ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 07, pp.54800-54804, July, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

CHALLENGE OF ANTIMICROBIAL RESISTANCE - POLICY RECOMMENDATIONS TO SAVE LIVES

[1]Dr. Shubha Ranjan Dutta, [2,*]Dr. Deepak Passi, [3]Dr. Laxman Malkunje, [4]Dr. Manisha Devi, [5]Dr. Sameer Gupta and [6]Dr. Yoshi panwar

[1]Department of Oral and Maxillofacial Surgery, M. B. Kedia Dental College, Chhapkaiya, Birgunj-2, Nepal
[2]Department of Oral and Maxillofacial Surgery, Inderprastha Dental College and Hospital, Sahibabad, Ghaziabad, India
[3]Department of Oral and Maxillofacial Surgery, S D Dental College and Hospital, Parbhani, Maharashtra, India
[4]Department of Oral and Maxillofacial Surgery, ESIC Dental College and hospital, Rohini, Delhi, India
[5]Private clinician, Dental Clinic, Rohini, Delhi, India
[6]Department of Oral and Maxillofacial Surgery, Maulana Azad Institute of Dental Sciences, New Delhi, India

ARTICLE INFO

Article History:
Received 17th April, 2017
Received in revised form
21st May, 2017
Accepted 19th June, 2017
Published online 31st July, 2017

Key words:

Antibiotic resistance (ABR),
Multidrug resistance (MDR),
Biofilm, Gastro instestinal tract (GIT),
Bacteriophages.

ABSTRACT

The extensive use of antibiotics since they were discovered has lead many bacterial species of human and animal origin to develop innumerable mechanisms that provide them resistant to some antibiotics and in a few cases to nearly all of them. There are numerous significant pathogens that are resistant to many antibiotic classes, and these multidrug resistant (MDR) organisms cause infections that are restricting treatment options and as a result compromising effective therapy. Thus, the emergence of antibiotic resistant bacteria population is a pertinent field of study in medical practice as well as in evolutionary and molecular biology. In recent times, the greatest challenge to the effective treatment of infectious disease, in the field of medicine, is the ability of all pathogens, without exception, to develop mechanisms for resistance to the action of antimicrobial drugs. Due to advancement in automation, clinical epidemiological research, and molecular biology, our wisdom of resistance has expanded at a confusing rate in recent years. Anyhow, antimicrobial resistance remains a significant medical, financial, and social issue. In this review we showcase some recent data and literature on molecular mechanisms of antibiotic resistance.

Citation: Dr. Shubha Ranjan Dutta, Dr. Deepak Passi, Dr. Laxman Malkunje, Dr. Manisha Devi, Dr. Sameer Gupta and Dr. Yoshi panwar, 2017. "Challenge of Antimicrobial Resistance - Policy Recommendations to Save Lives", *International Journal of Current Research*, 9, (07), 54800-54804.

INTRODUCTION

Globally antimicrobial resistance is now accepted as one of the major threats to human health (Walker *et al.,* 2009). The inherent mechanism developed by bacteria which render them resistant to certain antibiotics is called Antibiotic resistance (ABR). The antibacterial drug (antibiotic) is futile against resistant bacteria as they defy the effect of such drugs. On the other hand, antimicrobial resistance is a the resistance to drugs which is used for treatment of infection caused by other bacterial species, parasites and fungi (World Health Organisation). Multi drug resistance develops when microorganisms which are resistant to specific antimicrobial, develop resistance against others having identical pharmacological methods (Davies, 1996; Gold *et al.,* 1996).
In some hospitals there has been an alarming rise in the growth of Staphylococcus aureus resistant to customary conventional antibiotics (Park *et al.,* 2007; Manzur *et al.,* 2007). S. aureus is a bacterium that colonizes both the community and hospital settings (Estivariz *et al.,* 2003). Over a period of time Staphylococcus aureus (S. aureus) has confirmed its position as one of the most perpetual antibiotic resistant bacteria pathogens in society and hospital setup (Boucher and Corey, 2008). The rise in imputable mortality due to staphylococcal infections is related to Methicillin-resistant S. aureus (Cooper *et al.,* 2004). The data obtained via vigilance ambitions by the National Nosocomial Surveillance System (NNIS) and the European Antimicrobial Resistance Surveillance System (EARSS) shows that the rates of MSRA have been increasing globally (Fridkin *et al.,* 2002; Grundmann *et al.,* 2006; Tiemersma *et al.,* 2004; Turnidge and Bell, 2000).

Corresponding author: Dr. Deepak Passi,
Department of Oral and Maxillofacial Surgery, Inderprastha Dental College and Hospital, Sahibabad, Ghaziabad, India.

Resistance in hospitals and communities

Acinetobacter baumanii ,Hospital and community MDR strains of Mycobacterium tuberculosis, Enterococcus faecium,

Klebsiella pneumoniae, S. aureus, Enterobacter cloacae and Pseudomonas aeruginosa are the prominent universal examples of microorganisms which are resistant to hospital setup and prevalent in communities (Levy, 1998; Walsh and Amyes, 2004; Weinstein, 2001; Anonymous, 2002). More deaths are associated with MRSA than with methicillin-sensitive strains (Cosgrove *et al.,* 2003). Now a day's more cases of treatment failure are being reported due to persistently increasing, small percentage of MSRA which is showing low level resistance to even Vancomycin (the drug of choice) (Hiramatsu, 1998; Fridkin, 2001). To treat MSRA, vancomycin-resistant enterococci, and vancomycin- resistant S. aureus we have some recently developed drugs like daptomycin, linezolid and the streptogramin combination, dalfopristin/quinopristin. However some strains have sprouted with resistace against dalfopristin/quinopristin (Jones *et al.,* 1998; Meka and Gold, 2004).

Causes drug resistance

The two primary components of the resistance problem that we are facing today comprises of , the genetic makeup of the bacteria which renders them the resistance against antimicrobial drug and the second component is the antibiotic which inhibits the susceptible microorganisms and select or spare the ones which are resistant to that particular antibiotic (Levy, 1994 & 2000). The genes which provide resistance property to microorganisms against antibiotics can be transferred from one bacterium to another and to different ecological groups by means of conjugation, transduction, plasmids, transposons and bacteriophages, thus making this whole process of drug resistance quite portable (Levy, 2002 & 1989). In bacteria usually there is a gradual development from low level to mid level resistance through sequential mutation in chromosomes but in the presence of plasmids and transposons resistance is generally mediated at high level (Wang *et al.,* 2001; Schneiders *et al.,* 2003).

Behavior and the economics of antimicrobial resistance

Micro-organisms which are resistant to one antimicrobial agent can also develops resistance to others antimicrobial agents having similar pharmacology, leading to multi-drug resistance (Davies, 1996; Gold, 1996). It is a very crucial and evident fact that the treatment cost of infections caused by antimicrobial resistant organisms are far higher when compared to those which are susceptible to antibiotics, but the aptness of economics to this enigma of antimicrobial resistance extend far beyond (Cosgrove, 2006). The well certified and attested human nature for immediate delight and gratification is probably a very important contributor to resistance problem which we have not seen documented anywhere (Laibson, 1997; O'Donoghue and Rabin, 1999). In addition to all this excessive use antibiotics in aquaculture, food animals and agriculture are also playing a contributory factor to AR, with adverse results for preserving antimicrobial potency in human medicine (World Health Organization, 2010; Schneider and Garrett, 2009; Laxminarayan *et al.,* 2007).

Biofilm resistance to antibiotics and to host defense mechanisms

The biological properties of bacterial cells of mature biofilm differ from those of planktonic cells of the same bacterial strain. The ability of biofilm hidden bacteria to survive in nature, particularly in hostile microenvironment is due to these acquired properties. This adaptation has significant diagnostic and therapeutic consequences (Costeron *et al.,* 1999; Drenkard, 2003). Moreover, bacterial biofilms are resistant to phagocytosis and other mechanisms of innate and adaptive immune system (Park *et al.,* 2009). First, the increase in generation of antibiotics resistant phenotypes of bacteria is due to the increased number of mutations in bacterial genetic material which is directly linked to biofilm growth and these mutated genes which are involved in antibiotic resistance are associated with biofilm phenotype (Mah and O'Toole, 2001). Second, the production of the exopolysaccharide matrix contributes to an increased cell survival by slowing down antimicrobial diffusion speed. Third, the inclines of nutrient and oxygen availability are established by the differences in the density of bacteria throughout the biofilm, which leads to differences in metabolic activity among bacteria

Mechanisms of antibiotic resistance in gram-negative pathogens

Problematic pathogens such as P. aeruginosa and A. baumannii thrive because they employ a variety of antibiotic resistance mechanisms (Rice, 2006). The extraordinary cellular adaptability and survival of P. aeruginosa, honed over millennia, has now created states of pan-resistance at many medical centers (Bonomo and Szabo, 2006). The theatrical reduction in the antibiotic options against various infections that we are experiencing today is because of the plasmids which are responsible for ESBL production, these plasmids regularly carry genes that are responsible for various resistance mechanism and various ESBL enzymes target diverse antibiotic groups (Stein, 2005). Studies have shown that a shift in empirical therapy to the carbapenems, due to the presence of ESBL producers, is associated with emerging resistance in P. aeruginosa, A. baumannii, and the ESBL-producing organisms themselves (Rahal *et al.,* 1998; Meyer *et al.,* 1993).

Acquisition and spread of resistances

There have been studies which state the transfer of antibiotic resistance among LAB and bifidobacteria which indicate that resistant strains from animal and human colons are quite usual, that validate the transfer of resistance between commensal organisms in the intricate habitat of Gastro instestinal tract (GIT) (Ammor *et al.,* 2007). There is a saying that such microorganisms can carry genes that may lead to opportunistic infections (Tompkins *et al.,* 2008). The possibility for transmigration, colonization and harmful immunological consequences are the theoretical risks that have been brought up in relation to the use of probiotics with in human gastrointestinal tract (Snydman, 2008). Also there is availability of some data in relation to antimicrobial resistance pattern in food associated LAB such as lactobacilli but it is generally supported by non regulated approach and methodologies and/or it has been obtained only for a few number of strains (Huys *et al.,* 2008).

Biochemistry of antibiotic resistance

To understand the exact mechanisms of antibiotic resistance is significant achievement since lasts years and today there is plenty of information about bacteria drug resistance in medical literature (Mobashery and Azucena, 1999; Walsh, 2000). Resistance is created by few mechanisms:

- Inactivation of antibiotic - It is due to direct inactivation of the active antibiotic molecule (Wright, 2005)
- Modification of Target – It is due to alteration in the sensitivity to the antibiotic by modification of the target (Lambert, 2005)
- Efflux pumps and outer membrane permeability changes – Reduction in the concentration of drug without modification of the compound itself (Kumar and Schweizer, 2005)
- Target bypass mechanism– Microrganism become refractory to specific antibiotics by bypassing the inactivation of a given enzyme.

Genetics of antibiotic resistance

Resistance to antibiotics by bacteria can be its intrinsic property or it may be acquired. Mutation of cellular genes, attainment of foreign resistance genes or a combination of both can be the reasons for acquired bacterial antibiotic resistance. Thus acquired antibiotic resistance can be due to mutation in different chromosomal loci and it can be through transfer of resistance genes from other microorganisms (horizontal gene transfer) (Aminov and Mackie, 2007).

Genetics of resistance

Several studies have been put forward related to genetic aspect of development of antibiotic resistance, such as heterologous expression, mutation, HGT and gene pick up. All these studies started due to the widespread appearance and distribution of antibiotic resistant pathogen in the community (Bushman, 2002; Funnell *et al.,* 2004; White *et al.,* 2005). The strains of bacterial pathogen that were isolated prior to "antibiotic era" demonstrated that plasmids associated with antibiotic resistant were common but their genes were unique (Datta *et al.,* 1983). This was in consistent with the concept of the recent evolution of antibiotic resistance plasmids and multi resistant strains. The various genetic mechanisms that are responsible for evolution of antibiotic-resistant populations have been described by laboratory studies; the roles of plasmids, phages, and transformation are well established, but other processes may exist. For example, in intricate mixed microbial community bacterial cell-cell fusion might be preferred, for example those found in biofilms (Gillings *et al.,* 2009). But, there can be cases where partial protection is provided from an antagonist by low level expression of resistant gene in a new host (Allou *et al.,* 2009); subsequent gene tailoring by mutation with selection would lead to improved expression. Gene uptake is promoted due to physical vicinity by immobilization on agar surface or filter and by various other environmental factors. It is worth noting that antibiotics, especially at sub inhibitory concentrations, may facilitate the process of antibiotic resistance development (Davies *et al.,* 2006). In the development of recombinant DNA methods which are said to be the experimental foundation of modern biotechnology industry, studies related to antibiotic resistance mechanisms and their associated gene transfer in pathogens have played a very vital role (Helinski, 2004).

Bacteriophage therapy: A potential solution for the antibiotic resistance crisis

There has been surge in interest for finding alternatives to conventional antimicrobials due to emergence of multiple drug resistant bacteria. The use of bacteriophages as antimicrobial agents can be a feasible replacement option for antibiotics. Phage therapy is an important alternative to antibiotics in the current era of drug resistant pathogens. Phage preparation has been used in effective elimination of pathogenic bacteria which cause gastrointestinal diseases and this ha been proved by numerous studies that aimed primarily on the therapeutic use of phages (Marinelli *et al.,* 2012). To combat livestock associated pathogens such as toxinogenic E. coli, Campylobacter, and Salmonella, the current strategies that are followed today focus on targeting the bacteria in animals before slaughtering them. These strategies are direct extensions of "classical" phage therapy approach which follow the same principle (Sheng *et al.,* 2006). Western countries (Kim *et al.,* 2007). There can be exploitation of phages for their use as a delivery system for bacterial molecules due to their specificity of targeting. Engineered non lytic phages produce antimicrobial proteins which were effective in E. coli systematic mouse model (Westwater *et al.,* 2003). Treatment of MSRA by using phages has been reported by many studies (Schless, 1932), which can be achieved by local application for local infections or, if required for systemic infections, we can do it with substantially more caution and with more systemic dosing intraperitoneally (Straub and Applebaum, 1933). Also, the US Food and Drug Administration have long postponed the process of issuing workable guidelines to companies which will speed up the process of planning antibiotic clinical trials. Moreover, physicians are reluctant in prescribing a new antibiotic to their patients which is fresh in market, due to fear of drug resistance. They reserve it only for worst cases (Facts about Antibiotic Resistance, 2012).

Conclusion

Antibiotic resistance is one of the more confusing problems the FDA has faced. However, the FDA is in a peculiar position to play a positive and definite role. For one, the FDA is an organization that deals with all legal, social and judicial issues related to drugs. People will expect from the FDA to deal with the enigma involving antibiotics because FDA has that expertise and authority over drugs. Second, unlike other agencies, FDA is special as it has public respect and faith on it. The FDA can act as a mediator where physicians, scientists and manufacturers can come to a common platform to reach solutions to this intricate problem. In bringing different groups together on this controversial topic of antibiotic resistance, the role of FDA will be crucial. Antibiotic resistance poses a threat to mankind. It's not the matter whether this threat of menace is indirect and argued as the harm feared because of genetically engineered food or animal drugs or more direct and straight forward, as it is in the case of irrational use of antibiotics by people, the FDA can play a pivot role in curbing this threat. The only solution is to act promptly before the potential and actual damage is done.

REFERENCES

Allou, N., E. Cambau, L. Massias, F. Chau, and B. Fantin. 2009. Impact of low-level resistance to fluoroquinolones due to qnrA1 and qnrS1 genes or a gyrA mutation on ciprofloxacin bactericidal activity in a murine model of Escherichia coli urinary tract infection. *Antimicrob. Agents Chemother.,* 53:4292–4297.

Aminov, R.I., R.I. Mackie, 2007. Evolution and ecology of antibiotic resistance genes, *FEMS Microbiol. Lett.* 271, 147– 161.

Ammor, M.S., Belén Flórez, A. and Mayo, B. 2007. Antibiotic resistance in non-enterococcal lactic acid bacteria and bifidobacteria. *Food Microbiology,* 24(6): 559-570.

Anonymous, 2002. European Antimicrobial Resistance Surveillance System. EARSS Annual Report 2002.

Bonomo, R.A., Szabo, D. 2006. Mechanisms of multidrug resistance in Acinetobacter species and Pseudomonas aeruginosa. *Clin Infect Dis.,* 43(Suppl 2):S49–S56.

Boucher, H.W., Corey, G.R. 2008. Epidemiology of methicillin-resistant Staphylococcus aureus. *Clinical Infectious Diseases,* 46(Suppl 5):S344–S349.

Bushman, F. 2002. Lateral DNA transfer. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

Cooper, B.S., Medley, G.F., Stone, S.P., Kibbler, C.C., Cookson, B.D., Roberts, J.A., Duckworth, G., Lai, R., Ebrahim, S. 2004. Methicillin-resistant Staphylococcus aureus in hospitals and the community: stealth dynamics and control catastrophes. Proceedings of the National Academy of Sciences of the United States of America 101:10223–10228.

Cosgrove, S.E. 2006. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin. Infect. Dis.,* 42, S82-S89.

Cosgrove, S.E. et al. 2003. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. *Clin. Infect. Dis.*, 36, 53–59.

Costeron, J.W., Stewart, P.S., Greenberg, E.P. 1999. Bacterial biofilms: a common cause of persistent infections. *Science*, 284: 1318-1322.

Datta, N., and V. M. Hughes, 1983. Plasmids of the same Inc groups in enterobacteria before and after the medical use of antibiotics. *Nature*, 306:616–617.

Davies, J. 1996. Bacteria on the rampage. *Nature*, 383, 219-220.

Davies, J. 1996. Bacteria on the rampage. *Nature*, 383, 219-220.

Davies, J., G. B. Spiegelman, and G. Yim.2006. The world of subinhibitory antibiotic concentrations. *Curr. Opin. Microbiol.,* 9:1–9.

Drenkard, E. 2003. Antimicrobial resistance of Pseudomonas aeruginosa biofilms. *Microbes Infect,* 5: 1213-1219.

Estivariz, C.F., Park, S.Y., Hageman, J.C., Dvorin, J., Melish, M.M., Arpon, R., Coon, P., Slavish, S., Kim, M., McDougal, L.K., Jensen, B., McAllister, S., Lonsway, D., Killgore, G., Effler, P.E, Jernigan, D.B. 2003. Emergence of community-associated methicillin resistant Staphylococcus aureus in Hawaii, 2001-2003. *J Infect.,* 54: 349-357.

Facts about Antibiotic Resistance, 2012. Infectious Diseases Society of America. Available at: http://www.idsociety.org/AR_Facts. Accessed on December 12, 2012.

Fridkin, S.K. 2001. Vancomycin-intermediate and -resistant Staphylococcus aureus: what the infectious disease specialist needs to know. *Clin. Infect. Dis.,* 32, 108–115.

Fridkin, S.K., Hill, H.A., Volkova, N.V., Edwards, J.R., Lawton, R.M., Gaynes, R.P., McGowan, J.E. Jr, 2002. Intensive Care Antimicrobial Resistance Epidemiology (ICARE) Project Hospitals, Temporal changes in prevalence of antimicrobial resistance in 23 US hospitals. Emerging Infectious Diseases, 8:697–701.

Funnell, B. E., and G. J. Phillips (ed.).2004. Plasmid biology. ASM Press,Washington, DC

Gillings, M. R., M. P. Holley, and H. W. Stokes, 2009. Evidence for dynamic exchange of qac gene cassettes between class 1 integrons and other integrons in freshwater biofilms. *FEMS Microbiol. Lett.,* 296:282–288.

Gold, H.S., Mollering, R.D. 1996. Antimicrobial-drug resistance. *N. Engl. J. Med.,* 335, 1445-1453.

Gold, H.S., Mollering, R.D. 1996. Antimicrobial-drug resistance. *N. Engl. J. Med.,* 335, 1445-1453.

Grundmann, H., Aires-de-Sousa, M., Boyce, J., Tiemersma, E. 2006. Emergence and resurgence of meticillin-resistant Staphylococcus aureus as a public-health threat. The Lancet 368:874–885.

Helinski, D. R. 2004. Introduction to plasmids: a selective view of their history, p. 1–21.In B. E. Funnell and G. J. Phillips (ed.), Plasmid biology. ASM Press, Washington, DC.

Hiramatsu, K. 1998. Vancomycin resistance in staphylococci. Drug Resist. Updat. 1,135–150.

Huys, G., D'Haene, K., Danielsen, M., Mättö, J., Egervärn, M. and Vandamme, P. 2008. Phenotypic and molecular assessment of antimicrobial resistance in Lactobacillus paracasei strains of food origin. *Journal of Food Protection,* 71 (2): 339-344.

Jones, R.N., Ballow, C.H., Biedenbach, D.J., Deinhart, J.A. and Schentag, J.J. 1998. Antimicrobial activity of quinupristin-dalfopristin (RP 59500, Synercid) tested against over 28,000 recent clinical isolates from 200 medical centers in the United States and Canada. *Diagn. Microbiol. Infect. Dis.* 31, 437–451.

Kim, K.P., Klumpp, J., Loessner, M.J. 2007. Enterobacter sakazakii bacteriophages can prevent bacterial growth in reconstituted infant formul a. *Int J Food Microbiol.,* 115: 195-203.

Kumar, A., H.P. Schweizer, 2005. Bacterial resistance to antibiotics: Active efflux and reduced uptake, *Adv. Drug Deliv. Rev.,* 57, 1486–1513.

Laibson, D. 1997. Golden eggs and hyperbolic discounting. *Quart. J. Econ.,* 112, 443-477.

Lambert, P.A. 2005. Bacterial resistance to antibiotics: Modified target sites, *Adv. Drug Deliv. Rev.,* 57. 1471–1485.

Laxminarayan, R., Malani, A., Howard, D., Smith, D. 2007. Extending the Cure: Policy responses to the growing threat of antibiotic resistance. Resources for the Future (RFF) Report; RFF: Washington, DC, USA. Available online: http://www.rff.org/RFF/Documents/ETC_fullreport.pdf/ (accessed on 24 February 2010).

Levy, S. The Antibiotic Paradox: How Misuse of Antibiotics Destroys their Curative Powers (Perseus Cambridge, 2002).

Levy, S.B. & Miller, R.V. (eds.) Gene Transfer in the Environment (McGraw Hill, New York, 1989).

Levy, S.B. 1994. Balancing the drug resistance equation. *Trends Microbiol.,* 2, 341–342.

Levy, S.B. 1998. The challenge of antibiotic resistance. Sci. Am. 278, 46–53.

Levy, S.B. 2002. The 2000 Garrod lecture. Factors impacting on the problem of antibiotic resistance. *J. Antimicrob. Chemother.* 49, 25–30.

Mah, T.F., O'Toole, G.A. 2001. Mechanisms of biofilm resistance to antimicrobial agents. *Trends Microbiol.,* 9: 34-39.

Manzur, A., Vidal, M., Pujol, M., Cisnal, M., Hornero, A., Masuet, C., Peña, C., Gudiol, F., Aziza, J. 2007. Predictive factors of methicillin resistance among patients with Staphylococcus aureus bloodstream infections at hospital admission. *J Hosp Infect.,* 66: 135-141.

Marinelli LJ, Fitz Gibbon S, Hayes C, Bowman C, Inkeles M, Loncaric A, Russell DA, Jacobs Sera D, Cokus S, Pellegrini M, Kim J, Miller JF, Hatfull GF, Modlin RL (2012) Propionibacterium acnes Bacteriophages Display Limited Genetic Diversity and Broad Killing Activity against Bacterial Skin Isolates. *mBio.,* 3: 5-12

Meka, V.G. and Gold, H.S. 2004. Antimicrobial resistance to linezolid. *Clin. Infect. Dis.,* 39, 1010–1015.

Meyer, K.S., Urban, C., Eagan, J.A., Berger, B.J., Rahal, J.J. 1993. Nosocomial outbreak of Klebsiella infection resistant to late-generation cephalosporins. *Ann Intern Med.,* 119(5):353–358.

Mobashery, S., E.F. Azucena, 1999. Bacterial Antibiotic Resistance. In: Encyclopedia of Life Sciences, Nature Publishing Group, London, UK, (http://www.els.net).

O'Donoghue, T., Rabin, M. 1999. Doing it now or later. *Amer. Econ. Rev.,* 89, 103-124.

Park, D.W., Kim, M.J., Yang, J.A., Jeong, H.W., Sohn, J.W., Chun, B.C. 2007. Risk factors for isolation of low-level mupirocin-resistant versus - susceptible methicillin-resistant Staphylococcus aureus from patients in intensive care units. *J Infect,* 54: 337-342.

Park, Q.M., Young, R.L., Poch, K.R., et al. 2009. Neutrophil enhancement of Pseudomonas aeruginosa biofilm development: human F-actin and DNA as targets for therapy. *J Med Microbiol.,* 58: 492-502.

Rahal, J.J., Urba, C., Horn, D., Freeman, K., Segal-Maurer, S., Maurer, J., et al. 1998. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial Klebsiella. *JAMA*, 280(14):1233–1237.

Rice, L.B. 2006. Challenges in identifying new antimicrobial agents effective for treating infections with Acinetobacter baumannii and Pseudomonas aeruginosa. *Clin Infect Dis.,* 43(Suppl 2):S100–S105.

Schless, R.A. 1932. Staphylococcus aureus meningitis: treatment with specific bacteriophage. *Am J Dis Child.,* 44: 813-822.

Schneider, K., Garrett, L. 2009. Non-therapeutic Use of Antibiotics in Animal Agriculture, Corresponding Resistance Rates, and What Can be Done About It; Council on Foreign Relations. Center for Global Development: Washington, DC, USA, 2009; Available online: http:// www.cgdev.org/content/article/detail/1422307/#v/(accesse d on 24 February 2010).

Schneiders, T., Amyes, S.G.B. & Levy, S.B. 2003. Role of AcrR and RamA in fluoroquinolone resistance in clinical Klebsiella pneumoniae isolates from Singapore. Antimicrob. *Agents Chemother.,* 47, 2831–2837.

Sheng, H., Knecht, H.J., Kudva, I.T., Hovde, C.J. 2006. Application of bacteriophages to control intestinal Escherichia coliO157:H7levels in ruminants. *Appl Environ Microbiol.,* 72: 5359-5366.

Snydman, D.R. 2008. The safety of probiotics. Clinical Infectious Diseases 46 (SUPPL. 2).

Stein, G.E. 2005. Antimicrobial resistance in the hospital setting: impact, trends, and infection control measures. *Pharmacother*, 25(10 Pt2):44S–54S.

Straub, M.E., Applebaum, M. 1933. Studies on commercial bacteriophage products. J Am Med Assoc 100: 110-113.

Tiemersma, E.W., Bronzwaer, SLAM., Lyytik¨ainen, O., Degener, J.E., Schrijnemakers, P., Bruinsma, N., Monen, J., Witte, W., Grundman, H. 2004. European Antimicrobial Resistance Surveillance System Participants, Methicillin-resistant staphylococcus aureus in Europe, 1999–2002. *Emerging Infectious Diseases,* 10:1627–1634.

Tompkins, T.A., Hagen, K.E., Wallace, T.D. and Fillion-Forté, V. 2008. Safety evaluation of two bacterial strains used in asian probiotic products. *Canadian Journal of Microbiology,* 54 (5): 391-400.

Turnidge, J.D., Bell, J.M. 2000. Methicillin-resistant Staphylococcal aureus evolution in Australia over 35 years. *Microbial Drug Resistance,* 6:223–229.

Walker, B., Barrett, S., Polasky, S., et al. 2009. Environment. Looming globalscale failures and missing institutions. *Science*, 325:1345–6.

Walsh, C. 2000. Molecular mechanisms that confer antibacterial drug resistance, *Nature*, 406, 775–781.

Walsh, F.M. and Amyes, S.G.B. 2004. Microbiology and drug resistance mechanisms of fully resistant pathogens. *Curr. Opin. Microbiol.*, 7, 439–444.

Wang, H., Dzink-Fox, J.L., Chen, M. & Levy, S.B. 2001. Genetic characterization of highly fluoroquinolone-resistant clinical Escherichia coli strains from China: role of acrR mutations. Antimicrob. Agents Chemother. 45, 1515–1521.

Weinstein, R.A. 2001. Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. *Emerg. Infect. Dis.* 7, 188–192.

Westwater, C., Kasman, L.M., Schofield, D.A., Werner, P.A., Dolan, J.W., Schmid, M.G., Norris, J.S. 2003. Use of genetically engineered phage to deliver antimicrobial agents to bacteria: an alternative therapy for treatment of bacterial infections. *Antimicrob Agents Chemother,* 47: 1301-1307

White, D. G., M. N. Alekshun, and P. F. McDermott (ed.). 2005. Frontiers in antimicrobial resistance: a tribute to Stuart B. Levy. ASM Press, Washington, DC

World Health Organisation, Antimicrobial resistance Fact sheet, http://www.who.int/mediacentre/factsheets/fs194/en/

World Health Organization. Use of antimicrobials outside human medicine and resultant antimicrobial resistance in humans. Fact sheet N°268; WHO: Geneva, Switzerland, 2002 Available online: http://www.who.int/mediacentre/ factsheets/fs268/en/ (accessed on 24 February 2010).

Wright, G.D. 2005. Bacterial resistance to antibiotics: Enzymatic degradation and modification, *Adv. Drug Deliv. Rev.,* 57, 1451–1470.

****