Prevention of Antibiotic Resistance / Antibiotic Misuse - Abuse

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ABSTRACT

The emergence and spread of resistance to antibiotics among common pathogenic bacteria is an important healthcare concern. Today, the magnitude of the problem has become so great that it is threatening to reverse the scientific progress made so far. Several factors contribute to the problem including misuse on the part of physicians and patients, widespread use of antibiotics with high resistance potential, use of antibiotics as animal growth promoters and in household products. Resistance once established cannot be reversed, but prudent use of antibiotics can minimize the further development of resistant strains. Therefore, effective measures should be taken to combat antibiotic resistance. These include education of consumers and prescribers about the use and misuse of antibiotics, promoting the use of antibiotics with little or no resistance potential, and discouraging the use of antibiotics in animal husbandry. The role of surveillance of bacterial resistance is of paramount importance in helping physicians to choose appropriate antibiotics and for policy makers in formulating guidelines for the treatment of common infections.

INTRODUCTION

Antibiotic resistance with some microorganisms has become a worldwide concern. After World War II, penicillin resistance among gonococci and staphylococcal strains was first noted.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) emerged in the 1970's. Aminoglycoside-resistant *Pseudomonas aeruginosa* was noted after the widespread use of gentamicin, while ceftazidime-resistant and ciprofloxacin-resistant *P. aeruginosa* remains a concern today. There has been a rapid increase in antibiotic resistance among respiratory pathogens. Penicillin resistance in *Streptococcus pneumoniae* has increased in an epidemic manner in the past 10 years.[2,3] Resistance to macrolides, doxycycline, trimethoprim-sulfamethoxazole and second and third-generation cephalosporins are also on the rise.

A distinction must be made between increased prevalence versus the emergence of resistant organisms, which is the case with enterococci. In the past, *Enterococcus faecalis* was the commonest pathogenic enterococci (i.e. sensitive to ampicillin and vancomycin). Now, *Enterococcus faecium* has emerged as a commoner pathogen and it constitutes nearly all vancomycin-resistant enterococci (VRE) strains. This is not an example of increasing antibiotic resistance but rather a change in the selective pressures of the fecal flora favoring the widespread emergence of VRE as a colonizer.[4]

Major problems are also being faced in the treatment of tuberculosis due to emergence of resistance against multiple drugs. It has been estimated in a recent global survey that 9.9% of *M. tuberculosis* isolates from previously untreated patients are resistant to one of the first-line drugs (rifampicin, isoniazid, ethambutol, streptomycin).[5]

Resistance is emerging due to the increasing exposure of microorganisms to antimicrobial agents. Exposure of microbes to antimicrobials tempt them to develop strategies to survive in the hostile environment and become resistant. Pressure on the bacteria to mutate and become "hardy" develops due to (i) inappropriate and excessive use of antibiotics in treating infection, (ii) widespread use of antibiotics in animal husbandry and (iii) use of antimicrobials / antiseptic agents in agriculture and for domestic purposes. Once resistance is established, it cannot be reversed, but proper use of antibiotics minimizes the flourishing of resistant strains. Therefore, measures should be taken to promote appropriate prescribing and minimizing the development and spread of resistant bacteria.

FACTORS LEADING TO ANTIBIOTIC RESISTANCE

Antibiotic Misuse

Antibiotics are often used as a panacea for viral respiratory tract infections, to treat obscure febrile illnesses that are not infectious, and to treat infections for which antibiotics usually are ineffective (e.g. infected abscesses and implant-associated or device-associated foreign body infections). By withholding antibiotics, physicians are often subjected to concerns of infective complications and impaired health outcomes in patients. This and the fear of litigation, often pressurize a physician to prescribe

Table 1: Antibiotic resistance: Key concepts

Antibiotic resistance is agent-specific

- Antibiotic resistance is not related to antibiotic class
- Antibiotic resistance is not related to volume of use
- Antibiotic resistance is not related to duration of use

Antibiotic (agent-specific) resistance occurs early, not later

- If antibiotic resistance to a specific antibiotic develops, it occurs early (during preclinical trials or within 2 years after general use)
- Antibiotics showing resistance early (within 2 years) continue to have resistance problems as long as the antibiotic is used.
- Antibiotics that do not develop resistance problem within 2 years of use do not develop resistance later, even after prolonged high volume use

Clinical significance:

- Antibiotics with high resistance potential should be restricted or used minimally

  Examples include:
  - Ampicillin
  - Carbenicillin
  - Gentamicin
  - Tetracycline
  - Ciprofloxacin
  - Imipenem
  - Ceftazidime

Vancomycin usage should be restricted to prevent the increased prevalence of *E. faecium* (VRE)

- Antibiotics with little or no resistance potential should not be restricted.

Examples include:

- Piperacillin
- Amikacin
- Doxycycline
- Minocycline
- Quinolones (except ciprofloxacin)
- Third-generation cephalosporins (except ceftazidime)
- Cefipime
- Meropenem

Data from Cunha BA: Antibiotic resistance: Myths, truths, and a rational formulary approach 1999;34:644.

antibiotics. Patient's expectation and demands for antibiotics have also shown to have a strong association with excess antibiotic use.

Many patients in the ICU receiving mechanical ventilation are treated with antibiotics for weeks because of unexplained low grade fever, leukocytosis and ill-defined pulmonary infiltrates.

Antibiotic misuse also occurs when patients take shorter than prescribed course of antibiotics, and if a patient takes a reduced number of doses and/or at irregular timings. Recent study shows evidence that low serum drug levels may be associated with an increased risk of selecting resistant mutants for a variety of bacteria.[6] The easy, over-the-counter availability of antibiotics in developing countries further perpetuates the problem of drug resistance. Indiscriminate use of antibiotics not only subject the patient to antibiotic side-effects and drug interactions but if an antibiotic with a high resistance potential is used, the possibility of proliferation of resistant organisms is a potential complication.[7,8]

Antibiotic Resistance – Agent-Specific

Among antibiotic class there are one or more drugs which have more potential to cause antibiotic resistance, although this is not a class phenomenon. For example, among the third-generation cephalosporins, only ceftazidime has been associated with resistant *K. pneumoniae, Enterobacter* and *P. aeruginosa*, all other third-generation cephalosporins have not been associated with significant resistance problems with these or other organisms.[9,10] Similarly, among aminoglycosides, gentamicin[11] and among fluoroquinolones ciprofloxacin[12] have been associated with clinically significant resistance to various organisms. It is therefore prudent to use antibiotics with low resistance potential and restrict the use of antibiotics with high resistance potential (Table 1).

Antibiotic Resistance – Volume and duration of antibiotic use

It is a common misconception that the more an antibiotic is used the more it is likely to develop resistance. This is true only for antibiotics with high resistance potential. However, antibiotics not associated with high resistance (e.g. nitrofurantoin, doxycycline, minocycline, meropenem, cefipime, cefotaxime, ceftriaxone, levofloxacin, amikacin and piperacillin) have not been associated with widespread resistance problems after prolonged and extensive use.[7,8,13]

Similarly, duration of antibiotic use in years is not a predictor of antibiotic resistance. If antibiotic resistance to a specific antibiotic develops, it occurs early (within 2 years of general use). Antibiotics that do not develop resistance problems within 2 years of use do not develop resistance later, even after prolonged high volume use.[8] As neither volume nor duration of antibiotic use is a determinant or predictor of antibiotic resistance, there is no rationale for reserving an antibiotic with little or no resistance potential for future use.[14,15,16]

Antibiotic-Supplemented Animal Feeds

Antibiotics are commonly added to animal feeds to prevent infection and promote growth. There is little evidence that the incorporation of antibiotics into animal feeds reduces infections in animals raised for consumption, but there is good evidence that this practice has untoward effects in terms of antimicrobial resistance. The antibiotics most commonly used (e.g. tetracyclines and ciprofloxacin) are those known to be associated with antimicrobial resistance.[17] The use of avoparcin, a glycopeptide growth promoter, has selected for vancomycin-resistant enterococci among animals and the same clones of enterococci has also been found in humans.[18,19] Likewise, the use of growth promoter virginiamycin has selected for enterococci with resistance to it, but more important, to quinupristen daltopristin, an antibiotic that was recently approved for use in humans.[20] These bacteria armed with resistance to multiple drugs can gain entry into the human body through the food chain and cause resistance against many antibiotics.

Table 2: Common agent-specific resistance problems

High-resistance-potential antibiotics	Usual resistant organisms	Low resistance replacement antibiotic
Ceftazidime*	• Ceftazidime-resistant *P. aeruginosa* (not third-generation cephalosporin-resistant *P. aeruginosa*)	Cefepime
	• Ceftazidime-resistant *K. pneumoniae* or *Enterobacter* owing to extended-spectrum β-lactamases (ESBL) production	Meropenem
Ciprofloxacin*	• Ciprofloxacin-resistant *S. pneumoniae* (not fluoroquinolone-resistant *S. pneumoniae*) • Ciprofloxacin-resistant *P. aeruginosa* (not fluoroquinolone-resistant *P. aeruginosa*)	Levofloxacin
Imipenem*	• Imipenem-resistant *P. aeruginosa* (not carbapenem-resistant *P. aeruginosa*)	Meropenem
Gentamicin*	• Gentamicin-resistant *P. aeruginosa* (not aminoglycoside-resistant *P. aeruginosa*)	Amikacin

*Use also associated with an increased prevalence of methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecium* (VRE). Adapted from Cunha BA: Antibiotic resistance: Control strategies. *Crit Care Clin North Am* 1999;8:309-328.

Therapeutic use of Antibiotics in Animals

Today, the therapeutic use of antibiotics in animals is also a growing concern. Although the need may be real, this practice may lead to the selection of resistant strains of consequence to human health, especially if the use in animal does not follow the same standards of rational and appropriate use applied to human therapy. The reason for concern is genuine because soon after fluoroquinolones were given to animals in Netherlands, fluoroquinolone resistance appeared in another zoonotic organism, *Campylobacter*.[21] Resistant strains of *Campylobacter* are also appearing in the United States.[22] More important, *Typhimurium* DT104 that is resistant to fluoroquinolones has emerged in Europe.[23]

Antibacterial Household Products

Use of antibacterial containing surface products in households can affect resistance in the environment, as these agents leave residues and remain in sewers and on household surfaces, where resistant bacteria can develop. Triclosan, an antibacterial household product targets the same enzyme as does the experimental antibiotic diazoborine and isoniazid[24] and thus has a potential of causing resistance to these drugs.

As disposal of antibiotics into the environment can change the microbiology of a region, antimicrobial resistance is now being viewed as an "ecological problem". In addition, the increased rate of travel has also led to widespread and global dissemination of resistant microbes.

PREVENTION OF ANTIBIOTIC RESISTANCE

Public awareness

The International Forum on Antibiotic Resistance (IFAR) colloquium, 2002 recommended education for health care professionals and the public to promote prudent antibiotic use.

Several studies have shown that public-education campaigns can change knowledge and attitudes. In Canada, "Members of the Do Drug Need Bugs?" intervention community were significantly less likely to expect antibiotics for cold/influenza, more likely to mention hand washing as a measure to prevent infection, more likely to recognize that antibiotics offer no advantage in the treatment of colds or influenza, and more likely to define antibiotic resistance correctly.[25] Hence, large scale public education campaigns targeting relevant groups, using clear and consistent messages concerning bacterial versus viral infection, prudent antibiotic use, symptomatic treatment and infection control measures (e.g. handwashing) should be promoted.

Education of Health Care Professionals

As antibiotic resistance is agent-specific, limiting the use of high resistance potential antibiotic is the only resistance control measures that has been proved effective.[7,8,13] Given similar spectrum, pharmacokinetics, safety profile, and cost, clinicians should always select the antibiotic with little or no resistance potential. One of the tenets of antibacterial chemotherapy is that if the infecting bacterium has been identified, the most specific chemotherapy possible should be used. The use of a single agent with a narrow spectrum of activity against the pathogen diminishes the alteration of normal flora and thus limits the overgrowth of resistant nosocomial organisms. However, certain circumstances call for the use of more than one antibacterial agent (e.g. tuberculosis). Healthcare professionals should be encouraged to avoid needless treatment of viral illness and non-infectious disease with antibiotics. The principles of prudent antibiotic prescribing must be taught to undergraduate and postgraduate medical trainees.

As decreasing community use of antibiotics is an important strategy for combating the increase in community–acquired antibiotic-resistant infection. The need of the hour is to provide clinicians with evidence-based recommendation for the evaluation and treatment of various common infections. Physicians should be encouraged to believe that by following guidelines antibiotics can be safely withheld in certain patients. The Centers for Disease Control and Prevention (CDC) has initiated activities for decreasing inappropriate antibiotic use by publication of "practice guidelines" in the treatment of upper respiratory tract infection.

While prudent prescribing of antibiotic by doctors must be advocated, the issue of patient compliance to therapy cannot be ignored. There is evidence that the use of short duration, once or twice daily dosing regimens for community acquired infection can improve patient compliance,[26,27] thereby improving outcome and helping to reduce resistance.

Control Measures in Hospital and ICU/CCU

Antibiotics with known resistance problem should be removed from formulary or be made available only on a restricted basis. A properly limited hospital formulary is the best antibiotic resistance control measure.[7,8] Antibiotic equivalents exist in most antibiotic classes in which resistance has been a problem. By substituting an antibiotic with an equivalent spectrum but little or no resistance potential (i.e. a vacuum cleaner antibiotic), the general hospital environment can be cleaned up and restored to a relatively resistance-free environment (Table 2).

This measure coupled with an effective infection control program can eliminate or minimize most resistance problems in the hospital setting. Control of outbreaks resulting from highly resistant organisms depends on an effective infection control program for containment of the highly resistant strains to prevent intra-hospital and inter-hospital spread and extension into the community.

Antibiotic prescribing is intense in ICUs, and such units are most frequently the generators of resistant organisms. Resistance problems in CCUs are compounded by the fact that antibiotic therapy is often prolonged and antibiotics with a high resistance potential are used, setting the stage for the emergence of highly resistant microorganisms. Antibiotic choice in the ICU patients should be governed by:

a. Knowledge of the site of infection and the likely organisms present at that site.
b. Knowledge of what antibiotics the patient has previously received.
c. Knowledge of what multiresistant organisms colonize the patient, and
d. Knowledge of local epidemiologic trends in antibiotic resistance.

Although limited formularies in the CCU and ICU do not solve the problem, a restricted formulary in the hospital decreases resistance problems in the ICU and CCU.

Rapid implementation of infection control precautions to limit or contain spread of resistant organisms in ICU and CCU is also effective.

Discontinuation of Antibiotic-Supplemented Animal Feeds

As antibiotic resistant bacteria from animal products make their way into human population, antibiotic supplementation of animal feeds should be discontinued. In 1997 in Berlin a group of World Health Organization consultants recommended the gradual discontinuation of the use of antibiotics as growth promoters in the face of newly documented risks to human health. Recently the European Union countries have barred the use of growth promoter Avoparcin. As therapeutic use of antibiotics can also lead to selection of resistant strains, adequate caution should be taken before approving these drugs for use in animals. Therapeutic use of antibiotics in animals should also follow the same standards of rational and appropriate use applied to human therapy.

Surveillance

Surveillance of bacterial resistance is essential to understand the magnitude of the problem and also to assess the impact of interventions in containing antimicrobial resistance.

Surveillance at local level is needed to detect the local resistance pattern and thereby help doctors to choose appropriate antibiotics. It can also generate data for national and international surveillance.

Surveillance at the national / international level is required to guide policy makers in framing treatment guidelines.

Surveillance should also be done at hospital level to periodically review changes in resistance pattern in the hospital and ICU and to report novel resistance pattern to local, state and national public health officials.

CONCLUSION

Antibiotic resistance, especially the development of bacteria resistant to multiple drugs, is a rapidly growing global problem.

Diverse factors, including patient's expectation, over-the-counter availability of antibiotics, rampant use of antibiotics with high resistance potential and use of antibiotics as growth promoters in animals contribute to the problem.

Effective strategies to control antibiotic resistance are: •

- Increasing public awareness through public education campaigns
- Promoting prudent use of antibiotics by health professionals
- Restricting the use of antibiotics with high resistance potential
- Checking over-the-counter sale of antibiotic
- Discouraging the use of antibiotics in animal husbandry and household products
- Formulating evidence-based guidelines for the treatment of common infections
- Surveillance at local and national level to assess the magnitude of the problem and effectiveness of interventions.

Interventions may have limited effect as long as other regions of the world continue to misuse antibiotics, select for resistant bacteria and spread them. Therefore, we must all join hands in this fight to return to the world of susceptible microbes.

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