

Commentary

Rotating antibiotics in the intensive care unit: feasible, apparently beneficial, but questions remain

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Abstract

Rotating antibiotics in the intensive care unit may result in less infections caused by resistant organisms and in even less mortality. The selection of super-resistant organisms associated with the rotation strategy cannot be excluded, however, and many practical issues will have to be addressed before antibiotic rotation can be routinely recommended.

Keywords antibiotic, resistance, rotation policy

Raymond *et al.* from the University of Virginia, USA published work into rotating empirical antibiotics in an intensive care unit in June 2001 [1]. This was the first time that a quarterly rotation of empirical antibiotics used for 1 year was compared with the previous year of non-protocol-driven use in critically ill patients. The research showed that rotation was associated with a significant reduction in infection episodes caused by Gram-negative, antibiotic-resistant organisms.

The paper also showed that rotating antibiotics resulted in a lower incidence of Gram-positive coccal infections, less methicillin-resistant *Staphylococcus aureus* (MRSA) and gentamicin-resistant enterococci infections, and a clear reduction in mortality associated with infection. In fact, antibiotic rotation was an independent predictor of survival.

The Raymond *et al.* paper was welcomed news because we are clearly facing an antibiotic crisis [2,3]. Bacterial resistance is progressing faster than the number of new antibiotics available to the clinician, resulting in higher costs and poorer outcomes [4]. To meet this challenge, new strategies that optimise the use of available antimicrobials are urgently needed. Rotating antibiotics is one possible approach.

How rotating antibiotics works

While the basic principle of rotating antibiotics is simple, behind it lie a number of conceptual and practical issues that

are much more complex. A first antibiotic regimen is chosen for a group of patients during a specific period of time, then a second regimen is selected for another period, and then perhaps a third, and even a fourth, regimen may follow [5]. The same sequence of antibiotic regimen is then repeated. The basic idea is that a bacterium that becomes resistant to the first regimen would remain susceptible to the second regimen. If it is resistant to the second regimen, the third regimen should cope with the resistance, and so on.

Acquiring successive mechanisms of resistance can have metabolic consequences for the bacterium. For instance, if the resistance comes from a plasmid, the bacterium may require more energy during bacterial multiplication or for producing large amounts of beta-lactamases. It may alternatively lead to variations in the bacterium's ability to take up nutrients. The multiplication of resistance mechanisms in the same bacterial cell line should hence be detrimental to its optimal propagation, allowing sensitive bacteria (with supposedly better fitness) to take over. The expected consequence would be a decline in resistance and easier management of infected patients.

Threats to rotation

Bacteria possess mechanisms that allow them to become resistant to several structurally unrelated antibiotics at once. Mobile genetic elements that encode for numerous

MRSA = methicillin-resistant *Staphylococcus aureus*.

resistance mechanisms can become incorporated into the stable genetic structures of bacteria. These could jeopardise the rotation strategy [6]. Besides the well-known plasmids, bacteriophages, and transposons, the more recently described integrons can capture multiple gene cassettes, express them, and then integrate them into the chromosome [7]. The genes found in integrons often encode antibiotic resistance, including proteins such as efflux pumps, acetyl-transferases, dihydro-folate reductases, and beta-lactamases [8]. Furthermore, co-selection of resistance determinants can be achieved by numerous other molecular mechanisms of resistance, representing additional threats to the rotation strategy. For instance, the combination of quinolone and methicillin resistance is often observed in *S. aureus* [9].

Multidrug active efflux systems can pump out an astonishing number of unrelated antibiotics, any of these substrates acting as a potential trigger [10]. Some efflux systems are co-regulated with outer membrane permeability. For example, activation of the MexE-MexF-OprN multidrug efflux system generates an OprD (the carbapenem porin) deficiency, so that ciprofloxacin, for instance, can select resistance to carbapenems in the absence of carbapenem exposure [11]. Extended-spectrum cephalosporin use is associated with infection and colonisation with vancomycin-resistant enterococci [12]. *Klebsiella pneumoniae* strains producing extended-spectrum beta-lactamases often harbour plasmids that encode resistance to other antibiotics [13] and that cross-resist to quinolones by mechanisms that are currently unclear [14]. Moreover, the metabolic consequences of some multiple resistances are questionable considering the remarkable stability of *mecA* in the MRSA, vancomycin-resistant determinants in the enterococci, or integrons in nature, even in the absence of antibiotic pressure.

Practical issues are also complex [15]. A general consensus has to be obtained between hospital administration, health carers, and pharmacists: all prescribers have to follow the guidelines; the different regimens used in the rotation must be chosen in the light of recent scientific knowledge; the duration of each cycle must be between the 'too short', the 'difficult to implement', and the 'too long', allowing the selection of resistance during therapy despite the rotation policy; and, above all, optimal infection control measures have to be ensured.

Conclusions

The few published studies that address the antibiotic rotation strategy gave positive signals. For example, an influence of the aminoglycoside in use on aminoglycoside resistance patterns was reported [15,16], and a diminution in the rates of ventilated associated pneumonia [17], including those caused by MRSA [18], was observed. A decline in faecal vancomycin-resistant enterococci colonisation was also reported [19]. None of these studies, however, investigated an actual rotation policy including a sufficient number of

cycles; that is why the paper by Raymond *et al.* was so welcomed.

Antibiotic rotation is feasible and apparently beneficial, but many questions remain unanswered. All the studies published, including that of Raymond *et al.*, used historical controls (before versus after studies), which is inappropriate considering the variable nature of bacterial epidemiology. The risk of selecting 'super-resistant bugs' during the rotations has not been specifically addressed. The time has come for large, co-operative international studies on these important issues.

Competing interests

None declared.

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