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Role of Global Surveillance in Combating Bacterial Resistance

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Abstract

In recent years, one of the more alarming aspects of clinical microbiology has been the dramatic increase in the incidence of antibacterial resistance among pathogens causing nosocomial as well as community-acquired infections. Numerous antibacterial agents have lost their *in vitro* activity as a result of selective pressure exerted by antibacterial usage. There is a general consensus on the fact that emergence and spread of resistance may be delayed by improving hygiene measures, reducing inappropriate use of antibacterials, and adopting successful empirical therapy based on sound epidemiological data. As a consequence, worldwide international studies of antibacterial resistance surveillance have been established. Surveys such as the Alexander Project and the SENTRY Programme supply high quality data to participating countries, stimulate collaboration and provide the educational information required for clinical decision-making that may result in improved cure rates.

1. Resistance

The antibiotic era, spanning the past 50 years, has been associated with control, or perceived control, of bacterial diseases. However, the 1990s witnessed a worldwide resurgence of bacterial infections. Thus, for example, there has been a marked increase in the incidence and spread of bacterial conditions such as acute rheumatic fever, Lyme disease, food borne syndromes and tuberculosis.[1,2] Furthermore, an important factor in rendering even common infections more threatening has been the acquisition of antimicrobial-resistance genes by all major pathogens.[3,4] Within these micro-organisms, oxacillin-resistant staphylococci, penicillin-resistant pneumococci, vancomycin-resistant enterococci and staphylococci, extended-spectrum cephalosporin-resistant Enterobacteriaceae and carbapenem-resistant *Pseudomonas aeruginosa* are included.[5-7]

The driving force in the development of resistance has clearly been identified as the selective pressure exerted by drugs. In fact, genes expressing resistance to any specific antibacterial tend to predominate after the drug becomes widely used; however, the time necessary for resistance to emerge and disseminate cannot be predicted. In fact, the ultimate elements of the problem are resistance genes and resistant clones.[8,9] Their emergence initiates the problem and their spread determines its magnitude.[8]

Resistance progression could proceed slowly for years or accelerate, like an autocatalytic cascade. For instance, pneumococcal infections were treated with penicillin for about 30 years before penicillin resistance emerged, but during the last decade penicillin-resistant pneumococci have become a worldwide problem complicated by clone spreading.[10]

Both emergence and dissemination depend on many different events, such as the genetic mecha-

nisms of DNA mutation and exchange, ecological interactions and hygienic measures.[8,11,12]

For this reason, restricting the use of an agent everywhere to delay the emergence of resistance would not only be difficult to implement, but also questionable (for instance penicillin resistance in *Staphylococcus pyogenes* has still not appeared after more than half a century of use).

Dissemination of resistance can be retarded by improving infection control measures in order to interrupt the spread of particular bacterial populations.[13] In fact, as a result of the greatly increased mobility of the population today, these multiple-resistant strains have rapidly become disseminated throughout the world, with the result that the antibacterial use in one place can affect distant places.[14]

Emergence could be delayed by reducing the selective pressure exerted by widespread, and often inappropriate, use of antibacterial agents. Situations where inappropriate use is manifest include the treatment of viral diseases with antibacterials and the administration of prolonged courses of drugs in chemoprophylaxis,[15] a practice which is currently widely established, at least in Europe.[16] In addition, significant problems have been caused by the immense amount of antibacterials which have, perhaps unwittingly, found their way into food production as a result of their use as growth promoters in animals.[17] Other factors, including the expanding size of the populations at high risk, the widespread use of invasive medical procedures and devices (e.g. catheters), and the prolonged survival of patients with chronic debilitating diseases, have all amplified the problem to one of global dimensions.[1]

Resistance, as assessed *in vitro*, has a number of serious consequences in clinical situations. Treatment failures are common when an inappropriate drug has been prescribed and this, in turn, may lead to hospitalisation of patients who normally would have been treated on an outpatient basis, to longer hospital stay for inpatients (for instance, the development of a wound infection requires additional days of hospitalisation), and to the use of alternative drugs, which may be more expensive and produce more adverse effects. These factors all contribute to increased healthcare costs, morbidity and mortality.[18]

Microbiological procedures may identify the causative pathogen and provide the physician with the appropriate susceptibility pattern, thus reducing the chances of therapeutic failures. However, for a number of reasons including cost, even in hospitals, not to mention general practice, infections are seldom diagnosed on an aetiological basis.[15]

Therefore, the success of the empirical therapy usually adopted depends on factors including age, risk factors, the overall condition of the patient and the severity of the infection. Furthermore, it depends on the ability of the physician to guess correctly the putative pathogen and its resistance pattern so that they may select a drug that will overcome this hurdle. For the clinician, the picture is further compounded by the fact that, owing to strikingly divergent prescribing habits,[15,16] the incidence of resistance to a given drug in a certain bacterial species may vary profoundly among different geographical locations.

Most of the information we need could come from routine antimicrobial susceptibility tests performed by the innumerable diagnostic laboratories distributed around the world, but there are obstacles to the use of these data for epidemiological purposes. Their quality and comparability are uncertain because of a lack of uniform methodology. In addition, these studies are time consuming and not feasible for laboratories not equipped for computer data analysis. It is noteworthy that for this purpose the World Health Organization has prepared a program (WHONET), available at no charge.[8,11]

Walker and Thornsberry[19] have recently underlined that data obtained from tests performed in diagnostic laboratories are less useful for surveillance studies. In fact, generally, results are reported only in terms of the susceptibility category. These authors suggested that for epidemiological purposes, the minimum inhibitory concentration (MIC) value is a more appropriate parameter. Studies providing MIC values allow not only calculation of

percentages of susceptibility or resistance but also highlight changes in the degree of susceptibility or resistance year after year. However, MIC determination limited to concentrations that are at or near the break-point are not very useful for this purpose. An increase in the modal MIC values to a certain drug, even if not associated with a parallel reduction in the percentages of susceptible micro-organisms, could represent an omen for an evolutionary process toward resistance. Early detection of decreased susceptibility could offer the opportunity to initiate timely educational and or restrictive measures.

Information regarding MIC values is not lacking. In fact, we possess an enormous volume of MIC data derived from hundreds and hundreds of published studies on bacterial susceptibility to antibacterial agents. However, possibilities to compare resistance patterns have been limited because of variations in antibacterials tested and the range of concentrations, laboratory methods (broth microdilution, macrodilution, agar dilution methodologies), interpretative criteria, absence or use of different quality control strains and time spans.

2. Surveillance Systems

Adequate systems of surveillance are therefore essential to supply comparable information and provide a foundation for clinical decision-making.

These surveys must in fact be designed to generate accurate, timely and clinically relevant data on the incidence of resistance in those microorganisms that represent the major threats in community-acquired as well as nosocomial infections. These detailed results may guide antibacterial choices that can cure patients without extending the spread of resistance determinants and resistant clones.

Similar information has been provided recently by studies such as the National Nosocomial Infection Surveillance (NNIS) system,[20,21] the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) programme,[22-25] the Intensive Care Antimicrobial Resistance Epidemiology (ICARE),[7] the Surveillance of Invasive *Streptococcus pneumoniae* (SIREVA),[26] and the Asian Network for Surveillance of Resistant Pathogens (ANSORP).[27] These programmes have been limited by focusing only on nosocomial infections (NNIS and SCOPE), by the lack of validated identification and antibacterial susceptibility testing performed in a central laboratory (NNIS and ICARE), and by considering only one pathogen or only one continent (SIREVA, ANSORP).

The most comprehensive surveillance studies organised in the 1990s were the Alexander Project[28,29] and the SENTRY programme.[30-35]

The Alexander Project is an ongoing, longitudinal, multicentre, international study of trends in the antimicrobial susceptibility of pathogens commonly associated with lower respiratory tract infections which started in 1992. It was undertaken in response to a need perceived by the scientific community for high quality surveillance data in order to control increasing antibacterial resistance and is being supported by SmithKline Beecham Pharmaceuticals.

By using reproducible, standardised methods,[28] the Alexander Project compares the activity of the most commonly used antibacterials against major respiratory pathogens.

During the period 1992 to 1995 isolates were collected from geographically separate centres in EU countries (UK, France, Belgium, The Netherlands, Spain, Italy and Germany) and various states in the US. In 1996, the project was extended to centres in Mexico, Brazil, Saudi Arabia, South Africa, Hong Kong and other European countries not previously included. In all, more than 30 000 organisms have been characterised and stored. Data have been systematically collected over this time for *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*.

The methods used in the Alexander Project are standardised to minimise variation. They therefore allow coherent comparison of isolates from different centres and over time.[36,37] In fact, all centres deliver strains to a single co-ordinating laboratory located in London, England, where re-identification

and microbroth dilution susceptibility testing are performed in the same conditions.[28]

SENTRY is a 5- to 10-year prospective, longitudinal multinational microbial surveillance programme, founded by Bristol-Myers-Squibb, that tests pathogens to commonly prescribed antimicrobial agents.

The SENTRY Program began in 1997 and was established to monitor the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of sentinel hospitals distributed by geographical location and size. The monitored infections include bacteraemia and fungaemia (objective A), outpatient and inpatient respiratory infections (objectives B and C, respectively), and wound (objective D) and urinary tract (objective E) infections in hospitalised patients. The participating institutions include 72 medical centres in the US (30 sites), Canada (8 sites), South America (10 sites) and Europe (24 sites). In 1998 the study was extended to Asia, Australia, New Zealand and South Africa.

Each participating hospital contributed results (organism identification, date of isolation, hospital location) on consecutive isolates (one isolate per patient) judged to be clinically significant. All isolates were stored in agar slants and sent to the 3 coordinating centres: Iowa City (US) and Utrecht (The Netherlands), which cover North/South America and Europe, respectively, and Adelaide (Australia), which is responsible for Asia, Australia, New Zealand and South Africa. At the central laboratories, strains are re-identified and tested against a number of drugs employing National Committee for Clinical Laboratory Standards (NCCLS) standardised procedures.

Both these surveillance programmes solved the problem concerning data comparison between different countries, thus reducing variability, by introducing a central laboratory and standardised methods. At the same time, these studies play an educational role drawing attention to the antibacterial resistance problem and stimulating collaboration involving more and more participating countries. Global surveillance, by providing a snapshot of many and sometimes distant nations, may help in understanding the different trends and possible evolution of antibacterial resistance possibly correlating data with the prescribing habits in each country. This information may anticipate what could happen in selected areas and base clinical choices on solutions previously adopted effectively in other countries.[38,39]

Recently, interest has turned to whether antibacterial policies can reduce the spread of resistance and even reverse current high levels. In fact, increases of erythromycin-resistant group A streptococci and penicillin-resistant pneumococci have been controlled by prescription restriction of such drugs in Japan, Hungary, Finland and Iceland.[40-44] Longitudinal surveillance programmes are able to follow resistance trends over the years and trace the relationship between antibacterial consumption and variations in antibacterial susceptibilities. In addition, the availability of a large number of isolates has been found to be of great utility in comparing the activity of the most used agents,[45] but it could be also useful to test new antibacterials.

However, what are the limitations of global surveillance programmes? Rules for patient recruitment should be improved; for instance with *S. pneumoniae*, differences in the percentage of resistance between centres could be observed if centres included different proportions of paediatric and adult patients. Variations in the population sampled should be evidenced by reporting epidemiological data related to the patients, i.e. inpatient/outpatient, age, gender, clinical diagnosis and previous antibacterial therapy if received. This clinical information still seems difficult to obtain.[31] Rules for strain inclusion should also improve; in fact microorganisms are generally judged to be clinically significant according to local and not to standardised criteria.

Clonal spread of a single strain may produce misleading conclusions; in fact a rapid increase of resistance observed at one centre could be due to an outbreak and not be representative of the general situation.

Organisation of complex surveillance programmes, achievement and publication of results could proceed slowly, delaying timely rapid communication and dissemination of information, that is an important component for epidemiological study.

What is the real clinical impact of global surveillance information? The final aim of these studies is to guide physicians towards appropriate agents, but what kind of message reaches clinicians about the possibility of whether or not to use a certain drug?

In the above-mentioned studies, a relationship between rate of resistance and rate of correlate therapeutic failure does not exist. *In vivo* studies demonstrated that cure can be obtained against micro-organisms resistant to the antibacterial agent used (i.e. *S. pneumoniae* and penicillin, *S. pyogenes* and macrolides).[46,47] In addition, for obvious reasons, these international surveys include a limited number of centres (1 or 2) for each country and the percentages registered at one site become representative of a whole nation. This may lead the clinicians to over- or underestimate the problem in their area. This phenomenon has been well documented in our experience with *S. pneumoniae*.[48] Since 1992, our Institute has participated in the Alexander Project and from 1996 as the only Italian centre. As a consequence, data concerning Italy came from a restricted geographical area. In 1997 a multicentre study (50 sentries) was established to fill this gap: the Italian Epidemiological Observatory supported by SmithKline Beecham Pharmaceuticals. The results of this analysis showed a great and unpredictable variability among centres with percentages of penicillin resistance ranging from 3.8 to 42.9%. Our results suggest that data coming from a single centre must be substantiated by more extended studies. For this reason the most important monitoring and management appears to be that done at the local level. We strongly recommended that international surveillance programmes always be coupled with local surveillance survey and comparative data published in local journals. This kind of publication seems more likely to reach clinicians.

3. Conclusions

Among all possible strategies to be implemented in our attempt to limit bacterial resistance, the establishment of surveillance systems seems the more complex to carry out. This is because of the great variability among many parameters that have to be taken into account, such as criteria for strain inclusion, patient clinical information and the number and distribution of participating centres.

On the other hand, only epidemiological data on antibacterial resistance provide the educational information required for clinical decision-making that may result in improved cure rates.

In order to obtain consistent information and significant conclusions, surveillance systems have to be improved to reduce variability. In addition, all clinical information should be gathered as part of these studies to obtain a critical data analysis for each geographical location. One or 2 centres for each country might be representative of a whole nation only if they collect and analyse strains originating from a broader area. On the other hand, expanding the number of participating centres might cause an excessive increase in the complexity of these studies. A balanced solution is represented by an integrated network of national and international surveillance systems.

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