Key Issues In Developing Antibiotic Policies: From Institution to Europe-wide

ESGAP Subgroup 3

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INTRODUCTION

Establishment of a rational antibiotic policy (RAP) is a key issue for both better care of patients and combating antimicrobial resistance (1, 2, 3, 4, 5). The problem of rational antibiotic use is complex (6, 7) and requires coordination of the activities of health care authorities, institutions and individual practioners. Furthermore, on a community basis it involves restriction of non-human usage of antibiotics (8), awareness of society about both the useful and harmful effects of antibiotics (9) and on a national basis, participation of governmental (10) and non-governmental (11) organizations in collaboration with European and International medical societies (12, 13, 14). The rational use of antibiotics should be established in both hospital and ambulatory settings (10). Institutional, regional, national and global aspects of antibiotic policies should be considered (2).

NATIONAL ANTIBIOTIC POLICY

A national expert committee on antibiotic policies should be established in each country. The committee should develop guidelines for creating and auditing RAPs as well as considerations of content. They should consider both hospital and primary care settings as well as veterinary and agriculture use. Guidelines should be widely discussed through professional meetings of multidisciplinary groups, involving clinicians, microbiologists and pharmacologists/pharmacists. Some important issues to be included are (3, 12, 15,):

- Existing laws should be enforced to prevent non-prescription over the counter (OTC) sale of antibiotics
- Guidelines on the principles of antibiotic use (for treatment and prophylaxis) should be prepared by national experts and adapted institutionally at a local level)
- Consumption of antibiotics should be monitored in both the public and private sectors of health care to estimate the national consumption of antibiotics
- A national antimicrobial resistance surveillance system should be established and co-ordinated

with international surveillance systems

- A national control of infections programme should be implemented
- Educational programs should be elaborated:
  - for health care practitioners including veterinarians, junior doctors, nurses, medical students
  - for the wider audience (antibiotic consumers)
- Collaboration should be established with appropriate International organizations like WHO, APUA, the Medical Council of the European Commission (EC), ESGAP and pharmaceutical companies

- Appropriate funding should be made available by the government, health insurance organisations, the EC and international organizations

INSTITUTIONAL ANTIBIOTIC POLICY

Each health-care institution should have a therapeutics committee (TC), which should develop a local antibiotic policy based on national recommendations. This committee should be multidisciplinary so that the policy is acceptable to all sections of the institution. It should monitor the implementation of the policy, receive feedback information, assess the outcome and discuss it with the doctors (1, 6, 9, 12, 16, 17, 18). The policy should be revised each year, based on the experience of prescribers and the susceptibility reports of the microbiology laboratory. Audit targets should be set both for the RAP and the TC itself (19, 20).

The TC should consist of experts in antimicrobial chemotherapy, infectious diseases, internal medicine, surgery, paediatrics, clinical microbiology, pharmacology and hospital pharmacy. The guidelines should include consideration of activity, spectrum, pharmacokinetics, pharmacodynamics, potency to select resistance/to have adverse effects, costs and special needs of

individual patient groups (6, 12, 21, 22). It is advisable for the document to have different sections for treatment and prophylaxis including surgical procedures, as well as how to treat different infections – e.g. severe infections/immunocompromised hosts, hospital acquired infections, community-acquired infections, different infections by anatomic sites etc (12).

Three levels for antibiotic prescribing are generally recommended: (i). first choice antibiotics, to be prescribed by all doctors; (ii). restricted choice – for multiply-resistant pathogens, polymicrobial infections, some patient conditions that need special attention and/or more expensive antibiotics, to be prescribed after discussion with head of department or TC representative; (iii). reserve antibiotics – reserved for life-threatening infections and/or antibiotics known to select more resistance - to be used after permission from a TC member. The RAP should be discussed with all hospital staff, before becoming an official hospital policy.

Some hospitals have computerized prescribing of antibiotics (23), which, in the future, should become more commonplace (13, 17). This and other innovations such as the antibiotic order form and automatic stop form can be useful to control antibiotic usage (6, 21) and improve the quality of prescribing. Good collaboration between clinicians, the clinical microbiology laboratory, the committee for infection control and the pharmacy is necessary for achieving all the goals of a RAP (17, 18) and a multi-disciplinary antibiotic team (MAT) should be formed to ensure this is the case (1) (24)

CLINICAL PRACTICE

Prescribing of antibiotics should be done upon strict indications. Therapeutic decisions are best made depending upon the clinical situation:

1. The urgent situation in severely ill patients eg septic shock, endocarditis, meningitis, necrotizing cellulitis, osteomyelitis, need immediate therapy

2. Moderately ill patients with focal infection (eg pneumonia, urinary, biliary tract infection) where therapy should be administered within 2h.

3. Minor bacterial infection, which is not self-limiting but where therapy can await laboratory confirmation.

4. Prophylaxis upon specified medical or surgical indications

A careful assessment of the benefits of prescribing against the risks of non-prescribing of antibiotics should be considered including:

- patient cure/improvement against failure/mortality
- development of resistance in pathogens infecting the patient
- risks for spread of resistance (other patients, family-, society- members, more selective pressure in ICU etc)
- suppression of normal flora
- development of resistance in normal flora
- risks for superinfection

Other factors than antibiotics which may help the outcome should be considered; drainage of abscess, catheter replacement (10, 25), immunostimulation or reduced immune suppression, vaccination (2), reduced duration of ventilatory assistance, minimizing the use of central venous catheters, patient isolation (3, 26, 27).

Before starting antibiotic treatment, appropriate specimen should be taken, wherever possible, from the patient and sent for relevant laboratory examination including culture, species identification of probable pathogens(where possible) and antimicrobial susceptibility (3, 17). The results obtained should be used to guide/adjust the antibiotic therapy (3, 21), wherever possible stepping down from

broad to narrow spectrum (28) and from intravenous to oral agents (29). In urgent clinical situations helpful information to guide empiric therapy includes data about; localisation and source of infection nosocomial/community acquired, prior antibiotic therapy, prior invasive procedures, prior cultures, current relevant resistance patterns (25).

When making a decision about prescribing and choice of antibiotic, the doctor should answer the following questions (21, 25):

- 1. What is my rational in prescribing an antibiotic to this patient – does he really need it? - is it for empiric therapy or prophylaxis?

- 2. If there is confirmation of a bacterial infection, what is the causative organism(s) and probable susceptibility?

- 3. How ill is the patient, how quickly does treatment need to be given and what route is appropriate.

Other factors that it is very often relevant to consider include:

- in vitro susceptibility
- antibiotic spectrum and the need for combination therapy
- antibiotic activity: bactericidal/bacteriostatic
- site of infection and achievable antibiotic concentrations
- dosage regimen and modern pharmacodynamic principles (e.g. for beta-lactams – concentration >MIC for 40 % of the dosage interval; for quinolones - AUC: MIC ratio of > 125 (Gram-negative organisms) and > 30 (Gram-positive organisms); for aminoglycosides – a high C_{max} : MIC ratio (>16) and AUIC of >125 (30))

- dosing regimen and host factors (age, weight, immunosuppression, underlying disease, renal/hepatic dysfunction, allergy).

- cost/effectiveness ratio (22)
- adverse events, including drug interactions and those due to poor absorption of many oral agents

During the treatment the physician has to consider the relevance of

- bacterial identification/susceptibility testing report
- appropriateness of the antibiotic chosen
- appropriateness of the dose, route and duration
- are there any adverse effects
- patient status: improvement/failure
- are there any indications to change therapy eg antibiotic combination, streamlining, oral switch.

In hospitalised patients this evaluation should be on a daily basis, always stopping the antibiotic at the earliest opportunity to minimise unecessary antibiotic exposure (31)

Finally evaluation should be performed with respect to (3, 21):

- therapeutic response: cure, improvement, failure, death (analyze the reasons)
- any specific event to note: adverse effect, resistance during therapy, reinfection, superinfection

It is always worth emphasising that a careful clinical diagnosis, where possible with specific therapy is better than an uncertain diagnosis and treatment with broad spectrum agents (32).

For clinicians involved in prophylaxis, similar questions should be (12, 33):

- What is the need to give antibiotic prophylaxis in this patient?
- Which microorganisms have to be covered with prophylaxis?
- Which antibiotic?
- When to start the antibiotic?
- What is the dosage?
- How long should antibiotic prophylaxis last?

- The need to repeat the dose in surgical prophylaxis eg if the operation is prolonged.
- Is there any evidence for bacterial infection after the patient has been operated

CLINICAL MICROBIOLOGY LABORATORY

The clinical microbiology laboratory should identify the infecting organisms and their antimicrobial susceptibilities (10, 34) in as short a time period as possible, commensurate with accuracy (17, 18). Susceptibilities should not be reported on isolates of doubtful pathogenicity as this may encourage unnecessary use of antibiotics. Clinical microbiologists should be trained in giving advice to physicians about appropriate choices of antibiotic (1, 34) as well as collection and transport of the most appropriate specimens. Great emphasis should be put on timely reporting of results and audit of their impact on patient care (20, 35). An important task of the laboratory is to perform resistance surveillance, to analyze the results and inform clinicians and the antibiotic policy committee about current resistance rates and trends (10) The laboratory should be able to recognize emerging microorganisms/mechanisms of resistance (3, 26)**.** It should work in close harmony with the hospital pharmacy and only report these agents in the hospital policy and formulary on a routine basis (5),

PHARMACY

Pharmacy should routinely stock and dispense only those agents in the antibiotic formulary (5) . Pharmacists should participate in the RAP development, its control and periodic revision. They should monitor antibiotic consumption in order to analyze its association with development of resistance and highlight inappropriate use. Pharmacy should have computer facilities for quick connection with clinical and microbiology departments (17, 22) to facilitate these functions and look to implementations of electronic prescribing in the near future to make audit of quality of prescriptions easier (23).

INFECTION CONTROL COMMITTEE/TEAM (ICC/T)

They should work very closely with pharmacy and microbiology in the control of multiply-resistant organisms (17, 34). Their responsibilities also include all barrier precaution measures, control of hygiene, disinfection, sterilization, wards design, special monitoring in the ICU, isolation of patients infected/colonized by problematic microorganisms (such as MRSA, VRE), analyses of outbreaks (3, 18, 26, 27). Members of this committee should also be authorized to advise the healthcare administration when to make changes to prevent infections. Close liaison with the MAT is important to adopt antibiotic policies at short notice for the control of epidemic, multiply-resistant strains (31).

HEALTHCARE ADMINISTRATION

The Healthcare Administration should be closely involved in order to support all activities for improvement of the RAP (9). Clinical wards, the clinical microbiology laboratory, the pharmacy, and the ICC/T need adequate financing to perform their strategic goals. New diagnostic methods, for rapid diagnosis (3, 18) and computer programs (23) for better antimicrobial prescribing should be funded whenever possible. Special attention has to be given to the continued medical education of the staff, especially of junior doctors (9, 12).

PRIMARY CARE SETTING

A similar or identical TC should elaborate complementary RAP guidelines for general practice and also oversee their implementation and audit (10, 18)**.** Such TCs are often developed through area prescribing committees in collaboration with local microbiologists and general practitioners (GPs) (2). An appropriate system for audit and feedback enables the health authority to follow changes over time and target individual practices whose prescribing appears inappropriate. Doctors in Scotland have their own arrangements involving a set of 12 indicators, two of which relate to

antibiotic prescribing and data are available electronically (PRISM) (2). Special attention has to be paid to specialized institutions, especially residential ones for elderly people (36).

The most important community prescribing problem that needs to be solved, is the prescribing of antibiotic for viral infections such as URTI and other mild infections, that are self-limiting. This is especially important in pediatric practice (9, 10). In this regard it is important for GPs not to indulge patient (parental) demands for unnecessary antibiotics (35). The availability of laboratory facilities for primary care would improve the rational use of antibiotics as about 80 % of antibiotic use is in the ambulatory setting (37). In the current antibiotic resistance crisis, an evidence based, etiologic approach to the treatment of infectious diseases becomes more and more important (38). In this area, antimicrobial resistance surveillance is of special value.

Community ICTs should be established to prevent the dissemination of diseases and educate health care staff and patients in prophylactic and hygiene measures. Guidelines for community infection control management should be developed (2). Every health authority should have at least one infection control nurse (10). They are especially needed for nursing and residential homes.

In the community, pharmacists are often the first point of contact with patients and they are strategically placed to advise them about the risks of self-medication and necessity to see a doctor (2). They also provide services to nursing homes and should monitor the antimicrobial use. They should adhere to laws on OTC availability of antibiotics and only supply these in medical emergencies, where medical help is not available (39). Many more possibilities have to be given to the GPs to develop their qualifications through post-graduate education courses such as those provided by SWAB, STRAMA and APUA (11) and to ensure expert advice via computer-net systems (10). A good example is the computer-based decision support system PRODIGY (2).

Patient education is also important, especially about the hazards of misuse and over-use of antibiotics (as in self medication and/or OTC purchase) leading to treatment failure, chronic infection, suppression of normal flora and selection of resistant bacteria (40). The importance of patient's compliance should be emphasised, especially for long course therapy, such as for tuberculosis (9, 18) . Nowadays DOTS (directly observed treatment, short course) is recommended for treatment of tuberculosis to aid compliance and to minimize the risk of resistance (41). Finally, encouraging vaccination is important in preventing morbidity and mortality (2)**.**

TOWARDS A EUROPEAN ANTIBIOTIC POLICY? (EAP)

The Copenhagen Recommendations on The Microbial Threat (1) suggest that all states should:

- set up a European surveillance system of antimicrobial resistance and should collect data on antibiotic consumption
- make coordinated research on antimicrobial resistance a high priority
- develop educational programs
- improve practices to prevent the spread of resistance pathogens
- promote appropriate antibiotic use.

A Resolution of the 51st World Health Assembly, Emerging and Communicable Diseases: Antimicroial Resistance (42), requested the Director-General:

- to support countries to control antimicrobial resistance
- to assist in the development of sustainable national policies for rational antibiotic use
- to encourage sharing of knowledge and research to combat antimicrobial resistance
- to develop information and education programs for prescribers and users of antimicroial agents
- to encourage promotion of research and development of new antimicrobial agents

At the Nijmegen experts conference on a European strategy for controlling antibiotic resistance, Nijmegen, Holland, 1999 (13), it was concluded that it is a European priority to collate existing data on resistance rates, antibiotic consumption, antibiotic stewardship, infection control and molecular typing methods. On this basis suggestions would be provided about controlled intervention studies and a minimum set of common approaches for harmonization of strategies to control antibiotic misuse. Tackling antimicrobial resistance is not a short term activity: it is a long haul task, requiring partnerships between Government(s) and a wide range of organizations and individuals across many disciplines (2) (8).

On the basis of the philosophy behind the above statements, we believe there are crucial areas in the control of infectious disease, including multiply-resistant organisms, where harmonisation across Europe can contribute by improving the standard of antibiotic prescribing and infection control. At the same time we accept there are limitations to this approach. Firstly, local resistance problems dictate different solutions and different prescribing, even within a single country. Secondly, huge economic and social differences between different European countries, necessitate different approaches at different levels.

Establishment of European collaboration is of paramount importance for healthcare development and conserving the activity of antibiotics particularly in the developing countries of Europe. This would improve the clinical and laboratory standards. As postulated in the WHO Report on Infectious Diseases 2000 (43), essential drugs should be made available to poor people and alliances and partnerships should be established. Similarly, recommendations have been addressed to the WHO, through its Division of Emerging and other Communicable Diseases Surveillance and Control, to equip professionals and regulators in the developing countries to respond appropriately to pharmaceutical promotions (2). Development of a EAP should be a major step forward in achievement of the goal of global appropriate usage of antibiotics.

Although defined at a very preliminary stage, the minimum standards of a EAP should be:

- Establishment of a European antimicrobial resistance surveillance system (on a computer-based programme, e.g. WHONET) to provide data about antibiotic usage, resistance and linked clinical information.
- Establishment of European guidelines for good clinical practice
- Support of European educational programs for practitioners (under- and post- graduate-education) and consumers
- Establishment of an infection preventive and control policy
- Support of research: Disincentives such as intellectual property protection, regulatory approval procedures and antitrust law limitation on collaborative research and development constrain private investment (44).
- Supply of funds for developing countries eg from WHO and the World Bank (43,45, 46).

CONCLUSIONS

It is difficult to see how much more can be done at a National or International level to grapple with the overuse of antibiotics. Legal and political hurdles are soon met and negative reactions from prescribers who feel that their clinical freedom has been infringed are likely to be counter productive. Self regulation of the profession, through continuous professional development, clinical governance and peer review audit of clinical standards is seen as the way forward (47). Certainly it must be given a chance and enthusiastically implemented.

More formal regulations such as restricted distribution and modifying current labelling strategies may ultimately be considered essential although current thinking is that this is likely to be counterproductive (42). Variations in subsidies has been tried with some effects (48).

Ultimately there will always be a conflict between the public health aspects of antibiotic prescribing and the clinicians desire to do his best for individual patients (49). Perhaps authorities can take due care of the legal implications of this by underwriting any legal liabilities?

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