Antibiotic policies to control hospital-acquired infection

I. M. Gould*

Department of Medical Microbiology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB25 2ZN, Scotland, UK

Antibiotic use is widely accepted as being responsible for the selection and maintenance of antibiotic resistance. It is less obvious, however, that it is also responsible for increasing transmissibility and pathogenicity of many multiresistant bacteria and may actually be increasing the number of hospital-acquired infections (HAIs). Antibiotic stewardship should be given much more emphasis in the fight against HAI.

Keywords: MRSA, stewardship, Clostridium difficile, randomized controlled trials

Despite record resources being directed to infection control (IC), hospital-acquired infection (HAI) seems to be an ever increasing problem. Most of the high profile organisms are multidrug-resistant (MDR) either with acquired, e.g. methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum β-lactamase (ESBL) producers, or natural resistance (Clostridium difficile), and some such as MRSA are not merely replacing methicillin-susceptible S. aureus (MSSA) but are an additional burden of infection. Why is this and what can be done about it? Is it a case of IC measures not working or not being applied properly, or are the pressures of antibiotic use just too much? Is it possible to control MDR with antibiotic policies?

A recent Cochrane review, while emphasizing the poor quality of the evidence base for interventions to improve antibiotic prescribing in hospitals, did confirm previous reviews and mathematical models, indicating that modulating prescribing can reduce resistance, although the number of robust studies is no more than a dozen and more evidence is required on clinical outcomes to ensure that no harm is being done. The evidence is strongest for a reduction in third-generation cephalosporin (3GC) use, leading to reduction in MDR Gram-negatives and C. difficile. Most importantly, there were no data included in the Cochrane review to support control of MRSA by antibiotic modulation. The review did stop its evidence base in 2003 though, and there have been several robust studies published subsequently that back up an increasing number of less robust uncontrolled studies that consistently suggest that reducing fluoroquinolone and cephalosporin use can reduce MRSA rates. At first, this might seem surprising given the traditional view that MRSA is mainly an IC problem.

Considering other types of data does, however, lend support to the importance of antibiotic prescribing at all stages in the development of MDR, including MRSA. Clearly, Darwinian theories of evolution and survival of the fittest suggest that the selection and maintenance of MDR bacteria would not happen without antibiotic exposure and the heavier the exposure, the greater the resistance problem. It is also possible that in transmission of MDR from patient to patient, antibiotic pressures may be as important as failures in IC. First, antibiotic exposure can increase the bioburden of MDR bacteria in a patient through suppression of normal flora, allowing multiplication of the MDR bacteria. This increased bioburden makes the patient more likely to contaminate the environment, staff and other patients. Furthermore, antibiotics including the quinolones are known to modulate phage induction and horizontal gene transfer, both of which can spread virulence factors such as toxin production (α toxin, TSS toxin and SSS toxin in the case of S. aureus) and further antibiotic-resistance determinants. Similarly, quinolones are known to increase the expression of fibronectin-binding proteins and adherence in S. aureus, allowing even greater increases in transmissibility. Persistence of infection by increasing biofilm formation and small colony variants are further problems induced by various antibiotics in, for example, S. aureus. All this should be seen in the context of a typical hospital run on a daily diet of cephalosporins, quinolones and macrolides, which retain a high degree of activity against MSSA. Meanwhile, MRSA, which is usually resistant to these agents, is given a huge advantage, with prescription of such agents allowing its proliferation, increased transmissibility and increased virulence.

Such antibiotic-induced changes in microbial ecology, pathogenicity and transmissibility are not only concerning but also provide further evidence to argue for improved quality of antibiotic prescribing. Evolving data that the majority of nosocomial infections may be endogenous rather than transmitted also argue for restrained, short-term use of prophylactic antibiotics in carriers of known MDR pathogens to reduce the shift from colonization to infection. Concerns of further resistance must raise caution about the widespread implementation of measures such as selective digestive decolonization. Moreover, the poor...
evidence base that informs much of our traditional IC adds further importance to controlling prescribing.16,17

Unfortunately, current practice and likely future trends in hospital and community antibiotic prescribing give much cause for concern. In the community, although the number of scripts and even volume (as measured by defined daily doses) have reduced significantly in recent years,18,19 quinolone use is rising in many countries, often for the treatment of resistant pneumococcal infections.20 The advent of community-acquired MRSA will also put tremendous pressure on primary care and emergency department doctors to broaden their choice of antibiotic prescription for skin soft tissue infections.21 Community outbreaks of ESBL producers will lead to increased carbapenem use.22 This latter issue is perhaps the most problematic for hospital practice given the absence of likely alternatives to carbapenems for treatment of serious HAI by carbapenemase producers.23

In many hospitals, quinolone resistance in Enterobacteriaceae and Pseudomonas aeruginosa is now at such a high level that quinolones cannot be relied on for empirical monotherapy.24 For similar reasons, neither can broad-spectrum cephalosporins. Even carbapenems are under serious threat in many countries and carbapenemase-producing, polymyxin- and aminoglycoside-resistant P. aeruginosa and Acinetobacter baumannii are increasingly described.25,26 This is a real doomsday scenario as there are few, if any, drugs currently in development to address this problem. Although new drugs for MDR Gram-positives seem to be more likely,27 MRSA, vancomycin-resistant S. aureus, vancomycin-resistant enterococci and C. difficile continue to pose problems.21 Meanwhile, guidelines continue to recommend empirical combination therapy for community-acquired pneumonia28,29 and hospital-acquired pneumonia (HAP).30 In the former, the routine use of a broad-spectrum cephalosporin or a β-lactam inhibitor combination plus a macrolide makes little microbiological or clinical sense, but has almost certainly caused huge resistance problems.31 Recommendations of carbapenem–aminoglycoside–glycopeptide combinations for HAP typify the tendency to continue this spiral of therapeutic empiricism, which has to stop sometime.32

Sooner rather than later there has to be a consideration of the ecological damage of such regimes rather than just the perceived need to cover all possible pathogens in patients who present with serious infections. Moreover, proper patient severity assessment,33 streamlining and step down34 must continually be emphasized. There needs to be more realization that prescription of agents to which bacteria are resistant will encourage their proliferation, with consequences both for the patient themselves in terms of developing infection from colonization and for the hospital in terms of increased spread to other patients. This is most obvious perhaps with C. difficile but must also be emphasized for other organisms with major pathogenic and transmissible potential such as MRSA. Currently, conventional wisdom condemns the use of antibiotics in viral infections and minor bacterial infections. With the dearth of new antibiotics coming to the marketplace and the advance of MDR bacteria, it is not difficult to see untreatable life-threatening bacterial infection becoming common. But, it is now clear that the harmful properties of antibiotics extend beyond selecting and maintaining resistance and we should be particularly cautious about which antibiotics are prescribed to patients already colonized or infected with MDR bacteria.


