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Analysis of pharmacodynamic and pharmacokinetic interactions between antibiotics and corticosteroids in bacteria and human corneal epithelial cells

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Analysis of pharmacodynamic and pharmacokinetic interactions between antibiotics and corticosteroids in bacteria and human corneal epithelial cells

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ABSTRACT

The wide range of integrated treatment process of antibiotics and corticosteroids could be crucial for the proper treatment in ophthalmic field. The impact of the co-administration of antibiotics and corticosteroids in ophthalmology is not studied well. This research focus on in vitro pharmacodynamic and pharmacokinetic interaction to find out the outcome of several type of antibiotics that administered together with corticosteroids. For determining the pharmacodynamic and pharmacokinetic interactions we selected four bacteria, seven antibiotics, and four corticosteroids. The drug interaction and the corrected area under the curve (cAUC) method was established for quantitative evaluation. When corticosteroids were administered with a minimum inhibitory concentration of antibiotics, the antibacterial effect of the antibiotics decreased as the concentration of corticosteroids was increased. An associated application of antibiotics and corticosteroids was found to be changed the intracellular drug concentrations from 0.56 to 3.04 times and from 0.57 to 2.66 times, respectively, compared with individual application. The cAUC determined by using the intercellular drug concentration results ranged from 1.3 to 378.9. Polymyxin with corticosteroid showed the lowest unaffected antibacterial effect for Gram-negative bacteria and moxifloxacin for Gram-positive, on the other hand, ofloxacin combined with corticosteroid showed the most affected against all bacteria. Loteprednol combination with antibiotics showed the lowest influence on antibacterial effects of antibiotics, whereas others showed significant influence on antibacterial effects. In accordance with the result of this study, it is to be mentioned that, the continuous use of antibiotics and corticosteroids affect the intracellular concentration of each other's and can modify the antibacterial effect. Furthermore, based on cAUC, we suggest that the drug interaction explanation can be useful in the rational selection of appropriate antibiotic and corticosteroid combinations for the treatment of corneal infection.

Key Words: Drug Interaction, Intercellular Concentration, Pharmacodynamic, Pharmacokinetic, Bacteria, Antibiotics, Corticosteroids, cAUC.

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ABBREVIATION

AUC: Area Under the Curve

CFU: Colony Forming Unit

cAUC: Corrected Area Under the Curve

CME: pseudophakic cystoid macular edema.

DMEM: Dulbecco's Modified Eagle's Medium

FBS: Fetal Bovine Serum

MIC: Minimum Inhibitory Concentration

MRSA: Methicillin-Resistant Staphylococcus Aureus

1. INTRODUCTION

Drug-drug interaction is an important topic in the field of systemic drug therapy. There are pharmacodynamic and pharmacokinetic interactions between seven antibiotics and four corticosteroids were widely used against four bacteria in human corneal epithelial cells which were investigated in this study. There are a lots of research work ongoing and numerous article published on the basis of in vitro, in vivo and in slilco prediction. However, drug-drug interaction study data is not enough yet to give a definitive treatment in ophthalmology, especially in corneal infection.

Recently, the synergistic and antagonistic interaction between antibiotics and other drugs are applied as a strategy for the evaluation of drug resistance.[1] In aqueous humor, the topical drug administration can enhance the post-surgical intraocular drug concentrations when drug interaction with intraocular lens.[2] New drugs are now developed using such information, resulting more sophisticated treatment approaches.[3,4] Although multiple topical ophthalmic medications are routinely administered to patients simultaneously or sequentially in ophthalmology. it is rare for ophthalmologist to pay attention to drug interaction.[5] Nowadays, ophthalmologists are most likely to encounter drug interactions when prescribing two eye drops at the same time, conventional antibiotics can suppress bacterial infection, corticosteroids can also reduce eye inflammation. As a routine practice, antibiotics are routinely prescribed to prevent serious postsurgical complication, such as endopthalmitis, which can lead to significant vision loss and in extreme cases, the loss of the eye.[6] The use of corticosteroid is essential with antibiotics to control intraocular inflammation in cataract surgery. Specially, steroid is effective to prevent or reduce the severity of pseudophakic cystoid macular edema(CME). But, co-administration of these two drugs may causes CME in patient.[7, 8] Additionally, to treat bacterial keratitis, Conventional antibiotics are commonly used on the ocular surface in combination with corticosteroids.[7,8,9] In order to control corneal infection, antibiotics are the crucial part of this treatment. In addition, corticosteroids also recommended to reduce corneal tissue damage and to restore vision.[12,13] In this combination treatment, it is necessary to ascertain which corticosteroid have incremental effect with the

antibiotics, or at least steroid do not interfere the activity of antibiotics. Therefore, the data on antibiotics-corticosteroid interaction study could serves as a basic source of evidence to prevent treatment failure.

Until now, there is little systematic information available regarding drug interactions in the eye. In this study, the efficacy of antibiotics and four corticosteroids which are commonly used in the treatment of ophthalmic disease such as corneal infection was evaluated against four bacteria[14]. In vitro experiments were conducted to assess, whether various combinations of antibiotics and corticosteroids influence the antibacterial effects of antibiotics essential for the treatment of bacterial keratitis without considering immunologic reactions that can be common scenarios in corneal infections. Pharmacodynamic and pharmacokinetic changes were observed on the basis of drug-drug interaction and the best combination of antibiotics and corticosteroids was determined accordingly.

2. MATERIALS AND METHODS

2.1 Materials

The Human corneal epithelial cell line was purchased from American Type Culture Collection (ATCC; Rockville, MD). Fetal bovine serum (FBS) were purchased from Gibco (Grand Island, NY, (USA). Dulbecco's modified eagle's medium (DMEM, LM001-05, was purchased from Welgene, Korea. Gram negative bacteria (*Pseudomonas aeruginosa*) and gram positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pneumoniae*) were kindely provided by the department of microbiology and the department of laboratory medicine at Yonsei University school of Medicine. The bacterial growth media LB Broth (L3022) were purchased from Sigma-Aldrich, (USA), BHI (MB-B1008) were purchased from kisanbio, (Korea). Mueller Hinton Agar (MB-M1033, MBcell). Gatifloxacin (1288408), levofloxacin (28266), moxifloxacin (SML1581), neomycin (N6386), ofloxacin (O8757), polymyxin (P4932), tobramycin (T4014), dexamethasone (D4902), fluorometholone (F9381), loteprednol (SML0547), and prednisolone (P6004) were all purchased from Sigma-Aldrich. Trypsin-EDTA solution (LS015-10, Welgene) and PBS (IBS-BP007,) were purchased from Intron biotechnology, (Korea).

2.2 Methods

2.2.1 Cell line management

2×10^5 cells were seeded on 60mm dish and cells was initially cultured in Dulbecco's modified eagle's medium (DMEM) media supplemented with 10% fetal bovine serum was use to maintain human corneal epithelial cells. Cells was grown at 37 in humidified atmosphere of 5% CO_2.

2.2.2 Bacterial Strains and Culture

We selected four bacterial species that caused most of the ocular infections based on a10-year review of patients with bacterial keratitis who had been diagnosed with the bacterial keratitis (Table 1).[14] *P. aeruginosa* and *S. aureus* were grown on Luria-Bertani (LB) Broth media whereas *S. epidermidis* and *S. pneumoniae* were grown on Brain Heart Infusion(BHI) Broth media. Bacteria were stored at 4 , after grown in liquid media. Liquid media containing bacteria were used for the experiments. The bacterial strains were cultured at 37 , 150 rpm, for 18 hours in shaking incubator. All the bacterium strains were preserved in cryogenic vials using media containing 25% glycerol at 70 .

2.2.3 Colony forming unit counting

A colony-forming unit (CFU) is a unit used to estimate the number of bacterial cells in a sample. Colony forming units (CFU) were measured as shown as Kim et al[15.] Mueller Hinton Agar was used for the management of colony forming units. Purified water were used to made MHA suspension. Using agitator to dissolved components completely and autoclaved at 121°C for 15 minutes. Used 20-25ml of autoclaved MHA in 90mm dish. Then stored MHA plate at 4-8 . Serial diluted bacteria were seeded on MHA plate using a glass rod stirrer. The CFUs of bacteria were determined after 16 hours of incubation at 37 . The bacterial solutions were prepared at 1×10^6 CFU/mL and for the final concentration of 5×10^5 CFU/mL was used throughout in the study .

2.2.4 Minimum inhibitory concentration values

Minimum inhibitory concentration (MIC) testing were utilized in separating antibiotics that do and do not have an effect on the bacterium and developing the combinations of drugs in the research. Minimum inhibitory concentration values(MIC) were measured as shown as Kim et al[15.] The MICs were measured followed by modified broth microdilution assay. To determine the Minimum inhibitory

concentration, 1ml of bacterial stock was dissolved in 25-30 ml of Media and incubated overnight 150rpm, at 37 . The final concentration of $5X10^5$ CFU/ml of each bacteria was prepared thought in this study. Seeded 50 µl of bacteria ($5X10^5$ CFU/ml) into 96-well plate with 50 µl of antibiotic from different concentration. Incubate at 37 , for 20-24 h. Each strain of bacteria was inoculated individually with $5X10^5$ CFU/mL of different antibiotic concentrations in a 96-well plate. A microplate spectrophotometer (Epoch, Biotek, USA) was used to analysis optical density (OD 600) at 600 nm after 24 h and investigated microbial growth.

2.2.5 Antibiotics and corticosteroids interaction analysis

Seven antibiotics (gatifloxacin, levofloxacin, moxifloxacin, neomycin, ofloxacin, polymyxin, and tobramycin) and four corticosteroids were selected for this study which are commonly used in ophthalmology. Antibiotic and corticosteroids interaction analysis was determined as shown as Kim et al and Laishram et al. where described checkerboard assay.[15,16] In the checkerboard assay, compounds are combined to determine if they display enhanced pharmacodynamic effects, providing empirical support for selecting promising combinations. To investigate the combination effect, 1ml of bacterial stock was dissolved in 25-30 ml of Media and incubated overnight 150rpm, at 37℃. The final concentration of $5X10^5$ CFU/ml of each bacteria was prepared thought in this study. 50 µL of media was applied to every well of a 96-well plate and 50 µL of serially diluted antibiotic solution were added from row A to row G of the 96-well plate. The final concentrations of antibiotic were 8 MIC (row A), 4 MIC (row B), 2 MIC (row C), MIC (row D), 1/2 MIC (row E), 1/4 MIC (row F), 1/8 MIC (row F) and 0 (row H). Following that, 50 µL of corticosteroid was applied to each column in different concentrations (0 to 1000 µM). As a final step, 100 µL of bacteria was applied to a final concentration of 5×10^6 CFU/ mL to each well. A microplate spectrophotometer was used to measure optical density at 600 nm (OD 600) after 24 h of incubation at 37°C.

2.2.6 Evaluation of Intercellular drug concentration using LC-MS/MS

Human corneal epithelial cells were seeded at a density of 2×105 cells plate on 60 mm dishes and maintained at 37 in a humidified incubator with 5% CO2. After 24 hours, the cells were treated with 100μM of antibiotics and corticosteroids for 48 hours. Trypsin-EDTA solution (LS015-10, Welgene), 0.25% was used to harvest cells and washed with PBS (IBS-BP007, Intron biotechnology, Korea). 4×10^5 cells were transferred to Eppendorf tubes and centrifuged at 3000 rpm for 3 minutes. After that the supernatant was discard the cells were stored at -70 .

Next, 200 μl of distilled water was added to the cell pellet and mixed gently, after ultrasonicated for 1 to 2 minutes. Lysis buffer (50 μL) and internal standard solution (methyltestosterone 100 ng/ mL in methanol, 10 μL) were then added, and mixed for 3 second. Then methanol (50 μL) was added and the solution was mixed again for 30 seconds. The samples were centrifuged at 12,000 rpm for 2 min at 4 . Formic acid (0.1%, 80 μL) was added to the supernatant to give a final volume of 320 μL. After the samples were mixed well, 20 μL was used for the experiment

LC-MS/MS analysis was conducted using the systems AB SCIEX 4000 Q Trap LC-MS/MS and Shimadzu LC 20A. Intracellular drugs were expressed as fmol/cell. The amount of intracellular drug was converted into log scale and analyzed as t-test (Figure 1).

2.2.7 Drug interaction evaluation system

The pharmacodynamic interactions were quantified using Area Under the Curve (AUC). The antibacterial effect is better when the AUC value is smaller. Based on the checkerboard assay method, the linear trapezoidal rule was applied to the interaction evaluation graph of antibiotics and corticosteroids to obtain the AUC. When the x-axis was the concentration of anti-inflammatory agent concentration and the y-axis was the survival rate (%) of bacteria.

$$AUC_{0-last} = \sum_{0}^{last-1} \frac{(y_{n+1} + y_n)}{2} \cdot (x_{n+1} - x_n)$$

Using the formula, the AUC of the resulting graph was obtained when the antibiotic concentrations were ½ MIC, MIC, 2 MIC, and 4 MIC, respectively. The AUC of the MIC was taken as the baseline. A linear regression analysis was performed to analyze the differences in antibacterial effects depending on the combined corticosteroid concentration. LC-MS/MS was used to determine pharmacokinetic interactions by measuring intracellular antibacterial agent concentrations. As compared to the administration of antibiotics alone, corticosteroids combined with antibiotics reduced the amount of antibacterial agent in cells to 78 %, the applied MIC was 0.78 MIC. The AUC value at 0.78 MIC is calculated by applying it to the AUC values at 1/2 MIC, MIC, 2 MIC, and 4 MIC. Figure 5 illustrates our data in a representative manner. The final value calculated using this method was referred to as the cAUC.

3. RESULTS

3.1 Pharmacodynamic interactions

The minimum inhibitory concentration (MIC) values of antibiotics against four bacteria were determined before the interaction experiment. Figure 2A shows the survival rates of bacteria based on antibiotic concentration. An elaborate summary of the MIC values is shown in Figure 2B.

In general, the MIC value of *S. pneumoniae* was the most effective among seven different antibiotics. Figure 3 shown the antibacterial effect on bacterial survival rate after the treatment of the drug. The bacterial survival rate revealed from 0 to 1,000 μM concentration of corticosteroids and the MIC value of antibiotics, which were indicated in a red circle and line. AUC can be used to evaluate the antibacterial effect of corticosteroids when administered in combination; the lower the value, the greater the antibacterial effect (Table 2). The minimum inhibitory concentration values of antibiotics decreased the bacterial growth ideally, which means the AUC in the context of the MIC can be used to confirm negative interactions with the reduction of drug efficacy. Among the best combinations (minimum negative interactions) of antibiotics, neomycin-dexamethasone (AUC 1.69) was most stable for Gram-negative bacteria (*P. aeruginosa*) and ofloxacin-prednisolone (mean AUC 2.52) was most stable for Gram-positive bacteria (*S. epidermidis*, *S. pneumoniae* and *S. aureus*). In Gram-negative bacteria, gatifloxacin-fluorometholone (AUC 63.01) and tobramycin-loteprednol for Gram-positive bacteria (mean AUC 55.26) both showed the greatest reduction in effectiveness due to the presence of corticosteroids.

The efficacy of antibiotics tends to decrease with increasing corticosteroid concentration in most combination of antibiotics. The regression analysis of the antibacterial blot results shown in a straight line, in which a statistically significant positive slope indicates that the effect of antibiotics decreases as the corticosteroid concentration increases (Table 3). The combination effect of neomycin and dexamethasone, with the lowest AUC for Gram-negative bacteria, has a minimum slope, but as the

corticosteroid concentration increases, the antibacterial effect tends to be decreased ($y = 0.003324x + 0.0307$, $p < 0.0001$). Meanwhile, the combination of gatifloxacin-fluorometholone, with the highest AUC for Gram-negative bacteria, can be viewed as having an interaction with a reduced antibacterial effect, regardless of corticosteroid concentration ($y = 0.01531x + 15.17$, $p = 0.1694$). Among all the combinations, the highest affected by corticosteroids concentration was ofloxacin-fluorometholone for *S. aureus* (AUC 33.86, $y = 0.05708x + 2.22$, $p < 0.0001$). The survival rate of *S. aureus* in MIC of ofloxacin surpasses 50% when ofloxacin is combined with 1000 μM fluorometholone (red and orange in Figure 3).

Even positive interactions can be confirmed, if the evaluation is surpassed to a minimum concentration than the MIC. However, such positive interactions were rarely observed within the combinations studied. The neomycin-dexamethasone and tobramycin-dexamethasone combinations for *S. pneumoniae* showed a pattern of potentiation, a type of positive interaction. When dexamethasone was administered alone, *S. pneumoniae* grew better as the concentration increased (black in Figure 3M). Whatever, when 1/2 MIC of neomycin and dexamethasone were co-administered, the antibacterial effect became more strong when the concentration of dexamethasone was increased, and the survival rate of bacterial decreased by 4.2% even the neomycin was administered together with 1000 μM dexamethasone (Figure 3M, blue line). In Figure 3M, the orange graph below shows the effect of neomycin concentration with concomitant administration of 1000 μM dexamethasone. Compared with neomycin alone (black graph), neomycin plus dexamethasone showed a similar pattern of activity. The combinations of tobramycin-dexamethasone and neomycin-prednisolone also have similar potentiation effects on *S. pneumonia*.

3.2 Pharmacokinetic interactions

Human corneal epithelial cells were treated for 48 hours with antibiotics and corticosteroids (each 100 μM) which were observed to accumulate antibiotics within the cells, as shown in figure

4A&B. Statistical significance is broadly influenced by several factor, including the method of analysis, the cutoff point, and the number of experiment repetitions. As a result, in this study, statistical significance was applied only for reference and analyzed based on the intracellular drug concentration change ratio. Almost all combinations did not affect the intracellular drug levels significantly, but a few combinations produced noticeable changes. Compared to the combination of polymyxin-loteprednol, the concentration of intracellular antibiotics increased by more than three times; in the combination of moxifloxacin-loteprednol and in the combination of tobramycin-loteprednol, the concentration increased by more than two times (figure 4C). Combinations of ofloxacin-dexamethasone, ofloxacin-prednisolone, ofloxacin-fluorometholone, and gatifloxacin-fluorometholone decreased the concentration of intracellular antibiotics by more than 20%. In combinations of tobramycin-loteprednol, moxifloxacin-fluorometholone, levofloxacin-dexamethasone, and gatifloxacin-loteprednol, the concentration of intracellular corticosteroids was more than double (figure 4D). In combinations of tobramycin-prednisolone, gatifloxacin-fluorometholone, tobramycin-fluorometholone, and moxifloxacin-prednisolone, the concentration of intracellular corticosteroids was reduced by more than 20%.

3.3 Assessment of drug interactions incorporating pharmacodynamic and pharmacokinetic interactions

In this study, Pharmacodynamic interactions were assessed using the AUC values. Based on the pharmacokinetic and pharmacodynamic interactions together, the corrected area under the curve (cAUC) was calculated. Antibiotics and corticosteroids are applied together to determine the drug concentration by their pharmacokinetics interaction in a large framework, then refined by their pharmacodynamics interaction. For example, the amount of intercellular drugs is set as the reference point MIC, when the neomycin is applied alone. In the case of neomycin administered with dexamethasone, the concentration of neomycin in the cell was found to be 0.91 times higher than that of neomycin administrated alone.

Therefore, the AUC at the 0.91 MIC is the cAUC value. However, due to the lack of bacterial survival rate experiment was not conducted at 0.91 MIC, the AUC value was calculated by using the proportional expression of the AUC values of MIC and 1/2 MIC (Figure 5).

For *P. aeruginosa*, the AUC for neomycin-dexamethasone was the lowest at 1.69, but the cAUC reflecting neomycin concentration was 28.0, which lies in the middle of the range for *P. aeruginosa*. Among the combinations of ofloxacin and prednisolone for Gram-positive bacteria, the AUC for the combination of 2.52 was the lowest, while the AUC for the application of a 0.61 AUC change in the concentration of ofloxacin was the highest at 242.8. Polymyxin-dexamethasone had the lowest cAUC showing a stable antibacterial effect for Gram-negative bacteria (cAUC 3.3) and moxifloxacin-prednisolone had the lowest cAUC showing a stable antibacterial effect for Gram-positive bacteria (cAUC 2.0) (figure 6C). In both cases, intracellular antibiotics concentration increased significantly (1.25 and 1.83 times, respectively), and the pharmacodynamic interaction was stable at the MIC (3.12 and 4.87, respectively) (Table 2 and figure 4C). According to the cAUC, the preferred antibiotics in combinations of antibiotics and corticosteroids in Gram-negative bacteria are polymyxin and moxifloxacin for Gram-positive bacteria (mean cAUC 8.2 and 13, respectively). When combined with corticosteroids, moxifloxacin, polymyxin, and tobramycin all were retained their perfect antibacterial properties. Among the bacteria tested, ofloxacin was found to be least effective (mean cAUC 223.9 and 181.6 for Gram-positive and Gram-negative bacteria, respectively) (Figure 6A).

Corticosteroids showed that loteprednol was the most suitable against all the bacteria tested in this study and the other corticosteroids also had suitable co-administration effects (loteprednol, cAUC 17.8 for Gram-negative bacteria; 29.6 for Gram-positive bacteria). Nevertheless, this is an assessment based on the average value, and it should not be overlooked which separately are shown suitable combinations, for example, polymyxin-dexamethasone for Gram-negative bacteria and moxifloxacin-prednisolone for Gram-positive bacteria (Figure 6B).

3.4 Drug interactions analysis

The cAUC has been calculated to determine the effect of antibiotics and corticosteroids against bacteria. With cAUC values, drug interactions can be intuitively assessed at the overall concentrations and in various combinations. Moreover, the cAUC value alone is difficult to understand in detail the pattern of interactions. Table 4 shown the final in-depth analysis of drug interactions based on the pharmacodynamic and pharmacokinetic data collected so far, and the analysis of all combinations is listed here. There are changes in the antibacterial effects of MICs of antibiotics based on corticosteroid concentration patterns (red in Figure 3), changes in antibiotic effects when the concentration increases (green and purple in Figure 3), changes in intracellular antibiotic and corticosteroid concentrations (Figure 4), as well as a final conclusion considering all three components. For instance, in a detailed investigation of the moxifloxacin-prednisolone combination for Gram-positive bacteria that received the most evaluation in cAUC can be determined as follows. When prednisolone concentrations increase, the effectiveness of moxifloxacin decreases by up to 41.4% only for *S. epidermidis* and stabilizes as moxifloxacin concentration increases. Therefore, the antibacterial effect is stable as moxifloxacin concentrations increase by 82.4%, and prednisolone concentrations decrease by up to 25%. In the same way, a detailed investigation of the ofloxacin-prednisolone combination for Gram-negative bacteria that received the lowest cAUC assessment as follows. When prednisolone concentrations increase, the effectiveness of ofloxacin decreases by up to 24.1% and stabilizes as ofloxacin concentration increases. However, there is a possibility that ofloxacin effectiveness is decreased when it is administered along with prednisolone since its concentration decreases by up to 37.9%.

4. DISCUSSION

The pharmacodynamic and pharmacokinetic interactions between antibiotics and corticosteroids were investigated in human corneal epithelial cells which are widely used against bacterial infection. The cAUC value was used to analyze the drug interactions that incorporated both pharmacodynamic and pharmacokinetic drug interactions. On the basis of the cAUC, calculated from the detailed patterns of pharmacodynamic and pharmacokinetic data, we were able to reveal in vitro hidden interactions between antibiotics and corticosteroids which ophthalmologists should be aware of when selecting best combination of antibiotics with corticosteroids.

In the ophthalmic field, only a small number of reports have noticed the combined effect of antibiotics and corticosteroids. The results of in vitro evaluations cannot be successively anticipated in vivo conditions. A study in vitro was conducted to determine the effects of antibacterial and anti-inflammatory agents against bacteria and fungi from keratitis.[17] However, there is no overlap between our research and that study's experimental conditions, so it is not possible to compare that study with our research. The level of anti-inflammatory agent was investigated in rabbit cornea and aqueous humor after simultaneous administration of antibacterial agents and anti-inflammatory eye drops[5] However, the previous reports did not mention pharmacodynamic and pharmacokinetic interactions among antibiotics and corticosteroids. As a consequence, the study aimed to evaluate the drug interactions between seven antibiotics (gatifloxacin, levofloxacin, moxifloxacin, neomycin, ofloxacin, polymyxin, and tobramycin) and four corticosteroids (dexamethasone, fluorometholone, loteprednol, and prednisolone) by calculating the intracellular concentrations of every drug in human corneal epithelial cells and the viability of four different type of bacteria cultured with 28 pairs of antibiotics and corticosteroids. In addition, a new indicator for evaluation of antibiotic-corticosteroid interactions has been proposed, in which the new indicator cAUC value would recommended a quantitative measurement for combination interactions that incorporate pharmacodynamics as well as

pharmacokinetics. The interval between administrations for each combination of antibiotics and corticosteroids was not established, so both two drugs were administered simultaneously.

There are several possibilities to explain the changes in intracellular drug concentrations after drug co-administration. Overexpression of the efflux transporters (ABC transporters) is frequently cited as a leading mechanism at the cellular level.[18,19] In the present study, the concentrations of fluorometholone and gatifloxacin decreased significantly when administered together. Preliminary study shows that the transporters such as ABCB1, ABCC1, ABCC2, and ABCG2 overexpressed when both drugs were administered together. Since P-gp (ABCB1) and MRP2 (ABCC2) are transporter of gatifloxacin, so it is likely that the drug might have been leaked out of the cell (Figure 7).[20] Further study on transporter mechanisms associated with other combinations involving changes in intracellular drug concentration might be help us better understand this pharmacokinetics drug interaction.

Polymyxin-dexamethasone in combination had the lowest cAUC which showed a stable antibacterial effect for Gram-negative bacteria (cAUC 3.3), and the moxifloxacin-prednisolone combination had the lowest cAUC which also showed a stable antibacterial effect for Gram-positive bacteria (cAUC 2.0). A pressure patch is usually applied with neomycin and polymyxin B sulfates along with dexamethasone ophthalmic ointment (Maxitrol, Alcon Inc., Fort Worth, Tx, USA) within one day after intraocular surgery. Dexamethasone, the active ingredient in this combination ointment, has anti-inflammatory properties, while polymyxin B and neomycin have an anti-infective property. When polymyxin administered with a corticosteroid, polymyxin effectively killed *P. aeruginosa* and *S. aureus*. In addition the combination of polymyxin with dexamethasone is the highest effective way to kill *S. epidermidis* among 28 combinations of antibiotics and corticosteroids. So these are the best combination for the treatment of ophthalmic diseases. The combination of antibiotics and corticosteroids are usually prescribed on the first day after surgery, for at least 2 weeks or more. Moxifloxacin-prednisolone is widely used in combination. We found moxifloxacin-prednisolone to have a stable antibacterial effect against Gram-positive and Gram-negative bacteria (cAUC 2.0 and cAUC 9.4 respectively). As polymyxin was the most preferred combination antibiotic for Gram-negative bacteria and moxifloxacin

was the most preferred combination antibiotic for Gram-positive bacteria (mean cAUC 8.2 and 13, respectively), it is recommended to apply moxifloxacin in combination with prednisolone for the prevention of microbial infection and the reduction of inflammation following intraocular surgery. As a matter of fact, that the Gram-positive bacteria, moxifloxacin concentration increased twofold, prednisolone concentration remained unchanged, and pharmacodynamic interactions were stable at MIC 4.87.

On the basis of cAUC values, moxifloxacin, polymyxin and tobramycin were found to be shown excellent antibacterial effects regardless of all types of bacteria when administered in combination with corticosteroids. Tobramycin combined with dexamethasone effectively kills most bacteria but it does not kill *S. epidermidis*. The ophthalmic ointment of tobramycin and dexamethasone (Tobradex, Alcon Inc.) has anti-infective properties in the presence of tobramycin and anti-inflammatory properties in the presence of dexamethasone. The component of the combination that contains antibiotics is more effective against susceptible organisms. In vitro studies have represented that tobramycin is effective against susceptible bacterial strains of *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *P. aeruginosa*, and others. On the other hand, the cAUC value of the tobramycin-dexamethasone combination was the highest against *S. epidermidis* compare with other bacteria, as shown in our study. However, in vitro study demonstrated that tobradex ointment is a good combination when antibiotics and corticosteroids were administered.

The combination eye drops have advantages when it contains antibiotics and corticosteroids. For example, better patient compliance, reduced costs, and reduced potential washout effects and ocular toxicity through reduced preservative exposure. [21,22,23] An alternative eye drop that contains gatifloxacin 0.5%, prednisolone acetate 1%, and bromfenac sodium 0.075% is combination eye drops.[23] Preventing postoperative complications with combination therapy and separate drop therapy is equivalently effective. Another study found similar results when both prednisolone acetate and gatifloxacin hydrochloride were used in combination as well as individually.[22] In contrast, in the present study, we found that gatifloxacin and prednisolone acetate had no effect on killing Gram-positive bacteria. After

cataract surgery, the instillation of a combination of dexamethasone and netilmicin is also safe and effective for controlling postoperative inflammation.[24] Even though netilmicin was not included in our study, it has shown a wide spectrum of activity against methicillin-resistant *S. aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCoNS), and multiresistant coagulase-negative staphylococci with negligible to the ocular toxicity.[25, 26, 27] Against all types of bacteria, ofloxacin was found to be the lowest effective antibiotic (mean cAUC was 223.9 for Gram-negative bacteria and 181.6 for Gram-positive bacteria, respectively). Surprisingly, gatifloxacin combined with fluorometholone or dexamethasone did not significantly improve the effectiveness of treatment against all types of bacteria, but gatifloxacin combined with loteprednol significantly improved treatment against *P. aeruginosa* and *S. aureus*. The result suggests that loteprednol revealed a perfect combined administration effect for all types of bacteria, which can be indicated by the cAUC values.

In this study, we used an in vitro system to analyze the interactions between effective corticosteroids and antibiotics and also determined whether the included corticosteroids decrease the effectiveness of antibiotics at concentrations above the MIC. However, it is difficult to investigate whether antibiotics can really be improved in their effectiveness. The antibacterial was determined over the period of 48 hours, and therefore the experimental design could not measure where the antibacterial effect was accomplished faster due to the use of adjuvent corticosteroids concentrations above the MIC of antibacterial agents. On the other hand, this study investigated whether effective corticosteroids lower the efficacy of antibiotics. Based on the cAUC values presented for the first time, we believe that the ophthalmologist can quickly become aware of the interactions between antibiotics and corticosteroids. Furthermore, to learn more about the interactions between antibiotics and corticosteroids, refer to table 4, which provides a qualitative evaluation of the interactions between antibiotics and corticosteroids.

we believe that the cAUC, incorporating pharmacodynamic and pharmacokinetic effect between corticosteroids and antibiotics, which may applicable to further in vivo studies and be useful in clinical practice. We expect that future clinical studies will more accurate design using our results.

5. CONCLUSIONS

In this study, it was confirmed that the simultaneous use of antibiotics and corticosteroids affects intracellular concentration of each drugs and influence the efficacy of antibacterial agent. The pharmacodynamic and pharmacokinetic interactions were evaluated by using the cAUC values. The Ophthalmologists could use these cAUC values in drug selection for the treatment of corneal infection. We proposed that the appropriate drug combination can guide the most effective therapeutic selection in the future.

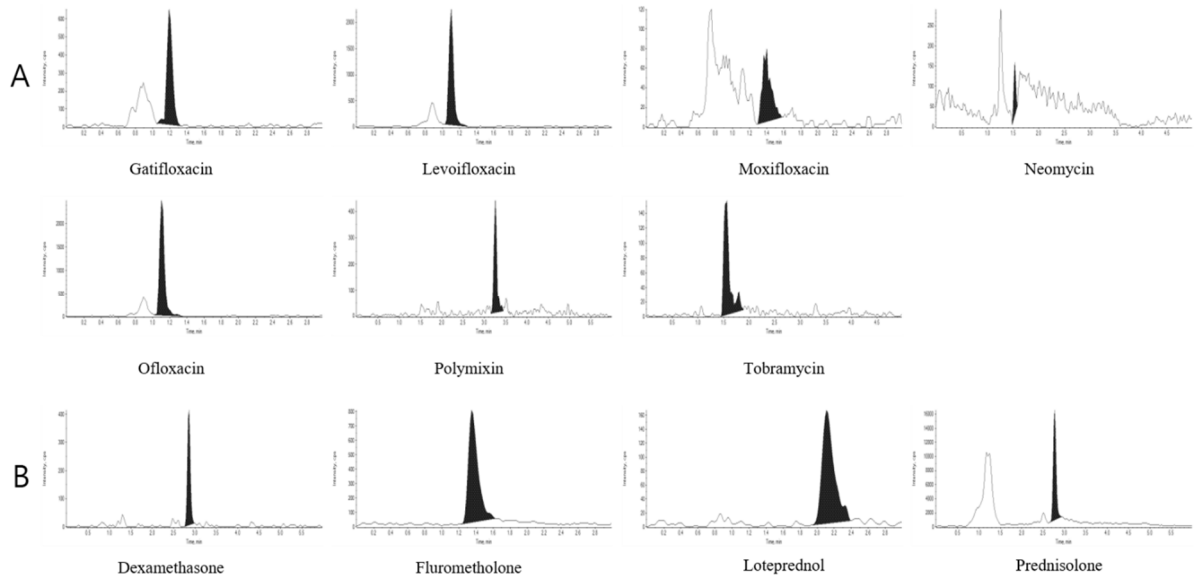
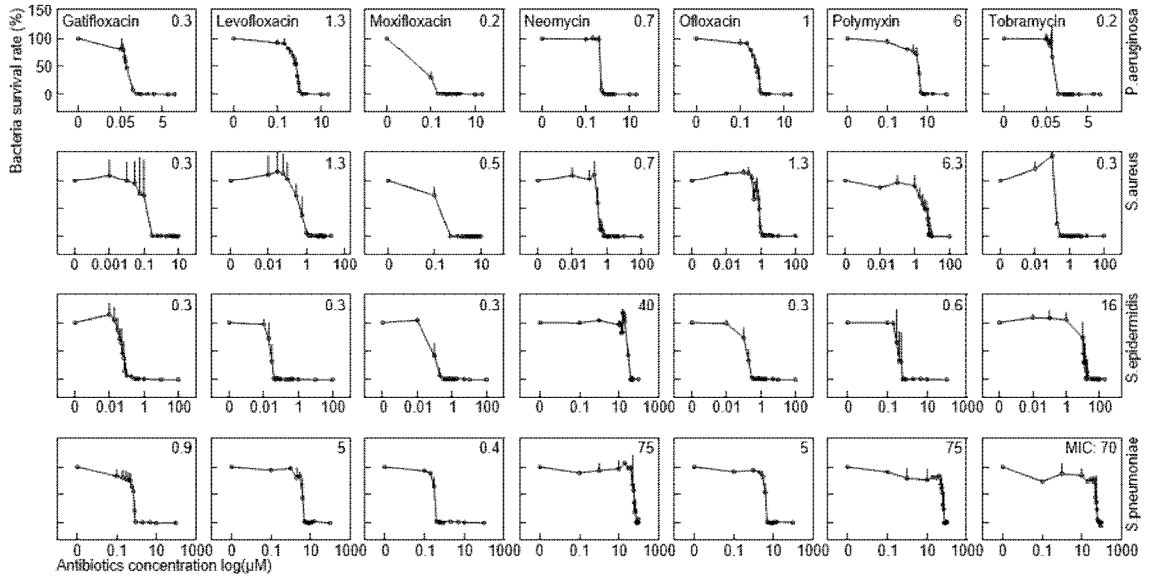


Figure 1: Intercellular antibiotics and corticosteroids concentration measured using LC-MS/MS

LC-MS/MS chromatogram of seven antibiotics and four corticosteroids were measured the intracellular drug concentrations compared with methyltestosterone as the internal standard. The concentration of intercellular drugs was expressed as an amount per cell. The drug name is written in the lower middle of all graphs. Experiments were performed at least three to six times.

A

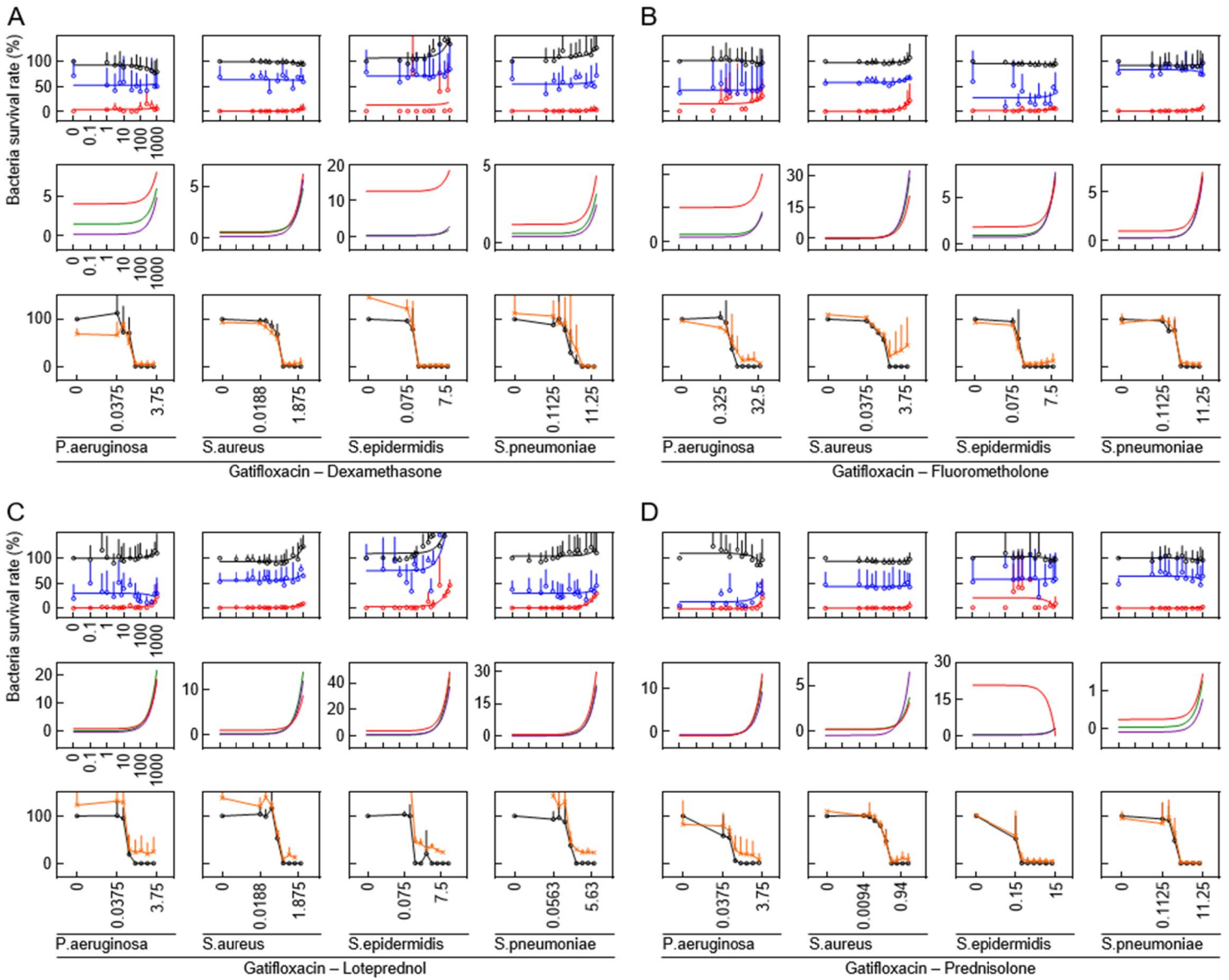


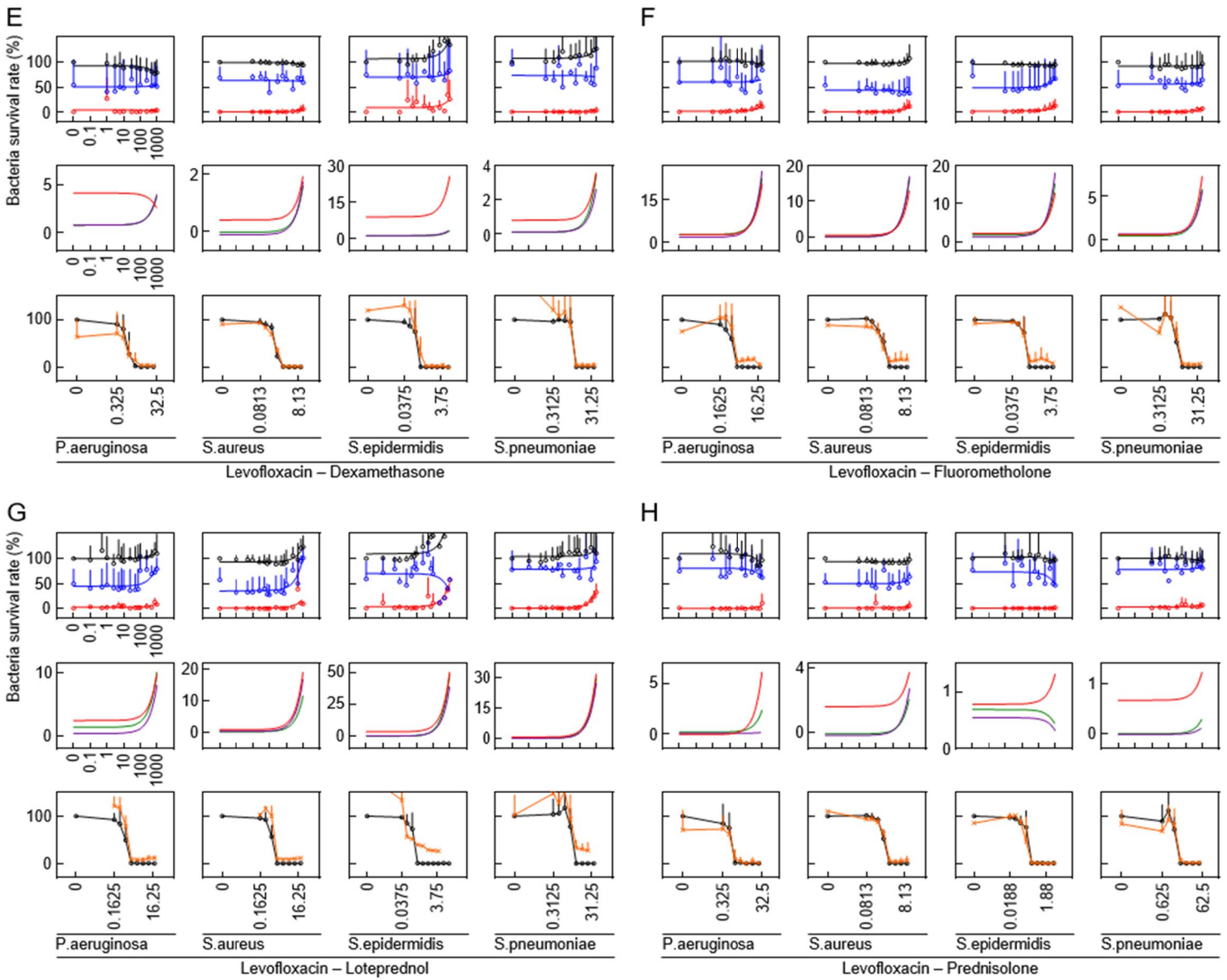
B

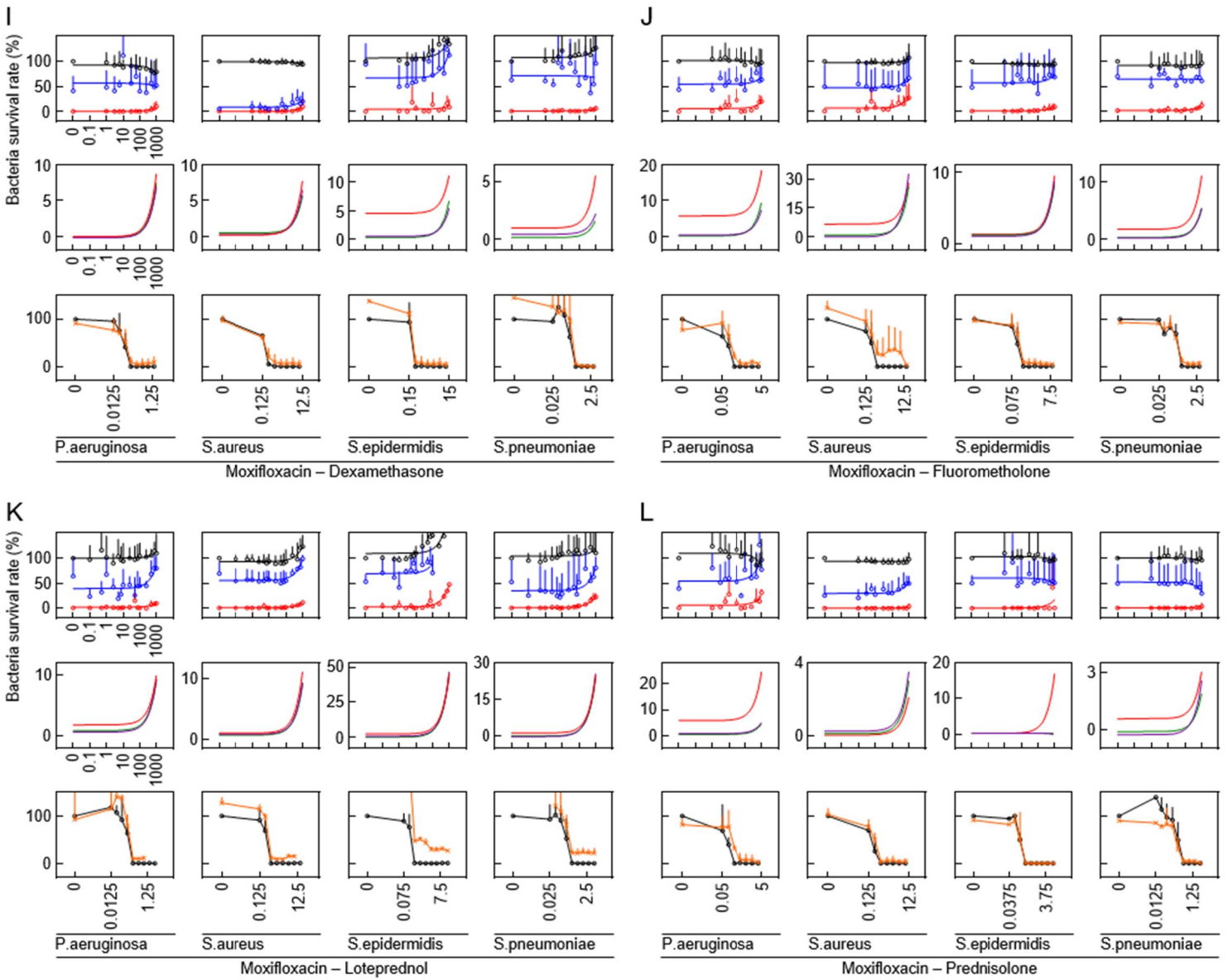
	P. aeruginosa	S. aureus	S. epidermidis	S. pneumoniae
Gatifloxacin	0.3	0.3	0.3	0.9
Levofloxacin	1.3	1.3	0.3	5
Moxifloxacin	0.2	0.5	0.3	0.4
Neomycin	0.7	0.7	40	75
Ofloxacin	1	1.3	0.3	5
Polymyxin	6	6.3	0.6	75
Tobramycin	0.2	0.3	16	70

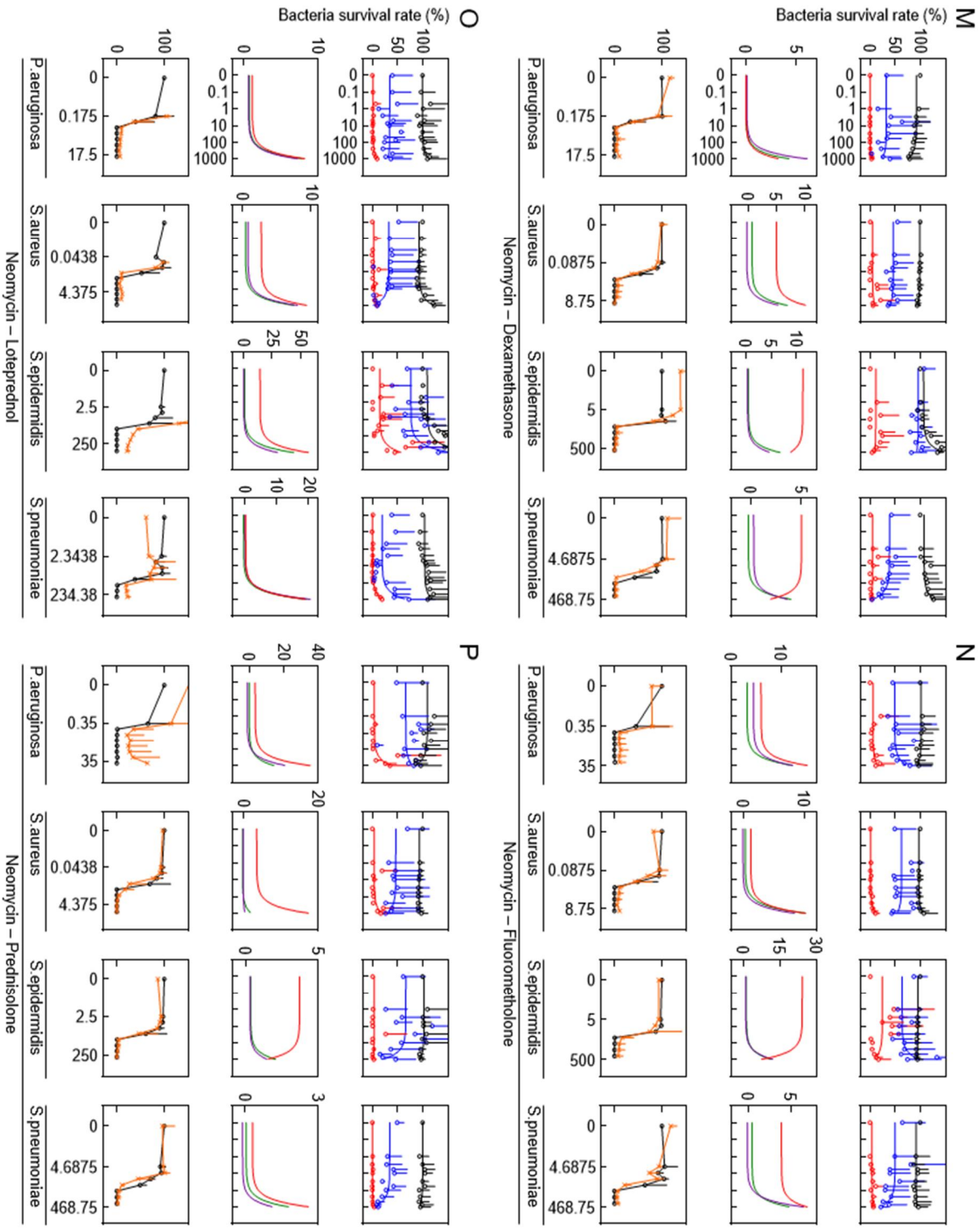
Figure 2. Determination of the minimum inhibitory concentration (MIC) of antibiotics using the survival rates of bacteria in a dose-dependent manner

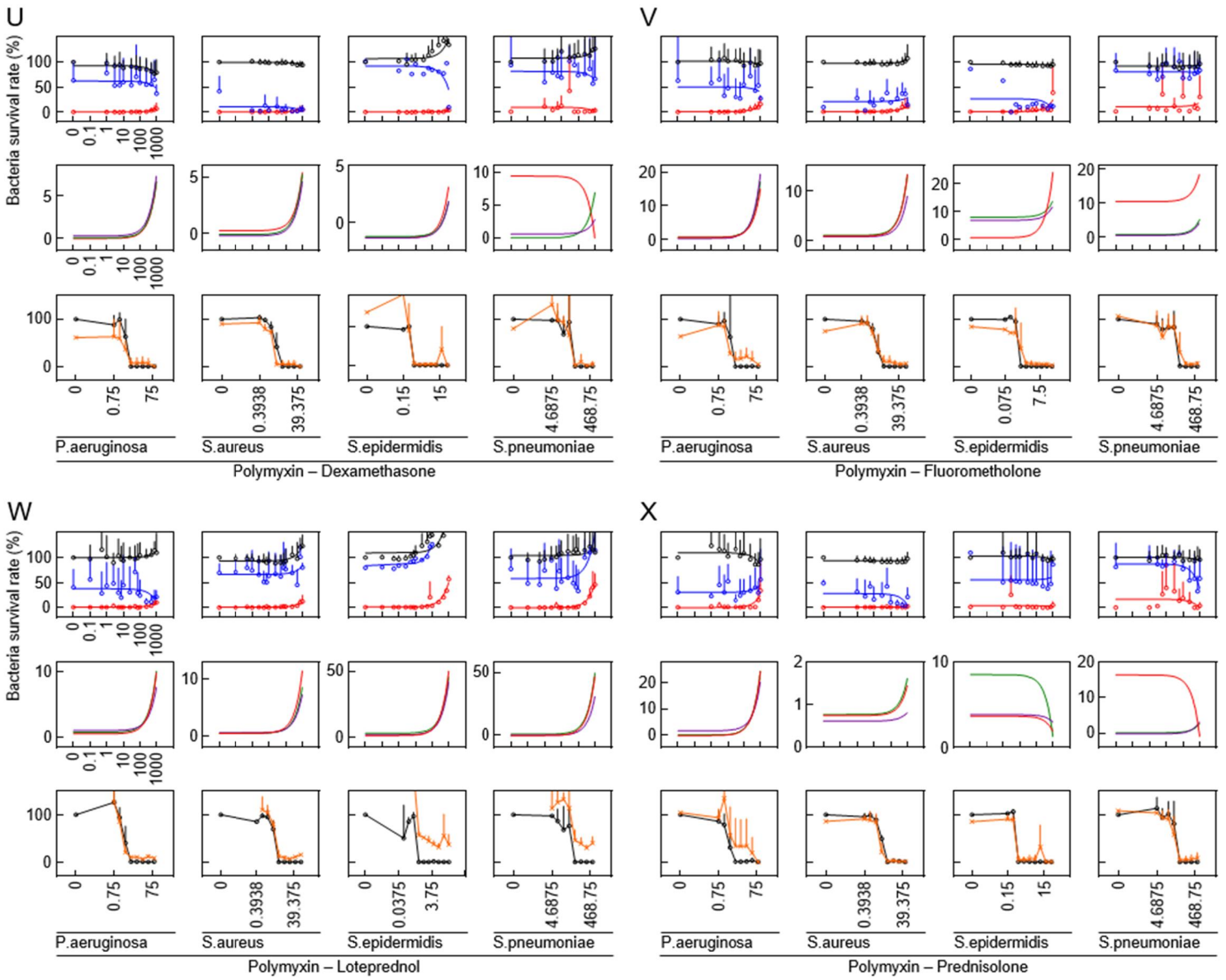
(A) The results of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pneumoniae*, are represented in rows 1, 2, 3, and 4, respectively. The results of gatifloxacin, levofloxacin, moxifloxacin, neomycin, ofloxacin, polymyxin, and tobramycin are represented in Column 1, 2, 3, 4, 5, 6, and 7 respectively. MIC values (μM) are shown in the upper right corner of all graphs. The X-axis represent the concentration of antibacterial agents and Y-axis represent the survival rate of bacteria in a logarithmic scale. (B) The results of antibiotics MIC values are summarized for four bacteria. Experiments were performed independently and repeated at least three to a maximum of eight times.

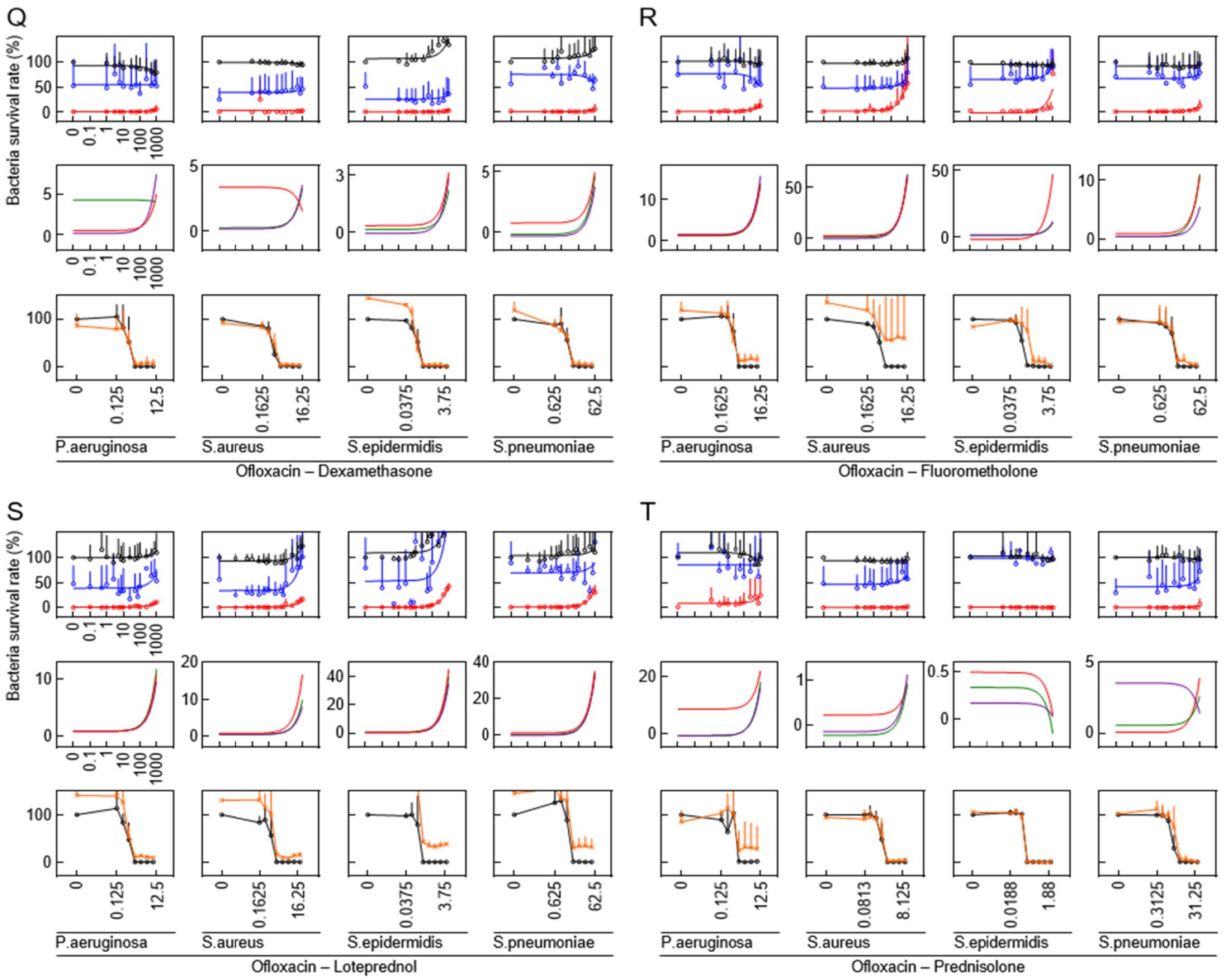

A
B
C
D
Bacteria survival rate (%)
P.aeruginosa
S.aureus
S.epidermidis
S.pneumoniae
Gatifloxacin – Dexamethasone
Gatifloxacin – Fluorometholone
Gatifloxacin – Loteprednol
Gatifloxacin – Prednisolone

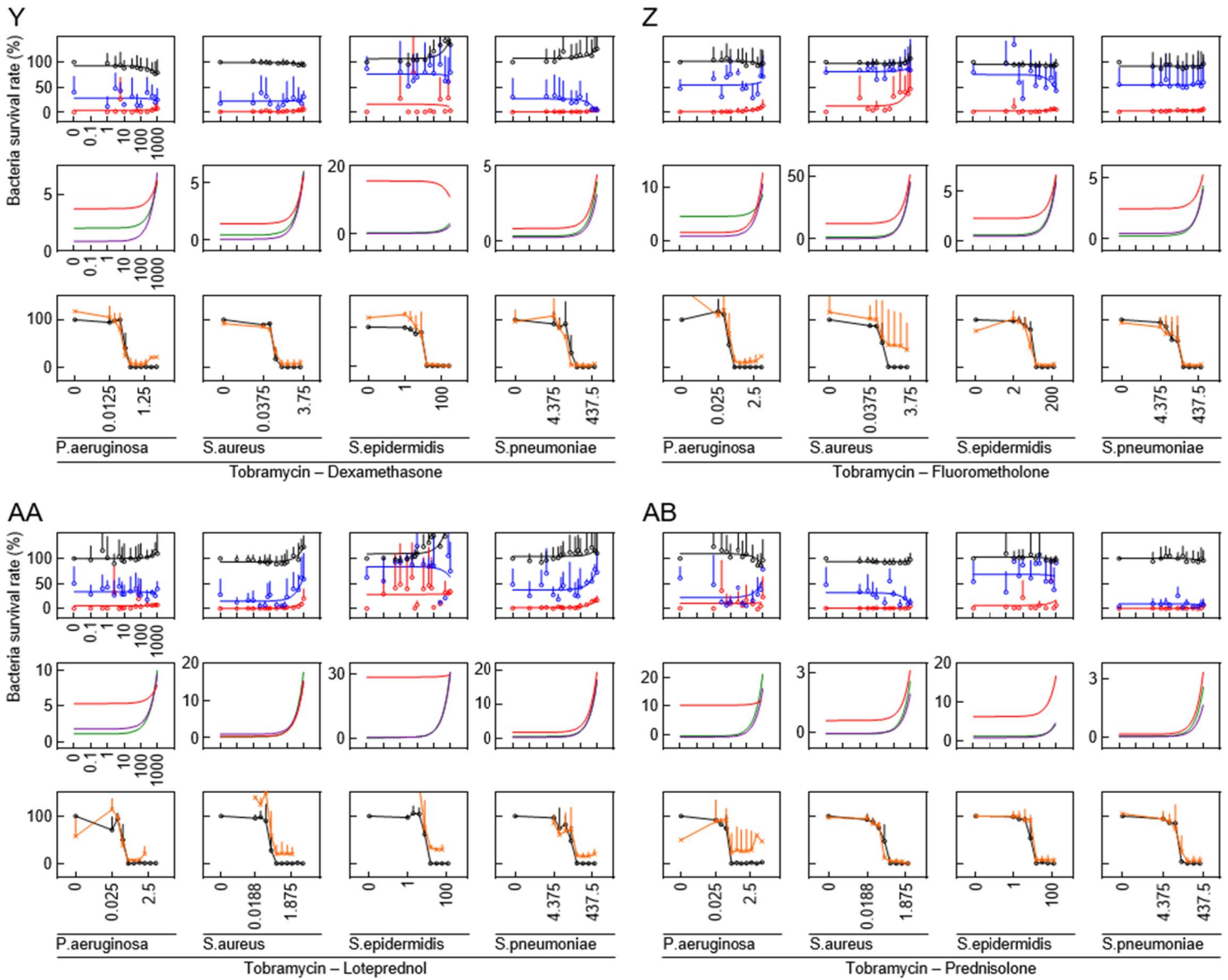

E
F
G
H
Bacteria survival rate (%)
P.aeruginosa
S.aureus
S.epidermidis
S.pneumoniae
Levofloxacin – Dexamethasone
Levofloxacin – Fluorometholone
Levofloxacin – Loteprednol
Levofloxacin – Prednisolone


I
J
K
L
Bacteria survival rate (%)
P.aeruginosa
S.aureus
S.epidermidis
S.pneumoniae
Moxifloxacin – Dexamethasone
Moxifloxacin – Fluorometholone
Moxifloxacin – Loteprednol
Moxifloxacin – Prednisolone


M
Bacteria survival rate (%)
P.aeruginosa
S.aureus
S.epidermidis
S.pneumoniae
Neomycin – Dexamethasone
N
Neomycin – Fluorometholone
O
Neomycin – Loteprednol
P
Neomycin – Prednisolone


U
V
W
X
Bacteria survival rate (%)
P.aeruginosa
S.aureus
S.epidermidis
S.pneumoniae
Polymyxin – Dexamethasone
Polymyxin – Fluorometholone
Polymyxin – Loteprednol
Polymyxin – Prednisolone


Q
R
S
T
Bacteria survival rate (%)
P.aeruginosa
S.aureus
S.epidermidis
S.pneumoniae
Ofloxacin – Dexamethasone
Ofloxacin – Fluorometholone
Ofloxacin – Loteprednol
Ofloxacin – Prednisolone


Y
Z
AA
AB
Bacteria survival rate (%)
P.aeruginosa
S.aureus
S.epidermidis
S.pneumoniae
Tobramycin – Dexamethasone
Tobramycin – Fluorometholone
Tobramycin – Loteprednol
Tobramycin – Prednisolone

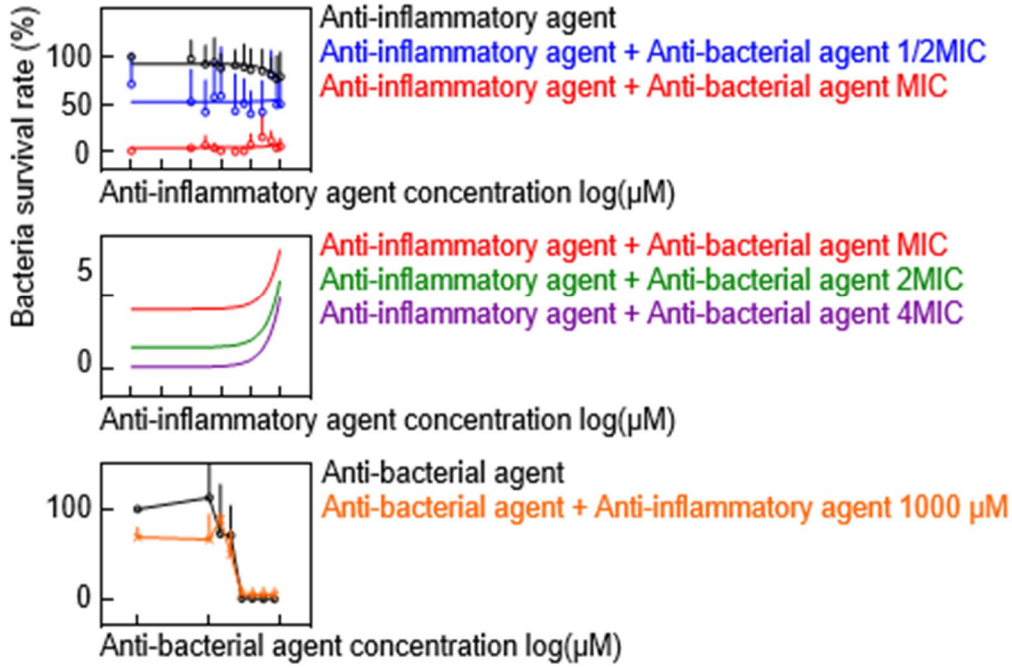
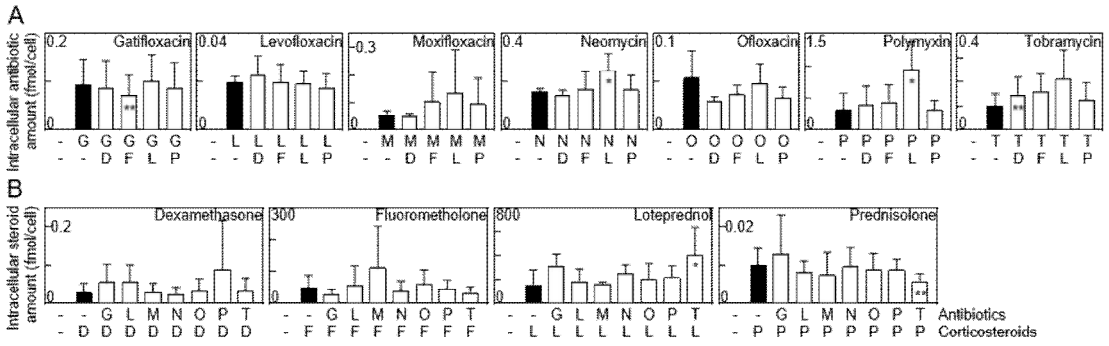


Figure 3. Pharmacodynamic interactions between antibiotics and corticosteroids.

Antibacterial agent-free (black), 0.5 MIC antibacterial agent (blue), and MIC antibiotic combined with corticosteroids (red) are presented bacterial survival rate in row 1. Logarithmic corticosteroid concentrations are depicted on the x-axis, with a point representing a value at each concentration of corticosteroid, and a straight line representing a linear regression. In the straight line graph, row 2 shows a linear regression analysis of bacterial survival in studies with combinations of corticosteroids and antibiotics at MIC levels (red), 2 MIC levels (green), and 4 MIC levels (purple). A logarithmic corticosteroid concentration is shown on the x-axis. Raw 3 presents bacterial survival rates when treated by antibiotic alone (black) or with 1000 μM of corticosteroid combined (orange). Logarithmic antibiotic concentrations are depicted on the x-axis. This analysis shows that *Pseudomonas aeruginosa* results in column 1, *Staphylococcus aureus* results in column 2, *Staphylococcus epidermidis* results in column 3, and *Streptococcus pneumoniae* results in column 4. All experiments were performed in triplicate.



C

Corticosteroids		-	Dexamethasone	Fluorometholone	Loteprednol	Prednisolone
Antibiotics	Gatifloxacin	0.095	0.087 (0.857)	0.072 (0.531)	0.101 (0.880)	0.088 (0.857)
	Levofloxacin	0.020	0.023 (0.545)	0.02 (0.987)	0.019 (0.829)	0.017 (0.488)
	Moxifloxacin	0.052	0.05 (0.876)	0.103 (0.385)	0.134 (0.345)	0.095 (0.401)
	Neomycin	0.158	0.144 (0.289)	0.168 (0.815)	0.245 (0.058)	0.166 0.819)
	Ofloxacin	0.054	0.03 (0.151)	0.037 (0.295)	0.049 (0.779)	0.033 (0.229)
	Polymyxin	0.311	0.388 (0.711)	0.424 (0.579)	0.945 (0.046)	0.312 (0.994)
	Tobramycin	0.099	0.142 (0.395)	0.159 (0.237)	0.21 (0.149)	0.125 (0.580)

D

Antibiotics		-	Gatifloxacin	Levofloxacin	Moxifloxacin	Neomycin	Ofloxacin	Polymyxin	Tobramycin
Corticosteroids	Dexamethasone	0.028	0.055 (0.350)	0.058 (0.272)	0.03 (0.935)	0.025 (0.842)	0.033 (0.851)	0.089 (0.390)	0.032 (0.858)
	Fluorometholone	50.4	29.9 (0.360)	56.4 (0.864)	111.8 (0.351)	38.7 (0.644)	59.1 (0.750)	47.8 (0.911)	32 (0.421)
	Loteprednol	151.0	311.3 (0.071)	179.8 (0.728)	162.5 (0.888)	252.8 (0.198)	201.5 (0.570)	216.5 (0.477)	401.7 (0.055)
	Prednisolone	0.0099	0.0128 (0.549)	0.0083 (0.466)	0.0075 (0.495)	0.0096 (0.912)	0.0088 (0.655)	0.0087 (0.579)	0.0056 (0.115)

Figure 4. Pharmacokinetic interactions between antibiotics and corticosteroids.

Human corneal epithelial cells were treated with antibiotics and corticosteroids in combination, and their intracellular concentrations were determined. Different antibiotic concentrations are demonstrated in (A) and different corticosteroid concentrations in (B). "*" demonstrates the area where statistical significance is investigated using an unpaired t-test (and "**" for paired t-test) in the combination-treated group compared to the single drug group. The drug name is shown in the upper right corner of all graphs. (C) The quantitative evaluation of intercellular concentration of antibiotics alone and in combination with corticosteroids. (D) The quantitative evaluation of intercellular concentration of corticosteroids alone and in combination with antibiotics. The numbers in parentheses p-value. Experiments were performed independently and repeated at least three to a maximum of six times.

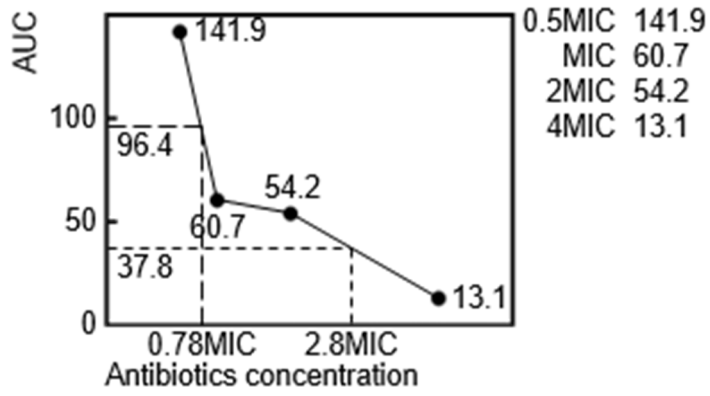
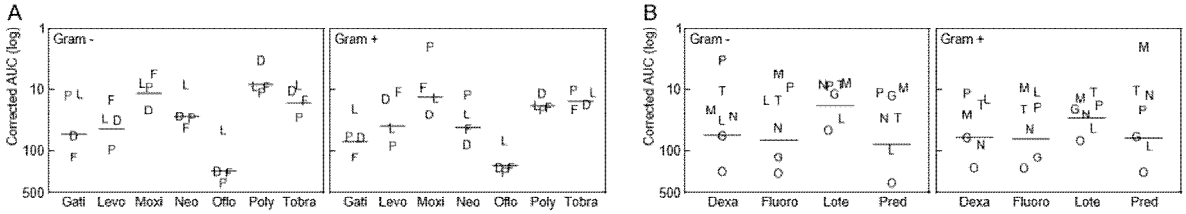


Figure 5. Methods for Calculating corrected AUC values considering intracellular concentration of antibiotics.

The intracellular antibiotic concentrations that was applied to the AUC values for every antibiotic concentration in Table 2 which shown in Figure 4. The ratio of intracellular antibiotic concentrations co-treated with corticosteroid shown in figure 4. The cAUC was calculated based on the proportional expression of AUC at ½ MIC, MIC, 2MIC and 4MIC.



C

		Gatifloxacin	Levofloxacin	Moxifloxacin	Neomycin	Ofloxacin	Polymyxin	Tobramycin
P. Aeruginosa Gram(-)	Dexamethasone	59.5	33.1	22.1	28.0	234.7	3.3	10.7
	Fluorometholone	134.5	15.0	5.5	44.2	250.6	9.2	15.4
	Loteprednol	12.0	31.2	7.9	8.4	48.1	8.8	8.5
	Prednisolone	12.7	100.1	9.4	30.7	362.1	11.5	30.1
S. Aureus Gram(+)	Dexamethasone	53.6	2.9	8.0	64.9	166.4	3.4	6.7
	Fluorometholone	142.2	9.7	16.0	10.0	171.4	9.8	49.6
	Loteprednol	9.0	28.6	7.3	10.8	47.2	5.7	8.5
	Prednisolone	35.0	66.3	1.9	20.2	177.9	3.5	3.8
S. Epidermidis Gram(+)	Dexamethasone	90.8	35.1	41.6	131.9	130.1	1.4	42.0
	Fluorometholone	75.6	16.0	8.2	114.8	219.8	19.9	8.3
	Loteprednol	37.4	60.7	22.6	59.1	81.9	29.7	15.4
	Prednisolone	102.2	90.8	2.9	14.4	378.9	14.4	25.1
S. Pneumonia Gram(+)	Dexamethasone	47.3	5.4	29.9	51.7	319.3	30.8	4.7
	Fluorometholone	191.3	7.9	4.1	14.3	229.2	29.7	6.7
	Loteprednol	16.7	45.0	12.1	8.6	85.1	20.2	10.1
	Prednisolone	47.3	106.1	1.3	2.8	171.5	48.4	2.2

Figure 6. Assessment of anti-bacterial activity based on corrected AUC.

Pseudomonas aeruginosa was derived from AUC values for (Gram-negative bacteria), and AUC values for Gram-positive bacteria were derived from an average of *Staphylococcus aureus, Staphylococcus epidermidis, and Streptococcus pneumoniae*. (A) Corrected AUC values for a combination of antibiotics with corticosteroids. (B) Corrected AUC values for a combination of four corticosteroids with antibiotics. (C)The quantitative evaluation of corrected (AUC) values of antibiotics and corticosteroids in combination. D, dexamethasone; F, fluorometholone; L, loteprednol; P, prednisolone; D, dexamethasone; F, fluorometholone; L, loteprednol; P, prednisolone.

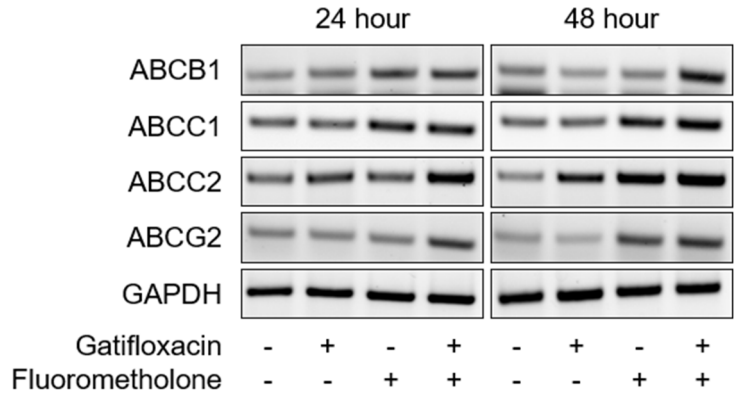


Figure 7. Effect of Gatifloxacin and fluorometholone on mRNA expression patterns of major efflux transporter.

20 μM gatifloxacin and 50 μM fluorometholone were administered to human corneal epithelial cells for 48 hours. After 24 hours and 48 hours of drug treatment, mRNA was extracted. And the expression proportion was ascertained by RT-PCR method. The internal control was the GAPDH.

Table 1: The four bacteria that commonly causes ophthalmic diseases.

Bacteria	10 years infection ratio (%) of bacterial keratitis
Pseudomonas aeruginosa	10.28
Staphylococcus aureus	12.15
Staphylococcus epidermidis	8.41
Streptococcus pneumoniae	8.41

The data were adopted from Mun et al.[14]

Table 2. Area under the curve (AUC) values of the combination of antibiotics and steroids calculated for four types of bacteria

		4MIC							2MIC							MIC							1/2MIC						
		Gati	Levo	Moxi	Neo	Oflo	Poly	Tobra	Gati	Levo	Moxi	Neo	Oflo	Poly	Tobra	Gati	Levo	Moxi	Neo	Oflo	Poly	Tobra	Gati	Levo	Moxi	Neo	Oflo	Poly	Tobra
P.Aeruginosa	Dexa	2.99	5.11	3.01	3.50	4.25	4.26	7.64	8.81	4.63	3.91	2.06	16.80	3.69	8.27	20.60	37.79	4.41	1.69	4.38	3.12	12.58	273.9	250.4	259.1	141.9	267.7	316.9	135.0
	Fluoro	12.47	3.53	5.26	23.35	12.79	9.58	7.83	15.13	3.53	4.91	28.52	10.08	10.20	18.37	63.01	12.95	26.48	45.23	10.70	8.63	10.99	214.8	305.9	263.3	244.1	385.0	265.3	278.0
	Lote	7.14	5.10	7.38	6.58	6.47	8.87	16.04	10.22	10.63	8.15	6.96	8.06	8.67	7.98	12.07	15.16	11.40	10.08	8.31	7.14	23.82	154.6	243.5	216.8	176.6	218.9	185.4	167.9
	Pred	1.73	0.50	5.12	7.01	6.21	26.87	4.78	2.45	2.98	5.09	8.20	6.80	12.06	8.95	3.11	3.29	29.38	31.78	50.12	11.50	37.66	67.8	408.7	305.0	324.1	461.8	153.5	174.2
S.Aureus	Dexa	3.19	0.40	4.44	2.33	2.63	1.56	2.84	5.70	0.71	4.70	6.85	3.28	2.39	4.60	4.98	3.24	4.97	25.10	12.38	3.69	8.30	322.2	156.2	48.6	237.4	188.4	61.3	103.8
	Fluoro	14.62	7.77	15.48	3.89	27.46	6.78	20.69	12.61	7.87	15.51	6.32	31.88	9.96	24.59	10.16	8.25	33.59	10.23	33.86	9.67	87.32	290.7	222.5	253.4	322.3	248.4	105.4	408.8
	Lote	5.94	10.59	7.96	6.79	5.82	5.63	9.63	6.89	7.41	7.05	5.62	6.12	5.86	8.41	9.11	14.68	9.21	17.05	11.06	6.95	7.65	282.3	212.8	298.8	154.6	202.5	345.3	98.6
	Pred	1.26	0.83	2.76	0.62	0.05	3.83	0.92	3.04	1.05	1.99	0.85	-0.31	5.15	1.24	2.19	7.29	1.51	21.12	1.59	3.47	4.68	223.3	254.5	147.9	227.8	234.2	142.8	155.5
S.Epidermidis	Dexa	2.01	6.67	4.99	3.57	1.50	1.45	2.21	2.38	6.23	5.18	5.86	1.97	1.38	3.03	43.57	39.83	18.09	49.10	3.09	1.34	71.59	351.3	356.0	357.3	490.7	148.3	437.5	388.2
	Fluoro	6.35	12.69	8.33	10.54	10.61	25.11	4.66	7.26	13.19	8.15	11.00	11.05	31.52	5.52	10.57	14.26	9.01	121.50	17.28	13.32	12.45	148.7	262.9	283.6	341.5	333.3	192.9	388.0
	Lote	20.77	18.04	24.89	15.52	18.42	26.05	15.40	22.62	21.30	21.67	25.83	23.01	33.61	15.36	38.38	41.16	31.17	99.31	23.19	24.50	141.70	453.4	319.4	278.3	398.4	334.0	349.8	375.7
	Pred	4.14	2.76	1.42	1.67	0.82	14.47	5.79	5.22	3.32	1.54	2.71	1.17	24.47	8.50	66.00	4.44	9.14	15.00	2.78	14.40	31.05	309.8	365.9	301.6	271.5	499.1	308.1	295.4
S.Pneumonia	Dexa	3.08	1.53	2.93	3.61	0.72	3.33	2.87	4.19	2.24	1.57	1.00	1.89	3.43	3.05	7.65	5.94	7.23	22.13	6.80	39.71	5.87	266.0	371.1	334.8	179.7	364.0	387.4	128.5
	Fluoro	4.15	5.38	3.40	2.85	3.86	3.58	3.33	4.47	4.55	3.81	3.44	6.70	5.13	3.12	8.04	5.93	12.44	15.03	8.82	43.69	12.18	397.3	293.1	311.7	249.8	352.6	395.9	272.8
	Lote	10.51	12.99	11.71	9.83	14.18	13.12	9.65	12.31	15.11	12.32	7.41	17.24	27.79	10.13	16.95	18.36	17.01	10.12	21.55	19.74	16.44	160.1	397.4	201.3	145.6	357.9	335.9	206.7
	Pred	0.18	0.03	0.45	0.53	11.74	0.95	0.94	0.98	0.76	0.69	2.22	3.07	2.31	1.59	1.89	14.21	3.97	2.85	3.19	48.60	2.44	307.7	399.0	257.3	162.2	225.3	417.7	43.2

Table 3. Linear regression analysis values calculated from four types of bacteria.

Pseudomonas aeruginosa	Gatifloxacin		Levofloxacin		Moxifloxacin		Neomycin		Ofloxacin		Polymyxin		Tobramycin	
	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value
Dexamethasone only	y = -0.01749x + 92.2	0.0007	y = -0.01749x + 92.2	0.0007	y = -0.01749*x + 92.2	0.0007	y = -0.01749x + 92.2	0.0007	y = -0.01749*x + 92.2	0.0007	y = -0.01749x + 92.2	0.0007	y = -0.01749x + 92.2	0.0007
Dexamethasone + antibiotic 1/2MIC	y = 0.002989x + 52.35	0.8003	y = 0.004375x + 50.46	0.5627	y = -0.008192x + 56.38	0.6649	y = -0.008768x + 32.82	0.5466	y = 0.0001258x + 54.68	0.9891	y = -0.01494x + 61.77	0.1009	y = -0.004718x + 28.56	0.7005
Dexamethasone + antibiotic MIC	y = 0.004255x + 4.019	0.3177	y = -0.001634x + 4.121	0.8149	y = 0.008867x - 0.04268	<0.0001	y = 0.003324x + 0.03077	<0.0001	y = 0.004488x + 0.4726	<0.0001	y = 0.006679x - 0.07224	<0.0001	y = 0.002576x + 3.727	0.7097
Dexamethasone + antibiotic 2MIC	y = 0.004756x + 1.433	0.004	y = 0.003093x + 0.7591	0.0002	y = 0.007697x - 0.1053	0.004	y = 0.00432x + 0.02626	<0.0001	y = -0.0002498x + 4.259	0.9752	y = 0.006726x + 0.03433	<0.0001	y = 0.004196x + 2.028	0.3239
Dexamethasone + antibiotic 4MIC	y = 0.004874x + 0.08617	<0.0001	y = 0.003257x + 0.7655	0.0009	y = 0.007268x - 0.1958	<0.0001	y = 0.006057x + 0.1082	<0.0001	y = 0.007417x + 0.1476	<0.0001	y = 0.007152x + 0.2469	<0.0001	y = 0.006136x + 0.8562	<0.0001
Fluorometholone only	y = -0.008799x + 101.7	0.0339	y = -0.008799x + 101.7	0.0339	y = -0.008799x + 101.7	0.0339	y = -0.008799x + 101.7	0.0339	y = -0.008799x + 101.7	0.0339	y = -0.008799x + 101.7	0.0339	y = -0.008799x + 101.7	0.0339
Fluorometholone + antibiotic 1/2MIC	y = 0.004132x + 42.68	0.5359	y = 0.005544x + 59.94	0.7033	y = 0.01403x + 54.36	0.1399	y = 0.02426x + 49.3	0.0824	y = -0.02712x + 76.66	0.1244	y = -0.01086x + 50.18	0.4572	y = 0.007829x + 54.13	0.652
Fluorometholone + antibiotic MIC	y = 0.01531x + 15.17	0.1694	y = 0.01198x + 1.83	<0.0001	y = 0.0128x + 5.735	0.0788	y = 0.009457x + 6.047	0.1329	y = 0.01233x + 1.224	<0.0001	y = 0.01466x + 0.4976	<0.0001	y = 0.01129x + 1.492	<0.0001
Fluorometholone + antibiotic 2MIC	y = 0.009407x + 3.126	0.0355	y = 0.01345x + 1.924	<0.0001	y = 0.009575x + 0.129	<0.0001	y = 0.009346x + 3.286	0.0291	y = 0.01256x + 1.095	<0.0001	y = 0.01702x + 0.5184	<0.0001	y = 0.004073x + 4.519	0.6328
Fluorometholone + antibiotic 4MIC	y = 0.01154x + 1.997	<0.0001	y = 0.01572x + 1.308	<0.0001	y = 0.007254x + 0.365	<0.0001	y = 0.007956x + 4.575	0.1118	y = 0.01404x + 1.369	<0.0001	y = 0.01952x + 0.1606	<0.0001	y = 0.009949x + 0.7959	<0.0001
Loteprednol only	y = 0.01284x + 99.46	0.0193	y = 0.01284x + 99.46	0.0193	y = 0.01284x + 99.46	0.0193	y = 0.01284x + 99.46	0.0193	y = 0.01284x + 99.46	0.0193	y = 0.01284x + 99.46	0.0193	y = 0.01284x + 99.46	0.0193
Loteprednol + antibiotic 1/2MIC	y = -0.009216x + 30.05	0.4155	y = 0.04092x + 44.56	0.0006	y = 0.04584x + 39.26	0.0016	y = -0.002568x + 34.68	0.8083	y = 0.02906x + 38.67	0.0321	y = -0.02667x + 37.73	0.0506	y = -0.00389x + 33.82	0.6072
Loteprednol + antibiotic MIC	y = 0.01772x + 0.923	<0.0001	y = 0.007346x + 2.46	0.0012	y = 0.008146x + 1.904	0.0219	y = 0.007268x + 1.241	0.0001	y = 0.01015x + 0.8217	<0.0001	y = 0.00947x + 0.5816	<0.0001	y = 0.002672x + 5.36	0.7243
Loteprednol + antibiotic 2MIC	y = 0.02164x + 0.1541	<0.0001	y = 0.00873x + 1.411	<0.0001	y = 0.008411x + 0.9535	<0.0001	y = 0.007279x + 0.8271	<0.0001	y = 0.01084x + 0.898	<0.0001	y = 0.009377x + 0.8325	<0.0001	y = 0.009001x + 1.106	<0.0001
Loteprednol + antibiotic 4MIC	y = 0.01838x - 0.1785	<0.0001	y = 0.007655x + 0.4234	<0.0001	y = 0.008669x + 0.7112	<0.0001	y = 0.006677x + 0.7507	<0.0001	y = 0.008881x + 0.8552	<0.0001	y = 0.00676x + 1.09	0.0025	y = 0.007834x + 1.782	0.036
Prednisolone only	y = -0.02457x + 109.5	0.0114	y = -0.02457x + 109.5	0.0114	y = -0.02457x + 109.5	0.0114	y = -0.02457x + 109.5	0.0114	y = -0.02457x + 109.5	0.0114	y = -0.02457x + 109.5	0.0114	y = -0.02457x + 109.5	0.0114
Prednisolone + antibiotic 1/2MIC	y = 0.02506x + 12.75	0.0372	y = -0.01704x + 80.06	0.267	y = 0.0444x + 53.98	0.0392	y = 0.01427x + 66.38	0.5222	y = -0.001146x + 84.78	0.9528	y = 0.0154x + 30.6	0.1594	y = 0.03627x + 21.68	0.0785
Prednisolone + antibiotic MIC	y = 0.01462x - 1.018	0.001	y = 0.006351x - 0.07907	0.0076	y = 0.01893x + 5.864	0.0415	y = 0.03218x + 3.722	0.0216	y = 0.01353x + 8.472	0.0266	y = 0.02505x - 0.3475	0.0003	y = 0.0019x + 10.32	0.8485
Prednisolone + antibiotic 2MIC	y = 0.01308x - 0.9684	0.0014	y = 0.002183x + 0.1676	0.0941	y = 0.004228x + 0.441	0.0141	y = 0.0146x + 0.2061	0.0017	y = 0.019x - 0.9544	0.072	y = 0.02494x - 0.1856	0.0002	y = 0.0223x - 0.5156	0.0002
Prednisolone + antibiotic 4MIC	y = 0.01013x - 0.804	0.0126	y = 0.0001074x + 0.0324	0.7796	y = 0.004411x + 0.7389	0.006	y = 0.02282x - 0.9493	<0.0001	y = 0.01722x - 0.8077	0.0132	y = 0.01921x + 1.501	0.0139	y = 0.01726x - 0.9113	0.0015

Staphylococcus aureus	Gatifloxacin		Levofloxacin		Moxifloxacin		Neomycin		Ofloxacin		Polymyxin		Tobramycin	
	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value
Dexamethasone only	y = -0.005859x + 98.94	0.0002	y = -0.005859x + 98.94	0.0002	y = -0.005859x + 98.94	0.0002	y = -0.005859x + 98.94	0.0002	y = -0.005859x + 98.94	0.0002	y = -0.005859x + 98.94	0.0002	y = -0.005859x + 98.94	0.0002
Dexamethasone + antibiotic 1/2MIC	y = -0.001526x + 63	0.8753	y = 0.006334x + 31.23	0.2625	y = 0.0146x + 8.608	0.0058	y = -0.006859x + 46.42	0.302	y = 0.007431x + 38.9	0.175	y = -0.008679x + 10.32	0.3928	y = 0.004631x + 21.46	0.5641
Dexamethasone + antibiotic MIC	y = 0.005688x + 0.4913	<0.0001	y = 0.001558x + 0.3959	0.0154	y = 0.007759x + 0.1935	<0.0001	y = 0.005329x + 5.019	0.4148	y = -0.001874x + 3.36	0.7729	y = 0.005178x + 0.2596	<0.0001	y = 0.004218x + 1.412	0.0003
Dexamethasone + antibiotic 2MIC	y = 0.004266x + 0.5946	<0.0001	y = 0.00165x - 0.03412	0.0001	y = 0.005338x + 0.4656	<0.0001	y = 0.006312x + 0.7354	<0.0001	y = 0.00303x + 0.2598	<0.0001	y = 0.005292x - 0.04978	<0.0001	y = 0.005601x + 0.4272	<0.0001
Dexamethasone + antibiotic 4MIC	y = 0.005508x + 0.1471	<0.0001	y = 0.001895x - 0.1224	<0.0001	y = 0.006271x + 0.2469	<0.0001	y = 0.005803x - 0.1693	<0.0001	y = 0.003408x + 0.175	<0.0001	y = 0.00485x - 0.1899	<0.0001	y = 0.005825x + 0.05726	<0.0001
Fluorometholone only	y = 0.007584x + 96.77	0.0033	y = 0.007584x + 96.77	0.0033	y = 0.007584x + 96.77	0.0033	y = 0.007584x + 96.77	0.0033	y = 0.007584x + 96.77	0.0033	y = 0.007584x + 96.77	0.0033	y = 0.007584x + 96.77	0.0033
Fluorometholone + antibiotic 1/2MIC	y = 0.00972x + 57.63	0.0112	y = -0.006035x + 44.27	0.2165	y = 0.01718x + 47.59	0.0012	y = -0.009154x + 62.68	0.5766	y = 0.02431x + 47.75	<0.0001	y = 0.008491x + 20.68	0.412	y = 0.00887x + 80.78	0.2851
Fluorometholone + antibiotic MIC	y = 0.02069x + 0.1259	<0.0001	y = 0.01257x + 0.4732	<0.0001	y = 0.02179x + 6.646	0.0011	y = 0.00902x + 1.281	<0.0001	y = 0.05708x + 2.22	<0.0001	y = 0.01239x + 0.8983	<0.0001	y = 0.03963x + 12.13	0.0031
Fluorometholone + antibiotic 2MIC	y = 0.02966x - 0.2965	<0.0001	y = 0.01649x + 0.1086	<0.0001	y = 0.02527x + 0.9912	<0.0001	y = 0.01004x + 0.4128	<0.0001	y = 0.05964x + 1.053	<0.0001	y = 0.01221x + 1.097	<0.0001	y = 0.04409x + 1.126	<0.0001
Fluorometholone + antibiotic 4MIC	y = 0.03316x - 0.1923	<0.0001	y = 0.01702x + 0.008401	<0.0001	y = 0.03311x + 0.1173	<0.0001	y = 0.008522x + 0.008533	<0.0001	y = 0.06266x - 0.2625	<0.0001	y = 0.008309x + 0.7935	<0.0001	y = 0.04581x + 0.01636	<0.0001
Loteprednol only	y = 0.02936x + 92.78	<0.0001	y = 0.02936x + 92.78	<0.0001	y = 0.02936x + 92.78	<0.0001	y = 0.02936x + 92.78	<0.0001	y = 0.02936x + 92.78	<0.0001	y = 0.02936x + 92.78	<0.0001	y = 0.02936x + 92.78	<0.0001
Loteprednol + antibiotic 1/2MIC	y = 0.01391x + 55.27	0.0123	y = 0.06794x + 35.25	<0.0001	y = 0.04077x + 55.42	<0.0001	y = -0.03131x + 33.04	0.0101	y = 0.07238x + 33.52	<0.0001	y = 0.01683x + 66.11	0.1452	y = 0.0509x + 14.6	<0.0001
Loteprednol + antibiotic MIC	y = 0.007887x + 1.062	<0.0001	y = 0.01839x + 1.101	0.0187	y = 0.01016x + 1.037	<0.0001	y = 0.006835x + 2.818	0.0396	y = 0.01594x + 0.8714	<0.0001	y = 0.01114x + 0.4886	<0.0001	y = 0.01529x + 0.2692	<0.0001
Loteprednol + antibiotic 2MIC	y = 0.01385x + 0.2646	<0.0001	y = 0.01143x + 0.3987	<0.0001	y = 0.008552x + 0.7162	<0.0001	y = 0.00716x + 0.5163	<0.0001	y = 0.009314x + 0.4589	<0.0001	y = 0.008185x + 0.5059	<0.0001	y = 0.01772x + 0.1703	<0.0001
Loteprednol + antibiotic 4MIC	y = 0.01202x + 0.1734	<0.0001	y = 0.01678x + 0.4786	0.0075	y = 0.008465x + 0.8413	<0.0001	y = 0.007322x + 0.8652	<0.0001	y = 0.007656x + 0.5736	<0.0001	y = 0.006935x + 0.5895	<0.0001	y = 0.0145x + 0.9103	0.0003
Prednisolone only	y = 0.0004832x + 93.39	0.8582	y = 0.0004832x + 93.39	0.8582	y = 0.0004832x + 93.39	0.8582	y = 0.0004832x + 93.39	0.8582	y = 0.0004832x + 93.39	0.8582	y = 0.0004832x + 93.39	0.8582	y = 0.0004832x + 93.39	0.8582
Prednisolone + antibiotic 1/2MIC	y = 0.003273x + 43.15	0.3127	y = 0.008638x + 49.75	0.3615	y = 0.02327x + 29.75	0.0005	y = -0.01849x + 46.79	0.0981	y = 0.0184x + 46.35	0.0121	y = -0.02279x + 28.11	0.0955	y = -0.02507x + 31.68	0.0562
Prednisolone + antibiotic MIC	y = 0.00309x + 0.1222	0.0023	y = 0.002171x + 1.62	0.4715	y = 0.002127x + 0.04568	0.0047	y = 0.01414x + 3.742	0.0412	y = 0.0006881x + 0.2274	0.1738	y = 0.000722*x + 0.7495	0.2007	y = 0.002562x + 0.6212	0.0054
Prednisolone + antibiotic 2MIC	y = 0.003634x + 0.1376	0.008	y = 0.002228x - 0.06894	0.0071	y = 0.002929x + 0.118	0.0072	y = 0.002286x - 0.07199	0.0073	y = 0.001174x - 0.226	0.0391	y = 0.0008603x + 0.7752	0.2368	y = 0.002702x - 0.05513	0.0093
Prednisolone + antibiotic 4MIC	y = 0.007209x - 0.5456	0.0022	y = 0.0029x - 0.1647	0.0069	y = 0.003306x + 0.2531	0.0089	y = 0.0005845x + 0.04662	0.1337	y = 0.001297x - 0.1496	0.0711	y = 0.0002076x + 0.6226	0.637	y = 0.002019x - 0.02982	0.0069

Staphylococcus epidermidis	Gatifloxacin		Levofloxacin		Moxifloxacin		Neomycin		Ofloxacin		Polymyxin		Tobramycin	
	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value
Dexamethasone only	y = 0.0412x + 106.7	0.0011	y = 0.0412x + 106.7	0.0011	y = 0.0412x + 106.7	0.0011	y = 0.0412x + 106.7	0.0011	y = 0.0412x + 106.7	0.0011	y = 0.0412x + 106.7	0.0011	y = 0.0412x + 106.7	0.0011
Dexamethasone + antibiotic 1/2MIC	y = 0.01194x + 70.39	0.0712	y = 0.009317x + 69.95	0.1699	y = 0.05216x + 66.78	0.0072	y = -0.003462x + 95.8	0.6944	y = 0.007158x + 26.07	0.4377	y = -0.04729x + 91.75	0.0206	y = -0.004681x + 75.99	0.7166
Dexamethasone + antibiotic MIC	y = 0.006254x + 12.64	0.7916	y = 0.01701x + 9.076	0.082	y = 0.006839x + 4.535	0.2622	y = -0.002563x + 11.36	0.7753	y = 0.002798x + 0.3289	<0.0001	y = 0.003661x - 0.07282	<0.0001	y = -0.005043x + 15.6	0.8215
Dexamethasone + antibiotic 2MIC	y = 0.00168x + 0.309	0.0005	y = 0.00209x + 1.3	0.0829	y = 0.00659x + 0.2948	<0.0001	y = 0.006318x + 0.5262	<0.0001	y = 0.002117x + 0.1195	0.0001	y = 0.002531x + 0.003715	0.0003	y = 0.003035x + 0.3706	<0.0001
Dexamethasone + antibiotic 4MIC	y = 0.002761x + 0.1315	<0.0001	y = 0.002538x + 1.335	0.0492	y = 0.005058x + 0.5016	<0.0001	y = 0.004555x + 0.3577	0.0001	y = 0.003006x - 0.09054	<0.0001	y = 0.002633x - 0.09378	<0.0001	y = 0.00234x + 0.203	<0.0001
Fluorometholone only	y = -0.002708x + 94.99	0.2212	y = -0.002708x + 94.99	0.2212	y = -0.002708x + 94.99	0.2212	y = -0.002708x + 94.99	0.2212	y = -0.002708x + 94.99	0.2212	y = -0.002708x + 94.99	0.2212	y = -0.002708x + 94.99	0.2212
Fluorometholone + antibiotic 1/2MIC	y = 0.008913x + 27.7	0.5884	y = 0.02005x + 48.74	0.0219	y = 0.01567x + 57.25	0.1171	y = 0.03274x + 63.93	0.1054	y = 0.0268x + 64.95	0.0004	y = -0.02165x + 26.61	0.3597	y = -0.03108x + 75.11	0.2272
Fluorometholone + antibiotic MIC	y = 0.00512x + 1.856	0.0072	y = 0.01093x + 2.155	<0.0001	y = 0.008245x + 1.257	<0.0001	y = -0.01682x + 24.38	0.3129	y = 0.04915x - 1.758	0.0022	y = 0.0235x + 0.6434	0.0033	y = 0.004359x + 2.274	0.1299
Fluorometholone + antibiotic 2MIC	y = 0.006489x + 0.9442	<0.0001	y = 0.01393x + 1.74	<0.0001	y = 0.007227x + 1.183	<0.0001	y = 0.01041x + 1.415	<0.0001	y = 0.009447x + 1.445	<0.0001	y = 0.005945x + 8.038	0.6283	y = 0.005819x + 0.6062	<0.0001
Fluorometholone + antibiotic 4MIC	y = 0.007016x + 0.7523	<0.0001	y = 0.01716x + 1.304	<0.0001	y = 0.007859x + 1.026	<0.0001	y = 0.0113x + 1.166	<0.0001	y = 0.01033x + 1.439	<0.0001	y = 0.005281x + 6.925	0.6535	y = 0.005449x + 0.4772	0.0005
Loteprednol only	y = 0.09005x + 109	<0.0001	y = 0.09005x + 109	<0.0001	y = 0.09005x + 109	<0.0001	y = 0.09005x + 109	<0.0001	y = 0.09005x + 109	<0.0001	y = 0.09005x + 109	<0.0001	y = 0.09005x + 109	<0.0001
Loteprednol + antibiotic 1/2MIC	y = 0.134x + 74.42	<0.0001	y = -0.03673x + 69.72	0.0775	y = 0.1971x + 68.69	0.1689	y = 0.07956x + 76.16	0.0155	y = 0.1427x + 52.6	0.0005	y = 0.446x + 83.76	<0.0001	y = -0.02082x + 83.17	0.4197
Loteprednol + antibiotic MIC	y = 0.04573x + 3.332	<0.0001	y = 0.04756x + 3.477	<0.0001	y = 0.04323x + 2.551	<0.0001	y = 0.04273x + 14.7	0.0232	y = 0.0447x + 0.5437	<0.0001	y = 0.04984x + 1.031	<0.0001	y = 0.001135x + 28.62	0.9462
Loteprednol + antibiotic 2MIC	y = 0.04504x + 0.2109	<0.0001	y = 0.04975x - 0.2697	<0.0001	y = 0.04597x + 0.1166	<0.0001	y = 0.0433x + 1.134	<0.0001	y = 0.03993x + 0.9313	<0.0001	y = 0.04339x + 2.888	<0.0001	y = 0.03124x + 0.2184	<0.0001
Loteprednol + antibiotic 4MIC	y = 0.03717x + 0.7443	<0.0001	y = 0.0397x + 0.05951	<0.0001	y = 0.04601x + 0.7837	<0.0001	y = 0.02965x + 0.4346	<0.0001	y = 0.03537x + 0.4447	<0.0001	y = 0.04114x + 1.562	<0.0001	y = 0.03079x + 0.2448	<0.0001
Prednisolone only	y = -0.009467x + 103	0.0306	y = -0.009467x + 103	0.0306	y = -0.009467x + 103	0.0306	y = -0.009467x + 103	0.0306	y = -0.009467x + 103	0.0306	y = -0.009467x + 103	0.0306	y = -0.009467x + 103	0.0306
Prednisolone + antibiotic 1/2MIC	y = 0.002922x + 57.6	0.8481	y = -0.02541x + 72.92	0.1326	y = -0.01146x + 60.15	0.3495	y = -0.04562x + 66.91	0.1133	y = 0.001483x + 97.9	0.8587	y = 0.006213x + 55.09	0.747	y = -0.004037x + 68.18	0.8469
Prednisolone + antibiotic MIC	y = -0.02086x + 21.06	0.2676	y = 0.0005399x + 0.7842	0.1648	y = 0.01669x + 0.2771	0.1116	y = -0.00231x + 3.766	0.7449	y = -0.0004593x + 0.4962	0.0869	y = -0.001822x + 3.693	0.7856	y = 0.01058x + 6.297	0.4751
Prednisolone + antibiotic 2MIC	y = 0.002682x + 0.7499	0.0063	y = -0.0002685x + 0.6898	0.2198	y = 6.958e-006x + 0.3048	0.9675	y = 0.001768x + 0.3232	0.0204	y = -0.0004906x + 0.3366	0.0823	y = -0.007312x + 8.558	0.574	y = 0.00322x + 1.202	0.0242
Prednisolone + antibiotic 4MIC	y = 0.002817x + 0.5464	0.0022	y = -0.0002304x + 0.5479	0.2527	y = -0.0003072x + 0.313	0.0517	y = 0.00122x + 0.2743	0.0182	y = -0.0001422x + 0.1692	0.5525	y = -0.0008962x + 3.867	0.9078	y = 0.004183x + 0.8572	0.0041

Streptococcus Pneumoniae	Gatifloxacin		Levofloxacin		Moxifloxacin		Neomycin		Ofloxacin		Polymyxin		Tobramycin	
	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value	Equation	p value
Dexamethasone only	y = 0.01894x + 107.7	0.0061	y = 0.01894x + 107.7	0.0061	y = 0.01894x + 107.7	0.0061	y = 0.01894x + 107.7	0.0061	y = 0.01894x + 107.7	0.0061	y = 0.01894x + 107.7	0.0061	y = 0.01894x + 107.7	0.0061
Dexamethasone + antibiotic 1/2MIC	y = 0.007015x + 54.93	0.5061	y = -0.003618x + 73.11	0.8212	y = -0.003131x + 70.81	0.8714	y = -0.03282x + 38.94	0.0003	y = -0.01946x + 75.07	0.1272	y = -0.01652x + 80.94	0.2007	y = -0.02774x + 27.11	0.0002
Dexamethasone + antibiotic MIC	y = 0.003162x + 1.178	0.0002	y = 0.002869x + 0.8088	<0.0001	y = 0.00468x + 0.9802	0.0002	y = -0.003213x + 5.055	0.4959	y = 0.004238x + 0.7799	<0.0001	y = -0.009658x + 9.411	0.3744	y = 0.003581x + 0.8288	<0.0001
Dexamethasone + antibiotic 2MIC	y = 0.002617x + 0.5893	<0.0001	y = 0.003408x + 0.1095	<0.0001	y = 0.001568x + 0.1407	0.0001	y = 0.004252x - 0.2487	<0.0001	y = 0.004811x - 0.155	<0.0001	y = 0.006948x - 0.02112	0.0001	y = 0.003606x + 0.3103	<0.0001
Dexamethasone + antibiotic 4MIC	y = 0.002051x + 0.3974	<0.0001	y = 0.002557x + 0.1201	0.0068	y = 0.00179x + 0.4289	0.2792	y = 0.003418x + 0.3012	<0.0001	y = 0.004132x - 0.3057	<0.0001	y = 0.002266x + 0.5445	0.0013	y = 0.002894x + 0.2247	<0.0001
Fluorometholone only	y = 0.001621x + 91.56	0.6644	y = 0.001621x + 91.56	0.6644	y = 0.001621x + 91.56	0.6644	y = 0.001621x + 91.56	0.6644	y = 0.001621x + 91.56	0.6644	y = 0.001621x + 91.56	0.6644	y = 0.001621x + 91.56	0.6644
Fluorometholone + antibiotic 1/2MIC	y = -0.006022x + 82.95	0.3771	y = 0.003254x + 56.19	0.6419	y = -0.0007426x + 64.51	0.9202	y = -0.02884x + 50.06	0.055	y = 0.008306x + 66.91	0.2967	y = -0.00112x + 79.96	0.9202	y = 0.002539x + 54.45	0.5567
Fluorometholone + antibiotic MIC	y = 0.006126x + 0.9688	<0.0001	y = 0.006857x + 0.5801	<0.0001	y = 0.009498x + 1.746	<0.0001	y = 0.003015x + 3.928	0.3059	y = 0.009924x + 0.9103	<0.0001	y = 0.008409x + 10.4	0.4741	y = 0.002919x + 2.48	0.0064
Fluorometholone + antibiotic 2MIC	y = 0.00648x + 0.2662	<0.0001	y = 0.005534x + 0.4447	<0.0001	y = 0.005195x + 0.3213	<0.0001	y = 0.004425x + 0.489	<0.0001	y = 0.01074x + 0.3994	<0.0001	y = 0.004586x + 0.6847	<0.0001	y = 0.004185x + 0.2569	<0.0001
Fluorometholone + antibiotic 4MIC	y = 0.006187x + 0.2769	<0.0001	y = 0.005017x + 0.6468	<0.0001	y = 0.005262x + 0.1957	<0.0001	y = 0.00659x - 0.05178	<0.0001	y = 0.004997x + 0.4501	<0.0001	y = 0.00394x + 0.4737	<0.0001	y = 0.003675x + 0.4466	0.0002
Loteprednol only	y = 0.0144x + 104.1	0.0389	y = 0.0144x + 104.1	0.0389	y = 0.0144x + 104.1	0.0389	y = 0.0144x + 104.1	0.0389	y = 0.0144x + 104.1	0.0389	y = 0.0144x + 104.1	0.0389	y = 0.0144x + 104.1	0.0389
Loteprednol + antibiotic 1/2MIC	y = 0.008978x + 29.95	0.1963	y = 0.006223x + 78.05	0.5322	y = 0.04626x + 35.1	0.0005	y = 0.04681x + 19.41	0.0017	y = 0.02009x + 69.4	0.262	y = 0.0923x + 57.74	0.0006	y = 0.04058x + 37.25	0.0031
Loteprednol + antibiotic MIC	y = 0.02942x + 0.6237	<0.0001	y = 0.03136x + 0.7496	<0.0001	y = 0.02355x + 1.327	<0.0001	y = 0.01924x + 0.3068	<0.0001	y = 0.03473x + 1.065	<0.0001	y = 0.0483x - 0.4648	<0.0001	y = 0.01768x + 1.827	<0.0001
Loteprednol + antibiotic 2MIC	y = 0.02408x + 0.1507	<0.0001	y = 0.02986x + 0.2385	<0.0001	y = 0.02418x + 0.1674	<0.0001	y = 0.01993x - 0.2881	<0.0001	y = 0.03471x + 0.2134	<0.0001	y = 0.04915x + 0.7174	0.0006	y = 0.01612x + 0.5611	<0.0001
Loteprednol + antibiotic 4MIC	y = 0.02328x - 0.1179	<0.0001	y = 0.02711x + 0.09926	<0.0001	y = 0.02619x - 0.07884	<0.0001	y = 0.02062x + 0.1792	<0.0001	y = 0.034x - 0.2813	<0.0001	y = 0.03117x - 0.2833	<0.0001	y = 0.01709x + 0.3478	<0.0001
Prednisolone only	y = -0.005206x + 99.66	0.1984	y = -0.005206x + 99.66	0.1984	y = -0.005206x + 99.66	0.1984	y = -0.005206x + 99.66	0.1984	y = -0.005206x + 99.66	0.1984	y = -0.005206x + 99.66	0.1984	y = -0.005206x + 99.66	0.1984
Prednisolone + antibiotic 1/2MIC	y = -0.008264x + 63.99	0.309	y = 0.005519x + 77.69	0.5517	y = -0.01869x + 52.13	0.0004	y = -0.03151x + 34.86	0.0039	y = 0.0205x + 41.51	0.0714	y = -0.04902x + 87.05	0.0027	y = -0.003296x + 9.456	0.56
Prednisolone + antibiotic MIC	y = 0.001172x + 0.2529	0.0169	y = 0.002936x + 3.333	0.2005	y = 0.00255x + 0.5656	0.0004	y = 0.002324x + 0.3524	0.0054	y = 0.003911x + 0.06112	0.0097	y = -0.01761x + 16.47	0.1602	y = 0.003227x + 0.1563	0.0084
Prednisolone + antibiotic 2MIC	y = 0.001222x + 0.04941	0.0073	y = 0.001593x - 0.01999	0.0013	y = 0.002057x - 0.1118	0.0226	y = 0.001751x + 0.08727	0.0393	y = 0.002107x + 0.5545	0.1849	y = 0.002671x + 0.1302	0.0125	y = 0.002561x + 0.04446	0.0143
Prednisolone + antibiotic 4MIC	y = 0.0008576x - 0.07479	0.0202	y = 0.0007369x - 0.07253	0.0653	y = 0.00285x - 0.2785	0.0014	y = 0.001239x - 0.05568	0.0267	y = -0.002174x + 3.549	0.5443	y = 0.003596x - 0.1814	0.0042	y = 0.001679x + 0.02549	0.0213

Table 4. Qualitative assessment of antibiotics interactions with corticosteroids

Antibiotics	Corticosteroids	Gram-negative bacteria (*Pseudomonas aeruginosa).*	Gram-positive bacteria (*Staphylococcus aureus, Staphylococcus epidermidis,* and *Streptococcus pneumoniae).*
Gatifloxacin	Dexamethasone	As the concentration of dexamethasone increases, the efficacy of gatifloxacin decreases by up to 15% and stabilizes when the concentration of gatifloxacin increases. The concentration of gatifloxacin remains unchanged, but the concentration of dexamethasone increases by about twofold, so there is a possibility that the effect of gatifloxacin is slightly decreased when gatifloxacin and dexamethasone are administered together.	As the concentration of dexamethasone increases, the efficacy of gatifloxacin decreases slightly by about 5% and stabilizes when the concentration of gatifloxacin increases in all bacteria.
	Fluorometholone	Regardless of the fluorometholone concentration, the efficacy of gatifloxacin decreases by up to 35.5% and stabilizes when the concentration of gatifloxacin increases. The concentration of gatifloxacin decreases by more than 20%, so the effect of gatifloxacin is decreased when gatifloxacin and fluorometholone are administered together.	As the concentration of fluorometholone increases, the efficacy of gatifloxacin decreases by about 7% to 22%. The concentration of gatifloxacin decreases by more than 20%, so the effect of gatifloxacin is decreased when gatifloxacin and fluorometholone are administered together.
	Loteprednol	As the concentration of loteprednol increases, the efficacy of gatifloxacin decreases by up to 22.8% and shows a similar pattern even when the concentration of gatifloxacin increases. The concentration of gatifloxacin remains unchanged, but the concentration of loteprednol increases by about twofold, so there is a possibility that the effect of gatifloxacin is decreased when gatifloxacin and loteprednol are administered together.	Regardless of the loteprednol concentration, the efficacy of gatifloxacin decreases by up to 10% to 50% and shows a similar pattern even when the concentration of gatifloxacin increases. The concentration of gatifloxacin remains unchanged, but the concentration of loteprednol increases by about twofold, so there is a possibility that the effect of gatifloxacin is decreased when gatifloxacin and loteprednol are administered together.
	Prednisolone	Only at the high concentration of loteprednol, the efficacy of gatifloxacin decreases by up to 20.9% and shows a similar pattern even when the concentration of gatifloxacin increases. The concentration of gatifloxacin remains unchanged, but the concentration of loteprednol increases by up to 28.7%, so there is a possibility that the effect of gatifloxacin is decreased when gatifloxacin and loteprednol are administered together.	Regardless of the prednisolone concentration, the efficacy of gatifloxacin is stable. The concentration of prednisolone increases by 28.7%, but the antibacterial effect is stable.
Levofloxacin	Dexamethasone	Regardless of the dexamethasone concentration, the efficacy of levofloxacin is stable. The concentration of levofloxacin increases by 14%, so the antibacterial effect is stable.	Regardless of the dexamethasone concentration, the efficacy of loteprednol decreases by up to 34.4% only for *S. epidermidis* and stabilizes when the concentration of levofloxacin increases. The concentration of levofloxacin increases by 14%, so the antibacterial effect is stable.
	Fluorometholone	As the concentration of fluorometholone increases, the efficacy of gatifloxacin decreases by up to 12.9% and shows a similar pattern even when the concentration of levofloxacin increases. The concentration of levofloxacin remains unchanged, and the concentration of dexamethasone increases by 11.9%, so there is a possibility that the effect of levofloxacin is slightly decreased when levofloxacin and fluorometholone are administered together.	As the concentration of fluorometholone increases, the efficacy of gatifloxacin decreases by up to 7.3% to 12.5% and shows a similar pattern even when the concentration of levofloxacin increases. The concentration of levofloxacin remains unchanged, and the concentration of dexamethasone increases by 11.9%, so there is a possibility that the effect of levofloxacin is slightly decreased when levofloxacin and fluorometholone are

			administered together.
	Loteprednol	Only at the high concentration of loteprednol, the efficacy of levofloxacin decreases by up to 12.6% and stabilizes when the concentration of levofloxacin increases. The concentration of levofloxacin remains unchanged, but the concentration of loteprednol increases by up to 19%, so there is a possibility that the effect of levofloxacin is decreased when levofloxacin and loteprednol are administered together.	Only at the high concentration of loteprednol, the efficacy of levofloxacin decreases by up to 32.6% to 56.3% and stabilizes slightly when the concentration of levofloxacin increases. The concentration of levofloxacin remains unchanged, but the concentration of loteprednol increases by up to 19%, so there is a possibility that the effect of levofloxacin is decreased when levofloxacin and loteprednol are administered together.
	Prednisolone	Only at the high concentration of prednisolone, the efficacy of levofloxacin decreases by up to 10.7% and stabilizes when the concentration of levofloxacin increases. The concentration of levofloxacin decreases by up to 11.9%, so there is a possibility that the effect of levofloxacin is decreased when levofloxacin and prednisolone are administered together.	Regardless of the prednisolone concentration, the efficacy of levofloxacin is stable and becomes more stabilized when the concentration of levofloxacin increases. The concentration of levofloxacin decreases by up to 11.9%, so there is a possibility that the effect of levofloxacin is decreased when levofloxacin and prednisolone are administered together.
Moxifloxacin	Dexamethasone	As the concentration of dexamethasone increases, the efficacy of moxifloxacin decreases by up to 9.8% and shows a similar pattern even when the concentration of moxifloxacin increases. The concentrations of moxifloxacin and dexamethasone remain unchanged.	As the concentration of dexamethasone increases, the efficacy of moxifloxacin decreases by up to 6% to 18.4% and stabilizes when the concentration of moxifloxacin increases. The concentrations of moxifloxacin and dexamethasone remain unchanged.
	Fluorometholone	As the concentration of fluorometholone increases, the efficacy of moxifloxacin decreases by up to 19.9% and stabilizes when the concentration of moxifloxacin increases. The concentration of moxifloxacin increases by about twofold, but the concentration of fluorometholone increases by more than 20%, so the effect of moxifloxacin is slightly decreased when moxifloxacin and fluorometholone are administered together.	As the concentration of fluorometholone increases, the efficacy of moxifloxacin decreases by up to 9.1% to 27% and stabilizes slightly when the concentration of moxifloxacin increases. The concentration of moxifloxacin increases by about twofold, but the concentration of fluorometholone increases by more than 20%, so the effect of moxifloxacin is slightly decreased when moxifloxacin and fluorometholone are administered together.
	Loteprednol	As the concentration of dexamethasone increases, the efficacy of moxifloxacin decreases by up to 9.5% and shows a similar pattern even when the concentration of moxifloxacin increases. The concentration of moxifloxacin increases by about twofold, but the concentration of loteprednol remains unchanged.	As the concentration of loteprednol increases, the efficacy of moxifloxacin decreases by up to 11.6% to 47.3% and shows a similar pattern even when the concentration of moxifloxacin increases. The concentration of moxifloxacin increases by about twofold, but the concentration of loteprednol remains unchanged.
	Prednisolone	Regardless of the prednisolone concentration, the efficacy of moxifloxacin decreases by up to 31.5% and stabilizes when the concentration of moxifloxacin increases. The concentration of moxifloxacin increases by 82.4%, so the antibacterial effect is stable.	As the concentration of prednisolone increases, the efficacy of moxifloxacin decreases by up to 41.4% only for *S. epidermidis* and stabilizes when the concentration of moxifloxacin increases. The concentration of moxifloxacin increases by 82.4% and the concentration of prednisolone decreases by up to 25%, so the antibacterial effect is stable.
Neomycin	Dexamethasone	Regardless of the dexamethasone concentration, the efficacy of neomycin is stable, but as the neomycin concentration increases, the efficacy of neomycin decreases at a high concentration of dexamethasone. The	Regardless of the dexamethasone concentration, the efficacy of neomycin decreases by up to 16.6% to 24.7% and stabilizes when the concentration of neomycin increases. The concentration of

		concentration of neomycin remains unchanged, and the concentration of dexamethasone decreases by 11.7%.	neomycin remains unchanged, and the concentration of dexamethasone decreases by 11.7%.
	Fluorometholone	Regardless of the fluorometholone concentration, the efficacy of neomycin decreases by up to 21.5% and shows a similar pattern even when the concentration of neomycin increases. The concentration of neomycin remains unchanged, and the concentration of fluorometholone increases by 33.3%.	Regardless of the fluorometholone concentration, the efficacy of neomycin decreases by up to 11% to 47.5% and stabilizes slightly when the concentration of neomycin increases. The concentration of neomycin remains unchanged, and the concentration of fluorometholone increases by up to 33.3%.
	Loteprednol	As the concentration of loteprednol increases, the efficacy of neomycin decreases by up to 9.7% and shows a similar pattern even when the concentration of neomycin increases. The concentration of neomycin increases by up to 54.7%, but the concentration of loteprednol increases by up to 67.4%, so there is a possibility that the effect of gatifloxacin is slightly decreased when gatifloxacin and loteprednol are administered together.	Regardless of the loteprednol concentration, the efficacy of neomycin decreases by up to 12.7% to 79.8% and stabilizes at the low concentration of loteprednol when the concentration of neomycin increases. The concentration of neomycin increases by up to 54.7%, but the concentration of loteprednol increases by up to 67.4%, so there is a possibility that the effect of gatifloxacin is slightly decreased when gatifloxacin and loteprednol are administered together.
	Prednisolone	As the concentration of prednisolone increases, the efficacy of neomycin decreases by up to 50.7% and stabilizes slightly when the concentration of moxifloxacin increases. The concentrations of neomycin and prednisolone remain unchanged.	Regardless of the prednisolone concentration, the efficacy of neomycin decreases by up to 8.5% to 26.8% and stabilizes when the concentration of neomycin increases. The concentrations of neomycin and prednisolone remain unchanged.
Ofloxacin	Dexamethasone	As the concentration of dexamethasone increases, the efficacy of ofloxacin decreases by up to 5.3% and shows a similar pattern even when the concentration of ofloxacin increases. The concentration of ofloxacin decreases by up to 43.7%, so there is a possibility that the effect of ofloxacin is decreased when ofloxacin and dexamethasone are administered together.	Regardless of the dexamethasone concentration, the efficacy of ofloxacin is stable and becomes more stabilized when the concentration of neomycin increases. The concentration of ofloxacin decreases by up to 43.7%, so there is a possibility that the effect of ofloxacin is decreased when ofloxacin and dexamethasone are administered together.
	Fluorometholone	As the concentration of fluorometholone increases, the efficacy of ofloxacin decreases by up to 12.2% and shows a similar pattern even when the concentration of ofloxacin increases. The concentration of ofloxacin decreases by up to 32%, so there is a possibility that the effect of ofloxacin is decreased when ofloxacin and fluorometholone are administered together.	As the concentration of fluorometholone increases, the efficacy of ofloxacin decreases by up to 12.5% to 57.1% and stabilizes slightly when the concentration of neomycin increases. The concentration of ofloxacin decreases by up to 32%, so there is a possibility that the effect of ofloxacin is decreased when ofloxacin and fluorometholone are administered together.
	Loteprednol	As the concentration of loteprednol increases, the efficacy of ofloxacin decreases by up to 10.9% and shows a similar pattern even when the concentration of ofloxacin increases. The concentration of ofloxacin remains unchanged, but the concentration of loteprednol increases by up to 33.4%, so there is a possibility that the effect of ofloxacin is decreased when ofloxacin and loteprednol are administered together.	As the concentration of loteprednol increases, the efficacy of ofloxacin decreases by up to 16.2% to 42.3% and shows a similar pattern even when the concentration of ofloxacin increases. The concentration of ofloxacin remains unchanged, but the concentration of loteprednol increases by up to 33.4%, so there is a possibility that the effect of ofloxacin is decreased when ofloxacin and loteprednol are administered together.
	Prednisolone	Regardless of the prednisolone concentration, the efficacy of ofloxacin decreases by up to 24.1% and stabilizes only at the low concentration of prednisolone when the	Regardless of the prednisolone concentration, the efficacy of ofloxacin is stable and becomes more stabilized when the concentration of neomycin increases. The

		concentration of ofloxacin increases. The concentration of ofloxacin decreases by up to 37.9%, so there is a possibility that the effect of ofloxacin is decreased when ofloxacin and prednisolone are administered together.	concentration of ofloxacin decreases by up to 37.9%, so there is a possibility that the effect of ofloxacin is decreased when ofloxacin and prednisolone are administered together.
Polymyxin	Dexamethasone	As the concentration of dexamethasone increases, the efficacy of polymyxin decreases by up to 6.7% and shows a similar pattern even when the concentration of polymyxin increases. The concentration of polymyxin increases by up to 24.6%, but the concentration of dexamethasone increases by more than threefold, so there is a possibility that the effect of polymyxin is slightly decreased when polymyxin and dexamethasone are administered together.	Regardless of the dexamethasone concentration, the efficacy of polymyxin decreases by up to 41.9% only for *S. pneumoniae* and stabilizes when the concentration of polymyxin increases. The concentration of polymyxin increases by up to 24.6%, but the concentration of dexamethasone increases by more than threefold, so there is a possibility that the effect of polymyxin is slightly decreased when polymyxin and dexamethasone are administered together.
	Fluorometholone	As the concentration of fluorometholone increases, the efficacy of polymyxin decreases by up to 15.4% and shows a similar pattern even when the concentration of polymyxin increases. The concentration of polymyxin increases by up to 36.2%, but the concentration of dexamethasone remains unchanged.	Regardless of the fluorometholone concentration, the efficacy of polymyxin decreases by up to 11.6% to 38.8% and stabilizes slightly when the concentration of polymyxin increases. The concentration of polymyxin increases by up to 36.2%, but the concentration of dexamethasone remains unchanged.
	Loteprednol	As the concentration of loteprednol increases, the efficacy of polymyxin decreases by up to 10.3% and shows a similar pattern even when the concentration of polymyxin increases. The concentration of polymyxin increases by about threefold, and the concentration of loteprednol increases by up to 43.4%, so there is a possibility that the effect of polymyxin is slightly decreased when polymyxin and loteprednol are administered together.	As the concentration of loteprednol increases, the efficacy of polymyxin decreases by up to 12.1% to 56.7% and stabilizes slightly when the concentration of polymyxin increases. The concentration of polymyxin increases by about threefold, but the concentration of loteprednol increases by up to 43.4%, so there is a possibility that the effect of polymyxin is slightly decreased when polymyxin and loteprednol are administered together.
	Prednisolone	Only at the high concentration of prednisolone, the efficacy of polymyxin decreases by up to 34.1% and shows a similar pattern even when the concentration of polymyxin increases. The concentration of polymyxin remains unchanged, and the concentration of prednisolone decreases by up to 12.5%.	Regardless of the fluorometholone concentration, the efficacy of polymyxin decreases by up to 2.3% to 38.9% and stabilizes slightly when the concentration of polymyxin increases. The concentration of polymyxin remains unchanged, and the concentration of prednisolone decreases by up to 12.5%.
Tobramycin	Dexamethasone	As the concentration of dexamethasone increases, the efficacy of tobramycin decreases by up to 7.2% and shows a similar pattern even when the concentration of polymyxin increases. The concentration of tobramycin increases by up to 43.2%, but the concentration of dexamethasone increases by up to 14.3%, so there is a possibility that the effect of tobramycin is slightly decreased when tobramycin and dexamethasone are administered together.	Regardless of the dexamethasone concentration, the efficacy of tobramycin decreases by up to 4.1% to 79.5% and stabilizes when the concentration of tobramycin increases. The concentration of tobramycin increases by up to 43.2%, but the concentration of dexamethasone increases by up to 14.3%, so there is a possibility that the effect of tobramycin is slightly decreased when tobramycin and dexamethasone are administered together.
	Fluorometholone	As the concentration of dexamethasone increases, the efficacy of tobramycin decreases by up to 13% and shows a similar pattern even when the concentration of polymyxin increases. The concentration of tobramycin increases by up to 60.1%, and the	Regardless of the fluorometholone concentration, the efficacy of tobramycin decreases by up to 5.8% to 46.4% and stabilizes only at the low concentration of fluorometholone when the concentration of tobramycin increases. The concentration of

		concentration of fluorometholone decreases by up to 36.6%.	tobramycin increases by up to 60.1%, and the concentration of fluorometholone decreases by up to 36.6%, so there is a possibility that the interaction between the two drugs is slightly decreased when fluorometholone and tobramycin are administered together.
	Loteprednol	Regardless of the loteprednol concentration, the efficacy of tobramycin decreases by up to 32% and stabilizes only at the low concentration of loteprednol when the concentration of tobramycin increases. The concentrations of tobramycin and loteprednol increase by more than twofold, so there is a possibility that the effect of tobramycin is slightly decreased when tobramycin and loteprednol are administered together.	Regardless of the loteprednol concentration, the efficacy of tobramycin decreases by up to 17% to 61.8% and stabilizes only at the low concentration of loteprednol when the concentration of tobramycin increases. The concentrations of tobramycin and loteprednol increase by more than twofold, so there is a possibility that the effect of tobramycin is decreased when tobramycin and loteprednol are administered together.
	Prednisolone	Regardless of the loteprednol concentration, the efficacy of tobramycin decreases by up to 35.3% and stabilizes only at the low concentration of prednisolone when the concentration of tobramycin increases. The concentration of tobramycin increases by up to 26.3%, and the concentration of prednisolone decreases by up to 43.5%.	Regardless of the loteprednol concentration, the efficacy of tobramycin decreases by up to 55.2% only for *S. epidermidis* and stabilizes when the concentration of tobramycin increases. The concentration of tobramycin increases by up to 26.3%, and the concentration of prednisolone decreases by up to 43.5%, so there is a possibility that the antibacterial effect is stable.

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국문초록

안질환에서 항생제와 코르티코스테로이드의 병용 투여는 매우 중요한 치료 방법이다. 그러나 항생제와 코르티코스테로이드가 점안액으로 병용 투여될 경우 상호간에 미치는 영향에 대한 연구는 지금까지 체계적으로 이루어진 적이 없다. 본 연구는 체외 약력학 및 약동학 상호작용을 바탕으로 코르티코스테로이드가 함께 투여한 여러 종류의 항생제에 미치는 영향을 알아보기 위해 설계되었다. 약력학과 약동학의 상호작용을 확인하기 위해서 각막에 감염을 일으키는 세균 중 가장 빈번하게 발견되는 4종을 선정하였고, 치료에 주로 사용되는 항생제 7종류와 코르티코스테로이드 4종류를 선택하였다. 항생제와 코르티코스테로이드간 상호작용의 정량적 평가를 위해 보정 곡선하 면적 (cAUC)을 고안하여 사용하였다. 병용투여된 코르티코스테로이드의 농도가 증가함에 따라 항생제의 효과는 감소하는 양상을 보였다. 인간 각막 상피세포에 항생제와 코르티코스테로이드를 병용처리하면 단독투여시에 비해 세포내 항생제의 농도는 0.56에서 3.04배까지, 코르티코스테로이드의 농도는 0.57에서 2.66배까지 변동하였다. 약물의 효과 변동과 세포내 농도 변화가 모두 고려되어 계산된 모든 약물의 cAUC 계산값은 1.3에서 378.9 사이에서 형성되었다. 코르티코스테로이드와 병용 투여시 그람 음성균에 대해 가장 적은 항생작용을 보인 것은 폴리마이신이었고 그람 양성균에 대해 가장 적 항생작용을 보인 것은 목시플록

사신이었다. 두 종류의 박테리아에 가장 큰 영향을 보인 것은 오플록사신과 코르티코스테로이드의 병용 투여였다. 항생제와의 상호작용이 가장 적은 코르티코스테로이드는 로테프레드놀이었으며 나머지 코르티코스테로이드들은 항생작용에 유효한 영향을 미쳤다. 본 연구 결과로부터 항생제와 코르티코스테로이드의 병용 투여가 서로의 세포내 농도에 영향을 미치고 항생제의 효과에도 영향을 미쳤다는 사실을 확인할 수 있었다. 또한 본 연구에서 평가된 약물 상호작용 정보는 임상에서 각막 감염 치료 약물 선택에 도움이 될 수 있는 기초 자료가 될 수 있을 것이다.

Key Words: 약물 상호작용, 세포간 농도, 약력학, 약동학, 박테리아, 항생제, 코르티코스테로이드, cAUC.

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