Antimicrobial management

- - - the role of clinical pharmacists

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The second part of this month’s special feature examines the role of clinical pharmacists in promoting the rational prescribing of antimicrobial agents, setting out some aspects of good practice that can be further developed.

Micro-organisms resistant to antimicrobials, especially those with multiple resistances, are causing concerns within health care systems throughout the world. Infections become more difficult to treat and patients stay longer in hospital, with the associated increases in costs. Furthermore, because less safe antimicrobial agents have to be used when the more safe alternatives are no longer suitable due to resistance, the prevalence of unwanted effects of the medicines tends to increase.

The emergence of resistance represents adaptive selection by micro-organisms, which is an inevitable result of the therapeutic use of antimicrobial agents. Killing or suppressing drug-sensitive organisms allows naturally drug-resistant variants to emerge which can then not only spread, but also transfer their resistance to other organisms.

Whether a reduction in the use of antimicrobials will reduce the levels of resistance has not yet been demonstrated. But by reducing the use of antimicrobials, and by conserving selection wherever possible to narrow spectrum agents, it is hoped that there may be a slowing in the emergence of resistance to existing agents and to new drugs as they come into use.

Resistance problems are generally greatest in hospitals, reflecting the fact that:

- Many inpatients have severe underlying diseases that render them susceptible to infection by otherwise harmless ‘opportunist pathogens’ that have been adept at acquiring resistance
- Prescribing is concentrated in a small area, intensifying selection for resistance

Resistance to antimicrobials has been reported ever since the clinical use of the first agents used to treat infectious diseases. It has been estimated that in the United Kingdom (UK) at any one time, approximately one in 10 patients in acute hospitals have a hospital acquired infection. The cost of antibiotic resistant infections in hospitals has been estimated to be up to $7.7bn in the United States alone. This does not take into consideration the wider costs of this problem in the community.

In the UK around 70,000 people die each year from an infection. Hospital-acquired infections are estimated to cost the NHS about £1bn per year according to the House of Lords Scientific Committee into Antimicrobial Resistance and the Department of Health (DoH) report “The path of least resistance”. This report identified growing problems in the use of antimicrobials.

DOH action

Following a number of expert reports, the DoH launched its UK Antimicrobial Resistance Strategy and Action Plan in June 2000. The aims of this strategy are set out in Panel 1 (pp.395).

The Specialist Advisory Committee on Antimicrobial Resistance (SACAR) was set up in 2001 to advise the government on its antimicrobial strategy. SACAR is an independent advisory committee, chaired by Professor Richard Wise from Birmingham University, which provides expert scientific advice on resistance issues arising from medical, veterinary and agricultural use of antimicrobials. The terms of reference of SACAR are shown in Panel 2 (p.395).

A prescribing subgroup of SACAR focuses on aspects of the prudent prescribing of antimicrobials. The prescribing issues are to be addressed initially in hospitals, but subsequently across the whole of the NHS. Its remit is:

- To advise SACAR on the prudent use of antimicrobials in humans
- To promote good practice in the use of antimicrobials
- To ensure recommendations are consistent with a strategy that lowers the risk of antimicrobial resistance

The prescribing group of SACAR is also to oversee the £12 million of funding over a three-year period to create a national database for the use of antimicrobials in hospital and to promote prudent antibiotic prescribing through enhanced clinical pharmacy activity (the “pharmacy initiative”), announced by the chief medical and pharmaceutical officers for England in June 2003. (See Panel 3, p.400, for contact details for SACAR and other relevant organisations.)

Hospital database

Data on the use of antimicrobials in primary care is available through PACT (prescribing analysis and cost) data, and provided by the Prescription Pricing Authority. No such aggregated data are available for hospital prescribing, which comprises a significant proportion of the total antibiotic use and up to 25 per cent of a hospitals total expenditure on medicines.

It is therefore important to examine hospital antimicrobial usage rates to observe differences within the NHS and seek a com-
mon approach across the UK. Also, it will be useful to determine whether any links can be made between antimicrobial use and the development of microbial resistance using local surveillance data. Ways in which such data can be captured and aggregated nationally are currently being investigated.

The hospital antimicrobial database will need to include units of agent issued as well as the cost. Many surveys use costs of issue data as a predictor for usage. This is probably satisfactory for financial planning and resource allocation purposes and can be a crude indicator for consumption. However, cost alone is not precise enough because it fails to recognize variations in financial discounting or the use of antimicrobials in clinical trials where supplies are free.

Better numerator data are grams of antimicrobial or defined daily dose (DDD). The DDD has been used in many pharmacoepidemiological studies and is a valuable tool for estimating trends of medicines usage and proportions of a particular medicines or group of medicines within a therapeutic group. Population denominators that have been used include 1000 patients, for medicines usage within community populations, 100 bed days or finished consultant episodes (FCEs) for hospital inpatients.

**CLINICAL PHARMACIST’S ROLE**

Clinical pharmacy activities have developed widely in the UK and evidence is available to show that these activities lead to improved patient care and to the better, and often more cost effective, use of medicines. It is also generally recognised that clinical pharmacists provide a high quality input to the care of individual patients. The pharmacy initiative promotes a number of examples of good clinical pharmacy practice including:

- Monitoring prescribing in relation to policies
- Ensuring parenteral antibiotics are switched to oral use where appropriate
- Developing local evidence based guidelines in close liaison with consultant medical microbiologists
- Providing regular analysis with feedback to prescribers on antibiotic use.

It sets out to build on examples of existing good practice and develop them further. In particular, hospital trusts are expected to extend clinical pharmacy services to areas of high antibiotic use and to meet identified local issues. This will help to focus on key areas such as antibiotic use in surgical prophylaxis, antibiotic use in children, and infection control. Clinical pharmacists should work with microbiologists and prescribers to promote the following:

**Guidelines, formularies and policies** The pharmacy initiative recommends that hospital antibiotic policies should be in line with current best practice and be evidence based. This could take place through existing groups such as drugs and therapeutic committees or medicines management committees, and should be linked to clinical governance.

Similarly, the Standing Medical Advisory Committee (SMAC) report recommends that antimicrobial formularies should:

- State the date that the document was created or revised
- Be evidence based
- Contain information on antimicrobial, dose, frequency and length of course
- Point out any aspects where the local formulary varies from national guidelines
- Indicate the strength of the evidence for the recommendation

A review of antimicrobial formularies was undertaken in the south east of England in 1999. The authors noted there was considerable variation in content and quality. Most formularies had a clear lack of an evidence base and a need to revise them in line with current recommendations. SACAR is currently developing a template for anti-microbial guidelines.

**Panel 1: The UK Department of Health’s antimicrobial resistance strategy and action plan**

**Strategy**

In the face of the ability of micro-organisms resistant to antimicrobial agents to emerge and spread, the increasing prevalence of resistant strains and the dearth of new agents likely to be available for therapeutic use in the near future, to minimise the morbidity and mortality due to antimicrobial resistant infection and to maintain the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections in man and animals.

**Action plan**

- **Surveillance**: to monitor “how we are doing” and provide the data on resistant organisms, illness due to them and antimicrobial usage necessary to inform action both locally and nationally
- **Prudent antimicrobial use**: to reduce the “pressure for resistance” by reducing unnecessary and inappropriate exposure of micro-organisms to antimicrobial agents in clinical practice, veterinary practice, animal husbandry, agriculture and horticulture
- **Infection control**: to reduce the spread of infection in general (and thus some of the need for antimicrobial agents) and of antimicrobial resistant micro-organisms in particular

**Panel 2: SACAR terms of reference and remit**

**Terms of reference**

To provide scientific advice to the government on its strategy to minimise the morbidity and mortality due to antimicrobial resistant infection, and maintain the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections in man and animals.

**Remit**

- To advise the government on long-term measures necessary to minimise antimicrobial resistance. This will include measures to effect a reduction in antimicrobial prescribing by medical/veterinary professions and a matching reduction in the expectations of patients
- To advise on relevant research in the field of antimicrobial resistance and any encouragement necessary for the pharmaceutical industry to produce relevant new antimicrobial agents
- To “scan the horizon” for likely emerging problems in the field of antimicrobial resistance to ensure that government and healthcare (including veterinary) workers have systems in place to meet potential threats. To react in a timely and realistic way to acute problems in the field of antimicrobial resistance as they arise
- To advise the government on problems in the medical and veterinary fields
antimicrobials offer immediate high plasma levels of drug and are to be chosen for the initial treatment of seriously ill patients. In many instances patients can be switched from IV to oral therapy once the patient has started to improve. Switching to an effective oral therapy can allow earlier discharge, improves patient comfort and mobility, and potentially significantly reduces the cost of treatment. Patients may be considered for oral therapy if:

- There is sufficient microbiological information about the pathogen and its sensitivities
- The patient is haemodynamically stable with no signs of fever
- The patient is clinically improving
- The patient is able to take oral medicines
- The patient has a functional gastrointestinal tract with no malabsorption
- There are no conflicts or interactions with any other medications the patient

The switch to oral therapy should be delayed for two weeks or more in patients suffering from certain high-risk infections as well as liver abscesses, inadequately drained abscesses and empyemas, osteomyelitis or septic arthritis.

**Duration of treatment** Ideally, drug charts on which IV antimicrobials are written up should be reviewed daily, and the agent rewritten. Alternatively, a number of institutions operate an “automatic stop” after a defined period, after which the prescription is no longer valid. Others require prescribers to state the intended duration of IV therapy and to indicate what they think they are treating.

**Pharmacokinetics** An understanding of both the pharmacodynamics and pharmacokinetics of antimicrobial agents provides an important piece of the jigsaw for the effective selection and use of these drugs in order to maximise the benefit to patients. Knowledge of the absorption, distribution, metabolism and excretion can also provide considerable indicators for selection of agents to treat clinical infections.

**Surgical prophylaxis** Randomised, controlled trials have shown that prophylactic antibiotics are effective in preventing surgical-wound infections. The timing of the first dose of antibiotic is important for the prevention of wound infection. For example, a classic US study involving patients who underwent elective clean or “clean-contaminated” surgical procedures at a large community hospital showed that 0.6 per cent of the 1,990 patients who received their first dose of antimicrobial agent up to two hours pre-operatively subsequently had surgical wound infections, compared with three per cent of the 857 patients who received the first dose more than two hours before or more than three hours after the incision.11

Where guidelines for the timing of surgical antimicrobial prophylaxis exist, they are not necessarily adhered to. For example, an audit of 1,763 surgical procedures carried out by reviewing medical, anaesthetic and nursing records and medication charts at 13 Dutch hospitals between the year to January 2001 showed that guidelines for antibiotic choice were followed in 92 per cent of cases. The corresponding figures for duration, dose, dosing interval and timing of the first dose were 82 per cent, 89 per cent, 43 per cent and 50 per cent of cases. Overall adherence to all aspects of the guideline, however, was achieved in only 28 per cent of cases. The authors proposed that the most important barriers to local guidelines adherence were lack of awareness due to ineffective distribution of the most recent version of the guidelines, lack of agreement by surgeons with the local hospital guidelines, and environmental factors, such as organisational constraints in the surgical suite and in the ward.12 It might be expected that the situation in the UK would be similar. Guidelines for antibiotic prophylaxis in surgery have been produced by the Scottish Intercollegiate Guidelines Network (SIGN)13 and are presented in the British
National Formulary.14

One practical and effective way of ensuring that the first dose of an antimicrobial used for surgical prophylaxis is given at the right time is to agree with the attending anaesthetist or nurse that the agent should be given with the other intravenous medicine at induction. A ready made syringe or mini-bag containing the antimicrobial agent greatly helps this process.

**Resistance monitoring and sensitivity reporting** A key aspect to using antimicrobials rationally is identifying the microbial causes of infection and measuring the sensitivities of these to antimicrobials. Monitoring of trends in antimicrobial resistance is also important, and is one of the key elements of the DoH’s strategy to control antimicrobial resistance.

Reporting of sensitivities of microorganisms to antimicrobial agents offers a “marksman” approach to the selection of an appropriate treatment strategy. However, such reporting needs to be linked to the overall antimicrobial formulary and should be focused on the selection of the most appropriate agent, rather than giving information on a vast array of agents to which the micro-organism is sensitive. It is also better to recommend an agent with the narrowest spectrum of activity and the least effect on the body’s normal commensal flora, since this offers the best chance of limiting the spread of resistance while maintaining effective treatment. For example, selective reporting might report just trimethoprim for a urinary tract infection even though a whole range of other agents might have been sensitive but have been held back at the first stage. Information on the other sensitivities can be divulged at a later stage if the prescriber deems the information already received to be insufficient for the clinical management of the patient. This method of sensitivity reporting also acts as an educational instrument for prescribers because they receive information on the most appropriate treatments on a regular basis.

**IV antimicrobial preparation** As with other IV drugs, many potential hazards are associated with preparing and administering IV antimicrobial agents. These include:

- Drug administration errors
- Microbial contamination
- Drug and fluid incompatibilities
- Inadequate training of ward staff in drug preparation and administration15-17

A number of reports recognise that the addition of drugs to intravenous infusion fluids is an aseptic pharmaceutical procedure, which should be carried out in appropriate environmental conditions under the direct control of a pharmacist. For example, the recent “A spoonful of sugar” report...
by the Audit Commission recommends that “trust boards and senior managers should seek regular assurance that actual clinical practice reflects agreed protocols – in particular, the practice of making up aseptic preparations on hospital wards should be stopped.”18 In addition, EL (96) 95, “Aseptic dispensing in NHS hospitals” states that “trusts, chief executives of trusts, the pharmacist or anyone else working in the trust on the supply of medicinal products could be liable for prosecution under the Medicines Act 1968 if medicinal products supplied are not of the nature or quality expected” and “Preparation of parenteral medication at ward level in an open environment can increase the risk of microbial contamination of the product and medication errors by, for example incorrect dose calculation or product preparation.”19

Many papers have been published on the establishment and evaluation of centralised intravenous additive (CIVA) services. Most agree that the benefits of these services fall into five key categories:17,20

- The patient is assured that he or she receives the product in the full confidence that it has been formulated in the best possible way21
- Reduced number of preparation and administration errors of IV medicines because of the increased pharmacy control22
- Increased opportunity for clinical pharmacy activities, because clinical pharmacists will be able to assist in the appropriate selection of drug and advise on monitoring for optimal dosage modification on a seven-day-a-week basis
- Improved use of hospital resources by minimising wastage and promoting an appropriate use of skill mix within the organisation23-25
- Benefits to hospital management, because there is more control over the issue and use of high cost IV preparations. Consultant costings can also be identified through the pharmacy computer system

**IT prescribing support** Unlike in primary care, electronic prescribing and information technology support is in place in less than 5 per cent of UK hospitals. Hospital clinicians would benefit from the availability of computer-aided decision support systems, into which suitably adapted national prescribing guidelines could be integrated.

Recommendations have been made that studies be undertaken in selected hospitals to develop and test one or more prototype decision support systems. To be fully effective, these computer based advisory systems should include information from local antimicrobial sensitivity profiles. These in turn should feed into regional and national
The British Society for Antimicrobial Chemotherapy (BSAC) has recently launched a website on the management of hospital infection. The resource is aimed at ensuring those responsible for prescribing select the correct antimicrobial at appropriate doses to increase the chance of cure while limiting the spread of antimicrobial resistance. Visit www.bsac.org.uk/pyxis/

The Alliance for the Prudent Use of Antibiotics (APUA) is a non-profit, international organisation solely dedicated to preserving the power of antibiotics. Founded in 1981, APUA conducts educational, research and international networking activities to promote more appropriate use of antibiotics around the world: local branches tailor research and interventions to local customs and practices. For further details of the UK Chapter of APUA contact Professor Peter Davey at UK Chapter Co-ordinator, BSAC, 11, The Wharf, 16 Bridge Street, Birmingham B1 2JS, Tel 0121 633 0410, Fax 0121 643 9497 or visit www.tufts.edu/med/apua/index.html

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) is a non-profit organisation whose mission is to improve the diagnosis, treatment and prevention of infectious diseases by promoting and supporting research, education and training in the infection disciplines. This is achieved by scientific exchange, educational programmes, grants and awards, certification and consultation with professional and government agencies. Through its activities and publications ESCMID fosters professional exchange and stimulates an open and collaborative spirit nourished by the diversity of European culture. Visit www.escmid.org/sites/index.asp

The Specialist Advisory Committee on Antimicrobial Resistance (SACAR) is an independent advisory committee set up to provide expert scientific advice on resistance issues arising from medical, veterinary and agricultural use of antimicrobials. Visit www.doh.gov.uk/sacar/

surveillance databases.1

SUMMARY

Clinical pharmacists, in conjunction with prescribers and microbiologists, have an invaluable role in promoting the rational prescribing of antibiotics. The aim is to help reduce the growing problem of resistance to existing antimicrobial agents, and to new drugs as they come into use.

REFERENCES

15. Aesopic dispensing for NHS patients, Department of Health 1995
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Credit for learning

The answers to the credit for learning questions for July/August (epilepsy) will appear in the next edition of Hospital Pharmacist.