~~ENUMERATING~~ THE ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE BASED ON ANTI-MICROBIAL SUSCEPTIBILITYTESTING IN VARIOUS INFECTIONS IN A TERTIARY CARE HOSPITAL: A PROSPECTIVE STUDY

ABSTRACT

Introduction: Antibiotics are anti-microbial agents used for the management of various bacterial infections. Over use, inappropriate prescribing pattern leads to antibiotics resistance (AR). Antibiotic resistance leads to increase in health care cost. Our study was mainly to assess the economic burden due to antibiotic resistance based on antimicrobial susceptibility testing in various infections.

Methods: The data for the study was collected prospectively and recorded in a data collection form specially designed for the study based on inclusion and exclusion criteria obtained from the Department of General Medicine, NIMS Hospital, Neyyattinkara, Thiruvananthapuram of patients with infectious diseases during the period of 6 months from April 2021 to September 2021.

Results: ~~In our study out o~~f 128 patients studied, 53.1% (N=68) were males and 46.9% (N=60) were females and the most prominent age group was found to be between 46-60 years of age (35%,N=45).The most common infection seen in patients was urinary tract infection (20.3%, N=26). According to the Kuppuswamy scale of socioeconomic status, most of them belonged to lower- middle class (50%, N=64). Antibiotic sensitivity test was done in more than half of the patients (52.3%, N=67); and the patients with resistance (Rs.26530.81) had more mean cost than those without resistance (Rs.18412.01) and this mean difference was highly significant (p=0.001). We also demonstrated that the resistant patients without antibiotic sensitivity testing had (Rs.30193.14) a significantly higher mean total cost. There is significant relation between antimicrobial resistance and economic burden.

Conclusion: Our study demonstrated that the resistant patients without antibiotic sensitivity testing had a significantly higher financial burden. ~~So,~~ we strongly recommend the need to perform antibiotic sensitivity testing (AST) in patients with various infectious diseases. Also, patient should be well-informed about the details and the results of antibiotic sensitivity testing to ensure medication adherence and to avoid self- medication.

Key words: Antibiotics, resistance, antibiotic sensitivity testing, economic burden

Comment [MB1]: THE ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE BASED ON ANTIMICROBIAL SUSCEPTIBILITY TESTS IN VARIOUS INFECTIONS IN A TERTIARY CARE HOSPITAL: A PROSPECTIVE STUDY

Comment [MB2]: Antibiotics are antimicrobial agents used for the treatment of various bacterial infections. Excessive use and inappropriate prescription pattern conduct to antibiotic resistance (AR). Antibiotic resistance leads to an increase in the cost of medical care. Our study assess the economic burden due to antibiotic resistance based on antimicrobial susceptibility testing in various infections.

Comment [MB3]: All capital N must be n minuscule, sin denote part of the total.

Comment [MB4]: How you did this calculi? There is no reference on the methods.

Comment [MB5]: This is a discussion, no part of the results

Comment [MB6]: 128 patients were studied, 53.1% (n=68) were males and 46.9% (n=60) were females and the most frequent age range was between 46-60 years of age (35%, n=45).The most common infection seen in patients was urinary tract infection (20.3%, n=26). The socioeconomic status, (50%, N=64) belonged to lower- middle class. Antibiotic sensitivity test was done in (52.3%, N=67) and the patients with resistance (Rs.26530.81) had more mean cost than those without resistance (Rs.18412.01) showing highly significant difference (p=0.001). The resistant patients without antibiotic sensitivity testing had (Rs.30193.14).

Comment [MB7]: This is a conclusion/discussion, no part of the results.

Comment [MB8]: Conclusion: Our study demonstrated that the resistant patients without antibiotic sensitivity testing had a significantly higher financial burden. Therefore, we strongly recommend to perform antibiotic sensitivity testing (AST) in patients with infectious diseases. Also, patient should be well-informed about the details and the results of antibiotic sensitivity testing to ensure medication adherence and to avoid self- medication.

1. INTRODUCTION

The term antibiotic was derived from the word “antibiosis” meaning “against life” [1]. The introduction of antibiotics in the clinical field was one of the successful breakthroughs in the history of medicines. After discovering penicillin by Sir Alexander Fleming (a physician and microbiologist) in 1928, antibiotics have transformed into the era of modern medicine [2].

Antibiotic resistance is one of the major limitations of antibiotic use. Antimicrobial resistance occurs when bacteria change their response to the use of these medicines. The factors which lead to antibiotic resistance are antibiotic overuse, irrational prescribing of antibiotics and use of antibiotics in agricultural industry.

Comment [MB9]: Reference?

One of the major consequences of antibiotic resistance is the increase in cost for treatment (when first-line antibiotics are not effective, then, more expensive medicines are used). These increased costs are mainly due to prolonged length of hospital stay [3], increases in number of tests needed and increased medical and rehabilitation services provided. It also has an impact on morbidity and mortality, including significant increases in disease complications, increases side effects from the use of multiple and more powerful antibiotics.

Comment [MB10]: Reference

The fundamental goal of the cost of illness study is to evaluate the economic burden that illness imposes on society as a whole [4]. It combines the cost of healthcare services (direct costs), the value of the patient's reduced or lost productivity (indirect costs), and the cost of pain and suffering (intangible costs). Hospitalization, medicine, emergency transport, and medical care are all direct costs in the health sector. In addition, non-refunded payments for hospitalization, medical visits, and drugs; transportation of patient and family for health visits; transportation of family to visit the hospitalized patient; modifications at home as a result of illness; and costs for taking care of the patient at home are all costs directly related to the treatment of illness [5].Sickness, untimely mortality, side effects of illness or therapy, or time spent seeking treatment can all cause decreased or lost productivity.

Comment [MB11]: Reference

Comment [MB12]: Reference

Culture sensitivity test, also called susceptibility test, ~~and helps to~~ find out the most effective antibiotic to kill an infecting microorganism and to confirm whether the empirical antimicrobial agent is susceptible. If antibiotics are prescribed based on culture sensitivity reports, economic burden can be reduced to an extent. This is because effective antibiotics can be givenearly and shifting to costly antibiotics can be avoided. All these reduce length of hospital staythus minimizing the cost of illness.

Comment [MB13]: Reference

Comment [MB14]: Reference

Biomarkers are biological characteristics that are objectively measured and used as an indicator of a physiological or pathological pathway or a pharmacologic response to therapeutic interventions and they assist physicians in triaging, diagnosing, stratifying risk, and monitoring clinical course and antibiotic response [6]. The most often investigated and used biomarkers are C-reactive protein (CRP) and pro-calcitonin (PCT) [7]. In comparison to normal care, PCT-guided antibiotic therapy reduces the number of antibiotic prescriptions without affecting the clinical success or increasing mortality [8]. Antimicrobial resistance can be prevented to a certain extent by practicing certain measures: using antibiotics only when prescribed by the physician, maintain hygienic environment by washing hands, discourage the use of leftover antibiotics, prescribe antibiotics after doing culture sensitivity test, strengthening policies and programs, prescribing antibiotic only when needed, giving antibiotics to animals only under veterinary supervision.

Comment [MB15]: Sure? Maybe in your hospital.

Comment [MB16]: Reference

2.METHODOLOGY:

Comment [MB17]: Methods

Our study was carried out in 128 inpatients in the General medicine department of NIMS Medicity, Neyyattinkara, a tertiary care hospital in Trivandrum, Kerala. Data were obtained in a systematic manner utilizing a data collection form.

The data collection form includes details on patient's demographics, reason for admission, education, occupation, income, laboratory parameters ~~like~~ Hb, PCV, RBC, WBC, Platelet, Neutrophils, Lymphocytes, Eosinophils, Basophils, Monocytes, ESR, CRP, MCV, MCH, MCHC, urine analysis, sensitivity test, expenses related to medical condition and other expenses. The data was collected from the patient’s files of inpatients with infection and were prescribed at least one antibiotic throughout their stay of more than three days. Information regarding the study (patient demographics, education, occupation, monthly income, transportation cost, cost of meals, loss of income due to hospitalization) was collected by interviewing the patients, and patient caregivers.

The Modified Kuppuswamy Socio-economic scale was used to assess socioeconomic status. Cost of illness was calculated by interviewing the patients on direct medical and non-medical costs, including the cost of drugs, cost of laboratory test, cost of transportation, cost of rent, cost of food, and indirect non-medical costs like patient and bystander loss of wages. After the collection of data, it was recorded and analyzed using an MS Excel spreadsheet and SPSS version 13.

Comment [MB18]: Reference

This study is approved by the ethics committee of NIMS Medicity, Neyyattinkara and was certified by the Institutional Ethics Committee met and approved the proposal [ECR/218/Inst/Ker/2013/RR-16].

3.RESULTS AND DISCUSSION

Comment [MB19]: I suggest a continuous wording, without separating with statements. You must refer to the table number in your writing.

3.1 AGE WISE DISTRIBUTION.

Among 128 patients, age was categorized into five groups: 18-30 (10%, N=13), 31-45 (12%, N=15), 46-60 (35%, N=45), 61-75 (30%, N=39) and >75 (13%, N=16). The most prominent age group involved was found in between 46-60 years (35%, N=45).The mean age of patients involved in infection was 52 years.

Comment [MB20]: The same as before: must be n (minuscule)

Comment [MB21]: The most frequent age range was between 46-60 years of age (35%, n=45)

Table 1: Frequency and percentage distribution ~~of samples~~ according to age.

AGE IN YEARS	FREQUENCY (n)	PERCENTAGE (%)
18-30	13	10
31-45	15	12
46-60	45	35
61-75	39	30
>75	16	13

3.2 GENDER WISE DISTRIBUTION.

Out of 128 patients, 53.1% (N=68) were males and 46.9% (N=60) were females. Male gender was found to be infected at a higher rate than females.

Comment [MB22]: Men were found to have a higher rate of infections than women.

Table 2: Frequency and percentage distribution ~~of samples~~ according to gender.

GENDER	FREQUENCY (n)	PERCENTAGE (%)
Male	68	53.1
Female	60	46.9
Total	128	100.0

3.3 DISTRIBUTION OF SOCIO-ECONOMIC STATUS.

Out of 128 patients, 2.3% (N=3), 22.7% (N=29), 50% (N=64), 18.8% (N=24) and 6.3% (N=8) were upper, upper middle lower middle, upper lower and lower middle respectively. The most of the patients presented with infection were from lower middle class (50%, N=64), followed by upper middle class (22.7%, N=29).

Table 3 Frequency and percentage distribution ~~of samples~~ according to Socio-economic status.

SOCIO-ECONOMIC STATUS	FREQUENCY (N)	PERCENTAGE (%)
Upper	3	2.3
Upper middle	29	22.7
Lower middle	64	50
Upper lower	24	18
Lower	8	6

3.4 DISTRIBUTION OF EMPIRICAL THERAPY RESISTANCE.

Out of 128 samples, 41.4% (N=53) patients had empirical therapy resistance, while 58.6% (N=75) patients did not.

Table 4: Frequency and percentage distribution of samples according to empirical therapy resistance.

EMPIRICAL THERAPY RESISTANCE	FREQUENCY (N)	PERCENTAGE (%)
Yes	53	41.4%
No	75	58.6%

3.5 DISTRIBUTION OF ANTIBIOTIC SENSITIVITY TESTING.

Among 128 patients, antibiotic sensitivity test (AST) was conducted in 52.3% (N=67) and was not conducted in 47.7% (N=61).

Table 5: Frequency and percentage distribution of samples based on antibiotic sensitivity test conducted.

AST CONDUCTED	FREQUENCY (N)	PERCENTAGE (%)
Yes	67	52.3
No	61	47.7
Total	128	100.0

3.6 ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE.

3.6.1 COMPARISON OF DIRECT COST AGAINST EMPIRICAL THERAPY RESISTANCE.

The mean value of total cost for patients with resistance is 17349.68 and the mean value of total cost for those without resistance is 10827.49. The total mean value cost comparison is done with a *t-statistics* and it is found that the mean value difference according to empirical therapy resistance is statistically significant. t/F value =3.602 and significant value *p=0.001*.

Comment [MB23]: I suggest a continuous wording, without separating with statements. You must refer to the table number in your writing.

Comment [MB24]: What is the unit of measure, money? Fx?, Hospitalization days?...

Comment [MB25]: This is a method, must be explained on the methods.

Table 6. Distribution of direct cost against empirical therapy resistance.

EMPIRICAL THERAPY RESISTANCE	FREQUENCY (N)	MEAN OF DIRECT COST	STANDARD DEVIATION	STANDARD DEVIATION ERROR MEAN	t/F	P VALUE
YES	53	17349.68	10162.33	1395.90	3.602	0.001
NO	75	10827.49	9984.70	1152.93		

This means that the patients with resistance have more mean direct cost than those without resistance and this mean difference is highly significant. This financial burden faced by the empirical therapy resistance patient was due to the shifting of antibiotics from low cost to high cost or use multiple antibiotics for the same infection.

3.6.2 DISTRIBUTION OF INDIRECT COST AGAINST EMPIRICAL THERAPY RESISTANCE.

The mean value of total cost for patients with resistance is 9184.53 and the mean value of total cost for those without resistance is 7632.44. The total mean value cost comparison is done with a t-statistics and it is found that the mean value difference according to empirical therapy resistance is statistically significant. t/F value =1.79 and significant value p=0.077.

Table 7 Distribution of indirect cost against empirical therapy resistance.

EMPIRICAL THERAPY RESISTANCE	FREQUENCY (N)	MEAN OF INDIRECT COST	STANDARD DEVIATION	STANDARD DEVIATION ERROR MEAN	t/F	P VALUE
YES	53	9184.53	5223.25	717.47		
NO	75	7632.44	4231.81	488.65	1.79	0.077

This means that the patients with resistance has more mean indirect cost than those without resistance and this mean difference is highly significant. The patient who is resistant to treatment may have to stay in the hospital or be sick for a longer period of time. As a result, the number of productive days is reduced. This will have an impact on their pay. The bulk of the age group impacted by resistance in our study was 46-60 years old and male. Furthermore, the ~~vast~~ majority of these patients were from the lower middle class. Normally, these people rely on their daily salaries to keep their families operating smoothly. They are facing a financial burden of indirect costs as a result of the loss of their primary source of income.

3.6.3 DISTRIBUTION OF TOTAL COST AGAINST EMPIRICAL THERAPY RESISTANCE.

The mean value of total cost for patients without resistance is 18412.01 and the mean value of total cost for those with resistance is 26530.81. The total mean value cost comparison is done with a t-statistics and it is found that the mean value difference according to empirical therapy resistance is statistically significant. t/F value =3.46 and significant value p=0.001.

Table 8. Distribution of total cost against empirical therapy resistance.

EMPIRICAL THERAPY RESISTANCE	FREQUENCY (N)	MEAN OF TOTAL COST	STANDARD DEVIATION	STANDARD DEVIATION ERROR MEAN	t/F	P VALUE
No	75	18412.01	12443.386	1436.838	3.468	0.001
Yes	53	26530.81	13859.107	1903.695		

This means that the patients with resistance has more mean cost than those without resistance and this mean difference is highly significant. Antibiotic resistance is a naturally occurring mechanism that can be slowed but not totally eliminated because resistance is an unavoidable result of medication selection pressure.

Comment [MB26]: Reference

Antibiotic-resistant diseases add significant expenses to an already overburdened health-care system. When first-line and second-line antibiotic therapy alternatives are restricted or unavailable, doctors may be obliged to employ antibiotics that are both more harmful to patients and more expensive. Even when effective therapies are available, research shows that patients with resistant infections require much longer hospital stays, more doctor visits, and longer recovery times, as well as having a greater rate of long-term disability. According to a study by *Mauldin et a* [17], infections caused by antibiotic-resistant microorganisms have a higher total cost than infections caused by susceptible pathogens.

Comment [MB27]: Reference

Comment [MB28]: Reference

Comment [MB29]: References

Comment [MB30]: Just ONE study?

3.6.4 DISTRIBUTION OF HOSPITAL STAY AND COST.

The mean total cost was 11078.35(N=46), 23488.13 (N=55), 32431.60(N=15), 41592.42 (N=12) for patients with 3-6, 7-10,11-14 and more than 15 days of hospital stay. The mean direct cost was 5974.39(N=46), 14809.07 (N=55), 20293.73(N=15), 28155.67 (N=12) for patients with 3-6, 7-10, 11-14 and more than 15 days of hospital stay. The mean indirect cost was 5186.00 (N=46), 8679.05(N=55), 12137.87(N=15) and 13436.75(N=12) for patients with 3-6, 7-10, 11-14 and more than 15 days of hospital stay respectively. The relationship between hospital stay and cost is highly significant.

Table 9. Distribution of hospital stay against cost.

HOSPITAL STAYS	Frequency	Mean	SD	t/F	P-value
			TOTAL COST		
3-6 days	46	11078.35	5252.088	42.03	0.001
7-10 days	55	23488.13	11459.117		

11-14 days	15	32431.60	9924.438		
>15 days	12	41592.42	13283.479		
			DIRECT COST		
3-6 days	46	5974.39	4416.108	30.46	0.001
7-10 days	55	14809.07	9578.358		
11-14 days	15	20293.73	7788.747		
>15 days	12	28155.67	11355.174		
			INDIRECT COST		
3-6 days	46	5186.00	1696.182	22.43	0.001
7-10 days	55	8679.05	4292.395		
11-14 days	15	12137.87	4776.998		
>15 days	12	13436.75	5903.540		

A similar result was found in the study conducted by *Mauldin,etal*[17] where increased hospital stay attributed to an increased hospital cost (23%, *p=0.0003*). Similarly, a research by *Zhen et al*[25] found that increased overall costs ($77 billion) were associated with an increase in length of stay (95 percent, N=15105) owing to antibiotic resistance.

Patients who were in the hospital for a longer period of time had a higher mean total cost. This is because the cost of therapy, medicine, administration fees, laboratory costs, room rent, and other expenses rise when patients are admitted to the hospital for extended periods of time.

Comment [MB31]: References

3.6.5. DISTRIBUTION OF TEST DONE AND EMPIRICAL THERAPY RESISTANCE AGAINST DIRECT COST.

The mean value of direct cost for patients with test done and resistance developed is 12239.82 and the mean value of cost for patients with resistance but had not subjected to antibiotic sensitivity test is 19762.67. It is found that the mean value difference according to empirical therapy resistance and test done against direct cost is statistically significant. For patients with test done and resistance developed, t/f value=0.545 and p value =0.590.And for resistant patients without test done, t/f value=3.49 and significant p value=0.001.

Table 10. Distribution of test done and empirical therapy resistance against direct cost.

TEST DONE	EMPIRICAL RESISTANCE	FREQUENCY (N)	DIRECT COST			t/F	P VALUE
			Mean	Standard Deviation	Standard Error		
Yes	Yes	17	12239.82	9346.34	2266.82	0.545	0.590
	No	50	10774.30	10213.04	1444.31		
No	Yes	36	19762.67	9738.049	1623.01	3.49	0.001
	No	25	10933.88	9716.72	1943.34		

This means that the resistant patients without antibiotic sensitivity testing have a significantly higher mean direct cost. In most patients, clinical evidence of increased CRP and ESR is taken into account rather than antibiotic sensitivity test during antibiotic treatment. The physician may alter antibiotics based on clinical judgment if the patient's condition does not improve significantly. As a result, the cost of therapy, laboratory fees and drugs will rise and thus the direct cost also increased. So we recommend antibiotic susceptibility testing prior to antibiotic therapy.

3.6.6 DISTRIBUTION OF TEST DONE AND EMPIRICAL THERAPY RESISTANCE AGAINST INDIRECT COST.

The mean value of indirect cost for patients with test done and resistance developed is 6546.06 and the mean value of cost for patients with resistance but had not subjected to antibiotic sensitivity test is 10430.47. It is found that the mean value difference according to empirical therapy resistance and test done against indirect cost is statistically significant. For patients with test done and resistance developed, t/f value=0.726 and value p =0.475. And for resistant patients without test done, t/f value=2.320and significant value *p =0.024.*

Table 11. Distribution of test done and empirical therapy resistance against indirect cost.

TEST DONE	EMPIRICAL RESISTANCE	FREQUENCY(N)	INDIRECT COST			t/F	P VALUE
			Mean	Standard Deviation	Standard Error		
Yes	Yes	17	6546.06	5287.62	1282.44	0.726	0.475
	No	50	7575.96	4287.51	606.35		
No	Yes	36	10430.47	4772.26	795.38	2.320	0.024
	No	25	7745.40	4203.06	840.61		

This means that the resistant patients without antibiotic sensitivity testing have a significantly higher mean indirect cost. There was a significant association between total cost and resistance to empirical therapy. This might be due to a longer hospital stay, higher therapy cost before and after switching over of antibiotics, higher medication cost, transportation cost, laboratory fees and administration fees.

3.6.7 DISTRIBUTION OF TEST DONE AND EMPIRICAL THERAPY RESISTANCE AGAINST TOTAL COST.

The mean value of cost for patients with test done and resistance developed is 18775.29 and the mean value of cost for patients with resistance but had not subjected to antibiotic sensitivity test is 30193.14. The total mean value cost comparison is done with a t-statistics and it is found that the mean value difference according to empirical therapy resistance and test done is statistically significant. For patients with test done and resistance developed, t/f value=0.114 and p value p=0.910.And for resistant patients without test done, t/f value=3.560 and significant p value p=0.001.

Table 12. Distribution of test done and empirical therapy resistance against total cost.

TEST DONE	EMPIRICAL RESISTANCE	FREQUENCY (N)	TOTAL COST			t/F	VALUE
			Mean	Standard Deviation	Standard Error		
Yes	Yes	17	18775.29	13464.11	3265.53	0.114	0.910
	No	50	18350.26	12519.64	1770.55		
No	Yes	36	30193.14	12628.77	2104.79	3.560	0.001
	No	25	18535.52	12545.09	2509.02		

This means that the resistant patients without antibiotic sensitivity testing have a significantly higher mean total cost. An antibiotic sensitivity test is used to determine which antibiotic will be most successful against the bacteria or fungus infecting a given person.A "susceptible" result means that the patient's organism should react to treatment with that antibiotic at the usual dosage for that kind of infection and species. In contrast, an organism that is considered as "resistant" means that the organism in patient should not react to treatment with the antibiotic. This is an essential component of antibiotic therapy since it can minimize the expense and toxicity of antibiotics while also preventing the spread of antimicrobial resistance in the population.

Comment [MB32]: References

4. CONCLUSION

Antibiotics were undoubtedly the biggest medical breakthrough of the twentieth century, with their development and introduction into clinical usage. Despite their importance in preventing and treating infectious diseases, antibiotic misuse and overuse have led in an alarming rise in antibiotic resistance around the world. The study demonstrated that the resistant patients without antibiotic sensitivity testing had a significantly higher mean total cost. So, we strongly recommend the need to perform antibiotic sensitivity test in patients with various infectious disease and to inform the patients about the importance of antibiotic sensitivity testing, including its indications and patient management.

Comment [MB33]: References

CONSENT

Informed consent of the participants was collected.

ETHICAL APPROVAL

The study was approved by the ethics committee of NIMS Medicity, Neyyattinkara and was certified by the Institutional ethics committee met and approved the proposal.

REFERNCE

1. Etebu E, Arikekpar I, Etebu E, Arikekpar I. Antibiotics: Classification and mechanisms of action with emphasis on molecul1. Int J App Microbiol Biotechnol Res;2016;4;90-101

2. Luyt CE, Brechot N, Trouillet JL, Chastre J. Antibiotic stewardship in the intensive care unit. Crit Care. 2014;18(5):480

3. Sengupta S, Chattopadhyay MK, Grossart HP. The multifaceted roles of antibiotics and antibiotic resistance in nature;Front Micro-biol;2013;4;47.

4. Spellberg B, Gilbert DN. The future of antibiotics and resistance: A tribute to a ... [Internet]. 2015 [cited 2021Oct2]. Available from: https://www.researchgate.net/publication/264987208_The_Future_of_Antibiotics_and_Resi stance_A_Tribute_to_a_Career_of_Leadership_by_John_Bartlett.

5. Antimicrobial classifications: Drugs for bugs. In: Antimicrobial Susceptibility Testing Protocols. CRC Press; 2007. p. 21–66.

6. Klevens RM, Edwards JR, Richards CL Jr, Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep. 2007;122(2):160–6.

7. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018;4(3):482–501.

8. Lushniak BD. Antibiotic resistance: a public health crisis. Public Health Rep. 2014;129(4):314–316.

9. Read AF, Woods RJ. Antibiotic resistance management. Evol Med Public Health. 2014;2014(1):147.

10. Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health. 2014;2:145.

11. Centers for Disease Control and Prevention (U.S.). Antibiotic resistance threats in the United States, 2019. Centers for Disease Control and Prevention (U.S.); 2019.

12. Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics;Clin Infect Dis 2013;56(10);1445–1450.

13. Golkar Z, Bagasra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. J Infect Dev Ctries. 2014;8(2):129–36.

14. Martinez JL. General principles of antibiotic resistance in bacteria. Drug Discov Today Technol. 2014;11:33–9.

15. Gaynes R, Edwards JR, National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis. 2005;41(6):848–54.

16. Chancey ST, Zähner D, Stephens DS. Acquired inducible antimicrobial resistance in Grampositive bacteria. Future Microbiol. 2012;7(8):959–78.

17. Mauldin PD, Salgado CD, Hansen IS, Durup DT, Bosso JA. Attributable hospital cost and length of stay associated with health care-associated infections caused by antibiotic-resistant gram-negative bacteria. Antimicrob Agents Chemother. 2010; Jan;54(1):109-15.

18. Report of the ASM task force on antibiotic resistance. Antimicrob Agents Chemother. 1995;Suppl:1–23.

19. Schlaes D, Gerding D, TenoverF,JE M, Levy S, John J. Guidelines for the prevention of antimicrobial drug resistance in hospitals: joint statement by the Society for Health Care Epidemiology of America and the Infectious Diseases Society of America. Infect Control Hosp Epidemiol;1997;18:275–91.

20. Department of Health UK. Government Response to the House of Lords Select Committee on Science & Technology Report: Resistance to antibiotics and other antimicrobial agents (publication CM4172). London: The Stationery Office; 1998.

21. McGowan JE Jr. Do intensive hospital antibiotic control programs prevent the spread of antibiotic resistance?Infect Control Hosp Epidemiol;1994;15(7):478–83.

22. Liss RH, Batchelor FR. Economic evaluations of antibiotic use and resistance--a perspective: report of Task Force 6. Rev Infect Dis. 1987;9 Suppl 3:S297-312.

23. Lai KK, Kelley AL, Melvin ZS, Belliveau PP, Fontecchio SA. Failure to eradicate vancomycinresistant enterococci in a university hospital and the cost of barrier precautions. Infect Control Hosp Epidemiol. 1998;19(9):647–52.

24. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309–18.

25. Zhen X, StålsbyLundborg C, Sun X, Zhu N, Gu S, Dong H. Economic burden of antibiotic resistance in China: a national level estimate for inpatients. Antimicrob Resist Infect Control. 2021;10(1):5.

26. Shrestha P, Cooper BS, Coast J, Oppong R, Do Thi Thuy N, Phodha T, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. Antimicrob Resist Infect Control. 2018;7(1):98.