Review

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Antimicrobial Therapy and Antimicrobial Stewardship in Urosepsis

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Since the latest knowledge on the treatment and countermeasures for sepsis is being updated at a rapid pace, becoming familiar with the Surviving Sepsis guidelines is helpful for patient prognosis. Extended-spectrum beta-lactamases (ESBL) are important factors when selecting early empirical antibiotics for sepsis caused by urinary tract infections. For severe septic shock, prolonged infusion and combination therapy need to be considered.

Keywords: Antimicrobial therapy; Antimicrobial stewardship; Urosepsis

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INTRODUCTION

Recently, the concept and necessity of an Antimicrobial Stewardship Program (ASP) have been highlighted as an important methodology for reducing or preventing antibiotic resistance. As the bane of antibiotic resistance is increasing worldwide, ASP activation is one of the most important measures to overcome the crisis. ASP is generally defined as a coherent set of actions that promote the responsible use of antimicrobials. This definition can be applied to actions at the individual as well as to the national and global levels, and also across human health, animal health, and the environment [1-3]. ASP in hospitals is known to not only increase the treatment outcome of infectious diseases, but also reduce the risk of adverse effects and resistance to antibiotics, and reduce complications such as *Clostridioides difficile* infection, ultimately reducing the length of stay and medical costs [4-6].

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Prognosis is poor in the absence of immediate action [7]. The most credible guideline for sepsis is the Surviving Sepsis campaign; however, it is difficult to introduce it in the main text due to its vast contents. The 2021 revision has recently been issued and we urge the readers to become familiar with it [8].

The current article discusses the points to consider when selecting an initial empirical antibiotic for sepsis caused by urinary tract infection and switching to an appropriate antibiotic from the perspective of antibiotic stewardship after obtaining the microbiological test results.

MAIN BODY

1. Selection of Initial Empirical Antibiotics for Sepsis Caused by Urinary Tract Infection

Selecting the initial empirical antibiotics for infectious diseases is a more difficult and labor-intensive process than expected. Several factors need to be considered, but selecting a broad spectrum antibiotic (like carbapenem) without deliberating these factors may be easier for clinicians. However, this eventually takes a toll on the patient and the community at large.

1) What should be considered initially?

There is an endless list of things to consider initially, but

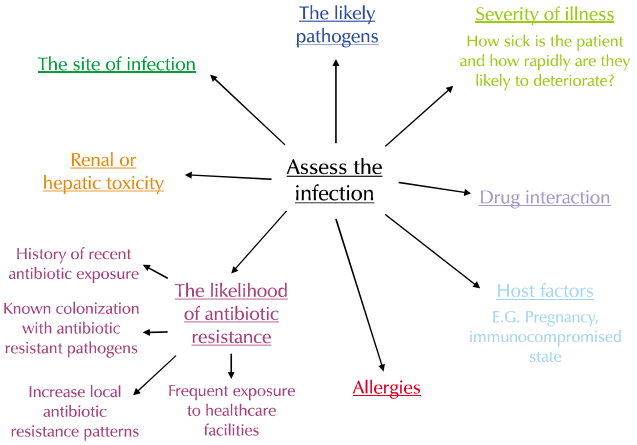

Fig. 1. Factors to consider when assessing initial infection.

the most important ones are as follows (Fig. 1) [9]:

(1) Immunocompromised: Paradoxically, recent advances in medicine have increased the proportion of immunosuppression, thereby increasing the probability of encountering immunosuppressed patients in clinical practice. In such immunocompromised patients or patients with neutropenia, antibacterial activity against *Pseudomonas aeruginosa* may be required in the early stage, or combination therapy with antibiotics may be considered.

(2) Severity: In case of unstable vital signs, such as hypotension at the time of visit or rapid deterioration within several hours, initial antibiotics can be used vigorously (wide range, combined). Once the microbiological test results are obtained, de-escalation to reduce the use of antibiotics can be considered.

(3) Pathogens: Since most urinary tract infections are caused by Gram-negative bacteria, the primary pathogen being *Escherichia coli*, antibiotics targeting Gram-negative bacteria should be selected. This means that it is not necessary to initially use antibiotics targeting Gram-positive bacteria unless there is a history of urinary tract infections caused by Gram-positive bacteria (Methicillin-resistant *Staphylococcus aureus*, Enterococcus), or there is a reason to suspect these bacteria are the causative pathogens.

(4) Infected site: A diagnosis of clinical sepsis is indicative of an upper urinary tract infection. In the case of renal abscess, appropriate drainage may be required through percutaneous drainage depending on the size. For complicated pyelonephritis related to urinary tract obstruction, percutaneous nephrostomy or double J stent insertion should be performed at the earliest. Percutaneous drainage or surgery may be required in some cases of emphysematous pyelonephritis.

(5) Resistance: Evaluating the possibility that pathogens are resistant to antibiotics is the most important factor in selecting the initial antibiotic. It is necessary to consider the probability of resistance by checking whether there is a history of recent exposure to antibiotics, whether there are previously colonized bacteria, what the recent community resistance dynamics are, and whether they are residents of long-term facilities such as nursing hospitals and nursing homes. The sensitivity of ciprofloxacin and trimethoprim-sulfamethoxazole (TMP-SMX) to *E. coli* isolated from patients with acute pyelonephritis in Korea has gradually decreased. According to recent reports, the rates are 78.7% and 72.2%, respectively, which are lower than those of the United States of America (82.9% and 75.8%, respectively) [10].

2) What are the possibilities of extended spectrum beta-lactamase?

Extended spectrum beta-lactamase (ESBL) is a type of beta-lactamase enzyme produced by Gram-negative bacteria, the primary causes of urinary tract infections, which include *E. coli* and *Klebsiella* species. These enzymes neutralize the very broad-spectrum beta-lactam antibiotics, thereby conferring resistance to the commonly used third-generation cephalosporin antibiotic. In the presence of ESBL, carbapenem-type antibiotics are the primary treatment; hence, it is imperative to save and maintain sensitivity to carbapenems as the last weapon and last resort. Therefore, the potential of ESBL should be clearly evaluated and carbapenem should be used only when required. Factors to consider when evaluating the possibility of ESBL has recently been published, and we introduce them in the current discussion [11]. However, it should be noted that they are for reference only; an increasing number of applicable items suggests a higher likelihood of ESBL but is in no way conclusive for ESBL positivity and the need to use carbapenem. A scoring system has yet to be established and can vary according to the epidemiology of each country, region, and hospital.

- Variables analyzed as ESBL risk factors
  - Duration and severity of symptoms
  - Presence of a urinary catheter at the time of admission

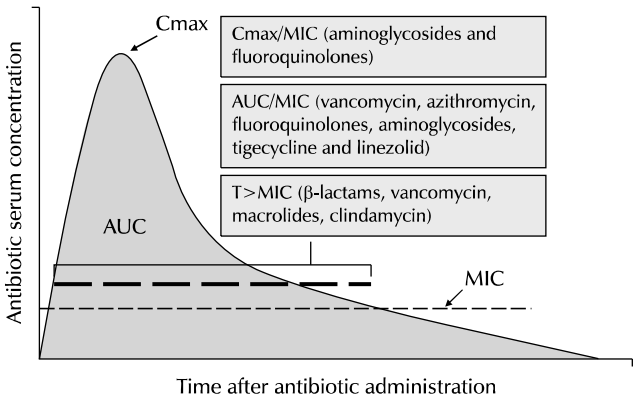

Fig. 2. Pharmacokinetic and pharmacodynamic parameters. AUC: area under the curve, MIC: minimum inhibitory concentration for a pathogen, AUC/MIC: ratio of AUC to MIC (time and concentration-dependent antibiotics), Cmax: peak antibiotic concentration, Cmax/MIC: ratio of peak concentration to MIC (concentration-dependent antibiotics), T>MIC: percentage of time that the antibiotic concentration remains above MIC (time-dependent antibiotics).

- Presence of concomitant bacteremia
- Need for admission to intensive care unit (ICU)
- Duration of ICU stay
- Preexisting medical problems: diabetes mellitus, congestive heart failure, chronic liver disease, chronic kidney disease
- History of recurrent urinary tract infections (defined as >3 episodes of urinary tract infections within the preceding year)
- History of renal stones, benign prostatic hypertrophy, urine outflow obstruction, urinary tract instrumentation or surgery, presence of neurogenic bladder
- History of stroke
- Travel outside North America within 3 months before index hospitalization
- Exposure to antibiotics within 3 months before index hospitalization
- Nursing home, long-term acute care facility, or other extended care facility residence at the time of admission

2. Antibiotic Stewardship for Sepsis Caused by Urinary Tract Infection

For patients with severe septic shock, antibacterial activity can be maximized by applying the following methods:

1) Prolonged infusion of beta-lactam antibiotics

The clinical effect of a drug shows a better correlation with plasma concentration than with the dose administered. After drug administration, a pharmacokinetic (PK) phase and a pharmacodynamic (PD) phase must be cleared before the drug reaches the receptor site and exhibits a medicinal effect. Animal experiments have proven that the correlation between the PK/PD indicators of antibiotics and the effect is closer than the correlation between the simple concentration and the effect of antibiotics. Recent human studies also support this theory [12].

Antibiotics are divided into time-dependent and concentration-dependent antibiotics. Time-dependent antibiotics are more effective when the effective blood concentration is maintained longer, whereas concentration-dependent antibiotics are more effective when the blood concentration is higher, which explains why a high concentration is administered in a single dose (Fig. 2) [13].

Time-dependent antibiotics, represented by beta-lactam antibiotics, become more effective as the time (T) maintained above the minimum inhibitory concentration (MIC) increases (T>MIC). Although there is no defined Korean term, the idea of prolonged infusion was conceived based on this activity [14]. The methodology varies for each antibiotic. In the case of the frequently used piperacillin-tazobactam, 4.5 g is injected over a prolonged period of 4 hours and the interval is written as 8 hours; for meropenem, 2 g is injected over 3 hours, with an interval of 8 hours.

Concentration-dependent antibiotics, represented by aminoglycosides, are more effective as the peak concentration (C_{max}) in blood increases. Therefore, the method of injecting a high dose once a day (once daily dose) rather than the traditional intermittent injection is advantageous in terms of PK/PD. In some animal experiments, it is said that this protocol reduces renal toxicity [15].

2) Combination therapy

Although combination therapy is not preferred by the Department of Infectious Diseases, considerations are given in the following special cases [16]:

(1) Severe infection or suspected polymicrobial infection (e.g., septic shock)
(2) When expanding the antibiotic range for possible causative bacteria during empirical treatment (e.g., *P. aeruginosa* infection)
(3) To prevent the development of resistance (e.g.,

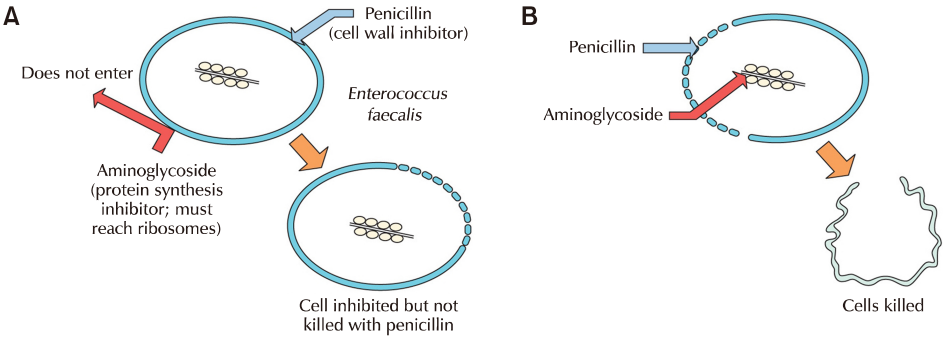

Fig. 3. Example of synergy between two antibiotics. (A) Either penicillin or an aminoglycoside is administered; the cells are inhibited but not killed. (B) When penicillin and an aminoglycoside are administered concurrently, the penicillin compromises the cell wall, enabling the aminoglycoside to enter the cell and reach the ribosomes to prevent protein synthesis, thereby killing the cells.

tuberculosis)

(4) For synergistic effects (e.g., beta-lactam+aminoglycoside)

(5) To administer a lower drug concentration (e.g., to reduce the maximum dose of each drug in the combination)

Synergistic effect means an effect greater than the combined individual effects (1 plus 1 is not 2 but >2). The most representative and applicable treatment for sepsis caused by urinary tract infection is the combination of beta-lactam antibiotics and aminoglycosides. Beta-lactam antibiotics mainly inhibit the synthesis of bacterial cell walls, and aminoglycosides interact with the 30S subunit of ribosomes in cells to selectively interfere with the transcription process and inhibit protein formation. When antibiotics are administered in combination, the cell wall is weakened by the beta-lactam antibiotic, and aminoglycosides enter the cell through the weakened gap, interfering with ribosomes and resulting in greater efficacy (Fig. 3) [16].

CONCLUSIONS

When prescribing antibiotics, each stage needs to be considered: from selecting the initial antibiotic, switching to an appropriate antibiotic after microbiological examination, and deciding the final duration of use. This process is particularly important in sepsis caused by urinary tract infections. The latest knowledge needs to be applied for appropriate treatment in sepsis as the basis when approaching sepsis caused by urinary tract infections. One needs to be familiar with the selection of early empirical antibiotics and additional methods that can be given to patients in severe septic shock.

After selecting the initial antibiotics by assessing the likelihood of ESBL, immediate switching to appropriate antibiotics must be performed upon obtaining results of the microbial antibiotic susceptibility test. In case of initial severe septic shock or no response to empirical antibiotics, prolonged infusion of beta-lactam antibiotics and combined treatment with aminoglycosides can be considered.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. 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.
2. McGowan JE Jr, Gerding DN. Does antibiotic restriction prevent resistance? New Horiz 1996;4:370-6.
3. Mendelson M, Balasegaram M, Jinks T, Pulcini C, Sharland M. Antibiotic resistance has a language problem. Nature 2017; 545:23-5.
4. Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis 2017;17:990-1001.
5. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2017;2: CD003543.
6. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E.

Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. Antimicrob Agents Chemother 2016;60:4840-52.
7. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
8. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med 2021;49:e1063-143.
9. British Society for Antimicrobial Chemotherapy. Principles of good prescribing [Internet]. London: FutureLearn [cited 2022 Nov 25]. Available from: https://www.futurelearn.com/info/courses/antimicrobial-stewardship-for-the-middle-east/0/steps/76625
10. Kang CI, Kim J, Park DW, Kim BN, Ha US, Lee SJ, et al. Clinical practice guidelines for the antibiotic treatment of community-acquired urinary tract infections. Infect Chemother 2018;50:67-100.
11. Goyal D, Dean N, Neill S, Jones P, Dascomb K. Risk factors for community-acquired extended-spectrum beta-lactamase-producing enterobacteriaceae infections-a retrospective study of symptomatic urinary tract infections. Open Forum Infect Dis 2019;6:ofy357.
12. Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin Infect Dis 2007;44:79-86. Erratum in: Clin Infect Dis 2007;44:624.
13. Al-Dorzi HM, Al Harbi SA, Arabi YM. Antibiotic therapy of pneumonia in the obese patient: dosing and delivery. Curr Opin Infect Dis 2014;27:165-73.
14. MacVane SH, Kuti JL, Nicolau DP. Prolonging β-lactam infusion: a review of the rationale and evidence, and guidance for implementation. Int J Antimicrob Agents 2014;43:105-13.
15. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. J Antimicrob Chemother 1996;37:645-63.
16. Wecker L. Brody's human pharmacology: mechanism-based therapeutics. 6th ed. Elsevier; 2018.