Antibiotic cycling or rotation: a systematic review of the evidence of efficacy

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Of the interventions designed to reduce antibiotic resistance rates in hospitals, one that is currently attracting considerable interest, particularly in the intensive care unit setting, is antibiotic cycling or rotation. Cycling is the scheduled rotation of one class of antibiotics with one or more different classes exhibiting comparable spectra of activity; in order to fulfill the definition, the cycle must be repeated. Following a search of the literature we identified 11 articles in which the authors claimed to have evaluated the efficacy of this intervention. Only four were suitable for review, but, owing to multiple methodological flaws and a lack of standardization, the results of these studies do not permit reliable conclusions regarding the efficacy of cycling. Further studies are therefore required in order to resolve this question. However, before such studies can be undertaken, there are a great many issues relating to cycling which must be addressed. For the time being, we advise against the routine implementation of this measure as a means of reducing antibiotic resistance rates.

Keywords: antibiotic resistance, interventions to optimize antibiotic prescribing, intensive care units

Introduction

The inexorable increases in antibiotic resistance rates have led to calls for reductions in the levels of inappropriate antibiotic prescribing. While the expected outcome is clear, the process by which it is to be achieved is not, there having been, to date, no published evidence-based guidelines on interventions to optimize antibiotic prescribing in either the community or hospitals. Many interventions have been proposed and evaluated, but there is currently no consensus regarding the measures or combination of measures that are likely to have the maximum impact on either prescribing rates or quality of care. One intervention that is currently attracting a considerable amount of interest, particularly in the intensive care unit (ICU) setting where antibiotic usage is high, is antibiotic cycling or rotation. We review here the literature relating to the efficacy of this strategy.

Cycling or rotation is the scheduled substitution of a class of antibiotics (or a specific member of a class) with a different class (or a specific member of that class) that exhibits a comparable spectrum of activity. This substitution may be followed after a fixed interval by a third, fourth or, indeed, any number of substitutions, but the ‘cycle’ must be repeated, with re-introduction of the original class/drug. Cycling/rotation should not be confused with scheduled changes or restrictions of antibiotic regimens without repeating the process (a common occurrence among both investigators and reviewers). The duration of each cycle is based on either local susceptibility patterns or a predetermined time period.

Cycling normally involves replacing an antibiotic belonging to one class with one or more belonging to different classes, as opposed to substituting one member of a class with another member of the same class. Although some investigators have withdrawn one aminoglycoside (gentamicin) and replaced it with another (amikacin), this practice is fraught with difficulties, as drugs belonging to the same class usually share resistance mechanisms. On the other hand, an antibiotic belonging to one class may select for resistance to drugs belonging to one or more unrelated classes as a result of genetic linkage of resistance determinants that encode resistance to multiple classes of antibiotics.

The principle underpinning cycling is that the more frequently an antibiotic is prescribed, the more likely it is that resistance to it will develop. Withdrawal of a class of antibiotics for a predetermined period will therefore limit the selective pressures exerted by those agents (and hence the emergence of resistance), thereby allowing resistance rates to the withdrawn drug to stabilize, or even fall, during the period of restriction and enabling it to be re-introduced at a later date with its efficacy intact. The outcome of the intervention will depend on the situation before its implementation. For example, if rates of resistance to a particular antibiotic are stable before the intervention is introduced, an increase (or decrease) in the volume of prescribing of that drug will result in a gradual increase (or decrease) in the incidence of resistance to it. However, if the baseline resistance rate was increasing before implementation, a reduction in the use of the antibiotic may or may not lead to an immediate decrease in
the rates of resistance; similarly, if the baseline resistance rate was falling, an increase in use may or may not be followed by an increase in the resistance rate. An equally important objective of cycling is to avoid the emergence of significant populations of organisms resistant to the substitute drug, and the duration of each cycle should be sufficiently short to ensure that this is the case.

Literature search

The literature relating to cycling was identified in the course of a wider search carried out in the context of a Cochrane review of interventions designed to optimize antibiotic prescribing in hospitals. Three independent electronic searches were undertaken. In the first, MEDLINE, EMBASE and the Cochrane database of clinical trials were searched from 1980 onwards with the following search terms: 'antibiotic use AND resistance'; 'antibiotic guidelines'; 'antibiotic guidelines AND implementation'; 'antibiotic policies'; 'antibiotic policies AND prescribing'; 'antibiotic policies AND antibiotic use'. All of these terms were then re-used, substituting 'antibiotic' with 'anticolic' and adding 'optional antibiotic/anticolic prescribing/use'. The second search was conducted by P. Gross (Department of Internal Medicine, Hackensack University Medical Center, Hackensack, NJ, USA) in MEDLINE (1966–2000), using PubMed and OVID, and the Cochrane database. The search terms were 'antibiotics' and 'premedication' which included 'antibiotic prophylaxis'. For the 'guideline' concept 'practice guidelines' and 'guidelines' were used as MESH terms. The publication types 'guideline' and 'practice guideline' were also used and the MESH terms 'clinical protocols', 'critical pathways' and 'evidence-based medicine' were used, together with 'guideline', as textwords. Finally, the third search was of the Cochrane Effective Practice and Organisation of Care (EPOC) specialized register which, itself, was compiled by searching MEDLINE (from 1966), Health STAR (from 1975) and EMBASE (from 1980). In addition to the electronic searches, the references section of every paper was reviewed and any articles not identified by electronic search were obtained and the manual search repeated. There were no language limitations.

Evidence

What published evidence supports the efficacy of cycling? The authors of 11 articles claim to have evaluated the efficacy of this intervention. However, three groups2–4 investigated only scheduled changes of antibiotic regimens. Four other studies5–8 are excluded from further consideration on the grounds that their designs do not fulfil the criteria for inclusion in a Cochrane review (only randomized controlled trials, controlled clinical trials, controlled before and after studies and interrupted time series with at least three data points before and after the intervention being eligible) (Cochrane Effective Practice and Organisation of Care Group, 2002); one was an uncontrolled before and after study6 and three were inadequate (i.e. fewer than three data points before and/or after the intervention) interrupted time series.5,3 Only four groups of investigators9–12 genuinely investigated cycling and carried out studies, the designs of which make them eligible for inclusion in a Cochrane review.

In response to increasing rates of resistance to gentamicin among aerobic Gram-negative bacilli (AGNB), Gerdinger & Larson9 described four successive changes in the use of aminoglycosides at the Minneapolis Veterans’ Affairs Medical Center; the design of the study was an interrupted time series. During an initial 4-month period during which gentamicin was the predominant aminoglycoside in use, the incidences of resistance to gentamicin and amikacin were 12% and 3.8%, respectively (baseline data). During the following 26 months, amikacin replaced gentamicin as the predominant aminoglycoside and the incidence of resistance to gentamicin fell to 6.4% (P < 0.001), whereas that to amikacin was 3.2% (not a statistically significant difference). Gentamicin was re-introduced and over the next 12 months the rate of resistance to it increased to 9.2% (P < 0.001); the rate of resistance to amikacin was 3.9% (not a statistically significant difference) during that period. Finally, amikacin again became the predominant aminoglycoside during the subsequent 12 months and resistance to gentamicin declined to 5.4% (P < 0.001), whereas that to amikacin also fell to 2.8% (P < 0.005). It was not at the outset the intention of the investigators to undertake a study of cycling. The changes were not pre-arranged, but rather evolved in response to emerging patterns of resistance to aminoglycosides and expenditure on these drugs.

Young et al.10 cycled the use of aminoglycosides at the Houston Veterans’ Administration Medical Center in response to increasing rates of resistance to gentamicin among AGNB; the study was designed as an interrupted time series. During a 4-month baseline period when gentamicin was the principal aminoglycoside used and amikacin administration was restricted, the incidence of resistance to gentamicin was 14% (the corresponding figure for amikacin being 2.4%). For the next 15 months, amikacin became the predominant aminoglycoside and gentamicin usage was restricted. The incidence of resistance to gentamicin declined to 9.2% (P < 0.005) (the resistance rate for amikacin remaining at 2.2%). During a 21-month follow-up period when all restrictions on aminoglycoside usage were lifted (although, in practice, prescriptions of amikacin approximated the baseline level owing to it being markedly more expensive than gentamicin) the rate of resistance to gentamicin rose to 15.3%; the incidence of resistance to amikacin increased to 4% (P < 0.000001).

Bradley et al.11 cycled an interrupted time series in which the empirical antibiotic therapy of febrile neutropenic patients was rotated. The impetus for the study was the high incidence of colonization of patients on a haematological malignancy unit with glycopeptide-resistant enterococci (GRE). During an initial 4-month period when baseline data were collected (phase 1), patients received standard therapy, ceftazidime; the incidence of GRE colonization was 57%. For the next 8 months (phase 2) ceftazidime was replaced by piperacillin/tazobactam and aggressive infection control measures were implemented. The rate of colonization with GRE during the first 4 months of phase 2 (phase 2a) was 29% (P < 0.002 compared with phase 1) and that during the second 4 months (phase 2b) was 8% (P < 0.001 compared with phase 1). During the subsequent final 4 months of the study (phase 3) ceftazidime was re-introduced (the enhanced infection control measures were maintained) and the incidence of colonization with GRE increased to 36% (not a statistically significant difference compared with phase 1). Infections attributed to GRE were observed only during phases 1 and 3. The authors acknowledge that the reduction in the GRE carriage rates during phase 2 could have been, at least in part, the result
of improved infection control measures, but concluded that the increase in the incidence of colonization following the re-introduction of ceftazidime, at a time when the colonization rate was very low and the enhanced infection control measures were being maintained, make it likely that the switch to ceftazidime accounted for the change.

The final study was a controlled clinical trial which was undertaken to determine whether antibiotic rotation leads to reduced colonization with multidrug-resistant AGNB among patients on a neonatal intensive care unit. During a 1-year period, patients with proven or suspected infections caused by AGNB were assigned to a study or control group. Those in the former group received empirical antibiotic therapy on a monthly rotating basis; the antibiotics which were cycled were gentamicin, piperacillin/tazobactam and ceftazidime. Those in the latter group were given empirical antibiotics according to the preferences of the prescribers. No baseline data were collected. At the end of the study, differences in total antibiotic usage, the incidence of colonization with multidrug-resistant AGNB and the incidences of nosocomial infections and mortality between the two groups were not statistically significant.

In summary, three of the four studies demonstrated that cycling was beneficial in terms of a reduced incidence of isolation of antibiotic-resistant bacteria when the drugs that allegedly precipitated the resistance were withdrawn; the fourth study failed to identify such a benefit. Only one of the studies evaluated the effect of cycling on clinical outcome; no significant difference between the control and intervention groups was reported. Moreover, in all three of the former studies, rates of resistance to the initial (precipitating) antibiotics returned to baseline levels when these drugs were re-instated. The results of these studies do not permit meaningful conclusions regarding the efficacy of cycling to be drawn owing to lack of standardization and multiple methodological flaws. For example:

(i) The settings of the studies were not standardized; two involved entire hospitals, one a neonatal intensive care unit and one a haematology malignancy unit.
(ii) Two studies involved cycling of drugs belonging to the same class (aminoglycosides).
(iii) The durations of the cycles were not standardized and varied both from study to study and within individual studies; in the study by Gerdig & Larson, this arose because the study was reactive rather than proactive, the interventions having evolved in response to increasing antibiotic resistance rates in the hospital. The durations of individual cycles ranged from 1 month to 26 months, most cycles being ≥4 months. Although the optimal duration for each cycle has not been determined, 1 month may be too short, whereas ≥4 months may be too long.
(iv) Interpretation of the impact of cycling on resistance rates is undermined owing to the effects of confounding variables, in particular, the role of infection control measures, variations in the patient populations studied and the administration of 'off-cycle' antibiotics to large numbers of patients.
(v) No attempt was made in any of the studies to differentiate between community- and hospital-acquired isolates.
(vi) No attempt was made in any of the studies to determine whether antibiotic-resistant clinical isolates represented colonization or infection. Moreover, few such organisms circulating in intensive care units are actually detected on the basis of recovery from clinical specimens.

It is not possible to reach reliable conclusions regarding the efficacy of cycling as a means of controlling antibiotic resistance rates on the basis of the existing published literature. The studies that will need to resolve the issue of efficacy will have to be adequately powered in order to overcome confounding variables and will need to employ high-quality epidemiological tools, sophisticated techniques for determining resistance mechanisms and carrying out molecular typing and effective infection control measures.

Future studies

Before additional trials to assess the efficacy of cycling can be undertaken many issues need to be addressed:

(i) When should cycling be implemented in a hospital or hospital unit? On the one hand, owing to the high costs associated with cycling, it could be argued that this intervention should not be introduced where there is not a serious resistance problem. On the other hand, the impact of cycling might be maximized by introducing it before such a problem develops by preventing the emergence and dissemination of resistance determinants. A caveat to this latter argument is that "... sequential antimicrobial exposure runs the risk of simply adding newer resistance determinants into already active resistance gene clusters in transposons... As such, cycling strategies that encourage serial overuse of antimicrobial agents are likely to aggravate, rather than alleviate, the problem of resistance."

(ii) Should trials be limited to single centres/units or should they be multicentre? Limiting studies to a single centre/unit may undermine efforts to generalize the findings.

(iii) On which units in the hospital should cycling be introduced? Specialized care units, such as ICUs, lend themselves to cycling because of the high frequency of serious infections and the high rates of antibiotic prescribing and multidrug-resistant bacterial pathogens.

(iv) Resistance to an antibiotic may not be the result of selective pressures arising from the persistent use of that particular drug, but rather to the use of antibiotics belonging to completely different classes, resistance determinants frequently being found on plasmids that mediate resistance to several unrelated classes. Consequently, despite withdrawal of an antibiotic from a hospital environment, resistance rates to that drug may not fall owing to co-selection for other resistance determinants.

(v) Factors other than the selective pressures associated with antibiotic usage may contribute to the emergence and persistence of resistance determinants, such pressures being only one of the forces that promote bacterial change.

(vi) Can antibiotics that have been withdrawn from usage because of high or increasing rates of resistance to them be reintroduced without leading to the re-emergence of resistant strains? The results of three studies suggest otherwise.

(vii) Should cycling be based on time interval, patient or category of infectious disease?

(viii) Which patients should be entered into the cycling protocol?

(ix) What are the optimal equivalent agents/regimens that should comprise each cycle?

(x) If a trial is conducted in several centres, how is it possible to ensure that the regimens comprising the cycles meet the requirements of each unit or institution in terms of appropriate empirical antibiotic therapy? In principle, the regimens must be
tailored to individual units/institutions, based on local susceptibility patterns.

(xii) What is the optimal duration of each cycle? If cycles are too short, changes in resistance rates may not be detected. For example, in the study carried out by Bradley et al., the reduction in the incidence of colonization with GRE was most marked in the latter half of the second phase of the cycling protocol. On the other hand, too long a duration may be associated with high risks of resistant strains emerging during the cycle.

(xiii) Should the duration of each cycle be the same? (Does resistance to different antibiotics develop at the same rate?)

(xiv) How can the effects of confounding variables, including infection control measures, the use of off-cycle antibiotics and the introduction of multidrug-resistant organisms into a unit from elsewhere in the same hospital or from outside the hospital, be eliminated?

(xv) Which outcome measures should be monitored (resistance rates, clinical outcome, including mortality rates, length of stay, cost-effectiveness)?

(xvi) How should antimicrobial resistance, in relation to specific antibiotics and organisms, be defined?

(xvii) How should hospital-acquired isolates be distinguished from community-acquired isolates?

(xviii) Should usage and rates of resistance to antibiotics other than those which are cycled be monitored?

Mathematical modelling

It is unlikely that these issues will be resolved in the near future, if, indeed, at all, and, until they have been satisfactorily addressed, it will be impossible to conduct the ‘ideal’ clinical trials necessary to determine whether or not cycling is beneficial. Under such circumstances, mathematical modelling may represent an alternative means of evaluating the efficacy of this intervention. Although mathematical models may not yield a definitive answer to the question of efficacy they may provide a rational basis for designing and interpreting the results of clinical trials. Specifically, they may define the conditions under which cycling is most likely to be beneficial. With this information, the ‘ideal’ clinical trials can then be designed and executed. A small number of such models have been described to date.

Bonhoeffer et al. used mathematical modelling to compare three treatment protocols involving two different antibiotics: periodic cycling of the drugs (cycling); administration of each drug (only one per patient) to equal proportions of the infected host population (50–50 or ‘mixed’ treatment); and simultaneous administration of both drugs to each infected host (combination therapy). They concluded that, when more than one antibiotic is employed, both 50–50 treatment and combination therapy are always superior to cycling, irrespective of how frequently the drugs are cycled. The theoretical superiority of ‘mixed’ antibiotic use over cycling was confirmed by Lo et al. who used a stochastic mathematical model to compare the efficacies of the two interventions in terms of preventing colonization with multidrug-resistant bacteria in the ICU setting.

Conclusion

In the light of the many unresolved issues relating to cycling, the poor quality of the majority of clinical trials evaluating its efficacy, the failure of a very small number of adequately designed trials to establish definitively the efficacy of cycling and the conclusions of two mathematical modelling studies, we do not believe that this intervention should be implemented routinely as a means of optimizing antibiotic prescribing and reducing antibiotic resistance rates in hospitals.

References


