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From the Editor-in-Chief



ძვირფასო კოლეგებო!

შემოთავაზებული სამეცნიერო ნაშრომთა ჟურნალი განკუთვნილია მედიცინის, ეკონომიკის, მენეჯმენტის, ფიზიკური მედიცინისა და რეაბილიტაციის დარგის სპეციალისტებისათვის.

ჩვენ ვიმედოვნებთ, რომ ავტორთა მიერ წარმოდგენილი ნაშრომები ხელს შეუწყობს სამეცნიერო პოტენციალის გაძლიერებას.

მარინა ფირცხალავა
ბიოლოგიურ მეცნიერებათა დოქტორი,
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Dear colleagues!

The proposed scientific journal is intended for specialists in medicine, economics, management, physical medicine, and rehabilitation.

We hope that the works presented by the authors will help to strengthen the scientific potential.

Marina Pirtskhalava
Doctor of Biological Sciences,
Professor, Academician,
Rector of University Geomedi

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Telemedicine and telehealth: an Italian and UK perspective

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Abstract

Background

On January 30, 2020, the Director-General of the World Health Organization (WHO) declared the international outbreak of new coronavirus 2019-nCoV (Public Health Emergency of International Concern -PHEIC), as enshrined in the International Health Regulations (IHR, 2005).

The current pandemic has uncovered our vulnerability and fears turning our lives upside down.

We have been forced to a more resourceful approach with a view to contain and limit potential damage.

The current events have put significant strain on hospital organisations all over the world.

Objective

At a time when, in the absence of specific therapy to treat cardio patients and a vaccine only recently approved, social distancing is one of the main measures used to combat the COVID-19 pandemic, telemedicine is gaining ground as a key technology for safe and efficient communication between doctors and patients.

The aim is to highlight the major role played by telemedicine and telehealth during the pandemic with reference to the potential implications for the foreseeable future.

Methods

We have attempted to give a survey on telemedicine and telehealth applications in Italy and UK before and during the management of the pandemic.

Results

Some examples of the application of telemedicine and telehealth with reference to their impact and relationship with end users have been highlighted.

Conclusion

Telemedicine and telehealth are likely to become more established in the future. We may have to reconsider our current working patterns towards a more beneficial and cost-effective way of living and working.

Key words: Telemedicine, Telehealth, COVID-19, Cardiovascular Disease.

Introduction

The world is on its knees. This is the utter reality and it would be foolish to deny it.

The recent events have confirmed how vulnerable and unprepared we are to face a viral illness that is claiming thousands of lives despite our highly advanced level of technology and knowledge.

Our daily activities and jobs have been suddenly forced to a complete rearrangement. Small and large businesses forced to stop. Whole countries in lockdown in an attempt to slow down and contain an invisible killer we do not know much about. Hospitals, GP surgeries and other primary care centres have been forced to redirect the available resources to fight against the new “black death”. Those who have read “The Betrothed” by Alessandro Manzoni may well understand the similarities.

In a matter of days, we have witnessed a complete revolution in telemedicine in Europe and the United States.

The World Health Organization (WHO) itself has mentioned telemedicine as one of the essential services in its policy of "strengthening the response of health systems to COVID-19" [1]. According to a new WHO policy, as part of the action to optimise service delivery, telemedicine should be one of the alternative models for clinical services and clinical decision support. However, it should be noted that telemedicine does not replace traditional medicine but supports and integrates it with new communication channels and innovative technologies, with the aim to improve healthcare and help patients access and obtain the best possible care.

Despite the initial scepticism, virtual consultations have become the “new normal” in order to maintain social distancing but at the same time to keep tracking of those patients in need because of other diseases. With fears running high, there is a need to treat anyone who can afford to remain at home with a video session or a phone call. The strict rules about privacy and data protection had to be reviewed in response to the pandemic. Microsoft Teams has soon become the virtual communication system for clinicians during Covid-19 pandemic in relation to hand-over between shifts, MDT meetings for decision-making and communication between “dirty” and “clean” areas. Nevertheless, face-to-face contact has been maintained whenever required in the context of social distance measures.

Although all this is happening in the heat of the moment, concerns remain about the limitations related to patient examination, potential for missing diagnosis and allocation of resources.

Material and Methods

To avoid confusion is important to understand the meaning of telehealthcare and telemedicine, which are often misleading because used without clear boundaries.

Telehealth is a collection of means or methods for the enhancement of health care, public health and health education delivery and support the use of telecommunications technologies.

Telehealth encompasses a broad variety of technologies and tactics to deliver virtual medical, health, and education services. Telehealth is not a specific service but a collection of means to enhance care and education delivery.

Telehealth is different from telemedicine in that it refers to a broader scope of remote healthcare services than telemedicine. Telemedicine refers specifically to remote clinical services, while telehealth can refer to remote non-clinical services.

Telehealth is personalised treatment delivered over a distance with data transfer between patient and medical professional, who gives advice after review. Chronic conditions like asthma/COPD, diabetes and hypertension may well be suitable for this approach, which reduces travelling to hospital and saves time. The disadvantage is a breakdown in patient/healthcare professional relationship although the problem may also arise from poor interpersonal skills and/or poor mastery of the technology used. Nevertheless, a new referral would still require a traditional face-to face appointment at the beginning for a thorough clinical examination and timely discussion [2,3].

Telemedicine is mainly related to information sharing between clinicians or hospitals over a distance [3]. For example, MDT meetings with imaging review and discussion for decision-making between referring and treating clinician; continuing medical education programmes; distant training and simulation with exchange of experience between groups of professionals. Another aspect currently not being addressed is the potential of telemedicine during earthquakes or flooding as a more direct interaction between rescuers on site and hospital specialists in relation to triage and advice.

Healthcare systems worldwide are facing significant challenges in the context of an aging population with an increasing number of chronic conditions, increasing expectations and difficulty with healthcare delivery in remote areas and resource availability. Telemedicine and telehealthcare may offer a solution to these problems but acceptance, effectiveness and safety must be taken into account. The evidence for cost-effectiveness remains limited at present [3-5] although a more recent analysis highlights the genuine potential for cost-effectiveness [6].

The OECD (Organisation for Economic Co-operation and Development) states that telemedicine may be divided into three categories and combined as appropriate (see [7] for major details):

- 1) Remote monitoring, i.e. employing mobile devices in order to carry out routine tests and make results available to healthcare professionals in real time.
- 2) Storage and forwarding applications. They are comparable to the previous category although they are employed for those kind of data, which does not require a short time between transmission and answer.
- 3) Real time interactive telemedicine. In such a case HC professionals and patients need real time communication.

We have sought to give an overview of this approach and make some considerations about pros and cons.

Results

There are examples of how telemedicine and telehealth have been applied with reference to their impact and relationship with end users. Telemedicine and telehealth have played a major role during the pandemic with reference to the potential implications for the foreseeable future. The current events may have fast-forwarded a process that had already started at slow pace but without clear direction.

The introduction of telemedicine and telehealthcare in the **UK** has been slow in view of political, organisational and safety issues although a recent national strategy has addressed this aspect of healthcare delivery for the immediate future [5,8,9]. The UK has seen a rapid growth in telemedicine in the last years. A significant amount of funding has been allocated to many different programs devoted to research and application in universities, hospitals, and health institutes (see [10]). The Royal Society of Medicine in London is the main medical organization supporting these developments through its Telemedicine Forum with meetings, conferences (annual Telemed conferences), and publications (Journal of Telemedicine and Telecare) [11]. As reported in [techweb], other more recent professional organizations, such as TEAM (Toward Education for ALL with Multimedia), are contributing to global collaboration in clinical care, telemedicine teaching and research with the provision of global health education using all forms of information technologies, such as the World Wide Web and teleconferencing.

An example of established telemedicine in the UK is based at Airedale NHS Foundation Trust in West Yorkshire, which provides a unique range of digital healthcare solutions developed by close cooperation between clinicians and patients. There has been a true commitment to fully understand patients' needs and continue to improve the quality and safety of patients' experience.

The telemedicine service is delivered through the Digital Care Hub. Such a hub was

established in 2011, becoming immediately leader in UK by offering “a single point of access to expert clinical and social assessment, diagnosis, advice and support through a 24/7 system operating 365 days per year.” [12].

The service employs a multidisciplinary team with different backgrounds. The variety of available skills is a relevant asset to be considered, together with the experience and the high training level of the different professionals involved.

The service branches out in three key directions.

The first one is the “Goldline”, available 24/7 by telephone. It is provided by nurses and it is devoted to terminal patients – mainly at home - and their caregivers.

The “Careline” provides telemedicine support to people restricted to prisons and youth offender institutions.

“Immedicare” is a telemedicine service regarding chronic patients and over 500 residential and nursing homes (see [12] for more details).

Italy has an earlier history of telemedicine applications [13]. The first example was in the early Seventies when one of the main University Hospitals in Rome established a telephone service providing teleconsulting for the treatment of poisonous intoxications. Initially run on a local network area, the service is nowadays available all over Italy.

In 1976, Bologna University developed a prototype aimed at acquiring and transmitting ECG by phone.

Also in this year, CSELT in Turin set up an experimental service of teleconsulting between two hospitals of the Piedmont region: San Giovanni in Turin and Susa in the province.

In 1982, the Italian government acknowledged the strategic relevance of telemedicine and its potentialities for Health Care improving and cost reductions. The role of telemedicine as a research tool in medical informatics with a view to enhance diagnosis and treatment was also emphasized.

In the late Eighties the Ministry conceived a “National plan for research and training in telemedicine” [13] with funding up to 100 billion lira (50 million Euros).

Despite these early and promising applications, the use of telemedicine has not lived up to its expectations with unmet needs. Nevertheless, the pandemic has witnessed a surge of this approach by necessity but also the need for appropriate guidelines for its use, which may be instrumental for the National Health System if adequately funded. Conversely, the Italian Armed Forces has implemented military telemedicine systems for both military operations and humanitarian missions, while the Civil Defence has developed telemedicine models to manage emergencies and catastrophes.

"Innova Italia" is a recent initiative promoted by the Ministry of Economic Development, the Ministry of University and Research, the Ministry for Technological Innovation and Digitization and the Ministry of Health. A total of 504 proposals of digital solutions for the remote management of patients suffering from COVID-19 and/or other chronic diseases

have been submitted and reviewed by a ministerial commission with the selection of five best apps and technical remote assistance solutions (Table 1), for active patients' surveillance at home during isolation for suspected or confirmed COVID-19 diagnosis.

Table 1	
Solution	Proponent
Co4Covid-19	Dedalus Italia S.p.A.
Smart Axistance Covid-19 Control	ENEL X Italia in costituendo RTI
eLifeCare Covid-19	Exprivia S.p.A.
LazioDoctor	LAZIOcrea S.p.A.
Ticuro Reply	REPLY S.p.A.

“Co4Covid-19” is a responsive web-app made available to individuals to complete both a pre-triage questionnaire and clinical self-assessment in the quarantine or self-isolation phase. There is a system for television, including psychological assessment, and tele-monitoring, which includes clinical and environmental sensor kits, chat-box, tutorial, reminder, diary, info, exams. All information is collected in a clinical repository and made available to the operations centre.

“Smart Axistance Covid-19 Control” is a CE/MED certified telemedicine platform registered with the Ministry of Health and available to public health facilities and General Practitioners to monitor the health status of individual patients and their relatives. Remote monitoring consists of a series of vital parameters, both for the management of COVID -19 and chronic diseases. “ASL Roma 2” has used this system for more than a year for chronic diseases.

The “eLifeCcare Covid-19” telemedicine platform is specifically configured for remote assistance of COVID-19 patients. It is aimed at COVID-19 patients during home isolation / quarantine. Key parameters such as body temperature, saturation and heartbeat are monitored and acted upon if clinical conditions deteriorate.

“LazioDoctor” gives quick and safe access to health care services in the event of a suspected infection and, if positive, the subsequent management of the entire cycle of care is remotely provided by GPs, primary care organizations and specialists. The app allows data collection to monitor the health status of patients in isolation, who have tested positive or have come into contact with positive patients.

“Ticuro Reply” allows automatic and manual collection of parameters that feed a clinical diary, which can be accessed regularly for monitoring and treatment. Alarms are automatically generated if the values are outside the target range. With “Televisita” a direct audio/video/chat contact with a doctor is available to share documents and access the clinical diary with a view to treatment plan supported by interactive questionnaires and video tutorials.

Discussion and future prospects

Telemedicine is giving a significant contribution to healthcare professionals during the current pandemic although certain limitations remain and must be acknowledged. There is a chance that telemedicine may contribute to hospitals being overwhelmed if used inappropriately, though we are learning to adapt accordingly.

The ability to screen patients remotely enables the triage of those who do not need immediate medical intervention and can receive care at home. This helps lower the risk of transmitting the infection to other patients and healthcare staff. At the same time, care can be provided for those patients with chronic diseases who are at risk if exposed to the virus. Finally, healthcare professionals who are self-isolating or in quarantine because tested positive can still provide remote care for patients if needed [14]. Nevertheless, this approach may need modification to help manage early testing, diagnosis and admit those patients who require in-hospital treatment.

All this sounds really great but the reality is different considering that telemedicine has not been used traditionally in response to public health major events. Therefore, many hospitals and GP surgery are not completely fit for purpose. There is a learning curve for the use of telemedicine in the traditional patient/doctor relationship. A telephone call remains at present the way to notify patients about rescheduling of appointments with remote consultation.

Most hospitals operate at full or near full capacity, therefore telemedicine may well be the way forward to relieve additional burden provided it is implemented appropriately.

Hospitals usually prepare for adverse events or crises like winter flu but telemedicine is not something we are accustomed to. The recent events are forcing more and more hospitals to use this type of technology for patients' follow-up and adapt to a certain extent as far as training is concerned.

Telemedicine is not a new concept and has been previously considered [15-17] but its implementation has been slow and difficult to take off [4].

There is no question about the potential benefit of telemedicine in relation to access to quality healthcare for rural communities, monitoring of long-term conditions from a distance, offer of effective advice and enhanced communication between healthcare professionals and relatives [2,18]. This is very attractive for patients who are willing to accept telemedicine as an additional tool [4,17]. What about the healthcare professionals? The key points are the perceived usefulness, the perceived ease-of-use and the intention to use [4]. This is quite an important aspect highlighting the need to consider telemedicine for those patients who would benefit the most and avoid its regular use [3,19].

The attitude towards telemedicine and telehealthcare is changing and the current pandemic (COVID-19) is a clear example. Nevertheless, the effective and safe implementation of this type of technology in NHS Trusts must be clear since the beginning to avoid disappointment and in line with the available resources. Aims like access

improvement to available facilities, increased satisfaction and avoidance of emergency admissions based on close monitoring and cost reduction may be justified as long as safety is not compromised in the absence of face-to-face consultations. Type of disease, type of technology, age of patients and their ability to interact with technology and also clinicians' expertise and ability to interact with technology should be considered. Finally, cost-benefit evaluation remains a limiting factor in the context of ongoing limited funding availability. Another important issue is the shared decision making process, which is highly dependent on clear, honest and unhurried communication. This is essential to patient-centred care but how to best implement it remains unknown. Would a shift toward telehealth reduce or increase healthcare disparities? There is evidence to suggest that a trusting relationship with shared decision-making can be achieved over a telephone consultation although this precludes the use of additional material or behavioural attitude that can be achieved in an in-person consultation. Videoconferencing technology may well help to overcome this barrier. Nevertheless, potential disparities introduced by telehealth are likely to be related to age, digital readiness, income, level of education and race [20]. The resurgence of telemedicine has to be acknowledged but there has to be a commitment to realise its full potential taking into account its advantages and limitations [21-24].

The economic burden to develop and run a national Tele-health network cannot be compared to the efforts required to face a serious environmental adverse event. The COVID-19 pandemic has required significant resources for the treatment of patients affected by the disease in all European countries with serious impact on general and specialist patient care. Additional healthcare burden will be added to restore balance for the treatment of patients with chronic conditions, particularly cardiovascular disease and cancer. The lockdown has put serious strain on the economy and healthcare of European countries. The availability of an integrated and efficient Tele-health network may have helped reducing the negative effects observed during the current pandemic. It is likely that the current trend is going to continue but the issues discussed must be taken into account to maintain a drive to change [25,26].

Telemedicine may have a role to play in the event of out-of-hospital cardiac arrest according to the following survival chain:

1. Early recognition and call for help
2. Early cardiopulmonary resuscitation
3. Early defibrillation
4. Post-resuscitation care

Future developments will see the contribution of our research group to key areas of research as follows:

1. Artificial Intelligence (AI)
2. Telemedicine (support from a distance)
3. Wearable Devices
4. Simulation

5. E-learning

Studies focusing on the first stage of the survival chain have already led to some AI applications with further solutions potentially available in a non distant future in relation to support from a distance. As far as “Wearable Devices” is concerned, the development of a T-shirt with different sensors integrated in its material would allow patient’s mobility without fear of losing the transmission signal.

Our “Telecardiology & Clinical Application of Numerical Modelling of Biological Systems” research unit based at the National Institute for Cardiovascular Research (Bologna, Italy) is quite active in Simulation and E-learning applications [27-29]. More specifically, we are developing numerical models of the cardiovascular system for trend evaluation of key parameters usually requiring invasive measurement. The aim is the reduction of complications in elderly patients and/or neonates.

Our models allow simulation and evaluation of the effect of drug administration on haemodynamic and energetic parameters. The integration of these models into a simulation software with particular reference to a telecardiology platform will allow long-distance training of medical professionals, paramedics, medical students and residents [30-33].

CARDIOSIM[®] [28,29,34] remains our main platform simulation software of the cardiovascular system, where different numerical models are available to simulate mechanical ventilation and circulatory support [34-37]. Further integration with a telecardiology set up will help clinicians with treatment optimisation of critical heart failure patients [38-41].

Conclusion

We have been forced to adapt and be more resourceful during the ongoing pandemic. Therefore, we should give serious thoughts to reconsider our current working patterns towards a more beneficial and cost-effective way of living and working.

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Conflict of Interest

The authors declare no conflict of interest.

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ტელემედიცინა და ტელეჯანდაცვა: იტალიისა და დიდი ბრიტანეთის პერსპექტივა

მასიმო კაპოჩია, კლაუდიო დე ლაცარი, დომენიკო მ. პიზანელი, ზეატრიცე დე ლაცარი

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აბსტრაქტი

2020 წლის 30 იანვარს, ჯანდაცვის მსოფლიო ორგანიზაციის (WHO) გენერალურმა დირექტორმა გამოაცხადა ახალი კორონავირუსის საერთაშორისო ეპიდემია 2019-nCoV (International Health Emergency of International Concern-PHEIC), ჯანმრთელობის საერთაშორისო რეგულაციებზე დაყრდნობით (IHR, 2005). მიმდინარე პანდემიამ ჩვენი დაუცველობა და შიში გამოავლინა. შიში იმისა, რომ ჩვენი ცხოვრება შეიძლება მოულოდნელად უარესობისკენ შეიცვალოს. ამიტომ იძულებულნი გავხდით ისეთი შემოქმედებითი მიდგომები გამოგვეყენებინა, რომლებიც შეგვაჩერებინებდა და შეგვამცირებინებდა ვირუს COVID-19 პანდემიით გამოწვეულ ზიანს. მიმდინარე მოვლენები მძიმე ტვირთად დააწვა ჰოსპიტალურ სექტორს მთელი მსოფლიოს მასშტაბით. იმის გათვალისწინებით, რომ არ არსებობს Sars-Cov-2 ინფიცირებული პაციენტების მკურნალობის სპეციფიკური თერაპია და ვაქცინებიც ახლახან იქნა დამტკიცებული, სოციალური დისტანცირება COVID-19 პანდემიასთან ბრძოლის ერთ-ერთი მთავარი ღონისძიებაა. აქედან გამომდინარე, ტელემედიცინამ შეიძინა კიდევ უფრო დიდი მნიშვნელობა როგორც ექიმებსა და პაციენტებს შორის უსაფრთხო და ეფექტური კომუნიკაციის ტექნოლოგიამ. ჩვენი მიზანია პანდემიის დროს ტელემედიცინისა და ტელეჯანდაცვის მთავარი როლის ხაზგასმა, ახლო მომავალში პოტენციურ შედეგებზე დაყრდნობით. შევეცადეთ ჩაგვეტარებინა კვლევა ტელემედიცინასა და ტელეჯანდაცვის გამოყენებაზე იტალიასა და დიდ ბრიტანეთში პანდემიის დაწყებამდე და პანდემიის მართვის პერიოდში. შედეგებში ვაჩვენებთ ტელემედიცინისა და ტელეჯანდაცვის გამოყენების რამდენიმე მაგალითს მათი გავლენისა და მომხმარებელთან ურთიერთობის შესახებ.

ჩვენი დასკვნით, ტელემედიცინა და ტელეჯანდაცვა კიდევ უფრო პოპულარული გახდებიან ახლო მომავალში. ასევე, შესაძლებელია, მოგვიწიოს ჩვენი სამუშაო რეჟიმის გადახედვა უფრო ხელსაყრელი და ეკონომიური ცხოვრების წესის მიმართულებით.

საკვანძო სიტყვები: ტელემედიცინა, ტელეჯანდაცვა, COVID-19, გულ-სისხლძარღვთა დაავადებები.

Телемедицина и телездравоохранение: перспектива Италии и Великобритании

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Абстракт

30 января 2020 г. Генеральный директор Всемирной организации здравоохранения (ВОЗ) объявил о международной вспышке нового коронавируса 2019-nCoV (чрезвычайная ситуация в области общественного здравоохранения, имеющая международное значение-РНЕИС), как это закреплено в Международных медико-санитарных правилах (ММСП, 2005 г.).

Текущая пандемия выявила нашу уязвимость и страхи, перевернувшие нашу жизнь с ног на голову. Мы были вынуждены использовать более изобретательный подход с целью сдерживания и ограничения потенциального ущерба. Текущие события стали серьезным бременем для больничных организаций по всему миру.

В то время, когда из-за отсутствия специфической терапии для лечения кардиологических пациентов и вакцины, одобренной только недавно, социальное дистанцирование является одной из основных мер, используемых для борьбы с пандемией COVID-19, телемедицина получает все большее распространение как ключевая технология для безопасной и эффективной общении между врачами и пациентами. Цель состоит в том, чтобы подчеркнуть важную роль телемедицины и телездравоохранения во время пандемии с указанием потенциальных последствий в обозримом будущем.

Мы попытались провести обзор приложений телемедицины и телездравоохранения в Италии и Великобритании до и во время борьбы с пандемией. Были выделены некоторые примеры применения телемедицины и телездравоохранения с учетом их воздействия и взаимоотношений с конечными пользователями.

Телемедицина и телездравоохранение, вероятно, станут более популярными в будущем. Возможно, нам придется пересмотреть наши текущие модели работы в направлении более выгодного и экономичного образа жизни и работы.

Ключевые слова: телемедицина, телездравоохранение, COVID-19, сердечно-сосудистые заболевания.

Can Au/Ag/Fe nanoparticle composition restore blood cell counts in terms of DMH-induced colon adenocarcinoma?

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Abstract

Scientific interest in nanomedicine nowadays is constantly growing, and nanomaterials have found wide application in diagnosis and treatment of various diseases. The most promising seem to be metal nanoparticles (NP). Some of them are actively studied in separate and there are favorable results considering their ability to normalize blood cell counts, but their co-work as a composite is still not well known. This opens a great perspective for studying NP as the blood homeostasis corrector, which could help in developing treatment schemes for many threatening diseases followed by the blood cell count disorders, especially malignant tumors. As colorectal cancer is third most commonly diagnosed, this study was focused on evaluation of blood cell counts changes in rats with DMH-induced colon adenocarcinoma *in situ* along with the assessment of Au/Ag/Fe NP composition corrective effect. Colon adenocarcinoma was induced by introducing N,N-dimethylhydrazine hydrochloride during 30 weeks. After pathohistological verification of developing colon adenocarcinoma *in situ* in DMH-treated rats Au/Ag/Fe NP composition was administered during 3 weeks. Introducing NP to the DMH-injured rats lead to increasing RBC and HGB and decreasing pathologically high-leveled MCV, MCH and MCHC to normal references. Assessed NP composition normalized the neutrophils rate, LMR and gave us a PLT rate particularly the same, as in the control group animals. Taking into account the previously proven biosafety of gold, silver and iron NP on their own and as a result the predicted biosafety of their composition we can consider further amplification of preclinical study on this NP composition of high significance, as it might be possibly used as following therapy of non-metastatic forms of colon cancer.

Keywords: Experimental carcinogenesis, nanoparticles, blood cell count, rat.

Introduction

The achievements of nanotechnology have significantly affected the development of nanomedicine and nanobiotechnology, where nanomaterials have found wide application

in the treatment and diagnosis of diseases of various etiologies, in biotechnological industries and sensory technologies¹⁻³. The key property of the substance in the nanoscale range lays in increased pharmacological and biological activity. The most promising seem to be metal nanoparticles (NP), which can be used as vectors for targeted therapy in oncology and cardiology, antimicrobial drugs in medicine and veterinary medicine, components of immunobiological drugs (probiotics and vaccines), stimulants in biotechnological industries (for example, in the processes of lyophilization - rehydration of bacterial strains-producers). At the current stage of development of nanomedicine and nanobiotechnology, the creation of a bank of biosafe nanomaterials, in particular, metal NP, is especially relevant⁴.

Metal NP possess high bioactivity and recently have become of great perspective for diagnosing and treating different ethiology diseases, especially cancer⁵⁻⁹. Among the studied NP of metals are recommended as biosafe: iron NP (INP) of size 77 nm, gold - 30 and 45 nm, silver - 30 nm⁴. Gold NP (GNP), in comparison with other metals, are characterized by unique physical, chemical, biological properties and functional activity¹⁰⁻¹⁴. The nanoparticle size and shape substantially define their properties¹⁵⁻¹⁹.

High affinity to tumor cells, surface modification ability and special optical properties create the basis for effective usage of GNP as vectors for target antitumor drug delivery^{20, 21}, in cancer photothermal therapy²²⁻²⁴, as contrasting agents in magnetic resonance and computer tomography^{25, 26}. It was found, that GNP in form of water dispersions possess significant and specific size-dependent bioactivity *in vitro* and *in vivo*. Synthesized GNP *in vitro* expressed size-dependent modulation of Na⁺K⁺-ATP-ase activity in U937 tumor cells membranes. *In vivo* GNP introduced via i.v. injection have shown high affinity to tumor cells. These *in vitro* and *in vivo* results open great perspectives of using GNP in cancer treatment and diagnostics, although the size-dependent biological safety level of GNP concerning normal organs should be taken into account²⁷.

Drugs and diagnostics based on INP and their oxides are actively created. Among the areas in which INP are used, a special place is occupied by the development of drugs with antianemic action²⁸. Recent studies have shown that after a ten-day course of oral administration of INP at a dose of 12 mg / kg / day in experimental animals, normalization of hemoglobin concentration, transferrin saturation and serum iron saturation was observed²⁹. According to the data obtained, NSAIDs when administered orally to rats did not cause an increase in serum urea and creatinine compared to controls, which indicates their safety for the kidneys - one of the key organs - targets of toxic effects of nanomaterials³⁰. The test substance NSAID was also characterized as safe for the kidneys and liver in terms of total bilirubin concentration and activity of LF, ALT and LDH²⁹. The results of another study indicate a high antianemic activity of the substance of NP of zero-

valent iron in the experimental treatment of model iron deficiency anemia under intravenous administration. Of particular note is the fact that INP showed antianemic activity both in the conditionally therapeutic dose and in 1/10 of the conditionally therapeutic dose. This will contribute to the achievement of rapid therapeutic efficacy of the antianemic drug, its high therapeutic safety and prolonged preservation of the antianemic effect²⁸.

Despite the constantly growing number of recent research papers on various metal NP, it was not yet investigated, how they could work together as a composite. Promising results considering normalizing blood cell counts open a great opportunity for using NP as the blood homeostasis corrector, which could help in developing and widening treatment schemes for many threatening diseases that are followed and worsened by the blood cell count disorders, especially malignant tumors.

It was investigated, that due to many factors of a complicated cascade of tumor pathogenesis it is often accompanied by anemia. In addition, growing evidences have emerged in recent years that inflammation may be the origin of many malignancies. Being third most often diagnosed malignant tumor in the world, colorectal cancer (CRC) represents a growing number of cancers associated with inflammation. Thus, CRC is characterized by infiltration of heterogeneous immune cells and peripheral hematologic profile disorder, which configure the complicated microenvironment affecting tumor development³¹.

In some recent studies the prognostic impact of peripheral blood leukocyte in the context of intra-tumoral immune profile was investigated. Leukocytosis was validated as a prognostic factor predicting survivals and tumor response to adjuvant chemotherapy in patients with colorectal cancer³².

Given all mentioned above this study was devoted to exploring the changes of blood cell counts in rats with DMH-induced colon adenocarcinoma and evaluating the Au/Ag/Fe NP composition influence on these indicators.

Materials and Methods

Animals

The research was carried out on 160 white mature outbred male rats with body weight 190 ± 5 g. The experimental animals were kept in standard conditions of vivarium. Animal survival and body weights were monitored throughout. Rats were provided with free access to drinking water and basal diet *ad libitum*. All animal experiments of this study conformed to internationally accepted standards and were approved by the Bioethical Committee of Ternopil National Medical University. All manipulations with animals were performed according to the requirements of the "European Convention for the protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg, 1986)³³. The rats

were randomly allocated into 4 groups: 1st – 80 control animals, 2nd – 80 animals with modeled colorectal adenocarcinoma *in situ*. Afterwards 30 of injured animals received NP Au/Ag/Fe intragastrically for 21 day (3rd group). 4th group – 10 control animals received NP Au/Ag/Fe in the same manner. At the end of the experimental period, colon adenocarcinoma *in situ* was histologically identified in all DMH-treated rats.

Colorectal Cancer Model

N,N-dimethylhydrazine (DMH) is known as well-known and widely used model of chemically induced colon cancer in animals. It has several morphological and molecular characteristics with human sporadic CRC. DMH-induced colon adenocarcinoma was modeled by introducing N,N-dimethylhydrazine hydrochloride (Sigma-Aldrich Chemie, Japan, series D161802) dissolved in isotonic sodium chloride solution. The carcinogenic substance was subcutaneously injected into the interscapular region at a dose of 7.2 mg/kg body weight (based on active substance) once a week for 30 weeks. Animals of the control group obtained subcutaneous injections of 0.1 ml physiological saline with the above frequency to simulate the possible stress effects³⁴.

NP dosage and administration

Composition of spherical silver (d=30 nm), gold (d=30 nm) and iron (d=40 nm) NP with a concentration in 1 ml: 1.6 mg Ag; 0.1mg Fe; 3.088 µg Au was used in the study. Initial water dispersion of the used silver NP was synthesized via reduction of silver nitrate (AgNO₃) by tannin (tannic acid) at the presence of potassium carbonate (K₂CO₃); gold NP were synthesized via reduction of the tetrachloroauric (III) acid (HAuCl₄ · 3H₂O) (≥99.9% trace metals basis, Sigma-Aldrich) by sodium citrate tribasic dehydrate at the presence of potassium carbonate; iron NP were synthesized via reduction of iron (III) chloride by sodium borohydride. Composition of the NP NP Au/Ag/Fe used in the work was obtained via the mechanical mixture of the water dispersions of silver, gold and iron NP. Metal NP used to obtain the experimental composition as well as the received mixture were characterized as biosafe according to the criteria of genotoxicity (comet assay), cytotoxicity (MTT-test), mutagenicity (Allium-test) and immunotoxicity under *in vitro* tests.

Animals received water dispersion of NP Au/Ag/Fe intragastrically one time a day for 21 days at a dose 0.842 mg Ag/0.0526 mg Fe/ 1.625 µg Au per 1 kg of rats body weight. Before the intragastric administration initial water mixture of NP Au/Ag/Fe was diluted by sterile distilled water at a ratio 1:10.

Blood samples collection and analyzation

Blood samples collecting was provided a day after the last DMH administration to DMH-only treated rats, three days after the last NP administration to the rats that underwent

nanocorrection along with the control animals of the same age. Experimental animals were deeply anesthetized with Thiopental (50 mg/kg, intraperitoneally, Arterium, NUA/3916/01/02) and sacrificed by cervical displacement and exsanguination. Blood samples were collected into EDTA and proceeded using the Yumizen H500 CT automatic hematology analyzer.

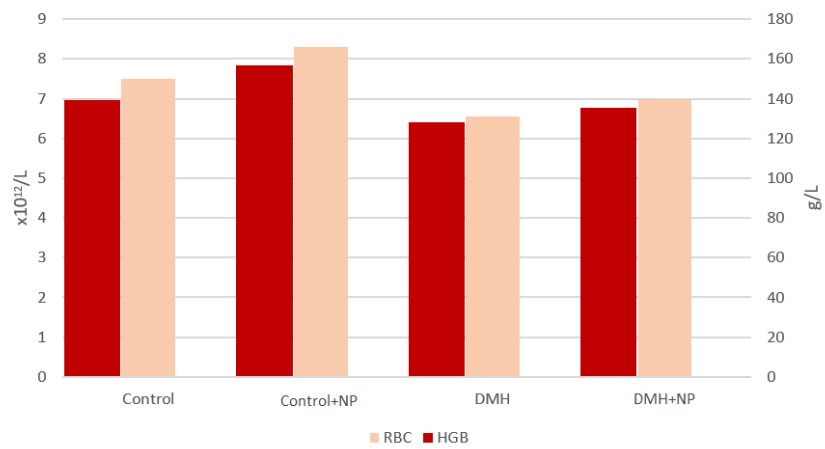
Results and Discussion

To check the effect of introducing Au/Ag/Fe NP on the blood cell count in healthy animals and to exclude any negative influence of this combination, we administered it to the healthy animals, which obtained only saline. It was investigated that the RBC count and the HGB rate was credibly increased in the nano-treated rats (Pic. 1). It can be suggested that the nanoparticle composition was an additional source of iron that promoted heme synthesis and RBC production in a natural way. The group of animals that received only Au/Ag/Fe NP had a slightly higher (6.94 %) PLT number, than the control group rats. We have estimated an increase in WBC number with the administration of the NP, mainly due to the neutrophils fraction that in this group is 1.64 times higher than the control (Pic. 3). One more subgroup, which is significantly higher, is the eosinophils – 1.42 times higher than the control. This can be explained as a physiological reaction to the introduction of foreign substance, which were the Au/Ag/Fe NP.

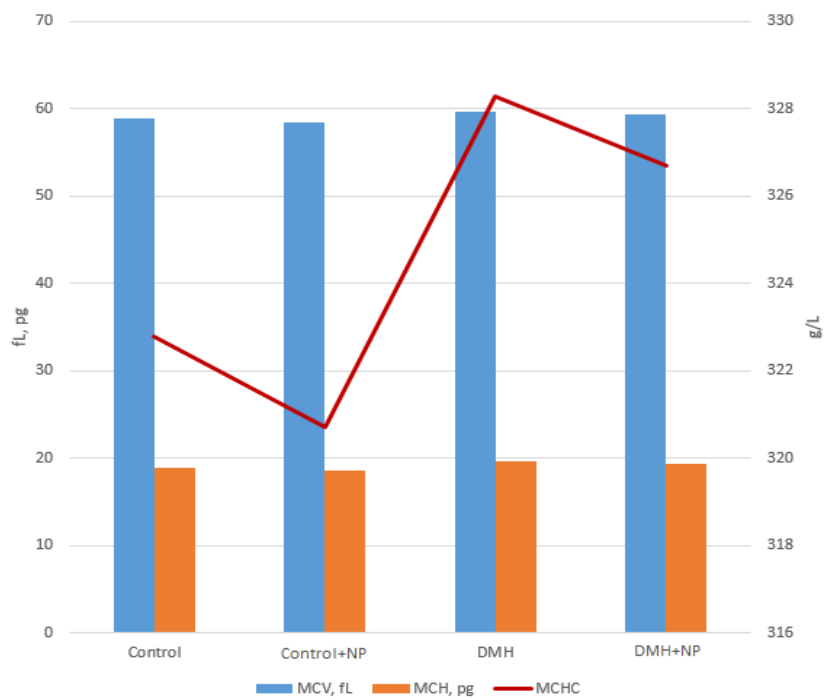
Modeling the CRC by introducing DMH after 30 weeks lead to the decrease of RBC and HGB. All three qualitative indicators – MCV, MCH and MCHC – slightly increased, probably as an adaptation reaction to the decreased number of RBC and general HGB rate (Pic. 2). Those animals that were treated with DMH had a credibly lower (59.4 %) level of PLT, comparing to the control. The WBC count, as well as its subgroups, has undergone significant changes. DMH treatment lead to the increase in WBC number mostly with the loss of lymphocytes. Thus, the WBC rate was 1.54 times lower in the DMH injured rats than the same indicator in the control group animals with the 1.73 times decrease in the number of lymphocytes (Pic. 3). In addition, the LIC count has tripled in comparison to the control group. NLR clearly shows the shift towards the neutrophils in DMH-injured animal group and LMR in the same group is 15.5 % higher comparing to the control (Pic. 4).

Nanoparticle correction helped in slightly increasing the erythrocyte number and returning the HGB rate almost to the level of control animals. Introducing NP to the DMH-injured animals lead to the decrease in MCV, MCH and MCHC, however, they did not return to the control group level (Pic. 2). Moreover, administration of NP gave us a PLT rate particularly the same, as in the control group animals. The Au/Ag/Fe NP correction has normalized the neutrophils rate. Moreover, the lymphocyte number is 26% higher in DMH+NP group rats, than in the DMH-only. However, the lymphocyte rate is still lower comparing to the control and the total WBC count in the group of DMH+ NP resumed 19 % lower, than in the control group animals. NLR remains increased even after the NP

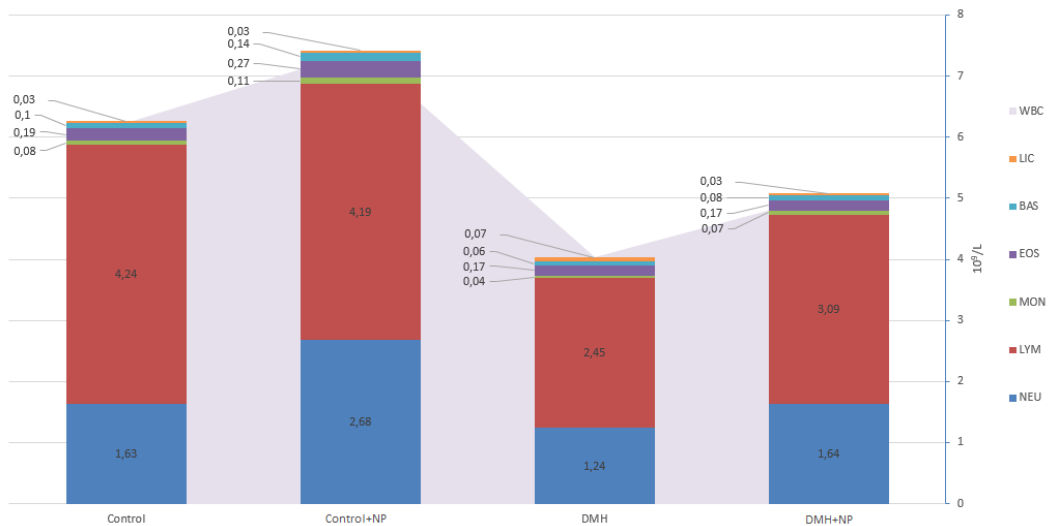
correction despite the normalization of the absolute number of the white cells (Pic. 3). On the other side, Au/Ag/Fe NP correction decreased the LMR and in this group it is even lower, than in the group of control animals (Pic. 4).



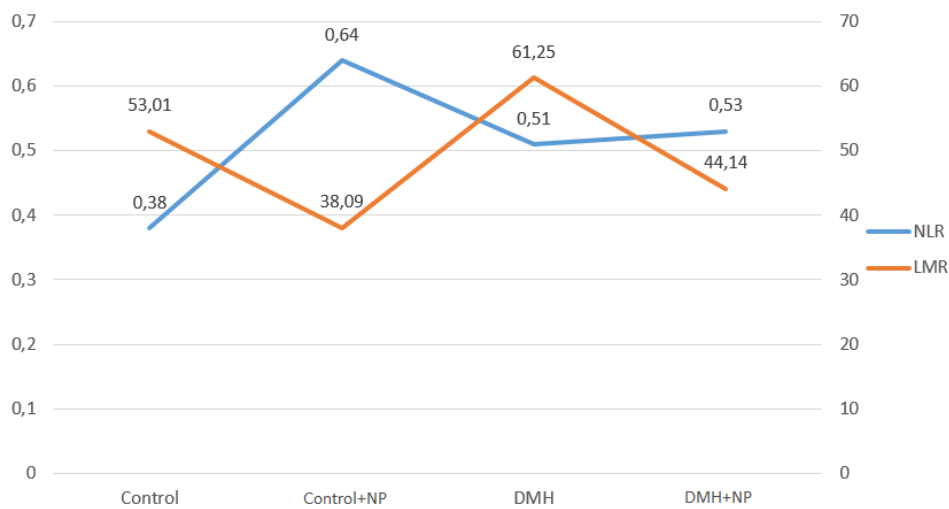
Pic. 1. RBC count and HGB rate in different experimental groups.



Pic. 2. MCV, MCH, MCHC in different experimental groups.



Pic. 3. Redistribution of WBC subgroups.



Pic. 4. NLR and LMR in different experimental groups.

Neutrophils are the most majority of peripheral leukocyte and react first to the sites of inflammation, playing an essential role in tumor development and progression. In fact, at the early stage of colorectal tumorigenesis, infiltration of neutrophils has been detected, as neutrophils infiltrated in colorectal adenomas much more than in adjacent normal mucosa and the count of neutrophils was positively correlated with the size of tumor. In addition, it was established that increased levels of these intra-tumor leukocytes correlated with poor prognosis through inducing metastasis. Neutrophils may be considered responsible as they are producing N-nitrosamines, known to be carcinogenic³¹. Additionally, activated neutrophils can induce replication errors in colon epithelial cells via hMSH2-dependent G2/M checkpoint arrest³⁵. These findings are consistent with other observations, indicating leukocytes as an adverse prognostic factor in cancer progression. In addition, inflammation leading to immunosuppression provided a preferred niche for tumorigenesis. Besides the

external causes of inflammation in cancer patients like bacterial and viral infections, there are internal causes like cancer mutations through the malignant transition in way of inflammatory cytokines. Key mediators of inflammation-induced cytokines included NF-kappa B, STAT3 pathways, reactive oxygen/nitrogen species and prostaglandins^{32,35}.

Other recent findings demonstrated that in CRC patients who underwent curative resection preoperative MCV ≥ 80.5 fL, NLR ≥ 5.5 , and LMR < 3.4 has been determined as predictors of poor RFS in II and III stage of the disease³⁶. The volume of RBCs indicated by MCV and is often used for diagnosing megaloblastic or iron-deficiency anemia. Meanwhile, recent studies found a prognostic implication of MCV in esophageal and liver cancer³⁷. It was previously reported that MCV was a prognostic factor for RFS in patients who underwent R₀ resection for stage I/II/III CRC, independent of the tumor stage³⁸; microcytosis (MCV < 80 fL) was associated with better outcomes. It was reported that Hb and MCV lowered in short terms before diagnosing the CRC, and association of low MCV and CRC patients survival was weak³⁹. CRC often plays along with iron-deficiency anemia that leads to decreased MCV. The mechanism responsible for the association between MCV and disease relapse is unknown, although several hypotheses have been proposed. The first is about oxidative stress, and the antioxidant capacity of the body had been related with the size of the circulating RBCs. Because an elevated MCV or macrocytosis may reflect structural or functional disorders of RBCs, a misbalance in antioxidant capacity can explain poor relapse outcomes after R₀ resection for CRC. In addition, affected RBCs deformability because of oxidative stress can damage the microcirculation and tissue oxygenation. On the other hand, macrocytosis may be a sign of disturbed hematopoiesis due to the dysfunction of bone marrow. It was investigated that mesenchymal stem cells out of bone marrow play crucial role in the repair of several damaged vital organs^{38, 39, 40}. A relatively high MCV is a marker of deficiency in folic acid or vitamin B12. Moreover, tumor location can be related with MCV. J.P. Väyrynen et al. (2018) reported that proximal tumor location was associated with predominant microcytic anemia⁴¹. T. Ueda et al. (2013) investigated the blood cell components in patients with acute decompensated heart failure and showed that the counts of WBC and PLT were credibly lower in the group with macrocytosis than in the non-macrocytic group⁴².

It was shown that the NLR was the second important prognostic factor among the blood cell markers³⁶. Inflammatory cytokines and mediators associated with carcinogenesis may stimulate inflammatory responses, which leads to tumor growth, infiltration, and formation of metastases. Lymphopenia can serve as a strong marker for misbalanced cell immunity, and neutrophilia is a response to systematic inflammation⁴³. Lymphocytes participate in cytotoxic cell death and inhibition of tumor cell proliferation and migration⁴⁴. The NLR had been reported to be an indicator of systemic inflammatory response in CRC. Many studies showed that a high NLR, with cutoff values ranging between 2 and 5, was

associated with poor long-term outcomes in patients with CRC⁴⁵⁻⁵⁰.

Monocytes can be responsible for tumor progression and metastasis as well. Tumor-associated macrophages (TAM) that evolve from circulating monocytes possess ability to suppress adaptive immunity along with the angiogenesis, invasion, and migration promotion⁴⁷. Increased level of circulating monocytes reflect the increased rate of TAM and is associated with worse prognosis. However, the level of circulating monocytes had not been widely used as a biomarker of CRC. The LMR is the ratio of lymphocyte to monocyte count in absolute number in blood. Recent studies have indicated that low LMR between 3.0 and 4.8 was associated with unfavorable long-term outcomes in CRC patients^{45, 51, 52}.

Conclusion

In this research it was established, that introducing the nanoparticle Au/Ag/Fe composition increased RBC count and the HGB rate in only-nano treated rats, which is more likely because the nanoparticle composition was an additional source of iron that promoted heme synthesis and RBC production in a natural way. Also, this group of experimental animals developed an increase in eosinophil rate being a physiological reaction to the introduction of foreign substance, which were the Au/Ag/Fe NP. Introducing NP to the DMH-injured animals lead to increasing the erythrocyte number and HGB rate, as well as to decreasing in MCV, MCH and MCHC to normal references. Moreover, administration of NP has normalized the neutrophils rate, LMR and gave us a PLT rate particularly the same, as in the control group animals. Thus, introducing the nanoparticle Au/Ag/Fe composition lead to normalizing the blood cell homeostasis in experimental animals with modelled non-metastatic colon adenocarcinoma. Taking into account the previously proven biosafety of the NP of gold, silver and iron on their own and as a result the biosafety of their composition we can consider further amplification of preclinical study on this nanoparticle composition of high significance, as it might be possibly used in future in curation of non-metastatic forms of colon cancer.

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შეიძლება თუ არა Au/Ag/Fe ნანონაწილაკებმა ადადგინონ სისხლის უჯრედების რაოდენობა დიმეთილჰიდრაზინით გამოწვეული მსხვილი ნაწლავის ადენოკარცინომის შემთხვევაში?

ნატალია ლისნიჩუკი, სვიტლანა დიბკოვა, ლიუდმილა რიზნიჩენკო, ზორიანა ვიგჩარი

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აბსტრაქტი

ნანომედიცინის მიმართ სამეცნიერო ინტერესი მუდმივად მზარდია. დღეისათვის ნანომასალებს ფართო გამოყენება აქვთ სხვადასხვა დაავადებების მკურნალობასა და დიაგნოსტიკაში; როგორც ჩანს, ყველაზე პერსპექტიული ლითონის ნანონაწილაკებია (NP). ზოგიერთი მათგანი ცალკეა შესწავლილი და

მიღებულია იმედის მომცემი შედეგები, რომლის მიხედვითაც მათ აქვთ სისხლის უჯრედების რაოდენობის ნორმალიზების უნარი, თუმცა კომბინაციაში ჯერ კიდევ არ არიან შესწავლილი. ეს კი იძლევა ნანონაწილაკების შესწავლის პერსპექტივას, როგორც სისხლის ჰომეოსტაზის მარეგულირებელნი. მრავალი დაავადების დროს, რომლებიც სისხლის უჯრედების შემადგენლობის დარღვევებითაა გამოწვეული, შესაძლებელია მათი გამოყენება მკურნალობის სქემებში, განსაკუთრებით კი ავთვისებიანი სიმსივნეების დროს.

ვინაიდან, კოლორექტალური კიბო რიგით მესამე, ყველაზე ხშირად დიაგნოსტირებადი კიბოა, ჩვენ შევისწავლეთ ვირთაგვებში Au/Ag/Fe ნანონაწილაკების კომბინირებული ეფექტი სისხლის უჯრედების შემადგენლობაზე *in situ*, DMH-ით გამოწვეული მსხვილი ნაწლავის ადენოკარცინმის დროს. ნაწლავის ადენოკარცინომა გამოწვეული იყო დიმეთილჰიდრაზინის ჰიდროქლორიდის შეყვანით 30 კვირის განმავლობაში. როდესაც პათოჰისტოლოგიურად დადასტურდა DMH-ით გამოწვეული *in situ* მსხვილი ნაწლავის ადენოკარცინომა ვირთაგვებში, მოხდა Au/Ag/Fe ნანონაწილაკების კომპოზიციის ადმინისტრირება 3 (სამი) კვირის განმავლობაში. ამ ნანონაწილაკების კომბინირებულმა გამოყენებამ გამოიწვია HGB-ის და RBC უჯრედების გაზრდა, ხოლო პათოლოგიურად მაღალი დონის MCV-ის, MCH-ის და MCHC-ის შემცირება ნორმასთან მიმართებაში. აგრეთვე, მოახდინა ნეიტროფილების, LMR შემადგენლობის ნორმალიზება, ხოლო PLT იყო იგივე, როგორც საკონტროლო ჯგუფის ცხოველებში. იმის გათვალისწინებით, რომ ადრე ჩატარებულ კვლევებში ოქროს, ვერცხლის და რკინის ნანონაწილაკების დამოუკიდებლად გამოყენება იყო უსაფრთხო, მათი კომბინაცია შეგვიძლია ჩავთვალოთ ბიოლოგიურად უსაფრთხოდ და მათი კომბინირებული გამოყენება შეიძლება განვიხილოთ როგორც მსხვილი ნაწლავის კიბოს არამეტასტაზური ფორმების თერაპიის საშუალება.

საკვანძო სიტყვები: სისხლის უჯრედების რაოდენობა, ნანონაწილაკები, ექსპერიმენტული კანცეროგენეზი, ვირთხა

Может ли композиция наночастиц Au / Ag / Fe восстанавливать количество клеток крови при аденокарциноме толстой кишки, вызванной ДМН?

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Абстракт

Научный интерес к наномедицине в настоящее время постоянно растет, и наноматериалы нашли широкое применение в диагностике и лечении различных заболеваний. Наиболее перспективными представляются наночастицы металлов (НЧ). Некоторые из них активно изучаются по отдельности, и есть положительные результаты, учитывая их способность нормализовать количество клеток крови, но их совместная работа в качестве составной части все еще недостаточно известна. Это открывает большие перспективы для изучения НП в качестве корректора гомеостаза крови, что может помочь в разработке схем лечения многих угрожающих заболеваний, за которыми следуют нарушения подсчета клеток крови, особенно злокачественных опухолей. Поскольку колоректальный рак является третьим по частоте диагностируемым, это исследование было сосредоточено на оценке изменений количества клеток крови у крыс с ДМН-индуцированной аденокарциномой толстой кишки *in situ*, а также на оценке корректирующего эффекта состава Au / Ag / Fe NP. Аденокарциному толстой кишки вызывали введением N, N-диметилгидразина гидрохлорида в течение 30 недель. После патогистологического подтверждения развития аденокарциномы толстой кишки *in situ* у крыс, получавших ДМГ, в течение 3 недель вводили композицию Au / Ag / Fe NP. Введение NP крысам с ДМН приводит к увеличению RBC и HGB и снижению патологически высокоуровневых MCV, MCH и MCHC до нормальных значений. Оцененный состав NP нормализовал уровень нейтрофилов, LMR и дал нам частоту PLT, в частности, такую же, как у животных контрольной группы. Принимая во внимание ранее доказанную биобезопасность НЧ золота, серебра и железа как таковую, и, как результат, прогнозируемую биобезопасность их состава, мы можем рассматривать дальнейшее усиление доклинических исследований этого состава НЧ, имеющее большое значение, поскольку оно может быть использовано в качестве после терапии неметастатических форм рака толстой кишки.

Ключевые слова: экспериментальный канцерогенез, наночастицы, количество клеток крови, крыса.

Prematurity and Language Developmental Outcomes in Preschool Age

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Abstract

Global progress in child survival and health cannot be achieved without addressing preterm birth, because every year an estimated 15 million babies are born preterm. Over 1 million children die each year due to complications of preterm birth. Complications highly associated with prematurity include acute respiratory, gastrointestinal, immunologic, central nervous system, as well as longer-term motor, cognitive, behavioral, social-emotional, health, growth and language problems. The aim of the study was assessment of language skills at school aged children born premature and identification of risk factors affecting language development outcomes. Case-control retrospective study was conducted in Child Developmental Center of M. Iashvili Children's Central Hospital (Georgia, Tbilisi). We evaluate language skills in 72±3 months old children (n=134). Children were divided into study (n=80) and control (n=54) groups. Groups were homogenous based on child age, gender, maternal health, maternal education, household income, family structure. Statistical analysis was based on SPSS 20. The difference in language development assessment among the full-term and late preterm children shows low correlation and is not significant (Cramer's V is 0,118; Pearson Chi-square data 0,098 (p>0,05). While the language assessment data in early and moderate preterm group compared to term infants show significant difference (Cramer's V is 0,354, Pearson Chi-square data 0,004). Statistical analysis show medium correlation, value (p<0,05), which tell us, that language development is a significantly associated with gestational age. So, small gestational age is correlated with language development problems. Early detection of minimal delays and starting early intervention services can improve developmental outcomes of preterm children. High-quality and stable child care is important for all infants, but especially to those who may be at risk of prematurity.

Keywords: language development outcomes, early and late preterm, preschool age.

Introduction

The future of human societies depends on children being able to achieve their optimal growth and psychological development. Early childhood development is considered to be the most important phase in life which determines the quality of health, well-being, learning and behavior across the life span [1]. Global progress in child survival and health to 2016 and beyond cannot be achieved without addressing preterm birth, because every year an estimated 15 million babies are born preterm and preterm birth rates are increasing

in almost all countries with reliable data. Preterm birth is one of the most significant problems in perinatology. Over 1 million children die each year due to complications of preterm birth [2]. Moreover, striking inequalities exist between developed and developing countries in terms of the survival chances and developmental outcomes of a preterm infant [4]. Many survivors face a lifetime of disability, including learning disabilities and visual and hearing problems. Complications highly associated with prematurity include acute respiratory, gastrointestinal, immunologic, central nervous system, as well as longer-term motor, cognitive, behavioral, social-emotional, health, growth and language problems [3]. Disadvantaged children in developing countries who do not reach their developmental potential are less likely to be productive adults [5,12].

One of the main aspects of child development is language and communication skills. Learning to talk is one of the most visible and important achievements of early childhood. A child's speech and language skills allow them to communicate ideas and share and express thoughts and emotions with those around them. Several studies have attributed language impairments in premature infants, especially those born extremely preterm, to a general cognitive deficit affecting several areas of functioning [6]. The study of Foster-Cohen S¹, Edgin JO, Champion PR, Woodward LJ reveal that associations between gestational age at birth and language outcomes. Specifically, children born extremely preterm (<28 weeks' gestation) tended to perform less well than those born very preterm (28–32 weeks' gestation), who in turn performed worse than children born full term (38–41 weeks' gestation). This pattern of findings was evident across a range of outcomes spanning vocabulary size and quality of word use, as well as morphological and syntactic complexity. These findings demonstrate language developmental delay in children born very preterm. They also highlight the importance of gestational age for predicting later language developmental risk in this population of infants [7,12].

According to Rossetti, infants who are born prematurely and have a low birth weight are at risk for many medical complications that could impede later development in areas such as communication. The degree of prematurity significantly impacts children born before 32 weeks, defined as extremely premature, and are six times more likely than their full-term peers to be receiving special education services by the time they reach school age [8]. Study of Jansson-Verkasalo conclude that at two years of age the toddlers born premature had less complex expressive language skills in addition to producing significantly less words than the full-term group. Some studies have revealed a much higher percentage of persistent language problems in children diagnosed with expressive language delays in the preschool years [9]. The study of Melissa Woythaler, Marie C. McCormick, at al. shows, that late preterm infants have worse outcomes at school entry, and development is variable during the early school years. The study also reveal that socioeconomic status, gender, language spoken in the home, maternal education and prematurity (even late preterm) have a large impact on language development.

Most Scientific studies regarding long term outcomes of preterm infants cover early preterm children and show the great impact of early intervention services on developmental outcomes, while the studies regarding the developmental outcomes in late preterm children is quite rare. Assessment of long term outcomes in late preterm children and revealing risk factors has a great importance for working out recommendations for improvement of developmental outcomes in this group of children [12].

Evidence suggests that infants born LPT are at an increased risk of neurodevelopmental delay between 1 and 18 years of life when compared to those born at term. The delay is most evident in the cognitive domain of neurodevelopment. Children born LPT are also at a risk of delayed language development, motor development, and lower academic performance [10]. In recent years, LPIs have increasingly been regarded as “at-risk” rather than “low-risk” infants. They are born developmentally immature and with increased neonatal health concerns compared with term infants. The impact of early neonatal care on longer-term outcomes has not yet been well considered. Study show, that LPIs have more favorable outcomes than very preterm infants but less favorable outcomes than term infants [11,12].

Aim

The aim of the study was assessment of language skills at school aged children born premature and identification of risk factors affecting language development outcomes.

Materials and methods

Case-control retrospective study was conducted in Child Developmental Center of M.Iashvili Children’s Central Hospital (Georgia, Tbilisi). We evaluate language skills in 72 \pm 3 months old children (n=134). Children were divided into study (n=80) and control (n=54) groups. Control group included 54 healthy, children born term (37 to 42weeks). Study group -was divided into 2 sub groups: I /consists from 46 late preterm born children (34 % to 36 % weeks) and II /included 34 early preterm children born at 26-33 weeks of gestation (very (26% -31%weeks) + moderate 32%-33% weeks) preterm children. Inclusion criteria were child’s age (72 \pm 3months), gestational age and weight at birth, child’s and family’s informed concept. Children with congenital anomalies, genetic disorders, special health care needs, autism-spectrum disorders, cerebral palsy, chronic health problems and children of non-Georgian speaking parents or parents refusing participation in study were excluded from study. Children with single parent also were excluded. Study and Control groups were homogenous based on child age, gender, maternal health, maternal education, household income, and family structure. Information of birth records were collected and parental interview were conducted for every investigated child, that include gestational age, and weight, complications during pregnancy and neonatal period and postnatal history: gathering information from parents, family complains about child’s speech and

language, history of middle ear infections, family history of language difficulties. The parental assessment of child development was conducted based on PEDS (Parents Evaluation of Developmental Status).

We evaluate language skills using 1) Formal and 2) Informal/natural assessment of language development.

1) **Formal Assessment** was based on specific part (communication part) of The Vineland Adaptive Behavior Scales, Second Edition (Vineland-II). We assess only one from the four main domains of this test, Communication part, which includes expressive and receptive language skills assessment.

2) **Informal/Natural assessment** included observation, oral examination, play-based assessment, play behaviors, interest in books, checklists and parent interviews. In most cases we used hearing screening. As a result of evaluation, considering the specific raw scores and children chronological age, we identified special scores of V-scale with the help of basic tables, which shows the range of Vineland test sub-areas data, and is important indicator for weak and strong sides in language development. Magnitude of V interchanges from low range $V < 9$, till medium (13-17) or high (21 and more) data. Expressive and receptive sub-areas are the important parts of communication sphere, which itself is the main part of assessment of child development. Each individual result for data by general level of language development: High, Medium and elementary levels and basic foundation for rate was magnitude of V-scale scores.

Table 1. The demographic and social characteristics of study cohort:

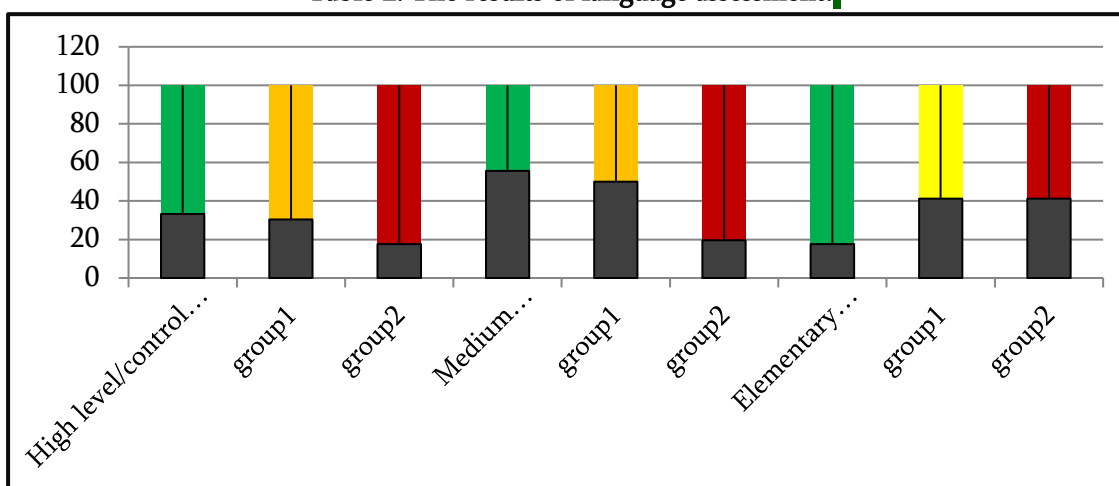
Characteristics:		Control group	I group	II group
Gestational age	Weeks	37-42	34-36	<34
Gender	Boy	29*-53,7%	26*-56,5%	18*-52,9%
	Girl	25*-46,3%	20*-43,5%	16*-47,1%
Family income	Low	9*-16,7%	6*-13,1%	4*-11,8%
	Middle	45*-83,3%	40*-86,9%	30*-88,2%
Mother education	Less than secondary	5*-9,2%	6*-13,1%	4*-11,8%
	Secondary and above	49*-90,8%	40*-86,9%	30*-88,2%
Father education	Less than secondary	7*-12,9%	8*-17,4%	3*-8,8%
	Secondary and above	47*-87,1%	38*-82,6%	31*-91,2%
Family size	1-4 members	34*-62,9%	37*-80,4%	28*-82,3%
	5 and more	20*-37,1%	9*-19,6%	6*-17,6%
Number of children	N=	54*	46*	34*

Child *

Result: Overall, of all 134 children – 40,3% (n=54) were full term, 34,3%(n=46) were late preterm, 25,4% (n=34) were early + moderate preterm. The demographic and social characteristics of study cohort are summarized in table1.

Our study revealed that children born preterm have significantly lower language skills. Results show that children with high and medium scores (were 80,4% in group I (late preterm children),58,8% in group II(moderate +early preterm children) while in control group accordingly 88,9%. Children with elementary scores were in group I- 19,6%, in group II-41, 2% and in control group 11,1%. So, our study shows that LPIs have more favorable outcomes than very preterm infants but less favorable outcomes than term infants. There seems to be a continuous relationship between decreasing gestational age and increasing risk of adverse outcomes such as language development. The results of language developmental data are presented in Table 2.

Table 2. The results of language assessment:



	High level	Medium level	Elementary level
Control group	18*-33,3%	30*-55,6%	6*-11,1%
I Group (n=46*)	14*-30,4%	23*-50%	9*-19,6%
II Group (n=34*)	6*-17,6%	14*-41,2%	14*-41,2%

Child *

After assessment we analyzed that 21,64% (n=29) of children had different kind of important problems. Group I – expressive language problems, receptive language problems. Group II -expressive language problems, receptive language problems. Control group expressive language problems, receptive language problems. At the same time 50% of all study children (n=67) had medium data, that means they had slight interruption in language skills. Only 28, 36 % (n=38) had problem-free results.

We also analyze our data by t-test, the independent-samples test which compares the means between two unrelated groups. We compare language development assessment results and groups with different gestational age and get such results: Sig 0,571; ($p > 0,05$); mean difference 1,446; Std. error difference 1,104; This value is not significant, so gestational age (34-36 weeks) is not associated with child's language development. Effect size $r = 0,1$ (small effect) explains 1 % of the total variance; Sig 0,037; ($p < 0,05$); Mean difference 5,038; Std. error difference 1,228; We got a significant value and it means, that child's language development is highly linked with small+ moderate gestational age. Effect size $r = 0,3$ (medium effect) – the effect accounts for 9% of the total variance; (r^* - effect size: is an objective and standardized measure of the magnitude Of observed effect. Effect size provides an objective measure of tve importance of an effect. Value: from 0=to 1; effect size=0 means, that, there is no effect).

Table 3. Group statistics:

Groups	N	Mean	Std. Deviation	Std. Error Mean
Control / Full Term	54	16.19	5.129	.698
Group1/ Late Preterm	46	14.74	5.893	.869
Control/Full Term	54	16.19	5.129	.698
Group2/Early Preterm + Moderate preterm	34	11.15	6.301	1.081

The difference in language development assessment among the full-term and late preterm children shows low correlation and is not significant (Cramer's V is 0,118; Pearson Chi-square data 0,098 ($p > 0,05$)). While the language assessment data in early and moderate preterm group compared to term infants show significant difference (Cramer's V is 0,354, Pearson Chi-square data 0,004. Statistical analysis show medium correlation, value ($p < 0,05$), which tell us, that language development is a significantly associated with gestational age. So, small gestational age is correlated with language development problems (table 3).

Table 4.
Pearson Chi-square Gramer`s V Correlation

Control group → GROUP I	Sig.0,498 ($p > 0,05$)	0,118	Low
Control group → GROUP II	Sig.0,004 ($p < 0,05$)	0,354	Medium

Children's language development is influenced by many different factors; In our study we focus on: gender, feeding type, family income, family size and parental education. Male gender is considered as one of the risk-factors for language development. We find that overall girls (n=61) have better language skills, then boys (n=73). Parents and family members play a crucial role in a child's language development. Parents' education and socio economic status has a great impact on children's global development. We found, that overall children from low-SES families often begin school with significantly less linguistic knowledge ($p < 0.05$). We did not find significant correlation between family size and school readiness scores ($p > 0.05$). In our study about of children 75,37% (n=101) had attended preschool. We compare children inside each group, and our data shows, that preschool education significantly improves language development. We also analyzed association between the child language skills and feeding practices. 62% (n=83) of study population were breastfeed and 38% (n=51) formula feed. We found little relationship between infant feeding practices and the cognitive development, the difference was not significant ($p > 0.05$), that can be explained by small sample size. During our study we reveal, that study participants who watch TV and play an electronic tablet more than 4 hour a day, had worse data, than children with rich, mutually satisfying verbal interactions with parents and peers.

Discussion: Our results showed correlation with prematurity and language development. The results of Allison M. Tanner study indicated that the children born premature consistently performed at a lower level than the children that were born full-term in receptive and expressive vocabulary, expressive language, and phonological short-term memory for non words and digit sequences [1,7,2]. Preterm birth poses risks for the language development of children, especially in the first years of life and they are at substantial risk of language-based learning disabilities that may not be detected until school age, but there are considerable individual differences in outcomes [4,5].

Our results showed correlation with prematurity and language development. The same results were found in several studies: Study of Amanda B. Zerbeto confirms an association between prematurity and language development. In studies that made comparisons between preterm and term infants, there was evidence that preterm infants had poorer performance on indicators of language. It was also observed that children born with lower birth weight had a poorer performance on measures of language when compared to children with higher weight and closer to 37 weeks of gestational age. Regarding the type of language assessed, expression proved to be more impaired than reception. Higher parental education and family income were indicated as protective factors for the development of language. Conversely, lower birth weight and higher degree of prematurity emerged as risk factors. Language difficulties are prevalent in premature children and

include articulation problems and expressive language delays, which can manifest themselves as poor vocabulary and grammar. Difficulties with phonological awareness are also common and predict later poor reading and writing. In fact, preterm birth is likely to have long-term consequences, affecting linguistic development beyond preschool (7). The results of Allison M. Tanner study indicated that the children born premature consistently performed at a lower level than the children that were born full-term in receptive and expressive vocabulary, expressive language, and phonological short-term memory for non words and digit sequences. [11,12]. Study of Inge L. van Noort-van der Spek et al reveals, that Preterm-born children scored significantly lower compared with term-born children on simple ($P < .001$) and on complex ($P < .001$) language function tests, even in the absence of major disabilities and independent of social economic status. For complex language function (but not for simple language function), group differences between preterm- and term-born children increased significantly from 3 to 12 years of age ($P = .03$). And while growing up, preterm-born children have increasing difficulties with complex language function. The results of Allison M. Tanner study indicated that the children born premature consistently performed at a lower level than the children that were born full-term in receptive and expressive vocabulary, expressive language, and phonological short-term memory for non words and digit sequences [12]. Study of Cusson RM¹ shows Language development is delayed in preterm infants. Maternal sensitivity is positively associated with enhanced infant language [11]. Study of NZ Rabie; TM Bird; EF Magann; RW Hall; SS McKelvey shows, that Rates for all outcome variables were statistically significant and elevated for LPI, but adjusted hazard ratios (AHRs) were only significant for the risk of developmental speech and/or language delay. So, late preterm and early term deliveries have adverse long-term neurodevelopmental outcomes, and these outcomes should be considered when determining the timing of delivery. In recent years, LPIs have increasingly been regarded as “at-risk” rather than “low-risk” infants. They are born developmentally immature and with increased neonatal health concerns compared with term infants. The impact of early neonatal care on longer-term outcomes has not yet been well considered; comorbidities, neonatal admission, and surrounding factors have not been fully explored. Systematic measurement of early childhood outcomes, such as those already considered for extremely preterm infant groups, is lacking in the late-preterm population. There is a real need for focused long-term follow-up studies to investigate early childhood development after late-preterm birth [12].

Many children in developing countries are exposed to multiple risks for poor development including poverty and poor health and nutrition. The children will subsequently do poorly in school and are likely to transfer poverty to the next generation. We estimate that this loss of human potential is associated with more than a 20% deficit in adult income and will have implications for national development. (3) The study found little-to-no relationship

between infant feeding practices and the cognitive development of children with less-educated mothers. Instead, reading to a child every day and being sensitive to a child's development were significant predictors of math and reading readiness outcomes [5, 6]. Some studies suggest that a longer duration of breast feeding benefits cognitive development [7]. The meta-analysis of American Pediatric Academy indicated that, after adjustment for appropriate key cofactors, breast-feeding was associated with significantly higher scores for cognitive development than was formula feeding [28]. The study of Hartley and Sutton, have recently reported that especially boys develop gender stereotypes according to which girls are perceived as academically superior with regard to motivation, ability, performance, and self-regulation [9]. Some studies show gender-dependent differences in the development of infants assessed during the first 2 years of life [3,8]. Our data shows, that preschool education had positive role in achievement of language development. Reading and writing skills are better in preschool attended children. Studies show that that preschool attendance have an impact on school readiness and school performance. [3,1,12]

Conclusion based on results of our study early and moderate preterm children are at increased risk for low level of language development up to 6 years of age, while late preterm infants does not show significant difference from term population. Male gender, absence of preschool education and low family socioeconomic status can be considered as risk factors for language development. Too many children enter school with physical, social, emotional and cognitive limitations that could have been minimized or eliminated through early attention to child and family needs. Addressing the risk factors and inclusion of early and moderate preterm children in early intervention and preschool services will improve their developmental outcomes. Interventions are required before and around school age to facilitate preterm children to perform at their potential. So daily reading, maybe 15 minutes per day, is an important contribution to the child's developmental outcomes. Since 15 minutes per day adds up to more than 90 hours per year, this can be a substantial investment in helping children reach their full potential in language learning. High-quality and stable child care and preschool education services is important for all infants and toddlers, but especially preterm born children. Inclusion of children in preschool improves global development [12].

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დღენაკლულობა და მეტყველების განვითარება წინასასკოლო ასაკში
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აბსტრაქტი

ბავშვის ჯანმრთელობისა და გადარჩენის გლობალური პროგრესი ვერ მიიღწევა ნაადრევი მშობიარობის პრობლემის გადაჭრის გარეშე, რადგან ყოველწლიურად დაახლოებით 15 მილიონი ბავშვი იბადება ნაადრევად. ყოველწლიურად 1 მილიონზე მეტი ბავშვი იღუპება ნაადრევი მშობიარობის გართულებების გამო. ნაადრევი მშობიარობის დაკავშირებული გართულებები მოიცავს მწვავე რესპირატორულ, კუჭ-ნაწლავის, იმუნოლოგიურ, ცენტრალურ ნერვულ სისტემის, ასევე გრძელვადიან მოტორულ, კოგნიტურ, ქცევით, სოციალურ-ემოციურ, ჯანმრთელობის, ზრდის და ენის პრობლემებს. კვლევის მიზანი იყო ნაადრევად დაბადებული სასკოლო ასაკის ბავშვების ენობრივი უნარების შეფასება და ენის განვითარების შედეგებზე მოქმედი რისკ-ფაქტორების იდენტიფიცირება. რეტროსპექტიული (Case control ტიპის) კვლევა ჩატარდა მ.ი.აშვილის სახელობის ბავშვთა ცენტრალური საავადმყოფოს ბავშვთა განვითარების ცენტრში (საქართველო, თბილისი). ენობრივ უნარებს ვაფასებდით 72±3 თვის ბავშვებში (n=134). ბავშვები დაყოფილი იყო საკვლევ (n=80) და საკონტროლო (n=54) ჯგუფად. ჯგუფები იყო ერთნაირი ბავშვის ასაკის, სქესის, დედის ჯანმრთელობის, დედათა განათლების, ოჯახის შემოსავლის, ოჯახის სტრუქტურის მიხედვით. სტატისტიკური ანალიზისთვის გამოყენებული იქნა SPSS 20. ენის განვითარების შეფასების სხვაობა სრულწლოვან და გვიან დღენაკლულ ბავშვებს შორის აჩვენებს დაბალ კორელაციას და არ არის მნიშვნელოვანი (კრამერის V არის 0,118; Pearson Chi-square მონაცემები 0,098 (p>0,05). მაშინ, როცა ადრეული და საშუალო ასაკის დღენაკლულ ჯგუფში ენის შეფასების მონაცემები ვადამდელ ახალშობილებთან შედარებით აჩვენებს მნიშვნელოვან განსხვავებას (კრამერის V არის 0,354, Pearson Chi-square მონაცემები 0,004). მაშინ როცა ენის შეფასების მონაცემები ადრეულ და ზომიერ დღენაკლულ ჯგუფში ვადამდელ ახალშობილებთან შედარებით აჩვენებს მნიშვნელოვან განსხვავებას (კრამერის V არის 0,354, Pearson Chi-square მონაცემები 0,004). სტატისტიკური ანალიზი აჩვენებს საშუალო კორელაციას, მნიშვნელობას (p<0,05), რაც გვეუბნება, რომ ენის განვითარება მნიშვნელოვნად ასოცირდება ორსულობის ეტაპთან. ასე რომ, მცირე ორსულობის საწყისი ეტაპი დაკავშირებულია ენის განვითარების პრობლემებთან. მინიმალური ჩამორჩენის ადრეული გამოვლენა და ადრეული ჩარევის სერვისების დაწყებამ შეიძლება გააუმჯობესოს ნაადრევი ბავშვების განვითარების შედეგები. მაღალი ხარისხის დასტაბილური ბავშვის მოვლა მნიშვნელოვანია ყველა ჩვილისთვის, განსაკუთრებით მათთვის, ვინც შეიძლება იყოს ნაადრევი მშობიარობით

გამოწვეული გართულებების რისკის ქვეშ.

საკვანძო სიტყვები: ენის განვითარების შედეგები, ადრეული და გვიანი დღენაკლულობა, სკოლამდელი ასაკი.

Недоношенность и результаты языкового развития в дошкольном возрасте

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Абстракт

Глобальный прогресс в области выживания и здоровья детей не может быть достигнут без решения проблемы преждевременных родов, поскольку ежегодно около 15 миллионов детей рождаются преждевременно. Ежегодно более 1 миллиона детей умирают из-за осложнений, связанных с преждевременными родами. Осложнения, в значительной степени связанные с недоношенностью, включают острые респираторные, желудочно-кишечные, иммунологические, заболевания центральной нервной системы, а также долгосрочные двигательные, когнитивные, поведенческие, социально-эмоциональные проблемы, проблемы со здоровьем, ростом и речью. Целью исследования являлась оценка языковых навыков недоношенных детей школьного возраста и выявление факторов риска, влияющих на результаты языкового развития. Ретроспективное исследование «случай-контроль» было проведено в Центре развития детей Центральной детской больницы им. М. Иашвили (Грузия, Тбилиси). Мы оценили языковые навыки у детей в возрасте 72 ± 3 месяцев ($n = 134$). Дети были разделены на основную ($n = 80$) и контрольную ($n = 54$) группы. Группы были однородными в зависимости от возраста ребенка, пола, состояния здоровья матери, образования матери, дохода домохозяйства, структуры семьи. Статистический анализ был основан на SPSS 20. Разница в оценке языкового развития среди доношенных и поздно недоношенных детей показывает низкую корреляцию и не является значимой (V Крамера составляет 0,118; данные хи-квадрат Пирсона 0,098 ($p > 0,05$)). Данные языковой оценки в группе недоношенных на раннем и умеренном сроках по сравнению с доношенными детьми показывают значительную разницу (V Крамера составляет 0,354, данные хи-квадрат Пирсона 0,004). Статистический анализ показывает среднюю корреляцию, значение ($p < 0,05$), которые говорят нам, что Языковое развитие в значительной степени связано с гестационным возрастом. Таким образом, малый гестационный возраст связан с проблемами языкового развития. Раннее обнаружение минимальных задержек и

начало оказания услуг раннего вмешательства могут улучшить результаты развития недоношенных детей. всем младенцам, но особенно тем, кто подвержен риску недоношенности.

Ключевые слова: результаты языкового развития, ранние и поздние недоношенные, дошкольный возраст.

Emotional Intelligence among the Health Care Providers Working in a Tertiary Level Hospital

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Abstract

Emotional intelligence (EI) is the ability to be aware of and control one's emotions and empathize with others. EI is essential for the well-being of a health care provider and their professional practice. A health care provider's empathy is important in building a strong relationship with the patient which results in enhanced positive service outcomes. Emotional intelligence competence can be acquired through training and implementation in our own life. As every person is unique, he or she needs to learn concepts that will be suitable for him or her. The objective of the study is to assess the emotional intelligence among health care providers working in a tertiary level hospital and also to understand the association of emotional intelligence with demographic variables of work experience and age of health care providers working in a tertiary level hospital. A descriptive cross-sectional research design was conducted in the Tertiary Level Hospital of Kathmandu District, Nepal to assess the emotional intelligence among health care providers. Through convenience non-probability sampling technique 100 health care providers were selected and to assess the status of emotional intelligence Standard Self-Report Emotional Intelligence Test (SSEIT) was used. Results of the study revealed that the highest forty per cent of the respondents have a low level of emotional intelligence and only thirty-two per cent of respondents have a high level of emotional intelligence. Lower in the level of EI among the health workers may be due to the lack of awareness on EI There was also significant association between the level of emotional intelligence with the respondent's age ($p= 0.003$). which shows with the increasing age, individuals have different working exposures that improve in their maturity, which may support increasing the level of EI, and there is no significant association with respondent's working experience.

Key words: Emotional intelligence, stress, compassion, fatigue, interference, intervention.

Introduction

Emotional intelligence is the competency of health care providers working in a tertiary level hospital which helps to understand and regulate emotions of self as well as others (Goleman, 2001). There is a significant relationship between emotional intelligence,

happiness and mental health in addition to making a contribution to achievement in maximum endeavours (Sasanpour, Khodabakhshi, & Nooryan, 2012). It additionally performs an essential element in forming successful human relationships, establishing a therapeutic nurse-patient relationship (McQueen, 2004). Emotional intelligence and patient-centred care increasing stress as a part of health care policy and practice (Birks & Watt, 2007). It may be taught, learned, and modified in medical care packages for better patient-doctor relationships (Basem Abbas Al, 2018).

Materials

There is a significant positive correlation between emotional intelligence and subjective well-being (Rema & Gupta, 2021; Sánchez-Álvarez, Extremera, & Fernández-Berrocal, 2016). There is an association of higher emotional intelligence with a positive mood and higher self-esteem (NS Schutte, JM Malouff & Hollander, 2002). Nurses with higher EI will contribute to a more productive and harmonious work environment. There is a significant positive relationship between job performance and emotional intelligence (Li et al., 2021; Patrianus Khristian Smule, 2012). It did not differ significantly from clinical nursing experience and was positively significant with age (Intelligence, 2018). Four common paradigms; self-awareness, self-management, social awareness and relationship management are the main ingredients for increasing the well-being of health care providers. It helps to increase the quality and positive outcomes of personal and professional life (Raghubir, 2018). Intervention, in order to increase emotional intelligence, can be powerful in improving empathetic communication, clinical performance, the relationship between patient and health care providers, and improve clinical outcomes.

Objectives

To identify the level of Emotional Intelligence among health care providers.

To identify the association between emotional intelligence with selected socio-demographic variables of age.

To identify the association between emotional intelligence and working experiences.

Research Methods

A descriptive cross-sectional research design was adopted to conduct the study in the Tertiary Level Hospital of Kathmandu District, Nepal to assess the emotional intelligence among health care providers. The study includes convenience non-probability sampling techniques and 100 healthcare providers were included in the study. The dependent variable was emotional intelligence and independent variables were health background, age, gender, years of experience and training on EI. A Standard Self-Report Emotional Intelligence Test (SSEIT) was used to collect data. It comprises a self-report on a 5-point Likert scale: 1- strongly disagree, 2- disagree, 3- neutral, 4- agree, 5- Strongly agree. It is a

33-items Likert scale. It is a valid tool with internal consistency (Cronbach's alpha= 0.90) (Schutte et. al., 1998). For analyzing the study data, Statistical Package of Social Sciences (SPSS), descriptive statistics analysis (Frequency and Percentage) and Pearson Chi-Square test and Fisher's Exact Test was used to measuring the association between level of emotional intelligence with selected variables.

Results

Table no.: 1

Socio-demographic variables of respondents

n=100

Variables	Frequency	Percentage (%)
Healthcare Provider		
Nursing	60	60.0
Others Paramedical (Lab, Radiographer, HA & Pharmacy)	40	40.0
Age		
18-27 years	9	9.0
28-37 years	69	69.0
38 years and above	22	22.0
Gender		
Male	21	21.0
Female	79	79.0
Year of working experience		
1-5 years	77	77.0
6-10 years	14	14.0
11-15 years	7	7.0
16 years and above	2	2.0
Emotional Intelligence Training Status		
No (not take any training on EI by the respondents)	100	100.0

Table no. 1 displays information about socio-demographic variables of the respondents and it revealed that the majority (60%) of the respondents were nurses and (40%) were paramedical staffs (i.e. Lab technologist, Radiographer, Health Assistant and Pharmacy). The majority (69%) of the respondents were from 28 to 37 years of age whereas 22% of respondents were 38 years and above and 9% respondents were from 18- 27 year group. The majority (79%) of the respondents were female whereas the remaining (21%) of the respondents were male. The majority (77%) of the respondents had 1-5 years of work experience whereas a few (14%) of the respondents had 6-10 years of work experience and only (2%) of respondents had work experience of 16 years and above.. All the respondents

who were included in the study had not taken any training related to emotional intelligence.

Table no.: 2

Level of Emotional Intelligence

n=100

Level of Emotional Intelligence	Frequency	Percentage (%)
Low	40	40.0
Average	28	28.0
High	32	32.0

Table no. 2 shows the level of emotional intelligence and revealed that the highest number (40%) of respondents has a low level of emotional intelligence whereas 32% of respondents have a high level of emotional intelligence and whereas the rest (28%) has an average level of emotional intelligence.

Table no.: 3

Association between Emotional Intelligence and Age

n=100

Level of EI	Age			Total	P value
	18-27	28-37	38 and Above		
Low	5 (12.5%)	20 (50%)	15 (37%)	40 (100%)	0.003
Average	2 (7.1%)	25 (89.3%)	1 (18.8%)	28 (100%)	
High	2 (6.2%)	24(75%)	6 (18.8%)	32 (100%)	
Total	9 (9%)	69 (69%)	22(22%)	100 (100%)	

Table no.: 3 demonstrates the outcome of Chi-square and Fisher's exact test analysis carried out to find out the association between level of emotional intelligence and selected Socio-demographic variables which revealed that there is a significant association between level of emotional intelligence with respondent's age (p= 0.003).

Table no.:4

Association between Emotional Intelligence and working experiences

n=100

Level of EI	Health care provider		Total	P value
	Nursing	Others (Lab, Rad. &HA)		
Low EI	21 (52.5%)	19(47.5%)	40 (100%)	0.501
Average EI	18 (64.3%)	10 (35.7%)	28 (100%)	
High EI	21 (65.3%)	11(34.4%)	32 (100%)	
Total	60 (60%)	40 (40%)	100 (100%)	

Table no.: 4 demonstrates the outcome of Chi-square and Fisher’s exact test analysis being carried out to find out the association between level of emotional intelligence and working experience which revealed that there is no significant association between level of emotional intelligence with respondent’s working experience (p= 0.247).

Table no.:5

Association between Emotional Intelligence and Health care provider

n=100

Level of EI	Working Experience				Total	P-value
	1-5 yrs	6-10 yrs	11-15 yrs	16 yrs and above		
Low EI	31 (77.5%)	7 (17.5 %)	2(5%)	0	(100%)	0.247
Average EI	25 (89.3%)	2 (7.1%)	1(3.6%)	0	(100%)	
High EI	21 (65.6%)	5 (15.6%)	4(12.5%)	2 (6.2%)	(100%)	
Total	77 (77%)	14(14%)	7 (7%)	2 (2%)	100 (100%)	

Table no.: 5 demonstrates the outcome of Chi-square and Fisher’s exact test analysis being carried out to find out the association between level of emotional intelligence and health care provider which revealed that there is no significant association between level of emotional intelligence and Health care provider(p= 0.501).

Conclusions

Emotional intelligence is fundamental to health workers practices. Concepts EI are central to nursing practices and affect critical thinking, decision making, quality of patient care and patient outcome (Bulmer, Profetto-mcgrath, & Cummings, 2009). In addition, people with a higher level of emotional intelligence are found more successful as compared to those who were low at the emotional intelligence scale (Transactions, Sciences, & Volume, 2013). Based on the finding the study concluded that forty per cent have a low level of emotional intelligence and only thirty-two per cent of respondents had a high level of emotional intelligence. Having low level of EI among the health workers may be due to the lack of awareness on EI. The study also shows a significant association between the level of emotional intelligence with respondent’s age (p= 0.003). Various studies also support the significant relationship between age and emotional intelligence (Chapman & Jr, 2006; Date, 2020; Sliter, Chen, & Withrow, 2013; Well-being, 2017). With the increasing age, individuals have different working exposures that improve in their maturity, which may support to increase their level of EI. Emotional intelligence contributes in the better performance of the staff, hence makes the workplace environment better. So, it is urgent and necessary to orient and train the health workers in the EI which will ultimately support the well-being of healthcare service providers and also the wellbeing of patients.

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ემოციური ინტელექტუალური ჩარევის მნიშვნელობა მედიცინის ფაკულტეტის სტუდენტებში

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აბსტრაქტი

ემოციური ინტელექტი (EI) არის უნარი აცნობიერებდე და აკონტროლებდე საკუთარ ემოციებს და უთანაგრძნო სხვებს. ემოციური ინტელექტი აუცილებელია ჯანდაცვის სფეროს წარმომადგენლების კეთილდღეობისთვის და მათი პროფესიული პრაქტიკისთვის. ჯანდაცვის მუშაკის თანაგრძნობა მნიშვნელოვანია პაციენტთან ძლიერი ურთიერთობის დასამყარებლად, რაც იწვევს მომსახურების გაძლიერებულ პოზიტიურ შედეგებს. ემოციური ინტელექტის კომპეტენცია შეიძლება შექმნილი იყოს ტრენინგის და მისი ჩვენს ცხოვრებაში დანერგვის გზით. ვინაიდან თითოეული ადამიანი უნიკალურია, მან უნდა ისწავლოს ცნებები, რომლებიც მისთვის შესაფერისი იქნება. კვლევის მიზანია შეაფასოს ემოციური ინტელექტი მესამე დონის საავადმყოფოში მომუშავე ჯანდაცვის პროვაიდერებს შორის და ასევე გაიგოს ემოციური ინტელექტის კავშირი სამუშაო გამოცდილების დემოგრაფიულ ცვლადებთან და მესამე დონის საავადმყოფოში მომუშავე ჯანდაცვის პროვაიდერების ასაკთან. ჯვარედინი კვლევის დიზაინი ჩატარდა ნეპალში, კატმანდუს ოლქის მესამე დონის საავადმყოფოში, ჯანდაცვის პროვაიდერებს შორის ემოციური ინტელექტის შესაფასებლად. მოხერხებული არაალბათური შერჩევის ხერხით შეირჩა 100 ჯანდაცვის პროვაიდერი და ემოციური ინტელექტის სტატუსის შესაფასებლად გამოყენებული იქნა ემოციური ინტელექტის სტანდარტული თვითშეფასების ტესტი (SSEIT). კვლევის შედეგებმა აჩვენა, რომ რესპონდენტთა 40%-ს აქვს დაბალი ემოციური ინტელექტი, ხოლო გამოკითხულთა მხოლოდ 32%-ს აქვს ემოციური ინტელექტის მაღალი დონე. ჯანდაცვის მუშაკებს შორის ემოციური ინტელექტის დაბალი დონე შეიძლება გამოწვეული იყოს მის შესახებ ინფორმირებულობის ნაკლებობით. ასევე იყო მნიშვნელოვანი კავშირი ემოციური ინტელექტის დონესა და რესპონდენტის ასაკს შორის ($p= 0.003$). რაც გვიჩვენებს ასაკის მატებასთან ერთად, ინდივიდებს აქვთ სხვადასხვა სამუშაო გამოცდილებები, რაც აუმჯობესებს მათ სიმწიფეს, რამაც შეიძლება ხელი შეუწყოს ემოციური ინტელექტის დონის ამაღლებას და არ არის მნიშვნელოვანი კავშირი რესპონდენტის სამუშაო გამოცდილებასთან.

საკვანძო სიტყვები: ემოციური ინტელექტი, სტრესი, თანაგრძნობა, დადლილობა, ინტერვენცია.

Эмоциональный интеллект медицинских работников, работающих в больнице третичного уровня

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Абстракт

Эмоциональный интеллект (ЭИ) - это способность осознавать и контролировать свои эмоции и сопереживать другим. EI имеет важное значение для благополучия врача и его профессиональной деятельности. Сочувствие медицинского работника важно для построения прочных отношений с пациентом, что приводит к улучшению положительных результатов обслуживания. Компетентность в области эмоционального интеллекта может быть приобретена путем обучения и применения в нашей собственной жизни. Поскольку каждый человек уникален, ему или ей необходимо изучить концепции, которые будут ему подходить. Целью исследования является оценка эмоционального интеллекта среди медицинских работников, работающих в больнице третичного уровня, а также понимание связи эмоционального интеллекта с демографическими переменными опыта работы и возрастом медицинских работников, работающих в больнице третичного уровня. Описательный кросс-секционный план исследования был проведен в больнице третичного уровня округа Катманду, Непал, для оценки эмоционального интеллекта среди медицинских работников. Благодаря удобному методу не вероятностной выборки было отобрано 100 поставщиков медицинских услуг, и для оценки состояния эмоционального интеллекта был использован стандартный тест эмоционального интеллекта с самоотчетом (SSEIT). Результаты исследования показали, что самые высокие сорок процентов респондентов обладают низким уровнем эмоционального интеллекта и только 32 процента респондентов обладают высоким уровнем эмоционального интеллекта. Более низкий уровень EI среди медицинских работников может быть связан с недостаточной осведомленностью об EI. Также была значимая связь между уровнем эмоционального интеллекта и возрастом респондента ($p = 0,003$), который показывает, что с возрастом люди имеют различные рабочие воздействия, которые улучшаются по мере их зрелости, что может способствовать повышению уровня EI, и нет существенной связи с опытом работы респондента.

Ключевые слова: эмоциональный интеллект, стресс, сострадание, усталость, вмешательство.

Isolation and Study of Bacteriophages Specific Against Multidrug Resistant *Salmonella* spp. and Assessment of their Therapeutic Potential

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Abstract

Within the scope of the study, clinical non-typhoidal *Salmonella* were isolated in Armenia and Georgia and identified based on conventional microbiological methods and MALDI-TOF MS. These isolates were further analysed by serotyping (White-Kauffmann-Le Minor scheme) and their antimicrobial susceptibility profiles were defined. A total of 40 antibiotic resistance profiles were identified, of which 35 were characteristic of clinical strains. Out of a total of 345 isolates, 238 strains from Georgia, Armenia and Ireland were eventually selected for our study. Using the strains of this collection, 13 new bacteriophages were isolated, characterized by biological and genetic features. Based on the data obtained, phages were classified and the peculiarities of their life cycle were determined (virulent-lytic, moderate-lysogenic).

Analysis of the sequencing results showed that only one of the 12 phages identified as temperate phage (vB_GEC_TR), it belongs to the family Podoviridae, genus Laderbergvirus. While the other 11 phages are virulent, they are related to well-known and characterized phages, which are used in various phage preparations. Analysis of their genomes did not show any lysogeny associated genes. Among the virulent phages, 6 are members of Myoviridae family (vB_GEC_B1, vB_GEC_B3, vB_GEC_MG, vB_GEC_BS, vB_GEC_NS7, vB_GEC_7A) and 5 of the Siphoviridae family (vB_GEC_N5, vB_GEC_N8, vB_GEC_M4, vB_GEC_M5, vB_GEC_Hi). *In vitro* tests revealed that the phages - vB_GEC_B1, vB_GEC_BS, vB_GEC_B3, vB_GEC_NS7, vB-GEC-N8 showed high activity (60% to 80%) against the examined strains. The phages have been shown to be more effective against clinical strains (≈90%) than against veterinary strains (≈70%). The strains susceptible to these phages were mainly *S.typhimurium* and *S. Enteritidis* serovars and are largely of clinical origin. Based on our research we can conclude that the application of phages as an additional tool for the treatment of MDR *Salmonella* infections seems to be plausible. Phages are natural and specific antibacterial agents, which can lyse bacteria

irrespective of their AMR status, whilst leaving the commensal microflora unharmed. This is one of the main advantages of phages in comparison to antibiotics. The phages tested in this study showed potential for application in phage therapy against MDR *Salmonella* infections.

Key words: bacteriophages, salmonella, bacteria, resistance to antibiotics.

Introduction

Salmonella is a ubiquitous, increasingly resistant bacterium which can survive several weeks in a dry environment and even several months in water. Infections caused by various salmonella pose a serious threat to both human and animal health. According to the World Health Organization's report (WHO), 550 million people are infected with diarrhea each year, including 220 million children under the age of five¹. *Salmonella* is one of the leading causes of foodborne infections. Antibiotic resistance is a growing process in non-typhoid salmon and has been monitored since 1996². Since 2017, Fluoroquinolone-resistant *Salmonella* spp. was included in the list of high-priority pathogens by the World Health Organization (WHO)³. Invasive infections caused by non-typhoid salmonella are prevalent globally, but the number of cases varies by geographical location. About 1% of enteric infections caused by non-typhoid *Salmonella* are complicated by bacteremia, although the true extent of bacteremia is unknown because many major enteric infections are not microbiologically diagnosed. Infants and people over the age of 65 are more likely to develop bacteremia. Concomitant diseases increase the risk of complications from bacteremia⁴.

Bacteriophages, or phages, are increasingly being considered as a primary or auxiliary / complementary means of combating highly resistant bacteria. Although phages have been used for therapeutic purposes in Georgia, Poland and Russia for almost a century⁵. However, existing commercial drugs cannot be used globally because they do not meet Western regulations and standards for pharmacological drugs. Consequently, there was a need to study bacteriophage-based preparations in more depth, taking into account their genetic, physiological and biochemical characteristics.

Materials and Methods

Isolation and identification of *Salmonella* isolates

The first phase of our work involved collection of non-typhoid *Salmonella enterica* subsp. *enterica* strains from different countries and from different location of pathogen habitat. Some of the strains were obtained from different countries, which were isolated from both animals and human samples with salmonellosis (feces, blood) as well as from foods contaminated with *Salmonella*. A total of 345 strains were collected and sent to our institute for further work.

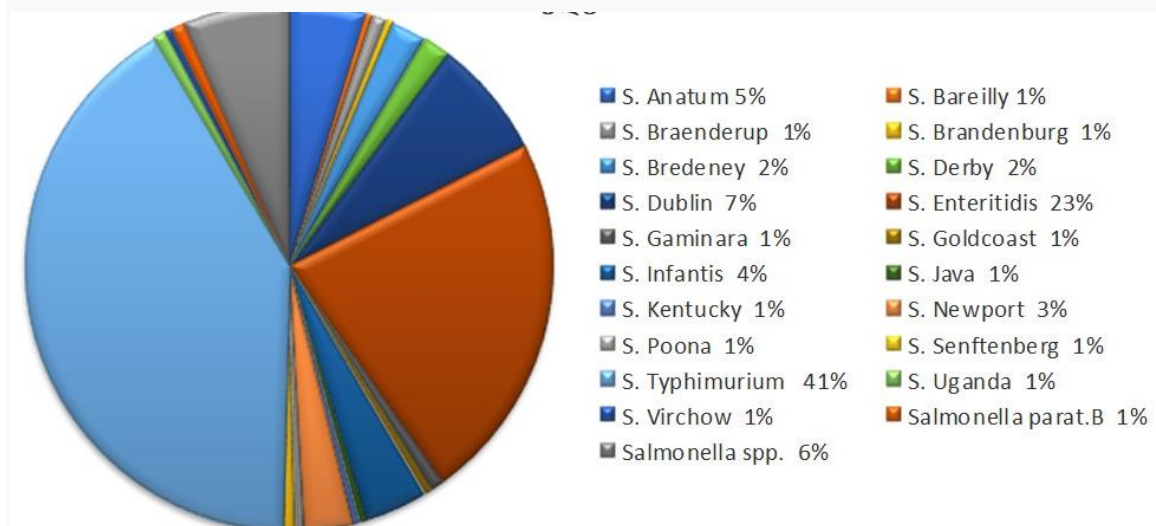
After identification using primary, microbiological and biochemical methods, all isolates belonged to the species *Salmonella enterica*.

For reliable identification species of clinical isolates obtained from Georgia, Armenia and Tajikistan, were analyzed by **matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS)**. The analysis revealed that 25 isolates (14 from Tajikistan, 5 from Georgia and 6 from Armenia) did not belong to the genus *Salmonella*. They belonged to the species: *Escherichia coli* (9), *Hafnia alvey* (5), *Morganella morganii* (4), *Enterobacter cobay* (1), *Enterobacter ludwigi* (1), *Comamonas kerstersii* (1), *Citrobacter freundii* (1), *Citrobacter braakii* 2), *Proteus vulgaris* (1). Accordingly, these isolates were not used for further work.

Serotyping was performed according to the White-Kaufman scheme. Of the 91 Georgian and Armenian isolates, 54% belonged to the serotype *S. Typhimurium*, 32% - *S. Enteritidis* and 5% could not be accurately identified, so they are referred to as - *Salmonella spp* ⁶. Also, according to the Kaufman-White scheme, the strains that our laboratory received from Ireland were serotyped. *Salmonella Typhimurium* is the most abundant of these isolates, followed by *Salmonella Dublin* and *Salmonella Enteritidis*. The collection also includes such rare serotypes as *Salmonella Uganda* and *Salmonella Goldcoast*.

Picture № 1.

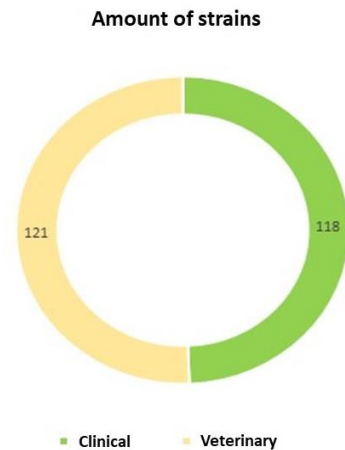
Distribution of strains used in the study by serotypes



As can be seen from the picture, most of the strains (41%) belong to *S. typhimurium* serotype, followed by serotype *S. enteritidis* -23%, serotype *S. dublin* - by 7%, *S. anatum* by 5%, and other serotypes by -Represented as a percentage. And unidentified serotypes, *Salmonella spp.* 6%, *S. anatum* 5%, while other serotypes are represented by 1 or 2 strains. (Picture 1.)

In total, 240 strains were used in our study, of which 118 were clinical strains and about 121 were veterinary strains, including strains from Georgia, Armenia and Ireland. 148 strains from Ireland, 20 strains from Georgia, 71 - from Armenia. (Picture 2.)

Picture № 2.



Antimicrobial Susceptibility Profiles of Salmonella Isolates

Eleven antibiotics were used to determine the susceptibility of the strains to antibiotics: ampicillin (A), amoxicillin + clavulanic acid (Au), azithromycin (Az), ceftriaxone (Cx), chloramphenicol (Cm), ciprofloxacin (Cip), nalid (Su), streptomycin (Sm), tetracycline (Tc), trimethoprim-sulfamethoxazole (T / S).

As the study showed, only 3 clinical strains obtained in Georgia were found to have multiple antibiotic-resistant genotypes, 2 of these strains belong to *S. Typhimurium*, one - *S. Enteritidis*. Among them was *S. enteritidis* 104, which was later used to create an animal infectious model.

74.64% of clinical isolates isolated in Armenia were found to be multidrug-resistant, of which 44 were *S. Typhimurium*, 5 - *S. Enteritidis*, 2 - *S. Derby*, 1 - *S. Kentucky*, and 1 *S. Newport*.

The analysis of the results showed that the highest rate of resistance is observed to Nalidixic acid (synthetic quinolone) - 68.13%, the rate of resistance to other antibiotics is as follows: sulfonamide - 61.54%, ampicillin (a Penicillin) - 52.75%, amoxicillin + clavulanic acid - 47.25%, ceftriaxone (a cephalosporin) - 41.76% and ciprofloxacin (a fluoroquinolone) - 14.29%. Significant amounts of isolates (13 strains) showed resistance to fluoroquinolones and third-generation cephalosporins (11 strains).

Only 9 isolates from strains isolated in Georgia and 5 isolates from strains isolated in Armenia were found to be sensitive to all antibiotics. None of the isolates were found to be resistant to all antibiotics used. The maximum number of antibiotics to which they were found to be isolated was 9, and only four isolates of *S. typhimurium* isolated in Armenia

showed such high resistance. (Table №1)

Table №1
Antibiotic resistance profiles of non-typhoid Salmonella serotypes

N	Antibiotic resistance Profile	MDR ^a	Number of isolates	Isolate identification number	Serotype	Year of isolation	ESBL ^b
A) Clinical antibiotic-resistant isolates isolated in Armenia n=53							
1	AAu*CxN	4	12	105 [†]	Typhimurium	2011	+
				645 [†]	Typhimurium	2006	+
				678 [†]	Typhimurium	2011	+
				1214	Typhimurium	2013	+
				1349	Typhimurium	2013	+
				2324	Typhimurium	2012	+
				2503	Typhimurium	2016	+
				2730	Typhimurium	2013	+
				3128	Typhimurium	2013	+
				4216	Typhimurium	2011	+
				8019	Typhimurium	2012	+
8130	Typhimurium	2014	+				
2	AAu*CxCip*N	4	6	3017 [†]	Typhimurium	2013	+
				3109	Typhimurium	2013	+
				3175 [†]	Typhimurium	2016	+
				5084	Typhimurium	2011	+
				5703	Typhimurium	2012	+
				5730	Typhimurium	2012	+
3	ACxN	3	5	60 [†]	Typhimurium	1996	+
				69 [†]	Typhimurium	2006	+
				684 [†]	Typhimurium	1996	+
				1051	Typhimurium	2012	+
				1726	Typhimurium	2013	-
				58			

4	AAu*CxAz*Cip*N	5	3	115 [†]	Typhimurium	2011	+
				3194 [†]	Typhimurium	2012	+
				3406 [†]	Typhimurium	2012	+
5	AAuCx Cip*N	4	2	1328 [†]	Typhimurium	2013	+
				5943	Typhimurium	2013	+
6	AAu*CxCip*NT/S	5	2	6004 [†]	Typhimurium	2013	+
				8011 [†]	Typhimurium	2014	+
7	CipNSmTcSu	4	2	4649 [†]	Derby	2016	-
				4970 [†]	Derby	2016	-
8	SmTcSu	3	2	5064 [†]	Typhimurium	2016	-
				8239 [†]	Typhimurium	2016	-
9	AAuCxAzNSmTc*CmT/S	9	1	3040 [†]	Typhimurium	2016	+
10	AAuCxAzNSm*Tc*CmT/S	9	1	3725 [†]	Typhimurium	2016	+
11	AAuCxAzCip*NSmTc*CmT/S	9	1	3246 [†]	Typhimurium	2016	+
12	AAuCxAz*Cip*NSm*TcCmSu	9	1	3889 [†]	Typhimurium	2013	-
13	AAuCip*NTcCmT/S	6	1	1722 [†]	Typhimurium	2013	-
14	AAuCxCip*NCmSu	6	1	3854	Typhimurium	2013	-
15	AAuCip*NSmCmT/S	6	1	5923 [†]	Typhimurium	2011	-
16	A*CxNCmTcSu	6	1	5962 [†]	Typhimurium	2012	+
17	AAu*CxNSu	5	1	1320	Typhimurium	2016	+
18	AAu*NTc*	4	1	2017	Typhimurium	2013	+
19	ACxCip*N	4	1	5048	Typhimurium	2011	+
20	NTcCm	3	1	2330	Typhimurium	2012	-
21	AAu*CxNT/S	5	1	126 [†]	Enteritidis	2011	+
22	ACip*NT/S	3	1	588 [†]	Enteritidis	2016	-
23	ANSm*Cm	4	1	6059 [†]	Enteritidis	2016	-
24	A*TcCm	3	1	6187 [†]	Enteritidis	2016	-
25	ACx*CipN	3	1	7201 [†]	Enteritidis	2016	-
26	AAu*Cip*N	3	1	478 [†]	Kentucky	2016	-
27	A*NTm/Su	3	1	7187 [†]	Newport	2013	-

B) Antibiotic-resistant isolates isolated in Georgia, n=3							
28	AAu*CxSu	4	1	104 [†]	Enteritidis	2016	-
29	AAu*NCmSu	5	1	311 [†]	Typhimurium	2016	-
30	AAu*SmT/S	4	1	1150 [†]	Typhimurium	2016	-

Notes: ampicillin (A), amoxicillin+clavulanic acid (Au), azithromycin (Az), ceftriaxone (Cx), chloramphenicol (Cm), ciprofloxacin (Cip), nalidixic acid (N), sulfonamide (Su), streptomycin (Sm), tetracycline (Tc), trimethoprim-sulfamethoxazole (T/S).

Isolation and characterizations of bacteriophages used in this study

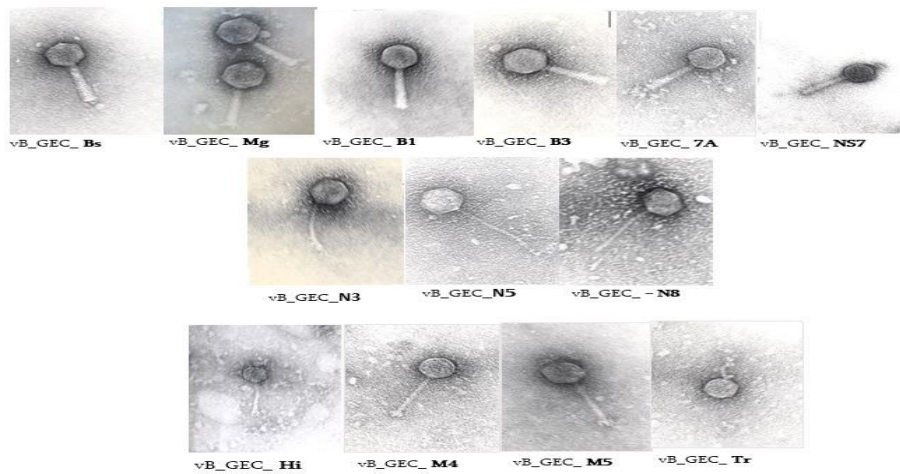
Isolation of *Salmonella* specific phages was performed using the bacterial strain enrichment method ⁷. Ten ml of 10× concentrated lysogeny broth (LB, Oxoid Limited, Basingstoke, UK) was pipetted into a 125 mL Erlenmeyer flask, 90 mL of the water/milk sample was added and the mixture was inoculated with 1 mL of overnight culture of host bacteria. The flask was incubated for 18 h at 37 °C. Then the mixture was centrifuged at 6000× *g* for 30 min at 4 °C and supernatant was filtered through 0.45 or 0.22 µm filters and tested for the presence of phages by a spot test on bacterial streaks⁸. Overnight host bacterial cultures were diluted in the sterile LB to a final concentration of 10⁷ colony forming units (cfu)/mL and streaks were made on 2% LB agar plates using a 10 µL loopful of each strain, and air-dried for 10–15 min. Ten µL of each filtered enrichment sample was applied on each streak. The plates were incubated at 37 °C for 18 h and phage presence was assessed based on visualization of clear spots on the bacterial growth⁹.

13 bacteriophages were identified and studied, of which 6 phage clones belong to the Siphoviridae family: - vB_GEC_N3, vB_GEC_N5, vB_GEC_N8, vB_GEC_M4, vB_GEC_M5 and vB_GEC_Hi; The Myoviridae family includes 6 clones: vB_GEC_Mg, vB_GEC_Bs, vB_GEC_NS7, vB_GEC_7A, vB_GEC_B1 and vB_GEC_B3; And the Podoviridae family has only one phage - vB_GEC_TR. It should be noted that among the phages used in the study, only this phage (vB_GEC_TR) was found to be a lysogenic or moderate phage.

Each phage was examined for morphological (negative colony and virion structure), biological (for host bacterial spectrum, temperature and pH resistance), and genetic traits. When annotating phage genomes, special attention was paid to the identification of genes that indicated the lysogenic nature of phages. For the phage genome sequence the next generation sequencing technologies were used ¹⁰

Picture №3

Transmission electron micrographs of bacteriophages used in this study

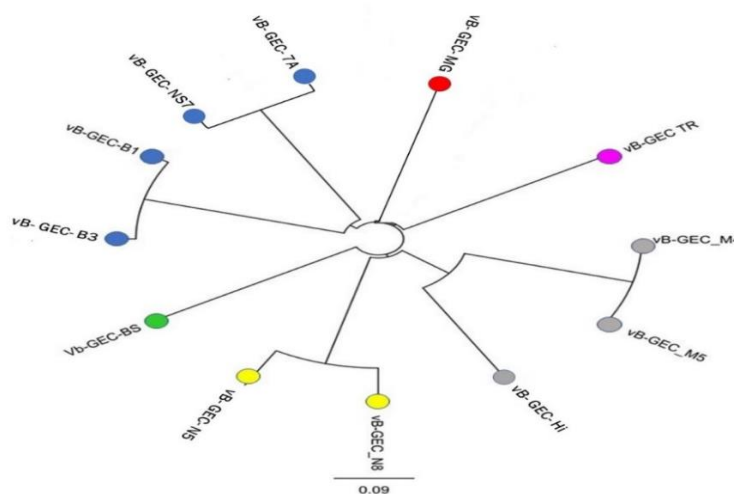


Comparative characterization of phages

In order to establish the relationship between the phages used in the study, their genomes were compared, for which we used the program – Geneious (<https://www.geneious.com/>). The layout of the phages on the genetic tree is as follows: They show high similarity to each other and the phages vB-GEC-B1, vB-GEC-B3, vB-GEC-NS7 and vB-GEC-7A are placed close to the genetic tree, all four of them are members of the family Myoviridae, genus-Felixounavirus; Phages vB-GEC-N8 and vB-GEC-N5, both are representatives of the family Siphoviridae and genus -Tequintavirus. vB-GEC-Hi also belongs to Siphoviridae, united in the genus - Jerseyvirus, phages vB-GEC-M4 and vB-GEC-M5 are united in the same genus;

Diagram №1

Phylogenetic tree showing relatedness between phages used in the study



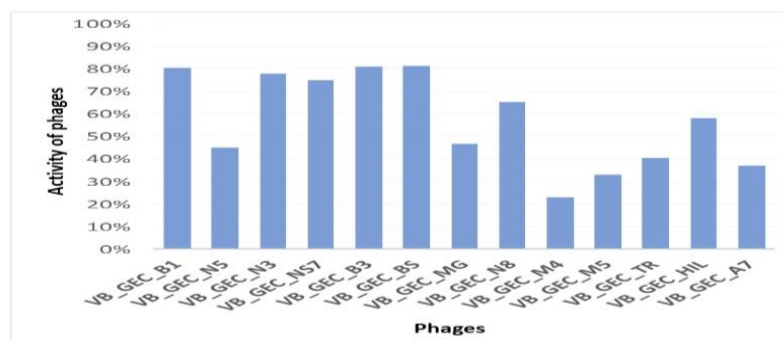
Thus, in terms of the relatedness, the phages were arranged in several groups:

1. The group of Felixounaviruses- vB-GEC-B1, vB-GEC-7A, vB-GEC-B3, vB-GEC_NS7.

2. The group Jerseyviruses from the family Siphoviridae - **vB-GEC-Hi**, **vB-GEC-M4** and **vB-GEC-M5**.
3. The group of Tequinta viruses (T5 -Tequintavirus) -**vB-GEC-N5** and **vB-GEC-N8**.
4. Genus - Tequatrovirus (T4 phages)- only one phage is representing this group - **vB -GEC -Mg**.
5. Genus Viunaviruses - only one phage is the representative of this genus - **vB -GEC -Bs**.
6. Podoviridae, genus Lederbergvirus, moderate phage - **vB -GEC-TR**.

Diagram №2

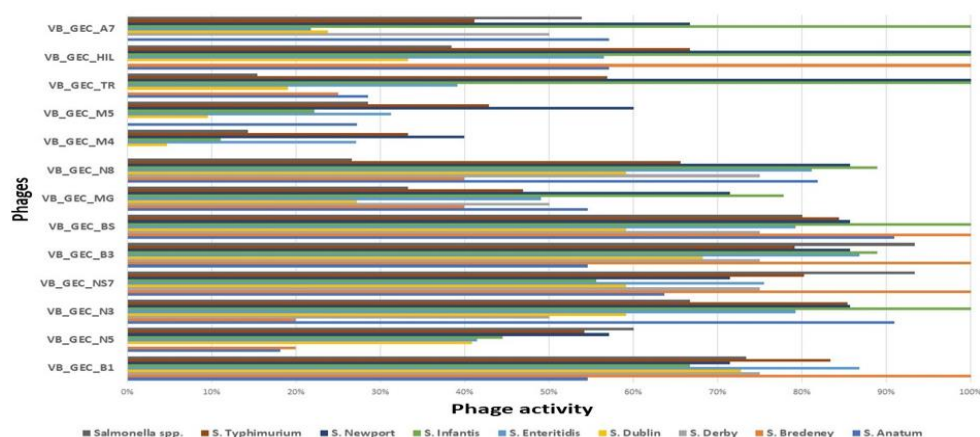
Activity of phages used in the study against to the total number of study strains (239 strains)



Comparison of the spectrum of action of phages used in the study revealed so-called highly active phages - vB-GEC-B1, vB-GEC -Bs, vB-GEC-B3, vB-GEC-N3, vB-GEC-NS7, vB-GEC-N8, the activity of which is defined from 60% to 80%. (Diagram №2)

Diagram №3

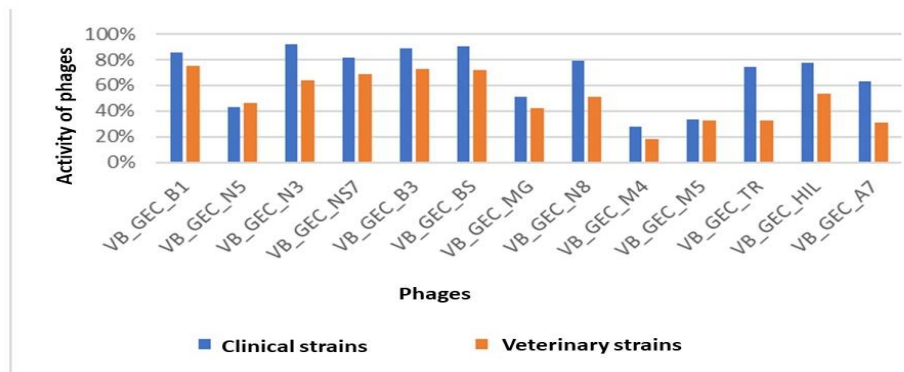
Activity of phages used in the study against different serotypes of the study strains



Interestingly, these phages were found to be more effective against clinical strains (~ 90%) than strains of veterinary origin (~ 70%). It should be noted that most of these strains which appeared to be sensitive to phages were characterized by multiple antibiotic-resistant (MDR) profiles. (Diagram №3)

Diagram №4

Activity of phages against clinical and veterinary strains



Conclusions

- From the newly isolated Salmonella specific bacteriophages - 6 belongs to the Myoviridae family - (vB_GEC_B1, vB_GEC_B3, vB_GEC_Mg, vB_GEC_Bs, vB_GEC_NS7, vB_GEC_7A), 5 – to the Syphoviridae family - vB_GEC_N5, vB_GEC_N8, vB_GEC_Hi, vB_GEC_M4, vB_GEC_M5;
- Phages with high activity are as follows - vB-GEC-B1, vB-GEC-Bs, vB-GEC-B3, vB-GEC-N3, vB-GEC-NS7, vB-GEC-N8, activity of which was defined as 60% to 80%;
- From 12 newly isolated and characterized phages 11 are lytic (virulent) phages and only one phage - vB_GEC_Tr appeared to be moderate (lysogenic);
- The strains that were susceptible to the phages isolated and characterized by us were mainly *S. typhimurium* and *S. enteritidis* serovars and were largely of clinical origin;
- Since all phages show varying degrees of efficacy against;
- 240 antibiotic-resistant Salmonella strains’.
- Since our studies did not reveal any phages to which all strains were resistant and did not detect any strains to which all phages were inactive, this also indicates the possibility of using them as prophylactic / therapeutic agents;
- Phages are natural and specific antibacterial agents, which can lyse bacteria irrespective of their AMR status, whilst leaving the commensal microflora unharmed. This is one of the main advantages of phages in comparison to antibiotics. The phages tested in this study showed potential for application in phage therapy against MDR *Salmonella* infections.

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მულტირეზისტენტული *Salmonella* spp. -ს სპეციფიკური ბაქტერიოფაგების გამოყოფა,
მათი შესწავლა და თერაპიული პოტენციალის შეფასება

ხათუნა მაკალათია, ელენე კაკაბაძე, ნინო გრძელიშვილი, ნატა ბაკურაძე, ლუკა
სანიკიძე, ნინა ჭანიშვილი

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აბსტრაქტი

კვლევის ფარგლებში მოხდა კლინიკური, არა-ტიფოიდური *Salmonella*-ს იზოლატების გამოყოფა სომხეთსა და საქართველოში, ჩატარდა მათი იდენტიფიკაცია მიკრობიოლოგიური/კულტურალური მეთოდების, სეროტიპირებისა და მატრიცაში ლაზერის სხივის დესორბცია იონიზაციაზე დაფუძნებული მასს სპექტროსკოპიის (MALDI-TOF MS) საშუალებით (White-Kauffmann-Le Minor scheme). სულ გამოვლინდა 40 ანტიბიოტიკორეზისტენტობის პროფილი, საიდანაც 35 კლინიკური შტამებისთვის იყო დამახასიათებელი. 345 *Salmonella* spp. სავარაუდო იზოლაციდან საბოლოოდ კვლევისთვის გადაირჩა 239 შტამი, საქართველოდან, სომხეთიდან და ირლანდიიდან.

აღნიშნული კოლექციის შტამების გამოყენებით მოხდა 13 ახალი ბაქტერიოფაგის გამოყოფა, მათი შესწავლა ბიოლოგიური და გენეტიკური მახასიათებლების მიხედვით. ჩატარდა 12 ფაგის ნუკლეოტიდური თანმიმდევრობის გაშიფვრა და ანალიზი, რომლის საფუძველზეც მოხდა მათი კლასიფიკაცია და სასიცოცხლო ციკლის თავისებურების დადგენა (ვირულენტური, ზომიერი).

მიღებული შედეგების ანალიზმა აჩვენა, რომ 12 ფაგიდან მხოლოდ ერთი ფაგია ე.წ. ზომიერი ფაგი - **vB_GEC_TR**, იგი განეკუთვნება ოჯახს **Podoviridae**; გვარი - **Lederbergvirus**. ხოლო დანარჩენი 11 ფაგი ვირულენტურია, მათ გენომში არ იქნა ნანახი ლიზოგენობის განმსაზღვრებელი გენები. ისინი ენათესავენ იან უკვე კარგად ცნობილ, შესწავლილ და სხვადასხვა ფაგურ პრეპარატებში შემავალ ვირულენტურ ფაგებს. ვირულენტურ ფაგებს შორის 6 Myoviridae -ს ოჯახის წარმომადგენელია - **vB_GEC_B1**, **vB_GEC_B3**, **vB_GEC_Mg**, **vB_GEC_Bs**, **vB_GEC_NS7**, **vB_GEC_7A**, ხოლო 5 Siphoviridae -ს ოჯახის - **vB_GEC_N5**, **vB_GEC_N8**, **vB_GEC_Hi**, **vB_GEC_M4**, **vB_GEC_M5**. მრავალრიცხოვანი *in vitro* ტესტების საფუძველზე დადგინდა, რომ **vB-GEC-B1**, **vB-GEC -Bs**, **vB-GEC-B3**, **vB-GEC-N3**, **vB-GEC-NS7**, **vB-GEC- N8** მაღალაქტიურ ფაგებს განეკუთვნებიან და მათი მოქმედების სპექტრი განისაზღვრა 60% დან 80 % მდე. აღნიშნული ფაგები უფრო ეფექტურნი აღმოჩნდნენ კლინიკური შტამების მიმართ (~90%), ვიდრე ვეტერინარული წარმოშობის შტამების მიმართ (~70%). შტამები, რომლებიც მგრძობელობას ავლენდნენ აღნიშნული ფაგების მიმართ, ძირითადად, *S. Typhimurium* და *S. Enteritidis* სეროვარებს მიეკუთვნებოდნენ და მეტწილად კლინიკური წარმომავლობის გახლდათ.

ჩვენს მიერ ჩატარებულ კვლევაზე დაყრდნობით, შეგვიძლია დავასკვნათ, რომ ფაგების, როგორც დამატებითი/დამხმარე ან ანტიბიოტიკის ალტერნატიული საშუალების გამოყენება მრავლობით რეზისტენტული *Salmonella* ინფექციების მიმართ მიზანშეწონილია და იმედის მომცემი. ფაგები ბუნებრივი, მადალსპეციფიკური ანტიბაქტერიული აგენტებია, რომელთაც აქვთ უნარი მოახდინონ ბაქტერიული უჯრედის ლიზისი, მისი ანტიბიოტიკო-რეზისტენტობის სტატუსის მიუხედავად. ამავდროულად, ანტიბიოტიკებისაგან განსხვავებით, ფაგები არავითარ ზიანს არ აყენებენ კომენსალურ მიკროფლორას. ჩვენი კვლევის ფარგლებში შესწავლილმა ფაგებმა აჩვენეს ძლიერი პოტენციური მულტირეზისტენტული *Salmonella* ინფექციების წინააღმდეგ საბრძოლველად.

საკვანძო სიტყვები: ბაქტერიოფაგები, სალმონელა, ბაქტერიები, ანტიბიოტიკების მიმართ რეზისტენტობა.

Выделение и изучение бактериофагов, специфичных в отношении *Salmonella* spp. С множественной лекарственной устойчивостью. и оценка их терапевтического потенциала

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Абстракт

В рамках исследования клинические нетифоидные сальмонеллы были изолированы в Армении и Грузии и идентифицированы на основе традиционных микробиологических методов и MALDI-TOF MS. Эти изоляты были дополнительно проанализированы путем серотипирования (схема Уайта-Кауфмана-Ле-Минора) и определены их профили чувствительности к противомикробным препаратам. Всего было идентифицировано 40 профилей устойчивости к антибиотикам, из которых 35 характерны для клинических штаммов. В конечном итоге для нашего исследования были отобраны из 345 изолятов 238 штаммов из Грузии, Армении и Ирландии.

Используя штаммы этой коллекции, выделено 13 новых бактериофагов, характеризующихся биологическими и генетическими особенностями. На основании полученных данных были классифицированы фаги и определены особенности их жизненного цикла (вирулентно-литические, умеренно-лизогенные). Анализ результатов секвенирования показал, что только один из 12 фагов, идентифицированных как умеренный фаг (vB_GEC_TR), принадлежит к семейству

Podoviridae, род-Laderbergvirus. В то время как другие 11 фагов вирулентны, они связаны с хорошо известными и охарактеризованными фагами, которые используются в различных фаговых препаратах. Анализ их геномов не выявил каких-либо генов, связанных с лизогенией. Среди вирулентных фагов 6 принадлежат к семейству Myoviridae (vB_GEC_B1, vB_GEC_B3, vB_GEC_MG, vB_GEC_BS, vB_GEC_NS7, vB_GEC_7A) и 5 - к семейству Syphoviridae (vB_GEC_N5_M_G_G_G_M_, vB_GEC_N5_, vB_G_G_G_G_M_, vB_GEC_N5_, vB_G_G_G_M_, vB_GEC_N5_, Тесты *in vitro* показали, что фаги vB_GEC_B1, vB_GEC_BS, vB_GEC_B3, vB_GEC_NS7, vB-GEC-N8 проявили высокую активность (от 60% до 80%) в отношении исследуемых штаммов. Было показано, что фаги более эффективны против клинических штаммов (~90%), чем против ветеринарных штаммов (~70%). Штаммы, чувствительные к этим фагам, были в основном сероварами *S.typhimurium* и *S. Enteritidis* и в основном имеют клиническое происхождение. Основываясь на наших исследованиях, мы можем сделать вывод, что применение фагов в качестве дополнительного инструмента для лечения инфекций, вызываемых сальмонеллами с множественной лекарственной устойчивостью, представляется правдоподобным. Фаги - это природные и специфические антибактериальные агенты, которые могут лизировать бактерии независимо от их статуса AMR, не повреждая при этом комменсальную микрофлору. Это одно из главных преимуществ фагов перед антибиотиками. Фаги, испытанные в этом исследовании, показали потенциал для применения в фаговой терапии против инфекций, вызываемых сальмонеллами с множественной лекарственной устойчивостью.

Ключевые слова: бактериофаги, сальмонеллы, бактерии, устойчивость к антибиотикам.

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