International Journal of Antimicrobial Agents 43 (2014) 319–322

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Discussion

Of stewardship, motherhood and apple pie

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ARTICLE INFO

Article history:
Received 13 January 2014
Accepted 14 January 2014

Keywords:
Antibiotic stewardship
Cephalosporins
β-Lactamase inhibitor combinations
Antibiotic cycling
Antibiotic heterogeneity
Gonorrhoea

ABSTRACT

Antibiotic stewardship is universally agreed to be desirable, but optimal models for stewardship remain uncertain. UK stewardship targets the particular antibiotic families—cephalosporins and fluoroquinolones—blamed for the selection of *Clostridium-difficile*-associated disease. To balance this there have been dramatic increases in the use of penicillin–β-lactamase inhibitor combinations. By channelling selection pressure in this way, we hazard destroying the utility of these antibiotic classes in turn, as happened with gonorrhoea where penicillins, fluoroquinolones and cefixime were sequentially lost as therapies. Strikingly, in context, almost all carbapenemase-producers are highly resistant to penicillin–β-lactamase inhibitor combinations, which may select for them. There is an urgent need to explore an alternative stewardship model, seeking to limit total antibiotic use but to maintain heterogeneity in what is used, avoiding concentrated selection pressure. There is also a great need to improve and accelerate diagnostics for infection and resistance, reducing or removing the need for protracted empirical treatment with broad-spectrum agents.

Antibiotic stewardship, like motherhood and apple pie, is now universally agreed to be a 'Good Thing'. It aims (i) to ensure patients receive appropriate and timely antibiotics, (ii) to minimise unnecessary antibiotic use and (iii) to maintain regular audit of antibiotic use, with education and feedback to prescribers [1,2]. These aims clearly are laudable, and there is evidence, including a Cochrane review, that stewardship programmes improve and reduce antibiotic use [3,4]. Nevertheless, it is legitimate to ask whether we have got stewardship 'right', just as it is legitimate to debate what makes a good mother or a good apple pie.

It is easy to recognise the *opposite* of good stewardship—profligate use, inappropriate regimens and long prophylaxis. But what is '*good*' stewardship, or motherhood, given that long- and short-term consequences may diverge? [Apple pie is simpler!]. Critical here is the issue of whether stewardship should concentrate on total usage, or target specific antimicrobial classes, as in the UK.

From the mid 1980s to around 2005–2006, injectable cephalosporins, alone or combined with macrolides or metronidazole, were the standard UK treatment for community-acquired pneumonia, urinary tract infections and intra-abdominal sepsis. Subsequently they, and fluoroquinolones, have been blamed for selecting *Clostridium-difficile*-associated disease, which rose from a few hundred cases per year in the early 1990s to over 50,000 by 2007–2008 [5]. Consequently, cephalosporins (and, to a degree, fluoroquinolones) have been particularly targeted by UK stewardship, with the use of second- and third-generation analogues reduced by >50% and 22%, respectively, between 2004 and 2009 [1,6], with many hospitals now claiming reductions exceeding 80%. Other agents are used instead, particularly piperacillin/tazobactam (TZP) and amoxicillin/clavulanic acid, but also carbapenems [1].

The immediate consequences are positive: reported *C. difficile* cases fell from 55,498 in 2007–2008 to 14,689 in 2012–2013 [5], whilst the proportions of Enterobacteriaceae with cephalosporin and quinolone resistance have stabilised (*Escherichia coli*) or declined (*Klebsiella* and *Enterobacter* spp.) [6]. Reductions in cephalosporin-resistant Enterobacteriaceae have not been seen elsewhere in Europe, where cephalosporins are not restricted so forcefully, implying causality [6]. So far there is no countervailing increase in resistance to TZP (Public Health England, data on file). Nevertheless, it is striking and worrisome that carbapenemase-producing Enterobacteriaceae—a gradually rising problem—are more consistently and highly resistant to TZP, with minimum inhibitory concentrations (MICs) of >128 mg/L [6], than to carbapenems themselves. Might the switch to TZP be driving the accumulation of these challenging pathogens?

A further aspect is whether UK stewardship now leads to cephalosporins being denied to patients for whom they are the most appropriate treatment. This point applies for ceftazidime, as still the most consistently active β-lactam against *Pseudomonas*

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http://dx.doi.org/10.1016/j.ijantimicag.2014.01.011

aeruginosa [7], and to ceftaroline and ceftobiprole, which potentially (further studies are needed) bring the antistaphylococcal advantages of β-lactams to the treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) infections [8,9]. This issue is set to become more acute with the expectation, by 2015, of two new cephalosporin combinations with unique features.

Ceftolozane/tazobactam is even more active than ceftazidime against *P. aeruginosa* [10,11] and appears less prone to select mutational resistance [12], whereas ceftazidime/avibactam is the sole β-lactam consistently active against Enterobacteriaceae with OXA-48 and KPC carbapenemases [13]. It will be unreasonable if patients are denied these agents simply 'because they are cephalosporins'; yet the perceived risk of *C. difficile* infection when using a cephalosporin, together with the need to deliver *C. difficile* reduction targets, is reportedly dissuading UK centres from undertaking clinical trials with these new cephalosporins [14].

The potential for narrowly-focused stewardship to misfire is illustrated by gonorrhoea [15,16]. The compliance of genitourinary physicians with treatment recommendations has been exemplary; in 2000, 80% of UK gonorrhoea patients received ciprofloxacin, switching to >80% receiving cefixime by 2008 [17] and 79% receiving ceftriaxone + azithromycin by 2011 [18], all in compliance with then-extant guidance. Moreover, (i) only patients with diagnosed gonorrhoea are treated, (ii) most patients are young and lack the physiological malfunctions that may confound antimicrobial pharmacodynamics, and (iii) patient compliance is ensured by directly observed single-dose therapy. Yet, despite these advantages, this standardised 'stewardship' has led to sequential destruction of the usefulness of ciprofloxacin and cefixime, not to their conservation [15–18]. It may be objected that gonorrhoea is a special case (i) because it is a classical infectious disease, (ii) because resistant strains may be imported from developing countries, perhaps originally selected, e.g. in commercial sex workers practicing routine prophylaxis, and (iii) because single-dose therapy constitutes undertreatment. These objections have merit but are not unique to gonorrhoea. (i) Clones of opportunist bacteria, e.g. *E. coli* sequence type 131 (ST131) variants with cephalosporin and fluoroquinolone resistance, likewise spread in the community, giving reservoirs for future infection [19–21], (ii) highly resistant bacteria, including Enterobacteriaceae with extended-spectrum β-lactamases (ESBLs) and carbapenemase, are repeatedly imported to the UK via patient transfers [21–23] and (iii) many other antibiotic regimens are suboptimal. In short, gonorrhoea is not unique.

Is there a better mode of stewardship? There are two obvious alternatives: cycling and heterogeneity. In cycling, a unit rotates its preferred empirical regimen at intervals, typically quarterly; in heterogeneity, the unit allocates patients to different but equivalent regimens. Both strategies aim to avoid narrowly focused selection pressure. There have been many studies of cycling, with little evidence of reliable short-term reduction in resistance [24,25]. A recently study does suggest longer-term benefit, with reduced resistance to cephalosporins, TZP and imipenem when these were cycled over a 6-year period in a surgical intensive care unit (ICU) [26], but the authors acknowledge possible confounders. Heterogeneity, which mathematical models suggest should be less selective than cycling [27], has been less evaluated [28]. A hint of potential benefit nevertheless is given by the work of Sandiumenge et al. (Fig. 1) [29]. In successive 11-month periods from 2000 to 2003 at a single ICU in Spain, these authors tested the effects of (i) antibiotic choice based on patient-specific factors, (ii) cycling of cephalosporins, TZP and carbapenems, (iii) restriction of one of these drug classes for 4-month periods and (iv) allocating successive patients to the different antibiotic regimens. There are many potential confounders, notably underlying national resistance trends. Nevertheless, the results suggest that resistance and infection rates were highest when selection pressure was most concentrated, and least when use was heterogeneous. Further studies are needed to test these conclusions, which support very different models of stewardship to those now standard in the UK.

It should be added that most cycling and heterogeneity studies have been undertaken in ICUs, which have higher resistance rates than general wards and which concentrate vulnerable patients, increasing the cross-infection risk. Might they work better in medical admissions units or geriatric wards? Or in gonorrhoea, where until 2000 ciprofloxacin, spectinomycin and cefixime were all reliably active [16,17]? Should we have sequentially allocated

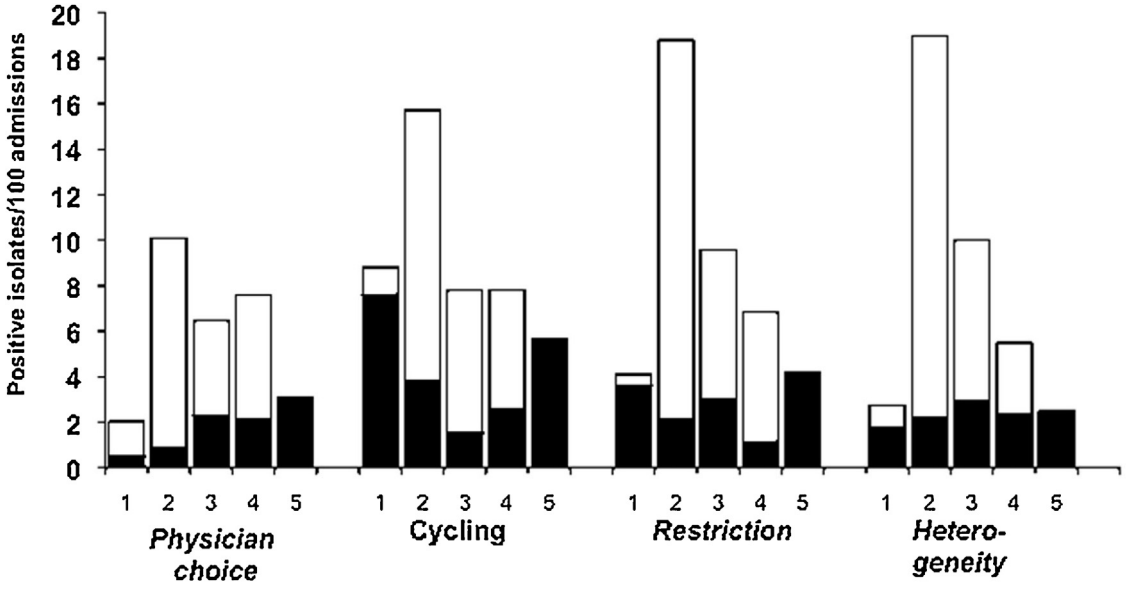

Fig. 1. Isolation of key resistance types from ventilator-associated pneumonia patients at an intensive care unit in northern Spain from 2000–2003. The white bars are total incidence and the black bars indicate the proportion with the key resistance: 1, *Acinetobacter*, carbapenem resistance; 2, Enterobacteriaceae, extended-spectrum β-lactamases; 3, *Pseudomonas aeruginosa*, any resistance; 4, *Staphylococcus aureus*, meticillin resistance; and 5, *Enterococcus faecalis*, irrespective of resistance. The empirical agents rotated in the cycling period, or sequentially withheld in the restrictive period, were carbapenems, piperacillin/tazobactam and oxyimino-cephalosporins.
Redrawn from Sandiumenge et al. [29].