Surveillance of Resistant Pathogens and Rational Use of Antibiotics: General Remarks

Jacques F. Acar

Surveillance of resistant pathogens should lead to improved treatment of patients and to a rational use of antibiotics. The process for decision making between microbiology, general practice and health policy is still to be documented with careful studies.

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We have learned from the past history of antibiotic resistance that bacterial resistance to antibiotics affects all bacterial species and all antibiotics and will continue to evolve. The emergence of a resistant gene, amplification and dissemination intra- and inter-species are three sequential stages which may occur at different rates, and with different clinical visibility (Acar et al. 1997).

It is now clearly documented that multiple mechanisms of resistance to the same antibiotic or class, and multiple resistance to different antibiotics are the rule in most pathogens. However, the incidence of resistance is highly variable between different locations. Two hospitals in the same city can be very different, as well as cities in the same countries... (Levy, 1998).

The high incidence of resistant and multi-resistant strains and their medical consequences have been what triggered concern in so many organizations. We have to live with resistant bacteria, provided that we can keep them at low incidence and that we can treat them with an adequate antibiotic when necessary (Williams and Heymann, 1998).

The simple idea that reducing or stopping the use of the selector antibiotic will reduce the incidence of resistance, or even prevent its emergence has become the ultimate bridge between the prescriber behaviour and the dynamic of a microbial resistant population.

True or not, this idea is very popular and is involved in many guidelines, protocols or studies. The major predictable consequence is a decrease in the general expenditure for antibiotics. This economic advantage is infringing on the careful scientific studies required to measure the effect of reducing the use of antibiotics on the incidence of resistance (Butler et al. 1998; Turnidge, 1998).

I would like to point out here the problems which are worthy of exploration in order to improve our intervention in bacterial antibiotic resistance: The clinical relevance of resistance traits is often weakly established, overlooked or neglected, and is replaced by a sort of authoritative statement on the part of the microbiologist (Finch, 1998). The most unfortunate thing happens when a breakpoint is agreed upon and the word 'resistant' replaces the MICs; thus clinical judgement can no longer take place. For example, the breakpoint given to penicillin G for Streptococcus pneumoniae was important and indicative in cases of meningitis. Most clinicians have since forgotten that a strain of S. pneumoniae with an MIC of 2 µg/mL to penicillin isolated from a sputum is not necessarily resistant. This strain,
although abnormal, might be successfully treated with penicillin or amoxycillin. No study has yet established the penicillin breakpoint for \textit{S. pneumoniae} isolated from respiratory infections. Three other examples can be given here: (i) The low level resistance of \textit{Salmonella} to ciprofloxacin, which fueled discussions about the role of antibiotics given to animals in human pathogen resistance, has not been explored sufficiently to establish its role in therapeutic failure; (ii) The intermediate level vancomycin-resistant MRSA were discovered in patients who did not respond to vancomycin therapy; the concern of physicians was immediate and the worldwide search for such strains was promptly started. Is it right to keep calling them intermediate? (iii) Should \textit{Enterobacteriaceae} producing extended-spectrum \(\beta\)-lactamases be considered clinically resistant to monobactams and all third and fourth generation cephalosporins? No clinical studies have established the lack of clinical efficacy of all compounds, or to the contrary, any efficacy of those of them which are poor substrate to the enzyme.

When clinical studies are difficult or impossible for ethical reasons or statistical significance, those studies should be replaced with animal experiment studies.

The second problem to consider is the interpretation of the strain with all its characteristics: resistance traits, clinical significance, etc... From the laboratory side, the resistance trait is frequently seen as resistance to one antibiotic. In fact, each resistance trait should be characterized according to its expression toward the other antibiotics of the same class; its link to other resistance affecting another class of antibiotics, and when possible, according to its biochemical mechanisms and its genetical structure (Struelens, 1998). The adequate treatment to suggest to the clinician should guarantee a full clinical efficacy. In \textit{Streptococcus pyogenes} for example, resistance to erythromycin brings into question the possible cross-resistance to other macrolides, and for clindamycin as well; the possible linked resistance to tetracyclines. Penicillins remain the preferred antibiotic for therapy. In multiple-resistant \textit{Enterobacter cloacae}, the interpretation and the choice are more difficult. Outer membrane alterations and cephalosporinase derepression create the risk of the emergence of resistance to 3rd- and 4th-generation cephalosporins, carbapenems, or quinolones; moreover, resistance to aminoglycosides is frequently present. The effect of combined antibiotics might be explored.

Epidemiological survey would benefit from exploring the 'resistance profiles' and their prevalence rather than studying the incidence of each resistance independently. Linking the resistance profile to the treatment and outcome of infection, to the patient and to the ward would be significantly more informative than a passive review of the percentage of resistant strains.

The third problem on which I would insist is that treating the patient adequately is an ethical obligation. The observation of a high incidence of resistance to a particular antibiotic, as mentioned before, suggests banning its empirical use, or its use as a first line therapy. Such a decision cannot be useful in itself, if two other options are not considered: (i) Alternative antibiotic(s) should be identified for adequate treatment of the patient and eradication of the pathogen. This is crucial both ethically with respect to the patient and to control the resistant strains by reducing dissemination from the patient-reservoir. The dose and duration of treatment must be clearly defined since they are important factors in the emergence of resistance (Guillemot \textit{et al.} 1998). The implementation of change in current prescribing behaviour is a very difficult task. In hospitals it will require a consensus process with the prescribers. In the community, there are few countries where communication between general practitioners and health authorities is extensive enough to consistently change the behaviour of prescribers; (ii) An evaluation system must be established in order to provide feedback information on the incidence of resistant pathogens targeted in the program. It is important to note that the criteria to consider will be different according to the patient setting, the epidemiological mode of infections, the number of resistance traits in the pathogen and the indirect selective pressure by other antibiotics and antiseptics (Salyers and Arnable-Cuevas, 1997).

Surveillance of resistance is a task distinct from the one intended to improve the rational use of antibiotics. Surveillance should move from passive surveillance of the percentage of resistance to a structured active surveillance where denominators related
to the patient, the antibiotic(s) and the bacterial strain will be easily accessible in the data base. Rational use of antibiotics should be promoted as an ethical obligation both to the patient and to society.

The bridge between the use of antibiotics and bacterial populations and the distribution of the resistant subset, is a research task. This will contribute to the recognition of factors necessary to stabilizing or decreasing the incidence of resistance, and for circumventing the emergence of new resistance mechanisms.

REFERENCES

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