The Indian Journal of Pediatrics (November 2020) 87(11):937–944
https://doi.org/10.1007/s12098-019-03180-3

REVIEW ARTICLE

Antibiotic Resistance — A Cause for Reemergence of Infections

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Received: 8 October 2019 / Accepted: 31 December 2019 / Published online: 5 February 2020

Abstract

This article can rightly be called 'the rise of the microbial phoenix'; for, all the microbial infections whose doomsday was predicted with the discovery of antibiotics, have thumbed their noses at mankind and reemerged phoenix like. The hubris generated by Sir Alexander Fleming's discovery of Penicillin in 1928, exemplified best by the comment by William H Stewart, the US Surgeon General in 1967, "It is time to close the books on infectious diseases" has been replaced by the realisation that the threat of antibiotic resistance is, in the words of the Chief Medical Officer of England, Dame Sally Davies, "just as important and deadly as climate change and international terrorism". Antimicrobial resistance threatens to negate all the major medical advances of the last century because antimicrobial use is linked to many other fields like organ transplantation and cancer chemotherapy. Antibiotic resistance genes have been there since ancient times in response to naturally occurring antibiotics. Modern medicine has only driven further evolution of antimicrobial resistance by use, misuse, overuse and abuse of antibiotics. Resistant bacteria proliferate by natural selection when their drug sensitive comrades are removed by antibiotics. In this article the authors discuss the various causes of antimicrobial resistance and dwell in some detail on antibiotic resistance in gram-positive and gram-negative organisms. Finally they stress on the important role clinicians have in limiting the development and spread of antimicrobial resistance.

Keywords Antimicrobial resistance · Antibiotic use · Antimicrobial stewardship · Reemergence of infections

Introduction

To get a perspective on the problem of antimicrobial resistance (AMR), readers are encouraged to look at these statistics:

- Antibiotic resistant bacteria cause more than 23,000 deaths in the USA [1] and European Union every year [2].
- 20,00,000 deaths per annum are projected to occur in India due to AMR by the year 2050 [3], while presently, more than 50,000 newborns in India are expected to die from sepsis due to microbes resistant to first-line antibiotics [4]

The enormous impact of AMR in children is further highlighted by the following factsheet:

- *Klebsiella* and *E. coli* were the most common Gram-negative bacteria in newborns with sepsis from a hospital in India in 2011, and over one-third of them were Extended Spectrum Beta Lactamase (ESBL) producers, both in community and hospital settings [5].
- The mortality rate amongst 78 newborns (< 7 d old) infected with *Acinetobacter* was to the tune of approximately 50% (37 out of 78 died).
- 71% of the bacteria were resistant to all antibiotics except Polymixin [6]
- In an outbreak in India, 4 babies developed New Delhi metallo-beta-lactamase1 (NDM-1) producing *E. coli* bacteremia and sepsis, and all 4 died [7].

Apart from their direct effects on infections, the indirect effects of antibiotics in every aspect of modern healthcare cannot be underestimated. Immunosuppression in treatment of malignancy and organ transplant will not be possible without the availability of antibiotics. Transplantation medicine, joint replacement surgery and stem cell therapy, to name just a few, would die a slow death if infections cannot be treated. The problem of antibiotic resistance is compounded further by two more issues: first, microbes are transferred readily

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between individuals and between the environment and the individual, making antibiotic resistance truly a One Health issue. Second, while genetic information in humans is spread vertically, the 'one -step- ahead' microorganisms transfer antimicrobial resistance horizontally not just between bacteria but even to unrelated species [8].

What Causes AMR?

Antibiotic resistance is simply defined as "bacteria changing in ways that reduce or eliminate the effectiveness of antibiotics" [1] and the causes are both microbial and human.

Microbial Causes

It is interesting to note that the majority of the antimicrobials in use today, barring a few like sulfa & oxzolidinones, originated in natural products, usually microbes themselves, to defend against attack by other microbes. These natural products have been subsequently isolated, commercially produced and later modified to create additional or amplified antimicrobial activity [9]. So antibiotic resistance genes arose in microbes long ago in response to naturally occurring antibiotics produced by their fellow brethren [10]. Resistance can arise spontaneously from mutation with subsequent generations inheriting the resistance. By removing the drug sensitive competitors, antibiotics increase the natural selection of resistant bacteria.

Additionally and ingeniously, bacteria can acquire resistance genes from "non relatives" on mobile genetic elements, for *example*, plasmids. This 'horizontal gene transfer (HGT)' can occur between very different species of bacteria without the originator claiming any 'patent rights'.

It is humbling to realise that mobile adaptive genes are exchanged by horizontal transfer to not just within but between microbial species; this thus changes the adaptive capability of entire microbial community.

Human Causes

Antimicrobial use in Agriculture

Antimicrobial use is rampant in agriculture, both in livestock and in crops, and this practice leads to significantly increased agricultural yield. The flip side is that these antimicrobials lead to death of susceptible bacteria and proliferation of antibiotic resistant bacteria which can then be transferred to humans *via* the food chain.

Human Population and Interconnectedness in the Global Village

While it took 200,000 years of human history for the world population to reach 1 billion, it took only 200 more years to reach 7 billion, with the figure reaching 7.7 billion in April 2019 [11]. This huge pool coupled with urbanisation induced close proximity among humans provides a fertile environment for rapid proliferation of infectious diseases.

The global humanity is now effectively a single biological population. While humans can travel anywhere in the planet within 1-2 d, so do the attendant microbes and pathogens, thus permitting globalisation of the drug resistant microbe.

Overuse of the Antimicrobials

It has been clearly demonstrated that many of the microbial adaptive processes leading to antimicrobial resistance are directly proportionate to the intensity of the selective challenge [12]. It is therefore intuitive that if we can reduce the exposure of the microbes to antimicrobials, the speed of development of AMR and its dissemination will be greatly reduced.

Perusal of any literature on AMR reveals that the pipeline of new antibiotics is drying up, due to variety of economic and regulatory obstacles, and this is emphasized as an important factor contributing to the threat posed by resistant microbes. Thus, unless we learn the lessons of the past, any significant advantage accruing out of the introduction of a new antimicrobial will be short lived.

AMR Contributing to Reemergence of Infections

In 2013, the Centers for Disease Control (CDC), Atlanta, ranked the antimicrobial resistant bacteria (& fungi) that have the most impact on human health into 3 categories: urgent, serious & concerning (Table 1). The threats were assessed according to seven factors - health impact, economic impact, prevalence, 10 y projection of prevalence, ease of transmission, availability of effective antimicrobial agents, and barriers to prevention.

The list is long and a detailed discussion on each of them is beyond the scope of this article. A few infections with great relevance to office practice as well are detailed below.

Resistance in Gram-Positive Organisms

Methicillin Resistant *Staphylococcus aureus* (MRSA)

Very soon after the introduction of methicllin in 1959, *Staphylococcus aureus* isolates resistant to the agent were

Table 1 CDC assessment of antibacterial resistance threats [13]

Urgent threats
- *Clostridium difficile*
- Carbapenem-resistant *Enterobacteriaceae* (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious threats
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBLs)
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella typhimurium*
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning threats
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

reported. Since then MRSA has emerged as a major nosocomial as well as a community acquired pathogen. The Clinical Laboratories Standards Institute (CLSI) defines methicillin resistance as an oxacillin minimum inhibitory concentration (MIC) ≥ 4 mcg/ml. Oxacillin and methicillin resistance is a surrogate marker for resistance to all beta lactam agents, including cephalosporins; exceptions include ceftraroline and ceftobiprole. Though traditionally classified into healthcare associated MRSA (HA MRSA) and community associated MRSA (CA MRSA), these distinctions are getting less distinct now with community onset MRSA sharing features of both HA MRSA and CA MRSA (CO-HA-MRSA).

With both HA MRSA and CA MRSA, resistance is conferred by PBP2a (a penicillin binding protein) encoded by the mec gene, which is located on a mobile genetic element (MGE). HA MRSA strains have MGEs (gene casettes) which confer resistance to multiple classes of antibiotics. CA MRSA are often susceptible to trimethoprim sulfamethoxazole (TMP-SMX) and clindamycin; while resistance to TMP/SMX is still relatively uncommon, there is now increasing resistance of CA MRSA to clindamycin [14].

While mupirocin ointment application to anterior nares and chlorhexidine baths have been used for decolonisation as an infection prevention measure somewhat successfully, resistance to both mupirocin and chlorhexidine have begun to emerge [15].

Streptococcus pyogenes

One of the important silver linings in the AMR saga, has been the continuing universal susceptibility of *Sreptococcus pyogenes* to penicillin. But the organism has not shared this benevolence with macrolides. The widespread use of macrolides for all upper respiratory infections has led to a selective pressure and thus spread of macrolide resistant strains. Incidence of macrolide resistance differs geographically based on use of macrolides with 53% macrolide resistance reported from India recently [16].

Streptococcus pneumoniae

Till the mid 1970s pneumococci had remained uniformly susceptible to all classes of antibiotics that had been active against these organisms. Since the appearance of penicillin resistant pneumococci in 1977, they have become widespread and have progressively developed resistance to other commonly used antibiotics including beta lactams, macrolide, lincosamides (clindamycin), tetracycline, TMP/SMX and fluoroquinolones. The risk factors for acquisition of drug resistant pneumococci include [17]:

- Recent hospitalisation
- Day care attendance
- Previous antibiotic use

Today most non-meningeal pneumococcal infections can be treated by standard doses of amoxicillin/ampicillin as the new CLSI breakpoints for penicillin are different for meningeal and non-meningeal sites. This change was brought about because there was no difference in the clinical outcome of non-meningeal infections in patients who were drug resistant by the earlier breakpoints.

Vancomycin Resistant *Enterococcus*

Enterococcus fecalis and *Enterococcus fecium* account for most enterococcal infections, while occasionally *Enterococcus gallinarium* has been associated with outbreaks. Systemic enterococcal infections are treated with ampicillin (if the isolate is susceptible) or vancomycin, in combination with an aminoglycoside, which provides synergy. Due to rampant use of vancomycin, resistance in *enterococci* has become very common. The genes responsible for vancomycin resistance (known as van genes) are located on plasmids and/or transposons. *Enterococcus* isolates being very hardy organisms, can withstand conventional cleaning methods and this is responsible for the spread of vancomycin resistant *enterococcus* in healthcare settings [18].

Linezolid or daptomycin are options for treatment of infection due to vancomycin resistant enterococci (VRE). The risk factors for VRE colonisation/infection are:

- Long periods of hospitalisation
- Use of multiple broad spectrum antibiotics
- Liver or stem cell transplant recipients

Resistance in Gram-Negative Organisms

In our battle against antimicrobial resistance, gram-negative pathogens are especially worrisome as many of them are now pan antibiotic resistant thus making the post antibiotic era seem like the pre antibiotic era. The most serious of these infections occur in healthcare settings, with the *Enterobacteriaceae* group of organisms being the most notorious (mostly *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter*).

Not to be left behind, even community acquired gram-negative pathogens are increasingly multidrug resistant, extended spectrum beta lactamase producing *E. coli* being a notable example [19].

We will now discuss some of the tools that the gram-negative pathogens possess that make them so difficult to treat.

Extended Spectrum Beta Lactamases (ESBLs)

Beta lactamases are enzymes which inactivate beta lactam antibiotics by opening the beta lactam ring. The initial beta lactamases were narrow spectrum beta lactamases TEM1 & TEM2, for *example*, which hydrolyze penicillins and narrow spectrum cephalosporins. In response to the clinicians' fascination for broad spectrum antibiotics, the microbes retorted by producing ESBL. ESBL enzymes are enzymes produced by gram-negative bacilli that have the ability to inactivate beta lactamases containing an oxyimino group, *viz*. third generation cephalosporins and aztreonam.

ESBLs are plasmid derived enzymes found exclusively in gram-negative organisms primarily *Klebsiella pneumoniae, E. coli, P. mirabilis* and other gram-negative bacilli. Many different varieties of ESBLs exist, differing in their activity against particular beta-lactam substrates. ESBLs are detected based upon the resistance conferred to third-generation cephalosporins and the ability of beta lactamase inhibitor, usually clavulanate, to block this resistance. They are heterogenous, with some showing *in vitro* susceptibility to certain third-generation cephalosporins, but *in vivo* therapeutic failures occur. This is due to inoculum effect in that the MIC of the extended spectrum cephalosporins rises as the inoculums of the organisms increases. Thus the CLSI has adjusted susceptibility breakpoint recommendations for gram-negative bacilli which often precludes the need to identify the ESBL in order to make treatment decisions [20].

The best therapeutic option for ESBL producing organisms are carbapenems (imipenem and meropenem). The use of cephalosporins including cefepime and piperacillin-tazobactam should be avoided even if the organism demonstrates *in vitro* susceptibility. The plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes like aminoglycosides, making the ESBL producing organisms multidrug resistant.

Restriction of use of third-generation cephalosporins and barrier protection are important measures to contain the spread of ESBL producing organisms.

Amp C Beta Lactamases

These enzymes are chromosomal or plasmid mediated. The organism producing these enzymes are clinically grouped through the acronym 'SPACE' - serratia, pseudomonas or proteus, acinetobacter, citrobacter and enterobacter. While production of amp C beta lactamses can be constitutive, inducible production can occur on exposure to particular beta lactams like cephalosporins. Thus the organism can become resistant on treatment. In contrast to ESBLs, amp C beta lactamases are not inhibited by beta lactamase inhibitor such as clavulanic acid, thus rendering beta lactam - beta lactamase combination ineffective. Cefepime and carbapenems are the available treatment options [21].

Carbapenemase

Carbapenems, for long considered the last defence in our armamentarium against resistant gram-negative pathogens, is now often rendered ineffective with the rise of carbapenemase (carbapenem hydrolysing beta lactamase) producing organisms. The two important groups of carbapenemases are the *Klebsiella pneumoniae* carbapenemases (KPC) and the metallo-beta-lactamases.

The KPC enzymes reside on transmissible plasmids and can be transmitted from *Klebsiella* to other genera like *E. coli, P. aeruginosa* and enterobacter spp. [22]. These enzymes confer resistance to most beta lactamases [23]. Metallobetalactamases (MBLs), so named because of their dependence on zinc for effective hydrolysis of beta-lactam, can be chromosomally encoded, naturally occuring, or acquired, residing on plasmids.

The New Delhi MBL, was first described in December 2009 in a Swedish patient hospitalised in India with a *Klebsiella pneumoniae* infection [24]. The gene for this betalactamase (NDM-1) has been identified in strains that possess other resistance mechanisms, contributing to their multidrug resistance.

Carbapenemase producing organism can arise from previously carbapenemase negative strains by acquiring genes from other bacteria through mobile genetic elements.

Use of broad spectrum cephalosporins and/or carbapenems is an important risk factor for infection or colonisation with these 'superbugs' [25] though prior receipt of carbapenems is not essential for acquisition of these strains. Isolates resistant to cephalosprins and carbapenems with retained susceptibility to aztreonam should be suspected of carrying an MBL.

Treatment of these infections is very difficult and the antibiotics should be chosen based on antimicrobial susceptibility test results. For KPCs, ceftazidime - avibactam or meropenem - vaborbactam are options, and in case these are not available a polymixin based regime is an alternative. For MBLs a polymixin based regime can be used if the isolate is susceptible, in which case a second active agent should be used in combination.

Combating Antimicrobial Resistance- How Clinicians Can Play an Important Role?

"4-y-old master SB is hospitalised in the pediatric ward for high grade fever of 4 d duration. He has no obvious focus of infection, and is active and cheerful in the interfebrile period. He has no urinary tract symptoms but his urine microscopy reveals 8 polymorphs per HPF. His urine culture is sent and he is started on injection ceftriaxone.

His gut microbiome is full of benign commensals including *Clostridium difficile*. Most of the commensals die due to ceftriaxone but *Clostridium difficile* is resistant to ceftriaxone and now proliferates and thrives in the competition free environment. Urine culture is reported negative, ceftriaxone is stopped, but by now *Clostridium difficile* diarrhea has set in. Unbeknownst to the healthcare provider, on exposure to ceftriaxone, some of the *E. coli* in the gut have been generously donated some ESBL carrying plasmid by a few commensals in the gut. Next to his bed is a 10-y-old girl, Miss SK, hospitalised with diabetic ketoacidosis. The nurse taking care of both of them is lax with her hand hygiene. While changing master SB's soiled bedsheets she carried the ESBL armed *E. coli* to Miss SK who now gets infected with and develops sepsis due to ESBL producing *E. coli*."

Though the above case is purely fictional, it is the unseen true story unfolding in our hospitals on a daily basis. The case wonderfully illustrates many important points in our fight against AMR:

1. There was no urgent need to start an antibiotic, a broad spectrum injectable one at that, for a child with 8 polymorphs/HPF in the urine without any urinary tract symptom. Waiting for the culture report would not have done any harm.
2. What protects us from major infections is the competition the microbes face from benign commensals. Get rid of them at your own peril.
3. The camaraderie that exists between unrelated microbes, leading to horizontal transfer of antimicrobial resistance rivals any human ingenuity.
4. All research, all literature, is a waste unless hand hygeine is practised with diligence.

Some Guidelines on Antimicrobial Use

With the threat of the post antibiotic era becoming like the preantibiotic era (nothing available to treat infection), looming large, there is now action at the global, international and national level to tackle the problem of antimicrobial resistance. The CDC has launched the Antibiotic Resistance Solution Initiative [26], and the WHO has come up with the Global Action Plan on antimicrobial resistance [27]. The Indian government has also awakened to the threat of AMR and launched the National Action Plan on AMR (NAP-AMR), where stakeholders from the ministries of health, environment, water, agriculture and science & technology will work together, underscoring the important contribution of multiple factors, for *example*, agricultural use of antibiotics and effluents of antibiotic waste from pharmaceutical industries polluting water bodies, among other things towards AMR. While these initiatives underline the importance of the multidimensional approach to AMR, this section would only discuss what a clinician can do in his daily practice to contribute in his own small way towards the fight against AMR.

1. *Use of antibiotics for upper respiratory tract infections:* Despite the knowledge that most upper respiratory tract infections are viral in origin, surveys indicate that 40 to 75% of adults and children seeking care for viral respiratory infections are treated with antibacterial agents [28] and almost similar statistics are available from India [29]. Use of FeverPAIN score will identify the minority of pharyngitis patients with streptococcal infection reducing inappropriate antibiotics use in pharyngitis. The authors who derived this score performed an implementation study suggesting it can safely reduce antibiotic use by 30% [30]. It has been validated for use in children above 3 y of age and should not be used in those under 3 y.
2. *Use of antibiotics in diarrhea:* Antibiotic use in diarrhea competes strongly with unwarranted use of antibiotics in upper respiratory tract infections for the pole position in irrationality! Despite guidelines galore from WHO, Government of India, Indian Academy of Pediatrics, to name the well known ones, a study [31] has shown that antibiotics were prescribed in 71% of prescriptions and

often in illogical fixed dose combinations. One such illogical combination, ofloxacin with ornidazole, was the most frequent oral antibiotic prescribed [31], and this combination is seductively acronymized to suggest it is the vital breath of life. A big dent in our fight against AMR could be made if only the guidelines for the management of acute diarrhea were disseminated by education of practitioners of all systems of medicine.

3. *How to use adverse prognostic indicators in guiding empiric antibiotic treatment [32]:* Confronted with a patient with suspected or confirmed bacterial infection, the decision regarding the level of medical intervention needed (broad spectrum or narrow spectrum antibiotics, oral or intravenous antibiotics) is usually based on clinical judgement. Though guidelines exist for many of the clinical syndromes, pneumonia for *example*, these are usually disease specific or require detailed data and are difficult to use in clinical practice. A simple tool that requires minimal data and which can be used in combination with clinical judgement, is the systemic inflammatory response syndrome (SIRS). SIRS is present when two or more of the following exist:

   a. Core temperature < 36° or > 38.5 °C
   b. Tachycardia (age defined)
   c. Tachypnea (age defined)
   d. Leukocyte count, elevated or depressed for age

Sepsis is SIRS in the presence of suspected or proven infection and there is a continuum of severity from sepsis to severe sepsis, septic shock or multiorgan failure [33] and mortality increases along the continuum. These criteria can be used to decide whether the patient needs only first-line antibiotics (for *example* a patient with only SIRS) or whether he or she should be covered for a suspected resistant pathogen (for *example* a patient with a risk of a resistant pathogen and severe sepsis).

4. *Shorter courses:* The antibiotic course has had its day! - This provocative title from a BMJ article [34] is hopefully the forerunner for shorter courses of therapy in many clinical syndromes.

Selection of antibiotic resistance in microbes occurs through one of two mechanisms:

a. Target selection: for some organisms like *Mycobacterium tuberculosis*, Human immunodeficiency virus (HIV), malaria and *Salmonella typhi*, spontaneous resistance conferring mutants may be selected during treatment. For such organisms, completing a course of therapy and often polytherapy is essential to cover for spontaneous resistant mutations that may arise on treatment.
b. Collateral selection: Most of the bacterial species now posing the greatest problems do not develop resistance through target selection. The threat is from microbes like *E. coli, Staphylococcus aureus, Klebsiella, Acinetobacter spp*, which are all found harmlessly in us, on us and in our environment [34]. When an individual takes antibiotics, the antibiotic sensitive organisms are killed and are replaced by the resistant strain in the competitor free environment, ready to cause infection in the future [35]. Hence, the longer the antibiotic exposure, the greater the pressure to select for antibiotic resistance. Thus indication specific recommendation based on poor evidence can hopefully be replaced by biomarker, for *example*, procalcitonin, based guidance on when to stop antibiotic treatment [36].

5. *Role of vaccines in the prevention of AMR:* Use of pneumococcal vaccine has reduced the prevalence of AMR in *pneumococci* and this benefit is extended even to unvaccinated individuals by herd immunity [37]. Even vaccines that prevent viral infections such as the flu, help in preventing AMR indirectly. Viral infections need not be treated with antibiotics, but the practice continues in the absence of reliable quick diagnostic tools, and the inappropriate use, thereby contributing to antimicrobial resistance.

Antibiotic Stewardship to Improve Hospital Based and Outpatient Based Antibiotic Use

An essential step forward to tackle the antibiotic crisis is the implementation of antimicrobial stewardship programmes both in hospitals and in outpatient settings. The core elements of these programmes are well elucidated by the CDC [38] and recently by the Indian Council of Medical Research [39]. Details of the antimicrobial stewardship programme is beyond the scope of this article, but suffice it to say that it will go a long way in promoting optimal antimicrobial use as regards empiric therapy, tailoring antimicrobial therapy, transitioning from intravenous to oral therapy and using the shortest effective duration of therapy.

In outpatient settings such programmes will help in not using antimicrobials where not indicated (*e.g.*, common cold, [40], non bloody diarrhea), using appropriate antimicrobial for a specific condition and in adopting a policy of watchful waiting or delayed prescribing can be appropriate, for *example*, acute otitis media and acute uncomplicated sinusitis [41].

Hope for the Future

Genetic Engineering

An interesting novel approach to combat HGT-acquired AMR is the use of naturally occuring barriers to the transfer of

resistance genes. Bacteria have xenogenic defence mechanisms, both innate and adaptive (CRISPR-Cas) systems which recognise and destroy incoming non self DNA [42]. These systems often protect the bacteria against resistance carrying parasitic mobile elements, such as bacteriophages. The key challenge is to develop and engineer CRISP-Cas based system which can then genetically manipulate pathogen population getting rid of the resistance carrying mobile genetic elements [43] thus ensuring the development of 'evolution proof' antibiotics.

Rapid Diagnostics

Howsoever much we wail and rail at the inappropriate use of antimicrobials driving antimicrobial resistance, there will be no respite from empiricism inherent in clinical practice, unless the clinician gets a definitive answer to the question - "can I be certain that my patient does not have a bacterial infection?" Therein lies the importance of R&D in the area of rapid diagnostics. While C-reactive protein (CRP) and procalcitonin levels are somewhat useful, they are not sensitive and specific enough to override clinical judgement. Molecular diagnostics promises to be the holy grail of rapid diagnostics, providing us with rapid, even point of care, detection of specific microbes to permit immediate pathogen specific treatment. The success story of cartridge based nucleic acid amplification test (CBNAAT) based microbial diagnosis of tuberculosis is an encouraging portend for the future.

Summary

There is no denying that antimicrobial resistance has assumed humungous proportions and threatens to strike a big blow to all therapeutic advances made in the last century, discovery of antibiotics, organ transplantation and cancer chemotherapy, to name just a few. Just like climate change, we owe it to the future generations to curtail this menace before it is too late. The first step towards this would be replacing the slogan of war against microbes with the slogan of peaceful coexistence.

Human inventiveness is no match for microbial ingenuity; horizontal gene transfer being a prime example of ingenuity and generosity combined together. Limiting the use of antibiotics so as to decrease the selection pressure is the only long term solution. Discovery of new antimicrobials can only be a short term measure till the microbes develop resistance, as they inevitably will. Fortunately, though belatedly, the medical community is seized of the problem. The CDC, USA, WHO and the ICMR have all come up with antimicrobial stewardship guidelines, which if implemented with diligence can reverse the trend of antimicrobial resistance.

It is also imperative on the part of clinicians, across the spectrum, to contribute in their own way by limiting the use of antibiotics. Hopefully, genetic engineering and rapid diagnostic tests, could prove to be the proverbial light at the end of the tunnel.

Authors' Contribution GS did literature review and wrote the manuscript, MG critically reviewed the manuscript and edited it. GS will be the guarantor for this paper.

Compliance with Ethical Standards

Conflict of Interest None.

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