Review article

Multiple drug resistance and bacterial infection

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Abstract

Drug resistance is becoming a great problem in developing countries due to excessive use and misuse of antibiotics. The emergence of new pathogenic strains with resistance developed against most of the antibiotics which may cause, difficult to treat infection. To understand the current scenario in different mode of infection is most important for the clinicians and medical practitioners. This article summarized some common infections and antibiotic resistance pattern found among these pathogens.

Keywords: Drug resistance; Bacteria; Infection

INTRODUCTION

Antimicrobial agents are being used to treat various infections for about five decades, they have been hailed as miracle drugs-magic bullets, able to destroy disease-causing bacteria. But with each passing decade, bacteria that resist not only single, but multiple, antibiotics, making some diseases particularly hard to control. The evolution of drug resistance is becoming a global problem [1-3]. Enterococci is important nosocomial pathogen causing different infections including gastrointestinal [4-6]. In fact, according to the Centers for Disease Control and Prevention (CDC), virtually all significant bacterial infections in the world are becoming resistant to the antibiotic treatment of choice. For some of us, bacterial resistance could mean more visits to the doctor, a lengthier illness, and possibly more toxic drugs. For others, it could mean death. The CDC estimates that each year, nearly 2 million people in the United States acquire an infection while in a hospital, resulting in 90 000 deaths. More than 70 percent of the bacteria that cause these infections are resistant to at least one of the antibiotics commonly used to treat them.

Antibiotic resistance, also known as antimicrobial resistance, is not a new phenomenon. Just a few years after the first antibiotic, penicillin, became widely used in the late 1940s, penicillin-resistant infections emerged that were caused by the bacterium *Staphylococcus aureus* (*S. aureus*). These "Staph" infections range from urinary tract infections to bacterial pneumonia. Methicillin, one of the strongest in the arsenal of drugs to treat staph infections, is no longer effective against some strains of *S. aureus*. Vancomycin, which is the most lethal drug against these resistant pathogens, may be in danger of losing its effectiveness; recently, some strains of *S. aureus* that are resistant to vancomycin have been reported.

Although resistant bacteria have been around a long time, the scenario today is entirely different from even just a few years ago. The number of bacteria resistant to different classes of antibiotics has increased, in many cases, tenfold or more. Even new drugs that have been approved are confronting resistance, fortunately in small amounts, but we have to be careful about their proper usage.

Colonization with methicillin resistant *Staphylococcus aureus* (MRSA)

MRSA is a major cause of health care associated infections. Transmission from unrecognized reservoirs

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of MRSA, is one of the major cause to spread MRSA[7,8]. Furthermore, patients with gastrointestinal colonization by health care associated pathogens may serve as important sources of transmission, since they often contaminate environmental surfaces which may acts as big source for hospital workers to contaminate their hands and gloves [9-11]. Nearly 10 % of patients who had stool specimens submitted for *C. difficile* toxin test had gastrointestinal tract colonization with MRSA. Boyce et al[12] found that more than 50 % patients with gastrointestinal carriage had no MRSA colonization or infection. Transmission of MRSA from such nonisolated patients is found to happened about fifteen times as frequently as from patients who are cared for using protective measures[7].

A number of researchers have reported that overgrowth of enterotoxin-producing MRSA strains in the stool may be associated with enterocolitis or antibiotic-associated diarrhea [13]. In spite of these reports, it is rare that MRSA causes enterocolitis or antibiotic-associated diarrhea [11]. But it is well known fact that nosocomial antibiotic -associated diarrhea is caused by enterotoxin producing MRSA strain and it is not being attributed to *C difficile* , other enteric bacteria or medications. Such MRSA strains were found to be unrecognized gastrointestinal colonization with this multidrug resistant pathogens.

Emergence of vancomycin-resistant *Enterococci* (VRE)

The primary inciting factor was likely the use of orally administrated vancomycin for treating antibiotic-associated diarrhea in hospitals. VRE infections have been identified frequently in the patients in adult intensive care whereas in pediatric patients it is seldom [14,15]. Young children have undergone gastrointestinal infection with VRE, may transmit this organism by fecal-oral spread. How does the infection spread in hospital setting is a question of debate. There was no correlation between the rooms to which patients were admitted during and PFGE Pattern obtained from isolates [16]. Vancomycin resistance is caused by one of the two operons, Van A or VanB. These operons even acquired by enterococci to show resistance against vancomycin. The major reason for this acquisition is comprabale percent GC content in Van B operon and enterococcal genes [1].

More than 95% of VRE recovered in United State are *E faecium*. These isolates are also resistant to ampicillin. The strong association of VRE with ampicillin resistant *E faecium* attributed to genetic linkage. The resistance is spread through transposon (Tn 5382). Both markers are located within a large mobile element that was able to transfer between *E. faecium* strains. *E faecium* is not as pathogenic as *E. faecalis*, infact, many VRE infections resolve without active antimicrobial drug therapy [17].

Clostridium pereringens and drug resistance

C perfringens is a gram-positive rod shaped anaerobic spore forming bacterium, some strains produce toxin which cause food poisoning. In United States it is the third most common cause of food born illness diarrhea and 5-20% of all cases of antibiotic associated diarrhea [18]. *Clostridium difficle* is implicated in the most severe cases of antibiotic associated diarrhea [19]. In past few decades enterotoxigenic strains of *Clostridium perfringens* have been identified as important agent of diarrhea. Most of the studies carried out have been on out break and have involved adults. Clostridium perfringen has also been shown to be associated with antibiotic associated diarrhea[20]. Drug resistance have been reported in *C. difficle* by Sebaihia et al 2006 [21] gyr mutations in fluoroquinolone resistant clostridium difficile have been demonstrated by Denise et al 2007 [22].

Drug resistant-*bacillus cereus*

Bacillus cereus is gram positive aerobic or facultatively anaerobic spore forming rods. It causes food poisoning, which is frequently associated with the consumption of rice based dishes. The organism produces an emetic or diarrhoal syndrome induced by an emetic toxin and enterotoxin, respectively. *B cereus* produces beta lactamases and so is resistant to beta-lactam antibiotics, it is usually susceptible to treatment with clindamycin, vancomycin and erythromycin [23].

Halicobacter pylori infection and drug resistance

H pylori has strong association with gastritis, gastric

and duodenal ulcers, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. Its infection is quite common amongthe population of developing countries up to 70% - 90%. Whereas, this rate is reduced by 50% in developed countries[24]. Most common mode of infection is through fecal-oral and oral-fecal transmission [25]. It has been considered as class I carcinogen.

Triple therapy is recommended to eliminate *H pylori*. It comprises a proton pump inhibitor in combination with two other antibiotics, includind amoxicillin, clarithromycin, or metronidazole [26, 27]. Resistance against clarithromycin is of great concern since this is a key drug for the eradication of *H. pylori* [25]. Thus, macrolide resistance is a frequent cause for failure of *H. pylori* eradication therapy[26]. Resistance rate against clarithromycin is higher in developing countries (20%-50%), while in USA (5%-10%), in Europe (10%) [26, 28, 29]. Clarithromycin resistance in *H pylori* is caused by single mutation in three adjacent nucleotides of 23s rRNA (2 142,2 143,2 144). these substitution cause decreased affinity of the ribosomes for several macrolides and hence resistance is increased.

Role of P-glycoprotein (PGP) in *H. pylori* infection

Pgp is multidrug transporter that pumps out cytotoxic substances, found on the gastrointestinal tract epithelium. Their mechanism of action being based on binding a broad spectrum drugs to the membrane polypeptide chain and through it out from the cell by using ATP energy. ATP dependent efflux proteins usually belong to the ABC transporter family [30,31]. Efflux pump as a mechanism of drug resistance has been described in gram negative bacteria in 1980[32]. In *H pylori*, LmrA transporter protein was identified as homologous to human multidrug transporter[33]. Pgp is expressed on a vide variety of cells. The evidence that Ppg inhibits the gastrointestinal absorption of orally taken drugs has been provided by several researchers [34-37]. Pgp activity is used as a good parameter for measuring the effect therapy. Increased Pgp activity may contribute to the drug induced effect on gastric cells after along therapy. It was also observed that Pgp pump activity was also increased during *H. pylori* infection. Therefore, this activity is being used to assess the therapeutic failure during the therapy in patients and also help to determine the potential of new therapeutic protocols.

Drug resistance in *campylobacter* species

It was in 1970s that the significance of campylobacter species in enteric diseases have revealed that more than 90% of infections are caused by *C jejuni*. *C lari* comprises < 1% of the strains isolated, with other species, such as *C. upsaliensis* and *C fetus*, only occasionally seen in clinical isolates [38]. Usually antibiotics are not prescribed in most of the diarrhoael cases caused by Compylobacter species but in severe or prolonged illness the use of erythromycin or ciprofloxacin is recommended [39]. *C jejuni*, is least resistant against erythromycin compare to *C. coli* which has been found more resistant [40]. *C. jejuni* and *C. coli* were found to have highest susceptibility against aminoglycosides. One of the reports by Thawits and Frost et al (1999) showed that 15 strains of *C. lari* out of 25 tested were resistant to kanamycin and tetracycline. This fact also strengthens the hypothesis that kanamycin resistance is usually plasmid mediated along with tetracycline marker [41].

Salmonelia infection

Salmonella is one of the most common and widely distributed disease and constitutes a major public health problem. It is generally contracted through consumption of contaminated food of animal origin (mainly meat, poultry, eggs and milk). A total of 2 501 different Salmonella serotypes have been identified that can cause disease in humans. While all serotypes can cause disease in humans, they are often classified according to their adaptation to animal hosts. A few serotypes have a limited host spectrum affecting only one or a few animal species for example *Salmonella typhi* in primates, *S. Dublin* in cattle and *S choleraesuis* in pigs. When these strains cause human disease it is often invasive and can be life threatening. Most serotypes have broad host spectrum such strains usually cause gastroenteritis often uncomplicated and needs no treatment but can be severe in elderly and immuno compromised individuals.

Antimicrobial drug resistance in *salmonella*

Strains of *Salmonella* spp with resistance to antimicrobial drugs are now widespread in both developed and developing countries. Resistance to the fluoroquinolones has emerged as a result of mutations in bacterial genome, while resistance to other antimicrobials have spread by transfer of DNA between bacterial strains. In some cases multidrug resistance is transferred by plasmid of particular concern to public health is the continuing worldwide epidemic spread of Salmonella enterica serovar. *S typhimurium* phagetype DT104 harbouring a genomic island called Salmonella genomic Island (SGI-1) This island contain an antibiotics gene cluster conferring resistance to ampicillin, chloramphenicol, florfinicol, Streptomycin, sulfonamides and tetracyclines. These resistance genes are assembled in mosaic pattern, indicative of several independent recombinational events. Multidrug resistant Salmonella were reported in European countries by Salmonella enterica serotype type isolates were found to be resistant to nalidaxic acid by Le et al 2007 [42]. The mechanism of nalidicxic acid resistance was due to mutation in the quinolone resistance determining chromosomal region of gyrA leading to amino acid substitution Ser83Phe, while plasmid mediated quinolone resistance was detected by Hopkins et al, 2007, qnrS1, qnrS2 genes were present on plasmids [43]. Multidrug resistance in *Salmonella typhi* and Salmonella non typhi were found to 2% and 18.9% respectively by Al-Tawfiq, 2007[44], Kato et al, 2007, also report multidrug resistance *Salmonella typhi* from India. They found 66.66% of strains to multidrug resistant [45].

Cholera a diarrhoeal disease by vibrio cholerae

Cholera is caused by gram negative bacterium Vibrio cholerae that belong to the O1 or O139 serogroup. The organism enters into the host during ingestion of contaminated water or food that colonizes the small intestine and produces enterotoxin (cholera toxin). Colonization of the gut is facilitade through the expression of bundle forming pilus structure (toxin coregulated pilus [TPC]) on the surface of the bacterium[46].

Development of drug resistance in vibrio cholerae is reported from different parts of the world. In India Sharma et al, 2007 reported 100% resistance to furazolidone, nalidixic acid and 96.6% to trimethoprim sulphamethoxazole in *V. cholerae* O1. In *V cholerae* serotype Inaba multidrug resistance (three or more drugs) was 98.6% in gawa 98.3% whereas in *V. cholerae* O139 it was only 30.8%. It was found that drug resistance in *V. cholerae* is either chromosome encoded or plasmid mediated [47].

Drug resistance in *Shigelia* SPP.

Among the bacterial causes of dysentery *Shigella* spp. Continue to be the most important with high infectivity rate and development of antimicrobial drug resistance. The infective dose for sufficient to initiate infection [48]. Four *Shigella* spp. Are recognized human pathogens- *Shigella dysentriae*, *Shigella sonnei*, *Shigella flexneri*, and *Shigella boydii*. Of these *Shigella sonnei* and *S boydii* are associated with mild illness of short duration. Infection by *S.* flexneri is generally more severe and last longer. *S dysenteriae* type I causes the most severe illness associated with complications and high mortality. Epidemiological reports show that 140 million people suffer from infection with gram negative bacilli, Shigella with estimated 600 000 deaths per year worldwide (WHO 1998).

There is emergence of multidrug resistance to different antibiotics including ampicillin, trimethoprim-sulphamethoxazole and nalidixic acid [49]. Resistance to ampicillin, tetracycline, chloramphenicol, nalidixic acid, gentamycin, ciprofloxacin has been reported recently [50]. Multidrug resistant *Shigella* spp. Showed high susceptibility to Mecillinam, a beta lactam with preferred activity against gram negative penicillin binding protein [51].

Ampicillin resistance in *enterococci*

Enterococcal infections are mostly treated by ampicillin. Low level ampicillin resistance in *enterococci* is due to the production of a low affinity penicillin-binding proteion (PBP). PBP5 have been identified in several enterococcal species, *E. faecalis*, *E. faecium* and *E hirae*. Resistance against ampicillin was observed in the lactamase producing species. Another ampicillin resistance mechanism is alteration in expression of PBP5. *E faecium* is more susceptible to

the changes in PBP5 as a primarily clinical problem. PBP5 has major role in cell wall synthesis, which is proved by an observation that *enterococci* could grow normally in penicillin concentration enough to saturate all the PBPs except PBP5. It has also been reported that due to increased resistance against methicillin, vancomycin is being used extensively which has become ineffective against *Clostridium difficile* causing antibiotic-associated diarrhea and pseudomembraneous colitis [52].

Combating to resistance

A task force was established in 1999 by 10 federal agencies and departments, led by the Department of Health and Human Services, to solve the problem of antibiotic resistance. The task force along with CDC, the FDA, and the National Institutes of Health, issued an action plan in 2001. Task force agencies continue to accomplish the activities set forth in the plan. The success of the plan, known as the Public Health Action Plan to Combat Antimicrobial Resistance, depends on the cooperation of many entities, such as state and local health agencies, universities, professional societies, pharmaceutical companies, health care professionals, agricultural producers. In order to control antibiotic resistance problem all of these groups must work together. This is a very serious problem. Two things should be done, facilitate the development of new antimicrobial therapy while at the same time preserve the usefulness of current and new drugs.

Preserving antibiotics' effectiveness

Two main types of germs, bacteria and viruses, cause most infections, according to the Center for Disease Control. But while antibiotics can kill bacteria, they do not work against viruses and it is viruses that cause cold, the flu, and most sore throats. In fact, only 15 percent of sore throats are caused by the bacterium *Streptococcus*, which results in strep throat. In addition, it is viruses that cause most sinus infections, coughs, and bronchitis. And fluid in the middle ear, a common occurrence in children, does not usually warrant treatment with antibiotics unless there are other symptoms.

Nevertheless, "Every year, tens of millions of prescriptions for antibiotics are written to treat viral illnesses for which these antibiotics offer no benefits," says David Bell, M. D., the CDC's antimicrobial resistance coordinator. According to the CDC, antibiotic prescribing in outpatient settings could be reduced by more than 30 percent without adversely affecting patient health.

Reasons cited by doctors for over prescribing antibiotics include diagnostic uncertainty, time pressure on physicians, and patient demand. Physicians are pressured by patients to prescribe antibiotics, says Bell. "People don't want to miss work, or they have a sick child who kept the whole family up all night, and they're willing to try anything that might work." It may be easier for the physician pressed for time to write a prescription for an antibiotic than it is to explain why it might be better not to use one. But by taking an antibiotic, a person may be doubly harmed, according to Bell. First, it offers no benefit for viral infections, and second, it increases the chance of a drug-resistant infection appearing at a later time.

"Antibiotic resistance is not just a problem for doctors and scientists," says Bell. "Everybody needs to help deal with this. An important way that people can help directly is to understand that common illnesses like colds and the flu do not benefit from antibiotics and to not request them to treat these illnesses."

Following the prescription exactly is also important, says Bell. People should not skip doses or stop taking an antibiotic as soon as they feel better; they should complete the full course of the medication. Otherwise, the drug may not kill all the infectious bacteria, allowing the remaining bacteria to possibly become resistant.

While some antibiotics must be taken for 10 days or more, others are FDA-approved for a shorter course of treatment. Some can be taken for as few as three days. "I would prefer the short course to the long course," says Levy. "Reservoirs of antibiotic resistance are not being stimulated as much. The shorter the course, theoretically, the less chance you 'll have resistance emerging, and it gives susceptible strains a better chance to come back."

Another concern to some health experts is the increasing use of antibacterial soaps, detergents, lotions, and other household items. Good soap and

water is sufficient in most cases. Antibacterial products should be reserved for the hospital setting, for sick people coming home from the hospital, and for those with compromised immune systems.

To decrease both demand and over prescribing, the FDA and the CDC have launched antibiotic resistance campaigns aimed at health-care professionals and the public. A nationwide ad campaign developed by the FDA's Center for Drug -Evaluation and Research emphasizes to health-care professionals the prudent use of antibiotics, and offers them an educational brochure to distribute to patients.

The FDA published a final rule in February 2003 that requires specific language on human antibiotic labels to encourage doctors to prescribe them only when truly necessary. The rule also requires a statement in the labeling encouraging doctors to counsel their patients about the proper use of these drugs.

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