Antibiotic cycling: more than it might seem?

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In the present battle against the rising tide of resistance, several interventions have been proposed to help control the situation. One of these is a process of planned antibiotic restriction, introduced through cycling drug selection based on local surveillance. Although such antibiotic cycling has been the subject of much discussion for 20 years, there are relatively few data available to assess its worth. A recent systematic review found only four studies worthy of inclusion and concluded that antibiotic cycling could not, at present, be promoted as a methodology to control resistance. This paper considers the complete literature and through demonstrating consistent benefits across the breadth and depth of the findings, suggests that whereas further work is required, nevertheless antibiotic cycling—as part of a suite of control measures—is a valid option.

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It is widely recognized that inappropriate antimicrobial prescribing is common and results in the generation of antibiotic resistance. However, there are few good data to assess the impact of a wide variety of interventions that have been claimed to be of benefit in preventing this and the subsequent spread of such antibiotic-resistant pathogens. It is now appreciated that any effort to control antimicrobial resistance must be underpinned by effective infection-control practices.1 Beyond this, many different interventions have been constructed.2,3 Firstly, techniques have been devised to enlist the support of prescribers in managing the resistance problem. This includes promoting understanding about the linkage between antibiotic prescribing and resistance, as well as the concept of ‘antimicrobial stewardship’. Secondly, schemes have been pursued to persuade patients and the public that pressurizing doctors to prescribe antibiotics inappropriately is harmful to both the individual and the greater good. Thirdly, measures have been invented to improve antimicrobial administration to patients. These include the production of antibiotic policies, computer-assisted prescribing and ‘stop’/’switch’ orders etc. Finally, strategies have been built around controlling drug choice. Examples of this are restricted antimicrobial availability or reporting, the use of special antimicrobial request forms and antibiotic cycling. Peculiarly, antibiotic cycling, which has been an identified concept for 20 years, actually has more reviews considering its potential than studies published assessing its effectiveness. Brown & Nathwani4 have presented an assessment of the efficacy of antibiotic cycling using the rigorous approach proposed by the Cochrane Group. Whereas there is no doubt that this has led to the best evidence being addressed, it has also meant that in doing so two-thirds of the published data on antibiotic cycling were excluded from consideration. This must pose the question about whether there is more to be said than can be found in the Cochrane approach.

Although a variety of descriptors have been used to describe the technique, antibiotic cycling is probably the most commonly adopted term. The idea at its simplest is that antibiotics are withdrawn from use for a period of time— with the intention of limiting resistance to the cycled agent—to be reintroduced later on. Basic questions can be asked of the principles underlying the concept of antibiotic cycling.5 Essentially, antibiotic cycling is a structured way of introducing antibiotic heterogeneity into prescribing practice, where mathematical modelling has demonstrated that heterogeneity, as opposed to availability restriction, is the most likely way to reduce selection pressures leading to antibiotic resistance.6 The intention is that a disciplined programme of usage will alter the emergence and persistence of resistant pathogens, by reducing antimicrobial selection forces. For this to be true, antibiotic cycling assumes that antimicrobial selection is the major impetus lying behind these phenomena, a position that is untested and unproven. Whereas it is generally accepted that there is a link between antimicrobial use and resistance, this is neither absolute nor directly proportional. Carbapenem resistance has been slow to develop in Gram-negative bacteria and has not been widely distributed amongst pathogens, but the fluoroquinolone experience is exactly the opposite, with a dramatic, rapid emergence and distribution of resistant strains. To hold up as true, the theory of antibiotic cycling must also address the issue of linked nosocomial resistance determinants. These developments are either the result of gene mutation, the acquisition of new genes or the mutation of acquired genes, with many such events involving pools of genetic material covering resistance for several antibiotic classes.7

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If antibiotic cycling is to be successful it must be applied in a way that avoids switching between such classes.

Unfortunately, whereas there is a broad agreement at a high level about the meaning of antibiotic cycling, other important issues of detail are not defined and so the schemes to date have been widely different.\textsuperscript{10–23} It has not been clear whether the cycling process applies between or within antibiotic classes. If it is to be within an antibiotic class then it must reflect issues about different mechanisms of action, since otherwise cross-resistance would make the cycling scheme fail. For example, within β-lactam agents subclasses could be defined for the various generations of cephalosporins and the β-lactam/β-lactamase inhibitor combinations. Equally, it is unspecified whether cycling means within a unit(s) or across an entire hospital, or whether it is equally relevant to apply the concept to both community and hospital scenarios. Furthermore, the duration of the withdrawal of the antimicrobial agent is undefined, as is the periodicity between repeats in the cycles. Finally, antibiotic cycling programmes have been assumed to be the same, whether they are applied where the process is being introduced to control developed resistance within an institution, as opposed to the intended primary prevention of the emergence of such problems. All of this has led to significantly varied studies conducted largely within projects pragmatically addressing resistance challenges. As such, Brown & Nathwani\textsuperscript{4} are right to question the strength of the findings and the appropriateness of merging these results to produce generalizations about the efficacy of antibiotic cycling.

Looking at the problem of resistance from a different dimension, influences other than just antimicrobial prescribing are now recognized to be important. Poorly cleaned wards allow an accumulation of dirt that can harbour resistant bacteria. The steady march of ever-increasing interventional practices promotes portals of entry and protected foci for resistant pathogens. It is recognized that the expression of resistance within strains can be associated with other factors, which cause the organism to have a reduced ability to survive in an antibiotic-free environment. Similarly, resistance expression has also been related to survival loss for organisms in the presence of a new antibiotic pressure. Finally, inducible resistance phenotypes may be more persistent than those that are expressed constitutively since their protective mechanisms are only activated when antibiotic is present to induce it. These organisms arguably have the best chance of survival in both the antibiotic-loaded as well as antibiotic-free environment. A key feature of the majority of trials on antibiotic cycling has been the introduction of the antibiotic restriction, in association with a variety of other measures that have included improvements in prescribing practice in terms of adherence to protocols, enhanced infection-control delivery, greater awareness through competent surveillance programmes and educational efforts to improve prescribing practice. Within this diverse and complex world of resistance, it is theoretically valid to view antibiotic cycling as a potential utilitarian tool that can be widely used with other interventions.

Whereas the literature review\textsuperscript{4} looked at just four papers, there are many more publications available on antibiotic cycling, and key features from these are presented in Table 1.\textsuperscript{10–23} Most of the work to date has been conducted in intensive care units (ICUs) and in adults, with just one paediatric trial\textsuperscript{21} and two neonatal studies.\textsuperscript{10,22} About half the available antibiogram studies follow its introduction in a reactive fashion due to the presence of an antibiotic-resistance problem. However, across both the reactive as well as proactive trials there is a consistent pattern: a reduction in resistance problems from Gram-negative organisms. Data on the implications for Gram-positive organisms are more scarce and confused. Whereas one study\textsuperscript{20} reported fewer nosocomial infections due to resistant Gram-positive organisms, another\textsuperscript{15} showed no effect on either colonization or bloodstream infection rates with such strains. In contrast, a project conducted outside an ICU, demonstrated an increase in Gram-positive bacterial sepsis, particularly due to enterococci.\textsuperscript{16} More recently, a trial rotating between ciprofloxacin and ceftazidime on a medical ICU demonstrated no adverse effect on either colonization or infection from vancomycin-resistant enterococci.\textsuperscript{17} In a linked vein, the only study that has explored the implications for wards receiving patients from an ICU employing antibiotic rotation techniques, demonstrated a broader institutional benefit with the non-ICU units. The study showed statistically significant reduced infection rates from hospital-acquired and resistant hospital-acquired episodes, whether due to Gram-positive or Gram-negative pathogens.\textsuperscript{24–27}

Summarizing their findings, Brown & Nathwani\textsuperscript{4} noted that antibiotic cycling was beneficial in three of the four studies, showing a reduced incidence of isolation of antibiotic-resistant bacteria. However, because of the unresolved issues they reported about antibiotic cycling, including the poor quality of the majority of the available clinical trials, they concluded that this intervention should not be routinely implemented as a means of optimizing antibiotic prescribing and reducing resistance rates. Interrogation of the data in Table 1 suggests a different inference, as there is a very consistent pattern of beneficial outcomes documented across the antibiotic cycling work. Only three studies,\textsuperscript{16,21,22} showed no gains and even two of these programmes claimed success as there was no increased resistance.\textsuperscript{21,22} These benefits can be identified as falling into three types. Firstly, in terms of the microbiology of antibiotic cycling, the studies that have evaluated the issue have uniformly shown a reduction in Gram-negative antibiotic-resistance patterns. Secondly, those papers reporting on therapeutic criteria have consistently demonstrated improved prescribing practices. Finally, the investigations that have looked at clinical outcomes have time and again reported reductions in the incidence of ventilator-acquired pneumonia, with two papers also finding lower mortality rates. Except for a single study that recorded an increase in enterococcal sepsis,\textsuperscript{16} no adverse effects from the technique have been identified in any of the antibiotic cycling literature. Two studies have explored the long-term effects of antibiotic cycling programmes, covering over 10 and 5 years experience, respectively,\textsuperscript{12,23} with both showing sustained benefits.

Certainly, the present clinical data on antibiotic cycling is narrow, having focused mainly upon ventilator-acquired pneumonia, although two studies have demonstrated effectiveness against a range of infections.\textsuperscript{20,23} Similarly, the scope of the available work is restricted, with the majority of the protocols assessing cycling between different classes of antibiotics. There is only a single β-lactam trial investigating a within-class effect\textsuperscript{15} compared to three such aminoglycoside trials.\textsuperscript{10–12} All these within-class studies demonstrated benefits. Widely varying cycle periods have been applied and, with the exception of the aminoglycoside study\textsuperscript{11} where a reintroduction of gentamicin after 12 months was related to an increase in resistance, the different
Table 1. Clinical trials of antibiotic cycling

<table>
<thead>
<tr>
<th>Reference</th>
<th>P/R</th>
<th>S/M</th>
<th>W/B</th>
<th>Venue</th>
<th>Cycle description</th>
<th>Cycle (months)</th>
<th>Findings</th>
</tr>
</thead>
</table>
| 10        | R    | S    | W    | neonatal ICU              | one cycle gentamicin to amikacin and back              | 5             | 1. ↓ colonization with gentamicin R<sup>d</sup> during amikacin use  
2. ↑ colonization with gentamicin R after switch back  
3. ↓ gentamicin and tobramycin R in clinical samples after amikacin reintroduction  
4. ↓ gentamicin and tobramycin R in clinical samples during amikacin use |
| 11<sup>f</sup> | R    | M    | W    | hospital wide             | two cycles of gentamicin to amikacin                   | first cycle 26 second cycle 12 | 1. ↓ colonization with gentamicin R<sup>d</sup> during amikacin use  
2. ↑ colonization with gentamicin R after switch back  
3. ↓ gentamicin and tobramycin R in clinical samples following gentamicin reintroduction  
4. ↓ gentamicin and tobramycin R in clinical samples after amikacin reintroduction |
| 12<sup>f</sup> | R    | S    | W    | hospital wide             | one cycle gentamicin to amikacin and back              | 15            | 1. ↓ colonization with gentamicin R in clinical samples during amikacin use  
2. ↑ colonization with gentamicin R after switch back  
3. ↓ gentamicin and tobramycin R in clinical samples after amikacin reintroduction  
4. ↓ gentamicin and tobramycin R in clinical samples during amikacin use |
| 13        | R    | S    | W    | hospital wide             | follow on to ref. 11 with gentamicin reintroduced      | 15            | 1. no ↑ colonization with gentamicin R in clinical samples following its second gradual reintroduction  
2. total aminoglycoside use ↓ over study  
3. ↓ incidence of resistance during the study period  
4. ↓ in enterococcal infections over study period |
| 14        | P    | S    | B    | cardiac surgery unit      | one cycle ceftazidime to ciprofloxacin                 | 6             | 1. ↓ incidence of VAP<sup>e</sup>  
2. ↑ incidence of VAP due to resistant organisms  
3. ↓ incidence of Gram-negative bacteraemia due to resistant organisms  
4. ↓ incidence of carriage of glycopeptide-resistant enterococci (GRE) during cycle  
5. ↓ incidence of carriage of GRE sepsis during cycle as compared to before and after |
| 15<sup>f</sup> | R    | S    | W    | haematological malignancy unit | one cycle ceftazidime to piperacillin/tazobactam and back | 4             | 1. no ↑ in resistance during the study period  
2. no ↑ in enterococcal infections over study period  
3. ↓ incidence of VAP<sup>e</sup>  
4. ↑ incidence of VAP due to resistant organisms  
5. ↓ incidence of resistance during the study period  
6. ↓ in enterococcal infections over study period |
| 16        | P    | M    | B    | haematology-oncology unit | ceftazidime/vancomycin to imipenem to aztreonam/cefazolin to ciprofloxacin/clindamycin | 6 to 4 to 5 to 4, respectively | 1. ↓ incidence of VAP<sup>e</sup>  
2. ↑ incidence of VAP due to resistant organisms  
3. ↓ incidence of inadequate antibiotics for Gram-negative organisms  
4. ↓ mortality rate for nosocomial infections |
| 17        | P    | M    | B    | medical ICU               | various β-lactams, aminoglycosides and fluoroquinolones | ≥1 for a total of 24 | 1. ↓ incidence of VAP<sup>e</sup>  
2. ↑ incidence of VAP due to resistant organisms  
3. ↓ incidence of resistance during the study period  
4. ↓ in enterococcal infections over study period  
5. ↓ in enterococcal infections over study period |
| 18        | P    | M    | B    | medical and surgical ICU  | ceftazidime to ciprofloxacin to cefepime              | 6 to 6 to 5, respectively | 1. ↓ incidence of VAP<sup>e</sup>  
2. ↑ incidence of VAP due to resistantorganisms  
3. ↓ incidence of empirical antibiotic selection  
4. ↓ in enterococcal infections over study period  
5. ↓ in enterococcal infections over study period |
| 19        | R    | M    | B    | medical ICU               | ceftazidime to ciprofloxacin                          | 6             | 1. no change in colonization with vancomycin-resistant enterococci during either cycle  
2. ↓ incidence R Gram-positive infections  
3. ↓ incidence R Gram-negative infections  
4. ↓ mortality rate  
5. ↓ in colonization with R organisms |
| 20        | P    | M    | B    | general, transplant, trauma ICU | 1 year non-protocol then 1 year rotating empirical selection | 12            | 1. no ↑ in colonization with R organisms  
2. no change in prevalence of bloodstream infections with R organisms  
3. ↓ incidence of VAP<sup>e</sup>  
4. ↑ incidence of VAP due to resistant organisms  
5. ↓ incidence of resistance during the study period  
6. ↓ in enterococcal infections over study period |
| 21        | P    | M    | B    | paediatric ICU            | imipenem to piperacillin/tazobactam to ceftazidime (cefepime)/clindamycin and back | 3 for a total of 18 | 1. no ↑ in colonization with R organisms  
2. no change in prevalence of bloodstream infections with R organisms  
3. ↓ incidence of VAP<sup>e</sup>  
4. ↑ incidence of VAP due to resistant organisms  
5. ↓ incidence of resistance during the study period  
6. ↓ in enterococcal infections over study period |
durations do not appear to have any demonstrable impact. Most of the recent programmes evaluated schemes where multiple cassettes of different antibiotics were being cycled, rather than a single switch with subsequent reintroduction of the original antibiotic, again with demonstrated benefits again being the norm.

Notwithstanding these very real qualifications on any conclusions, the available clinical trials, nevertheless, consistently point to benefits in the following areas:

(i) Where antibiotic cycling is introduced in response to a Gram-negative resistance problem, it can help to control that problem.

(ii) Where antibiotic cycling is introduced and no specific susceptibility problem exists, it can still reduce background levels of resistance. This has been consistently demonstrated for Gram-negative pathogens, although not for Gram-positive organisms.

(iii) Where antibiotic cycling is introduced, there is a reduction in ICU nosocomial infections. This has been consistently demonstrated for ventilator-associated pneumonia, although less convincingly for other types of sepsis.

(iv) Where antibiotic cycling is introduced, there is a reduction in the incidence of ICU nosocomial sepsis due to resistant organisms. This has been consistently demonstrated for Gram-negative pathogens, although not for Gram-positive organisms.

(v) Where antibiotic cycling is introduced, there is an improvement in effective antibiotic prescribing in ICU.

(vi) Where antibiotic cycling is introduced, there is a reduction in ICU mortality rates.

Accepting that these benefits are genuine, leaves open the question as to how they are produced. Proponents of the case for antibiotic cycling lay them at the door of this stratagem. Brown & Nathwani\(^4\) are correct in calling for better-designed trials to assess definitely the efficacy of antibiotic cycling, and they helpfully describe what these should look like. However, whereas their literature review led to a conservative, slightly negative conclusion, consideration of the whole evidence perhaps points to a brighter vision, and suggests that such work should be undertaken soon and with optimism and enthusiasm. Arguably, in the meantime, and particularly if faced with resistance problems, workers interested in this field should continue to view antibiotic cycling as a potentially employable intervention, since such tactics can reliably be expected to lead to improvements and at the worst will do no harm.

References


