What Is the Issue of Antimicrobial Resistance?

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Abstract

During the last decade, we have witnessed the evolution and dissemination of multi-drug resistant bacterial pathogens in hospitals and the community. This has resulted in limited options for the management of infections due to such pathogens, increased health care costs, as well as increased morbidity and mortality. Although much of the resistance problems we face today are the result of the misuse of antibiotics in humans, there is increasing evidence that the use of antibiotics in agriculture has contributed to this problem.

Examples include *Salmonella typhimurium* DT104 resistant to at least 5 antimicrobials in cattle, fluoroquinolone-resistant *Campylobacter jejuni* in poultry and vancomycin-resistant *enterococci* (VRE) in farm animals. Multidrug resistant *enterococci* are organisms found in both humans and animals as normal flora, causing disease in compromised patients. Vancomycin until recently had remained the mainstay of therapy.

However, in the late 1980s VRE were isolated in the UK and the USA. VRE has now established itself as a major nosocomial pathogen and threatens to provide a source for vancomycin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA). There is now compelling evidence that the use of a vancomycin-like drug, avoparacin, as a growth promoter in the European agriculture industry provided the selective pressure for the emergence of this resistant organism. The use of antibiotics in agriculture, without regard for their impact on resistance in human pathogens, may help to accelerate us to the post-antibiotic era.

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Introduction

Antibiotics were initially developed for the treatment of infectious diseases in people. Their miraculous effects led to the same antimicrobials being used for the treatment of animals and eventually plants. The powerful killing and growth inhibitory effects of antibiotics have reduced the numbers of susceptible strains, leading to the evolution and propagation

of resistant variants. Although much of the resistance problems we face today are the result of the misuse of antibiotics in humans, there is increasing evidence that the use of antibiotics in agriculture has contributed to this problem. Examples include *Salmonella typhimurium* DT104 resistant to at least 5 antimicrobials in cattle, fluoroquinolone-resistant *Campylobacter jejuni* in poultry, and vancomycin-resistant *enterococci* (VRE) in farm animals (Glynn *et al*., 1998; Smith *et al*., 1999; Stobberingh *et al*., 1999).

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How Have Bacteria Managed To Become Resistant To Antimicrobials?

The use of antimicrobials themselves do not cause resistance, but rather their presence creates a selective environment for resistant strains over their susceptible counterparts, allowing them to survive and to multiply. Equally important to the creation of the problem of antimicrobial resistance is the dissemination of these resistant microorganisms that have evolved. In order for a strain to disseminate it must be transmitted to a susceptible host that it can colonize and/or infect. Social changes have facilitated dissemination. For example, the establishment of daycares has facilitated the transmission of antimicrobial resistant pathogens amongst children. Migration and world travel have facilitated the global dissemination of resistant pathogens including: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and penicillin-resistant *Streptococcus pneumoniae* (Fukuda and Hiramatsu, 1999; Heisig 1996; Hoshino *et al*., 1994; Kataja *et al*, 1999; Tanaka *et al*., 1997). One of the major factors believed to be responsible for creating a large susceptible host population is the misuse of antibiotics (Gootz and Brighty, 1996). Antibiotics kill the normal flora that may protect the individual from being colonized with a resistant strain that they may come in contact with (Nikaido, 1998; Weigel *et al*., 1998; Zhao *et al*., 1997).

Resistance can be either inherent or acquired. Inherent resistance is a result of the normal genetic, structural, or physiologic state of a microorganism. This resistance is predictable and therefore recognized once the identity of the microorganism is known (Yoshida *et al*., 1990). Acquired resistance is when the organism has been able to either develop resistance by spontaneous mutation or has acquired a resistance mechanism from an external source. Acquired resistance can occur de novo or by acquiring resistance genes from other organisms.

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De Novo Resistance

De novo resistance is often the result of a single or multiple genetic mutations, such as is seen with the development of resistance of *Mycobacterium tuberculosis* to streptomycin, *Staphylococcus aureus* to fluoroquinolones, the development of extended spectrum b-lactamases (ESBLs) in Gram negatives and rifampin resistance (Deplano *et al*., 1997; Rasheed *et al*.,1997). All organisms suffer a certain number of mutations as the result of normal cellular operations or random interactions with the environment. Such mutations are called spontaneous or growth-dependent. Therefore, spontaneous mutations resulting in resistance may occur by chance. Mutations of any kind may be facilitated by "mutator" cell phenotypes (Bjorkman *et al*., 1998; LeClerc *et al*.,1996; Taddei *et al*.,1997). LeClerc (LeClerc *et al*., 1996) reported that the incidence of mutators among isolates of pathogenic *Escherichia coli* and *Salmonella enterica* was high (over 1 percent). They found defects in the methyl-directed mismatch repair system in all mutator phenotypes described. Of nine independently derived hypermutable strains, seven contained a defective mutS allele. They speculated that since these mutant alleles increase the mutation rate and enhance recombination among diverse species, this might help explain both the rapid emergence of antibiotic resistance and of virulence genes.

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Acquisition Of Resistance

Horizontal gene flow is a driving force in bacterial evolution. The implication is that complex and elegant resistance mechanism, which may have evolved eons ago, can be shared with other species within the same genus, and even with other genuses (Courvalin, 1996). Acquisition of foreign DNA occurs by three mechanisms: transduction, the bacteriophage-mediated transfer of genes from one bacterium to another; transformation, the introduction of extraneous DNA into a competent bacteria; and conjugation, transfer of genetic material from one cell to another by means of cell-to-

cell contact (Courvalin, 1996). Transduction is limited to closely related species by the high degree of specificity of the adsorption step in bacteriophage invasion. Similarly, transformation may be confined to intrageneric transfer. However, unlike transduction and conjugation, transformation allows for the uptake of huge blocks of heterologous DNA (Coffey *et al*., 1998). *Streptococcus pneumoniae* and *Neisseria meningitidis*, can take up foreign DNA and incorporate it into their chromosomes. This mechanism has accounted for the creation of mosaic penicillin binding protein genes that have a reduced affinity for penicillin.

Many of the genes that mediate resistance are found on plasmids or on transposons that can be disseminated among various bacteria by conjugation. Conjugative plasmids carrying resistant determinants can efficiently transfer among Gram positive or Gram negative bacteria belonging to different genera but not between the two groups of microorganisms (Courvalin, 1996). Conjugative transposons are self-transmissible elements that are normally integrated into a chromosome or plasmid but can excise themselves and transfer by conjugation to a recipient. They represent an efficient mode of transfer of antibiotic resistance genes to a broad host range. Conjugative transposons are capable not only of transferring themselves but also of driving the transmission of other resistant elements (Salyers *et al*., 1995).

One of the mechanisms by which plasmids and transposons acquire multiple antibiotic resistance determinants is by site-specific integration (Sandvang *et al*., 1998). This recombination is mediated, in part, by a distinct family of DNA elements referred to as integrons (Recchia and Hall, 1997). Integrons are elements that contain the genetic determinants of the components of a site-specific recombination system that recognizes and captures mobile gene cassettes. Cassettes normally include only one complete gene, which encodes for a resistant mechanism, followed by a recombination site. Multiple cassette insertions can occur. Each cassette is not only a discrete unit but is also mobile. This allows the spread of resistance genes from one integron to another. The cassettes do not have promoters and in order to be expressed they are dependent on an upstream promoter of the integron. When more than one cassette is present, the position of the cassette in the array influences the level of antibiotic resistance expressed by the cassette gene. The resistance level is highest when the gene is in the first cassette (Collis and Hall, 1995). The introduction of new cassettes preferentially insert closest to the integron and the promoter and are therefore expressed preferentially over the other cassette that may be present (Hansson *et al*., 1997). *S. typhimurium* DT104 have the ampicillin- and streptomycin resistant genes in two integrons as gene cassettes.

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Does Antimicrobial Usage Influence Antimicrobial Resistance?

Several investigators have reported the direct relationship between fluoroquinolone consumption and the emergence of quinolone-resistant strains. Chen *et al*. (1999) found that fluoroquinolone prescriptions increased from 0.8 to 5.5 per 100 persons per year between 1988 and 1997. The prevalence of *pneumococci* with reduced susceptibility to fluoroquinolones increased from 0 percent in 1993 to 1.7 in 1997-1998 (P = 0.01). The prevalence of resistant strains was higher in isolates from older patients (2.7 percent in those ³ 65 years vs. 1.0 in those 15 to 64 years, P < 0.001) and in those from Ontario vs those from the rest of Canada (1.5 vs. 0.4 percent, P = 0.001) where quinolone consumption was highest. Aguiar *et al*. (1992) related the increased consumption of quinolones to the presence of quinolone-resistant strains of *E. coli* isolated from community-acquired urinary tract infections over a four-year period (1988-1991). During this period the consumption of quinolones more than doubled.

Huovinen (Huovinen *et al*., 1997) found in Finland that, in specific areas, use of erythromycin had affected significantly the level of erythromycin resistance in group A *streptococci*. Resistant isolates occurred most often among children younger than 5 years: the age group where the use of erythromycin was the highest. Attempts to reduce erythromycin use were initiated in 1991-92. Recommendations were published in the Finnish Medical Journal in December 1991. Following the recommendations, macrolide consumption in Finland decreased by 40% between 1991 and 1994, and macrolide resistant group A *streptococci* decreased from 16.5% in 1992 to 8.6% in 1996 (Seppala *et al*., 1997).

The relationship between antibiotic use and antimicrobial resistance is not always so clear. Chiew *et al*. (1998) monitored streptomycin resistance in *Enterobacteriaceae* in their hospital in 1991, about 20 years after the cessation of the use of this agent. They found that up to 20% of isolates were resistant to streptomycin. Four years after the prohibition of the use of tetracycline as a food additive to promote growth in pigs, there was no significant reduction in percentage of pigs harboring tetracycline resistant *E. coli* (Smith, 1975). This is important since it suggests that once resistance has emerged simply reducing antimicrobial use may not always eliminate or reduce resistance.

Antimicrobial use can not only directly influence the emergence of resistance in those pathogens to which it is directed, but indirectly do so through the process of selection. A risk factor for the acquisition of VRE is the administration of broad-spectrum antibiotics. Use of multiple antibiotics in patients colonized with low numbers of VRE allows enterococcal overgrowth with increased risk of dissemination (Woodford *et al.,* 1995).

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What Is The Consequence Of Antimicrobial Resistance?

Although it is often difficult to measure the effect of inappropriate treatment of an infection with an antibiotic to which the offending organism is resistant, there are important potential consequences for some infectious syndromes.

Potential consequences of infections caused by antimicrobial resistant pathogens:

- Increased likelihood of treatment with inappropriate antimicrobial with resulting increased morbidity and mortality
- Need to change empiric therapy to potentially less effective, more expensive, and more toxic alternative
- Increased length of illness
- In the hospital:
    - increased length of hospital stay
    - increased laboratory costs
    - increased infection control costs

There are a number of clinical infectious syndromes for which the benefit of antimicrobial therapy is questionable. Criteria, which determine the resistance of an organism to a particular antimicrobial, or group of antimicrobials, may not always correlate with treatment outcomes. When attempting to determine if treatment failure is due to antimicrobial resistance, co-morbid illnesses or physiological processes are often not accounted for.

Infections that are caused by organisms that are resistant to the antimicrobial used may appear to respond because the natural history of the infection is often to resolve spontaneously. Examples include acute sinusitis and mild to moderate acute exacerbation of chronic bronchitis (Anthonisen *et al*., 1987; Gonzales *et al*., 1997; McCaig *et al*.,1995; van Buchem *et al.*, 1997). Van Buchen *et al*. (1997) randomized patients that had been diagnosed as having acute maxillary sinusitis to placebo or amoxicillin. They found that amoxicillin did not influence the clinical course or the frequency of relapses. Anthonisen *et al*. (1987) found that antibiotics were ineffective in mild acute exacerbations of chronic bronchitis. They did however find a difference in success rate between antibiotic and placebo for the more severe exacerbations and in those patients, deterioration was over twice as common with placebo as with antibiotic. The benefit of antimicrobial therapy has been clearly established for bacterial pneumonia (Austrian and Gold, 1964). In the pre-antibiotic era, over 80% of the CAP were due to *S. pneumoniae*, with mortality rates of 20 to 40% (Austrian and Gold 1964; Bullowa 1935). In the antibiotic era, the overall mortality rates for CAP are < 6% and for *S. pneumoniae* are < 15% (Fine *et al*., 1996; Fine *et al*., 1997).

The clinical relevance of resistance in vitro may depend on the site of infection and the degree of resistance. What constitutes resistance of an organism to an antibiotic in vitro may not be relevant for the site at which the organism is causing the infection. Penicillin therapy is frequently ineffective in meningitis caused by *pneumococci* exhibiting intermediate resistance because of the relatively low concentrations of penicillin achievable in the cerebrospinal fluid (CSF). However, there is no convincing evidence that therapy with penicillin or an equally active b-lactam antibiotic is ineffective in pneumonia or bacteremia due to *pneumococci* that are intermediately or highly resistant to penicillin since adequate levels of a b-lactam are achieved at these sites (Klugman, 1996).

Finally, when trying to assess the relationship between antibiotic activity and outcome, several factors have to be taken into consideration, including the type of pathogen, the physiological response by the host, and underlying comorbid illnesses. Mortality is closely associated with the etiology of the infection. Patients with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and enteric gram-negative rod pneumonia (e.g., *Klebsiella* spp. and *E. coli*) have overall mortalities of > 30% (Fine *et al*., 1996). Austrian and Gold (Austrian and Gold, 1964) found that the mortality rate for type I *pneumococcal* bacteremia was 8% for all cases whereas that for type III infection was 55%. Despite the benefit seen with the use of antibiotics for the treatment of *S*. *pneumoniae* bacteremia, we have failed to alter the mortality in the first

five days of the illness (Austrian and Gold, 1964). Austrian and Gold (Austrian and Gold, 1964) found that the percentage of patients that had died with bacteremic *pneumococcal* pneumonia was similar for those patients that were untreated, or treated with penicillin, tetracycline or serum therapy during the first five days of the diagnosis of their illness. In addition, they found that 60% of all deaths among patients treated with penicillin occurred in this first five-day period, despite treatment often being initiated on the first or second day of illness. This suggests that factors, in addition to the pathogen, such as the physiological response by the host, are important with regards to outcome. Factors that are independently associated with mortality include: age more than 50 years, neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, and liver disease (Fine *et al*., 1997).

Despite these observations, there is evidence for the benefit of the use of an antibiotic to which the pathogen is susceptible and deleterious effects seen when the pathogen is resistant. Leroy *et al*. (1996) found that ineffective antimicrobial therapy was a predictor of mortality for severe community acquired pneumonia. Jamulitrat *et al*. (1994) found in patients with nosocomial blood stream infections that death was associated with inappropriate antibiotic therapy. Mosdell *et al*. (1991) reviewed 480 patients with secondary bacterial peritonitis and found that inadequate empiric antibiotic therapy was associated with poorer outcome than any other type of treatment.

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Antibiotic Use in Agriculture and Its Consequence to Humans: The VRE Debate

Resistance to glycopeptides such as vancomycin or teicoplanin in clinical isolates of *enterococci* (VRE) was first reported in Europe in 1988, are emerging as a global threat to public health (Uttley *et al*., 1988). The incidence of VRE infection and colonization among hospitalized patients has increased rapidly. From 1989, the year VRE was first identified in the United States, through 1993, the proportion of VRE reported to the National Nosocomial Infections Surveillance System increased 20-fold (Centers for Disease Control and Prevention, 1993). Infection with VRE may be associated with increased mortality (Linden, 1996), and no effective antimicrobial therapy is available for many VRE. Although the nosocomial prevalence of infections caused by VRE has increased significantly in the United States, virtually no VRE have been found in the gut flora of healthy people.

The epidemiology of VRE in Europe differs from that in the United States. In Europe the rate of fecal carriage of VRE in the community is much higher (e.g., 2 to 28%) than that in the United States, where VRE seem to be more or less absent outside hospitals (Coque *et al.*, 1996). The prevalence of VRE in Europe is low among strains causing hospital-associated infections, while VanA-positive enterococci can easily be detected outside the hospital in several European countries (Stobberingh *et al*., 1999). A possible source of VRE is the food chain. In Europe a diversity of VRE types has been isolated from sewage, animal waste, meat and meat products, and feces of healthy persons, suggesting a pool of VRE outside hospitals (Bates 1997, Klare *et al.*, 1995). It has been suggested that the use of the antibiotic avoparcin, also a glycopeptide, as a feed additive in animal husbandry in numerous European countries has resulted in the selection of vancomycin resistance in strains from farm animals (Stobberingh *et al*., 1999). This is consistent with the lack of non-hospital-associated VRE in the United States, where the use of avoparcin has not been permitted (McDonald *et al*., 1997). Because of the concern that avoparcin was a risk factor for carriage of VRE in food animals, its use as a growth promoter was suspended in the European Union in 1996. Since then, Klare *et al*. (1999) have documented a decreasing number of VRE in frozen and fresh poultry meat (chickens and turkeys) from German producers. A decline of VRE prevalence was also observed in the gut flora of healthy persons in the same region of Germany, having fallen from 12% in 1994 when avoparcin was being used to 6% (6/100) in 1996 and 3% (13/400) in 1997 after it was discontinued.

These findings provide strong evidence that the selective environment, which led to the emergence of VRE, was the use of glycopeptides as feed additives in agriculture and that discontinuation of their use resulted in a lowered prevalence of VRE which may minimize its introduction into the hospital community.

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Conclusion

Since the introduction of antibiotics, we have witnessed the relentless evolution and dissemination of resistance to them. This has been a result in part to previous exposure of organisms to antibiotics produced by other bacteria, by the

inappropriate and overuse of antibiotics in agriculture and in humans, and to societal problems. Unfortunately, even if we were able to ensure the appropriate use of antibiotics today, it may take years before we would see a decline in the levels of resistance, since many bacteria have been able to reduce the costs associated with resistance. This means that we must continue to develop new antimicrobials and to develop better ways of preventing or slowing the emergence of these Superbugs by ensuring their judicious use.

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