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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS
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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.
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WEBSITE
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К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman** (**Кириллица**), ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

Yuliya Tyravska, Dmytro Maltsev, Valentyna Moyseyenko, Vitalii Reshetylo, Volodymyr Yakymenko.
IMMUNOMODULATORS IN THE TREATMENT OF ATHEROSCLEROSIS AND OTHER CHRONIC HEART DISEASES: PROSPECTS ANDRISKS………………………………………………………...……….………………………..6-16

Aldabekova G, Khamidullina Z, Abdrashidova S, Musina A, Kassymbek S, Kokisheva G, Suleimenova Zh, Sarsenbieva A, Kamalbekova G.
ASSESSMENT OF THE IMPLEMENTATION OF WHO INFECTION PREVENTION AND CONTROL (IPC) CORE COMPONENTS IN KAZAKHSTAN: FINDINGS BASED ON THE IPCAF TOOL……………...……………17-22

Madina Madiyeva, Gulzhan Bersimbekova, Gulnur Kanapiyanova, Mariya Prilutskaya, Aray Mukanova.
ANALYSIS OF RISK FACTORS AND THEIR IMPACT ON BONE HEALTH STATUS IN KAZAKH POPULATIONS……………...…23-30

Bilanishvili I, Barbakadze M, Nikabadze N, Andronikashvili G, Nanobashvili Z.
AUDIOGENIC SEIZURE SUPPRESSION BY VENTRAL TEGMENTAL AREA STIMULATION………...............................…………31-37

Yan Wang, Yulei Xie, Chong Yin, Qing Wu.
EXPLORING THE MECHANISM OF ACTION OF HEMP SEEDS (CANNABIS SATIVA L.) IN TREATING OSTEOPOROSIS USING NETWORKPHARMACOLOGY…………………………………………………..…………38-43

Marzhan Myrzakhanova, Gulshara Berdesheva, Kulsara Rustemova, Shynar Kulbayeva, Yuriy Lissitsyn, Zhuldyz Tleubergenova.
TRANSFORMING MEDICAL EDUCATION IN KAZAKHSTAN: THE POTENTIAL OF VIRTUAL REALITY FOR ENHANCING THE LEARNINGEXPERIENCE………………………………………………...………………………………44-51

Malinochka Arina D, Khupsergenov Emir Z, Avagyan Artyom A, Kurachenko Yulia V, Britan Inna I, Hvorostova Serafima V, Koipish Vladislav S, Siiakina Anastasiia E, Vasileva Vasilisa V, Mikheenko Diana D, Fomenko Danila A.
LATE DIAGNOSIS OF ACROMEGALY IN THE SETTING OF A SOMATOPROLACTINOMA…………...................................………52-54

Serhii Lobanov.
ONTOGENETIC AND PSYCHOSOCIAL DETERMINANTS OF ADDICTIVE BEHAVIOR FORMATION AMONG UKRAINIAN YOUTH ………………………………………………………………………………………………...……………..55-62

Emzar Diasamidze, Tamaz Gvenetadze, Giorgi Antadze, Iamze Taboridze.
THE IMPACT OF ANEMIA ON THE DEVELOPMENT OF INCISIONAL HERNIA, PROSPECTIVE STUDY……………..............…...63-67

Karapetyan A.G, Ulusyan T.R, Danielyan M.H, Avetisyan E.A, Petrosyan A.A, Petrosyan S.S, Grigoryan V.S.
RESEARCH OF HEMATOLOGICAL CHANGES IN INDIVIDUALS EXPOSED TO IRRADIATION FROM THE CHERNOBYL NUCLEAR POWER PLANT…………………………………..…………………………………………...…68-71

Yaji Chen, Yin Wang.
THE RELATIONSHIP BETWEEN SOCIAL CAPITAL AND WORKERS' MENTAL HEALTH IN CONTEMPORARY CHINA……....72-78

Begaidarova R.Kh, Alshynbekova G.K, Kadyrova I.A, Alshimbayeva Z.Ye, Nassakayeva G.Ye, ZolotaryovaO.A, Omarova G.M.
CASE REPORT OF INFLUENZA A (H1N1) PDM 09 STRAIN / KARAGANDA/ 06/2022 IN A CHILD AGED 3 YEARS…..........……..79-86

Fahad Saleh Ayed AL-Anazi, Albadawi Abdelbagi Talha.
ANTIBIOGRAM OF URINARY CATHETER-ASSOCIATED BACTERIAL PATHOGENS IN INTENSIVE CARE UNIT, KING KHALID GENERAL HOSPITAL, HAFER AL-BATEN, SAUDI ARABIA…………...……………………87-95

Serik Baidurin, Ybraiym Karim, Akhmetzhanova Shynar, Tkachev Victor, Moldabayeva Altyn, Eshmagambetova Zhanna, Darybayeva Aisha.
COEXISTENCE OF APLASTIC ANEMIA AND PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: DIAGNOSTIC CHALLENGES AND THERAPEUTIC STRATEGIES - CASE REPORT………..……………………96-101

Lika Leshkasheli, Darejan Bolkvadze, Lia Askilashvili, Maria Chichashvili, Megi Khanishvili, Giorgi Tsertsvadze, Nana Balarjishvili, Leila Kvachadze, Elisabed Zaldastanisvhili.
PHENOTYPIC CHARACTERIZATION OF FIVE PHAGES ACTIVE AGAINST ANTIBIOTIC-RESISTANT *KLEBSIELLA PNEUMONIAE*…………………………………………..................................……………………………………………………102-112

Aliya Manzoorudeen, Marwan Ismail, Ahmed Luay Osman Hashim, Abdelgadir Elamin Eltom.
ASSOCIATION BETWEEN GALECTIN-3 AND MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS: A COMPARATIVE STUDY……………………………………………………………………………………..113-119

Gulmira Derbissalina, Zhanagul Bekbergenova, Ayagoz Umbetzhanova, Gulsum Mauletbayeva, Gulnara Bedelbayeva.
BIOMARKERS OF CARDIOMETABOLIC RISK IN PATIENTS WITH ARTERIAL HYPERTENSION: A CROSS-SECTIONAL PILOT ST UDY……………..……………………………………………………………………………120-126

Madina Rashova, Saule Akhmetova, Berik Tuleubaev, Dinara Turebekova, Amina Koshanova, Adilet Omenov, Bakdaulet Kambyl, Yekaterina Kossilova.
ASSESSMENT OF CLINICAL SYMPTOMS OF ACUTE TOXICITY FOLLOWING THE IMPLANTATION OF A NANOCELLULOSE-BASEDBIOCOMPOSITE………………...…………………………………………………..…127-137

Dali Beridze, Mariam Metreveli, Avtandil Meskhidze, Galina Meparishvili, Aliosha Bakuridze, Malkhaz Jokhadze, Dali Berashvili, Lasha Bakuridze.
STUDY OF THE BIOACTIVE COMPOUND COMPOSITION, ANTIMICROBIAL, AND CYTOTOXIC ACTIVITIES OF ENDEMIC PLANT SPECIES OF ADJARA-LAZETI………………………………...……………………………….138-152

Faisal Younis Shah, Reece Clough, Fatima Saleh, Mark Poustie, Ioannis Balanos, Ahmed Najjar.
FACTORS AFFECTING MORTALITY IN PATIENTS WITH HIP FRACTURES AND SHAH HIP FRACTURE MORTALITY SCORE: A RISK QUANTIFICATION TOOL………………………………...………………………..153-159

Anas Ali Alhur, Layan S. Alqahtani, Lojain Al Faraj, Duha Alqahtani, Maram Fahad, Norah Almoneef, Ameerah Balobaied, Rawan Alamri, Aseel Almashal, Fatimah Alkathiri, Lama Alqahtani, Lama Al-Shahrani, Hani Alasmari, Nouran Al Almaie, Sarah Alshehri.
GLOBAL RESEARCH TRENDS IN MRI SAFETY AND PATIENT AWARENESS: A BIBLIOMETRIC ANALYSIS (2000–2025)…160-167

Virina Natalia V, Kuchieva Lana M, Baturina Yulia S, Fizikova Aliya B, Gereeva Madina M, Bitiev Batraz F, Apakhaeva Karina K, Manukhova Natalia M, Rasulova Fatima Z, Kornev Egor M, Rodionova Ekaterina A.
DANIO RERIO (ZEBRAFISH) - A UNIQUE AND INTEGRATIVE PLATFORM FOR 21ST CENTURY BIOMEDICAL RESEARCH…………………………………………………………………………………………….....................................……………….168-173

Salah Eldin Omar Hussein, Shamsa Murad Abdalla Murad, Ogail Yousif Dawod, Elryah I Ali, Shawgi A. Elsiddig, Rabab H.Elshaikh A, Awadh S Alsubhi, Tagwa Yousif Elsayed Yousif, Siednamohammeddeen Nagat, Amin SI Banaga, Salah Y.Ali, Marwan Ismail, Ayman Hussien Alfeel.
BIOCHEMICAL ASSOCIATION BETWEEN CALCIUM HOMEOSTASIS AND SERUM URIC ACID LEVELS IN PATIENTS WITH HYPOTHYROIDISM: A COMPARATIVE EVALUATION WITH 25-HYDROXYVITAMIN D……………………………………….174-179

Markova OO, Safonchyk OI, Orlovska IH, Kovalchuk OM, Sukharieva AO, Myrza SS, Keidaliuk VO.
PROTECTION OF CONSUMER RIGHTS IN THE FIELD OF ELECTRONIC COMMERCE OF MEDICINES………...………………180-187

Ilona Tserediani, Merab Khvadagian.
ENDONASAL ENDOSCOPIC DACRYOCYSTORHINOSTOMY USING RADIOFREQUENCY (RF) IN CHRONIC ABSCESSED DACRYOCYSTITIS: A PROSPECTIVE STUDY………...…………………………………………………188-189

Nadezhda Omelchuk.
HYPERCORTICISM IN THE PATHOGENESIS OF ACUTE RADIATION SICKNESS AND CONDITIONS OF INCREASED RADIORESISTANCE……………....................................……………………………………………………………………………190-196

Anas Ali Alhur, Raghad Alharajeen, Aliah Alshabanah, Jomanah Alghuwainem, Majed Almukhlifi, Abdullah Al Alshikh, Nasser Alsubaie, Ayat Al Sinan, Raghad Alotaibi, Nadrah Alamri, Atheer Marzouq Alshammari, Nawal Alasmari, Deema Alqurashi, Shahad Alharthi, Renad Alosaimi.
THE IMPACT OF VISION 2030 ON PHARMACY STUDENTS' CAREER OUTLOOKS AND SPECIALIZATION CHOICES: A CROSS-SECTIONALANALYSIS…………..…………………………………………………………197-203

Fitim Alidema, Arieta Hasani Alidema, Lirim Mustafa, Mirlinde Havolli, Fellenza Abazi.
LDL-CHOLESTEROL LOWERING WITH ATORVASTATIN, ROSUVASTATIN AND SIMVASTATIN: RESULTS OF A RETROSPECTIVE OBSERVATIONAL STUDY……………..............................……………………………………………………204-209

Ainur Amanzholkyzy, Yersulu Sagidanova, Edgaras Stankevicius, Ainur Donayeva, Ulziya Sarsengali.
HEAVY METAL TOXICITY VERSUS TRACE ELEMENT PROTECTION IN WOMEN'S REPRODUCTIVE HEALTH - A SYSTEMATIC REVIEW………………………………………………...……………………………………210-216

Marwan Ismail, Mutaz Ibrahim Hassan, Assiya Gherdaoui, Majid Alnaimi, Raghda Altamimi, Srija Manimaran, Mahir Khalil Jallo, Ramprasad Muthukrishnan, Praveen Kumar Kandakurthi, Jaborova Mehroba Salomudinovna, Shukurov Firuz Abdufattoevich, Shawgi A. Elsiddig, Tagwa Yousif Elsayed Yousif, Asaad Babker, Ahmed L. Osman, Abdelgadir Elamin.
ASSOCIATION BETWEEN EXERCISE MODALITIES AND GLYCEMIC CONTROL IN TYPE 2 DIABETES………..……………..217-223

Tamar Zarginava, Zaza Sopromadze.
THE PRIORITY OF CONTEMPORARY MEDICAL UNIVERSITY MODELS IN SUBSTANTIATING BENCHMARKING OF MARKETINGSOCIO-ETHICALSTANDARDS………………………..……………………224-230

Svetlana Shikanova, Altynay Kabdygaliyeva.
THE SIGNIFICANCE OF INTERLEUKIN-22 AND HOMOCYSTEINE IN THE PROGNOSIS OF PREMATURE ANTEPARTUM RUPTURE OF MEMBRANES IN PREGNANT WOMEN…………………..……………………231-242

Shahad A. Badr, Taqwa B. Thanoon, Zeina A. Althanoon, Marwan M. Merkhan.
CHARACTERISTICS AND MANAGEMENT OF RESPIRATORY AILMENTS IN PAEDIATRICS: A PROSPECTIVE CLINICAL STUDY ……………………………………………………………………………………….............................………………………243-247

Ulviyya Z. Nabizade, Orkhan Isayev, Gunel R. Haci, Kamal İ. Kazimov, Gulmira H. Nasirova, Rezeda R. Kaziyeva, Elchin H. Guliyev, Isa H. Isayev.
EVALUATION OF THE DEEP INSPIRATION BREATH-HOLD TECHNIQUE TO IMPROVE DOSIMETRIC OUTCOMES IN RADIOTHERAPY FOR STAGE III NON-SMALL CELL LUNG CANCER………………...……248-252

Galina Battalova, Yerkezhan Kalshabay, Zhamilya Zholdybay, Dinara Baiguissova, Bolatbek Baimakhanov.
NON-INVASIVE QUANTITATIVE CT PERFUSION OF THE LIVER IN AUTOIMMUNE HEPATITIS…………….......................…253-260

Lachashvili L, Khubua M, Jangavadze M, Bedinasvili Z.
MiR-29a, miR-222 AND miR-132 IN THE BLOOD PLASMA OF PREGNANT WOMEN AS PREDICTORS OF GESTATIONAL DIABETES…………………………....................................………………………………………………………………………261-265

Mohanad Luay Jawhar, Hadzliana Binti Zainal, Sabariah Noor Binti Harun, Baraa Ahmed Saeed.
OMEGA-3 POLYUNSATURATED FATTY ACIDS AND HYPERTENSION: A REVIEW OF VASOACTIVE MECHANISMS AND IMPLICATIONS FOR CARDIOVASCULAR DISEASE……………………..……………266-271

Dimash Davletov, Mukhtar Kulimbet, Indira Baibolsynova, Sergey Lee, Ildar Fakhradiyev, Alisher Makhmutov, Batyrbek Assembekov, Kairat Davletov.
ESTIMATING THE PREVALENCE OF FAMILIAL HYPERCHOLESTEROLEMIA IN STROKE AND TRANSITORY ISCHEMIC ATTACK POPULATION: A SYSTEMATIC REVIEW AND META-ANALYSIS………………...……272-281

Anas Ali Alhur, Abdullah Saeed, Anas Almalki, Hawra Alhamad, Hafez Meagammy, Norah Al Sharaef, Sarah Alakeel, Saeed Alghamdi, Abdulaziz Alqarni, Mohammed Alqarni, Muhannad Alshehri, Naif Alotaibi, Salman Almutairi, Rayan Alajhar, Adel Al-Harthi.
IS HEALTH AT RISK? A QUANTITATIVE STUDY ASSESSING THE IMPACT OF EXCESSIVE MOBILE APPLICATION USE ON PHYSICAL AND MENTAL WELL-BEING AMONG ADULTS IN SAUDI ARABIA……………......................................……………282-288

Khatuna Kudava.
ONYCHODYSTROPHIES IN PEDIATRIC DERMATOLOGY……………......................……………………………………………….…289-292

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PHENOTYPIC CHARACTERIZATION OF FIVE PHAGES ACTIVE AGAINST ANTIBIOTIC-RESISTANT *KLEBSIELLA PNEUMONIAE*

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Abstract.

Widespread antibiotic resistance represents an increasingly significant burden for healthcare systems worldwide. One of the primary contributors to this pressing issue is *Klebsiella pneumoniae*, a pathogen of major clinical concern. Here we describe five distinct phages that infect antibiotic-resistant *K. pneumoniae* strains. A total of 100 clinical bacterial strains were systematically assessed for their antibiotic- and phage susceptibility profiles. Notably, 94 of these strains demonstrated high levels of antibiotic resistance across multiple drug classes. The five described phages, which target nearly all studied strains, were comprehensively characterized regarding their virion morphology, their lytic spectra, their intracellular growth parameters, and their potential to trigger development of phage-resistant bacterial forms. Two Siphoviridae phages exhibited remarkably low rates of phage-resistant form development during the study period. While such rates were comparatively higher for the three Myoviruses tested, bacterial forms that acquired resistance to these particular phages subsequently became sensitive to other phages in the collection. In conclusion, the studied phages effectively targeted 93 out of 100 bacterial strains tested. Such broad coverage of diverse clinical strains by these phages strongly underscores their considerable potential in therapeutic settings, particularly for treating multidrug-resistant infections.

Key words. *Klebsiella pneumonia*, bacteriophage, phage therapy, infectious diseases, bacterial infections.

Introduction.

Klebsiella species are a group of Gram-negative bacteria belonging to the *Enterobacteriaceae* family. *K. pneumoniae* as well as other species of the *Klebsiella* genus are responsible for a wide range of infectious diseases in humans [1]. *Klebsiella*-associated diseases include urinary tract infections, pneumonia and bloodstream infections, particularly in immunocompromised patients [2]. *K. pneumoniae* strains are notorious for their ability to acquire antibiotic-resistance against a wide range of antibiotics including beta-lactams, aminoglycosides and carbapenems. This makes *Klebsiella*-associated infectious diseases increasingly difficult to treat [3,4]. As a result, the emergence of multidrug-resistant *Klebsiella* strains have become a major concern in various clinical settings [5]. These pathogens are responsible for community- as well as hospital-acquired infections, with a fairly high mortality rate, which tends to be particularly high in hospital settings [6-9].

To combat the growing threat from *Klebsiella*-associated infectious diseases, phages have emerged as one of the most promising alternative therapeutic approaches – both independently and in combination with antibiotics [10-15]. Phages represent the largest group of viruses on earth. They can be found in various environments such as air, soil, water and especially wastewater [16]. Phages, as natural predators of bacteria, have demonstrated their therapeutic potential in human healthcare as early as in the beginning of the XX century [17,18]. The golden era of antibiotics overshadowed phage use. However, treatment options for antibiotic-resistant bacteria are now diminishing [19]. Therefore, phages are once again regarded as antibacterial agents of great potential [20,21].

A number of traits highlight great potential and advantages of phages over antibiotics. Phages are widely distributed in nature and their isolation from the environment does not require significant financial resources. Phages are highly specific to their target bacteria, often on species or even on strain level. Such specificity ensures that mammalian cells and healthy microbiota remain untargeted by phage therapy [22-24]. Phages have virtually no side effects; their high specificity to targeted pathogens as well as the fact that due to their widespread presence phages are non-foreign entities for humans, makes phages safe therapeutic agents [25-28]. Presence of target bacterial cells leads to the multiplication of phage particles – increasing their concentration and preventing further spread of the pathogen. Phages can easily penetrate and move within the body, making them successful at reaching sites which are otherwise not so easily accessible – including bacterial biofilms [29,26,30]. While phage-resistance does emerge in clinically relevant bacteria, it is considered less alarming, than the development of antibiotic resistance. Phages are in constant arms race with their hosts, often being successful at overcoming resistance. In phage therapy, one of the strategies for suppressing emergence of phage resistance is combining therapeutic phages in cocktails.

Recent research on *Klebsiella* phages has mainly focused on their isolation, characterization and study of their therapeutic potential. The diversity of *Klebsiella* phages, their genetic plasticity and their ability to evolve quickly to counteract bacterial resistance mechanisms are important factors that make

them a promising therapeutic tool in the fight against bacterial infections [13].

Despite the promising potential of *Klebsiella* phages, there are challenges that need to be addressed before they can be routinely used in clinical settings. These include bacterial potential to develop resistance against phages. Here we characterize five *Klebsiella* phages in terms of their biological properties. We also evaluate the rates at which phage-resistant bacterial forms arise against them and we estimate their potential therapeutic use.

Materials and Methods.

Bacterial strains and their cultivation:

100 *Klebsiella pneumoniae* strains of clinical origin were used in this study. All strains had been provided by the Bacteriophage analytical-diagnostic center "Diagnosi 90". The full list of strains and their origin can be found in Table S1.

Bacteria were cultivated at 37 °C for 18-24 hours. Incubation of cultures (both solid and liquid) took place in static conditions. Lysogeny Broth (LB) with and without agar was used as growth medium.

Antibiotic susceptibility testing of bacterial strains:

Bacterial strains were tested for their antibiotic susceptibility with disk diffusion method according to EUCAST recommendations [31]. Susceptibility evaluation experiments included 23 antibiotics from different groups: Penicillins – 5 antibiotics; Cephalosporins – 6 antibiotics; Carbapenems – 4 antibiotics; Monobactam – 1 antibiotic; Fluoroquinolones – 4 antibiotics; Aminoglycosides – 3 antibiotics. Additionally, the activity of trimethoprim-sulfamethoxazole and chloramphenicol were also tested, bringing the total to 25 antibacterial agents (Table S2).

PCR detection of β-lactamase-encoding genes:

In all bacterial strains of interest, the presence of four β-lactamase encoding genes (Table 1) was detected by conventional PCR. 2 µl of heat-extracted DNA was used as a template. All primers are listed in Table 1. DreamTaq Green PCR Master Mix (Thermo Scientific) was used in all reactions and PCR products were analysed on 1 % agarose gel.

Genotyping of *K. pneumoniae* strains:

K. pneumoniae clinical strains of interest were genotyped through pulsed-field gel electrophoresis (PFGE) approach [39]. Agarose-embedded DNA samples were treated with lysis buffer (1 mg/mL lysozyme, 100 µg/m proteinase K, 6 mM Tris-HCl (pH 8.0), 1 M NaCl, 100 mM EDTA (pH 8.0), 0.2% deoxycholate, 0.5% N-Lauroylsarcosine). Restriction endonuclease XbaI (NEB) was used for DNA fragmentation. Electrophoresis took place at 14 °C for 18 hours in 1 % agarose and 0.5 x Tris-borate EDTA (TBE) in a pulsed field gel electrophoresis apparatus Gene Navigator™ System (Amersham). Pulse parameters were: 10-50 seconds, 200 volts (6 V/cm). Fragment analysis was conducted using Freetree and TreeView softwares [40].

Isolation of bacteriophages:

Phages were isolated from environmental water samples by the enrichment method [41]. 90 ml of water sample was enriched with 10 ml of times concentrated LB and 1 ml of bacterial suspension of strain(s) of interest. After incubating the sample at 37 °C for 18 hours, samples were centrifuged at 9 000 rpm for 20 min. Supernatant was filtered through 0.22 µm pore sized filters and was spotted on bacterial lawn.

Plaque formation and morphology:

The double-layer agar method was used to analyse phage plaque morphology [41]. Ten-fold diluted phage samples were mixed with 0.1 ml of a suspension of the host bacterial strain (10^9 CFU/ml) and 3 ml of semi-solid (0.5 %) LB agar. The mixture was spread on a Petri dish containing solid (1.5 %) LB agar. After incubation at 37 °C for 18-24 hours, the morphology and number of phage colonies were recorded.

Phage host range and efficiency of plating:

The host range of bacteriophages was studied using the spot-test assay [42]. 100 clinical isolates of *K. pneumoniae* were employed as target strains. 10 µl of phage suspensions (with phage titters of 10^7 PFU/ml) were spotted on bacterial soft-agar lawns. The plates were incubated at 37 °C, after which the presence of lysis zones was observed. The following designations were used to assess the degree of antibacterial activity of bacteriophages: CL - the phage causes complete lysis of bacteria; SCL - the phage causes complete lysis, but single bacterial colonies are observed in the lysis zone; OL - the phage does not cause complete lysis of bacteria and there is secondary bacterial growth in the droplet zone; R- bacteria were resistant to phage. The efficiency of plating (EOP) of phages was calculated as average PFU on bacterial strains of interest divided by the average PFU obtained from the original host strain. EOP values from the original host strain were considered a reference - 100%. The EOP was classified into high (≥ 0.5), medium (0.1–0.5), or low (0.001–0.1) [43].

Transmission electron microscopy:

For the visualization of phage particles negative staining Drop-to-Drop method was used [44]. Briefly, 0.05 ml of phage suspension (with a titre of 10^9-10^{10} PFU/ml) was spotted on a formvar and carbon covered copper grid (Electron Microscopy Sciences). After 1 min of incubation extra liquid was blotted with filter paper. Copper grid was then placed on to the 2% phospotungstic acid (pH 7,2) droplet for 1 min. extra liquid was blotted with filter paper again and the grid was allowed to air dry. Prepared sample was examined using transmission electron microscope JEOL 100- SX (Jeol, Akishima-Shi, Tokyo, Japan).

One-step growth experiments:

For the one-step growth curve experiment, phages and their host bacterial strains were mixed in LB broth at a multiplicity of infection (MOI) of 0.1. The mixture was incubated at 37 °C in a water bath for 5-15 minutes to allow phage adsorption. To assess the number of unadsorbed phages at 5-minute intervals, 0.1 ml of the sample was transferred into pre-cooled 9.9 ml of LB broth containing chloroform and immediately placed on ice for 10 minutes. The sample was then analyzed using the double-layer agar method. The proportion of adsorbed phages was determined by calculating the percentage of non-adsorbed phage particles, which corresponded to the plaque count. Once the maximum adsorption level was reached, the mixture was diluted 1000 times in fresh LB broth and incubated under the

same conditions. To track phage propagation, sample aliquots were taken at 5-10 min intervals and were plated using the double-layer agar method.

Phage latent period was defined as the shortest time required for the phages to complete their replication cycle, from adsorption to bacterial lysis and progeny release. The burst size was calculated as the ratio of the phage count before and after lysis, indicating the number of new phages released per infected bacterial cell [41,45].

Evaluation of the frequency of the development of phage-resistant bacterial forms:

To estimate the frequency at which phage-resistant forms were created, both solid- and liquid culture approaches were used. In solid culture approach 0.1 ml bacterial culture (10^7-10^8 CFU/ml) was plated onto the LB agar plates pre-treated with phage suspensions (10^9-10^{10} PFU/ml). After 18 hours of incubation at 37 °C, the number of phage-resistant bacterial colonies formed on the plates was recorded. The frequency of resistance formation was calculated as the CFU of resistant colonies divided by the CFU of colonies from a control experiment (bacteria plated on untreated agar) [41,46]. In liquid culture approach, 96 well microtiter plates were inoculated with 0.1 ml of phage suspension (10^9-10^{10} PFU) and with 0.05 ml phage host strains (10^4-10^3 CFU). Absorbance was recorded at 590 nm every 20 min for 18 h while shaking at 37 °C.

Results.

Characterization of bacterial strains.

Antibiotic susceptibility of *K. pneumoniae* strains:

100 *K. pneumoniae* clinical strains, which were studied in this work had been isolated from various clinical samples of both, local and travelling patients. About one third were isolated from urine samples (30 %), followed by faecal isolates (29 %). 16 % of strains have unknown origin. Isolation sites of the remaining 25 strains are as follows: sputum and throat swabs – 11 %, urogenital specimens – 7 % and wound swabs – 7 % (Table S1).

All strains were investigated in terms of their antibiotic resistance. Two most effective antibiotics were chloramphenicol and a combination of ceftazidime with avibactam. Only 17 % and 18 % of strains showed resistance to these two antibacterial agents, respectively (Table 2). In cases of 15 other antibiotics that were tested in this work, percentage of resistant strains always exceeded 50 % and even reached 100 % in case of Ticarcillin. Ticarcillin was followed by ampicillin, doripenem, piperacillin and cefepime, resistance rates to which were 99 %, 95 %, 93 % and 93 %, respectively (Table 2). 86 % of all strains showed resistance to ceftazidime. 78 % and 73 % of studied strains were resistant against ofloxacin and the combination of amoxicillin and clavulanic acid, respectively. Moxifloxacin, aztreonam and ciprofloxacin were ineffective against 64 %, 63 % and 61 % of strains, respectively. Resistance rates to the remaining five antibiotics did not exceed 58 % and were as follows: imipenem - 58 %, cefuroxime - 57 %, meropenem - 56 %, ertapenem - 53 % and ceftriaxone - 51 % (Table 2).

According to these results, most studied strains showed either extensively drug-resistant (XDR) or multidrug-resistant (MDR) phenotypes. Three strains were completely resistant to all tested antibiotics of all classes. From the remaining 97 strains 67 are XDR and 24 are MDR isolates.

Evaluation of the presence of selected β-lactamase encoding genes:

According to conventional PCR approach, we did not detect any of the four targeted *bla* genes in most of studied strains (70 %). Among the other 30 %, tested *bla* genes occurred either independently or in combination. 11 % of strains harbored bla_{KPC}. bla_{CTXM} gene was found in 8 % of strains. These two genes co-occurred in 2 strains. bla_{NDM} was found in 4 % of studied strains and in all of four cases bla_{CTXM} was also present. Only five strains were found to harbor bla_{OXA-48} gene. In one out of these five cases bla_{OXA-48} was co-detected with bla_{CTXM}. Since only a small set of genes was selected for PCR detection, PCR-negative strains could still bear antibiotic resistance-encoding genes, which have not been targeted by us. These may include potential alternative mechanisms related to the loss of porins or to the acquisition of different efflux pumps.

Pulsed-field gel electrophoresis (PFGE) fingerprinting:

By PFGE fingerprinting we defined phylogenetic relationships between studied *K. pneumoniae* isolates. The strains were grouped according to their origin: 50 strains from local patients in one group and 50 strains from non-Georgian residents – in another group. Strains were compared with other strains from their assigned group. XbaI digestion resulted in detectable and reproducible fingerprints in 96 cases, while DNA of 4 (Three local patients' strains and one strain form a patient from abroad) strains was repeatedly degraded by restriction digest. Obtained fingerprints were used for constructing dendrograms, where multiple clusters can be observed (Figure 1). Tight clusters represent strains with higher level of genetic relatedness. No big clusters or large groups of highly similar strains were detected – highlighting high genetic diversity among studied strains. No correlation was found between the clustering of strains and their antibiotic susceptibility patterns.

Characterization of phages.

Phage host range and efficiency of plating (EOP):

From an initial set of 31 candidate phages five were selected for subsequent experiments. Main selection criterion for these phages was their lytic spectra. Phage M222 showed activity against 74 (out of 100) isolates, phages S884 and S706/2 were active against 44 strains and 40 strains, respectively. Phages M66 and M143 were not distinguished because of their wide lytic activity, however, they showed activity against strains, which were otherwise resistant to the three other phages. This way we ended up with a set of five phages, which, collectively act against 93 out of 100 target bacterial strains (Table S1).

While some strains showed intermediate sensitivity (e.g. OL) towards phages of interest, only fully sensitive strains were selected for the evaluation of the efficiency of plating (EOP) experiments. All five phages showed high EOP (≥0.5) on roughly half of tested strains (Table 3). Phage M143, which was characterized by the narrowest host range, indeed showed plaque formation only on 4 out of 9 tested strains. Even in these

Table 1. *bla genes targeted by PCR. All primers and PCR setting were selected according to the sources cited in the table.*

Targeted genes	Primer sequence	Expected product size	References
bla_{KPC}	For: CGTCTAGTTCTGCTGTCTTG Rev: CTTGTCATCCTTGTTAGGCG	798 bp	[32-34]
bla_{CTXM}	For: AAAAATCACTGCGCCAGTTC Rev: AGCTTATTCATCGCCACGTT	415 bp	[35,36]
bla_{OXA-48}	For: CCAAGCATTTTTACCCGCATCKACC Rev: GYTTGACCATACGCTGRCTGCG	389 bp	[37]
bla_{NDM}	For: GCAGCTTGTCGGCCATGCGGGC Rev: GGTCGCGAAGCTGAGCACCGCAT	782 bp	[38]

Table 2. *Antibiotic susceptibility of clinical isolates of K. pneumoniae. Amount of resistant/susceptible strains are presented in percentages. Percent values are calculated from 100 tested strains.*

Antibiotic class	Antibiotic	Resistant strains (%)	Sensitive strains (%)
Penicillins	Ticarcillin	100	0
	Ampicillin	99	1
	Piperacillin	93	7
	Amoxicillin-clavulanic acid	73	27
	Ampicillin-sulbactam	50	50
Cephalosporins	Cefepime	93	7
	Cefuroxime	57	43
	Ceftriaxone	51	49
	Ceftazidime	86	14
	Cefotaxime	43	57
	Ceftazidime-avibactam	18	82
Carbapenems	Doripenem	95	5
	Imipenem	58	42
	Ertapenem	58	42
	Meropenem	56	44
Monobactam	Aztreonam	63	37
Fluoroquinolones	Ofloxacin	78	22
	Moxifloxacin	64	36
	Ciprofloxacin	61	39
	Levofloxacin	48	52
Aminoglycosides	Tobramycin	31	69
	Gentamicin	30	70
	Amikacin	30	70
Other	Trimethoprim-sulfamethoxazole	36	64
	Chloramphenicol	17	83

Table 3. *EOP of five tested phages. EOP of 0.5 or higher corresponds to high efficiency, EOP values between 0.1 and 0.5 is considered medium efficiency, while EOP of 0.1 or less is low efficiency.*

Bacteriophage	Number of bacterial strains tested	Quantitative distribution of strains according to the efficiency of each phage		
		EOP ≥ 0.5	**EOP < 0.5**	**EOP = 0**
vB_Kp M66	13	7	5	1
vB_Kp M222	29	14	9	6
vB_Kp M143	9	4	0	5
vB_Kp S884	29	13	10	6
vB_Kp S706/2	18	9	6	3

Table 4. *The rate at which phage resistant forms appear for each tested phage are presented. The rate is calculated by taking into account the initial amount of bacterial CFUs on phage-treated plates and the number of formed colonies.*

Bacteriophage	Rate of formation of phage-resistant forms
vB_Kp M66	$8x10^{-4}$
vB_Kp M222	$6x10^{-3}$
vB_Kp M143	$3x10^{-4}$
vB_Kp S884	$1.5x10^{-8}$
vB_Kp S706/2	$1x10^{-8}$

four cases plaques were not always fully transparent. The other four phages showed plaque formation on most tested strains. Phage M66 formed plaques on 12 out of 13 strains (with high efficiency on 7 strains), phage M222 and phage S884 both formed plaques on 23 out of 29 and 26 strains respectively (with high efficiency on 14 and 13 strains, respectively) and phage S706/2 formed plaques on 15 out of 18 strains (with high efficiency on 9 strains) (Table 3).

Phage virion and plaque morphology:

Phage virion morphology was studied via transmission electron microscopy (TEM). TEM investigation revealed two different phage morphologies. Phages M66, M222 and M143 showed morphology characteristic for the Myoviridae morpho group – all three phages having hexagonal heads and contractile tails (Figure 2 a, b, c – top left panels). On the other hand, phages S884 and S706/2 showed smaller heads and non-contractile tails, putting them in the Siphoviridae morphological group (Figure 2 d, e – top left panels).

Plaque formation varied among the studied five phages. Phage plaques on bacterial lawns differed in terms of their size and in terms of the presence or absence of halos around plaque centers. While phages M222, S884 and S706/2 formed small, clear plaques, in cases of phages M143 and M66 halo formation was also observed (Figure 2 b, c, bottom and right panels).

Phage one-step growth experiments:

In terms of their growth characteristics, all five phages showed different properties. Phages M222 and M143 proved to be the fastest absorbers, 95 % and 92 % of phage particles of M222 and M143, respectively successfully absorbing to host cells in 5 minutes. In all other aspects these two phages differed drastically. With 130 min, phage M143 has the longest (among the studied phages) latent period. Its burst size fluctuates between 90 and 100 PFUs per infected cell. These properties are quite similar to what we saw in case of phage M66, which is also characterized by long latent period (100-120 min) and a burst size of 100-120 PFUs per infected cell. It is noteworthy, that maximum adsorption by this phage takes place at 10 minutes (with 90 % of phage particles adsorbing to the host). Fast-adsorbing phage M222 has a much shorter latent period of 15-20 min and its burst size is 40 PFUs per infected cell. Adsorption of phage particles of S706/2 and S884 peaks at 10 minutes in both cases (with 95 % and 90 % of corresponding phage particles adsorbing at 10 min time point), however their latent period and burst size are significantly different. Phage S706/2 has a 50 min-long latent period concluded by the release of 90-100 PFUs from each infected cell, while phage S884 produces 30 PFUs per infected cell after a latent period of only 20-25 min.

Determination of the rate of formation of phage-resistant forms:

We studied the rate at which phage-resistant forms arise in target bacterial strains. For phages S884 and S706/2, the rate was very low ($1\text{-}1.5x10^{-8}$). This number was higher for the three other phages (Table 4). Importantly, in case of phage M222 (with a rate of $6x10^{-3}$), resistant forms were found to be unstable – already after the first round of cultivation, phage resistance was no longer detected. It is interesting to note, that phage-resistant forms, which developed against phage M222 as well

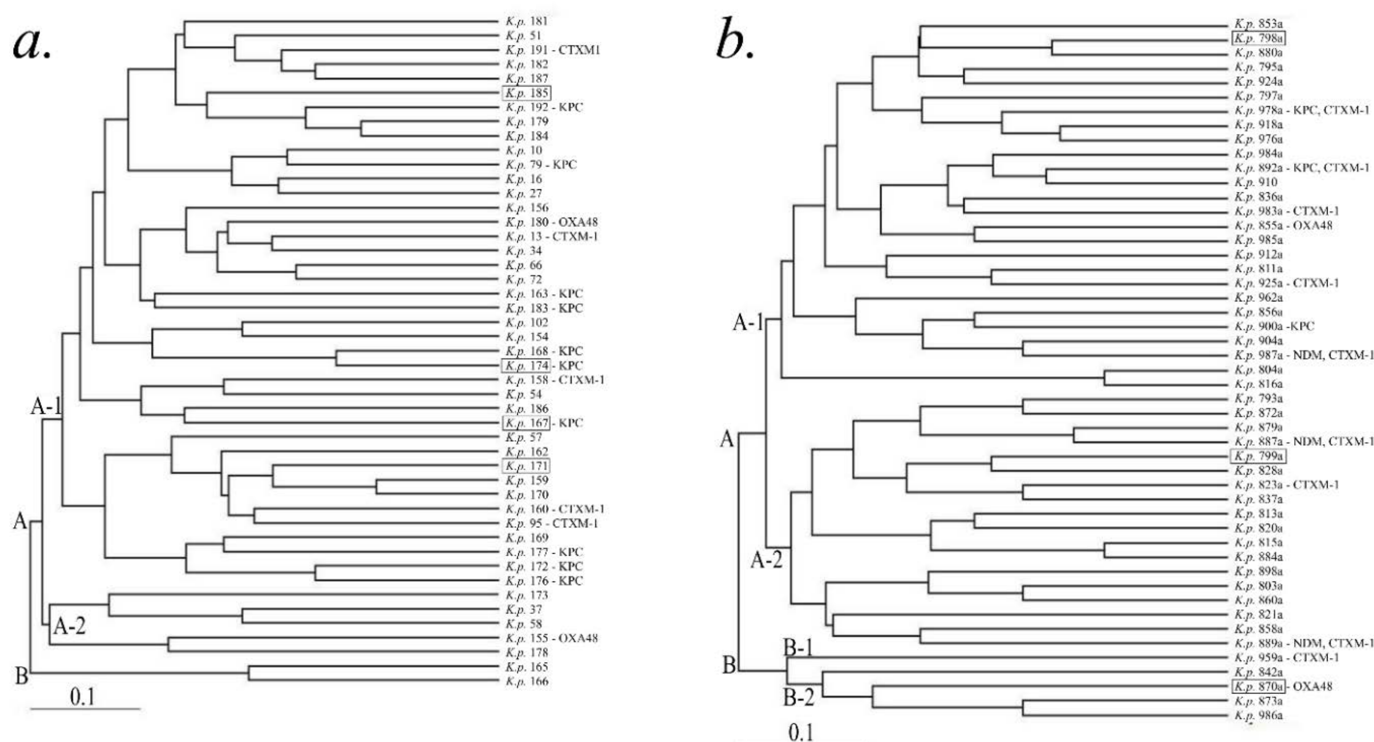

***Figure 1.** Dendrograms of XbaI digest-based PFGE fingerprinted strains of K. pneumoniae. Strains of local patients (a) and of patients travelling from abroad (b) are presented in two separate trees. Clusters A and B (and corresponding sub-clusters) are indicated for each dendrogram. Seven strains, which showed resistance to all five phages are boxed. Detected presence of β-lactamase encoding genes is indicated next to relevant strains.*

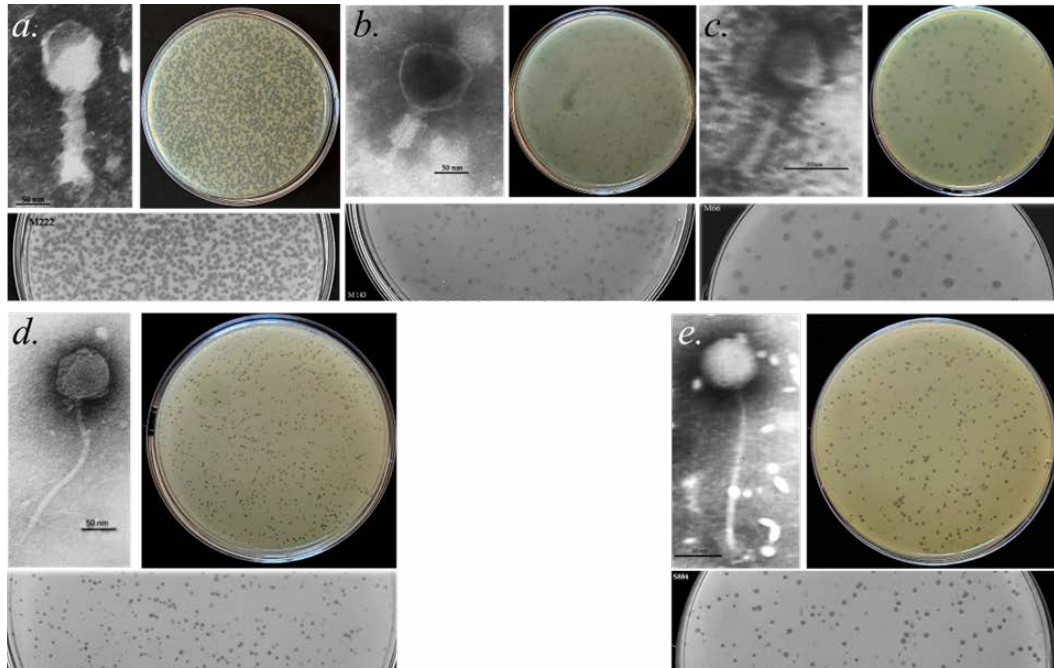

Figure 2. *Morphology of phage particles and plaques. Phage particles were visualized by transmission electron microscopy, at x320 000 magnification. Scale bar – 50 nm. Plaque morphology was assessed on double layered agar plated. For each phage top-left panel depicts its virion morphology, top-right panel shows a full plate with phage plaques and the bottom panel depicts magnified picture of plaque-containing plate in greyscale. a. Phage M222 – Myoviridae, approximate head and tail sizes: 108 x 87 nm and 135 35 nm, respectively. b. Phage M 143 – Myoviridae, approximate head and tail sizes: 105 x 106 nm and 102 x 30 nm, respectively. c. Phage M66 – Myoviridae, approximate head and tail sizes: 43.7 x 43.7 nm and 75 x 9.5 nm, respectively. d. Phage S706/2 – Siphoviridae, approximate head and tail sizes: 78 x 78 nm and 218 x 8 nm, respectively. e. Phage S884 – Siphoviridae, approximate head and tail sizes: 65 x 65 nm and 188 x 6 nm, respectively.*

as phages M143 (at the rate of $3x10^{-4}$) and M66 (at the rate of $8x10^{-4}$) acquired sensitivity to other phages, including phage M198 [47] (data not shown).

In accordance with the results obtained by plate-based assays (described above), we found that phage resistance against phages S884 and S706/2, but also against phage M222 did not occur in liquid culture experiments. Bacterial forms resistant to phages M143 and M66 only arouse after 8-12 hours of cultivation and even then, cell density remained low.

Discussion.

In this work we evaluated therapeutic potential of five phages targeting clinical strains of *K. pneumoniae*. *K. pneumoniae* is an important pathogen, with more and more cases of infections, where conventional antibiotics have failed [48-52]. Since the number of successful clinical cases, where *K. pneumoniae* has been effectively targeted by personalized phages, is on the rise, it is obvious, that *Klebsiella* phages represent a promising alternative to antibiotics [12,13,53-59]. The fact that there are no ready-made *Klebsiella*-targeting phage cocktails available on the pharmaceutical market, creates obstacles for rapid, effective and accessible phage therapy options for *Klebsiella*-related infections. We therefore believe, that characterization of phages for potential therapeutic application (for personalized use as well as for potential cocktail development) is an important step in this direction.

While the need for well characterized *Klebsiella* phages is apparent, we understand the limitations of current study. Phenotypically characterized phages, which are described in this work have not yet been studied in terms of their genetic characteristics. This is an important next step, which would allow us to confidently declare therapeutic potential of these phages – as we have recently done for another *Klebsiella* phage – Phage M198 [47].

Phenotypic tests suggest, that all five phages described in this work are most likely lytic phages, which effectively tagret clinical isolates of *K. pneumoniae*. Also, the fact that these five phages vary by their intracellular growth characteristics (most importantly by their adsorbtion times and latent periods), makes them good candidates for phage combinations. Relatively low rates of resistance formation is also an important aspect, which needs to be noted. While presented data does not allow to pinpoint any mechanisms behind emergence or loss of phage-resistance, these are long known, but not fully understood occurrences. Since we did not study genetic backgrounds of different generations of the bacterial host and neither did we assess heterogeneity of phage-treated populations, possible pseudolysogeny cannot be fully excluded. It is also plausible to assume, that what we observed are not true resistant mutants, but rather cells in a carrier state [60,61]. It would therefore be interesting to find out whether the cells in different generations respond to phage infection through receptor-involving mechanisms such as by adapting LPS synthesis pathways or through reversible phase-variation [62,63]. These aspects of the emergence and loss of phage resistance towards described five phages remains to be understood.

Importantly, characterized phages lyse strains, which proved to be extensively drug-resistant – highlighting their therapeutic potential. Also, phenotypic antibiotic resistance profiles or presence of resistance genes tested by us does not seem to correlate with phage susceptibility of studied strains.

It is interesting to note, that the distribution of detected beta-lactamase encoding genes was uneven between the two groups of strains tested here. KPC, which is responsible for resistance to carbapenems and which is often found on mobile genetic elements, was more frequently encountered in strains originating from Georgia. Since we have not studied how alternative processes could contribute to observed antibiotic resistance, we are unable to definitively identify the specific mechanisms responsible for phenotypically observed resistance to a wide range of antibiotics. However, previous studies suggest that loss of porins or acquisition of efflux pumps may contribute to resistance in strains, which, according to our limited PCR experiments, did not harbor beta-lactamase encoding genes. It has long been known, that outer membrane permeability is an important factor in drug resistance in *Klebsiella* [64]. Loss of outer membrane porins, such as OmpK35 and OmpK36 has been established as one of the factors contributing to resistance to beta-lactams, such es imipenem and ertapenem [64-66]. While efflux pumps are rarely the sole determinants of high-level antibiotic resistance, they are playing an important role in the development of multidrug resistance in *Enterobacteriaceae* [67]. It is therefore highly likely, that PCR-negative strains from this work possess mechanisms, not detectable by highly specific PCR used by us.

Our observation that these phages have covered 93 % of randomly selected drug-resistant, genetically diverse (according to PFGE fingerprinting) strains from different sources, suggests that they could be effective against a large variety of clinical isolates. However, we understand that the variety of targeted *K. pneumoniae* strains, being notorious for its capsule type diversity, needs to be confirmed by strain capsular typing. While such typing has not been a part of this project, we are planning to address this shortcoming in future work involving these phages.

Despite its shortcomings, we view this work as an important step towards ensuring that a large and diverse set of therapeutic *Klebsiella* phages are available. As a foundation for future experiments, this work would be followed by experiments, which would aim at phage cocktail design by more detailed characterization of phages as well as of their target strains.

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Authorship contribution statement

L.L.: writing – original draft (lead); writing - review and editing (equal); Methodology (lead).; Formal analysis (equal); Investigation (equal); Project administration (lead); Visualization (lead). D.B.: Investigation (equal). L.A.: Investigation (equal). M.Ch.: Investigation (equal). M.Kh.: Investigation (equal). G.Ts.: Investigation (equal). N.B.: Conceptualization (lead); Funding acquisition (lead); Project administration (supporting). L.K.: Conceptualization (supporting); Formal analysis (equal), Project administration (supporting); Visualization (supporting); Supervision (lead). E.Z.: writing – original draft (supporting); writing - review and editing (equal); Investigation (equal), Project administration (supporting); Visualization (supporting).

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Table S1. *List of 100 strains included in the study. Isolation source is indicated next to the strain ID. Strains resistant to all five phages tested in this work are highlighted in yellow. resistance (R) is indicated in purple, full and intermediate sensitivity – in blue (S and I, respectively). Next to each strain, its antibiotic-resistance status is shown: S – sensitive; MDR – multi-drug resistant; XDR – extensively drug resistant; PDR – pan-drug resistant.*

#	Strain ID	Isolation source	Phage					
			M66	M222	M143	S884	S706/2	
1	*K.p.10*	Stool	R	S	R	S	S	MDR
2	*K.p.13*	Urine	R	S	R	S	S	MDR
3	*K.p.16*	Urine	R	R	R	S	S	MDR
4	*K.p.27*	Stool	R	I	R	R	R	MDR
5	*K.p.34*	Stool	S	I	R	S	S	MDR
6	*K.p.37*	Throat swab	R	I	R	R	R	XDR
7	*K.p.51*	Urine	S	S	R	I	S	XDR
8	*K.p.54*	Sputum	I	I	R	I	I	S
9	*K.p.57*	Sputum	R	I	R	R	R	MDR
10	*K.p.58*	Stool	R	R	R	S	R	XDR
11	*K.p.63*	Urine	R	I	R	I	S	XDR
12	*K.p.66*	Wound swab	S	I	R	R	R	**PDR**
13	*K.p.72*	Stool	R	I	S	R	R	XDR
14	*K.p.79*	Stool	R	S	R	I	S	XDR
15	*K.p.95*	Wound swab	R	I	R	R	R	XDR
16	*K.p.102*	Unknown	R	I	S	S	S	XDR
17	*K.p.154*	Unknown	R	S	R	R	R	S
18	*K.p.155*	Wound swab	R	S	R	R	R	XDR
19	*K.p.156*	Urine	R	S	R	I	S	XDR

20	*K.p.158*	Urethra	R	R	R	R	S	XDR
21	*K.p.159*	Stool	R	I	R	R	R	MDR
22	*K.p.160*	Stool	R	I	R	I	S	XDR
23	*K.p.161*	Stool	R	S	R	R	R	MDR
24	*K.p.162*	Stool	R	R	S	R	R	XDR
25	*K.p.163*	Stool	R	S	R	S	S	XDR
26	*K.p.164*	Urine	R	S	R	R	I	MDR
27	*K.p.165*	Urine	R	S	R	R	R	MDR
28	*K.p.166*	Stool	R	I	R	R	R	XDR
29	*K.p.167*	Throat swab	R	R	R	R	R	XDR
30	*K.p.168*	Stool	R	I	R	R	R	MDR
31	*K.p.169*	Stool	R	R	S	R	R	MDR
32	*K.p.170*	Stool	R	S	R	R	R	XDR
33	*K.p.171*	Stool	R	R	R	R	R	MDR
34	*K.p.172*	Stool	R	I	R	S	I	XDR
35	*K.p.173*	Stool	R	R	R	I	R	MDR
36	*K.p.174*	Stool	R	R	R	R	R	MDR
37	*K.p.176*	Urine	R	S	R	S	S	XDR
38	*K.p.177*	Sputum	R	S	R	R	R	XDR
39	*K.p.178*	Wound swab	R	I	R	R	R	S
40	*K.p.179*	Unknown	S	R	S	R	R	S
41	*K.p.180*	Urine	R	S	R	I	S	XDR
42	*K.p.181*	Unknown	R	S	R	I	R	MDR
43	*K.p.182*	Stool	R	S	R	I	R	MDR
44	*K.p.183*	Stool	R	R	S	R	R	MDR
45	*K.p.184*	Throat swab	R	S	R	S	S	MDR
46	*K.p.185*	Vagina	R	R	R	R	R	MDR
47	*K.p.186*	Unknown	S	R	R	R	R	S
48	*K.p.187*	Stool	R	I	R	I	I	S
49	*K.p.191*	Stool	S	R	R	S	I	XDR
50	*K.p.192*	Sputum	R	I	R	R	R	XDR
51	*K.p.793a*	Urine	R	S	R	R	R	XDR
52	*K.p.795a*	Urine	R	S	R	R	S	XDR
53	*K.p.797a*	Urine	R	S	R	R	R	XDR
54	*K.p.798a*	Urine	R	R	R	R	R	XDR
55	*K.p.799a*	Urine	R	R	R	R	R	XDR
56	*K.p.803a*	Stool	S	I	R	R	R	XDR
57	*K.p.804a*	Stool	R	I	R	R	S	XDR
58	*K.p.811a*	Stool	R	S	R	R	R	XDR
59	*K.p.813a*	Urine	R	R	R	S	S	**PDR**
60	*K.p.814a*	Urine	R	S	R	R	R	XDR
61	*K.p.815a*	Unknown	R	R	R	R	S	XDR
62	*K.p.816a*	Unknown	R	S	R	R	R	XDR
63	*K.p.820a*	Urine	R	I	R	S	S	XDR
64	*K.p.821a*	Urine	R	S	R	I	R	XDR
65	*K.p.823a*	Urine	S	R	R	R	R	XDR
66	*K.p.828a*	Unknown	R	I	R	R	R	XDR
67	*K.p.836a*	Urethra	R	S	R	R	R	XDR
68	*K.p.837a*	Sperm	R	S	R	R	R	XDR
69	*K.p.842a*	Urine	R	S	R	I	I	XDR
70	*K.p.853a*	Unknown	S	R	R	I	R	XDR
71	*K.p.855a*	Unknown	R	S	R	S	S	MDR
72	*K.p.856a*	Wound swab	R	S	R	R	R	XDR
73	*K.p.858a*	Urine	R	S	R	I	R	XDR
74	*K.p.860a*	Unknown	R	S	R	R	R	XDR
75	*K.p.870a*	Unknown	R	R	R	R	R	XDR
76	*K.p.872a*	Throat swab	R	S	R	R	R	XDR
77	*K.p.873a*	Unknown	R	S	R	I	R	XDR
78	*K.p.879a*	Throat swab	R	R	R	R	S	XDR
79	*K.p.880a*	Unknown	R	R	S	R	R	MDR
80	*K.p.884a*	Urine	R	R	R	S	R	XDR
81	*K.p.887a*	Wound swab	R	S	R	S	S	XDR

82	*K.p.889a*	Wound swab	S	I	S	R	R	XDR
83	*K.p.892a*	Urine	R	I	S	R	R	XDR
84	*K.p.898a*	Sputum	S	S	R	I	I	MDR
85	*K.p.900a*	Sputum	R	S	R	S	S	XDR
86	*K.p.904a*	Urine	R	I	R	R	R	XDR
87	*K.p.910a*	Stool	R	S	R	S	S	XDR
88	*K.p.912a*	Stool	R	R	S	R	R	XDR
89	*K.p.918a*	Stool	R	I	S	R	R	XDR
90	*K.p.924a*	Sperm	R	S	R	S	S	XDR
91	*K.p.925a*	Urine	R	S	R	I	S	XDR
92	*K.p.959a*	Urine	R	S	R	I	R	XDR
93	*K.p.962a*	Urine	S	S	R	I	I	XDR
94	*K.p.976a*	Sperm	R	S	R	I	I	XDR
95	*K.p.978a*	Prostate	R	I	R	I	I	XDR
96	*K.p.983a*	Urine	R	S	R	R	R	XDR
97	*K.p.984a*	Unknown	R	I	R	I	S	XDR
98	*K.p.985a*	Urine	S	R	R	S	I	XDR
99	*K.p.986a*	Urine	R	I	R	S	S	MDR
100	*K.p.987a*	Unknown	R	I	R	R	R	**PDR**

Table S2. *List of antibiotics used in this work. Antibiotics are grouped according to their class.*

Antibiotic class	Antibiotic
Penicillins	Ticarcillin
	Ampicillin
	Piperacillin
	Amoxicillin-clavulanic acid
	Ampicillin-sulbactam
Cephalosporins	Cefepime
	Cefuroxime
	Ceftriaxone
	Ceftazidime
	Cefotaxime
	Ceftazidime-avibactam
Carbapenems	Doripenem
	Imipenem
	Ertapenem
	Meropenem
Monobactam	Aztreonam
Fluoroquinolones	Ofloxacin
	Moxifloxacin
	Ciprofloxacin
	Levofloxacin
Aminoglycosides	Tobramycin
	Gentamicin
	Amikacin
Other	Trimethoprim-sulfamethoxazole
	Chloramphenicol