YEAR 2000 BUGS: THE END OF THE ANTIBIOTIC ERA?*

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Dramatic changes are occurring in resistance of bacteria and other organisms to antimicrobial agents.[1] Antimicrobial resistance has become a major concern because it seems to be progressing faster than the tools for combating it are being developed.[2] The cost of infections caused by antibiotic-resistant bacteria is estimated to be between $4 and $5 million (US) per year.[2] A large part of this comes from the increase in multiresistant bacteria, which infect patients in acute care hospitals and other health care institutions (nursing homes, extended care facilities, ambulatory surgery clinics). The Director-General of the World Health Organisation, in the WHO Annual Report on Infectious Diseases for 2000, notes that 'if the world fails to mount a more serious effort to fight infectious diseases, antimicrobial resistance will increasingly threaten to send the world back to a pre-antibiotic age'.[3] The most effective strategy against antimicrobial resistance, according to WHO, 'is to give the right treatment at the start, to destroy microbes unequivocally'.[4]

It is the purpose of this article to explain that therapy, no matter how well delivered, will not alone prevent the development of antibiotic-resistant organisms. Rather, the pre-antibiotic age can only be avoided by combining treatment with efforts at prevention, using tools that are already developed or soon to be ready. This article details changes in resistance that cause concern today. Pathways are outlined for the development and spread of drug-resistant bacteria, which cause serious infections.[5] Prevention strategies available to the clinician are then considered.

RESISTANT ORGANISMS AND THEIR IMPORTANCE

In the 1960s and early 1970s, multiresistance emerged in hospitalised patients and caused nosocomial outbreaks, first of *Staphylococcus aureus*, then of a variety of Gram-negative bacilli.[6] These and similar events required physicians to change their practices for prescribing empiric therapy for infections that arose both in the hospital and in the community. As newer drugs such as the extended-spectrum cephalosporins and the fluoroquinolones were introduced, resistance to these classes of drugs also appeared.[7] Some strains of several species of bacteria, such as *Acinetobacter baumanii*, are now resistant to all approved antimicrobial agents.[8] Other organisms, such as *Enterococcus faecalis*, have had brief periods in which no therapeutic agents were available pending the introduction of new antimicrobial agents.[9] Infections due to these multiresistant organisms demand special attention.

FOUR DEVELOPMENTS OF CONCERN

Four new developments are of special concern when dealing with infection in the health care setting. These developments include: increasing resistance in more virulent organisms (e.g. glycopeptide-resistant *S. aureus*); spread of resistant organisms from the health care settings defined above to the community (e.g. methicillin-resistant *S. aureus*); spread of resistant organisms from the community to these health care settings (e.g. penicillin-resistant pneumococci) and presence of multiple resistance mechanisms in the same organism (e.g. *Klebsiella pneumoniae*).

New patterns of resistance in more virulent organisms

The appearance in the early 1990s of organisms that were resistant to all available antimicrobial agents has received considerable attention. The prominence of vancomycin-resistant enterococci (VRE) led to speculation about entering the 'post-antimicrobial era'.[10] However, the number of organisms so resistant as to be untreatable is very small.[11] Moreover, infections due to multiresistant VRE were concentrated in compromised hosts and rarely afflicted those with intact host defences.[12]

Since that time, resistance has emerged in more virulent organisms that are able to cause infection even in patients with intact host defences. Foremost among these organisms is *S. aureus*. Discovery of *S. aureus* strains with intermediate susceptibility to vancomycin raises the spectre of widespread nosocomial infection due to *S. aureus*, as occurred in decades past.[13] Reports of vancomycin-intermediate *S. aureus* (VISA) strains have come from Japan, Hong Kong, Europe and the US.[13-6] These strains should, by their proper name, be known as glycopeptide-intermediate *S. aureus* (GISA) strains, because they are resistant to other glycopeptides, such as teicoplanin, in addition to vancomycin.[13] Laboratory diagnosis of these organisms is a concern. For example, in US clinical laboratories responding to a survey by the Centers for Disease Control and Prevention (CDC), approximately 16% employed susceptibility testing methods unsuitable for detecting VISA strains.[17] The organisms raise infection control issues as well. In 1998, an update of earlier infection control recommendations for dealing with vancomycin-resistant strains of *S. aureus* was published; it stressed a vigorous approach to barrier isolation and hygiene.[18] All of these developments emphasise that newly resistant strains of organisms causing severe infection have implications not only for antimicrobial treatments but also for diagnostic laboratories and infection control programmes.[19]

Spread of resistant organisms from the health care setting to the community

Traditionally, most antimicrobial-resistant bacteria causing human infection have emerged in the acute care hospitals and then gradually become prevalent in the community. This was the case with penicillin-resistant strains of *S. aureus*. As the presence of MRSA (methicillin-resistant *S. aureus*) increased in health care institutions, it was anticipated that

Based on the lecture delivered at the symposium on Appropriate Antibiotic Prescribing held at the Royal College of Physicians of Edinburgh, on 16 June 2000

colonisation and infection with MRSA strains eventually would be found outside hospitals, as was noticed with penicillin-resistant *S. aureus*.[20] Infections in the community due to MRSA strains that appear to arise outside the health care setting are now reported from several parts of the world, including North America [21-3] and Australia.[24] The epidemiology and clinical presentation of infections associated with many of these community acquired (CA) strains of MRSA appear to be different than those of previously reported MRSA (Table 1).[25] The strains in earlier reports (middle column in Table 1) typically spread from health care facilities. Patients with these strains tended to be older individuals and infants who had been recently hospitalised. The sites of their infections included skin and soft tissue, but serious infections involving bacteremia and surgical site infection were prominent as well. Many of the patients had recently been in-patients in acute or chronic care hospitals or nursing homes, had previously received antimicrobials, or had histories of intravenous drug abuse. Thus, the likely mechanism by which these cases arose is transfer into the community from health care settings, with subsequent horizontal cross infection of contacts (e.g. other drug users, family).

By contrast, the recent reports of infection with CA-MRSA (right column of Table 1) described patients whose infections primarily involved skin and soft tissue. These patients, most frequently, were young adults living within relatively closed communities (e.g. Native American reservations, rural towns). Few patients had been in health care institutions or nursing homes, although some reported intravenous drug abuse. Thus, the main mode by which these cases emerged seems to be a horizontal transfer to contacts after introduction to the community by drug users or other source individuals carrying these organisms; introduction and person-to-person spread is known to occur in other closed communities, such as child care centres.[26] Colonisation or infection may occur in persons with no history of recent health care contact but who acquire the strain from a person who was inadvertently colonised with MRSA at the time of transplantation.[27]

Hospital strains of MRSA usually are multidrug-resistant, unsusceptible to other beta-lactams as well as to antimicrobials of several other unrelated chemical groups. Often vancomycin is the only tested drug to which the organisms are susceptible. Strains truly arising in the community, while resistant to other beta-lactam drugs, usually have been susceptible to a number of other antimicrobials in addition to vancomycin. Such drugs include macrolides, clindamycin, newer fluoroquinolones, and tetracycline.[28]

The susceptibility pattern of organisms causing CA-MRSA cases has a great impact on guidelines for empiric therapy of these infections. The CDC report of cases recommended that 'in critically ill patients with invasive infections, empiric treatment with vancomycin (in addition to a third-generation cephalosporin) pending culture result, may be necessary'.[23] However, in communities in which CA-MRSA cases are susceptible to other drug groups (e.g. macrolides, clindamycin, newer fluoroquinolones), empiric treatment should begin with those drugs, and vancomycin should be held in reserve. The extent to which CA-MRSA strains are found in the US and around the world is unclear. Studies are needed to determine the frequency of such organisms, to further describe in detail their susceptibility patterns, and to correlate clinical response with the *in vitro* testing of organism susceptibility to both currently available and investigational antimicrobials.

Spread of resistant organisms from the community to the health care setting

Penicillin resistance in *S. pneumoniae,* once unknown, has become common in the community. In 1997–8, the overall frequencies of penicillin-intermediate and penicillin-resistant strains of *S. pneumoniae* in a survey of clinical isolates at 34 US

TABLE 1
Type of community-acquired MRSA*

	Strains spreading from health care facilities	Strains arising independently in the community
Age group affected	older individuals and infants	children and young adults
Sites affected	bacteremia, skin and soft tissue infections, surgical site infections	skin and soft tissue infections
Risk determinants	prior hospital stay, prior receipt of antimicrobials, nursing home residence, intravenous drug abuse	closed communities, prior treatment with oral antimicrobials, intravenous drug abuse
Organism susceptibilities	usually resistant to other beta-lactams and many drug groups unrelated to beta-lactams, but susceptible to vancomycin	usually resistant to other beta-lactams, but susceptible to many drug groups other than beta-lactams and vancomycin
Empiric therapy	vancomycin for suspected severe infections due to these strains of *S. aureus*	organisms usually susceptible to erythromycin, clindamycin, etc. do NOT use vancomycin

**methicillin-resistant S. aureus, adapted from reference 25*

medical centres were 17.4% and 12.1% respectively.[29] The frequency of non-susceptible strains varies geographically in the US, but can be sizeable in some areas. For example, a survey from December 1997 to May 1998 found rates of penicillin-nonsusceptibility (intermediate and resistant strains classified together) to be as high as 44% in the South Atlantic region of the US.[30] Worldwide prevalence of resistance is increasing as well. For example, penicillin-resistance in pneumococci rose in England and Wales from under 1% in 1990 to 7.4% in 1997.[31]

Increasing pneumococcal resistance to penicillin in the community is now paralleled by resistance appearing in nosocomial isolates. *S. pneumoniae* was an infrequent source of nosocomial infection following the introduction of penicillin in the 1940s. However, this organism was once prominent in hospital-acquired respiratory infection and in infections following chest trauma. Resistant strains of pneumococcus are now associated with infection in the hospital as well as in nursing homes.[32] Multiresistant variants of pneumococci are also common, so vancomycin is being used more frequently than ever to treat patients with pneumococcal infection.[33]

The clinical impact of the appearance of these strains in the community is still not clear. Some reports suggest that *in vitro* resistance or intermediate testing results are not paralleled by patient response.[34] Data from 109 cases of pneumococcal meningitis in Atlanta, Baltimore, and San Antonio showed that 9% of the organisms were resistant to cefotaxime, and related infections showed no increased mortailty compared to susceptible strains.[35] Yet, a retrospective cohort study of medical outcomes for adult patients with bacteremic pnuemococcal pneumonia in 1994 showed that patients whose isolates were non-susceptible had a greater risk of suppurative complications.[36] The balance of evidence suggests that patients with pneumococcal pneumonia due to strains of pneumococci with minimum inhibitory concentration (MIC) values ≤1 mg/mL can be successfully treated with high doses of intravenous penicillin.[37, 38] However, the clinical outcome of treatment of such strains in other sites, or when more than the lower respiratory tract is involved, remains a concern for practitioners.

Two new patterns of concern about these organisms have now arisen. The first is the appearance in pneumococci of resistance to the newer fluoroquinolones.[39] *In vitro* studies now document emergence of resistance to all commonly employed fluoroquinolone agents when exposed to subinhibitory concentrations of drugs.[40] Studies in Canada and Hong Kong now document increasing prevalence of this resistance in isolates from humans.[41, 42]

A second finding of concern is the emergence of strains of *S. pneumoniae* that are tolerant to vancomycin. Novak *et al.* tested 116 clinical isolates from their community and found three strains to be tolerant to vancomycin.[43] The loss of function of the *vncS* histidine kinase of a strain in these organisms resulted in tolerance to vancomycin and other classes of antimicrobials. Sequence analysis of the *vncS* gene in these three isolates revealed a consistent substitution (valine for alanine at position 440). Since then, a patient, from whose cerebrospinal fluid vancomycin-tolerant pneumococcus was recovered, had recrudescent meningitis despite treatment with vancomycin and a third-generation cephalosporin.[44]

Presence of multiple resistance mechanisms in the same organism

In the past decade Gram-negative bacilli have become resistant to many antimicrobials through various mechanisms. A study of susceptibility of these organisms (isolated from blood culture in 24 European hospitals during 1997–8) identified potential presence of beta-lactamase enzymes in 0.3% of *E. coli* and 16.7% of *Klebsiella pneumoniae* strains studied.[45]

Dealing with Gram-negative organisms that have developed a single new mechanism of resistance to currently employed antimicrobials poses problems. For example, strains of *Pseudomonas aeruginosa* causing infections in outbreak fashion have demonstrated resistance to carbapenems due to the production of carbapenemases.[46] These strains differed from other strains resistant to carbapenems, which typically exhibit resistance through reduced drug uptake secondary to porin loss. On the other hand, organisms such as *Enterobacter aerogenes* are now resistant to carbapenem drugs because of the decreasing porin synthesis during therapy with imipenem. [47] Cessation of treatment with imipenem resulted in reversion of the organism to susceptibility and reappearance of porins in most of the organisms.

Even more difficult to deal with are organisms (especially Gram-negative aerobic bacilli) that are demonstrating presence in the same organism of multiple mechanisms of resistance. For example, a study from the US reported the demonstration of at least five different beta-lactamase genes in a multiply resistant strain of *K. pneumoniae*.[48] Most of the resistance genes were encoded on one large transferable plasmid, illustrating the complexity of multiply-resistant organisms and the difficulty involved in trying to determine resistance pathways.

HOW DO NEW RESISTANCE PATTERNS APPEAR?

The acquisition of resistance can be examined from several viewpoints. These include molecular mechanisms of resistance in the organism and more general pathways for appearance or spread of resistant bacteria in a specific setting (hospital, community etc.).

Molecular mechanisms of resistance often involve determinants arising from mutations in cellular genes, acquisition of new genes, or mutation of acquired genes. The ability of pathogenic bacteria to acquire and spread these resistance determinant genes is orchestrated by a variety of plasmids, bacteriophages, transposons, and integrons.[49] In Gram-positive organisms, this transfer primarily occurs through activity of plasmids, transposons, and insertion sequences.

Several independent pathways have been described for the appearance or spread of resistance in bacteria.[25, 50] Each of these (Table 2) may conceivably have a role in appearance or increase of resistant organisms in the acute care hospital, and many apply as well to other health care settings. These pathways may include the following.

Introduction from outside

New strains may be introduced by way of a patient from another unit of the same hospital or health care setting or from the community. For example, a study from Warsaw found horizontal transfer of a plasmid after possible introduction from another city in Poland.[51] Resistant organisms may also be introduced by a health care worker, or a contaminated commercial product. Introduction of

TABLE 2
Pathways by which resistance appears or is spread, and risk determinants for operation of each pathway.

Pathway*	Risk Determinants
1. Introduction	• Entry of patient with resistant organism by: – transfer from other institutions in health care system (acute care, extended care, etc.) – transfer from outside system – entry from community.
2. Mutation, genetic transfer	• Reservoirs with high organism concentration (and thus increased chance for random mutation or transfer, e.g. lung abscess, abdominal abscess, etc.).
3. Emergence, selection	• Selective pressures from antimicrobial use (note: whether prescribed appropriately or not).
4. Dissemination within ICU	• Improper or insufficient barrier isolation – lack of attention to major vectors of transmission (intravenous catheters, transducers, respiratory therapy equipment, etc.).

**adapted in part from reference 50*

resistant strains into hospitals from nursing homes and extended care facilities has become common for certain pathogens.

Genetic mutation and transfer

Resistance can be acquired by a previously susceptible strain from another species or genus.[49,52] Both genetic mutation and transfer of genetic material can produce this. Changes in chromosomal structure or control genes, in only a few base pairs, may result in substitution of one or a few amino acids in a crucial target (enzyme, cell structure, cell wall, etc.) this can affect chromosomal structure or control genes leading to new resistant strains.[53] The changed defence is often able to inactivate whole chemical groups of related antimicrobials. The genes that result can often spread widely. For example, clonal spread and horizontal transfer of vancomycin-resistance genes were reported in Finland shortly after widespread dissemination of strains with these genes were documented.[54] Studies suggested that vanA and vanB incorporated into an endemic ampicillin-resistant *Enterococcus faecium* strain that was vancomycin susceptible, through a conjugative transposon, resulted in a more difficult therapeutic decision for clinicians in the area. Many antibacterial resistance genes are on plasmids that can, and do, transfer themselves to another genus or species of bacteria, as has recently been demonstrated for fluoroquinolone resistant determinants and various streptococci.[55] Co-resistance to old and newer drugs can be produced by plasmid-mediated mechanisms: the presence of genes responsible for glycopeptide and streptogramin resistance linked on the same plasmid in *E. faecium* could be of clinical concern if the plasmid were to disseminate.[56]

Emergence

Chromosomal determinants for resistance may not be expressed until the organism comes in contact with a given drug.[50] When permissive conditions appear (e.g. new antibiotics in use, introduction of new conjugative plasmids), resistance can be manifested rapidly. For example, multi-resistant strains of *Pseudomonas aeruginosa* have emerged in patients in a stepwise fashion after exposure to anti-pseudomonal antibiotics, and these strains were associated with adverse clinical outcomes.[57] The trigger for this emergence may be the antimicrobial agent to which resistance is directed. In some cases, exposure to another antimicrobial results in induction or derepression of a determinant (enzyme etc.) that stimulates resistance to the studied drug.

Selection

Exposure to a stimulus that inhibits or kills the susceptible majority of a population allows a resistant subset of strains to grow at the expense of susceptible organisms. For example, even the brief period of antibiotic exposure associated with perioperative prophylaxis leads to rapid emergence of resistance in coagulase-negative staphylococci.[58] The selecting factor is usually the antibiotic to which the subpopulation is resistant, but on occasions a related agent can also have a great impact. Non-drug factors such as those stimulating activity of reactions like acetylation or glucuronylation can also provide a selective advantage to organisms. The relatively short time that may elapse between introduction of antimicrobial agents and the appearance of determinants that confer resistance to them has often been interpreted as evidence for a causal relationship, but this is more likely to be due to emergence or selection.[49] This consideration places extra emphasis on avoiding careless use of antimicrobials, which can provide a trigger or stimulus to the development of these types of resistance.

Cross-transmission and clonal dissemination

Organisms in hospitals can be spread in clonal fashion from patient to patient; from one patient to another via a health care worker (e.g. on the hands of ward personnel), in contaminated commercial products (e.g. antiseptics) and on other inanimate objects (e.g. stethoscopes, instruments or ventilators). While it varies from one health care system to another, the impact of such cross-transmission can be important. For example, a strain of MRSA introduced into a larger tertiary-care teaching hospital in Manitoba, Canada led to a sustained outbreak with transmission to two large long-term care facilities and a second hospital.[59] Rice points out that cross-infection is the major mechanism, if not the only mechanism, by which strains of methicillin-resistant *S. aureus* (MRSA) are spread in intensive care units (ICU) and in other health care settings.[60]

Cross-infection can also occur in settings in the community such as day care centres. Spreading in this fashion has been implicated in transfer of organisms such as penicillin-resistant *S. pneumoniae*.[61]

Today's pressing problem – multiple pathways in the same organism
Any or all of these pathways may have a role in the appearance or increase of resistant organisms in the acute care setting and in other health care settings. For example, establishment of endemicity of vancomycin-resistance in enterococci at one hospital over a six year period was found to involve clonal spread, transfer or genetic elements and introduction of new strains.[62] In a similar fashion, the rise of GISA strains probably relates to selection of resistant strains; the appearance of true community-acquired strains of MRSA may be related to the same pathway, as well as the introduction from health care institutions. The appearance of penicillin tolerance in health care institutions probably results in part from introduction from the community, after resistant strains have emerged in that setting. Sorting out these multiple and concurrent elements that lead to appearance and spread of resistance is an important but difficult problem.

Relating control measures to epidemiologic pathways
Once introduced, resistant organisms are difficult to eliminate. Weinstein has suggested that about 30–40% of resistant infections arise from cross-infection via hands of hospital personnel, 20–25% result from the selective pressure of antimicrobials, 20–25% represent introduction of new pathogens to the setting, and 20% arise from other or unknown pathways.[63]

Control of resistance – general considerations
The most obvious way to combat resistance is to develop new antimicrobials. However, the rate of appearance of new antimicrobials will be slow for at least the next few years. Other strategies must be developed to deal with this problem and to help preserve the useful life of the antimicrobials available now.[64]

Statements from professional societies, independent review groups and governmental agencies stress several control measures.[65-8] These include the need for professional educational programmes, enhanced microbiological surveillance, enhanced surveillance among patients, effective implementation of infection control procedures, development of vaccines against multiresistant organisms and prudent use of antimicrobial agents for treatment and prophylaxis. Surveillance is a key feature in determining the appropriate control measures needed in a given situation.[69] New rapid methods are becoming available to facilitate this important effort. The data generated by such surveillance must be relevant to the intended audience, as resistance varies widely in different areas.

The combination of measures used must be individualised to the specific organism, antimicrobial groups, health care institutions and care settings that are involved. There are at least two reasons why this is true.[5]

1. The reservoir for important resistant organisms varies dramatically, e.g. for MRSA, the reservoir is now in some communities as well as in health care facilities.[70] For others, like Gram-negative bacilli, containing extended-spectrum beta lactamase (ESBL) enzymes, acute care hospitals (especially their ICUs) and nursing homes are the main focus.[71]
2. The modes of spread for different organisms vary. For example, MRSA seems closely linked to person-to-person spread, while Gram-negative non-fermenting bacilli are often spread through contamination of liquids and respiratory therapy devices. Thus, global guidelines for dealing with resistant organisms are unlikely to be practical and effective.

Co-operative efforts will be necessary at times. For example, a survey of 15 hospitals in a single area of New York City (Brooklyn) found *Klebsiella* strains possessing ESBL enzymes to be present in all hospitals surveyed.[72] The authors concluded that 'citywide policies may have to be developed that supplement local institutional measures'. This may become more and more common as resistance becomes widespread.

Specific steps to deal with the problem can be divided into two: those dealing with the problem of resistance in general and those taken to optimise antimicrobial use.

IMPORTANT STEPS FOR DEALING WITH RESISTANCE
Control measures to deal with each of the resistance pathways presented below (Table 3) vary considerably, so efforts to prevent or control resistance problems depends in part on determining which pathways are operative in a given situation. However, several steps will be of use in most settings, and will involve a number of different groups of participants (Table 4).

TABLE 3
Interventions to deal with resistant organisms, according to the pathway* by which resistance appears or is spread.

1. Pathway: Introduction of Organism from External Source
   - surveillance and empiric isolation
     - survey for resistance in patients coming from known reservoirs of resistant organisms (chart flagged, etc.)
     - implement barrier isolation precautions for patients from known sites within or outside the health care system (discontinue only after cultures are negative)
2. Pathway: Mutation, Genetic Transfer
   - decrease reservoirs of organisms with potential for mutation (proper care of instruments, fluids, selective decontamination, etc.)
3. Pathway: Emergence, Selection
   - decrease antibiotic selective pressures
4. Pathway: Dissemination within the Institution
   - institute barrier isolation precautions to contain resistant organisms, maintain proper use of equipment and procedures (major risk determinants for spread)

**pathways are those described in Table 1*

Validate your laboratory methods for detection of antimicrobial resistance
The physician must be aware of the resources and limits of the clinical microbiology laboratory for detecting and reporting resistance. Several of the new resistance

mechanisms recognised in Gram-positive and Gram-negative bacterial organisms are difficult to detect with current laboratory methods. For example, vancomycin-intermediate *S. aureus* and penicillin-resistant *S. pneumoniae* can be difficult to detect by agar disk diffusion methods or by automated methods.[13, 73] Another continuing problem is the detection of cefotaxime, ceftriaxone and ceftazidime resistance in *K. pneumoniae* and *E. coli*, particularly when resistance is mediated by extended-spectrum beta-lactamases.[17] To counter these problems, groups like the National Committee for Clinical Laboratory Standards (NCCLS, Villanova, Pennsylvania) have developed guidelines and standards for testing to assure that resistant organisms posing new problems are handled appropriately.[37] However, growing restraints on the personnel and supply budgets in microbiology laboratories may hinder the widespread implementation of the tests. Thus, the physician and the microbiology director should work closely together to optimise the testing that is being done and the ways that such tests are reported.

TABLE 4
Strategies to deal with antimicrobial resistance, by target group.

Group	Strategy
1. Prescribers and administrators	Obtain support for efforts to deal with resistance.
2. Patients	Reassure that most infections remain treatable despite newly emerging patterns of resistance.
3. Prescribers, pharmacists	Promote team approaches to formulation of programmes to optimise nurses, laboratorians administration of antimicrobials to patients.
4. Antimicrobial use and quality assurance groups	Benchmark prevalence of antimicrobial resistance and antimicrobial use-frequency against available national and regional data.
5. Laboratory staff	Determine best approaches to detection and reporting of resistant isolates in the ICU.

Keep abreast of developments of new antimicrobial drugs and other therapeutic agents

The number of new antimicrobial agents approved for use decreased during the 1990s. Until recently, very few new classes of antibacterial agents were expected to surface, as many pharmaceutical manufacturers had abandoned antibacterial drug discovery programmes for several years, preferring to focus on identifying antifungal and antiviral drugs, or drugs for non-infection areas.[74] Now, however, there are several new combinations or classes of antimicrobial agents, including quinupristin/dalfopristin and oxazolidinones, which may be of value for therapy of infections due to several resistant bacteria.[75, 76] Other new compounds and variations on older molecules are entering clinical use or clinical testing as well.[77, 78] As usefulness of older drugs for treatment of certain pathogens diminishes, the clinician must stay aware of the status of these newer products of industry in terms of safety and efficacy.

Non-antimicrobial means to combat resistant organisms will also assume more importance. For example, appearance of strains of *S. pneumoniae* with relative or absolute resistance to penicillin and other beta-lactam drugs has increased attention to development of vaccines directed against the pneumococcus.[79, 80] Administration of such vaccines to adults as well as to children could potentially result in a triumph similar to the reduction of cases of severe illness due to *Haemophilus influenzae* when the vaccine against that organism was introduced.

Emphasise implementation of infection control measures

In view of the estimate by Weinstein that cross-infection is the major source for resistant infections in the hospital (see previous page), then hospital hygiene and isolation precautions are of great importance.[63] In support of this thesis, several hospitals in the US have been able to reverse epidemics of MRSA infection by instituting rigorous infection control measures.[81] A report from the Hospital Infection Control Practices Advisory Committee of the CDC stressed effective implementation of infection control procedures to deal with vancomycin-resistant enterococci (VRE).[82] This recommendation is also appropriate for control of other types of resistant organisms found in the hospital environment. Use of sterile examination gloves for contact with patients or their environment, encouragement of handwashing by appropriate facilities and use of an alcohol based hand-rub in between patient contacts, when appropriate handwashing facilities are unavailable, are all suggested by CDC and others as a starting point for programmes.[83] Adherence to isolation precautions is important throughout the health care setting, not just in acute care hospitals.

Benchmark resistance and use

Prevalence of resistance and frequency of antimicrobial use vary greatly among different hospitals. Several groups provide data on antimicrobial resistance in groups of US health care institutions. These include the Surveillance Network, the Alexander Project, the SCOPE project , the ResistanceWeb, the SENTRY project and Project ICARE.[45, 84-7] In addition, Project ICARE and ResistanceWeb provide information on antimicrobial use in networks of US hospitals. In the future, the National Nosocomial Infections Surveillance (NNIS) System of CDC will be including the surveillance done as part of Project ICARE as a routine part of their reporting. These sources provide a way to determine whether use and resistance in a given hospital is disproportionate to that in similar units or institutions: this can help in planning campaigns for dealing with resistance. Similar benchmarks are needed for other health care settings. PDAs (personal digital assistants) with direct internet access may help these efforts soon.[88]

Include control of resistance in your educational programme

Students, residents, hospital staff and others are frequently part of the health care team. Making sure that awareness

of the problem of resistance, and how to deal with it is part of educational programmes or inservice education and is a key part of obtaining the support of your associates in attempts at control. This holds for the ambulatory care setting as well as the hospital, nursing home, or other patient facility.

STEPS TO OPTIMISE ANTIMICROBIAL USE

Antimicrobial use is a major, although not the only, risk determinant for antimicrobial resistance.[89] Many strategies can be developed to improve antimicrobial use (Table 5).[5] Several of these will be discussed briefly.

TABLE 5
Strategies to improve antimicrobial use.

1. Enlist prescriber support for programmes and strategies to improve use.
2. Enlist support of patients and the public, especially in situations in which use of an antimicrobial is not likely to be helpful.
3. Develop and support teams to monitor and improve procedures for proper dosing (interval of administration, proper duration of treatment), monitoring for adverse effects, etc.
4. Customise antimicrobial use to your setting and pattern of resistance:
   a. improve empiric therapy by providing more useful data to prescriber at time of empiric choice (targeted susceptibility summaries, web-based information transfer, etc.); and
   b. improve peri-operative antimicrobial use (targeted practice guidelines, etc.).
5. Cautiously include programmes to control antimicrobial drug choice, such as:
   a. removal of specific antimicrobial drugs from formulary;
   b. restriction of specific antimicrobial drugs to certain groups of specialists;
   c. promotion of practice guidelines for use of specific drug groups and for treatment of specific types of infection; and
   d. scheduled change in use of antimicrobials for specific indications ('rotation' or 'cycling' of antimicrobials).

Enlist prescriber support

Overuse of antimicrobials comes about for several reasons. Perhaps the most important is that many prescribers fail to appreciate that good antimicrobial 'stewardship' entails more than consideration of the immediate benefit to the individual patient being treated.[90] It should also consider the effects of use on the continuing preservation of organism susceptibility in the practice population of each prescriber.[88] To accept this idea and change practise, prescribers must feel that their prescribing actions affect the overall control of resistance. Because multiple variables are involved, it is not always clear how any particular resistance mechanism will relate to use.[91] Sometimes there will be a straightforward relationship, sometimes the relationship will appear as nonexistent. This makes it difficult to deliver straightforward messages about the link to our prescribing colleagues. The antimicrobial improvement team often can obtain support from other prescribers by discussing these points in the course of establishing a unit policy on antimicrobial use that allows for input by all concerned.[66]

Enlist support of patients and the public

Overuse arises, in part, from demands for antimicrobials by patients who believe that such treatment is useful for every cold or sore throat or cough.[92] Patients expecting to receive antimicrobials need to learn that prescription of antimicrobial agents has a downside as well as a benefit.[93] At the same time, it is prudent to make sure that the public is not misled about the extent of the current problem.[5] There must be clear communication that today, the number of resistant organisms that are untreatable is very small. The public needs to hear that almost all of the infections that they are likely to acquire can still be dealt with effectively. It is a balance of communication that is needed. Our efforts to achieve this balance must increase.

Team up to deal with the details of antimicrobial administration

Measures taken to improve the way that antimicrobials are administered to patients are widely accepted. Programmes to monitor and improve procedures for proper dosing, proper interval of administration, proper duration of treatment, monitoring for adverse effects, etc. have all been undertaken and updated during the past few years.[94] These programmes generally have been well accepted by prescribers, pharmacists, administrators and others involved in the drug prescription process. These groups should be enlisted in a team to promote activities that are proven successful in improving use and indirectly decreasing resistance.

Customise antimicrobial use to your setting

Certain aspects of antimicrobial use must be adapted to local conditions and circumstances; among these are empiric therapy and peri-operative antimicrobial use.

Empiric therapy can be improved substantially by providing more information to the prescriber at the time of prescription.[95] Whether through targeted electronic or printed laboratory summaries, or through other means of communication, this laudable goal is being explored by several methods. Accurate local patterns of resistance can now be obtained in printed form, on hospital and laboratory information systems and in some cases over the internet by using PDAs with direct net access. This should facilitate good decisions about empiric drug choice.

Another area of proven success is targeted peri-operative antimicrobial use.[96] Careful efforts to provide the right drug at the correct time for the appropriate duration have been made. These have been widely hailed by surgeons and others interested in this area. Such work serves as a shining example of how to improve antimicrobial use. However, to succeed, it must take note of susceptibility patterns of hospital organisms in your area.

Be cautious about programmes that control drug choice

Recent interest has focused on attempting to improve antimicrobial use by controlling the choice of antimicrobials by individual prescribers. Three examples are: formulary restriction or prescriber restriction by specialty, use of practice guidelines and antimicrobial rotation or cycling.

A variety of papers from different parts of the world

now claim success for this change in drug-use as a means of dealing with outbreaks. For example, White and colleagues reported that requiring prior authorisation for selected antimicrobials produced several benefits.[97] Included were a dramatic decrease in expenditures for antimicrobials and an increase in susceptibilities to some antimicrobials in organisms from ICU patients. All this was accomplished without change in mean survival, in interval between positive blood culture and initial antimicrobial treatment, or in interval between positive blood culture and time of discharge from the hospital. However, it is not clear that this type of approach is effective in dealing with non-epidemic situations. Some authors suggest that the homogeneous use of drugs may be doing more harm than good.[95] Thus, further studies are needed to determine the utility of these measures.

Practice guidelines are a means of achieving uniformity of antimicrobial use which have been applied to many areas in addition to that of infectious diseases. Project ICARE (Intensive Care Antimicrobial Resistance Epidemiology) is a co-operative project of the National Nosocomial Infections System (NNIS) of the Centers for Disease Control and Prevention (CDC) and the Rollins School of Public Health of Emory University. The study measures antibiotic resistance and antibiotic use in a subset of hospitals that participate in the intensive care component of the NNIS system of CDC. Data being collected include:

1. overall resistance for selected target organism/drug combinations, stratified into CCU, non-CCU inpatient, and outpatient settings;
2. overall antimicrobial use, stratified into CCU and non-CCU inpatient settings; and
3. resistance mechanism and epidemiologic typing for selected organisms.

Phase 1 was a pilot study in eight NNIS hospitals (1995). Data here was collected from a sample of about 40 NNIS hospitals for a median of 12 months in 1996–7 (phase 2) and again in 1998–9 (phase 3). Data from this project about prevalence of resistance and frequency of antimicrobial use are available at the project website (**www.sph.emory.edu/ICARE**).

A survey in 1998 of 47 hospitals participating in Project ICARE revealed that clinical practice guidelines were reported most frequently (70% of hospitals) among the measures taken to improve antimicrobial prescribing practises.[98] In particular, they have been useful in reducing costs of therapy and total amounts of prescribing, while maintaining quality of care.[99] The current question is whether these efforts can reduce prevalence of resistance, and Gould notes that 'there have been some major successes in recent studies, both in the community and hospital'.[99]

Rotation or cycling of antimicrobial agents has been suggested for the various hospital units, especially ICU but to date few data are available to determine the impact of this tactic. The largest experience for this tactic was reported years ago with respect to changes in aminoglycoside use.[100] Since then, however, the potential of this strategy has not been adequately explored. Most studies of rotation of drugs have been done reactively rather than proactively as a response to an outbreak, and the value of rotation in the absence of an outbreak is unclear. The best choices of antimicrobials to be cycled, the duration of the cycles and the preferred order in which agents are cycled, is unknown, so defining the value of this approach will require further study.[101] Multi centre trials now being conducted may provide answers to this knotty question.

Convincing or compelling data are lacking on the value of these measures. Careful, controlled evaluations are needed to determine the outcome of these various types of interventions. Such studies must consider not only direct savings in drug acquisition cost but also indirect gains, such as those of increasing organism susceptibility.

SUMMARY

The effects of resistance are being noted on an increasing scale in all aspects of health care today. Multiresistant organisms are diminishing our ability to treat and to control the spread of infection. Yet, 'to send the world back to a pre-antibiotic age'[3] is not a likely outcome as long as preventive steps are taken now to deal with the problem. Strategies for control of resistant organisms must be based on the underlying pathophysiology of resistance mechanisms. Several steps needed to deal with resistant organisms and their consequences are in place today, i.e. assuring that drugs are administered in appropriate dose for appropriate duration of treatment is made easier today by co-operative efforts of physicians, nurses, pharmacists, and laboratory workers. Improving empiric treatment of infection requires similar co-operative efforts of others with the prescriber. However, evaluating other current strategies and developing new approaches will require further research. It is unlikely that many hospitals or health care systems will have sufficient resources on their own to develop useful data that can be widely applied. Funding for such efforts has been scarce to date. Members of this College have been prominent in research in this field, and should remain leaders in this effort.

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