Formularies and antimicrobial approval systems

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2.1 Key points

• Formularies can be used to influence patterns of antimicrobial use in hospitals. Each hospital should have a formulary for antimicrobial drugs, and the drug and therapeutics committee of the hospital should define rules that restrict access to particular antimicrobial agents.

• Restrictions on the use of antimicrobials have played an important role in aborting outbreaks of resistant bacteria.

• Antimicrobial approval systems have been shown to be effective in optimising antimicrobial use in a hospital setting — their use has been associated with reduced volumes of drugs used, reduced drug costs, fewer adverse drug reactions and shorter lengths of stay.

• Approval systems may be used for preprescription or postprescription approval.

• Experts providing the approval should be members of the antimicrobial stewardship teams or their nominees.

• Computerised systems have been found to be acceptable to clinicians as a means of facilitating antimicrobial approvals in hospitals.


2.2 Recommendations

2.2.1 Hospitals have a list of restricted antimicrobial agents and criteria for their use which is consistent with *Therapeutic Guidelines: Antibiotic*.19

2.2.2 Hospitals implement an antimicrobial approval system.

2.2.3 Compliance with the approval process is audited on a regular basis.

2.2.4 Expert advice is available 24 hours a day to guide clinicians in prescribing antimicrobials.

2.3 Strategies for antimicrobial stewardship

Strategies for antimicrobial stewardship (AMS) fall into ‘educative’ strategies, where prescribers are provided with guidelines and taught how to select antimicrobial agents more appropriately, and ‘restrictive’ strategies, in which prescribers are prevented from accessing particular antimicrobial agents unless criteria are met and formal approval is granted by a nominated person. Approval may be required preprescription, or postprescription within a specified time period (e.g. 48 hours).

Several leading guidelines on AMS endorse the use of both educative and restrictive strategies to facilitate comprehensive stewardship in hospital settings. This chapter will focus on describing different restrictive strategies for AMS.

Some authors have suggested that restrictive strategies have the greatest impact on prescribing behaviour. Dellit et al. in the Infectious Diseases Society of America and Society of Healthcare Epidemiology of America guidelines,1 and MacDougall and Polk in their comprehensive review,12 all recommend that antimicrobial restriction and specifically antimicrobial approval systems have a central place in any AMS program for hospitals.

The use of antimicrobial formulary and approval (pre-authorisation) systems to influence appropriate antimicrobial prescribing are described below. The roles of the different departments in supporting these restrictive strategies are further described in Chapters 7, 8 and 9. See Appendix 2, Section A2.1 for examples of restricted antimicrobial policies and guidelines from Australian hospitals.

2.4 Formulary systems

In its simplest form, a formulary is a list of drugs, including antimicrobial agents, that has been approved for use in a hospital. However, formulary systems can also be used to influence prescribing behaviour by restricting access to particular drugs and by applying rules governing drug use. A formulary that includes a list of restricted antimicrobials is an essential component of an AMS program.1, 12, 16-17, 20
The antimicrobial formulary should be appropriate to the needs of the hospital and should take into account the range of antimicrobials required, the clinical orientation of the hospital and local antimicrobial resistance. It should be updated periodically and compliance with it audited.\textsuperscript{17,20}

The responsibility for creating and maintaining a drug formulary usually lies with a hospital’s drug and therapeutics committee. The role of this committee is to evaluate the evidence regarding the efficacy, safety and cost of new agents before deciding whether to endorse their use in the hospital and list them on the formulary. The drug and therapeutics committee may have an antimicrobial subcommittee or may use the AMS team to evaluate requests for new antimicrobial agents or new indications for use, and to make recommendations for formulary listing.

In many circumstances, formulary decisions may have criteria attached to the approval for use of a drug in the hospital (e.g. use is approved only for a particular unit, for patients with a particular condition, or where other options are contraindicated due to intolerance or demonstrated failure). In the case of antimicrobial agents, certain drugs may be restricted for use only with approval by nominated expert prescribers (e.g. infectious diseases [ID] specialists or microbiologists).

It is important that antimicrobial formulary decisions are informed by local microbiologic information. If, for example, resistance to one antibiotic class has been emerging in local bacteria, then the drug and therapeutics committee may respond by directing prescribing towards alternative agents. This may require a change in criteria for approval to use the alternate agents. It is therefore important for microbiologists and ID physicians to provide continuous expert advice to drug and therapeutics committees (by membership of the committee or liaison with the AMS team).

2.4.1 The evidence for restricted formularies influencing antimicrobial prescribing

It has been well demonstrated that formularies dictate prescribing patterns in hospitals and direct prescribing away from some drug classes and towards others. This clearly affects drug consumption patterns and expenditure. For example, Aspinall et al.\textsuperscript{43} compared 15 hospitals in the United States, where 12 had free access to fluoroquinolones and 3 had restricted access as indicated in their respective hospital formulary. The study sampled 200 cases of acute respiratory infection presenting to each hospital and found that 17% of patients were treated with fluoroquinolones for respiratory tract infections at the unrestricted hospitals compared with just 6% at the hospitals with a formulary. Multivariate analysis of the factors that predicted the use of fluoroquinolones found that hospital site was strongly predictive and the study concluded that a formulary can have an important impact on prescribing practices. In turn, prescribing practices may have an impact on the local prevalence of some resistant pathogens.
Few published studies have directly examined the use of formularies to guide antimicrobial prescribing with the primary aim of tackling antimicrobial resistance. Studies that do address antimicrobial resistance usually incorporate some form of restriction of one class of drug, followed by an addition of another class to the formulary in an effort to ‘replace’ the first class. Such changes in formularies have been shown to be associated with changes in local rates of some antibiotic-resistant pathogens, but the authors tend to attribute the observed changes to the formulary switch by virtue of an association in time only. Unfortunately, most of these studies have occurred over short time periods and at single centres — studies run over longer time periods and at multiple centres would be preferable to better explore this complex association. Some examples of the studies are reported in Table 2.1.

Table 2.1  Effect of formulary changes on prevalence of multiresistant pathogens

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of sites</th>
<th>Description of intervention</th>
<th>Results</th>
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<tbody>
<tr>
<td>Landman et al. (1999)***</td>
<td>One hospital in the United States</td>
<td>Restriction on use of third and fourth-generation cephalosporins, clindamycin and vancomycin; approval required for their use. Beta-lactam–beta-lactamase combinations (piperacillin–tazobactam and ampicillin–sulbactam) were simultaneously added to the formulary without requirement for approval.</td>
<td>There was a shift in prescribing behaviour away from cephalosporin-based therapy and towards extended spectrum penicillin use. Concurrently, there were reductions in the rates of methicillin-resistant <em>Staphylococcus aureus</em> (MRSA), and ceftazidime-resistant <em>Klebsiella</em>, which the authors hypothesised were attributable to the change in prescribing patterns.</td>
</tr>
<tr>
<td>Walbrown et al. (2008)**</td>
<td>10 veterans’ affairs hospitals in the United States</td>
<td>A formulary change from levofloxacin to gatifloxacin with 12-month data collection, 6 months pre and postintervention.</td>
<td>A rise in <em>Clostridium difficile</em> infection (CDI) was noted, from 2.3 cases per 1000 antibiotic days (54% associated with previous fluoroquinolone use) to 3.4 cases per 1000 antibiotic days (67% associated with previous fluoroquinolone use). The study concluded that the formulary does dictate prescribing patterns and that different drugs within a class may have different effects on CDI rates.</td>
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Table 2.1  Effect of formulary changes on prevalence of multiresistant pathogens continued

<table>
<thead>
<tr>
<th>Author</th>
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<th>Description of intervention</th>
<th>Results</th>
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<tr>
<td>Winston et al. (2004)</td>
<td>One hospital in the United States</td>
<td>Formulary change from ticarcillin-clavulanate to piperacillin-tazobactam. Active surveillance of all patients at admission and discharge from the intensive care unit was undertaken.</td>
<td>There was a reduction in the vancomycin-resistant Enterococcus (VRE) acquisition rate (11.5% versus 7.6%, relative risk 0.68, ( P = 0.07 )) and a fall in clinical VRE isolates (0.58 per 1000 bed-days pre to 0.33 per 1000 bed-days post) with the change in formulary. The authors of this study proposed that the change in prescribing behaviour caused by the formulary switch led to the change in VRE rates.</td>
</tr>
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In summary, the evidence supports the inclusion of a formulary system in hospital AMS programs, with a list of restricted antimicrobial agents and criteria for their use. Examples of restricted formularies are provided in Appendix 2, Section A2.1.

2.5 Antimicrobial approval systems

The use of a restricted formulary and an approval system, which facilitates restriction of broad-spectrum antimicrobials to patients where use is clinically justified, are considered essential requirements of any antimicrobial stewardship program.\(^1,12,16\)

A formulary describes the agreed indications for use of particular antimicrobial agents and an approval system provides a mechanism through which the formulary restrictions can practically be enforced.

2.5.1 The evidence for antimicrobial approval systems

Several studies suggest that antimicrobial approval systems can reduce the volume of broad-spectrum antimicrobials prescribed, thereby reducing drug expenditure.\(^48-51\) A reduction in adverse drug reactions for patients has also been described.\(^48,52\) Effects on patient outcomes are less well described, although reduced lengths of hospital stay have been reported after the deployment of an antimicrobial approval system, as has the use of more appropriate empirical antimicrobial therapy.\(^52\)

Studies on the effectiveness of restrictive antimicrobial strategies in addressing the problem of antimicrobial resistance have generally been related to limiting the use
of a specific antimicrobial class to tackle an outbreak of a specific pathogen. For example, restricting:

- cephalosporins and vancomycin to deal with vancomycin-resistant *Enterococcus* (VRE)\(^{53}\)
- cephalosporins to tackle an outbreak of *Acinetobacter*\(^{50}\) or resistant *Klebsiella*\(^{54}\) or resistant *Enterobacter* and *Pseudomonas*\(^{55}\)
- cephalosporins to address outbreaks of *Clostridium difficile*\(^{41,42,56-57}\)

The effect of restricting a large number of antimicrobials on the endemic resistance profiles of several different bacterial pathogens has been described in some single-site studies. Paterson reported anecdotal evidence of an improvement in sensitivity patterns in local bacteria with the introduction of a restrictive stewardship system.\(^{29}\) Martin and Ofotokun\(^{58}\) showed that an antimicrobial control policy that reduced cephalosporin, vancomycin and carbapenem use led to a reduction in multidrug-resistant gram-negative pathogens. Cook et al.\(^{59}\) described no change in the antibiogram for gram-negative bacilli before and after an AMS program, but these data were only collected for a relatively short time period (two years either side).

In general, the effects of restrictive systems addressing multiple antibiotics on endemic antimicrobial resistance patterns of multiple bacteria over long time periods has not been widely reported. The relationship is likely to be complex, and more work is needed in this field.

### 2.5.2 Mechanisms for administering approval systems

The practical mechanisms for administering approval systems have varied, but basically some form of approval must be granted by an expert prescriber under a system that fits the workflow of the organisation. Preprescription approval may be by telephone or by filling in a drug order form. An example of a drug order form is provided in Section A2.1 in Appendix 2. Bamberger and Dahl\(^{55}\) described a system where written justification for the use of ceftriaxone or ceftazidime had to be submitted to the pharmacy before the drugs could be used. McGowan and Finland\(^{48}\) described a system that required prescribers to telephone the ID consultant to discuss a case before approval. Until recently, telephone approval has been the predominant method used by many Australian hospitals.

However, these methods have a number of drawbacks:

- Telephone approval can be onerous for staff who must be available to grant approval as it is required — they therefore receive continual interruptions.
- The advice provided may be inconsistent if different experts rotate the role.
- It can be difficult to keep a record of the advice given and to communicate the advice to others involved in a patient’s care, including pharmacy staff supplying the drug.
Postprescription approval systems usually entail a review of a patient prescribed a restricted drug by an expert prescriber within a given time period. Reviews may be carried out in some settings by a dedicated AMS team, including ID physicians, a microbiologist, and pharmacists who perform daily ward rounds. Such systems can be very successful as they provide individualised advice and direct interaction with prescribers face to face. The main difficulty with postprescription approval systems is that large resources are required to maintain them. In addition, communication advice usually needs to occur via the medical record and auditing can be difficult.

Some articles describe a mix of different strategies. In a study from Hong Kong, prescribers were required to fill in an antibiotic order form if they wanted to use one of 12 restricted antimicrobials beyond one day. Receipt of a form prompted review by an ID specialist and concurrent feedback was provided (i.e. a combination of preprescription approval and postprescription review). Woodward et al. described a multitiered system whereby some agents required preprescription approval before access was allowed, while other drugs could be used without preprescription approvals, but triggered an automatic postprescription review at 72 hours.

Restrictive strategies require close collaboration with pharmacy, clinical microbiology and ID staff to be successful. Approval systems have been shown to be cost-effective, even personnel-intensive systems. For example, in a study from Hong Kong that used an AMS team with a mix of pre and postprescription approvals, an economic analysis demonstrated an overall cost saving, if AMS program personnel costs (US$71 000 per year) were weighed against antibiotic costs (US$380 000 per year).

Some examples of antimicrobial approval systems are provided in Appendix 2, Section A2.1.

### 2.5.3 Automated approval systems

The practical implications of restricting large numbers of antimicrobials can be quite significant for hospitals. Personnel requirements (resources and time) can become onerous with telephone approval systems or an AMS team, because approvals may be required at any time of the day. This can lead to delays and frustration for both the prescriber and the authorised approver. Automation using computerised antimicrobial approval systems is a possible solution to this problem. Electronic approval systems for individual antimicrobial agents have been described in several centres. Both Richards et al. and Grayson et al. describe clinical electronic advice and approval systems introduced into Australian teaching hospitals that have significantly reduced the burden of a wholly telephone-based approval system for third-generation cephalosporin use.

Recently, electronic systems to manage larger numbers of antimicrobials have been reported. Some of these systems are large, institution-specific decision-support systems that trigger alerts for particular drugs and make recommendations, rather than restricting access to drugs. These have been successfully implemented at some major sites in the United States and are further described in Chapter 10.
A transferable web-based electronic antimicrobial approval system (Guidance DS), which covers several restricted antimicrobials, has had good uptake in Australia, leading to reduced drug consumption, improved resistance patterns in some gram-negative isolates in the intensive care unit and acceptable usability for clinicians. The system has been used to restrict the use of third and fourth-generation cephalosporins, carbapenems, extended-spectrum penicillins, aminoglycosides, fluoroquinolones and glycopeptides. Buising et al. evaluated trends in antimicrobial consumption for five years before the deployment of the system, and compared this with the patterns observed over two years after implementation in one Australian tertiary hospital. Reductions in the use of all classes of broad-spectrum antibiotics were observed, with the exception of extended-spectrum penicillins, as increased use was prompted by a change in hospital protocols for febrile neutropenia. The system was incorporated successfully into clinicians’ workflow, with between 200 and 250 uses per month in a 350-bed hospital.

An independent evaluation of the Guidance DS system demonstrated that clinicians and pharmacists found it easy to use and incorporate into their workflow. The reduced consumption of broad-spectrum antimicrobials was associated with a subsequent fall in multiresistant gram-negative bacteria in the intensive care unit over time. There was no negative impact on patient outcome (no increase in patient deaths or lengths of stay for gram-negative bacteraemia, despite the access limits to broad-spectrum antimicrobials). The Guidance DS system has been successfully transferred to other hospitals in Victoria and Tasmania, and the effect on prescribing in these sites will be the subject of ongoing study.

2.5.4 Advantages of electronic approval systems

Electronic approval systems can provide a number of benefits apart from reducing demands on personnel. The system can be accessed 24 hours a day and can be used to provide consistent advice regarding approved indications for drug use. The institution may nominate certain standard indications and durations for which approval may be obtained via the computer, and then require individual approval for more complex indications or prolonged durations of drug use. This process focuses the expert prescriber’s attention on the complex cases and does not burden them with ‘routine’ indications. However, the prescriber is still encouraged to think carefully about their own prescribing behaviour, which ensures that they are aware of hospital policy at the time of prescribing.

Electronic approval systems can provide access to guidelines at the time of prescription and thus address educative strategies for stewardship. They can generate electronic alerts or reminders, prompting review after a set period for complex patients being managed by the expert prescriber, and communicate advice explicitly to other clinical staff (doctors from other units, pharmacists, etc). Importantly, electronic approvals allow for easy data extraction and auditing of antimicrobial use, thereby facilitating feedback to individual prescribers, units and hospital committees.
Electronic approval systems do not function in isolation. They streamline the approvals process for general prescribers, pharmacists and nominated expert prescribers, and act as tools for AMS committees. They do not replace expert prescribers, but they can direct the attention of expert prescribers towards the most important patients.

2.5.5 Implementing electronic approval systems

The implementation of an electronic approval system requires careful planning. Important attributes of the system include high usability and meeting the needs of users within their context. In addition, the organisational structure surrounding the implementation of an electronic approval system needs to be assessed. Recently, Luu et al. assessed the readiness of hospitals in Victoria and Tasmania to adopt an electronic antimicrobial approval system.68 They explored the human, organisational and technical aspects of ‘readiness to change’ and identified a number of domains in which hospitals could be assessed to identify ‘gaps’ that might need addressing.

These included:

- technical readiness — integration requirements and access to information technology infrastructure
- resources — financial and human resources (e.g. provision of a project officer, antimicrobial pharmacist or ID specialist with dedicated time for stewardship activities)
- skills — training needs and prior experience of the project team and end users
- process readiness — project planning, system implementation, communication with staff, working rules, evaluation planning, feedback methods, and the ability to incorporate existing AMS strategies into the electronic workflow
- administrative readiness — executive support and high-level clinical champions.

Early observations from seven Victorian hospitals assessed in this way were that the hospitals differed significantly with regard to their readiness to adopt an electronic AMS system. Some hospitals had dedicated resources, but others lacked any additional staff time. Administrative support was generally high and most staff had the necessary skills to oversee implementation, but process readiness needed attention. Technical readiness was not identified as a barrier to readiness in any of the hospitals studied.68

Cultural factors are also important for successful implementation of electronic approval systems.68 In a hospital where ID physicians or microbiologists have not previously played a prominent consultative role, staff will face additional barriers compared with hospitals with existing telephone or paper-based approval systems. These barriers need to be identified during the planning phase of the project and managed during implementation.
2.6 Antibiotic cycling

Antibiotic cycling is a restrictive strategy that involves withdrawing some classes of drug from routine use for a period of time and replacing them with another class of drug for empirical therapy, then reintroducing the original class later. This cycling aims to limit the emergence of resistance to the reserved antimicrobial. Antimicrobial cycling has primarily been studied in the intensive care unit setting.

Early pre and postintervention studies showed encouraging results when antimicrobials were cycled, with a fall in ventilator-associated pneumonia (VAP) due to resistant gram-negative bacteria and a higher likelihood of appropriate initial empirical drug choice. However, the ‘before and after intervention’ methodology of these studies meant that none of them had concurrent control groups, so other practices (e.g. infection control) may have also been modified during the studies.

More recent studies have cast doubt on the antibiotic cycling strategy, as they have shown the selection of drug resistance during the periods of cycling of each antibiotic class. For example, in a study by Van Loon et al., cefpirome, piperacillin-tazobactam or levofloxacin were each cycled for 4-month periods. Pathogens resistant to a particular cycling antibiotic were shown to be selected during each of the cycling periods. Similarly, Warren et al. cycled four classes of antibiotic in 4-month blocks over two years and the proportion of bacteria resistant to the cycling class increased during the cycling periods.

Mathematical modelling studies now support heterogeneous antibiotic use rather than structured antibiotic cycling. Mathematical modelling by Bergstrom et al. suggested that cycling would probably not be effective — homogeneous drug use for blocks of time was shown to be more likely to select for resistant isolates. The authors concluded that it is preferable to have mixed prescribing within a unit. The opinion of most experts in this field is that the evidence does not support antibiotic cycling as an effective strategy to control antibiotic resistance.