

**ANTIMICROBIAL STEWARDSHIP PROGRAM
IN A DEVELOPING COUNTRY:
THE EPIDEMIOLOGICAL BARRIER**

Antimicrobial stewardship programs (ASPs) promote the appropriate use of antimicrobials to improve clinical outcomes by reducing the emergence of resistance, limiting drug-related adverse events, and minimizing the risk of unintentional consequences associated with antimicrobial use such as the risk of infection with *Clostridium difficile* (1).

The two core strategies proposed in the published joint guidelines of the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America for implementation of ASPs are formulary restriction and preauthorization and prospective audits with direct interaction and feedback to the prescriber (1). Supplements to these core strategies include education and generation of local guidelines and clinical pathways, among others.

We have developed an ASP in a medium complexity 140-bed university hospital located in Vicente López (Buenos Aires), Argentina. The program includes implementing a policy that requires prior approval from an infectious disease physician for selected antibiotics (cefepime, ceftazidime, ceftriaxone, colistin, imipenem, piperacillin-tazobactam, and vancomycin) (phase 1, 1 April 2007 to 31 March 2008). Pharmacists reviewed prescriptions every day and the team had discussions with prescribing physicians to follow hospital guidelines. After 1 year of implementing the program, we stopped the restriction policy and continued to work with the other tools of the program (phase 2, 1 April 2008 to 31 March 2009).

Supplemental strategies for implementing antimicrobial therapy for the most common community and hospital-acquired infections and for providing medical education in "bedside" discussions with the prescriber were developed during both phases. The strategy of the infectious disease team included: (a) follow-up of every infected patient together with the attending physician throughout the acute illness, (b) scheduled multidisciplinary meetings for acute patient management and discussion, (c) feedback to the prescriber concerning results of antibiotic usage, and (d) daily active presence of three infectious disease physicians for a 6-h period and availability of 24-h online assistance. No changes in the infection control team or in epidemiological measures were implemented between the phases.

To assess whether cessation of restriction was associated with an increase in antimicrobial usage, we measured antibiotic consumption during the first year

(phase 1) and for 1 year after we stopped restriction (phase 2). Antimicrobial consumption was measured by defined daily dose (DDD) normalized by 1 000 bed-days.

Several changes in consumption of selected antibiotics were observed in a comparison of phase 1 and phase 2. A significantly pronounced decrease was observed in the use of vancomycin, ceftriaxone, and ceftazidime (from 44.31 to 36.98, 40.00 to 32.07, and 17.56 to 12.57 DDD/1 000 bed-days, respectively; $P < 0.001$) (Table 1). The use of piperacillin-tazobactam remained unchanged (30.36 and 30.19 DDD/1 000 bed-days, $P = 0.9$). In contrast, the use of cefepime, imipenem, and colistin rose from 53.73 to 80.97, 14.11 to 21.65, and 9.25 to 19.50 DDD/1 000 bed-days, respectively ($P < 0.001$) (Table 1).

Consumption of four of the seven antibiotic agents did not increase after we stopped the restriction policy, while use of some agents did increase. These agents were those mainly prescribed in intensive care units and were associated with a numerical, but not significant, increase in invasive infections due to multidrug-resistant (MDR) nonfermentive Gram-negative bacilli (*Acinetobacter* spp. and *Pseudomonas aeruginosa*) during phase 2 (Table 2).

Our results suggest that, despite having implemented an ASP in which several of the recommended strategies (core and supplemental) were used by the infectious disease team, other factors may contribute to amplifying and disseminating the problem of bacterial resistance, mainly in the intensive care unit (2, 3). The increasing number of invasive measures and interventions as well as existing poor hygiene standards and inadequate nonmedicinal measures (e.g., hand disinfection) for infection prophylaxis appear to play a significant role in rates of bacterial resistance.

TABLE 1. Antibiotic consumption during two study periods, Argentina, 2007–2009

Antibiotic	DDD per 1 000 bed-days		% change	P value
	Phase 1	Phase 2		
Cefepime	53.73	80.97	+50.7	< 0.01
Ceftazidime	17.56	12.57	-28.4	< 0.01
Ceftriaxone	40.00	32.07	-19.8	< 0.01
Colistin	9.25	19.50	+110.8	< 0.01
Imipenem	14.11	21.65	+53.4	< 0.01
Piperacillin-tazobactam	30.36	30.19	-0.05	0.9
Vancomycin	44.31	36.98	-16.5	< 0.01

Note: DDD: defined daily dose, Phase 1: 1 April 2007 to 31 March 2008, Phase 2: 1 April 2008 to 31 March 2009.

TABLE 2. Incidence of invasive hospitalwide infections due to multidrug-resistant nonfermentive Gram-negative bacilli in intensive care unit, Argentina, 2007–2009

Phase	Invasive infections (No.)	
	Global ^a	MDR ^b -NFGN ^c
1	70	22 ^d
2	68	32 ^d

Note: MDR: multidrug resistant, NFGN: nonfermentive Gram negative, Phase 1: 1 April 2007 to 31 March 2008, Phase 2: 1 April 2008 to 31 March 2009.

^a Hospital-acquired pneumonia, surgical site infection, and bloodstream infection.

^b Isolates resistant to at least two of the following: piperacillin–tazobactam, cefepime, meropenem, and ciprofloxacin.

^c *Acinetobacter* spp. and *Pseudomonas aeruginosa*.

^d $P = 0.2782$ for phase 1 versus phase 2 (two-sample proportion test).

Spellberg et al. found that once the emergence of MDR bacteria is established, a comprehensively applied infection control program (i.e., hand hygiene, isolation precautions, and specific transmission-based measures) will interdict amplification and dissemination of the MDR nosocomial pathogens *P. aeruginosa* and *Acinetobacter* spp. (4). In that sense, Eagye et al. demonstrated in a retrospective, observational case-control study that the observed high proportion of meropenem-resistant *P. aeruginosa* was a consequence of ready transmission of an organism resident in their hospital rather than selective antibiotic pressure promoting its development (5). Although antibiotic use was shown elsewhere to promote the development of resistance in *P. aeruginosa*, their population of patients with high-level meropenem resistance had not received carbapenems (or any other class of agent) at a significantly different rate than those with susceptible organisms or no infection at all; in fact, carbapenem administration was nearly zero (5).

Although restriction of certain antibiotics (i.e., third-generation cephalosporins) is an effective method for controlling outbreaks of MDR pathogens, the success of such measures must be considered cautiously. It is well-established that there is a dynamic and temporal relationship between the prevalence of bacterial resistance and use of antibiotics (6); nevertheless, the best approach in settings with a high prevalence of MDR pathogens probably involves hand hygiene plus careful assessment of the institution's circumstances and application of more aggressive procedures such as patient isolation, staff cohorting, and active surveillance cultures (6).

We organized an ASP according to international guidelines using core and supplemental strategies; we devoted many hours to the education process and addressed the idea that the infectious disease consultant leadership may by itself produce significant changes in prescribing habits. Nevertheless, the epidemiologic profile of our institution limits, at least partially, the expected results.

How we can reduce the use of carbapenems and colistin in the face of, for example, an outbreak of MDR *Acinetobacter* spp.?

In summary, to reduce antimicrobial resistance in hospitals, it is necessary to have a good ASP team combined with optimal adherence to infection control measures such as rigorous hygiene protocols to prevent the survival and transfer of resistant bacteria in clinics and hospitals. However, in developing countries, this infrastructure is uncommon in most hospitals, and ASPs are based on individual efforts of infectious disease physicians who are willing to develop these programs as part of their activities as attending physicians (7).

Health authorities should promote programs aimed at revising the way antibiotics are prescribed accompanied by measurement of antibiotic consumption to help focus the program on particular agents and areas of the hospital and to reinforce other infection control measures.

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REFERENCES

- 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; 44:159–77.
- Patterson JE, Hardin TC, Kelly CA, Garcia RC, Jorgensen JH. Association of antibiotic utilization measures and control of multiple-drug resistance in *Klebsiella pneumoniae*. *Infect Control Hosp Epidemiol.* 2000;21:455–8.
- Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. *Clin Infect Dis.* 2001;32:1055–61.
- Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;46:155–64.
- Eagye KJ, Kuti JL, Nicolau DP. Risk factors and outcomes associated with isolation of meropenem high-level-resistant *Pseudomonas aeruginosa*. *Infect Control Hosp Epidemiol.* 2009;30:746–52.
- MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. *Clin Microbiol Rev.* 2005;18:638–56.
- Curcio D. Antibiotic stewardship: the “real world” when resources are limited. *Infect Control Hosp Epidemiol.* 2010;3:666–8.