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Succinct review on emergent crisis of antibiotics resistant (MDR) bacteria: impact on human health worldwide

Abstract

Multidrug resistance (MDR) has become an alarming global health menace due to either overuse or abuse of antibiotics. It has happened because of lack of proper diagnostic testing and absence of general medical awareness including overuse of antibiotics in livestock and animal husbandry. Indeed, increased MDR phenomenon is led to increase in global mortality and morbidity because of diseases treatment failures that impacted global healthcare costs. It is done due to inappropriate continual use of antibiotics in human therapies, in animal husbandry and aquaculture farming practices that resulted in increase the incidence of pathogenic bacteria becoming resistant to multiple drugs. Multidrug resistant (MDR) bacteria are very common to become prevalent causes of community-acquired infections that associated with increased morbidity, mortality and healthcare costs. Colonisation of foreign patients by MDR bacteria is found to major health concern as predisposing factors in hospitals. During hospitalization and ICU treatment of critically ill foreign patients including travellers/tourists are found to having increased risk of acquiring MDR bacteria when hospitalized abroad. Hence, all these multiple factors led to fuelling in antibiotic resistance of bacteria during pandemic crisis and causing lethal effect in cancer patients due to treatment. Antibiotic resistant pathogens to protect world human population from this global health threat. So, this stipulated review is highlighted the insight of various notable aspects of fuelling of antibiotic resistance in bacteria including their possible modes of actions and ingrained impacts on human health. Henceforth, it is the peak era to explore new sustainable therapeutic alternatives to curb increase in global MDR crisis.

Keywords: multidrug resistant bacteria, antimicrobial drugs, antibiotic susceptibility, foreign transmission risks, antibacterial resistance.

Kirti Rani

Associate Professor, Amity Institute of Biotechnology, Amity University, India

Correspondence: Dr. Kirti Rani, Associate Professor, Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, Sec-125, Gautam Buddha Nagar, Noida-201313 (UP), India, Tel +91-9990329492,
Email krsharma@amity.edu, kirtisharma2k@rediffmail.com

Introduction

Nowadays, multidrug resistance (MDR) is a globally recognized health concern that made therapeutic drugs ineffective against various treatable diseases like tuberculosis, malaria, urinary tract infection, gonorrhea and pneumonia when most of MDR bacterial strain became superbugs (Figure 1).[1–3]
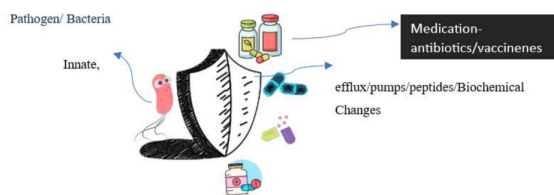
**Figure 1** Pictorial simplified portrayal of multidrug resistant bacteria.[1–3]

Multi-drug resistant (MDR) bacteria are found to rise due to prolonged hospital stay, ineffective treatment failure that led to increase morbidity and increased health burden globally.[4–7] Hitherto, it is need to prevent MDR bacteria transmission during hospitalization to keep suspected high risk patients in isolation following proper identification and preventive clinical policies by adopting more potent alternative of safe doses of antimicrobials.[8–10] MDR bacteria are found to cause many communicable diseases that are more prone to spread fast in pandemic. It became a cut throat medical challenge in those countries where medical services are more advanced and where various foreign medical travelers and tourists are used to visiting very frequently. Hence, WHO has been classified notable multidrug-resistant bacteria as "priority pathogens" or "ESKAPE pathogens,"

e.g. *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. These superbugs are reported to become difficult to kill due to having unique structural cell wall compositions including their respective increased density of drug efflux pumps.[11]

Survival of fittest strategies of multidrug-resistant bacteria against current proposing medications

All Bacteria are found to acquire antibiotics resistance by well depicted cellular mechanisms like drug inactivation process carried out due to β-lactamases group of enzymes that hydrolyse drugs as part of the inactivation process. Other reported cellular route is drug uptake reduction which carried out by lowering of bacterial cell permeability as an example: *Pseudomonas aeruginosa* found to consist monomeric 8-stranded β-barrel with a C-terminal periplasmic domain. It is observed that a rare oligomer form has large open β-barrels which belong to diffusion porin OmpF.[12,13] Another notable route of cellular mechanism is reported drug efflux take place outside the bacterial cell membrane. It is led to the characterization of drugs efflux pumps in various emerging superbugs like methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*, *Clostridium difficile*, *Enterococcus* spp., *Listeria monocytogenes*, *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, *Campylobacter jejuni*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Vibrio cholerae* and *Salmonella* spp.[14–16]

In last decade, many reported MDR bacterial strains are found to subject for studying their altered biochemical metabolic pathway which make them to escape their target site from binding to proposed antibiotics/drugs. This is led to decreases the affinity of antibiotic molecules while targeting against specific bacterial killing of bacterial strains that synthesize essential folic acid and nucleic acid from the para-amino benzoic acid (PABA) precursors. Hence, it is restricted the efficacy of antibiotics like sulphonamide that block PABA pathway, so that targeted bacteria became resistant against proposed antibiotics/therapeutic drugs (Figure 2).[17]
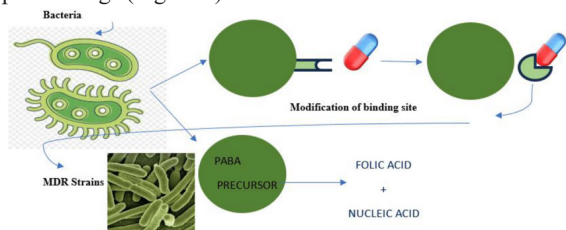
Figure 2 Pictorial delineation of defence mechanism of bacteria by modifying itself as MDR bacterial strain against proposed antibiotics.[17]

MDR bacterial pathogenic strains are found to have increased expression of active efflux pumps that in turn decreasing the drug permeability from the cell surface. This resulted in low susceptibility to antibiotics especially fluoro quinolones-based medications. Most of gram-negative bacteria are found to use this drug efflux mechanism whereas gram-positive bacteria lack this drug efflux mechanism because of not having lipopolysaccharides in their outer membrane. And, few of MDR gram-negative bacteria are also found to produce plasmid-mediated genes which are selectively bind with DNA gyrase or topoisomerase IV that make them protected from the quinolones-based antibiotics while given to patients during hospitalization as first line drug treatment.[18]

Medical tourism: a rising risks of MDR bacteria

Medical tourism is found to play a major role in spreading multidrug resistant bacteria (MDR) globally. A previous clinical cohort study is carried between 2009-2014 in Hadassah Medical Center that is known referral center for medical tourists worldwide and also for Palestinian Authority residents.[19–21] It was found that trade/travel tourists and patients from the Palestinian Authority suffered from high indexed rates of MDR positivity as MDR carriers when compared to Israeli patients than the resident population including antimicrobial resistance. Hospitalized foreign travellers are found at high risk of acquiring antimicrobial resistant bacteria in Europe report having MDRO carriage rates.[21–24] MDRO based clinical investigation was done in Finland where MRR found more prevalent in foreign hospitalized patients. It is also found to be more strongly associated with travellers from the Indian subcontinent followed by Southeast Asia, Africa and South America due to lack of proper clinical guidelines for medical tourism raising bloodstream infection (BSI): a life-threat and increasing health care costs as well.[25–28] The increasing burden of hospital-acquired BSI caused by Multidrug-resistant (MDR) pathogens are listed out in Table 1. Reported clinical studies was done to identity present bacterial etiology and predicting mortality in hospital acquired blood stream infections (BSI) in hospitalized patients and ICU admitted critical ill patients. Hence, MDR bacterial strains are found to be as potent independent predictor for calculating patients' mortality who diagnosed with blood stream infections upon abroad hospitalization.[29–31]

Table 1 A clinical report tabularized for confirming all isolated bacteria from BSI diagnosed patients are mostly types of MDR bacterial strains

S. No.	Organism causing BSI	Sensitivity pattern against drugs	Resistance against antibiotics	References
1.	*Acinetobacter baumanii*	Meropenem Piperacillin Tazobactum Polymyxin B Colistin	Ceftazidime Levofloxacin Doxycycline Ceftriaxone	Datta et al 2020[28]
2.	*Enterococcus faecium*	Vancomycin Linezolid	Gentamicin Piperacillin Tazobactam Penicillin	Kaur, Jasmine et al 2024[29]
3.	*Pseudomonas aeruginosa*	Meropenem Piperacillin Tazobactam Polymyxin B Colistin	Cotrimoxazole Ciprofloxacin Gentamicin Ceftrixone Ofloxacin	Kolayli F et al 2005[30]
4.	*Staphylococcus aureus*	Vancomycin Linezolid Piperacillin Tazobactam	Cotrimoxazole Gentamicin Levofloxacin Cefoxitin	Foglia F et al 2023[31]

Conclusion

This brief stipulated review is highlighted the various factors that lead to increase in incidence of MDR in exposed populations. Hospitalization of patients abroad including admitted in the ICU are found at higher risk of colonization and acquisition of MDR strain which must require proper screening and required isolation. So, increased medical tourism could lead to an increase MDR globally that lead to geographically dispersed outbreaks of various communicable diseases as well. Indiscriminate use of antibiotics and other overuse of antimicrobial agents have become mainstream cause of increasing MDR pathogens, "superbugs" in more suspected and exposed populations. Hence, we need to be more careful to control the spreading of MDR pathogenic bacterial strains in human population worldwide by adopting safe use of antibiotics and antimicrobial agents. National and International clinical governance must have to go ahead to analyzing and tracing these hazards and curtail ill effects of MDR on human health globally.

Acknowledgments

Conflicts of interest

The author declares that there are no conflicts of interest.

References

1. Centers for disease control and prevention. AR threats report. 2019.

2. Colson AR, Morton A, Årdal C, et al. *Antimicrobial resistance*: is health technology assessment part of the solution or part of the problem? *Value Health*. 2021;24(12):1828–1834.

3. Catalano A, Iacopetta D, Ceramella J, et al. Multidrug resistance (MDR): a widespread phenomenon in pharmacological therapies. *Molecules.* 2022;27(3):616.

4. Marston HD, Dixon DM, Knisely JM, et al. Antimicrobial resistance. *JAMA.* 2016;316(11):1193–1204.

5. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. 2014.

6. Toner E, Adalja A, Gronvall GK, et al. Antimicrobial resistance is a global health emergency. *Health Secur.* 2015;13(3):153–155.

7. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA*. 2018;115(15):E3463–E3470.

8. Siegel JD, Rhinehart E, Jackson M, et al. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control.* 2007;35(10 Suppl 2):S65–S164.

9. Bloom DE, Black S, Salisbury D, et al. Antimicrobial resistance and the role of vaccines. *Proc Natl Acad Sci USA*. 2018;115(51):12868–12871.

10. De Oliveira DMP. et al. Antimicrobial resistance in ESKAPE pathogens. *Clin Microbiol Rev.* 2020;33(3):e00181–e00219.

11. Sugawara E, Nestorovich EM, Bezrukov SM, et al. *Pseudomonas aeruginosa* porin OprF exists in two different conformations. *J Biol Chem*. 2006;281(24):16220–16229.

12. Sugawara E, Nikaido H. Pore-forming activity of OmpA protein of *Escherichia coli. J Biol Chem*. 1992;267(4):2507–2511.

13. Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. *Science.* 1995;267(5197):483–489.

14. Schindler BD, Kaatz GW. Multidrug efflux pumps of gram-positive bacteria. *Drug Resist Updat.* 2016;27:1–3.

15. Bloom DE, Black S, Salisbury D, et al. Antimicrobial resistance and the role of vaccines. *Proc Natl Acad Sci USA.* 2018;115(51):12868–12871.

16. Lade H, Kim JS. Bacterial targets of antibiotics in methicillin-resistant *Staphylococcus aureus*. Antibiotics. 2021;10(4):398.

17. Davin-Regli A, Bolla JM, James CE, et al. Membrane permeability and regulation of drug "influx and efflux" in enterobacterial pathogens. *Curr Drug Targets.* 2021;9(9):750–759.

18. Kaiser AM, Schultsz C, Kruithof GJ, et al. Carriage of resistant microorganisms in repatriates from foreign hospitals to the Netherlands . *Clin Microbiol Infect.* 2004;10(11):972–979.

19. Frost I, van Boeckel TP, Pires J, et al. Global geographic trends in antimicrobial resistance: the role of international travel. *J Travel Med.* 2019;26(8):taz036.

20. Angue M, Allou N, Belmonte O, et al. Risk factors for colonization with multidrug-resistant bacteria among patients admitted to the intensive care unit after returning from abroad. *J Travel Med.* 2015;22(5):300–305.

21. Kajova M, Khawaja T, Kantele A. European hospitals as source of multidrug-resistant bacteria: analysis of travellers screened in Finland after hospitalization abroad, *J Travel Med.* 2022;29(4):taac022.

22. Blomberg B, Manji KP, Urassa WK, et al. Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study. *BMC Infect Dis*. 2007;7:43.

23. Seboxa T, Amogne W, Abebe W, et al. High mortality from bloodstream infection in Addis Ababa, Ethiopia, is due to antimicrobial resistance. *PloS One*. 2015;10(12):e0144944.

24. Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol*. 2005;43(2):745–749.

25. Boyles TH, Davis K, Crede T, et al. Blood cultures taken from patients attending emergency departments in South Africa are an important antibiotic stewardship tool, which directly influences patient management. *BMC Infect Dis*. 2015;15:410.

26. Negussie A, Mulugeta G, Bedru A, et al. Bacteriological profile and antimicrobial susceptibility pattern of blood culture isolates among septicemia suspected children in selected hospitals Addis Ababa, Ethiopia. *Int J Biol Med Res*. 2015;6(1):4709–4717.

27. Laupland KB, Zygun DA, Davies HD, et al. Population-based assessment of intensive care unit-acquired bloodstream infections in adults: Incidence, risk factors, and associated mortality rate. *Crit Care Med*. 2002;30(11):2462–2467.

28. Swarnendu D, Chakrabarty U, Chakrabarty P, et al. Incidence of central venous and Foley's related bacteraemia, organisms responsible and antibiotic sensitivity pattern: in cardio-thoracic intensive therapeutic unit following elective surgery, in a tertiary care hospital of Kolkata, India. *Int J Adv Med*. 2020;7.

29. Kaur J, Singh H, Sethi T. Emerging trends in antimicrobial resistance in bloodstream infections: multicentric longitudinal study in India (2017-2022). *Lancet Reg Health Southeast Asia*. 2024;26:100412.

30. Kolayli F, Gacar G, Karadenizli A, et al. PER-1 is still widespread in Turkish hospitals among *Pseudomonas aeruginosa* and *Acinetobacter* spp. *FEMS Microbiol Lett.* 2005;249(2):241–245.

31. Foglia F, Rocca MTD, Melardo C, et al. Bloodstream infections and antibiotic resistance patterns: a six-year surveillance study from southern Italy. *Pathog Glob Health*. 2023;117(4):381–391.