DOI: 10.55522/ijti.V1I2.0007 *September - October 2023, Vol. 1 - Issue 2* *ISSN NO: 3048 - 4626*

IJTI | INTERNATIONAL JOURNAL OF THERAPEUTIC INNOVATION

Review article

Antibiotic resistance: overuse of antibiotics, context and potential solutions

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Received - 18-05-2023**, Revised** - 15-08-2023, **Accepted** - 10-10-2023 **(DD-MM-YYYY)**

Refer this article

Priyanka Joshi, Dinesh Kumar Bajpai. Antibiotic resistance: overuse of antibiotics, context and potential solutions, September - October 2023, V 1 - I 2, Pages - viii – xv. Doi: https://doi.org/10.55522/ijti.V1I2.0007.

ABSTRACT

Antimicrobial resistance is a global public health challenge, which has been accelerated by the overuse of antibiotics worldwide. Increased antimicrobial resistance is the cause of severe infections, complications; longer hospital stays, and increased mortality. Steps must be taken to reverse the damage that has already been done and prevent further resistance from developing. This work will examine the context and societal situations that led to this acceptance of antibiotic overuse and misuse seen in both healthcare professionals and the public, the biochemical and genetic pathways that allow a microbe to develop drug resistance, the consequences that could follow if this trend of antibiotic overuse is allowed to continue and the various methods and solutions that have been suggested to prevent and reverse this problem.

Keywords: Antibiotic resistance, Antimicrobial resistance, Overuse of Antibiotics, Evolution.

INTRODUCTION

Many physicians and other health care professionals prescribe antibiotics with little to no caution. It has become expected practice to prescribe antibiotics for common and minor bacterial infections such as Streptococcus pyogenes, the bacteria responsible for strep throat, which would normally be eliminated in approximately ten days by a healthy immune system. Antibiotic overuse is leading to drug resistance in microbes, resulting in bacteria that are impossible to treat with currently available antimicrobial medications.

Steps must be taken to reverse the damage already done and prevent further resistance from developing. This work aims to examine the context and societal situations that led to this acceptance of antibiotic overuse and seeming ignorance towards the issue seen in both healthcare professionals and the public, the biochemical and genetic pathways that allow a microbe to develop drug resistance, the various methods that experts have suggested to prevent and reverse this problem and the consequences that could follow if this trend of antibiotic overuse is allowed to continue. This manuscript will propose several solutions to this growing issue.

Brief history of antibiotics and antibiotic resistance

The first case of methicillin-resistant Staphylococcus aureus (MRSA) was identified in the United Kingdom in 1962. Vancomycin was used in 1972 for the treatment of methicillin resistance in both S. aureus and coagulase-negative staphylococci. In 1979 and 1983, cases of vancomycin resistance were reported in coagulase-negative staphylococci. Antibiotic development continued and increased throughout the following decades. Countless antibiotics are available for medical use: cephalosporins, tetracyclines, aminoglycosides, monobactam, carbapenems, macrolides, streptogramins, and dihydrofolate reductase inhibitors were all available in the early 1990s for the treatment of bacterial disease [2]. Penicillin, the first antibiotic discovered by Dr. Alexander Fleming in 1928 by fortunate accident [1] was believed to be a miracle drug,

saving the lives of thousands of soldiers in World War II and improving the quality of life for the public. However, shortly thereafter, penicillin resistance became a substantial clinical problem. In response, new beta-lactam antibiotics were discovered, developed, and deployed. Today, there are well over 100 classes of antibiotics, though most fall into the category of penicillin derivatives.

The plethoras of antibiotics now available are widely and readily prescribed by medical providers. All are being used in an alarmingly loose way that is fueling and contributing to the modern-day antibiotic crisis. This crisis is a result of many factors: pharmaceutical companies, prescribers, patients, agriculture, and the genetic abilities of bacteria.

Context leading to antibiotic resistance

Role of the pharmaceutical industry

Pharmaceutical companies discover, develop, and market new antibacterials. Clearly, it is in the best interests of pharmaceutical companies to promote the wide use of antibacterials in order to justify research and development costs. Big products produce big profits for companies and ensure the companies' commitment to that area of medicine. This fact, coupled with the willingness of some physicians to prescribe the latest antibacterial, has undoubtedly increased the frequency of resistance. Between 1988 and 2000, Antibiotics were plentiful and profitable during these years. Animal testing laws in particular were much easier to navigate around. Since 2003, only one new antibiotic per year on average has been approved by the FDA for medical treatment. The largest names in pharmaceuticals, including Wyeth, Eli Lilly, Procter and Gamble, Roche, Abbott Laboratories, and Aventis have either largely reduced their antibiotic research and development or terminated their antibiotic research entirely.

It is simply not as profitable to focus on antibiotics as other areas of research. These companies have shifted their research and development focus to medications with wider markets and higher profit margins. Drugs that are used in the treatment of chronic conditions are of particular interest to big pharmaceutical companies. Antibiotics are much more difficult and expensive to manufacture than medications for conditions such as diabetes, high cholesterol, depression, and arthritis. Antibiotics are far less profitable than other so-called maintenance medications. Antibiotics are only used for a short duration and will only be utilized periodically during a person's lifetime. It is understandably difficult to make any money on the development of a medication that will only be used for approximately ten days at a time every other year, especially when antibiotics are so hard to find, develop, and test. To make a long story short, there is a lot more money to be made from so-called blockbuster drugs than from antibiotics that will only be used periodically and for a short duration by patients. Pharmaceutical companies are very invested in the antibiotics that have already been produced. They desire to keep making money off the work they have already done [2].

A study published in the PLoS Medical Journal found that pharmaceutical companies spent roughly 1.6 billion dollars in 1998 to promote antibiotics to customers, hospitals, doctor's offices, and pharmacies [3]. This money could easily be spent in the pursuit of new antibiotics or on safe antibiotic usage campaigns. Sadly, it is being used only to market and encourage the further use of already well-established antibiotics.

Pharmaceutical companies have little incentive to investigate and produce new antimicrobial medications. They can make considerably higher profits by developing drugs for other conditions, especially those that are widespread and chronic such as diabetes and high blood pressure.

Role of medical doctors

Physician's decisions about prescriptions are very complex and determined by many factors. Clearly, in cases of infectious disease, the decision to treat is based on the diagnosis of a bacterial infection or the likelihood of a bacterial infection. The dose and type of antibacterial are chosen based on the likely pathogen and its local in vitro susceptibility, the severity of the infection, and the condition of the patient. In most situations, neither the pathogen nor its in vitro susceptibility is known. Antibiotic use is increasing substantially worldwide, though it is increasing to the largest degree in the United States and other highly developed countries [4].

Antibiotic over prescription is understood to be very expensive and known to contribute to the growing resistance of bacteria. Antibiotics are being vastly over-used and misused and are often prescribed for viral illnesses that will not be helped by antibiotic medication. Prescribing antibiotics for self-limiting illnesses is perhaps the main

reason for the emergence of antibiotic-resistant bacteria in the community setting [5]. It is perplexing to consider the reasons physicians, who are typically very highly educated individuals, choose to prescribe medications that will do more harm than good for the patient and society as a whole in the long run. This frightening trend has its roots in many factors. Despite their reasons, the truth remains that antibiotic prescription is very seldom based on clinical factors alone. It has been suggested that antibiotic over-prescribing can be correlated with the prescriber's personality and environment. Clinician characteristics that have been linked to unnecessary prescribing include years of practice, medical specialty, perceived patient expectations, and desire to please the patient [4].

General practitioners prescribe somewhere around ninety percent of the antibiotics prescribed in the United States for a given year and more than half of these are prescribed to treat respiratory tract infections [6]. Statistics are very close to these numbers for most highly developed European countries as well. Urinary tract infections are the second most common malady for which antibiotics are typically prescribed. It is estimated that more than fifty percent of patients who present to a primary care facility with symptoms of a urinary tract infection are treated right away with antibiotics, even though urinary tract infections are incredibly self-limiting and pose a very small threat to an individual's overall health and wellbeing [7].

Treating urinary tract infections with antibiotics before performing the necessary lab work is not only irresponsible from a microbial resistance point of view; it is also quite costly and ineffective in treating the illness. The patient may be given peace of mind knowing that he or she was prescribed something tangible, but the benefit will go no further. The harm done by prescribing antibiotics for urinary tract infections far outweighs the good it will do to the patient. The majority of the responsibility for the ineffective and irresponsible prescribing of antibiotics lies with the prescribers, whether they are physicians, physician assistants, or other medical faculty [8]. However, the patient also bears a portion of the blame and responsibility. It is indeed patient expectations and presuppositions that make doctors feel bullied or forced into prescribing antibiotics either just in case or to please a difficult patient who will not be satisfied unless they leave with a prescription.

A study was performed in Iceland to examine how often and in what contexts medical practitioners, specifically family and general practitioners prescribe antibiotic medications to patients who present with no clear or definite signs of bacterial infection. Arason calls this prescribing method "non-pharmacological prescriptions of antibiotics". The study found that the primary reasons doctors would prescribe antimicrobial drugs to a patient with a non-definite bacterial illness are all related to the ever-changing doctor-patient relationship. In the region studied, the reason for this fluctuation in doctor-patient relations was supposed to be the lack of continuity in medical care that most patients sought out. Pressure from patients in a stressful society, the physician's heavy work pressure, the prescriber's personality, any supplemental income or prescribing incentives they may be receiving from pharmaceutical companies, and the physician's lack of confidence or uncertainty in their diagnostic abilities were the main factors that resulted in a situation in which antibiotic prescriptions were prescribed as a kind of coping strategy for an uncomfortable situation with a patient.

A European study surveyed one thousand general practitioners about their prescribing habits and practices. Fifty-five percent of the general practitioners admitted to feeling under intense pressure from patients to prescribe antibiotics, even if the practitioner insisted and explained to them that the antibiotic was unnecessary and would be ineffective. Forty-four percent of the general practitioners further admitted to prescribing antibiotics to a difficult patient just to get them to leave the office [9].

The over-prescription of antibiotic medication is particularly prevalent among pediatric patients. A study in the *Scandanavian Journal of Primary Health Care* found that, in the region studied, children under the age of seven consumed nearly twenty percent of the total antibiotic medication sold, though they comprised only about 10% of the total family care office visits. Over half of these patients were prescribed antibiotics due to ear infections, which are seldom caused by bacterial infections.

They are almost always of a viral nature. A correlation was found between the amount of antibiotics an individual child consumed and the risk of that patient being a carrier of antibiotic-resistant microbes, specifically *penicillin non-susceptible pneumococci*, in the weeks following the medical treatment. Pediatric ear infections are some of the

most common illnesses that prescribers will prescribe an antibiotic to treat [10]. Upper respiratory tract infections are the leading cause of antibiotic overprescribing in the outpatient setting, both for pediatric and adult patients. Another study done in Sweden and published by the same journal found that after the implementation of more thorough diagnostic techniques, fewer patients were being diagnosed with bacterial upper respiratory infections. Shockingly, the proportion of patients who were prescribed an antibiotic did not decrease as may be expected. The proportion of patients who were prescribed an antibiotic increased over the period studied. This study shows fairly definitively that clinical factors such as lab workups are very low on the list of reasons a prescriber would prescribe antibiotic medication to a patient. A cause that may be a contributor to unnecessary antibiotic prescribing is the fact that antibiotic over-prescription has been shown to increase the likelihood that patients will return to a certain provider or office.

Knowing that one can go into a doctor's office and leave with definitive treatment, regardless of whether or not that treatment is appropriate for one's case and condition, will increase the likelihood of the individual bringing their business back to that provider. Patient loyalty is likely a contributing factor to the antibiotic crisis.

Role of Patient

Patients have become far more demanding and entitled in recent decades. They often believe that if they leave a doctor's office without an antibiotic or other tangible and definitive treatment, they are being short-changed or cheated in some way. Patients see prescribers as lazy and uncaring if they choose not to prescribe a medication for the individual's malady. Misconceptions and presuppositions abound within the public's belief as it pertains to antibiotics. A study done in Europe looked at what the general public believes about antibiotics and their effectiveness.

The study found that about half of the patients surveyed believed that antibiotics were fully effective in treating viruses, colds, and flu and should be prescribed in those cases. This is alarming because none of those illnesses will be improved by antibiotics. Antibiotics are effective only against bacterial infections, not against viruses like the ones that can cause ear infections, respiratory infections, flu, and the common cold.

Patient characteristics that coincide with excessive and unnecessary antibiotic prescribing include misperceptions about antibiotic effectiveness for viral illnesses, desire for a tangible product from the clinical encounter, age, ethnic and racial identification, and insurance status. Older patients, patients from underprivileged areas, and minority patients were the groups that received unnecessary antibiotics the most. Ackerman suggests that the listed characteristics incline these patients to be those with whom it is more difficult to converse and explain unpleasant or complicated information. These boundaries do make for a sometimes difficult provider-to-patient interaction, but to rectify the antibiotic crisis these obstacles will have to be surmounted. Social characteristics of the doctor-patient relationship as listed above must be considered when looking at the issue of antibiotic over-usage.

However, the ongoing cultural shift in the expected role of the patient from passive receiver of medical expertise to active medical "consumer" must also be heavily considered. People expect to be sold something and, when they are turned away without medication, they feel cheated or short-changed in some way. The consumer mindset of American culture is a definite contributing factor to the antibiotic crisis.

Role of Uncertainty

The uncertainty involved in diagnostic testing also contributes to overprescribing of antibiotics, particularly in the primary care setting. A Dutch study done in 2005 showed that the use of antibiotics was very strongly linked to physicians wanting to avoid uncertainty in diagnosing patients rather than actual clinical indications of a bacterial illness [11]. Physicians want to eliminate the possibility of withholding antibiotic treatment from a patient only to have them suddenly develop a serious bacterial infection and become severely ill or even die. The legal repercussions and moral questions weigh heavily on the backs of doctors facing these choices. The problem is that the likelihood of misdiagnosing a life-threatening bacterial infection as a self-limiting viral illness is incredibly small. By providing a "blanket coverage" antibiotic prescription just to ease the patient's worries or prevent repercussions for the physician, the crisis of antibiotic resistance is being further propagated. It is not beneficial to the patient or provider to practice antibiotic prescription for just in case scenarios.

Antibiotic Resistance

Antibiotic resistance is rising to dangerously high levels in all parts of the world and bacteria are becoming alarmingly antibiotic resistant. One bacterium in particular, *methicillin-resistant Staphylococcus aureus*, has gained quite a bit of infamy for being nearly impossible to treat. Neu states that in 1941, virtually all *Staphylococcus aureus* strains worldwide were susceptible to and treatable with penicillin. By 1944, *S. aureus* was capable of destroying penicillin by producing penicillinase (aka beta-lactamase). About fifty percent of *S. aureus* strains were resistant by the end of the 1940s [12]. Presently, over ninety-five percent of *S. aureus* is resistant to not only penicillin but also ampicillin and anti-pseudomonal penicillins [13]. Hospitals are breeding grounds for bacterial infections, not because of bad sanitation or filthy conditions, but because they provide an ideal environment for the development of multi-drug resistant bacteria by promoting the reproduction and growth of the particular strains of bacteria that carry the gene for drug resistance. *Clostridium difficile* is another perfect example of this phenomenon. When antibiotics are used unnecessarily or indiscriminately, the normal bacteria that live in the gut can be disrupted and killed, allowing for drug-resistant bacteria to move in. *C.difficile* is the most prominent of these bacteria, causing opportunistic infections in patients who have been treated with antibiotics and, on occasion, leading to a persistent and debilitating disease that is often incurable.

Antimicrobial treatment places selective pressure on bacteria. This pressure favors the emergence of strains of the microbe that will be resistant to the antibiotics in the environment and therefore able to survive and reproduce. Bacteria can resist antibiotics as a result of their genetic and mutational abilities. This can include chromosomal mutation, inductive expression of a previously latent chromosomal gene, exchange of genetic material through transformation, transduction by bacteriophage, or conjugation by plasmids which are extra chromosomal DNA [13]. Plasmids are a current target of a large amount of antibiotic research. Bacteria may also possess transposons. Transposons have been nicknamed “jumping genes” due to their ability to enter transmissible plasmids or chromosomes and thereby spread antibiotic resistance not only to other bacteria of the same species but to different species of bacteria. Gram-positive species have demonstrated the ability to transfer resistance to Gram-negative species, although the reverse is uncommon. This collaboration and cooperation of different species of bacteria is a wonderful testament and example to the intelligence and adaptation abilities of microbial life, given to them by their Creator.

Bacteria evade antibiotics in three major ways. They can inactivate the antibiotic by destroying it or modifying it in a way that makes it unable to negatively affect the microbe. Secondly, they can evade the antibiotic or prevent its access to the microbial body. Lastly, they can alter the antibiotic target site on their membrane surface, which will prevent the antibiotic from binding. Therefore, it will have decreased or no effect on the microbe [14].

Possible Consequences

What is of most concern is that common bacterial infections such as strep throat may once again become untreatable due to bacterial resistance [15]. The World Health Organization has outlined what a possible future could look like if antibiotic resistance grows any higher. They have named it the post-antibiotic world.

This world looks a lot less like Pasteur’s hope of the future destruction of disease and much more like the pre-penicillin era when infectious disease dominated. The WHO warns that antibiotic resistance may soon result in simple infections becoming unmanageable and potentially even fatal [16].

Potential Solutions

Several methods for the prevention of further drug resistance development have been suggested by scientists, physicians, and other professionals. These include educating the public about the proper use of antibiotics and the consequences of misusing them, holding physicians and health care professionals to a much higher standard when it comes to diagnosing and then treating patients with bacterial illness, putting stricter regulations in place for when antibiotics can and should be prescribed, and increasing the search for new antibiotics. Multifaceted interventions that attack the problem from several sides have shown to be the most effective in fighting back against antibiotic resistance.

The interventions that have shown the best results in countries worldwide include the enforcement of policies prohibiting the sale and purchase of antibiotics without a valid prescription from a qualified dispensing pharmacy, the use of stewardship programs explaining the importance of the proper use of antibiotics to the public, the enforcement of laboratory testing before prescribing antibiotics, teaching

physicians how to better manage patient interactions, and putting incentives in place for physicians who adhere to these guidelines and regulations. These steps, among others, are probably necessary to prevent society from being thrust back into the time before antibiotics.

Public Antibiotic Education

The public is seriously misinformed about when an antibiotic is necessary and when it is not. There is a clear need for education in this area.

Including material about antibiotics and their safe usage in public school curriculum plans could go a long way in informing the general public about the realities of antibiotic use. Informative pamphlets could be given out in government buildings such as the Social Security Office. Television could be particularly useful in this aspect. Documentaries and news stories could go a long way toward educating the public. Social media could also potentially be used as a platform in spreading the news about antibiotic resistance. Public intervention could include the publication of guidelines, freely offered educational sessions covering what illnesses antibiotics will and will not work for, the publication of local interviews with pharmacists, messages on radio, television, and other mass media platforms, etc. These public campaigns will certainly have a positive effect on reducing the antibiotic crisis, but educating the public will by no means solve the antibiotic crisis. It is simply a first step in the right direction [17].

Physician Programs and Interventions

Since bacterial infection is genuinely hard to distinguish from viral infection at times, physicians and providers must be encouraged and even required to run diagnostic tests before prescribing antibiotics to a patient [18]. Not only will this remove the guesswork and put the physician's mind and conscience at ease, but also it will make the subsequent, often uncomfortable explanation to a patient about the reason they are not being prescribed an antibiotic "just in case" a thing of the past.

The patient could be much less likely to put pressure on a provider to prescribe antimicrobials in situations in which they are not indicated or warranted. Diagnostic tests are, generally, quite simple. They usually entail taking a swab, blood sample, or urine sample and sending it to the laboratory. Diagnostic testing may take a little longer and seem like an inconvenience to the patient, but the time lost from their day will pale in comparison to the impending antibiotic crisis if these measures are not taken. This is not meant to trivialize a patient's concerns, but to help them understand how antibiotics can and should be properly used for the betterment of their health and the health of society as a whole. There may be cases that are too severe to call for diagnostic testing before giving patient antibiotics. This is a situational concern that allowances would need to be made for. Perhaps hospitals could have allowances for the prescription of emergency antibiotic medication.

Including antibiotic training as part of a physician's medical education could prove immensely valuable, particularly as it pertains to conversations with patients. Physicians must know how to discuss the correct use of antibiotics and know how to adequately explain to a patient with no medical background or understanding that antibiotics will not reduce the duration of viral or self-limiting diseases and that they may be contributing to the antibiotic crisis. The information given verbally by the provider could be backed up by informational leaflets or pamphlets that the patient can take home. It is also important that doctors can set realistic expectations for patients about the duration and severity of the illnesses they are experiencing. Four days is a common running time frame for ear infections, about a week for an acute sore throat caused by a virus, a week and a half for the common cold, two and a half weeks for a sinus infection, and up to three weeks for a severe cough or bronchitis. This is of particular importance because studies have shown that many patients believe that if they suffer symptoms for more than three days, antibiotics are not only warranted but necessary.

Regulations

The antibiotics currently in use must be conserved and protected while the search continues for other antibiotics. It may be necessary to only allow IV administration of antibiotics in life-threatening cases while a patient is in the hospital.

Oral antibiotics could be temporarily done away with to ensure that the medication is being taken only when necessary and in the correct dosages, for an adequate amount of time. This would remove the necessity of educating the public and trusting the common man to safely and responsibly use antibiotics. The ultimate goal of putting regulations into place regarding the acceptable use of antibiotics is not simply to reduce the number of antibiotics

being prescribed and utilized. It is primarily to encourage the rational use of antibiotics and to ensure that they are only being prescribed to patients who need the treatment and will benefit from it. The Centers for Disease Control (CDC) has already put a program into the works that would do just what is being proposed here. It is quite an aggressive plan aimed at reducing the unnecessary and frivolous use of antimicrobials so that antibiotics remain a viable tool for future generations to come. In fiscal year 2016, Congress appropriated nearly $160 million for the CDC to allot to different agencies and programs in the fight against antimicrobial resistance. With these investments, the CDC implemented the Antibiotic Resistance Solutions Initiative, which is improving national infrastructure to detect, respond to, and contain resistant infections across healthcare settings and communities. This plan does have its flaws. It is aimed primarily at hospital use of antibiotics, not towards general practitioners or family practitioners. Also, the CDC's proposed plan does not address the use of antibiotics in agriculture and livestock.

The CDC includes several categories of goals in the fight against antibiotic resistance. They hope to set national goals to improve antibiotic use, particularly to cut inappropriate prescribing practices by fifty percent in hospitals and twenty percent in the general practitioner and specialists' offices. They plan to encourage effective public information and antibiotic stewardship programs, focusing their efforts on doctors' offices, hospitals, and nursing homes. The CDC has provided funding to researchers who are studying antimicrobial resistance and those who are searching for new antimicrobial substances that could potentially be medicalized and used in the treatment of patients. Interestingly, they also have begun a program in support of the early recognition of sepsis [16]. All of these initiatives sound very noble and promising. However, the CDC has yet to set forth a practical approach to fighting antimicrobial resistance. All of their planning thus far has been focused on future initiatives, not the here and now. Unfortunately, the antibiotic crisis is happening today, not in the distant future.

Pharmaceutical companies must be removed from their place of authority in antibiotic production. They should be prevented from offering prescribing incentives to medical providers, potentially through legal action. This is probably one of the toughest issues to overcome. It may be impossible to remove pharmaceutical companies from their place of authority and power without putting the government in control of pharmaceutical production. Government control would undoubtedly be a worse alternative. For the time being, the role of unsavory "big pharma" must be recognized and possibly countered by public pressure and incentives.

Antibiotics for use in animals should be administered only by a licensed veterinarian directly or through writing a prescription that a pharmacy can fill. Antibiotics should by no means be sprayed onto crops or included in the food of livestock as a preventative measure. The link between animal health and human health must be recognized and integrated into the approach taken by health professionals, regulatory agencies, and the enforcing authorities.

Search for New Antibiotics

The search for new antibiotics is well underway, though it is moving at an alarmingly slow rate. It is much more difficult for researchers to find financial support from pharmaceutical companies to search for and develop these new drugs. The time delay between the discovery of a potential new antimicrobial substance and the approval to commercially produce it is on the magnitude of decades [17]. This has led many researchers to abandon the search for new antibiotics entirely, as there is not enough interest or funding.

CONCLUSION

Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics. This crisis is global, reflecting the worldwide overuse of these drugs and the lack of development of new antibiotic agents by pharmaceutical companies to address the challenge. Antibiotic-resistant infections place a substantial health and economic burden on the healthcare system and population. Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are greatly needed.

ACKNOWLEDGEMENTS

I would like to thank Pr. Khayati and Pr. Akrim, for their valuable contributions and timely advice that shaped this work.

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