Recommendations for Implementation of Antimicrobial Stewardship Restrictive Interventions in Acute Hospitals in Ireland

A report by the Hospital Antimicrobial Stewardship Working Group, a subgroup of the RCPI Clinical Advisory Group on Healthcare Associated Infection and Antimicrobial Resistance

Background

A 2005 Cochrane review of antibiotic stewardship interventions for hospitalised patients found overall rates of success for persuasive interventions (e.g. direct clinical review with intervention and feedback) were 64-75%, and 66-87% for restrictive interventions (e.g. formulary restriction and pre-authorisation requirements for specific agents). However, restrictive interventions had, on average, a more than three-fold greater effect compared to persuasive interventions. In a 2013 update, meta-analysis of 52 interrupted time-series studies was used to compare restrictive versus purely persuasive interventions. Restrictive interventions had significantly greater impact on prescribing outcomes at one month (32%, 95% confidence interval (CI) 2% to 61%, P = 0.03) and on microbial outcomes at 6 months (53%, 95% CI 31% to 75%, P = 0.001).

Both formulary restriction and preauthorisation requirements for use of clindamycin during nosocomial outbreaks of C. difficile infection have led to prompt cessation of the outbreaks. Pre-approval restriction of broad spectrum antimicrobials has led to increased susceptibilities among Gram-negative pathogens, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterobacter cloacae, during a 6–12-month period. In one centre, restriction of vancomycin and third-generation cephalosporins in response to increasing rates of vancomycin-resistant enterococci (VRE) was associated with a decrease in the faecal VRE point prevalence from 47% to 15% during six months.

There is an increasing prevalence of antimicrobial resistant pathogens causing invasive infection in Ireland (figure 1). In addition, an extensive national outbreak caused by multiple drug-resistant clones of Klebsiella pneumoniae has been identified (figure 2), along with increasing reports of infections caused by carbapenem-resistant enterobacteriacea (CRE).
Figure 1: Proportion of resistance to selected antimicrobials among key bloodstream infection isolates in Ireland, 2004 - 2013

![Proportion of resistance to selected antimicrobials among key bloodstream infection isolates in Ireland, 2004 - 2013](image1)

Figure 2: Number and proportion of *K. pneumoniae* bloodstream infections caused by multiple drug-resistant clones (i.e. isolates of *K. pneumonia* which are either ESBL-producers and non-susceptible to both ciprofloxacin and gentamicin AND/OR carbapenemase-producers), 2006 - 2013

![Number and proportion of K. pneumoniae bloodstream infections caused by multiple drug-resistant clones](image2)

In parallel with the increasing levels of antimicrobial resistance, there has been an upward trend in antimicrobial consumption in hospitals, from 78.2 defined daily doses (DDD) per 100 bed days used (BDU) in 2007 to 84.9 DDD/100BDU in 2013 (figure 3).

![Antimicrobial consumption in hospitals](image3)
Of particular concern is the increasing consumption of broad-spectrum antibiotics. For example, carbapenem consumption in hospitals has steadily increased over the past number of years, and this increase appears to be occurring in addition to (rather than instead of) consumption of other broad-spectrum antibiotics (figure 4).
Recommendations

The 2009 SARI Guidelines for Antimicrobial Stewardship in Hospitals in Ireland included restricted availability of antimicrobials and pre-authorisation among the high-impact interventions recommended for hospitals. These recommendations should be implemented in all acute hospitals in Ireland:

- Each hospital’s antimicrobial prescribing guidelines should include a list that stipulates which antimicrobials are unrestricted, restricted (approval of a specialist is required) or only permitted for specific conditions. Criteria for alert antimicrobials include spectrum of activity, potential toxicity, misuse or cost.
- The list of restricted antimicrobials should be reviewed on a regular basis, in light of the hospital’s antimicrobial usage data and rates of antimicrobial resistance. Restrictions may have to be reinforced, or applied to additional antimicrobial agents, in the setting of outbreaks caused by antimicrobial-resistant pathogens (e.g. *C. difficile*, VRE, MRSA).
- Restricted antimicrobials should only be available from the hospital pharmacy, and not included in medication ward stocks of those areas where access is restricted. However, hospitals should ensure that there is a mechanism for accessing restricted agents, when required, outside of normal working hours.
- Where possible, each hospital should have a process in place to allow pre-authorisation for the use of restricted antimicrobials by a member of the antimicrobial stewardship team (see Appendix for an example of such a system).
- Regardless of whether or not a system of pre-authorisation is in place, hospitals should have a system for identifying when restricted antimicrobials have been prescribed, and early review of such prescriptions by a member of the antimicrobial stewardship team.

The following antimicrobial classes, or specific agents, should be considered for inclusion in restricted lists following local agreement. These agents should require pre-authorisation by an infection specialist, or only be permitted for use as part of locally-agreed protocols for management of conditions in specific patient groups (e.g. neutropenic sepsis, acute exacerbations of cystic fibrosis):

- Carbapenems (e.g. meropenem, imipenem, ertapenem)
- Other specific beta-lactams (e.g. Aztreonam)
- Antipseudomonal penicillins (e.g. piperacillin-tazobactam; ticarcillin-clavulanic acid)
- Third, fourth and fifth generation cephalosporins (e.g. cefotaxime, ceftazidime, cefipime)
- Fluoroquinolones (e.g ciprofloxacin, ofloxacin, levofloxacin)
- Specialist anti-Gram positive agents (e.g. vancomycin, teicoplanin, linezolid, daptomycin, rifampicin)
- Lincosamides (e.g. clindamycin)
- Aminoglycosides (e.g. amikacin)
The above list is not exhaustive, and hospitals may choose to include other agents on restricted lists such as anti-fungal agents, anti-viral agents, or other antibiotics.

References


APPENDIX: Suggested Procedure for Requesting Restricted Antimicrobials

i. A member of the antimicrobial stewardship team will carry a designated pager and/or mobile phone 24 hours/seven days a week

ii. If a consultant or non-consultant hospital doctor is considering prescribing one or more restricted antimicrobial agents, he/she should contact the antimicrobial stewardship team member on-call. The prescriber should be able to provide the following information:
   a. Patient’s name, hospital medical record number and location
   b. Clinical indication for antimicrobial therapy
   c. Drug allergies and side effects to previous antimicrobials
   d. Microbiology culture results, if available
   e. Renal and hepatic function
   f. Weight and height of the patient

iii. The antimicrobial stewardship team member will respond to the prescriber in a timely manner, discuss the case with the prescriber and, on the basis of the above information, may:
   a. Recommend the use of the restricted agent(s)
   b. Recommend an alternative therapeutic option
   c. Recommend further investigations or clinical follow-up
iv. The prescriber must record the details of the consult in the patient’s clinical notes.

v. The antimicrobial stewardship team member will fill out an information card for all restricted antimicrobials requests. The information card contains the following:
   a. Patient’s name, medical record number and location
   b. Prescriber’s name, pager number, clinical service and position
   c. The prescribing consultant’s name and clinical service
   d. Reason for calling
   e. If for pre-authorisation, reason for authorisation
   f. Recommendations given
   g. Rationale for recommendations given
   h. Whether or not the infectious diseases or medical microbiology consultant was contacted