The crisis of antibiotic-resistance in bacteria

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ABSTRACT

Significant increases in the prevalence of resistance to antibiotics have been observed in common pathogen of humans worldwide. The consequences of the appearance and spread of antimicrobial resistance have included increasing morbidity, mortality, and cost of health care. The increasing use of antimicrobial agents promotes the appearance and spread of bacterial resistance. Strict clinical guidelines on antibiotic prescribing and firm guidance on the optimum length of treatment is required. These strategies can be utilized as a part of a multidisciplinary approach to limit the appearance and dissemination of antimicrobial resistance, in addition to, surveillance of antibiotic resistance rates both locally and nationally.

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The tremendous therapeutic advantage afforded by antibiotic is being threatened by the emergence of increasing resistant strains of microbes. Antimicrobial resistance has resulted in increased morbidity and mortality, as well as high health-care costs. Selective pressure favoring resistant strains arises from misuse and overuse of antimicrobials (specifically extended-spectrum cephalosporins), increased numbers of immunocompromised hosts, lapses in infection control, increased use of invasive procedure and devices, and the widespread use of antibiotics in agriculture and animal husbandry. The appearance and spread of antimicrobial resistance has not been limited to bacteria. Since the introduction of fluconazole, strains of Candida causing hospital-acquired fungal infections have changed from ones with predictable fluconazole susceptibility to those with significant resistance.[1] One study[2] of Candida bloodstream isolates has shown that the likelihood of resistance to fluconazole or amphotericin was directly related to the magnitude of fluconazole or amphotericin therapy the patient had received prior to recovery of Candida isolates. Increasing resistance to antimicrobials has been identified in other classes of human pathogens, such as the mycobacteria and viruses. Most important in this regard are mycobacterium tuberculosis and human immunodeficiency virus (HIV).[3] Tuberculosis (TB) is an infection that has experienced spectacular ups and downs in the prevalence, control, and response to antibiotics. Drugs were developed to treat it, complacency set in that it was beaten, and the disease resurged as patients stopped their medication too soon and infected others. Today, one out of 7 new TB cases are resistant to the 2 drugs most commonly used to treat TB (isoniazid and rifampicin), and 5% of patients die. When patients with TB were closely followed with nurses observing them take their pills, the relapse rate, which reflects antibiotic resistance, fell from 20.9-5.5%,[4] this is especially significant as it occurred as risk factors for spreading TB.

Consequences of antibiotic resistance. The adverse consequences of antibiotic resistance have been well documented. When outbreaks of bacterial infection were examined retrospectively,[5] those caused by antibiotic resistant strains were associated with rates of hospitalization, length of hospital stay, and mortality that were 2 times greater than those caused by antibiotic sensitive strains.

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Risk factors for developing antimicrobials resistant infections. The most important factor influencing the emergence of antibiotic-resistant bacterial infections has been the extensive use of antimicrobial agents both within hospitals and in the community setting. In human, antibiotics are often used when unnecessary, and when they are necessary, often the wrong antibiotics are prescribed, selecting for bacteria that have developed or received resistant mechanism. Antibiotics are necessary when an infection cannot be eliminated through the body's natural defenses' they are unnecessary when incorrectly prescribed for viral infection. According to a study carried out by the Center for Diseases Control [CDC], of the 150 million outpatients prescriptions each year in the United States of America (USA), 50, 000,000 were estimated to be unnecessary.[6] During hospital stays, patients are often prescribed broad-spectrum antibiotics, which kill all types of bacteria, rather than targeting a specific population of bacteria. Since broad-spectrum antibiotics affect all bacteria, they select for resistance in harmless bacteria giving them the potential to become pathogenic. For instance, 5-years ago, *Acinetobacter species*, and *Stenotrophomans species* were harmless bacteria, but today cause pathogenic infection.[7] A number of investigators have demonstrated a close association between the use of antibiotics and the emergence of antibiotic resistance, both in gram-negative and gram-positive bacteria.[8-12] Trouillet et al,[13] examined 135 consecutive episodes of ventilator-associated pneumonia, of which 77 (57%) were caused by potentially antibiotic-resistant bacteria (methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter baumanii, and Stenotrophomonas maltophilia*). According to logistic regression analysis, duration of mechanical ventilation for 7 or more days, prior antibiotic use, and prior use of broad-spectrum antibiotics (third-generation cephalosporins, fluoroquinolones, or imipenem, or both) were associated with the development of ventilator-associated pneumonia due to antibiotic-resistant pathogens. This investigation confirmed the importance of antibiotic exposure as a risk factor for nosocomial infections due to antibiotic resistant bacteria.[14,15] In addition to prior antibiotic exposure, other factors have been associated with emergence of antibiotic-resistant infections. Prolonged length of stay in the hospital appears to predispose to infection with antibiotic-resistant bacteria.[14] This may be due in part, to the greater likelihood of becoming colonized with such bacteria, from either horizontal nosocomial transmission, or endogenous emergence of resistance, the longer a patient remains in the hospital. Similarly, the presence of invasive devices, such as endotracheal tubes, intravascular catheters and urinary catheters may also predispose to infection with antibiotic-resistant and antibiotic-sensitive bacteria. Twenty percent of antibiotic prescriptions are received by hospitalized patients, while the rest occurs in the community. It has been estimated that 20-50% of all antibiotic prescriptions are unnecessary.[16] Unfortunately, doctors often prescribe antibiotics excessively and inappropriately, for various reasons.[17] Reasons doctors gave for over prescribing antibiotics: 1. Insufficient training, or lack of education in infectious diseases and antibiotic treatment. 2. Difficulty in selecting the appropriate antibiotic empirically 3. Insufficient use of microbiological information 4. Need for doctors to reassure themselves the treatment they prescribe will be effective 5. Fear of litigation which prompts the use of broad-spectrum drugs 6. Patient expectation. In addition, staff compliance with basic infection control practices, such as hand washing, is often inadequate. Furthermore, shortage of health-care staff and isolation facilities often make controlling the spread of antibiotic-resistant bacteria difficult in hospitals.

Mechanisms of antibiotic resistance. Resistance in bacteria can be intrinsic or acquired, and may occur by mutation or acquisition of DNA. Mutation is the most frequent mechanism of resistance development in *mycobacterium tuberculosis*.[18] Bacteria can protect themselves from antibiotics by 4 main mechanisms: 1. Antibiotic modification occurs when the sensitivity of the target within the bacteria remains the same but the antibiotic is prevented from reaching it. An example is the β-lactamase enzyme cleaving the 4-membered β-lactam ring of penicillin and cephalosporins, rendering the antibiotic inactive. 2. Some bacteria can prevent the antibiotic from entering the cell or are able to pump it out faster than it can flow in. Imipenem-resistant *Pseudomonas aeruginosa* lacks the specific D2 porin in its cell membrane, which confers resistance as imipenem cannot then penetrate the cell. Tetracycline resistant bacteria show increased efflux of the antibiotic via an energy-dependent transport pump. 3. Changes to the site of action may occur as of structural alteration in the molecules. Most strains of *Streptococcus pneumoniae* are highly susceptible to penicillin and cephalosporins, but they can acquire DNA from other bacteria (for example enterococcus), which changes the enzyme responsible for penicillin-binding proteins (PBP) production. 4. The final mechanism is the production of an alternative target (usually an enzyme) that is resistant to inhibition by the antibiotic. An example is the production of an alternative binding protein (PBP2a) which is produced in addition to the "normal" PBP by MRSA.

Several methods of genetic transfer allow bacteria to pass these mechanisms of resistance. Bacteria have special DNA elements called R plasmids that contain resistance genes and are easily passed to other bacteria. Bacteria may also take up random sequences of DNA encountered in their environment. If this DNA contains resistance genes, the bacteria could become resistant. Viruses can also serve as a means of bacterial transfer. Occasionally, when viruses are made in an infected bacterial cell, DNA with resistance genes may accidentally be encapsulated into a daughter virus particle. When this daughter virus infects another bacteria, DNA for antibiotic resistance is spread to that cell.[19] Selective pressure resulting from antimicrobial administration can lead to the other bacteria. Overgrowth of previously susceptible strains that have acquired resistance, or the overgrowth of strains that are intrinsically resistant. The emergence of Stenotrophomonas maltophilia during imipenem therapy is an example of selection of intrinsically antibiotic-resistant strain.

Resistance associated with community-acquired infections. Outside the hospital, resistance to previously standard therapy is emerging in several common pathogens. These include *Salmonella, Shigella, Neisseria gonorrhoeae*, *S. pneumoniae*, *Haemophilus influenzae,* and most recently *S. aureus*.[20] Pathogens associated with respiratory tract infections have significant impact as approximately 75% of oral antimicrobial use are for respiratory tract infection. Greater than 35% of *H. influenzae* strains, and 90% of Moraxella catarrhalis are now resistant to the early β-lactam agents, by virtue of the β-lactamase enzymes they produce.[21,22] β-lactamase inhibitors combined with penicillin can restore activity towards such strains. Rare strains of *H. influenzae* that are ampicillin resistant but β-lactamase negative have recently been identified.[21] Of greatest concern however, is the recent emergence of resistance in *S. pneumoniae*. Recent multicenter studies indicate that penicillin resistance rates in the USA are now approximately 24-34%, with high-level resistance rates of 9-14%.[23,24] In Europe, the prevalence of penicillin-resistant pneumococci varies significantly from 0-5% (Germany, Switzerland and Italy), to 11-17% in France and Spain.[25] In the Kingdom of Saudi Arabia and other neighboring countries 3-7% of Pneumococci are resistant to penicillin and 51% are intermediately resistant.[26-28] The clinical relevance of drug-resistant strains of Strep. pneumoniae in lower respiratory tract infections has been debated, but recent studies suggest in a correlation between the presence of high penicillin resistance and increased mortality in invasive *S. pneumoniae* pneumonia.[29] Risk factors associated with penicillin-resistant pneumococci include past and current antimicrobial use and the presence of a family member in the day-care center.

Resistance associated with nosocomial infections. Most studies show a higher rate of resistance associated with nosocomial pathogens, particularly from intensive care units (ICUs), than with community-acquired organisms.[30] The correlation between increasing antibiotic use and increasing prevalence of antibiotic resistance has been shown most clearly in the hospital. As a part of the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) project carried out in hospitals participating in the Center for Diseases Control (CDC), and National Nosocomial Infections Surveillance (NNIS) Survey, the prevalence of methicillin-resistant coagulase-negative *Staphylococcus*, methicillin-resistant *S. aureus,* ceftazidime-resistant Enterobacter, imipenem-resistant *Pseudomonas* and vancomycin-resistant *enterococci* were shown to rise progressively from outpatients to inpatients to patients hospitalized in the ICU, as did antibiotic use in each of these populations.[30]

Management of antimicrobial resistance. Various strategies to limit antimicrobial resistance have evolved and are based on 4 basic principles: containment of resistant species (such as isolation and colonization surveillance); infection prevention (such as appropriate use of antibiotic prophylaxis, vaccination, and limited utilization of invasive devices); infection eradication (such as appropriate diagnosis and treatment); and optimizing antibiotic utilization. The most basic goal of optimizing utilization is the appropriate utilization of antibiotic therapy. This involves accurately identifying infection episodes using standardized definition, obtaining appropriate culture and sensitivity data, applying appropriate treatment modalities, selecting the most appropriate antibiotic for therapy when indicated, and dosing antibiotic appropriately.[31] In addition, to selecting the most appropriate antibiotic, utilizing knowledge of hospital-specific and unit-specific antibiotic susceptibility patterns, treatment includes removal of invasive devices and prosthesis materials, drainage collection, and debridement of devitalized tissues. Various strategies have developed that entail the manipulation of antibiotic use to decrease the rates of antibiotic resistance. These strategies include alterations in antibiotic utilization, implementation of antibiotic guidelines/protocols, and formulary restriction.

Alterations of antibiotic utilization by antibiotic rotation or cycling. These are associated with alteration in antibiotic resistance patterns presumably through alterations in antibiotic selection pressure. Kollef et al[32] studied the effect of

a scheduled change in empiric antibiotic coverage of suspected gram-negative rod infection from ceftazidime to ciprofloxacin in 680 patients who had undergone cardiac surgery during two 6-month periods. The study revealed a significant reduction in the incidence of ventilator-associated pneumonia (VAP) (relative risk of VAP during the second 6-months periods: 0.58, 95% confidence interval (CI) 0.35-0.95; *P*=0.028) presumably due to significant reduction in VAP caused by antibiotic resistant-gram negative rods (relative risk: 0.23; 95% C.I., 0.076-0.80; *P*=0.0013). Additionally they were able to demonstrate improved antibiotic susceptibility profile of gram-negative isolates (48.8% resistant versus 20%; *P*=0.05). With the availability of new antibiotic agents for the treatment of gram-positive bacterial infections, the use of scheduled antibiotic changes can also be implemented at improving therapy for these infections.

Antibiotic guidelines, protocols and recommendations. The implementation of guidelines or protocols, have been shown to be a formal means of achieving the goal of appropriate antibiotic utilization, limiting unnecessary antibiotic use and, as result improving antibiotic susceptibility profiles.[33-37] For example, nationwide program to specifically reduce the use of penicillin was associated with reduction in the nationwide prevalence of penicillin resistance in *pneumococci* in Iceland.[38] Likewise, a reduction of erythromycin resistance was observed in group A. *Streptococci* after implementation of programs to reduce the nationwide use of erythromycin and other macrolides antibiotics in Finland.[34] Antibiotic use guidelines in the hospital settings which employ a computerized system in guiding clinicians use of antibiotics proved to be successful in identifying and minimizing the occurrence of adverse drug effects due to antibiotic administration, also has been shown to reduce the occurrence of inadequate empiric antibiotic administration, as compared with individual physician prescribing practices and stable antibiotic susceptibility patterns of nosocomial bacteria.[35-37]

Hospital formulary restrictions. Limiting access to an antibiotic through formulary restriction or antibiotic surveillance teams has been implemented in many centers, as a means of decreasing the inappropriate utilization of antibiotics, especially broad-spectrum agents (such as imipenem), rapid emergence of antibiotic resistance (such as third-generation cephalosporins), and readily identified toxicity (such as aminoglycosides) thus decreasing antibiotic selection pressure and therefore, improving resistance profiles. Such programs have been shown to be successful for limiting the spread of specific pathogens. Quale et al[39] demonstrated that restriction in the use of vancomycin and cefotaxime in addition to replacing third-generation cephalosporins with β-lactamase inhibitors resulted in a significance decline in the point prevalence of vancomycin-resistant enterococci (VRE) colonization (42% versus 15%; *P*<0.001) during a hospital-wide outbreak. Furthermore, Rice et al[40] restricted the use of ceftazidime to control an outbreak of ceftazidime-resistant *Klebsiella pneumoniae*, and Rahal et al[12] limited hospital-wide cephalosporin usage to decrease the rate of cephalosporin-resistant *Klebsiella species* by 44% (*P*<0.01). Restriction program has been shown to reduce drug cost, and adverse reactions[41] and may positively affect antimicrobial susceptibility patterns when part of a multidimensional program that includes physician education and antibiotic guidelines;[40,42] however, alone they may also decrease the heterogenecity of antibiotic use and, thus, enhance resistance as reported in the study of Rahal et al.[12] To date, due to methodological problems, it has been difficult to demonstrate that restricted hospital formularies are effective in curbing the overall emergence of antibiotic resistance among bacterial species. However, their use has been successful in specific outbreaks of infection with antibiotic-resistant bacteria, particularly in conjunction with infection control practices and antibiotic educational activities. Restricted formularies cannot be viewed on as alternative to more judicious overall use of antibiotics since the emergence of widespread resistance to the unrestricted antibiotics will likely occur when their prescription is not carefully managed.

Reducing the resistance of bacteria to antimicrobial agents depends on the clinicians, the patients who demand antibiotic for viral illness, and the pharmaceutical industry, which should, promotes antibiotics appropriately.[43,44] Physician education is an important part of an antibiotic-resistance-management program. Education-based intervention is most effective when the prescribing physician perceives it as assistance rather than as a restriction. Education can be accomplished by a variety of means. An antibiotic review sub-committee to the pharmacy and therapeutic committee can be created to engage in discussions at section meetings, circulate newsletters, and speak at grand rounds. Advantage of the educational approach over the restrictive formularies, or the requirement of prescription approval by an infectious disease specialist include, less conflict, a greater diversity in antibiotic prescribed, and the direct involvement of infection control specialists and microbiologist. The threat associated with antimicrobial resistance should serve as a strong incentive for responsible and

judicious use of antimicrobial agents. There is a need for both prudent use of antibiotics and stringent appropriate infection control policies to reduce the emergence of resistance.

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