10.30699/ijmm.17.2.267

Iranian Journal of Medical Microbiology | ISSN:2345-4342

Is the Antibiotic Era Joint the History?

Yara Elahi[1], Ramin Mazaheri Nezhad Fard[2,3*]

1. *Department of Genetics, Faculty of Life Sciences, Islamic Azad University Tehran North Branch, Tehran, Iran*
2. *Department of Pathobiology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*
3. *Food Microbiology Research Center, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran*

Keywords: Bacteria, Antibiotic resistance, Novel antibiotics, Mobile genetic elements

Received: 2022/8/28; **Accepted**: 2022/12/25; **Published Online:** 2023/03/30

Corresponding Information: **Ramin Mazaheri Nezhad Fard**, *Department of Pathobiology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran* Email: raminmazaheri@gmail.com

Elahi Y, Mazaheri Nezhad Fard R. Is the Antibiotic Era Joint the History?. Iran J Med Microbiol. 2023; 17(2):267-9.

Use your device to scan read the article online!

Dear Editor

For the last few years, antibiotic resistance has become one of the major concerns within medical society. On one hand, pathogens have mostly acquired resistance against the major conventional antibiotics used in the treatment of microbial infections. These included even first-line antibiotics, which are critical in the treatment of severe infections. This catastrophic situation has occurred due to the extensively irresponsible use of antibiotics in humans and veterinary medicines, agriculture, aquaculture and animal breeding. On the other hand, the long absence of novel antibiotic introduction to the market by the pharmaceutical industry has exacerbated the situation. In fact, industrial giants are not interested in, or at least have lost their fasci-nation with, the development of novel formulations. One of the greatest reasons that pharmaceutical industries are not fascinated by antimicrobial development is that the process is a greatly expensive wander since the development of novel antimicrobial drugs costs an estimated $1.5 billion **(1)** while incomes from the marketing of the antimicrobial agent include nearly $46 million annually. As far as it is known, very few novel antibiotics have been commercialized by the pharmaceutical industries within the last three decades, mostly semi or fully synthetic ones, while the necessity of these biochemicals is urgently felt. As a response to this failure, medical researchers have shifted to other antimicrobial alternatives, including bacteriophages, short peptides, bacte-riocins and herbals. However, the potential rapid effectiveness of conventional antibiotics may force researchers to rethink further investigations of microbial antibiotics. But (as always there must be a big “BUT”) why?

People usually do not wish to be fanatic about science; so, why they would like to take steps back into the somewhat failed history of chemical antimicrobials? Well, this sad story apparently reminds me of the oil story! This is natural (to some extent) that nobody looks for renewable, clean green (probably more expensive) energy sources as far as there are still possible dirty black-gold (also cheaper) crude-oil sources! Similarly, researchers have no desire to put their gold mine (available antibiotics) aside and search for alternatives as far as there is still little hope for the reinvention of current antibiotics! Let’s dig this a bit deeper. In addition to synthetic formulations, thanks to the development of bio-informatics and computer modeling, other modern techniques such as machine learning can help researchers with this. In contrast, recent inves-tigations have opened new horizons in front of us to possibly return to old-fashioned methodologies. One of these methods includes the fresh recovery of old microbes from ancient repositories **(2)**. As recently broadcasted, ancient bacteria have been isolated from harsh environments such as glaciers, permafrost, well-preserved fossils and Nordic and Chinese deep-sea sediments. More, space agencies optimistically

propagate the recovery of bacteria from space materials such as planet dust and meteorites, which mostly looks like sci-fi TV series! **(3)**. The current fundamental question is could bacteria open escape ways for the seemingly dead-ended antimicrobial resistance problem? Thus, we should answer this question before early celebrations. The major problem within the natural antibiotic investigation is associated with their rapid horizontal resistance, owing to the high activity of mobile genetic elements (MGE). These hyperactive elements can transfer resistance genes to any chemicals between the bacterial species and exert the associated drug resistance within relatively short time spans. As encoding resistance genes have resided in the bacterial genomes for millions of years, they just need to exert pressure by the use of any class of antibiotics to be reactivated. A possible explanatory mechanism includes the opening of the bacterial cell wall pores and further acceptance of MGEs by the bacterial hosts. It is noteworthy that integron (a common MGE) cassettes mostly carry on several resistance genes that are transferred together. Hence, the use of specific antibiotics may result in resistance to other antibiotics, including those newly investigated. However, other critical factors must not be ignored. For example, the investigation of novel antibiotics needs nearly 20 years of research as well as millions of dollars in the research budget. These high investments are currently questioned as the ineffectiveness of the new formulations can endanger industrial efforts.

By the way, recent news on the application of exciting ideas in drug industries for the development of novel antibiotics seems optimistically promising. Examples of these ideas include the use of artificial intelligence, machine learning, complementary therapies such as quorum-sensing pathways **(4)**, microdosing for a pharmacokinetic evaluation in epithelial fluid and subcutaneous tissue **(5)**, antibacterial nanofilms **(6)**, methods that focus on the bacterial enzymes or proteins that cause antimicrobial resistance **(7)** and antimicrobial peptides with no possible microbial resistance. In 2022, scientists at the University of Liverpool have made substantial progress in realizing therapeutic promises of a new family of strong antibiotics that may eradicate "superbugs" such as methicillin-resistant *Staphylococcus aureus* (MRSA) with no detectable resistance. Teixobactin is a biochemical by the bacteria to eliminate other bacteria in soil; from which, researchers have created a simpler synthetic copy. They have created and tested a one-of-a-kind library of synthetic variations of the antibiotic that has changed the game, optimizing key components of the medication to increase its efficacy and safety while lowering the costs of large-scale production **(8)**. So, could these be addressed as medical miracles of modern medical history, or just are struggling before the antibiotic ship is completely wretched? I think this question needs a relatively long time to be answered. In conclusion, although fresh ideas have sparked small lights in the darkness, tough decisions must be made by the administrators if they want to retry this classic way and back to the future.

Acknowledgment

Special thanks to Prof. Mary Barton, University of South Australia.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Towse A, Hoyle CK, Goodall J, Hirsch M, Mestre-Ferrandiz J, Rex JH. Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. Health Policy. 2017;121(10): 1025-30. [PMID] [DOI:10.1016/j.healthpol.2017.07.011]
2. Khelaifia S, Drancourt M. Susceptibility of archaea to antimicrobial agents: applications to clinical microbiology. Clin Microbiol Infect. 2012;18(9):841-8.[PMID] [DOI:10.1111/j.1469-0691.2012.03913.x]
3. Levy MG. Smithsonian Magazine. 2020.
4. Muller C. Antibiotics and antimicrobials resistance: mechanisms and new strategies to fight resistant bacteria. 2022. p. 400. [PMID] [PMCID] [DOI:10.3390/antibiotics11030400]
5. Oesterreicher Z, Eberl S, Wulkersdorfer B, Matzneller P, Eder C, van Duijn E, et al. Microdosing as a Potential Tool to Enhance Clinical Development of Novel Antibiotics: A Tissue and Plasma PK Feasibility Study with Ciprofloxacin. Clin Pharmacokinet. 2022; 61(5):697-707. [PMID] [PMCID] [DOI:10.1007/s40262-021-01091-1]
6. Modi S, Inwati GK, Gacem A, Saquib Abullais S, Prajapati R, Yadav VK, et al. Nanostructured Antibiotics and Their Emerging Medicinal Applications: An Overview of Nanoantibiotics. Antibiotics [Internet]. 2022; 11(6). [PMID] [PMCID] [DOI:10.3390/antibiotics11060708]
7. Murugaiyan J, Kumar PA, Rao GS, Iskandar K, Hawser S, Hays JP, et al. Progress in Alternative Strategies to Combat Antimicrobial Resistance: Focus on

Antibiotics. Antibiotics [Internet]. 2022; 11(2). [DOI:10.3390/antibiotics11020200][PMID] [PMCID]

8. University of Liverpool Website. Liverpool scientists develop synthetic antibiotics that could save millions of lives 2022. Available from: [https://news.liverpool.ac.uk/2022/03/29/liverpool-scientists-develop-synthetic-antibiotics-that-coul]