

TACKLING ANTIMICROBIAL RESISTANCE THROUGH PRESCRIPTION CONTROL IN HUMAN HEALTH

CÉLINE PULCINI, CHU DE NANCY, SERVICE DE MALADIES INFECTIEUSES, NANCY, FRANCE; UNIVERSITÉ DE LORRAINE, UNIVERSITÉ PARIS DESCARTES AND WORLD ALLIANCE AGAINST ANTIBIOTIC RESISTANCE



Antibiotic resistance is on the rise worldwide, as are antibiotic prescriptions. Antibiotic stewardship programmes are urgently needed in all settings, if we are to tackle bacterial resistance. Prescription control is one of the strategies used in antibiotic stewardship programmes. This article describes the main measures that could be implemented, and discusses the potential limitations and barriers to implementation of restrictive antibiotic stewardship strategies.

Antibiotic resistance is a growing international threat, and is gaining more and more attention (1, 2). The causal link between antibiotic use and bacterial resistance is well known (3, 4). We need to reduce antibiotic use if we are to tackle bacterial resistance, all the more since antibiotic use is on the rise worldwide (5) and because up to half of antibiotic prescriptions are considered to be either unnecessary or inappropriate (6-8).

We need to break the “vicious” circle: antibiotic overuse/misuse -> growing antibiotic resistance -> increased use of broad-spectrum antibiotics -> more selection of resistant bacteria. Antibiotics must be considered as special drugs, due to the collective impact of antibiotic resistance, and these precious drugs must be protected. Unnecessary prescriptions must be reduced to a minimum, and narrow-spectrum antibiotics must be preferred to broad-spectrum antibiotics whenever possible, for the shortest possible duration.

What is an antibiotic stewardship programme?

According to the Infectious Diseases Society of America (IDSA), the definition of antibiotic stewardship includes: optimizing the indication, selection, dosing, route of administration and duration of antibiotic therapy to maximize clinical cure or prevention of infection while limiting the collateral damage of antibiotic use, including toxicity, selection of pathogenic organisms (such as

Clostridium difficile) and the emergence of resistance (8). Antibiotic stewardship programmes are multifaceted, associating educative/persuasive and restrictive measures, including prescription control, as well as organizational/structure measures (Table 1). In the hospital setting, a recent meta-analysis supports the use of restrictive interventions when the need is urgent (e.g. a multi-resistant bacteria outbreak), but suggests that persuasive and restrictive interventions are equally effective after six months (9). In both outpatient and inpatient settings, multifaceted programmes are considered to be more effective than a single-component intervention (9, 10).

Antibiotic stewardship programmes have been shown to improve the appropriateness of antibiotic use, reduce patient morbidity and mortality, decrease antibiotic use and costs, and reduce bacterial resistance and *C. difficile* infections, both in the outpatient and the inpatient settings (6, 7, 9-11).

Who are the actors in prescription control ?

Antibiotic prescriptions are usually controlled by infectious diseases specialists, clinical pharmacists, clinical microbiologists, and/or clinicians with a training in infectious diseases (12). Adequate training and clinical expertise are crucial, as well as communication and teaching skills (6, 13). The organization of prescription control varies between

Table 1: Main antibiotic stewardship strategies recommended in the literature for hospital settings

Restrictive measures	<ul style="list-style-type: none"> - Hospital formulary with a limited number of antibiotics - Antibiotic order form - Automatic stop order - Formulary restriction and pre-authorization
Passive educational measures	<ul style="list-style-type: none"> - Local antibiotic guidelines - Educational sessions
Active persuasive / educational interventions	<ul style="list-style-type: none"> - Clinical rounds discussing cases - Prospective audit and feedback - Academic detailing
Structure/ organizational measures	<ul style="list-style-type: none"> - Multidisciplinary antibiotic stewardship teams (pharmacist, infectious diseases specialist, microbiologist, infection control specialist) - Consultancy service (infectious diseases, microbiology, pharmacy) - Computerized-decision support system - Regulating contacts with pharmaceutical representatives

countries and even between hospitals and structures (12, 14).

In some countries, such as France, the role of the “antibiotic expert” is clearly defined (role, competencies, time to be spent) and is part of the accreditation process of hospitals, but no specific funding has been allocated to this mission (http://www.sante.gouv.fr/IMG/pdf/12_286t0.pdf). In a cross-sectional survey involving 74 hospitals in France, time dedicated by the antibiotic expert was significantly associated with a decrease in fluoroquinolone use (15). Whether the antibiotic expert should be an infectious disease specialist or not is a matter of debate and depends on local resources (6). It is likely that a multidisciplinary antibiotic stewardship team, involving ideally at least an infectious diseases specialist, a clinical microbiologist and a clinical pharmacist, is likely to achieve more significant results than an antibiotic expert on his/her own (6, 8, 16, 17).

Nurses are more and more involved in antibiotic stewardship programmes (12). Regarding prescription control, they could play a significant role for certain strategies, for example IV-oral switch or helping in triggering the review of antibiotic prescriptions (18, 19).

Strategies for prescription control in hospitals

Most hospitals define a list of antibiotics that are available to the prescribers (hospital formulary). This was the case in 90% of the hospitals in the 2012 international survey conducted by ESGAP (the European Society of Clinical Microbiology and Infectious Diseases Study Group for

In some countries, such as France, the role of the “antibiotic expert” is clearly defined (role, competencies, time to be spent) and is part of the accreditation process of hospitals

Antibiotic Policies), even though this picture is likely to be an optimistic one, since the study was probably biased towards the most motivated hospitals, and since it was based on declarative data (8, 9, 12). A formulary is a list of antibiotics that have been approved for use in a hospital. Formularies are useful in influencing prescribing behaviour by controlling access to particular drugs (e.g. use is approved only for a particular department, for patients with a particular condition, or where other options are contraindicated). These restricted drugs require approval by nominated experts who are members of the antibiotic stewardship team (17).

Antibiotic order forms, i.e., a standardized form that is filled in by the prescriber in order to get the antibiotic from the pharmacy, are also very common (8, 9, 12).

Automatic stop orders can also be implemented in order to limit the duration of treatments, and to force the prescriber into reviewing his/her antibiotic prescription; they were in place in 46% of the hospitals in the 2012 ESGAP international survey (8, 9, 12). This means that the pharmacy delivers the treatment for a short period of time (e.g. three days) for each antibiotic order form.

Automatic therapeutic substitutions can also be in place at the pharmacy level (e.g. dispensing cefotaxime instead of ceftriaxone, since cefotaxime is thought to select less resistant bacteria than ceftriaxone).

Restricted prescriptions require expert approval for the pharmacy to dispense the treatment; this system was in place in 81% of the hospitals in the 2012 ESGAP international survey (12). Expert approval is usually needed for broad-spectrum and expensive antibiotics (e.g. carbapenems, daptomycin, fidaxomicin). Approval may be required pre-prescription (pre-authorization), or post-prescription within a specified time period, for example 48 hours (post-prescription review). Pre-authorization is sometimes needed to allow the dispensing of the first dose of treatment, but most of the time, it takes place just after first dose, to avoid delayed administration of the first dose of

Ideally, all prescriptions should be looked at, since there are no reliable predictors of antibiotic misuse. The best strategy depends, however, on the local context and resources

antibiotic. Pre-authorization requires 24-hour coverage and real-time expert advice (12). Post-prescription review of antibiotic prescriptions by an expert appears to be more effective than review by the prescriber on his/her own (6, 9, 20). In Turkey, the introduction of a new health-care regulation in 2003 requiring mandatory approval of specific parenteral IV antibiotics by dedicated infectious diseases specialists found some health-economic benefits (21), which have been shown by others (9, 17).

Experts can also provide unsolicited advice for certain situations, for example positive microbiological samples (multi-resistant bacteria, positive blood cultures) (6, 9, 12), giving more opportunities to review antibiotic prescriptions. In some hospitals, systematic review of all antibiotic prescriptions are planned regularly in certain units (e.g. twice weekly rounds in intensive care units) (12). All expert reviews provide an opportunity for additional education as well as feedback on the episode of care.

Table 2 gives practical examples of restrictive measures that could be implemented in hospitals, and that have been successfully tested by the author (22).

Ideally, all prescriptions should be looked at, since there are no reliable predictors of antibiotic misuse. The best strategy depends, however, on the local context and resources. Electronic medical records and electronic prescribing obviously facilitate prescription control, but they are not implemented in all hospitals (12). Sophisticated electronic antimicrobial approval systems have been implemented in some hospitals and look promising (17, 23).

Most experts recommend that the antibiotic stewardship programme should reside within the hospital's quality improvement and patient safety governance structure and should be included within the hospital's quality and safety strategic plan, thereby facilitating its implementation (17). As antibiotic stewardship is an important component of patient safety, its performance indicators should be measured and publicly reported, and hospitals and hospital executives should be accountable for these (17). Structure indicators for hospital antibiotic stewardship programmes have recently been validated across European hospitals (24).

Table 2: Practical examples of restrictive measures that could be implemented in a hospital

Hospital formulary	List of antibiotics available in the hospital with a specific list for restricted broad-spectrum antibiotics
Nominative antibiotic order form	Specific form to be filled in to get antibiotics from the pharmacy
Automatic stop order	The pharmacist delivers treatment for three days only, forcing the prescriber to review the prescription For surgical prophylaxis, the pharmacy delivers one day of treatment only
Expert approval	For all the following situations: <ul style="list-style-type: none"> • Restricted broad-spectrum antibiotics, before day three (post prescription review) and at day seven; • Multi-resistant bacteria (list to be defined); • Positive blood cultures; • Regular rounds of the antibiotic expert with systematic advice on all antibiotic prescriptions in some units (especially in those with high antibiotic use).

One of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) objectives is indeed to develop a common structure and process indicators for hospital antibiotic stewardship programmes (http://www.cdc.gov/drugresistance/pdf/TATFAR-Progress_report_2014.pdf).

In France and in Australia, for example, antibiotic stewardship has become a criterion for the accreditation of health services. In particular, hospitals are required to have an antibiotic stewardship programme in place and measureable clinical standards for stewardship (http://www.sante.gouv.fr/IMG/pdf/12_286t0.pdf and <http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-stewardship/>) (14, 17).

Strategies for prescription control in the outpatient setting

Controlling antibiotic prescriptions in the outpatient setting is even more challenging, since relationships between prescribers and an antibiotic stewardship team are uncommon.

To start controlling prescriptions, over-the-counter prescriptions must be banned (i.e. the pharmacist cannot deliver an antibiotic without a nominative prescription), and this is not the case in all countries (2).

Antibiotic formularies, i.e. the list of antibiotics that can be prescribed in the outpatient setting, should be available, in order to limit the prescription of some broad-spectrum antibiotics. The list needs however to be updated regularly,

to take into account current guidelines and resistance data.

Specific antibiotic order forms (i.e. forms dedicated to antibiotic prescriptions only), automatic stop orders and automatic therapeutic substitutions could also be used, but they are quite uncommon.

Expert approval is much more difficult to organize in the outpatient setting, and few countries have implemented such a strategy. In Australia, for example, the use of fluoroquinolones has long been restricted by guidelines favouring alternative options and the limitation of prescription subsidies for this antibiotic class by the Pharmaceutical Benefits Scheme to very specific indications are recognized by the guidelines (25).

Structural and organizational strategies can also be used. For example, in Slovenia, primary care prescribers pay a fine if certain antibiotic prescriptions (amoxicillin-clavulanic acid, fluoroquinolones, macrolides, third-generation cephalosporins) do not comply with existing national guidelines. The Slovene National Health Insurance is auditing medical records in order to enforce this policy (M Cizman and B Beovic, personal communication) (26, 27).

The example of Denmark also demonstrates how, at the national level, the authorities have a powerful tool in their reimbursement policy. Antibiotics are reimbursed differently, according to national decisions and this policy impacts significantly on prescribing (28).

Strategies for prescription control in long-term care facilities

The same strategies could also be used in long-term care facilities (7, 29, 30). However, antibiotic stewardship programmes in long-term care facilities tend to be less well-organized and less-resourced than in the hospital setting (7, 29, 30). National performance indicators for antibiotic stewardship in European long-term care facilities have recently been validated (31).

Limitations of and barriers to prescription control

Prescription control should be associated with educative and persuasive measures, within a multifaceted antibiotic stewardship programme (8, 9). This approach is more effective, and is also likely to lessen the barriers to prescription control from the prescribers. It is indeed well known that a prescription control approach on its own can lead to adaptation strategies from prescribers bypassing the restriction (32). There is no “magic bullet”, meaning that no single antibiotic stewardship model will deliver optimal antibiotic prescribing in every context. In addition to selecting the strategies that have the best efficacy, the

antibiotic stewardship team needs to consider which strategies are most likely to be successful in their specific context and how best to implement them (17).

Prescription control needs dedicated resources, since it is a time-consuming activity. In the ESGAP international survey conducted among 660 hospitals in 2012, less than 20% of hospitals had dedicated funding in place for their antibiotic stewardship team (12). Opposition from prescribers can also be an issue and that cannot be solved without strong institutional support (12). When expert approval is in place, the clinician in charge of the patient is usually free to comply, or not, with suggestions made by the expert, because of legal responsibility issues. The quality of the relationship between the expert and the clinician is therefore crucial to ensure a good level of compliance. Finally, since expert approval does not always involve a bedside consultation, the quality of exchanged information (by phone, fax, mail) has a direct impact on the quality of the given advice (33). Traceability of all exchanged information is needed.

Conclusion

Given the worldwide antibiotic resistance crisis, implementing antibiotic stewardship programmes in all settings is an emergency (12, 34, 35). Prescription control is one aspect of these programmes, and can be very useful to improve antibiotic prescribing; however, restrictive measures are currently not in place in all countries, and neither are they implemented in all settings (7, 12, 14, 29, 30, 34, 36). Establishing an international framework for antibiotic stewardship is urgently needed, as are regulatory measures enforcing the implementation of antibiotic stewardship programmes, including restrictive measures (12, 34, 35). ●

Acknowledgements

I am grateful to Jean Carlet, Inge Gyssens and Bojana Beovic for their helpful comments on the manuscript. No funding or conflicts of interest to declare.

Professor Céline Pulcini, MD, PhD is an infectious diseases specialist working in Nancy, France. She has been carrying out research on antibiotic stewardship for many years, and is actively involved in the World Alliance Against Antibiotic Resistance (WAAAR), a non-governmental non-profit association whose aim is to raise awareness regarding the bacterial resistance threat. She is also a member of ESGAP executive committee (ESCMID [European Society of Clinical Microbiology and Infectious Diseases] Study Group for Antibiotic Policies).

References

- World Health Organization. Antimicrobial resistance - Global report on surveillance. 2014. Available at: <http://www.who.int/drugresistance/documents/surveillancereport/en/>
- Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis*. 2013;13(12):1057-98
- Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis*. 2014;14:13
- Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet*. 2007;369(9560):482-90
- Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis*. 2014;14(8):742-50
- Pulcini C, Botelho-Nevers E, Dyar OJ, Harbarth S. The impact of infectious disease specialists on antibiotic prescribing in hospitals. *Clin Microbiol Infect*. 2014. [E-published ahead of print].
- Dyar OJ, Pagani L, Pulcini C. Strategies and Challenges of Antimicrobial Stewardship in Long-Term Care Facilities. *Clin Microbiol Infect*. 2014. [In press].
- Dellit TH, Owens RC, McGowan JE, Jr., Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44(2):159-77.
- Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2013;4:CD003543.
- Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev*. 2005(4):CD003539.
- Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2014;69(7):1748-54.
- Howard P, Pulcini C, Levy Hara G, West RM, Gould IM, Harbarth S, et al. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. *J Antimicrob Chemother*. 2014. [In press].
- Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. *Virulence*. 2013;4(2):192-202.
- Huttner B, Harbarth S, Nathwani D. Success stories of implementation of antimicrobial stewardship: a narrative review. *Clin Microbiol Infect*. 2014. [E-published ahead of print].
- Dumartin C, Rogues AM, Amadeo B, Pefau M, Venier AG, Parneix P, et al. Antibiotic usage in south-western French hospitals: trends and association with antibiotic stewardship measures. *J Antimicrob Chemother*. 2011;66(7):1631-7.
- Standford HC, Chan S, Tripoli M, Weekes E, Forrest GN. Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. *Infect Control Hosp Epidemiol*. 2012;33(4):338-45.
- Australian Commission on Safety and Quality in Healthcare. Antimicrobial stewardship in Australian hospitals. 2011. Available at: <http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-stewardship/book/>
- Fleet E, Gopal Rao G, Patel B, Cookson B, Charlett A, Bowman C, et al. Impact of implementation of a novel antimicrobial stewardship tool on antibiotic use in nursing homes: a prospective cluster randomized control pilot study. *J Antimicrob Chemother*. 2014;69(8):2265-73.
- Gillespie E, Rodrigues A, Wright L, Williams N, Stuart RL. Improving antibiotic stewardship by involving nurses. *Am J Infect Control*. 2013;41(4):365-7.
- Lesprit P, Landelle C, Girou E, Brun-Buisson C. Reassessment of intravenous antibiotic therapy using a reminder or direct counselling. *J Antimicrob Chemother*. 2010;65(4):789-95.
- Arda B, Sipahi OR, Yamazhan T, Tasbakan M, Pullukcu H, Tunger A, et al. Short-term effect of antibiotic control policy on the usage patterns and cost of antimicrobials, mortality, nosocomial infection rates and antibacterial resistance. *J Infect*. 2007;55(1):41-8.
- Mondain V, Lieutier F, Dumas S, Gaudart A, Fosse T, Roger PM, et al. An antibiotic stewardship program in a French teaching hospital. *Med Mal Infect*. 2013;43(1):17-21.
- Buising KL, Thursky KA, Robertson MB, Black JF, Street AC, Richards MJ, et al. Electronic antibiotic stewardship--reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. *J Antimicrob Chemother*. 2008;62(3):608-16.
- Buyle FM, Metz-Gercek S, Mechtler R, Kern WV, Robays H, Vogelaers D, et al. Development and validation of potential structure indicators for evaluating antimicrobial stewardship programmes in European hospitals. *Eur J Clin Microbiol Infect Dis*. 2013;32(9):1161-70.
- Cheng AC, Turnidge J, Collignon P, Looke D, Barton M, Gottlieb T. Control of fluoroquinolone resistance through successful regulation, Australia. *Emerg Infect Dis*. 2012;18(9):1453-60.
- Cizman M, Beovic B, Krcmery V, Barsic B, Tamm E, Ludwig E, et al. Antibiotic policies in Central Eastern Europe. *Int J Antimicrob Agents*. 2004;24(3):199-204.
- Cizman M, Srovin T, Pokorn M, Cad Pecar S, Battelino S. Analysis of the causes and consequences of decreased antibiotic consumption over the last 5 years in Slovenia. *J Antimicrob Chemother*. 2005;55(5):758-63.
- Sorensen TL, Monnet D. Control of antibiotic use in the community: the Danish experience. *Infect Control Hosp Epidemiol*. 2000;21(6):387-9.
- Moro ML, Gagliotti C. Antimicrobial resistance and stewardship in long-term care settings. *Future Microbiol*. 2013;8(8):1011-25.
- Rhee SM, Stone ND. Antimicrobial stewardship in long-term care facilities. *Infect Dis Clin North Am*. 2014;28(2):237-46.
- Cookson B, Mackenzie D, Kafatos G, Jans B, Latour K, Moro ML, et al. Development and assessment of national performance indicators for infection prevention and control and antimicrobial stewardship in European long-term care facilities. *J Hosp Infect*. 2013;85(1):45-53.
- Burke JP. Antibiotic resistance--squeezing the balloon? *JAMA*. 1998;280(14):1270-1.
- Linkin DR, Paris S, Fishman NO, Metlay JP, Lautenbach E. Inaccurate communications in telephone calls to an antimicrobial stewardship program. *Infect Control Hosp Epidemiol*. 2006;27(7):688-94.
- Carlet J, Piddock LJ, Pulcini C. Antibiotic resistance: A geopolitical issue. *Clin Microbiol Infect*. 2014. [E-published ahead of print].
- Carlet J, Jarlier V, Harbarth S, Voss A, Goossens H, Pittet D. Ready for a world without antibiotics? The Penseires Antibiotic Resistance Call to Action. *Antimicrob Resist Infect Control*. 2012;1(1):11.
- Huttner B, Goossens H, Verheij T, Harbarth S. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *Lancet Infect Dis*. 2010;10(1):17-31.