Antibiotic policy: a tool for controlling resistance of hospital pathogens

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Marc J. Struelens[1], *Baudouin Byl*[2], *and Jean-Louis Vincent*[3]

Departments of [1]Microbiology, [2]Infectious Diseases and Infection Control and
[3]Intensive Care Departments, Université Libre de Bruxelles-Hopital Erasme, Brussels, Belgium

Multiresistant Gram-negative bacilli, including strains of *Klebsiella pneumoniae, Enterobacter* spp, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, resistant to broad spectrum beta-lactams, aminoglycosides and fluoroquinolones, are recovered at increasing frequency from patients suffering from nosocomial infections, particularly from those receiving intensive care. The emergence and spread of resistant pathogens to endemic and epidemic levels has frequently been related in time and place to the intensive use of antibiotics to which these microorganisms have developed resistance, notably third generation cephalosporins and fluoroquinolones. Recent investigations have indicated that the prevalence of resistance can be reduced by scheduled changes of empiric treatment regimens, involving discontinuation of intensively prescribed drugs and substitution with newly introduced antibiotics of another class to which the prevalent resistant strains remain susceptible. Among these drugs, penicillins–beta-lactamase inhibitor combinations, 'fourth generation' cephalosporins and, where little used previously, fluoroquinolones, have been introduced successfully in high risk units where ceftazidime-resistant strains of *K.pneumoniae, Enterobacter* and *Citrobacter* spp or glycopeptide-resistant enterococci had become highly prevalent. However, these studies do not demonstrate a direct causal relationship between changes in prescribing practices and ecological improvements, because their observational design cannot be controlled. In most studies, several important factors influencing the dynamics of resistance were not monitored and the relative contribution of decreased emergence versus control of cross-transmission to the improved susceptibility rates is not clear. We propose that additional long-term studies are required to better track the ecological impact and to determine the optimal modalities of programmed changes of antibiotic prescribing as an antibiotic resistance prevention or control strategy.

Key words: antibiotic resistance, epidemiology, therapeutic guidelines, nosocomial infections

INTRODUCTION

The increasing antimicrobial resistance of hospital pathogens is today a cause of great concern to clinicians and microbiologists. Multiple antibiotic-resistant strains of Gram-negative bacilli and Gram-positive cocci are increasingly causing epidemic and endemic nosocomial infections, particularly in intensive care units [1,2]. Among the leading drug-resistant Gram-negative pathogens are *Enterobacteriaceae* resistant to extended spectrum cephalosporins (due to production of plasmid-encoded extended spectrum beta-lactamase, hyperproduction of chromosomal cephalosporinase, or both) and often cross-resistant to other major classes of antibiotics such as aminoglycosides and fluoroquinolones [3–4]. Multiple-drug-resistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are also increasingly encountered in critically ill patients [3,4]. In Belgium, *Enterobacter aerogenes* has recently been recognized as an emerging multiple-drug-resistant nosocomial pathogen, often associated with invasive disease, including pneumonia and bacteremia [4,5]. Certain clones of this microorganism have a remarkable propensity to spread to critically ill patients receiving prolonged antibiotic treatment and supportive care, despite specific infection control efforts [5].

Corresponding author and reprint requests:
M. J. Struelens, Service de Microbiologie,
Université Libre de Bruxelles-Hopital Erasme,
808, route de Lennik, 1070 Brussels, Belgium
Tel: +32 2 555 45 19 Fax : +32 2 555 64 59
E-mail: marc.struelens@ulb.ac.be

THE RELATIONSHIP BETWEEN INCREASED ANTIBIOTIC USE AND RESISTANCE

Resistance is emerging due to the selective pressure of antibiotic use which selects the bacterial subpopula-

tions harbouring advantageous resistance mutations or acquired mobile resistance determinants such as plasmids and transposons. Resistance becomes widespread as a result of dissemination of resistant clones or mobile genetic determinants, which are also directly favored by the intensity and homogeneity of antibiotic exposure in a patient population. The modification of the wild type endogenous flora by antibiotic treatment leads to a reduction in the colonization resistance and enhances the establishment of substitutive, exogenous, drug-resistant bacteria. Intensive use of antibiotics in the hospital is often associated with increasing prevalence of resistance [6,7]. This relationship has been explored by different study designs: case control studies and cohort studies have linked the emergence of colonization and infection of patients with antibiotic-resistant pathogens to specific risk factors, including the severity of underlying disease, intensity of care, presence of indwelling devices, exposure to broad spectrum antibiotics and treatment underdosing [1,5,8–10]. Other risk factors are admission to wards where resistant strains are epidemic or endemic and frequent exposure to nursing and invasive procedures [8–10]. Surveillance of resistance rates in hospitals has likewise revealed a direct correlation between the amount of broad spectrum antibiotics used and local prevalence of resistant strains during outbreaks. Such an observation has been reported by Rice et al, who found a strong correlation betweeen ward levels of ceftazidime use and the prevalence of clonally-related strains of *Klebsiella pneumoniae* harboring plasmid-mediated TEM-26 beta-lactamase during a hospital-wide outbreak [11].

In some studies, reduction in antibiotic use has been followed by a reduction of resistance [6,7,11]. This has been achieved either by reducing total consumption by restrictive antibiotic control programs [7] or by a drastic shift in the type of drugs used for empiric therapy [6,11]. This paper will focus on the following questions: How to measure accurately the impact of antibiotic policy interventions on the prevention or control of antibiotic resistance in hospitals? What evidence is provided by recent studies on the efficacy of antibiotic policy in reducing epidemic or endemic resistance problems?

HOW TO MONITOR THE IMPACT OF AN ANTIBIOTIC POLICY ON RESISTANCE RATES OF HOSPITAL PATHOGENS ?

Because resistance is a complex, multifactorial ecological phenomenon, merely recording the temporal trends in the frequency of decreased drug susceptibility among large groups of microorganisms does not accurately reflect the dynamics of emergence and spread of resistant clones and resistance genes that interact with the flora of the ever-mobile hospital patient population. Therefore, a number of predictor variables should ideally be recorded to monitor the various factors influencing resistance prevalence, some of which can be controlled by medical interventions. First, the amount of different antimicrobial drugs used by period must be measured. Rather than using crude amounts in grams or dose units as an indicator of use, the density of exposure can be expressed as the number of defined daily doses (DDD) or average local daily administrations (DDA) per 100 patient-days. The prevalence of carriers of resistant strains and the importation rate of admitted and transferred patients colonized by resistant strains in each ward are important indicators of the initial reservoir of resistance against which any control intervention must be measured, especially in the setting of highly transmissible, endemic, multi-resistant strains. Lastly, the patient case-mix and bed-occupancy rates, as well as staffing levels and infection control practices, need to be monitored as factors influencing patient-to-patient transmission of resistant strains.

Among the outcome variables that may be used to assess the clinical and ecological impact of the antibiotic policy, both prevalence and incidence indicators should be recorded. The prevalence of strains with decreased susceptibility can be determined by biologically relevant groups of bacteria, such as *Enterobacteriaceae* with inducible cephalosporinase or enterococci, but detailed frequencies should also be determined for bacterial species that may evolve into resistance phenotypes, either as independent entities or as communities of gene exchange. Moreover, molecular delineation of clones within each species showing a high frequency of resistance is required to properly interpret the dynamics of emergence and dissemination of resistant clones within and between wards [12]. Thus, the incidence of nosocomial acquisition of resistant strains by ward expressed as the number of new cases by 1000 admissions may be checked against the incidence rate of imported cases admitted to the unit. The ratio of nosocomial cases over prevalent and imported cases reflects the secondary transmission rate of resistant clones by ward. Clearly, these detailed indicators cannot be assessed solely based on routine laboratory data, but require an integrated approach by which prospective epidemiological inquiries and admission screening for carriage of problem organisms are coordinated.

EVIDENCE OF THE IMPACT OF HOSPITAL OR WARD ANTIBIOTIC POLICY INTERVENTIONS TO REVERSE RESISTANCE PROBLEMS

There is more ample opportunity to 'rotate' antibiotics

Table 1 Summary of studies documenting reduction of antibiotic resistance by antibiotic policy intervention

Reference	Resistance problem	Setting	Intervention	Outcome
11	Ceftazidime–resistant *K. pneumoniae* outbreak	VA* hospital	Ceftazidime replaced by piperacillin–tazobactam	75% reduction of resistant *K. pneumoniae* over 9 months
13	Glycopeptide–resistant *E. faecium*, endemic	VA hospital	Reduction of cefotaxime, clindamycin, vancomycin, introduction of piperacillin–tazobactam and ampicillin–sulbactam	70% reduction of resistant *E. faecium* over 8 months
14	Antibiotic-resistant Gram-negative bacteria causing nosocomial infection (bacteremia, pneumonia), endemic	SICU†	Ceftazidime replaced by ciprofloxacin	78% reduction of AB-resistant Gram-negative ventilator–associated pneumonia over 6 months
15	Ceftazidime-resistant inducible *Enterobacteriaceae*, endemic	Hematology ward	Ceftazidime replaced by cefepime–amikacin	80–100% reduction of resistant *Enterobacter* spp and *Citrobacter* spp over 3 years
16	Ceftazidime and ciproflaxocin-resistant *E. aerogenes*, endemic	ICU	Ceftazidime and ciprofloxacin replaced by cefepime	75% reduction of resistant *Enterobacteriaceae* Ten-fold reduction of incidence of resistant *E. aerogenes* over 1 year

*VA: Veterans Administration; †SICU, Surgical Intensive Care Unit.

to curb resistance among Gram-negative pathogens, against which a wider diversity of antimicrobials usually remains active as compared with the more limited alternatives to glycopeptides to treat resistant Gram-positive cocci. In the 1980s, studies showed that aminoglycoside resistance emerged and decreased in Gram-negative bacilli as the usage was rotated from gentamicin to amikacin [6]. Recent prospective studies reported an effective reduction of resistance by modifying usage of other classes of antibiotics within a ward or hospital. Tables 1 and 2 summarize the design, indicators used and major findings of five important studies of scheduled antibiotic policy changes, shifting from intensively prescribed antimicrobial drugs, mostly third generation cephalosporins, to another class of broad-spectrum antibiotics, such as a penicillin–beta-lactamase inhibitor combination, a fluoroquinolone or a 'fourth generation' cephalosporin.

Each of these five studies, which used historical controls, concluded that the antibiotic policy change led to a major reduction in the prevalence of resistant strains that were either associated with a hospital-wide outbreak [11] or had become endemic in a whole hospital [13] and in high-risk departments [14–16]. In three studies reporting evidence of cross-infection with resistant clones, infection control measures like patient isolation and use of barrier nursing precautions were either not attempted [11], or failed to control the spread after several months [13,16]. In two studies [13,14] the case-mix, severity of illness and exposure of patients to invasive procedures was compared between the baseline and new policy periods and, in one of these, a reduction in the incidence of infection was found to be significantly associated with the new antibiotic policy after controlling for these confounding factors by multivariable analysis [14]. In only a limited number of investigations was the incidence of nosocomial acquisition of resistant strains analysed and in only one were the dynamics of importation and transmission of resistant clones examined based on molecular typing (Table 2).

In our 870-bed university hospital, the consumption of third generation cephalosporins increased between 1993 and 1996 from 3.5 to 4.8 × 1,000 Defined Daily Administrations (DDA) and that of fluoroquinolones from 5 to 13.5 × 1,000 DDA annually, the latter change being in part related to an increase in daily dose. During that period, the rate of ceftazidime resistance among *Enterobacteriaceae* isolates recovered from patients admitted to the intensive care department, increased from 7% to 17% and the rate of resistance to ciprofloxacin rose from 3% to 20%. From mid-1994 onward, several imported clones of *E. aerogenes* resistant to ceftazidime, ciprofloxacin and amikacin caused outbreaks in the intensive care depart-

Table 2 Indicators used to monitor processes and outcome of antibiotic policy intervention studies

Reference	Antibiotic use		Case-mix	Antibiotic resistance			Molecular typing
	Total amount	Exposure density		Prevalence	Incidence	Importation	
11	YES	NO	NO	YES	NO	NO	YES
13	YES	NO	YES	YES	NO	NO	NO
14	YES	YES	YES	YES	YES	NO	NO
15	YES	YES	NO	YES	NO	NO	NO
16	YES	YES	NO	YES	YES	YES	YES

ments and became endemic hospital-wide despite the enforcement of screening and isolation of colonized patients [5].

Because these resistant strains were associated with significant nosocomial morbidity and because selection of resistance to carbapenems was observed during therapy [5], a scheduled change of antibiotic policy was implemented [16]. Cefepime was introduced for empiric therapy of infections in the intensive care department instead of ceftazidime and ciprofloxacin. Cefepime is a 'fourth generation' cephalosporin that is known to possess low affinity for a majority of beta-lactamases and to exhibit a low capacity for selection of mutants of *Enterobacter* spp. that hyperproduce cephalosporinase [17,18]. It has been shown to possess clinical efficacy for the treatment of infections due to strains of *Enterobacter* spp with decreased susceptibility to third generation cephalosporins mediated by hyperproduction of cephalosporinase [19]. In a previous study by Mebis and colleagues in a hematology ward with a high rate of colonization by ceftazidime-resistant *Enterobacter* and *Citrobacter,* replacement of ceftazidime by cefepime and amikacin was associated with a marked reduction of resistance [15]. In our evaluation, detailed monitoring of resistance among Gram-negative isolates recovered from clinical and surveillance specimens, as well as recording of importation and transmission rates of multiresistant *E. aerogenes*, were performed during a baseline six-month period before the scheduled change of policy and during two consecutive six-month periods thereafter [16].

The shift in antibiotic treatment in the department was temporally related to a significant, three-fold decrease in the ceftazidime and ciprofloxacin resistance rates among isolates of *Enterobacteriaceae*. More than 80% of the reduction in resistance rates appeared to be related to a decreased incidence of multiresistant *E. aerogenes*. Moreover, the ratio of new secondary cases per imported case of multiresistant *E. aerogenes* admitted to the intensive care department decreased significantly. No increase in resistance to cefepime was observed in the one-year follow-up among isolates of *Enterobacteriaceae*, although a high rate of resistance to this and other antipseudomonal drugs persisted during this period among *Pseudomonas aeruginosa* isolates recovered from patients admitted to the intensive care department.

PRACTICAL IMPLICATIONS

These studies provide encouraging results which sugges that scheduled reduction of intensively used antibiotic may be effective in reversing increased resistance i the hospital setting and complement infection contro efforts to limit the spread of multiresistant clones. I would, therefore, seem logical to attempt regular modi fication of empirical therapy prescription guideline either as a reactive intervention when resistance to particular antibiotic or class of antibiotics increase significantly, or even proactively with the aim c delaying the selection and spread of resistant strains i the local ecosystem of a unit or hospital. This so-calle 'antibiotic rotation' or 'antibiotic cycling' policy remair to be investigated in the long term, however, before i potential preventive efficacy can be established.

In fact, as pointed out by Niederman in a luci editorial [20], the currently available evidence on suc a strategy raises more questions than it provides answer regarding the mechanisms of prevention or its practic modalities. Some questions deal with the strength an plausibility of the evidence supporting this approach. I what proportions were the reported decreases in th frequency of recovery of resistant strains due t decreased emergence of resistant mutants and to contr of cross-colonization? Was the observed effect direct related to the intervention or to uncontrolled extr neous factors? Because natural fluctuations are observe in the incidence of cross-transmitted nosocom pathogens, a temporal relationship does not demo strate causal relationship. However, it appears extreme difficult to design more controlled experimental co ditions for this type of ecological study. Compr hensive, multifactorial statistical prediction models a probably the best available tools to estimate the preventi

efficacy of interventions from longitudinal studies using historical controls [14].

Secondly, if the measured beneficial effects were indeed caused by the intervention, was the specific antimicrobial drug selected responsible for the effect or would any other drug of a class different to that of the selecting agent have led to the same ecological changes? This question cannot be answered definitely, since every epidemiological setting of resistant nosocomial pathogens is different and such interventions cannot be easily stratified into comparable arms, as in a clinical trial. However, from the available studies, it appears that both beta-lactam–beta-lactamase inhibitor combinations and 'fourth generation' cephalosporins can be successfully used as an alternative to third generation cephalosporins or fluoroquinolones in the context of increasingly prevalent resistant enterococci or *Enterobacteriaceae* following intensive and prolonged use of the latter drugs. In one study, however, fluoroquinolones were also strikingly effective in a unit where they were previously little used (Table 1). It would therefore appear that the change of empiric regimen to a 'new' class of drugs may be more important than the particular drug regimen selected. Studies with a longer duration of follow-up of ecological changes in the local microflora are needed, to ascertain the extent of emergence of resistance to the newly introduced antimicrobial agents. The possibility of multicenter studies needs to be explored.

Thirdly, if scheduled changes of antibiotic treatment regimens were indeed helpful in reversing local resistance problems, should they be programmed whenever surveillance of the microbial flora detects a problem? If so, how early, and based on what threshold should the modification of prescription rules be introduced: as soon as any statistically significant change is detected in the colonizing flora or only when it becomes a major clinical problem impeding the expected efficacy of empiric regimens? Should they become a first-line control strategy, be associated with standard infection control precautions whenever cross-infection by resistant clones is documented, or should they be attempted only when the latter fail to control spread? It is likely that each institution will consider the practical advantages and disadvantages of these options on a case-by-case basis rather than embrace an all-out uniform strategy.

Fourthly, should scheduled changes of antibiotic treatment regimens become a true preventive, rather than control, strategy aimed at delaying the establishment of resistant strains? It is fairly difficult, given the poorly understood dynamics of resistance selection and spread, to define biologically meaningful time intervals at which this 'antibiotic crop rotation' would be best effective. At any rate, it is rather impractical to modify the prescription guidelines too often, such as, for instance, every other quarter. Prescription guidelines prove difficult enough to comply with for many hospital physicians even when they are designed to last for several years.

Whatever the 'reactive' or 'pro-active' approach one may attempt by periodically alternating classes of antimicrobials used for major indications in the treatment of infections in the hospital, it is essential to closely monitor the local epidemiology of resistance and to inform physicians about the prevalence trends and transmission of resistant microorganisms in their own units. In addition, any manipulation of the formulary can only be part of a more comprehensive, multidisciplinary system of prevention of antibiotic resistance by optimizing antibiotic usage and infection control efforts [1,20–21].

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