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# ANTIBACTERIAL THERAPY OF PLAGUE (literature review)

**Tatiana V MEKA-MECHENKO, https://orcid.org/0000-0002-6322-006,**
**Ziyat Zh ABDEL, https://orcid.org/0000-0003-4446-140X,**
**Elmira Zh BEGIMBAYEVA, https://orcid.org/0000-0003-3662-5806,**
**Galina G KOVALEVA, https://orcid.org/0000-0002-2673-2213,**
**Larissa Y LUKHNOVA, https://orcid.org/0000-0002-5818-8021,**
**Uinkul A IZBANOVA, https://orcid.org/0000-0002-4616-8728,**
**Zhandos S DALIBAYEV, https://orcid.org/0000-0002-6567-2225**

*M Aikimbayev National Scientific Center for Especially Dangerous Infections of the Ministry of Healthcare of the Republic of Kazakhstan, Almaty, Republic of Kazakhstan*

*Мека-Мечено Т.В.*

Population growth and its high migration activity cause a risk of the global spread of especially dangerous infectious diseases, including plague. Sensitivity to antibacterial drugs is an important feature of *Yersinia pestis* strains isolated in natural plague foci. The reported antibiotic resistance of plague pathogen decreases the effectiveness of specific antibiotic therapy for this infection. This paper reviews literary data on the antibacterial therapy of plague.

**The purpose of the study** was to analyze literary sources on antibacterial therapy of plague and describe the current state of the problem.

**Material and methods.** Literary review and source analysis covered the Scopus, Thomson Reuter, Google Scholar, e.library.ru, and PubMed databases. The search depth was 30 years (1988-2018). Out of 200 sources revealed, 39 (26 in English and 13 in Russian) were selected for further analysis.

Keywords used for inclusion in the study were: plague, antibacterial drugs and therapy, sensitivity, resistance, strains and *Y. pestis.*

**Results and discussion.** The data on the promptness and adequacy of antibiotic administration was reviewed. Such antibiotics as streptomycin, gentamicin, tetracycline or doxycycline, and chloramphenicol are commonly used in the clinic and recommended by the WHO. Fluoroquinolones, such as ciprofloxacin, were also efficient in animal and *in vitro* studies. Streptomycin has been the most effective and available clinical therapy. Gentamicin was an acceptable and preferred alternative to streptomycin in the United States and several other countries. Recently, several studies have suggested a drug combination that may be more effective – streptomycin or gentamicin combined with tetracycline or doxycycline.

**Conclusions.** Aminoglycosides are the leading group of drugs effective against plague infection. Streptomycin remains the reference drug used to compare the effectiveness of other antibiotics.

**Keywords**: plague, antibacterial drugs and therapy, sensitivity, resistance, strains, *Y. pestis*.

**For reference**: Meka-Mechenko TV, Abdel ZZh, Begimbayeva EZh, Kovaleva GG, Lukhnova LY, Izbanova UA, Dalibayev ZhS. Antibacterial therapy of plague (literature review). *Meditsina (Almaty) = Medicine (Almaty).* 2021;3(225):36-42 (In Russ.). doi: 10.31082/1728-452X-2021-225-3-36-42

## Т Ұ Ж Ы Р Ы М
## ОБАҒА ҚАРСЫ БАКТЕРИАЛЬДЫ ТЕРАПИЯ (әдебиетке шолу)

**Татьяна В. МЕКА-МЕЧЕНКО, https://orcid.org/0000-0002-6322- 006,**
**Зият Ж. ӘБДЕЛ, https://orcid.org/0000-0003-4446-140X,**
**Эльмира Ж. БЕГІМБАЕВА, https://orcid.org/0000-0003-3662-5806,**
**Галина Г. КОВАЛЕВА, https://orcid.org/0000-0002-2673-2213,**
**Лариса Ю. ЛУХНОВА, https://orcid.org/0000-0002-5818-8021,**
**Үйінкүл А. ІЗБАНОВА, https://orcid.org/0000-0002-4616-8728,**
**Жандос С. ДӘЛІБАЕВ, https://orcid.org/0000-0002-6567-2225**

*«М. Айқымбаев атындағы Аса қауіпті инфекциялар ұлттық ғылыми орталығы» ШЖҚ РМК, Алматы қ., Қазақстан Республикасы*

Халық санының артуына және оның көші-қон белсенділігінің жоғары болуына байланысты аса қауіпті жұқпалы аурулардың жаһандық таралу қаупі бар, олардың қатарына оба жатады. Бактерияға қарсы препараттарға сезімталдық обаның табиғи ошақтарында оқшауланған *Yersinia pestis* штаммдарының маңызды қасиеті болып табылады. Оба қоздырғышынан антибиотикке төзімділік анықталып отыр, бұл осы инфекцияның антибиотикалық терапиясының тиімділігінің төмендеуінің негізгі себептерінің бірі болды. Шолуда әдеби дереккөздерге сәйкес обаның бактерияға қарсы терапиясы туралы ақпарат берілген.

**Зерттеу мақсаты.** Обаның бактерияға қарсы терапиясы бойынша әдеби дереккөздерді талдау. Мәселенің қазіргі жағдайы туралы ақпараттандыру.

**Contacts:** Tatiana Vladimirovna Meka-Mechenko, Doctor of Medical Sciences, Chief Researcher of the Plague Laboratory «Masgut Aikimbayev's National Scientific Center for Especially Dangerous Infections» of the Ministry of Healthcare, Almaty, e-mail: tmekamechenko@gmail.com

**Контакты:** Татьяна Владимировна Мека-Мечено, доктор медицинских наук, главный научный сотрудник лаборатории чумы РГП на ПХВ «Национальный научный центр особо опасных инфекций им. М. Айкимбаева» МЗ РК, г. Алматы, e-mail: tmekamechenko@gmail.com

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**Материал және әдістері**. Scopus, Thomson Reuter, Google Scholar, e.library.ru, PubMed мәліметтер базасы бойынша әдеби шолу жасалды. Іздеу тереңдігі 30 жыл (1988-2018 жж.). 200 дереккөз табылды, олардың ішінен кейінгі талдау үшін 39: 26 ағылшын тілінде және 13 орыс тілінде таңдалды.

Зерттеуге қосу үшін мынадай түйінді сөздер негіз болды: оба, бактерияға қарсы препараттар және терапия, сезімталдық, резистенттілік, штаммдар, *Y. pestis*.

**Нәтижелері мен талқылауы**. Антибиотиктерді уақытылы және адекватты тағайындау туралы мәліметтерге шолу жасалды. Әдетте бұл клиникада жиі қолданылатын және ДДҰ ұсынған стрептомицин, гентамицин, тетрациклин немесе доксициклин және хлорамфеникол. Ципрофлоксацин сияқты фторхинолондар жануарларға жүргізілген зерттеуде және in vitro-да тиімділігін көрсетті. Клиникалық терапиядағы ең тиімді және қол жетімді стрептомицин болды. Америка Құрама Штаттарында және кейбір басқа елдерде стрептомицинге қолайлы балама ретінде гентамицин болып табылады. Соңғы жылдары бірнеше зерттеулер тиімді болуы мүмкін дәрі-дәрмектердің жиынтығын ұсынды: стрептомицин немесе гентамицин тетрациклинмен немесе доксициклинмен біріктірілген түрі.

**Қорытынды**. Аминогликозидтер - оба инфекциясы үшін тиімді дәрілердің негізгі тобы. Стрептомицин басқа антибиотиктердің тиімділігін салыстыратын анықтамалық препарат болып қала береді.

**Негізгі сөздер**: оба, бактерияға қарсы препараттар және терапия, сезімталдық, төзімділік, штамдар, *Y. pestis*.

## Р Е З Ю М Е
## АНТИБАКТЕРИАЛЬНАЯ ТЕРАПИЯ ЧУМЫ (обзор литературы)

**Татьяна В. МЕКА-МЕЧЕНКО, https://orcid.org/0000-0002-6322- 006,**
**Зият Ж. АБДЕЛ, https://orcid.org/0000-0003-4446-140X,**
**Эльмира Ж. БЕГИМБАЕВА, https://orcid.org/0000-0003-3662-5806,**
**Галина Г. КОВАЛЕВА, https://orcid.org/0000-0002-2673-2213,**
**Лариса Ю. ЛУХНОВА, https://orcid.org/0000-0002-5818-8021,**
**Уинкуль А. ИЗБАНОВА, https://orcid.org/0000-0002-4616-8728,**
**Жандос С. ДАЛИБАЕВ, https://orcid.org/0000-0002-6567-2225**

*РГП на ПХВ «Национальный научный центр особо опасных инфекций им. М Айкимбаева» МЗ РК, г. Алматы, Республика Казахстан*

В связи с ростом населения и его высокой миграционной активностью существует риск глобального распространения особо опасных инфекционных заболеваний, к числу которых относится чума. Чувствительность к антибактериальным препаратам является важным свойством изолированных в природных очагах чумы штаммов *Yersinia pestis*. У возбудителя чумы выявлена антибиотикорезистентность, ставшая одной из основных причин снижения эффективности антибиотикотерапии этой инфекции. В обзоре приведены сведения по антибактериальной терапии чумы по данным литературных источников.

**Цель исследования.** Анализ литературных источников по антибактериальной терапии чумы. Осветить современное состояние проблемы.

**Материал и методы.** Проведен литературный обзор-анализ литературы по базам данных Scopus, Thomson Reuter, Google Scholar, e.library.ru, PubMed. Глубина поиска 30 лет (1988-2018 гг.). Было найдено 200 источников, из них для последующего анализа было отобрано 39: 26 на английском языке и 13 – на русском.

Основанием для включения в исследование являлись ключевые слова: чума, антибактериальные препараты и терапия, чувствительность, резистентность, штаммы, *Y. pestis*.

**Результаты и обсуждение.** Представлен обзор данных о своевременности и адекватности назначения антибиотиков. Как правило, это стрептомицин, гентамицин, тетрациклин или доксициклин и хлорамфеникол, обычно используемые в клинике и рекомендованные ВОЗ. Фторхинолоны, такие как ципрофлоксацин, показали свою эффективность в исследованиях на животных и *in vitro*. Стрептомицин был самым эффективным и доступным в клинической терапии. В Соединенных Штатах и некоторых других странах приемлемой и предпочтительной альтернативой стрептомицину является гентамицин. В последние годы в нескольких исследованиях предложено сочетание лекарств, которое может быть более эффективным: стрептомицин или гентамицин в сочетании с тетрациклином или доксициклином.

**Выводы.** Аминогликозиды являются основной группой препаратов, эффективных при чумной инфекции. Стрептомицин остаётся эталонным препаратом, с которым сравнивают эффективность других антибиотиков.

***Ключевые слова:*** чума, антибактериальные препараты и терапия, чувствительность, резистентность, штаммы, *Y. pestis.*

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An antibioticogram for such an especially dangerous infection as plague should be obtained within the culture identification period. It determines the choice of specialized emergency prevention actions and etiotropic therapy of the infection.

Determination of the spectrum and range of sensitivity of *Y. pestis* strains of various origins against antibacterial agents remains important for selecting drug prevention and therapy despite the available antibacterial drugs with a known bactericidal and bacteriostatic effect on the plague pathogen.

**This study aimed** to analyze literary sources on antibacterial therapy of plague and the *Y. pestis* strains' sensitivity to antimicrobial drugs.

## MATERIALS AND METHODS

An online literature search on the sensitivity of plague strains to antibiotics and the effectiveness of antibacterial therapy against plague was performed in Scopus, Thomson Reuter, Google Scholar, e.library.ru, and PubMed databases.

The *inclusion criterion* was the description of scientific research on plague strains' antibiotic sensitivity and plague antibacterial therapy published in the last 30 years. The review included 39 papers meeting the *inclusion criterion*.

*Confidence and Data Extraction Assessment*

We reviewed 39 selected sources on the topic. The articles were assessed at random by key aspects, including sensitivity and resistance of *Y. pestis* strains, the effectiveness of plague antibacterial therapy.

## RESULTS AND DISCUSSION

Today, the issue of stability and expansion of the area of natural foci of dangerous infections intensifies due to the existing risk of the infections' global spread taking into account the global population growth and high migration activity. The situation on infectious diseases in the world becomes all more serious and less predictable, also in mature countries. New information on the phenotypic and genetic variability of microorganisms and the potential of parasitic systems to adapt to natural and anthropogenic factors add to the situation's seriousness. The detection of plague strains with reduced sensitivity to streptomycin and resistance to tetracycline and rifampicin causes concern [1].

*Y. pestis* strains resistant to chloramphenicol and insensitive to gentamicin were obtained from plague patients in Kazakhstan [2].

During a pulmonary plague outbreak in Tanzania, the pathogen culture was obtained from the sputum of patients treated with tetracycline or streptomycin plus tetracycline [3].

The emergence of antibiotic-resistant *Y. pestis* strains is a public health issue. Three antibiotic-resistant Malagasy *Y. pestis* strains were isolated from different patients at different times and from distant places. They had unrelated plasmids suggestive of independent horizontal acquisition of genetic material and demonstrated the ability to acquire antibiotic resistance plasmids in vivo. Therefore, we can expect the emergence of new *Y. pestis* strains with multidrug resistance posing a severe threat to health [4].

Bioterrorism is an urgent problem these days. According to A.A. Vorobyov, plague pathogen is the second most probable bioagent after the smallpox virus [6].

First-line (streptomycin, amikacin, gentamicin, doxycycline, ciprofloxacin (or ofloxacin, pefloxacin, lomefloxacin, levofloxacin), ceftriaxone, rifampicin, trimethoprim/sulfamethoxazole) and second-line (kanamycin, netilmicin, tobramycin, tetracycline, ampicillin, ceftazidime (or ceftibuten, cefixime, cefepime), aztreonam, nalidixic acid, chloramphenicol) drugs are used to treat plague in the CIS countries. The drugs from this list are used when studying the antibiogram of plague strains.

In the US, gentamicin and fluoroquinolones are the common first-line drugs with suspected plague. The treatment duration is 10 to 14 days or up to 2 days after the fever subsides. Regimens and treatments are indicative and may need an adjustment depending on the patient's age, medical history, underlying health conditions, or allergies [7-10].

CDC recommends streptomycin, gentamicin, levofloxacin, ciprofloxacin, doxycycline, moxifloxacin, or chloramphenicol as antibiotics against plague.

In response to the intense use of antibiotics since their discovery in the 1930s, bacteria develop an increasing resistance to these essential drugs. The state shall ensure a stock of antibiotics against bacterial plague. Governments shall also subsidize tests to determine the infections' nature and resistance, increase subsidies and spending on vaccination research, and gather more information about the magnitude and nature of the threat posed by resistant bacterial pathogens.

Routine assessment of antibiotic sensitivity by bacteriological laboratories does not provide a reliable forecast of sustainability to aminoglycosides. It also does not allow for long-term planning of the choice of antibiotics [11, 12].

Therefore, the study of resistance mechanisms to aminoglycosides in clinical isolates is of great importance to [13, 14].

Reshedko [15] studied the resistance to aminoglycosides based on the assessment of antibiotic resistance.

The choice of discs with antibiotics for microbial testing should be guided by the spectrum of action of antibiotics and the results of multicenter antibiotic susceptibility studies.

Li et al. [16] provided data on the timeliness and adequacy of antibiotic prescription. Streptomycin, gentamicin, tetracycline or doxycycline, and chloramphenicol are mainly used in clinical practice [17, 18] and recommended by WHO.

Fluoroquinolones such as ciprofloxacin were effective in animal studies [19] and *in vitro* [20]. Some physicians have also used moxifloxacin clinically to treat plague in China [19].

Streptomycin was the most efficient among the antibiotics mentioned above and available in clinical therapy [20, 21]. The Chinese CDC has proposed streptomycin 2 g as the starting dose and used it in China to treat pneumonic plague [19]. However, streptomycin should never be used during pregnancy for deafness development.

This drug is not always available in the US and some other countries. Gentamicin is an acceptable and preferred alternative to streptomycin, with proven efficacy in some instances [22, 23].

Li et al. describe a case of a toxic-infectious shock in a plague patient due to late diagnosis. Therefore, timely diagnosis and treatment are essential for disease prognosis [16]. Another patient received no antibiotic therapy, and the third one was treated with clindamycin which is ineffective against plague. Wrong treatment leads to high mortality, especially in pneumonic plague.

Several studies [24, 25] suggested a probably more effective combination of drugs: streptomycin or gentamicin plus tetracycline or doxycycline. In the case of streptomycin resistance [26], researchers tried to find alternatives to antibiotic treatment, for example, immunotherapy, treatment with phages and bacteriocins [27].

Kiersten et al. [28] analyzed 1,006 plague cases occurring in humans in the US over 113 years since the first case reported in 1900. Plague mortality has declined with the invention of effective treatment.

Antimicrobial therapy for plague is effective when started early in the disease and continued for at least three days after body temperature returns to standard values. Streptomycin is a preferred drug in such cases. However, it is not immediately available everywhere. Gentamicin is an acceptable alternative to streptomycin based on laboratory and animal studies and limited clinical observations in humans. Tetracyclines are also effective against plague, so they are widely used for therapy and prevention. Doxycycline twice a day is the most preferred oral drug due to its rapid gastrointestinal absorption. Chloramphenicol is used to treat various forms of plague, including plague pneumonia. It is also recommended against plague meningitis due to its ability to cross the blood-brain barrier. Fluoroquinolones are effective against plague in animal studies. Ciprofloxacin had nearly similar efficacy in mice studies as aminoglycoside antibiotics and tetracyclines. In laboratory studies, some fluoroquinolones have shown equivalent or even better action than aminoglycoside antibiotics and tetracyclines. Several sulfonamides (sulfathiazole, sulfadiazine, sulfamerazine, and trimethoprim-sulfamethoxazole) have been used successfully to treat and prevent plague. However, sulfonamides are less effective than streptomycin or tetracycline, especially in pneumonic plague. Sulfisoxazole should not be used due to its rapid urinary excretion. Penicillins, macrolides, and cephalosporins are clinically ineffective and not recommended to treat plague. Multiple drug resistance due to plasmid transfer was found in a single clinical isolate. The same refers to plasmid-associated streptomycin resistance. Some strains obtained in laboratories were resistant to antimicrobial drugs.

Smego et al. [17] emphasized the importance of efficient antibiotic treatment of plague due to high mortality from an untreated plague. A limited range of antibacterial agents used for treatment include streptomycin (alternatively gentamicin), chloramphenicol, and tetracycline (or doxycycline) [29].

Streptomycin administration for ten days is the preferred regimen, but its antibacterial activity may precipitate endotoxic shock. However, it was not a problem in cases of plague in Vietnam. Most patients showed an improvement in 3 days, but 10-day therapy was recommended to prevent relapses.

Tetracycline or doxycycline is a usually satisfactory alternative in uncomplicated bubonic plague. Streptomycin may be replaced with tetracycline or doxycycline in the risk of ototoxicity or renal toxicity. Chloramphenicol is used to treat plague meningitis and as an alternative to tetracycline or doxycycline in pregnant women and small children. Tetracycline or doxycycline is a usual choice for prevention purposes. In case of any contraindications due to age or pregnancy, trimethoprim-sulfamethoxazole is administered. Other previously used treatment agents with lower efficacy or higher toxicity include sulfonamides, trimethoprim-sulfamethoxazole, ampicillin, and kanamycin [18].

Pneumonic plague is highly contagious, and patients should be strictly isolated with appropriate precautions taken against the spread of the infection until 48 hours of antibiotic treatment is applied with a favorable outcome [30].

Antonov et al. [31] specify that infectious diseases are natural phenomena in human society; they develop and change with time. Their prevalence remains global despite significant advances in the fight against infectious diseases. Many people can become infected within a short period. Therefore, further improvement in the prevention of infectious diseases remains relevant. Emergency and specific prophylaxis are of great importance to prevent the development of infectious diseases.

An increased range of new, highly effective drugs is required to eliminate the natural and artificial infection foci. Fluoroquinolones are widely used to treat infections of various etiologies (anthrax, plague, tularemia) [32].

In the RK market, the fluoroquinolone class of chemotherapy drugs is presented by nine drugs.

New fluoroquinolones – sparfloxacin, moxifloxacin, imifloxacin, levofloxacin – are the most promising for experimental studies. The earlier representatives of this class – pefloxacin, ofloxacin, ciprofloxacin – have an extensive action against causative agents of dangerous and especially dangerous bacterial infections and are included in almost all relevant regulatory documents. The main task is to find drugs that are superior in efficiency to the earlier representatives of this class in the treatment of especially dangerous bacterial infections.

Some authors [33] have shown the high efficacy of levofloxacin and lomefloxacin against plague in white mice. These drugs could supplement the range of effective etiotropic medicines against plague.

Shchipeleva et al. [34] studied the problem of plague multidrug resistance. Nowadays, plague treatment might be complicated by the spread of multiply resistant forms of this pathogen. Many researchers have long proven the plague pathogen's ability to perceive and express R-plasmids in experiments. The etiotropic therapy effectiveness against plague depends on the timely initiation of adequate treatment. Late diagnostics and generalization of the process can cause death despite highly active antibacterial drugs and intensive pathogenetic therapy, as evidenced by still high mortality from the plague.

A comparative effectiveness study of many antibacterial agents in subcutaneously and aerogenically infected mice experiments has proven a high efficiency of etiotropic therapy at the early start of treatment (24 h after infection) and low efficiency – at a late start of treatment (after 48 or 72 h). The authors showed higher therapeutic activity of aminoglycosides and fluoroquinolones at a late start of treatment (but with a survival rate below 60%) [35, 36].

An infectious-toxic model of plague in white mice was used to study the clinical efficacy of different groups of antibacterial drugs to determine the ability of drugs recommended against plague to enhance or not aggravate the development of infectious-toxic shock [37].

The experiments showed the primary efficacy of aminoglycosides against plague. Streptomycin remains the reference drug used to compare the effectiveness of other medicines. Netilmicin [38], ciprofloxacin, and moxifloxacin [39] are promising in developing (developed) infectious-toxic shock.

At that, the therapeutic efficacy of gentamicin recommended to prevent and treat all forms of plague sharply decreases in the model of an infectious-toxic form of the infection. Gentamicin is inappropriate in advanced disease [37].

One of the most important directions of the national security policy in the Republic of Kazakhstan is to protect the population and counter biological threats. Further large-scale experiments are required to eradicate plague pathogens in case of an infection outbreak in any of its forms.

## CONCLUSIONS

A comparative study of the means to treat plague in global literature sources shows the primary efficiency of aminoglycosides against this disease. Streptomycin remains the reference drug used to compare the effectiveness of other antibiotics.

Constant monitoring of freshly isolated *Y. pestis* strains sensitivity to antibacterial drugs is required for timely detection of the resistance of the plague pathogen to antibiotics.

***Research transparency***

*The study was not sponsored. The authors are solely responsible for the submission of the final version to print.*

***Declaration of financial and other relationships***

*The authors did not receive royalties for the article.*

***Contribution of authors***

*Meka-Mechenko T.V., Abdel Z. Zh., Begimbayeva E. Zh. - development of the concept of the article and its writing, selection, translation, and analysis of literature, formation of the final version of the article.*

*Kovaleva G.G., Lukhnova L.Yu., Izbanova U.A., Dalibayev Zh.S. - literature sources' selection and analysis.*

***Conflict of interests***

*The authors declare that they have no conflicts of interest.*

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