74.
PUBMED | CROSSREF

69. Olans RN, Olans RD, DeMaria A Jr. The critical role of the staff nurse in antimicrobial stewardship--unrecognized, but already there. Clin Infect Dis 2016;62:84-9.
PUBMED | CROSSREF

70. Furuya EY, Dick A, Perencevich EN, Pogorzelska M, Goldmann D, Stone PW. Central line bundle implementation in US intensive care units and impact on bloodstream infections. PLoS One 2011;6:e15452.
PUBMED | CROSSREF

71. Huang WC, Wann SR, Lin SL, Kunin CM, Kung MH, Lin CH, Hsu CW, Liu CP, Lee SS, Liu YC, Lai KH, Lin TW. Catheter-associated urinary tract infections in intensive care units can be reduced by prompting physicians to remove unnecessary catheters. Infect Control Hosp Epidemiol 2004;25:974-8.
PUBMED | CROSSREF

72. Parry MF, Grant B, Sestovic M. Successful reduction in catheter-associated urinary tract infections: focus on nurse-directed catheter removal. Am J Infect Control 2013;41:1178-81.
PUBMED | CROSSREF

73. Flottorp SA, Oxman AD, Krause J, Musila NR, Wensing M, Godycki-Cwirko M, Baker R, Eccles MP. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. Implement Sci 2013;8:35.
PUBMED | CROSSREF