Experimental Research

Comparison of ciprofloxacin, cotrimoxazole, and doxycycline on *Klebsiella pneumoniae*: Time-kill curve analysis

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**ABSTRACT**

Background: Antibiotic resistance is a significant problem in the world, so optimization of antibiotic use is needed. *Klebsiella pneumoniae* is a Gram-negative bacterium that causes bacteremia, sepsis, UTIs, pneumonia, nosocomial infections and ESBL-producing bacterium. Ciprofloxacin, cotrimoxazole, and doxycycline are broad-spectrum antibiotics, including in WHO essential drugs.

Objective: The study tested antibiotics that most effectively inhibited *Klebsiella pneumoniae* non-ESBL, *Klebsiella pneumoniae* ESBL invito with time-kill curve analysis.

Method: This experiment used *Klebsiella pneumoniae* ATCC isolates, stored clinical isolates of *Klebsiella pneumoniae* non-ESBL, *Klebsiella pneumoniae* ESBL, and the control group. Isolates other than control were challenged with ciprofloxacin, cotrimoxazole, and doxycycline oral preparations with concentrations of 1, 2, 4 MIC at 0, 2, 4, 6, 8, 24 h. At each hour, the bacteria were cultured, incubated, calculated the number of colonies. The results were analyzed with time-kill curve and tested statistics. Statistical analysis used included ANOVA, post-Hoc, Mann Whitney, and Kruskal Willis tests with p < 0.05.

Results: Ciprofloxacin, cotrimoxazole, and doxycycline in this study had inhibition effects on *Klebsiella pneumoniae* non-ESBL and *Klebsiella pneumoniae* ESBL. Ciprofloxacin had the best inhibitory effect. Statistically, the most meaningful differences of antibiotics in ciprofloxacin and cotrimoxazole at four and 24 h (p < 0.001), in concentrations of 1 MIC and 4 MIC at 2 h (p < 0.001), and in *Klebsiella pneumoniae* ESBL and *Klebsiella pneumoniae* ATCC at 8 h (p = 0.024).

Conclusion: Ciprofloxacin is the best antibiotic to inhibit the growth of *Klebsiella pneumoniae* non-ESBL and *Klebsiella pneumoniae* ESBL compared to cotrimoxazole and doxycycline. The inhibitory effect increases with an increase in concentration.

1. Introduction

*Klebsiella pneumoniae (K. pneumoniae)* is a Gram-negative bacterium that can cause bacteremia, sepsis, urinary tract infections, pneumonia, and nosocomial infections [1]. A study conducted in hospitals in 10 Asian countries from 2008 to 2009 found *K. pneumoniae* as the most common cause of nosocomial infections, namely pneumonia associated with ventilator installation [2]. Antibiotics resistance has become a significant problem worldwide. In the era of increasing antibiotic resistance and the lack of discovery of new antibiotics, it is necessary to optimize the use of existing antibiotics to treat infections [3]. Antibiotic resistance of *Klebsiella* spp. is highest in Asia (>60%), reflecting an alarming increase in opposition to this bacterium. Increased resistance, especially to various classes of antibiotics classified by WHO as essential drugs, so the use of new and more broad-spectrum antibiotics must be limited if there are still narrower-spectrum and effective antibiotics [4].

The prevalence of *K. pneumoniae* infection was 13% in America, 5% in Pakistan, 64.2% in Nigeria, 33.9% in India, 17.4% in Denmark, and 14.1% in Singapore. *K. pneumoniae* Extended-Spectrum Beta-Lactamase (ESBL) infection in Indonesia was 35.35%, a total of 297 isolates from patients hospitalized from January–April 2005 and 38.5% of all isolates from October 2014–May 2015 at Surabaya [5,6]. In a study conducted in Turkey in 2016, there were 190 patients with nosocomial bacteremia caused by *K. pneumoniae* with a mortality rate of 47.9% [7]. Another
study in Taiwan in 2020 involving 150 patients with bacteremia caused by *K. pneumoniae* had a mortality rate of 20–40% [8].

Ciprofloxacin, cotrimoxazole, and doxycycline are antibiotics used for a long time and are included in WHO essential drugs because of their excellent efficacy, minimal side effects, and relatively inexpensive. There are also injection and oral dosage forms with good bioavailability making them easier to use and relatively easy to obtain. The 2021 hospital antimicrobial stewardship guidelines from the Ministry of Health also classify these antibiotics in the access group [9,10]. These antibiotics are still effective enough to treat various Gram-negative infections based on available data, including *K. pneumoniae*. The study in France with 40 samples of *K. pneumoniae*, 75% susceptible to ciprofloxacin, also analyzed the time-kill curve of ciprofloxacin against *K. pneumoniae* [11]. A study in China demonstrated the use of cotrimoxazole for *K. pneumoniae* in vitro. Of 812 isolates of *K. pneumoniae*, 175 (21.6%) isolates were resistant to cotrimoxazole [12]. A study in Mumbai, India, with a retrospective method involving 2951 samples collected from January 2017–December 2018 with 263 of these samples were isolates of *K. pneumoniae* from sputum, showed doxycycline susceptibility of 68.4% [13]. Clinical infectious disease stated that based on pharmacokinetic and MIC data for UTIs caused by *Enterobacter ESBL*, doxycycline could potentially be used for therapy [14].

Time kill curve can be used to study antimicrobial activity that depends on concentration and time-dependent, so this method serves as an alternative option that provides more detailed and dynamic information than MIC. Considering the sensitive profile data to ciprofloxacin, cotrimoxazole, and doxycycline antibiotics, this study aimed to compare the effectiveness of these antibiotics in vitro against *K. pneumoniae* and *K. pneumoniae* ESBL isolates at a hospital in the form of an analysis of the bacterial time-kill curve.

2. Method

The study used a case-control (experimental) analysis with a posttest control group design. The subjects used were *K. pneumoniae* ESBL and non-ESBL, replicated 6 times. Antibiotics used included ciprofloxacin, cotrimoxazole, and doxycycline. This study was conducted from June 2021 to May 2022. The antibiotic doses used in *K. pneumoniae* varied, including ciprofloxacin 0.25, 0.5, 1 p/mL, cotrimoxazole 2, 4, and 8 p/mL, and 4, 8, and 16 p/mL. Furthermore, the time-kill was evaluated for each antibiotic exposure, including 0, 2, 4, 6, 8, and 24 h.

Before the examination, the number of colonies in the CFU/mL log was calculated first. If clinical isolates were found stored with the identification of fungi, sterile culture results, and clinical isolates of *K. pneumoniae* non-ESBL and *K. pneumoniae* ESBL were identified and tested for antibiotic susceptibility. Manually, the isolate could not be used. The measurement results were analyzed using statistical product and service solution (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA). The analysis used were ANOVA, post-Hoc, Mann Whitney, and Kruskal Willis with p < 0.05.

3. Results

*K. pneumoniae* non-ESBL, *K. pneumoniae* ESBL, and *K. pneumoniae* ATCC on administering of ciprofloxacin, doxycycline, and cotrimoxazole 1 MIC at 2–8 h all showed bacteriostatic activity with a reduction in colony number of 1-2-log CFU/mL. *K. pneumoniae* non-ESBL, *K. pneumoniae* ATCC, administration of ciprofloxacin, doxycycline 2 MIC at 2–6 h showed bacteriostatic activity with a reduction in colony number of 1-2-log CFU/mL while at 8 h showed bactericidal activity with a reduction in the number of colonies by 3-log CFU/mL. In *K. pneumoniae* ESBL on the administration of ciprofloxacin 4 MIC at 2–6 h showed bacteriostatic activity with a reduction in the number of colonies by 1-2-log CFU/mL while at 8 h showed bactericidal activity with a reduction in colony number by 3-log CFU/mL. *K. pneumoniae* non-ESBL, *K. pneumoniae* ESBL, and *K. pneumoniae* ATCC on the administration of doxycycline 4 MIC at 2–6 h showed bacteriostatic activity with a reduction in the number of colonies by 1-2-log CFU/mL. Administration of cotrimoxazole 4 MIC at 2–8 h showed bacteriostatic activity with a reduction in the number of colonies by 3 log CFU/mL while at 8 h showed activity bactericidal with a reduction in colony number by 3-log CFU/mL. This study was conducted from June 2018 with 263 of these samples were isolates of *K. pneumoniae* from sputum, showed doxycycline susceptibility of 68.4% [13]. Clinical infectious disease stated that based on pharmacokinetic and MIC data for UTIs caused by *Enterobacter ESBL*, doxycycline could potentially be used for therapy [14].

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that all colonies began to grow back at 24 h. Results of the analysis of the effectiveness of time-kill *K. pneumoniae* could be seen in Tables 1 and 2.

4. Discussion

Various studies in antibiotics have been carried out clinically and in vitro to treat infections due to *K. pneumoniae*. This study tested and compared the oral antibiotics ciprofloxacin, cotrimoxazole, and doxycycline exposed to *K. pneumoniae* non-ESBL, *K. pneumoniae* ESBL, and *K. pneumoniae* ATCC at concentrations of 1 MIC, 2 MIC, and 4 MIC in vitro. Judging from the study’s results, ciprofloxacin was faster reaching bacterial concentrations at higher concentrations (2 MICs at 8 and 4 MICs at 6 and 8) as it is concentration-dependent [15] while at 1 MIC concentration ciprofloxacin only comes bacteriostatic. There were time-kill studies exposing ciprofloxacin to several strains of *K. pneumoniae* with the result that some strains of *K. pneumoniae* at 1 MIC only reached bacteriostatic [11].

Ciprofloxacin also affected *K. pneumoniae* ESBL, and the bactericidal concentration was only reached at a concentration of 4 MICs at 8 h, while the 1 MIC and 2 MICs were only bacteriostatic. ESBLs resist beta-lactam antibiotics, including third-generation cephalosporines and aztreonam. Genes encoding ESBL production may be chromosomal or plasmid-mediated. Usually, plasmids carrying ESBL production genes also have genes encoding other antibiotic resistance, including gyrA encoding quinolone resistance. There was a study linking ESBL production and ciprofloxacin resistance in *K. pneumoniae*, showing no association between ESBL production and ciprofloxacin resistance [16].

This study also showed that doxycycline affected *K. pneumoniae* non-ESBL, *K. pneumoniae* ESBL, and *K. pneumoniae* ATCC. Theoretically, doxycycline tends to be time-dependent rather than concentration-dependent and bacteriostatic. At concentrations of 2–4 MIC, there was bacteria inhibition. At higher concentrations of 8–16 MIC, doxycycline is concentration-dependent to kill bacteria [17]. Pharmacokinetic and pharmacodynamic data on doxycycline are rarely obtained and updated. Doxycycline’s advantages include its availability in oral form, broad antimicrobial activity, and mild side effects. Doxycycline has also
successfully treated *K. pneumoniae* MDR infection in UTIs [18]. In this study, doxycycline reached bactericidal concentrations at 2 MICs and 4 MICs at 8 h in *K. pneumoniae* non-ESBL and *K. pneumoniae* ATCC.

In contrast, *K. pneumoniae* ESBL reached bactericidal concentration at 4 MICs at 8 h. A studies showed that the time-kill doxycycline exposed to *Acinetobacter baumannii* might also be bactericidal [19]. Time-kill study of doxycycline monotherapy against *K. pneumoniae* carbapenem producer showed potential antibacterial activity [20]. There were time-kill studies of the same drug class, namely tigecycline, which at specific concentrations could also be bactericidal against *K. pneumoniae* [21].

Cotrimoxazole also affected *K. pneumoniae* non-ESBL, *K. pneumoniae* ESBL, and *K. pneumoniae* ATCC, at concentrations of 1 MIC, 2 MIC, and 4 MIC in the second, fourth, sixth, and eighth hours, all achieved bacteriostatic effect. Cotrimoxazole tends to be bacteriostatic and can also be bactericidal. In gram-negative, it is concentration-dependent, although there are few supporting data. Cotrimoxazole is not affected by beta-lactamase because of its chemical structure. Nevertheless, some studies suggest ESBL-producing organisms can also acquire resistance genes to cotrimoxazole which are often sul1 and sul2 [22]. Cotrimoxazole can be used in nosocomial infections caused by *Enterobacter*, which produces ESBL and is still susceptible. Even for UTIs, the results are as good as carbapenem therapy. Cotrimoxazole has the advantage that it is available in oral and injectable forms so that patients can go on an outpatient basis, and side effects are also relatively mild [23].

All colonies of *K. pneumoniae* non-ESBL, *K. pneumoniae* ESBL, and *K. pneumoniae* ATCC grew back at 24 h. This might be due to the decreased antibiotic concentration and could also be due to tolerance or persistence. Tolerance is one way for bacteria to survive antibiotics. The tolerant bacterial population has the same MIC as the susceptible population, but the passive population can stay at high antibiotic doses and is often much higher than its MIC. Tolerant bacterial population cannot grow or replicate under high antibiotic concentrations.
A subpopulation of bacteria that tolerate is called the persisters. Persisters are naturally present in almost every bacterial population, including *K. pneumoniae*. This is an attempt by the bacterial population to survive and live in unfavorable environmental conditions. Drug concentrations usually exceed 8–10 times the MIC to prevent persistence [24, 25].

Determining whether an antibiotic is bacteriostatic or bactericidal provides information about the action potential of the antibiotic in vitro. This information must be combined with pharmacokinetic and pharmacodynamic data to predict its efficacy in vivo [24].

The limitations of this study include the current time-kill studies, rarely using oral antibiotics, so further studies are needed with more varied types of antibiotics, more significant number of samples and observation times so that they can provide complete information for the treatment of *K. pneumoniae* infection.

5. Conclusion

Time-kill studies showed that ciprofloxacin and doxycycline achieved bactericidal activity, while ciprofloxacin appears more bactericidal than doxycycline, and cotrimoxazole completes the bacteriostatic activity. Therefore, these results show that ciprofloxacin inhibits the growth of *K. pneumoniae* non-ESBL and *K. pneumoniae* ESBL, *K. pneumoniae* ATCC 13883 better than cotrimoxazole and doxycycline. Ciprofloxacin, cotrimoxazole, and doxycycline inhibit the growth of *K. pneumoniae* non-ESBL, *K. pneumoniae* ESBL, and *K. pneumoniae* ATCC 13883. The most significant difference is between ciprofloxacin and cotrimoxazole, at 1 MIC and 4 MIC concentrations, in *K. pneumoniae* ESBL and *K. pneumoniae* ATCC 13883.

Ethical approval

We have conducted an ethical approval base on the Declaration of Helsinki with registration research at the Health Research Ethics Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

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None.

Author contribution

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Table 1

| Time to Kill | Antibiotic  | CI 95%     | p-value |
|-------------|-------------|------------|---------|
| 2           | Ciprofloxacin | 0.023–0.258 | 0.020   |
|             | Doxycycline  | –0.161 – 0.074 | 0.453   |
|             | Cotrimoxazole | 0.067–0.302 | 0.003* |
| 4           | Ciprofloxacin | 0.089–0.407 | 0.004* |
|             | Doxycycline  | 0.038–0.356 | 0.017   |
|             | Cotrimoxazole | 0.286–0.603 | <0.001* |
| 6           | Ciprofloxacin | –0.004 – 0.451 | 0.054   |
|             | Doxycycline  | –0.027 – 0.427 | 0.062   |
|             | Cotrimoxazole | 0.196–0.651 | 0.001* |
| 8           | Ciprofloxacin | –   | 0.015   |
|             | Doxycycline  | –   | 0.015*  |
|             | Cotrimoxazole | –   | 0.005*  |
| 24          | Ciprofloxacin | 0.241–0.818 | 0.001* |
|             | Doxycycline  | –0.075 – 0.502 | 0.140   |
|             | Cotrimoxazole | 0.454–1.032 | <0.001* |

Table 2

| Time to Kill | Antibiotic  | CI 95%     | p-value |
|-------------|-------------|------------|---------|
| 2           | 1 MIC 2 MIC | –0.027 – 0.187 | 0.136   |
|             | 1 MIC 4 MIC | 0.114–0.328 | <0.001* |
|             | 2 MIC 4 MIC | 0.034–0.248 | 0.012   |
| 4           | 1 MIC 2 MIC | –0.196 – 0.267 | 0.754   |
|             | 1 MIC 4 MIC | –0.081 – 0.381 | 0.193   |
|             | 2 MIC 4 MIC | –0.46 – 0.417 | 0.111   |
| 6           | 1 MIC 2 MIC | –0.125 – 0.368 | 0.321   |
|             | 1 MIC 4 MIC | –0.106 – 0.599 | 0.007*  |
|             | 2 MIC 4 MIC | –0.015 – 0.478 | 0.065   |
| 8           | 1 MIC 2 MIC | –   | 0.173   |
|             | 1 MIC 4 MIC | –   | 0.250   |
|             | 2 MIC 4 MIC | –   | 0.965   |
| 24          | 1 MIC 2 MIC | –0.292 – 0.479 | 0.662   |
|             | 1 MIC 4 MIC | –0.075 – 0.502 | 0.026   |
|             | 2 MIC 4 MIC | 0.454–1.032 | 0.073   |

Note.

* Significant <0.01.

Fig. 6. Time-kill graph of the number of colonies of *K. pneumoniae* non-ESBL, *K. pneumoniae* ESBL, and *K. pneumoniae* ATCC at 0, 2, 4, 6, 8, and 24 h against cotrimoxazole antibiotics at concentrations of 1 MIC, 2 MIC, 4 MIC.
Registration of research studies

Name of the registry: Health Research Ethics Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
Unique Identifying number or registration ID: 0371/KEPK/II/2022.
Hyperlink to your specific registration (must be publicly accessible and will be checked): -

Guarantor

Agung Dwi Wahyu Widodo is the person in charge of the publication of our manuscript.

Consent

All participants are required to fill out an informed consent.

Declaration of competing interest

Andy Setiawan, Agung Dwi Wahyu Widodo, and Pepy Dwi Endras underscore that they have no conflict of interest.

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