Original article
https://doi.org/10.18019/1028-4427-2025-31-5-587-601

# Antibiotic therapy for orthopedic infections caused by gram-negative pathogens over a 12-year observation period

**O.S. Tufanova[1]✉, S.A. Bozhkova[1], A.R. Kasimova[1,2], E.M. Gordina[1], A.N. Gvozdetsky[3], R.M. Tikhilov[1]**

[1] Vreden National Medical Research Center of Traumatology and Orthopedics, Saint Petersburg, Russian Federation
[2] Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russian Federation
[3] Mechnikov North-Western State Medical University, Saint Petersburg, Russian Federation

**Corresponding author**: Olga S. Tufanova, katieva@mail.ru

**Abstract**

**Introduction** Treatment of patients with orthopedic infection includes a combination of the optimal surgical debridement and adequate antibacterial therapy. Gram-negative bacteria are encountered in 13–28 % of orthopedic infections, and *A. baumannii, K. pneumoniae, P. aeruginosa* are significant bacteria notorious for its high and intrinsic antibiotic resistance and can be associated with worse outcomes.

The **objective** was to substantiate the choice of drug for targeted empirical and etiotropic antibacterial therapy based on the analysis of antibiotic resistance in leading gram-negative bacteria (*A. baumannii, K. pneumoniae, P. aeruginosa*) isolated from patients with orthopedic infection.

**Material and methods** Antibiotic sensitivity of leading Gram(–) microorganisms isolated from patients with orthopedic infection was retrospectively examined between 01.01.2011 and 31.12.2022. The average frequency of isolated resistant strains was examined and resistance trends of leading Gram(–) pathogens to various antimicrobialbacterial drugs (fluoroquinolones, co-trimoxazole, cephalosporins, carbapenems, monobactams, aminoglycosides, fosfomycin, colistin) determined.

**Results** Over a 12-year period, statistically significant trends were revealed towards an increase in the proportion of *A. baumannii* strains resistant to ciprofloxacin ($p = 0.024$) and levofloxacin ($p = 0.012$), and *P. aeruginosa* ($p = 0.018$) and *K. pneumoniae* ($p = 0.018$) strains resistant to ciprofloxacin. The predicted proportion of *A. baumannii* strains resistant to fluoroquinolones tends to 100 %. There was a significant increase in *A. baumannii* and *P. aeruginosa* strains resistant to cefoperazone+[sulbactam] ($p = 0.027$ and $p = 0.010$, respectively), *K. pneumoniae* strains resistant to meropenem and imipenem ($p = 0.037$ and $p = 0.003$, respectively), and *P. aeruginosa* strains resistant to imipenem ($p = 0.001$). No statistically significant trends were found for the remaining antibiotics; drug resistance of the pathogens remained stable or had a wave-like course over the 12-year period. Cefoperazone+[sulbactam] was the optimal drug active against Gram(–) bacteria.

**Discussion** There is an authoritative list of antimicrobiall drugs active against *A. baumannii, K. pneumoniae, P. aeruginosa* strains, mainly containing drugs for parenteral administration. The list is limited to one or two groups for resistant strains, and there are no drugs available in oral form. This causes difficulties in the infection control and a high rate of relapses. The negative dynamics in increasing antibiotic resistance of leading Gram(–) pathogens to fluoroquinolones, cephalosporins and carbapenems is a global problem necessitating the use of reserve antibiotics.

**Conclusion** Protected cephalosporin is more practical for targeted empirical initial antimicrobial therapy due to the lower risk of selected resistant strains. Fluoroquinolones and carbapenems can be used with the sensitivity known. Polymyxin B and fosfomycin should be considered as reserve drugs for the treatment of infections caused by strains resistant to other AB, and prescribed as part of combination therapy. Aminoglycosides and unprotected cephalosporins can be an alternative due to the pharmacokinetic characteristics and high level of resistance when more active drugs cannot be administered.

**Keywords**: implant-associated infection, orthopedic infection, periprosthetic joint infection, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii*, antibacterial therapy, antibiotic resistance, empirical therapy, etiotropic therapy

**For citation**: Tufanova OS, Bozhkova SA, Kasimova AR, Gordina EM, Gvozdetsky AN, Tikhilov RM. Antibiotic therapy for orthopedic infections caused by gram-negative pathogens over a 12-year observation period. *Genij Ortopedii*. 2025;31(5):587-601. doi: 10.18019/1028-4427-2025-31-5-587-601.

## INTRODUCTION

Peri-implant joint infections are among the most severe complications of musculoskeletal surgeries [1]. Gram(+) bacteria *S. aureus* and *S. epidermidis* are common pathogens causing orthopedic infections (OI), and gram-negative bacteria are encountered in 13–28 % [2, 3]. There may be specific local prevalence of the pathogens; microorganisms are reported to be as high as 61 % in some countries [4]. Gram-negative aerobes being most frequently isolated are the *Enterobacteriaceae* family (*K. pneumoniae* and E. coli) and non-fermenting bacteria (*P. aeruginosa, A. baumannii*).

Gram(–) bacteria *K. pneumoniae, P. aeruginosa* and *A. baumannii* are a group of common pathogens with documented critical and severe levels of antibiotic resistance designated as ESKAPE pathogens by the Infectious Diseases Society of America. Resistance to fluoroquinolones (FQ) antibiotics including cephalosporins (CS) and carbapenems (CP), which have traditionally been considered the drugs of choice, is a significant problem.

The involvement of Gram(–) bacteria in the etiology of implant-associated infection (IAI) is a poor prognostic sign. Relapses of the infections caused by Gram(–) bacteria are recorded in 50–60 % of patients with IAI during the first two years after debridement surgery [5, 6]. Researchers suggest a direct correlation between the antibiotic resistance of bacteria isolated from patients and the frequency of adverse outcomes [7]. The data substantiate the need for continuous local monitoring of the sensitivity of the microorganisms to antibacterial drugs to facilitate review of the options for initial empirical and etiotropic antibiotic therapy in hospital and at the outpatient stage.

Fluoroquinolones, unprotected and protected cephalosporins of the third and fourth generations, carbapenems, monobactams, aminoglycosides, fosfomycin, colistin and co-trimoxazole atr the main drugs with the spectrum of action including Gram(–) bacteria. The practical use of drugs of the groups has advantages and disadvantages, which will be discussed in this paper.

The **objective** was to substantiate the choice of drug for targeted empirical and etiotropic antibacterial therapy based on the analysis of antibiotic resistance in leading gram-negative bacteria (*A. baumannii, K. pneumoniae, P. aeruginosa*) isolated from patients with orthopedic infection.

## MATERIAL AND METHODS

A retrospective study of data on antibacterial resistance of common Gram(–) pathogens isolated from patients with OI was performed between January 1, 2011 to December 31, 2022. Common pathogens included microorganisms with prevalence exceeding 3.5 % in the total spectrum of OI pathogens according to previously published central monitoring [8].

Data on antibiotic resistance were obtained from the Microbiological Monitoring System Mikrob-2 program (MedProject-3, 2002–2020) and from the Across-Engineering laboratory information system (2021–2022). Bacteriological analysis of biomaterials obtained from patients was performed in accordance with accepted international standards of microbiological research (UK SMI). Species identification of grown cultures was produced with the biochemical method on Microlatest panels (Erba Lachema) using iEMS Reader MF (Labsistems, Finland) until 2021 and by the MALDI-TOF mass spectrometry method since 2021.

The sensitivity of the isolated strains of Gram(–) bacteria was determined to antimicrobial drugs included in the center's formulary list:

— *A. Baumannii*: to ciprofloxacin, levofloxacin, co-trimoxazole, cefoperazone+[sulbactam] (determined by cefoperazone), imipenem, meropenem, amikacin, gentamicin, colistin;

— *K. pneumoniae*: to ciprofloxacin, co-trimoxazole, ceftriaxone, cefoperazone+[sulbactam] (determined by cefoperazone), cefepime, imipenem, meropenem, aztreonam, colistin, fosfomycin (since 2017);

— *P. Aeruginosa*: to ciprofloxacin, levofloxacin, ceftazidime, ceftazidime+[avibactam], cefoperazone+[sulbactam] (determined by cefoperazone), cefepime, imipenem, meropenem, aztreonam, amikacin, gentamicin, colistin.

Throughout the 12-year period, susceptibility of strains was determined according to the breakpoints in the current version of EUCAST at the time of the initial microbiological study.

Absolute values and proportions of the whole (*n*, %) were used to describe categorical variables. Variables with a continuous distribution were described by the mean and standard deviation (M ± σ), discrete variables and ordered data were described by the median, 1–3 quartiles (Md [Q1; Q3]). The minimum and maximum values (|min; max|) were calculated.

The main trends in antibiotic resistance for the pathogens were presented by antibiotic groups including fluoroquinolones, co-trimoxazole, cephalosporins, carbapenems, monobactams, aminoglycosides, fosfomycin, polymyxin E (colistin). The resistance-time curve was modeled using the `mgcv` library. The proportion of resistant strains per year was used as the dependent variable, and time and bacterial species were used as independent variables. The nonlinear dependence was modeled using the cubic spline transformation method from time with the effect of interaction with group affiliation.

The beta distribution model was used with the dependent variable being in the range (0, 1). To exclude extreme values (0 and 1), the following transformation of the dependent variable was performed ($y \times (n - 1) + 0.5) / n$, where y is the dependent variable, n is the number of observations. The syntax of the model was as follows:

*gam (y ~ s(time, bs = 'cr', k = 5) + name + s(time, by = name, bs = 'cr', k = 5), family = betar()).*

The model was characterized by the pseudo-determination coefficient R2, normalized root of the mean square error (nRMSE), and degrees of freedom. the Linear trend hypotheses were tested to specify data with the models obtained. The average false discovery rate (FDR) was used to correct multiple hypothesis testing. All calculations were performed in the R v4.4.0 programming language.

## RESULTS

### *Fluoroquinolones (ciprofloxacin, levofloxacin)*

The mean resistance rate of A. baumannii, K. pneumoniae and P. aeruginosa strains was 83.7 % for ciprofloxacin [62.5–98.7], and 87.6 % for levofloxacin [50–98.6]. A statistically significant increase in the resistance rate of ciprofloxacin-resistant strains was observed for most common Gram(–) bacteria ($p = 0.024$) throughout the period. The proportion of resistant strains increased by 36.2 %, 25 % and 33.4 %, respectively, for *A. baumannii* ($p = 0.024$) (Fig. 1A), *K. pneumoniae* ($p = 0.018$) (Fig. 1B) and *P. aeruginosa* ($p = 0.018$) (Fig. 1C) between 2011 and 2022, and reached 98.7 %, 98.2 % and 66.7 %, respectively, by the end of the observation period.

A similar picture was observed with respect to levofloxacin. The general trend was characterized by a statistically significant increase in the proportion of *A. baumannii* strains resistant to the drug ($p = 0.012$). However, the isolation of levofloxacin-resistant *P. aeruginosa* strains had a wave-like pattern despite the predicted increase in the proportion of resistant isolates with no clear trend identified ($p = 0.461$).

The predicted isolation rate of fluoroquinolone-resistant *A. baumannii* will reach 100 % in the coming years. The level of 100 % will not be reached for *K. pneumoniae* and *P. aeruginosa* despite the obvious increase in resistance to fluoroquinolones.

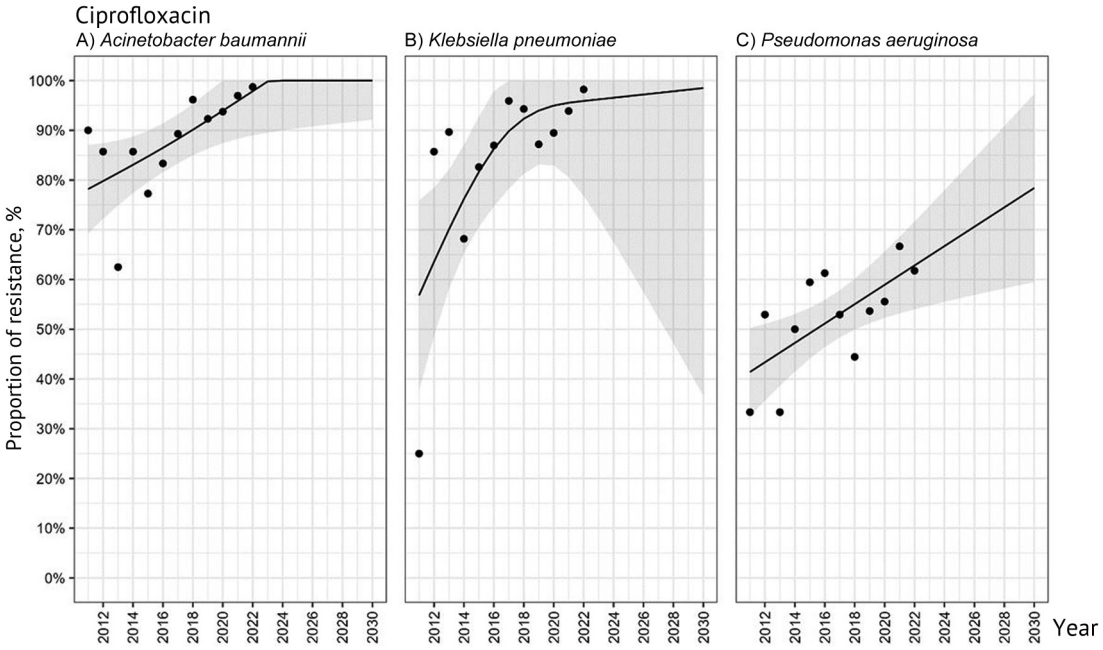



**Fig. 1** Prediction of resistance of *A. baumannii* (A), *K. pneumoniae* (B) and *P. aeruginosa* (C) to ciprofloxacin

### *Sulfamethoxazole-trimethoprim (co-trimoxazole)*

On average, 74.8 % [47.1–92.6] of *A. baumannii* strains were resistant to co-trimoxazole. There were two main trends in the dynamics of the isolation of resistant strains: the proportion of resistant isolates decreased by 38.9 % between 2011 and 2016 and increased by 45.5 % (Fig. 2A) between 2017 and 2022. Despite the predicted increase in the frequency of isolated resistant strains, a clear trend could not be identified ($p = 0.978$).

On average 81.9 % [52.4–97.1] strains demonstrated resistance to this antibiotic among *K. pneumoniae*. The frequency of isolation of co-trimoxazole-resistant *K. pneumoniae* strains was characterized by constant fluctuations. Despite a decrease in this indicator in the last three years of observation, the overall trend shows a statistically insignificant increase in the proportion of resistant strains ($p = 0.195$), which is likely to reach 100 % by 2030 (Fig. 2B).

### *Protected and unprotected cephalosporins*

The average proportion of *A. baumannii* strains resistant to cefoperazone+[sulbactam] was 53.3 % [18.8–83.3]. There was nonlinear dynamics in the indicator throughout the observation period (Fig. 3A); however, the overall trend over 12 years was characterized by a steady increase in the proportion of resistant strains ($p = 0.027$), which is predicted to reach 100 % by 2026. The frequency of isolation of *K. pneumoniae* strains resistant to cefepime and ceftriaxone remained almost steady over 12 years of observation and averaged to 86.3 % [76.2–97.4] and 85.0 % [76.9–96.4], respectively. The predicted frequency of isolation of resistant strains was close to average.

The dynamics in the isolated *K. pneumoniae* strains resistant to cefoperazone+[sulbactam] had a wave-like pattern; a decrease in this indicator was recorded between 2015 and 2017 (Fig. 3B). However, the overall trend demonstrated a statistically insignificant increase in resistance ($p = 0.225$). Against, Cefoperazone+[sulbactam] was most effective for *P. aeruginosa*, with 32.8 % [7.8–60.3] of the strains included in the study being resistant.

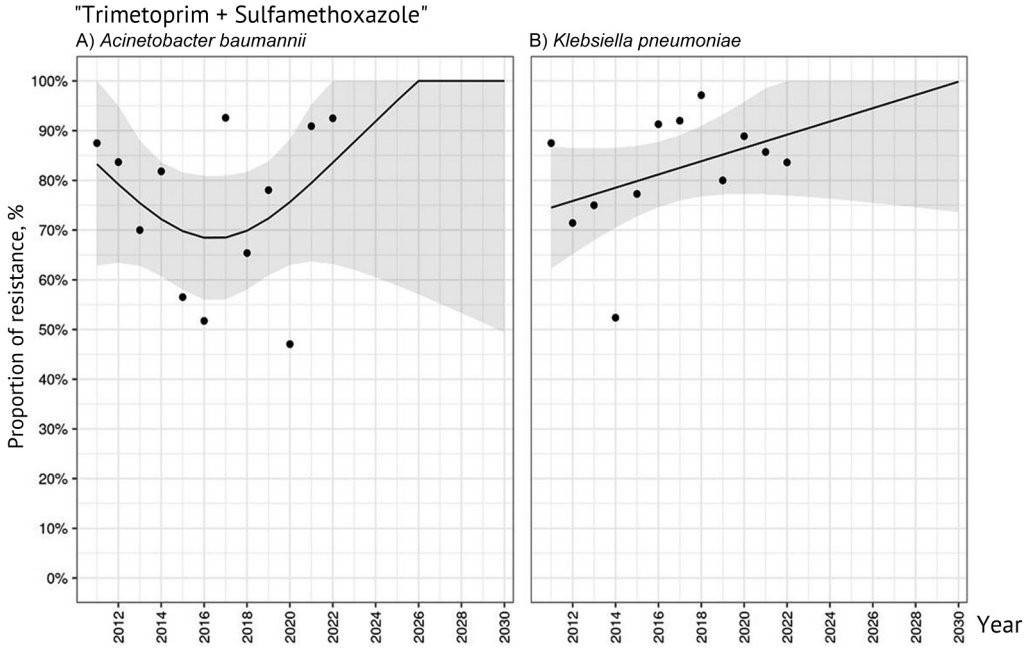



**Fig. 2** Predicted resistance of *A. baumannii* (A) and *K. pneumoniae* (B) for co-trimoxazole

For comparison, the average proportion of strains resistant to ceftazidime+[avibactam] was 41.2 % [25.4–50.0]; to ceftazidime, 45.9 % [17.3–75.0]; to cefepime, 49.1 % [19.2–75.0]. A negative trend of an increased proportion of resistant *P. aeruginosa* strains was revealed for cefoperazone+[sulbactam] ($p = 0.010$) (Fig. 3C). A minor increase in the proportion of resistant *P. aeruginosa* strains is predicted for ceftazidime, with no increase in the proportion of resistant *P. aeruginosa* strains predicted for cefepime.

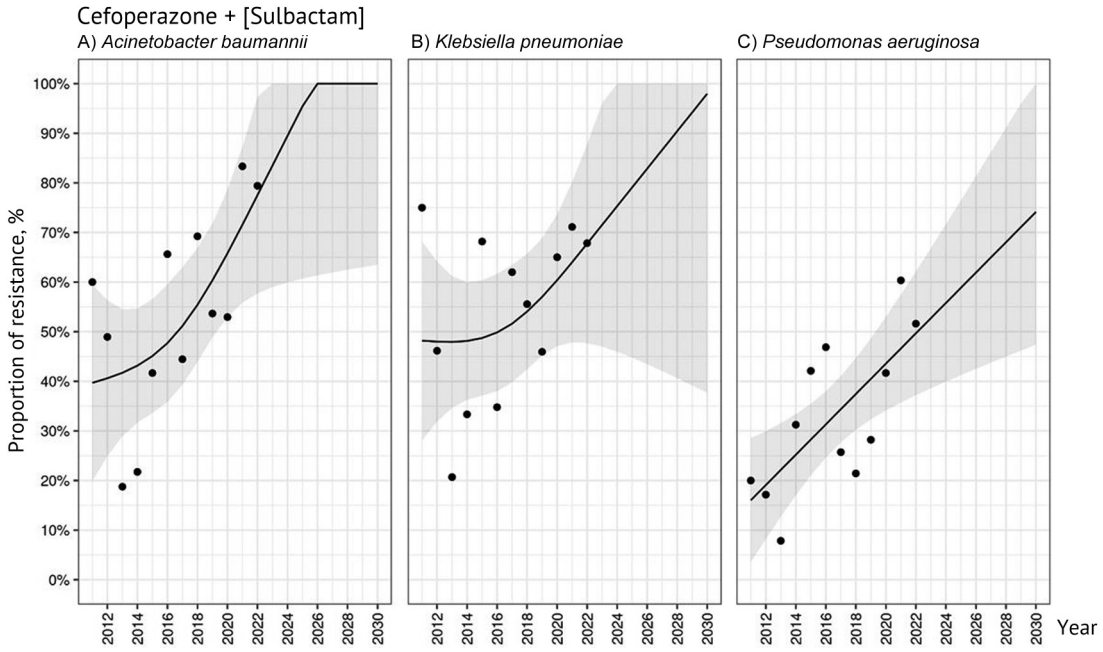



**Fig. 3** Predicted resistance of *A. baumannii* (A), *K. pneumoniae* (B) and *P. aeruginosa* (C) for Cefaperazone+[Sulbactam]

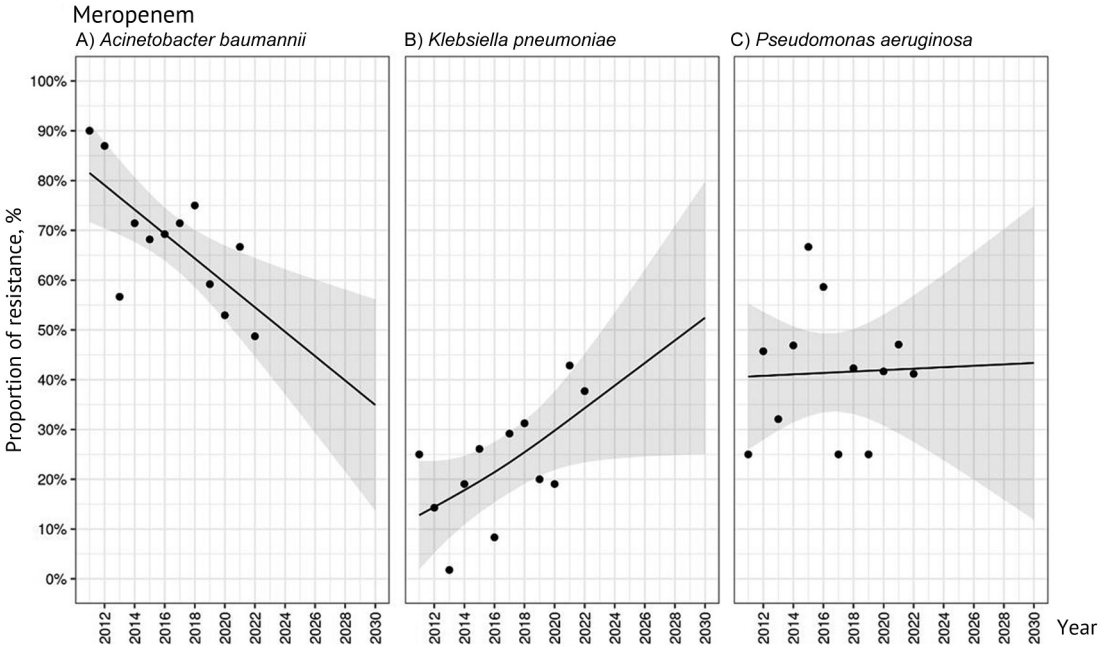
### *Carbapenems*

The average frequency of isolated imipenem-resistant *A. baumannii* was 56.7 % [33.3–75.0] with wave-like dynamics and no trend identified ($p = 0.877$). The predicted frequency of isolated resistant strains in the coming years will remain close to the average value. Despite the higher average proportion of meropenem-resistant *A. baumannii* strains compared to imipenem (68.0 %

[48.7–90.0]), the indicator decreased by 41.3 % during the observation period (Fig. 4A). A statistically significant decrease in the frequency of isolated meropenem-resistant strains was established ($p$ = 0.010) which is projected to decrease to 35 % by 2030.

The average resistance level of *K. pneumoniae* strains to imipenem and meropenem was identical and amounted to 23.0 % [3.6–42.9] and 22.9 % [1.8–42.9], respectively. The trends were comparable and characterized by a stable, statistically significant increase in the prevalence of *K. pneumoniae* strains resistant to imipenem ($p$ = 0.003) and meropenem ($p$ = 0.037) despite the wave-like course. More than 50 % of strains of the species will be resistant to CP by 2030 according to the forecast (Fig. 4B). The proportion of imipenem-sensitive *P. aeruginosa* strains decreased over 12 years of observation. The average proportion of resistant strains was 34.3 % [9.6–56.1] despite the lack of a linear trend. The overall trend can be characterized as a significant increase in the frequency of resistant strains ($p$ = 0.001), which was 50 % by 2022. About 75 % of *P. aeruginosa* strains are predicted to be resistant to imipenem by 2030. For meropenem, the mean proportion of resistant strains was 41.4 % [25.0–66.7], and the predicted isolation rate will be comparable at 45 % by 2030 (Fig. 4C).

**Fig. 4** Predicted resistance of *A. baumannii* (a), *K. pneumoniae* (b) и *P. aeruginosa* (c) for meropenem




### *Monobactams*

No dynamics in the level of resistance to aztreonam in *P. aeruginosa* and *K. pneumoniae* strains was identified. The average frequency of isolated aztreonam-resistant *P. aeruginosa* strains was 48 % [29.4–62.5], *K. pneumoniae* measuring 85.7 % [75–96.9]. No statistically significant trends in changes in the sensitivity of the pathogens to aztreonam were found.

### *Aminoglycosides (gentamicin, amikacin, tobramycin)*

The average frequency of isolated *A. baumannii* strains resistant to amikacin and gentamicin was similar and amounted to 78.1 % [40.0–97.4] and 78.2 % [50.0–98.1], respectively. The general trends were characterized by an increase in the proportion of resistant strains, which was statistically significant for amikacin ($p$ = 0.091) and insignificant for gentamicin ($p$ = 0.869). The predicted frequency of isolated *A. baumannii* strains resistant to aminoglycosides will reach 100 % by 2025–2026 (Fig. 5A).

On average, 52.5 % [13.0–87.5] of *K. pneumoniae* strains were resistant to amikacin. A steady decrease by 74.5 % was observed in the proportion of resistant strains between 2011 and 2016, and the opposite trend was observed between 2017 and 2021 (Fig. 5B). Despite a slight decrease in the resistant strains in 2022 compared to 2021, the overall trend can be characterized as an increase in the proportion of resistant strains ($p = 0.481$).

The dynamics in isolated amikacin-resistant *P. aeruginosa* showed less variability (Fig. 5C) than for *A. baumannii* and *K. pneumoniae*. On average, only 35 % [19.1–58.3] of cases of *P. aeruginosa* strains were resistant to it. The overall trend showed a decrease in the frequency of isolated resistant strains with low statistical significance of the prediction ($p = 0.762$). A persistent increase in resistant *P. aeruginosa* strains for gentamicin from 25 % to 83 % was identified between 2011 and 2017 with the average of 41.0 % [25.0–83.0]. The sensitivity of *P. aeruginosa* to gentamicin has not been determined since 2019.

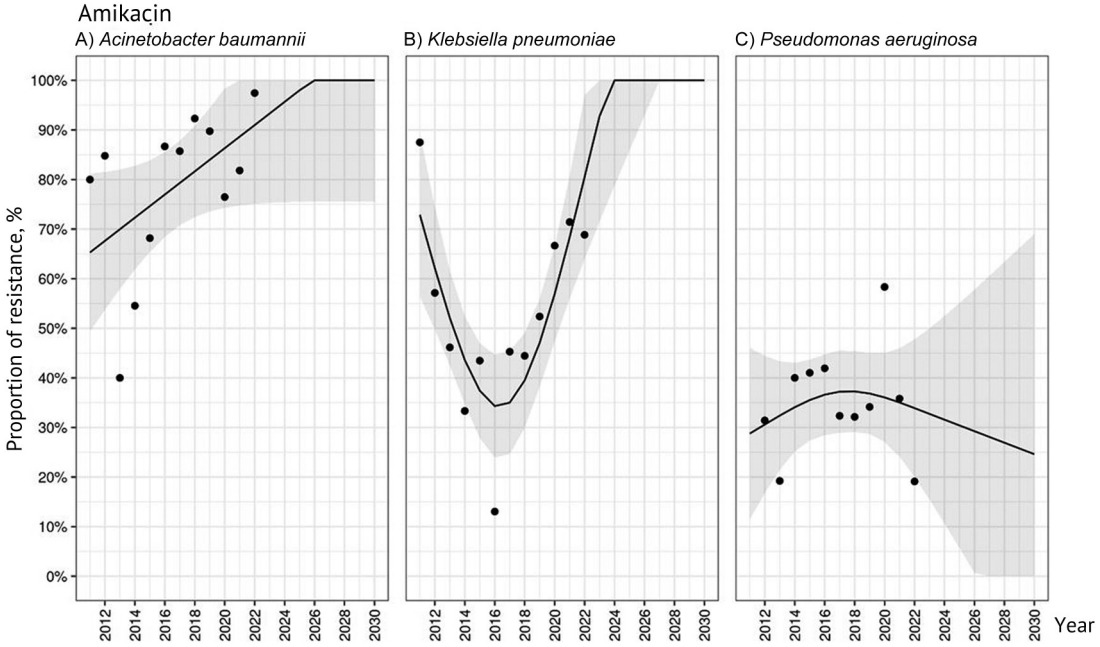



**Fig. 5** Predicted resistance of *A. baumannii* (A), *K. pneumoniae* (B) and *P. aeruginosa* (C) for amikacin

### *Polymyxin E (colistin)*

The average frequency of isolated colistin-resistant *A. baumannii* strains was 11.4 % [1.6–25]; *K. pneumoniae*, 13.2 % [6.7–30.8]; *P. aeruginosa*, 15.3 % [1.2–50].

There was a nonlinear frequency of isolated resistant *A. baumannii* strains between 2012 and 2015 with an increase in the proportion noted and the opposite trend observed in the following four years (Fig. 6A). The overall trend could be characterized as the absence of pronounced dynamics with the expected frequency of isolated colistin-resistant *A. baumannii* being close to the average ($p = 0.390$). The susceptibility of *K. pneumoniae* to colistin was determined since 2017. The nonlinear incidence of resistant strains was observed over the six years of observation (Fig. 6B) with a trend toward a statistically insignificant decrease in the resistance rate ($p = 0.151$). The proportion of colistin-resistant *P. aeruginosa* strains decreased throughout the observation period (Fig. 6C) reaching 1.2 % by 2022 ($p = 0.054$).

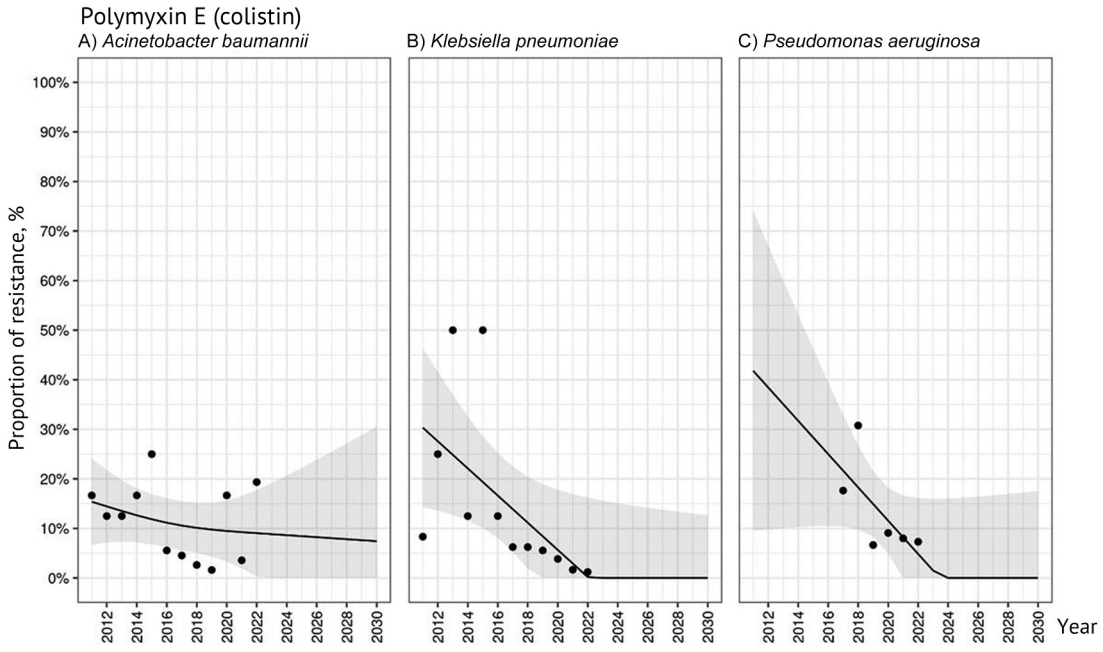



**Fig. 6** Predicted resistance of *A. baumannii* (A), *K. pneumoniae* (B) and *P. aeruginosa* (C) to polymyxin E (colistin)

### *Fosfomycin*

Fosfomycin susceptibility was determined only for *K. pneumoniae* starting from 2017. The average level of fosfomycin resistance of *K. pneumoniae* strains was 22.4 % over six years [3.6–48.7]. The incidence of fosfomycin-resistant strains decreased from 30 % to 5 % between 2017 and 2020 with a subsequent increase to 10 % by 2022. A trend could not be established due to the small number of observations.

## DISCUSSION

Infection associated with orthopedic implants requires a comprehensive approach including radical surgical treatment of the purulent focus, removal of the infected metal construct combined with etiotropic anti-inflammatory therapy. A prolonged antibiotic therapy for IAI would include a course of parenteral administration of drugs (7–14 days) and a course of oral administration (4–8 weeks). Treatment of patients with IAI caused by Gram(–) bacteria with MDR (multidrug-resistant) and XDR (extensively drug-resistant) susceptibility phenotypes can be associated with the limited choice of drugs that are active against pathogens. Antibiotics administered parenterally include CS, KP, monobactams, aminoglycosides, tigecycline, fosfomycin, polymyxin B, dioxidine and a list of oral drugs for stepwise ABT at the outpatient stage is limited to include FQ, co-trimoxazole, minocycline and cefixime.

The frequency of Gram(–) microorganisms with MDR and XDR phenotypes of antibiotic susceptibility reported by Benito et al. [9] was in line with that observed with our series. Our findings for the 12-year period 2011–2022 indicated Gram(–) pathogens including *K. pneumoniae* (4.78 %), *P. aeruginosa* (3.88 %) and *A. baumannii* (3.65 %) as most common [8]. Our data are generally comparable with the results reported by the Russian [2] and foreign [10] colleagues.

### *Fluoroquinolones (ciprofloxacin, levofloxacin)*

FH, cipro- and levofloxacin are drugs that are commonly used in the treatment of patients with OI. Ciprofloxacin is the drug of choice in the treatment of patients with IAI caused by Gram(–) bacteria including *P. aeruginosa*. The drug provides high concentrations in the bone having antibiofilm

activity (Table 1) with oral antibiotics being characterized by high bioavailability [12]. Step therapy is another positive aspect. Despite the fact that levofloxacin is slightly inferior to ciprofloxacin in terms of penetration into the bone [16], the concentration of levofloxacin in synovial fluid exceeds serum concentrations and ciprofloxacin and levofloxacin are characterized by similar levels of activity according to scientific publications. The pharmacokinetic features result in the widespread use of FQ in the treatment of patients with IAI caused by Gram(–) pathogens. Given the need to prescribe AB therapy for a long period the cardio- and neurotoxicity [13] of FQ are to be considered with a greater risk of tendon rupture, tendonitis, aortic aneurysm and mental disorders [12].

Table 1

Pharmacokinetic parameters of the main groups of antibiotics used in the treatment of patients with IAI

| INN | Residual/average concentration in blood (mcg/ml)[1] | Concentration in spongy/cortical bone (μg/ml) | Concentration in synovial fluid (mcg/ml) | Effect on biofilms | Possibility of step-by step ABT | Degree of expression HP[1] | References |
|---|---|---|---|---|---|---|---|
| Fluoroquinolones | Cipro — 0.2; levo — 0.6 | Cipro — 13.8/13.8; levo — 10/4.6 | cipro — penetrates well1; levo — 8,9 | yes | yes | + | [11–14] |
| Trimethoprim/ sulfamethoxazole | 1.3–2.8/32–63 | The serum to bone C ratio is 1.2 for trimethoprim; 0.36 for sulfamethoxazole. | | none | yes | ++ | [15–17] |
| III generation CA | ceftriaxone — 10.5; ceftazidime — 3 | ceftriaxone — ND/10.7; ceftazidime — 32.1/32.1 | ceftriaxone 60–100 % of plasma concentrations; ceftazidime — 25.6 | none | none | + | [11, 16, 18] |
| Cefoperazone + [sulbactam] | 69.23/6.49 | penetrates well[1] | penetrates well[1] | none | none | + | [19, 20] |
| Cefepime | 0.7 | 67.6/99.8 | does not penetrate well | none | none | + | [16, 21] |
| Carbapenems | meropenem — 8.0; imipenem — 1.0 | meropenem — 10.6/10.6; imipenem — 2.6/2.6 | meropenem — 12.5; imipenem — 13.8 | yes/none | none | + | [16, 22, 23] |
| Aztreons | does not exist; C max — 90 | 16 (20 % of C in serum) | 83 (95 % of C in serum) | yes | none | + | [16, 24] |
| Aminoglycosides | gentamicin — 2.0; amikacin — 10 | lOW C[1] | 25–50 % of C in serum | to immature | none | +++ | [16, 25, 26] |
| Polymyxin B | 2.0 | ND | does not penetrate well[1] | yes (*in vitro*) | none | +++ | [27–31] |
| Fosfomycin | 11.4 | penetrates well, bone to plasma C ratio 0.43 | penetrates well[1] | yes | none | ++ | [16, 32–37] |

*Note*: [1] Register of SmPC and LV of the EAEU, State Register of Medicines. Designations: C, concentration; ND, no data; C max, maximum serum concentration

According to the AMRmap platform, 93 % of P. aeruginosa strains isolated from patients with bone and joint infections in Russia between 2012 and 2022 were resistant to ciprofloxacin, which was 37 % higher than in the period between 2002 and 2012. Ciprofloxacin-resistant strains increased for *A. baumannii* and *K. pneumoniae* from 76 % to 93 % and from 66 % to 84 %, respectively [38]. A statistically significant trend towards increased resistance to ciprofloxacin was obtained for all of the above pathogens ($p = 0.025$ for *A. baumannii* and $p = 0.018$ for *K. pneumoniae* and *P. aeruginosa*) in our series. Increased resistance to levofloxacin was detected only for *A. baumannii* ($p = 0.012$). In recent years, the proportion of *A. baumannii* and *K. pneumoniae* strains resistant to ciprofloxacin has approached 100 % with the resistance of P. aeruginosa being 63 % by the end of the study period. The catastrophic growth of resistance to FCh of the main Gram(–) bacteria was reported by foreign researchers [39].

In addition to the high level of resistance there is another difficult question whether FQ can be used as monotherapy in cases where the infection is caused by an antibiotic-resistant strain of Gram(–) bacteria. Attempts to combine FQs with representatives of other groups of antibiotics in the presence of resistance are not convincing. Grossi et al. suggested that the additional administration of oral FQs to prolonged infusion of beta-lactam antibiotics being active against bacteria had no significant effect on the outcome of treatment of patients with IAI caused by strains resistant to FH during the entire treatment period (median 90 days) [40].

***Sulfamethoxazole-trimethoprim (co-trimoxazole)***

Co-trimoxazole is one of the alternatives to FH from the standpoint of stepwise ABT of OI caused by Gram(–) bacteria (except for naturally resistant *P. aeruginosa*). Co-trimoxazole has a bactericidal effect in relatively low concentrations due to the synergism of the components (trimethoprim and sulfamethoxazole) [41]. The drug penetrates bone tissue well (Table 1) and is indicated for acute and chronic osteomyelitis and can be prescribed as a step therapy. Unlike FQ, co-trimoxazole lacks antibiofilm activity [16].

There is a paucity of literature reporting co-trimoxazole to be used for the treatment of patients with OI caused by Gram(–) pathogens. The largest study of its effectiveness included 51 patients with bone and joint infection. However, the drug was mainly prescribed as part of a combination antibacterial therapy with no possibility to assess an individual contribution [42]. Co-trimoxazole used for treatment of outpatients with IAI caused by *K. pneumoniae* significantly improved the likelihood of a favorable outcome ($p = 0.038$) [43]. There are publications reported the experience with co-trimoxazole used for the treatment of patients with bone and joint infections caused by *E. cloacae, Burkholderia spp*. and *Stenotrophomonas maltophilia*. Long-term therapy with co-trimoxazole can be associated with side effects of varying severity primarily from the hematopoietic system and the skin [15].

According to Russian researchers, more than 70 % of *K. pneumonia*e and *A. baumanni*i strains isolated from OI patients are resistant to co-trimoxazole [2, 44]. According to the AMRmap platform, 50 % and 54 % of *A. baumannii* strains and 61 % and 69 % of representatives of the *Entrobacteriaceae* family isolated from patients with bone and joint infection were resistant to this drug in the periods between 2002 and 2012 and between 2012 and 2022, respectively, in Russia [38]. Our findings showed a more negative picture: resistance of *A. baumannii* to co-trimoxazole was 74.8 %, *K. pneumoniae* being 81.9 %.

***Beta-lactam antibiotics***

These drugs are generally characterized by good penetration into bone tissue (Table 1) and a varying activity against Gram(–) bacteria.

*Cephalosporins*

Third- and fourth-generation cefiximes, including inhibitor-protected forms, exhibit potential activity against Gram(–) bacteria. They are officially registered for the treatment of patients with bone and joint infections, with the exception of cefixime, the only orally administered third-generation cefixime. The use of cefixime for stepwise ABT in traumatology and orthopedics is significantly limited by poor penetration into bone tissue and the natural resistance of *P. aeruginosa* and some representatives of the *Enterobacteriaceae* family to the drug. The efficacy of this drug for outpatients with bone and joint infections remains under-explored. The proportion of drug-resistant Gram(–) bacteria strains was not examined in our series.

With the declared activity of ceftriaxone against some Gram(–) bacteria including representatives of the *Enterobactiaceae* family and *A. baumannii*, we did not find any publications devoted to its use in IAI of Gram(–) etiology. This is probably due to the high level of resistance to it (up to 90 % of strains) of A. baumannii and K. pneumoniae and natural resistance of P. aeruginosa. In our series, 85 % of *K. pneumoniae* strains were resistant to this drug by 2020–2022 [76.9–96.4].

For a long time, infection caused by *P. aeruginosa* was the main indication for ceftazidime. According to the ARMmap platform, the proportion of ceftazidime-resistant *P. aeruginosa* strains isolated from patients with bone and joint infection was 33–39 % for the period between 2002 and 2022. The susceptibility of *K. pneumoniae* and *A. baumannii* is not determined [38]. According to our data, resistance to ceftazidime in *P. aeruginosa* strains averaged 45.9 % without a specific trend throughout the observation period, which may be due to the limited use of this drug for the treatment of patients with OI.

The spectrum of action of cefoperazone includes predominantly Gram(–) bacteria, including *P. aeruginosa*, which distinguishes it favorably from ceftriaxone, and the drug penetrates well into the bone and the synovial fluid (Table 1). However, the combination of cefoperazone with the beta-lactamase inhibitor sulbactam is clinically more significant. This combination increases the antimicrobial activity of the drug including some KP-resistant strains of *A. baumannii*, and can be considered as a drug for targeted empirical ABT. Rou-Zhen et al. reported the effectiveness of cefoperazone+[sulbactam] in the treatment of patients with infection caused by Gram(–) bacteria being better in some cases than that with unprotected third-generation CS and carbapenems. The effect may be caused by a slower resistance with a lower risk of selection of resistant strains [17].

According to our data, the antibiotic retains greater activity against *P. aeruginosa*, and somewhat less against *A. baumannii* and *K. pneumoniae*. The statistically significant trend identified with increasing proportion of *A. baumannii* ($p = 0.027$) and *P. aeruginosa* ($p = 0.010$) strains resistant to cefoperazone+[sulbactam] is of concern with the sensitivity being higher than for other CS and comparable to KP. Hypocoagulation is one of the serious side effects that can be associated with the use of cefoperazone+[sulbactam] and must be taken into account with prescription to elderly patients and for a long course [20].

Cefepime is active against most Gram(–) microorganisms, with the exception of *Stenotrophomonas maltophilia*. According to the ARMmap platform, the proportion of *Enterobacteriaceae* strains resistant to this antibiotic isolated from patients with bone and joint infections increased from 43 % to 58 % over 20 years [38]. According to our data, resistance to cefepime was higher for *K. pneumoniae* and amounted to 86.3 % and 49.1 % for *P. aeruginosa* showing no significant changes throughout the observation period. Considering the poor penetration into synovial fluid (Table 1) and relatively high level of resistance of Gram(–) bacteria to the drug, Cefepime has no registered indications and is not indicated for patients with OI.

*Carbapenems*

CPs have the broadest spectrum of action among β-lactam antibiotics and have long been the antibiotic of choice for the treatment of patients with infections caused by Gram(–) bacteria producing ESBL (extended spectrum β-lactamases). Indications for imipenem+[cilastatin] include bone and joint infection caused only by *P. aeruginosa*, while meropenem does not have such an indication. Both carbapenems are widely used in the treatment of patients with OI caused by FC and CS-resistant Gram(–) bacteria. This is due to the fact that CPs reach sufficiently high concentrations in the bone and the synovial fluid (Table 1), allowing them to exceed the MIC for most Gram(–) bacteria.

In recent years, there is an increasing tendency for the proportion of Gram(–) bacteria demonstrating resistance to the drugs. According to the results of a multicenter study (2000–2015), ESBL-producing bacteria were isolated from 91 patients (72 %) with IAI with the resistance to CP recorded in 12 cases (9 %) [7]. According to the AMRmap platform, 70 % of *A. baumannii*, 25 % of *K. pneumoniae* and 40 % of *P. aeruginosa* strains isolated from patients with bone and joint infection between 2012 and 2022 were resistant to meropenem, with a marked increase in resistance observed for the three pathogens compared to the period 2002–2012. A similar trend was noted for imipenem [38]. A similar statistically significant increase in the proportion of *K. pneumoniae* ($p = 0.003$) and *P. aeruginosa* ($p = 0.001$) strains resistant to imipenem, which was absent for A. baumannii in our series. There was a statistically significant decrease in the proportion of *A. baumannii* strains resistant to meropenem ($p = 0.037$), which is not in line with the results of foreign and Russian authors and is probably a local finding that has no scientific role.

*Monobactams*

Aztreonam, the only current representative of the group, is naturally active against most Gram(–) bacteria, including ESBL producers, with the exception of *A. baumannii*. According to the ARMmap platform, 66.5 % of *Pseudomonas spp*. strains and 38.5 % of *Enterobacteriaceae* strains isolated from patients with bone and joint infections over the period between 2003 and 2022 retain sensitivity

to the drug, without any specific dynamics [38]. According to our study, 52 % of *P. aeruginosa* and 14.3 % of *K. pneumoniae* strains were susceptible to aztreonam. The resistance level remained stable throughout the observation period.

Aztreonam produces concentrations in synovial fluid comparable to serum concentrations, but penetrates the bone five times less (Table 1). A systematic review by Thabit et al. showed that bolus administration of a loading dose of the drug resulted in its concentration in cancellous bone tissue and synovial fluid exceeding the concentration of meropenem by 1.5 and 6.6 times, respectively [16]. However, the drug does not have a registered indication for the treatment of patients with bone and joint infection, and it is not used in routine clinical practice for the treatment of patients with intraocular infections and osteomyelitis. Existing publications evaluate the combined use of aztreonam with ceftazidime+avibactam in cases of intraocular infections caused by XDR strains of Gram(–) bacteria. Researchers recommend simultaneous, synchronous infusions through different catheter ports or through different venous accesses. This combination helps cover the maximum range of Gram(–) bacteria with extreme and pan-resistant resistance, even in the presence of resistance to each of them [24].

***Other reserve antibacterial drugs: aminoglycosides, fosfomycin, polymyxin B***

These drugs are not the treatment of choice for patients with acute respiratory infections, and are used in cases of pathogen resistance to fluoroquinolones, β-lactams, and co-trimoxazole as etiotropic antibiotics.

Aminoglycosides are antibacterial agents to which the vast majority of Gram(–) bacteria are naturally susceptible. Gentamicin and amikacin are commonly used for systemic antibiotic therapy in the Russian Federation. Aminoglycosides accumulate well in tissues with an active blood supply and much less so in bone tissue [16]. High doses of these drugs are needed for therapeutic concentrations of bone and synovial fluid increasing the risk of adverse reactions (Table 1), primarily nephro- [25] and ototoxicity [26]. Aminoglycosides are not commonly used in the treatment of patients with OI. According to the ARMmap platform, 76 % of *Acinetobacter spp*. strains and 60 % of *K. pneumoniae* strains isolated from patients with bone and joint infection during the period 2012–2022 were resistant to gentamicin [38]. Identical results were obtained in our series: 78.2 % of *A. baumannii* strains were resistant to gentamicin, with a statistically significant upward trend in the proportion of resistant strains.

Amikacin demonstrated slightly greater activity against the strains than gentamicin. According to the ARMmap platform, 33 % of *Pseudomonas spp.*, 30 % of *K. pneumoniae*, and 84 % of *Acinetobacter spp*. strains isolated from profile patients over the period 2012–2022 were resistant to amikacin, with negative dynamics compared to the period 2002–2012 [38]. According to our data, the level of resistance to amikacin was 78.1 % for *A. baumannii*, 35 % for *P. aeruginosa*, 52.5 % for *K. pneumoniae* which is generally comparable with the all-Russian data, but no specific trend identified.

Fosfomycin is active against a wide range of Gram(–) bacteria, including members of the *Enterobacteriaceae* family and some strains of *P. aeruginosa*, but is naturally inactive against *A. baumannii*. The drug is characterized by a pronounced synergistic effect when combined with beta-lactams, FQs, or aminoglycosides against a wide range of Gram(–) aerobic bacteria. Fosfomycin penetrates bone tissue well and has a registered indication for the treatment of patients with bone and joint infections (Table 1) [34].

The average incidence of fosfomycin-resistant *K. pneumoniae* strains was 22.4 % over 12 years at our center. However, no trend could be established due to the small number of observations: susceptibility to this antibiotic was determined only for strains with extreme resistance at the request of physicians. According to the AMRmap platform, only 14 % of *Enterobacteriaceae* strains isolated from patients with bone and joint infections were resistant to fosfomycin, and for 35 % of *Pseudomonas spp*. strains, the MIC of fosfomycin measured 64 mg/L [38].

Fosfomycin is commonly used for the treatment of patients with OI, but its use in monotherapy is not recommended due to the rapid development of resistance and decreased efficacy in the presence of a large amount of bacterial inoculum, which is typical for bone and joint infections [35]. Pronounced synergism of combined fosfomycin and colistin E in in vitro experiments against *K. pneumoniae* and *P. aeruginosa* in biofilms, with CP in the treatment of patients with infection caused by difficult-to-eradicate P. aeruginosa, is a serious justification for the use of fosfomycin as part of combination therapy [35].

Polymyxin B is active exclusively against Gram-negative bacteria. It cross-resists with colistin (polymyxin E), so susceptibility to polymyxin B is traditionally assessed using colistin. Resistance of Gram(–) bacteria to this drug reaches 10 % in some countries of Southeast Asia and the Mediterranean, however, in most countries, including the Russian Federation, polymyxin B retains its activity against the most problematic Gram(–) bacteria, including producers of various carbapenemases [29]. The frequency of isolated colistin-resistant strains was higher and averaged 11.4 % for *A. baumannii*, 13.2 % for *K. pneumoniae*, and 15.3 % for *P. aeruginosa* in our series. This was due to the determination of susceptibility only for multiresistant and panresistant strains. No significant dynamics in the level of resistance for *A. baumannii* and *K. pneumoniae* were observed due to the small number of observations.

The use of polymyxin B can be associated with the high frequency of adverse reactions including renal and urinary dysfunction, acute renal failure, and neurotoxicity. The drug poorly penetrates bone tissue and SF (Table 1), however, it exhibits pronounced antibiofilm activity due to its effect on metabolically inactive cells within the inner layers of the biofilm. The effect is observed with topical application of polymyxin; it is significantly weaker with systemic administration and higher doses of the antibiotic lead to an increased incidence of adverse reactions. Lora-Tamayo et al. recommend using a combination of colistin with other antibiotics active against Gram(–) bacteria: CS, KP, etc. [30].

The clinical efficacy of colistin has been confirmed by the results of multicenter studies. Papadopoulos et al. (2000–2015) performed a multicenter study and reported the frequency of favorable outcomes among patients with IAI caused by XRD strains, compared with MDR strains of bacteria treated by combination therapy with colistin as high as 66.7 % and 39.1 %, respectively ($p = 0.018$). The authors recommended the use of colistin in the absence of an alternative [7]. Another study demonstrated an advantage of using a combination of intravenous infusions of beta-lactams and polymyxin in the treatment of 44 patients with IAI caused by multidrug-resistant Gram(–) microorganisms, with adverse reactions occurring in 10 % of cases and being completely reversible [31]. Limitations of the study include the retrospective design and the local nature of the data. Predictions of microbial resistance to antibacterial drugs require confirmation in further studies.

## CONCLUSION

With negative dynamics in the increased proportion of strains of common Gram(–) bacteria resistant to cefoperazone+[sulbactam], meropenem and imipenem+cilastatin, the use of a protected cephalosporin for targeted empirical initial therapy appeared to be more practical due to the lower risk of selection of strains resistant to it. FH and KP can be used with the susceptibility proved. Polymyxin B and fosfomycin should be considered reserve drugs for the treatment of infections caused by strains resistant to other antibiotics and should only be prescribed as part of combination therapy. Aminoglycosides and unprotected cephalosporins are an alternative due to their pharmacokinetic properties and high levels of resistance when more active drugs cannot be used. The list of drugs (fluoroquinolones, co-trimoxazole) for oral administration remains limited at the outpatient stage; additional studies are needed to evaluate the effectiveness in the treatment of patients with IAI caused by resistant Gram(–) bacteria.

***Conflict of interest*** *The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.*

***Funding source*** *The authors received no financial support for the research and/or authorship of this article.*

***Ethics approval*** *Not applicable.*

***Consent for publication*** *Not required.*

## REFERENCES

1. Bozhkova SA, Tikhilov RM, Artyukh VA. Periprosthetic Joint Infection as a Socio-Economic Problem of Modern Orthopedics. *Annals of the Russian academy of medical sciences*. 2023. 78(6): 601-608. (In Russ.) doi: 10.15690/vramn8370.
2. Tsiskarashvili AV, Melikova RE, Novozhilova E.A. Analysis of six-year monitoring of common pathogens causing periprosthetic joint infection of major joints and the tendency to resistance. *Genij Ortopedii*. 2022;28(2):179-188. doi: 10.18019/1028-4427-2022-28-2-179-188.
3. Fisher C, Patel R. Rifampin, Rifapentine, and Rifabutin Are Active against Intracellular Periprosthetic Joint Infection-Associated Staphylococcus epidermidis. *Antimicrob Agents Chemother*. 2021;65(2):e01275-20. doi: 10.1128/AAC.01275-20.
4. Sebastian S, Malhotra R, Sreenivas V, et al. A Clinico-Microbiological Study of Prosthetic Joint Infections in an Indian Tertiary Care Hospital: Role of Universal 16S rRNA Gene Polymerase Chain Reaction and Sequencing in Diagnosis. *Indian J Orthop*. 2019;53(5):646-654. doi: 10.4103/ortho.IJOrtho_551_18.
5. Bozhkova S, Tikhilov R, Labutin D, et al. Failure of the first step of two-stage revision due to polymicrobial prosthetic joint infection of the hip. *J Orthop Traumatol*. 2016;17(4):369-376. doi: 10.1007/s10195-016-0417-8.
6. Pfang BG, García-Cañete J, García-Lasheras J, et al. Orthopedic Implant-Associated Infection by Multidrug Resistant Enterobacteriaceae. *J Clin Med*. 2019;8(2):220. doi: 10.3390/jcm8020220.
7. Papadopoulos A, Ribera A, Mavrogenis AF, et al. Multidrug-resistant and extensively drug-resistant Gram-negative prosthetic joint infections: Role of surgery and impact of colistin administration. *Int J Antimicrob Agents*. 2019 Mar;53(3):294-301. doi: 10.1016/j.ijantimicag.2018.10.018.
8. Kasimova AR, Tufanova OS, GordinaEM, et al. Twelve-year dynamics of leading pathogens spectrum causing orthopedic infection: a retrospective study. *Traumatology and orthopedics of Russia*. 2024;30(1):66-75. doi: 10.17816/2311-2905-16720.
9. Benito N, Franco M, Ribera A, et al. Time trends in the aetiology of prosthetic joint infections: a multicentre cohort study. *Clin Microbiol Infect*. 2016;22(8):732.e1-8. doi: 10.1016/j.cmi.2016.05.004.
10. Drago L, De Vecchi E, Bortolin M, et al. Epidemiology and Antibiotic Resistance of Late Prosthetic Knee and Hip Infections. *J Arthroplasty*. 2017;32(8):2496-2500. doi: 10.1016/j.arth.2017.03.005.
11. Morgan JR, Paull A, O'Sullivan M, Williams BD. The penetration of ceftriaxone into synovial fluid of the inflamed joint. *J Antimicrob Chemother*. 1985;16(3):367-371. doi: 10.1093/jac/16.3.367.
12. Azamgarhi T, Scarborough M, Peter-Akhigbe V, et al. Fluoroquinolones in orthopaedic infection: balancing risks and rewards. *J Antimicrob Chemother*. 2024;79(10):2413-2416. doi: 10.1093/jac/dkae286.
13. Hussen NHA, Qadir SH, Rahman HS, et al. Long-term toxicity of fluoroquinolones: a comprehensive review. *Drug Chem Toxicol*. 2024;47(5):795-806. doi: 10.1080/01480545.2023.2240036.
14. Belov BS. Ciprofloxacin in rheumatology: efficacy and safety questions. *Scientific and practical rheumatology*. 2004;42(1):43-47 (In Russ.) doi: 10.14412/1995-4484-2004-1382.
15. Sukasem C, Pratoomwun J, Satapornpong P, et al. Genetic Association of Co-Trimoxazole-Induced Severe Cutaneous Adverse Reactions Is Phenotype-Specific: HLA Class I Genotypes and Haplotypes. *Clin Pharmacol Ther*. 2020;108(5):1078-1089. doi: 10.1002/cpt.1915.
16. Thabit AK, Fatani DF, Bamakhrama MS, et al. Antibiotic penetration into bone and joints: An updated review. *Int J Infect Dis*. 2019;81:128-136. doi: 10.1016/j.ijid.2019.02.005.
17. Chen RZ, Lu PL, Yang TY, et al. Efficacy of cefoperazone/sulbactam for ESBL-producing Escherichia coli and Klebsiella pneumoniae bacteraemia and the factors associated with poor outcomes. *J Antimicrob Chemother*. 2024;79(3):648-655. doi: 10.1093/jac/dkae022.
18. Gergs U, Clauss T, Ihlefeld D, et al. Pharmacokinetics of ceftriaxone in plasma and bone of patients undergoing hip or knee surgery. *J Pharm Pharmacol*. 2014;66(11):1552-1558. doi: 10.1111/jphp.12282.
19. Wang Q, Wu Y, Chen B, Zhou J. Drug concentrations in the serum and cerebrospinal fluid of patients treated with cefoperazone/sulbactam after craniotomy. *BMC Anesthesiol*. 2015;15:33. doi: 10.1186/s12871-015-0012-1.
20. Miao W, Guo J, Cheng H, Zhao Q. Risk Factors for Cefoperazone/Sulbactam-Induced Coagulation Disorder. *Infect Drug Resist*. 2023;16:6277-6284. doi: 10.2147/IDR.S429706.
21. Tamma PD, Heil EL, Justo JA, et al. Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections. *Clin Infect Dis*. 2024:ciae403. doi: 10.1093/cid/ciae403.
22. Bondareva IB, Zyryanov SK, Chenkurov MS. Pharmacokinetic analysis of meropenem therapeutic drug monitoring data (TDM) in critically ill adult patients. *Antibiotics and chemotherapy*. 2021;66(11-12):31-38. (In Russ.) doi: 10.37489/0235-2990-2021-66-11-12-31-38.
23. Sidorenko SV, Partina IV, Ageevets VA. Imipenem: 30-Year Experience in Therapy. *Antibiotics and chemotherapy*. 2013;58(5-6):55-61. (In Russ.)
24. Popov DA, Zubareva NA, Parshakov AA. Aztreonam: clinical and pharmacological characteristics at the present stage. *Clinical microbiology and antimicrobial chemotherapy*. 2023;25(1):19-25. (In Russ.) doi:10.36488/cmac.2023.1.19-25.
25. Balakumar P, Rohilla A, Thangathirupathi A. Gentamicin-induced nephrotoxicity: Do we have a promising therapeutic approach to blunt it? *Pharmacol Res*. 2010;62(3):179-186. doi: 10.1016/j.phrs.2010.04.004.
26. Rutka J. Aminoglycoside Vestibulotoxicity. *Adv Otorhinolaryngol*. 2019;82:101-110. doi: 10.1159/000490277.
27. Eliseeva EV, Azizov IS, Zubareva NA. Review of the international consensus guidelines for the optimal use of the polymyxins. *Clinical microbiology and antimicrobial chemotherapy*. 2019;21(4):282-309. (In Russ.) doi:10.36488/cmac.2019.4.282-309.

28. Zhao Y, Chen H, Yu Z. Trough concentration may not be a good target for polymyxin B therapeutic drug monitoring. *Crit Care*. 2023;27(1):41. doi: 10.1186/s13054-023-04326-8.
29. Silva KED, Rossato L, Leite AF, Simionatto S. Overview of polymyxin resistance in Enterobacteriaceae. *Rev Soc Bras Med Trop*. 2022;55:e0349. doi: 10.1590/0037-8682-0349-2021.
30. Lora-Tamayo J, Murillo O, Ariza J. Clinical Use of Colistin in Biofilm-Associated Infections. *Adv Exp Med Biol*. 2019;1145:181-195. doi: 10.1007/978-3-030-16373-0_13.
31. Mancheño-Losa M, Murillo O, Benavent E, et al. Efficacy and safety of colistin plus beta-lactams for bone and joint infection caused by fluoroquinolone-resistant gram-negative bacilli: a prospective multicenter study. *Infection*. 2025;53(1):359-372. doi: 10.1007/s15010-024-02379-7.
32. Leonova MV. Fosfomycin: An old antibiotic and new perspectives. A review. *Consilium Medicum*. 2023;25(7):433–438. (In Russ.) doi: 10.26442/20751753.2023.7.202284.
33. Schintler MV, Traunmüller F, Metzler J, et al. High fosfomycin concentrations in bone and peripheral soft tissue in diabetic patients presenting with bacterial foot infection. *J Antimicrob Chemother*. 2009;64(3):574-578. doi: 10.1093/jac/dkp230.
34. Hashemian SMR, Farhadi Z, Farhadi T. Fosfomycin: the characteristics, activity, and use in critical care. *Ther Clin Risk Manag*. 2019;15:525-530. doi: 10.2147/TCRM.S199119.
35. Morata L, Soriano A. The role of fosfomycin in osteoarticular infection. *Rev Espanola Quimioter Publicacion Of Soc Espanola Quimioter*. 2019;32 Suppl 1(Suppl 1):30-36.
36. Kowalska-Krochmal B, Mączyńska B, Rurańska-Smutnicka D, et al. Assessment of the Susceptibility of Clinical Gram-Negative and Gram-Positive Bacterial Strains to Fosfomycin and Significance of This Antibiotic in Infection Treatment. *Pathogens*. 2022;11(12):1441. doi: 10.3390/pathogens11121441.
37. Konev VA, Bozhkova SA, Netylko GI et al. Results of the fosfomycin application for the impregnation of bone replacement materials in the treatment of chronic osteomyelitis. *Traumatology and Orthopedics of Russia*. 2016;22(2):43-56. (In Russ.) https://doi.org/10.21823/2311-2905-2016-0-2-43-56
38. Kuzmenkov AYu., Vinogradova AG, Trushin IV, et al. AMRmap – antibiotic resistance surveillance system in Russia. *Clinical microbiology and antimicrobial chemotherapy*. 2021;23(2):198-204 (in Russ.). doi:10.36488/cmac.2021.2.198-204.
39. Sulayyim HJA, Ismail R, Hamid AA, Ghafar NA. Antibiotic Resistance during COVID-19: A Systematic Review. *Int J Environ Res Public Health*. 2022;19(19):11931. doi: 10.3390/ijerph191911931.
40. Grossi O, Asseray N, Bourigault C, et al. Gram-negative prosthetic joint infections managed according to a multidisciplinary standardized approach: risk factors for failure and outcome with and without fluoroquinolones. *J Antimicrob Chemother*. 2016;71(9):2593-2597. doi: 10.1093/jac/dkw202.
41. Eyler RF, Shvets K. Clinical Pharmacology of Antibiotics. *Clin J Am Soc Nephrol*. 2019;14(7):1080-1090. doi: 10.2215/CJN.08140718.
42. Deconinck L, Dinh A, Nich C, et al. Efficacy of cotrimoxazole (Sulfamethoxazole-Trimethoprim) as a salvage therapy for the treatment of bone and joint infections (BJIs). *PLoS One*. 2019;14(10):e0224106. doi: 10.1371/journal.pone.0224106.
43. Tufanova OS, Kasimova AR, Astakhov DI, et al. Factors affecting the course and prognosis of implant-associated infection caused by Klebsiella spp. *Traumatology and orthopedics of Russia*. 2024;30(2):40-53. (In Russ). doi: 10.17816/2311-2905-16719.
44. Bozhkova SA, Kasimova AR, Tikhilov RM, et al. Adverse trends in the etiology of orthopedic infection: results of 6-year monitoring of the structure and resistance of leading pathogens. *Traumatology and orthopedics of Russia*. 2018;24(4):20-31. (In Russ.). doi: 10.21823/2311-2905-2018-24-4-20-31.

The article was submitted 11.08.2025; approved after reviewing 19.08.2025; accepted for publication 25.08.2025.

**Information about the authors:**

Olga S. Tufanova — Clinical Pharmacologist,
katieva@mail.ru, https://orcid.org/0000-0003-4891-4963, SPIN-code: 8704-9195;

Svetlana A. Bozhkova — Doctor of Medical Sciences, Head of the Scientific Department, Professor of Department,
clinpharm-rniito@yandex.ru, https://orcid.org/0000-0002-2083-2424, SPIN-code: 3086-3694;

Alina R. Kasimova — Candidate of Medical Sciences, Clinical Pharmacologist, Associate Professor of the Department,
kasi-alina@yandex.ru, https://orcid.org/0000-0001-6284-7133, SPIN-code: 3131-4385;

Ekaterina M. Gordina — Candidate of Medical Sciences, senior researcher,
emgordina@win.rniito.ru, https://orcid.org/0000-0003-2326-7413, SPIN-code: 9647-8565;

Anton N. Gvozdetsky — Candidate of Medical Sciences, Assistant Professor at the Department,
Gvozdetskiy_AN@hotmail.com, https://orcid.org/0000-0001-8045-1220, SPIN-code: 4430-6841;

Rashid M. Tikhilov — Doctor of Medical Sciences, Professor, Corresponding Member of the Russian Academy of Sciences,
Director, rtikhilov@gmail.com, https://orcid.org/0000-0003-0733-2414, SPIN-code: 3602-4912.

**Contribution of the authors:**

All authors made equal contributions to the study and the publication. All authors have read and approved the final version of the manuscript of the article. All authors agree to bear responsibility for all aspects of the study to ensure proper consideration and resolution of all possible issues related to the correctness and reliability of any part of the work.