Free combating antimicrobial resistance: a public health problem argumentative es...

Technology, Development

Introduction: Prior to the discovery of penicillin by Alexander Flemming millions of people worldwide succumbed to common infections. The influenza pandemic of 1918-1919 killed nearly 30 million people, which was higher than the population that succumbed to the First World War. Following the discovery of penicillin in 1928, a number of other antimicrobial agents were discovered from natural sources or synthesized in laboratories that led to treatment of many infectious diseases worldwide. It was believed at one point that these magic bullets could be used to target and kill any and all kinds of pathogenic microorganisms. However, soon after the widespread use of antimicrobial drugs occurred, most common of which include ‘ antibiotics’, the existence of resistance to these drugs was observed. Resistance to antimicrobial agents can be a natural phenomenon for some species. However, most incidence of drug resistance occur as result of two processes; genetic mutation in the microorganism or acquiring of resistance from other species. A key factor affecting the development of drug resistance is the duration of treatment. Many physicians recommend the completion of antibiotic regimen on conservative side, while many others believe that the medication can be stopped following clearance of symptoms. This reports compares and evaluates the effectiveness of these treatment strategies.

Description: The use of antibiotics and other antimicrobial agents is highly prevalent in the developing world. Patients do not need prescription from a doctor to get various antimicrobial agents. People consume antibiotics for treatment of cold, where antibiotics have no effect. Even in the developed world a lot antimicrobial agents are available in the form of household

cleaning products and animal feed. In addition to the over- use of medication non compliance, either in terms of time or dosage is another factor that can lead to ineffective treatment causing resistance.

Antibiotic and anti-viral resistance is the probably the greatest health concern of the 21st century. In some instances, resistance occurs when a sub-population of the bacteria develops resistance towards one or more antibiotics; however some bacteria develop resistance to almost all commonly known antibiotic agents, resulting in their becoming multidrug resistant (Livermore, 2004). These MDR organisms are commonly called the ‘ superbugs’. These superbugs can become resistant to not only first-line agents, but can develop resistance against second and third-line antibiotic drugs also. In India there have been reports of totally drug resistant (TDR) tuberculosis that are resistant to all known and available antibiotic agents. The resistance to antimicrobial agents can arise simply by means of ‘ selection pressure’. The phenomenon of selection pressure occurs as the susceptible bacteria are killed following treatment with an antibiotic agent allowing proliferation of the resistant bacteria. Some of the other commonly observed molecular mechanisms of antibiotic resistance include, modification of the structure of the antibiotic target protein, efflux or removal of antibiotic drug outside the bacterial cell by use of drug ejecting membrane proteins, molecular bypass in which an ubiquitous or key step or substrate is worked around by which the cell inhibiting antibiotic activity is circumvented and modification to the drug molecule is made rendering it inactive (Coates, 2012). The bacteria also acquire resistance from other bacteria by horizontal transfer of genes. The horizontal transfer of resistance

between bacteria can take place by conjugation, transformation or transduction. Plasmids or transposons that carry resistance genes can also transmit resistance gene between microorganisms (Wright, 2011). Virus like bacteria become resistant by acquiring genetic mutations. A single nucleotide mutation can alter a key amino acid sequence making the virus resistant to the anti-viral therapy. A selection pressure is also observed in virus where a sub population with less susceptibility to anti-viral agent gains a survival advantage. Viruses like HIV, influenza change constantly and have a greater possibility of developing resistance.

One main reason behind antibiotic resistance is failure of compliance. A large percentage of patients (10-44%) do not finish a given course of antibiotic as their symptoms get resolved. They simply stop taking the medicine within 2-3 days of improvement of their symptoms. However, in some infections the pathogen still exists even after the symptoms have resolved. The failure to take medicine within a given time and dosage results in suboptimal antibiotic concentration that raises the possibility of antibiotic resistance. An incomplete antibiotic course results in survival of the resistant pathogen which can relapse with more severe infection that is very difficult to treat. It has been shown that people are more compliant with the medication when they are required to take the medicine once daily as opposed to twice daily. A clinical study published in antimicrobial agents and chemotherapy in 1998 examined the relation between the pharmacokinetic parameters of the antibiotic and development of resistance among patients from nosocomial respiratory infections. In a sample of 128 pathogens, 32 were initially sensitive to antibiotic treatment however they developed resistance during

the study. It was demonstrated that the resistance to antimicrobial agents increased when the AUC was low as a result of suboptimal antimicrobial concentration (Thomas, et al., 1998). Another study published in the journal Age and Ageing looked at the effect of offering 1 single dose of trimethoprim vs. offering the medication for 5 days in 96 elderly patients with UTI. It was observed that a single dose had a 7 day cure rate of 67% as opposed to 95% with a five day course (Lacey et al., 1981). Finally, a stud in JAMA demonstrated the significance of complying with anti- HIV therapy. It was demonstrated that some patients who were on a triple anti-viral regimen failed to comply to didanosine schedule had resistance develop in nevirapine and zidovudine as well. Higher viral RNA levels were also observed due to the drug resistance (Montaner, Reiss, & Cooper, 1998). These studies demonstrated that it is vital for the antibiotic and antiviral drugs to reach the optimal concentration for an optimum time period to exert full antimicrobial activity and symptom resolution does not necessarily mean that all microbes have been terminated.

The other explanation (contrary to the first) for clinical development of antimicrobial (antibiotic and antiviral) resistance is the indiscriminate prescription and use of these drugs. It has been demonstrated that intake of even one dose of antibiotic drug can lead to increased resistance in the target microorganism for up to a year. A high proportion of patients who are prescribed antibiotics and antiviral agents do not really need them and increase the risk for resistance development. A number of published studies have demonstrated that the length of antibiotic treatment is correlated with increase in resistance in patients. A number of physicians advise against the

use of prescription if the patients are asymptomatic for 72 hours. It is recommended by many physicians that the medication should be prescribed for the lower timeline spectrum of clinically effective treatment. A study published in Archives of Internal medicine in 2004 looked at the effectiveness of levofloxacin in 87 patients with uncomplicated cellulitis. It was observed that 98% of patients who were either on 5 and 10 day antibiotics course had no recurrence of symptoms. The shorter 5 day course was equally effective in treating the infection as the10 day treatment course (Hepburn et al., 2004). Another meta analysis study was published in looking at the effect of treating " group A streptococcal (GAS) tonsillopharyngitis" with oral antibiotics for a period of either 5 or 10 days. It was observed that patients had a good treatment rate with a 10 day course of penicillin with Odds ratio of 1. 67 and 95% confidence; however when cephalosporin was offered for 3-5 days an improved cure rate (compared to 10 day penicillin) was observed(Casey, & Pichichero, 2005). This study demonstrates that selection of a potent appropriate antibiotic can result in an effective treatment in a shorter duration. It is also known facts that in many infectious conditions, such as the cold and the flu, the virus have to complete their course and subsequently resolve on their own. Treatment with an antiviral might not demonstrate any significant improvement as opposed to treatment with placebo. In a study performed on asthmatic children it was demonstrated that placebo demonstrated similar effectiveness as the flu vaccine (Bueving, et. al, 2004). A clinical study published in 1997 in Lancet demonstrated that treatment with an antibiotic, amoxicillin led to clinical improvement in 83% of patients compared to 77% in placebo treatment in

sinusitis patients (van Buchem, Knottnerus, Schrijnemaekers, & Peeters, 1997).

Discussion: The resistance to antimicrobial agents and specifically to antibiotics is a growing problem worldwide. A task force was formed to fight the war against antimicrobial resistance by the center of disease control (CDC). In the US nearly 2 million people get infected with bacteria that are resistant to one or more antibiotic agents. The issue of antiviral resistance also needs to be carefully addressed as it is usually observed in patients who are already immunocompromised. After performing literature review on this issue, the most important reason causing antimicrobial resistance, I believe is the indiscriminate and unnecessary prolonged use of antimicrobial agents. I think antibiotics should be taken for the minimal optimal period of time for non life threatening conditions. The patient should be reexamined by the physician to determine the appropriateness of stopping the medication or need of longer treatment. The medication can be safely discontinued for many infections when no symptoms are present for seventy two hours after intake of last dose. The termination of the treatment should be the decision of the doctor and not simply the choice of the patient. It also needs to be emphasized that there are some more serious infectious diseases such as HIV where completion of the treatment course is vital for the patient health. The use of a combination of anti-viral agents is a useful strategy as it can completely wipe out the presence of virus thereby preventing resistance development. However, in the combination treatment non compliance to even 1 drug can result in resistance against all combination agents. Adequate patient education can prevent antimicrobial resistance problem to

some extent. It is imperative that people be informed and educated about the significance of taking antimicrobial drugs properly and only for the optimal time period.

Conclusion: It is critical to understand the methodologies and clinical practices that can preserve the efficacy and activity of antimicrobial agents for a long time and prevent resistance.

References

Bueving, H. M., Roos M. D. Bernsen, Johan C. de Jongste, Lisette W. A. van Suijlekom-Smit, Guus F. Rimmelzwaan, Albert D. M. E. Osterhaus, Maureen P. M. H. Rutten-van Mölken, Siep Thomas, and Johannes C. van der Wouden. (2004)Influenza Vaccination in Children with Asthma. American Journal of Respiratory and Critical Care Medicine, 169, No. 4, 488-493.

Casey, J. R. & Pichichero, M. E. (2005). Metaanalysis of Short Course Antibiotic Treatment for Group A Streptococcal Tonsillopharyngitis. Pediatrics Inf. Dis. Journal. 909-917

Coates, A. R. M (2012). Antibiotic Resistance. Handbook of experimental pharmacology. NY. (ed.)68-87

Hepburn, M. J., Dooley, D. P., Skidmore, P. J., Ellis, M. W., Starnes, W. F., & Hasewinkle, W. C. (2004). Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med. 164: 1669–1674

Lacey RW, Simpson MHC, Lord VL, Fawcett C, Button ES, Luxton DEA, Trotter, I. S (1981). Comparison of Single-Dose Trimethoprim with a Five-day Course for the Treatment of Urinary Tract Infections in the Elderly. Age and Ageing 10 (3): 179-185

Livermore, D. M. (2004) The need for new antibiotics. Clin Microbiol Infect 10(suppl 4): 1–9

Montaner, J. S. G., Reiss, P & Cooper, D. (1998). A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. JAMA. 279: 930-937.

Pechere, J. C. (2001). Patients' Interviews and Misuse of Antibiotics. Clinical Infectious diseases. 33, S170-S173

Thomas, J., Forrest, A., Bhavnanai, S. M., Hyatt, J. M. Cheng, A., Ballow, C. H. & Schentag, J. J. (1998). Antimicrob Agents Chemother. 42(3): 521–527.

van Buchem, F. L., Knottnerus, J. A., Schrijnemaekers, V. J., & Peeters, M. F. (1997). Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet, 349, 9053, 683-687

Wright, G. D. (2011). Molecular mechanisms of antibiotic resistance. Chem. Commun. 47, 4055-4061