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Review

Antimicrobial stewardship in hospitals: Does it work and can we do it?

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ABSTRACT

Selection of resistant pathogens by antimicrobial use is probably the most important cause of antimicrobial resistance. Antimicrobial stewardship (AMS) refers to a multifaceted approach to optimise prescribing. The benefits of AMS programmes have been widely demonstrated in terms of reductions in antimicrobial use, mortality, *Clostridium difficile* and other healthcare-associated infections, hospital length of stay and bacterial resistance. Several kinds of interventions (i.e. restriction of drugs, pre-authorisation of certain antimicrobials, joint clinical rounds with prescribers, implementation of guidelines and education) have shown positive results. Regrettably, in most hospitals in Latin America, Asia and Africa as well as in a significant proportion of institutions in Europe and North America, essential human and material resources are scarce or absent, and teams are neither developed nor well functioning. Despite current or potential barriers, we should start or improve our already ongoing initiatives on AMS by considering the main specific problems and act accordingly with the available human and material resources. From supervising the use of specific classes of drugs to implementing more sophisticated decision support programmes, there is a wide range of possible useful interventions.

Contents

Antimicrobials are among the most commonly prescribed drugs in hospitals. In fact, about 30–50% of hospitalised patients receive at least one antimicrobial treatment [1,2]. Antimicrobial resistance is the product of a complex interaction of multiple factors, and selection of resistant pathogens by antimicrobial use is probably the most important.

Adverse effects associated with antimicrobial use result in more visits to the emergency room than other classes of drugs, including anticoagulants [3]. Antimicrobials are the most common drugs involved in the development of drug-induced liver injury, are a frequent cause of nephrotoxicity and are responsible for 13.7% of life-threatening anaphylactic reactions [4]. There are also concerns regarding the costs of antimicrobials, their high rates of misuse worldwide (25–70%), the impact of resistance on morbidity and mortality, the shortage of new drugs for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR)

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organisms, and the almost current catastrophic ecological situation. These issues have been previously well described and will not be addressed in depth in this article.

1. What is the meaning of antimicrobial stewardship?

Physicians have a double and somehow contradictory responsibility. First, physicians should do the best for their patients, which may lead to overuse of antimicrobials. However, they should also do their best for people and the community, aiming to minimise the selection of resistance [5].

AMS refers to the multifaceted approach (including policies, guidelines, surveillance, prevalence reports, education and audit of practice) to optimise prescribing. The aim of AMS programmes (ASPs) is to improve antimicrobial use in the context of every specific situation. This implies correct drug selection, with an adequate spectrum, prescribed at an appropriate moment, with the correct dose and route, and with an adequate duration of treatment [5].

2. Are antimicrobial stewardship programmes beneficial?

The benefits of ASPs have been widely demonstrated in terms of significant reductions in the following variables.

2.1. Antimicrobial use

Several studies, most of them from the USA, have shown a decrease of between 10% and 40% in antimicrobial use (with annual savings of US$200,000–900,000) with ASPs [1,2,6–9].

2.2. Mortality

The association between inadequate empirical antibiotic treatment and mortality has been assessed [10,11]. Many studies focusing on the treatment of ventilator-associated pneumonia (VAP) [12] demonstrated that treating episodes according to microbiological results and shortening the treatment duration significantly contributed to reducing mortality. One recent study [13] that evaluated local guidelines showed that patients receiving inadequate antibiotic therapy had a greater than two-fold increased likelihood of death within 30 days and a greater than six-fold increased risk of death within 1 week compared with patients who were adequately treated. The positive role of the consultation of an infectious diseases specialist has also been established [14].

2.3. Clostridium difficile-associated diarrhoea (CDAD)

In a Cochrane Review [15], three of five studies aimed to reducing CDAD showed positive results. These findings were recently confirmed in two studies where reductions in the use of several antibiotics significantly correlated with a reduction in CDAD [6,7].

2.4. Healthcare-associated infections

A recently published multifaceted programme combining cross-transmission prevention and AMS performed in France [16] showed that a 31% reduction in antibiotic consumption was associated with an 84% reduction in hospital-acquired meticillin-resistant *Staphylococcus aureus* (MRSA) colonisation and with a 93% reduction in bacteraemia caused by MRSA. Similar findings have recently been published from a 2000-bed tertiary hospital in South Korea [17].

2.5. Hospital length of stay

A 1-day study performed in six hospitals across the UK showed that an infection team review of prescriptions facilitated both intravenous-to-oral switch as well as reductions in antibiotic use, saving 481 bed-days [18]. One study on the treatment of VAP used a clinical pathway [19]. This tool included the adoption of a specific antimicrobial regimen that considered local minimum inhibitory concentration distributions and a pharmacodynamically optimised dosing strategy. Shorter duration of treatment, reduced length of hospital stay and lower hospital costs were observed.

2.6. Bacterial resistance

Whilst it seems logical that ASPs should decrease the development of resistance, it is difficult to measure its exact impact given that antimicrobial resistance grows rapidly and decreases slowly [20]. This may be explained by the fact that resistance mutations are generally persistent and easy to be transmitted from one bacteria to another without a significant fitness cost. Thus, a failure to reduce resistance should not be taken as evidence of programme failure.

Despite these issues, some positive results have been published. One 7-year study in an intensive care unit (ICU) at a tertiary teaching hospital demonstrated improved antibiotic susceptibility of Gram-negative isolates, including *Pseudomonas aeruginosa*, following an intervention to reduce consumption of broad-spectrum antibiotics [21]. In another study, a 56.6% reduction in ciprofloxacin use ($P < 0.001$) was associated with a significant decrease in the mean percentage of nosocomial ciprofloxacin-resistant *P. aeruginosa* (from 45.0% to 35.2%; $P < 0.002$) [22]. A survey of 670 US hospitals found that implementation of guideline-recommended practices to control antimicrobial use and to optimise the duration of empirical therapy was associated with less antimicrobial-resistant infections, including MRSA, vancomycin-resistant enterococci, fluoroquinolone-resistant *Escherichia coli* and ceftazidime-resistant *Klebsiella* spp. [23]. Another intervention resulted in improved susceptibilities of bacteria recovered in the ICU and other hospital units to all β-lactam and quinolone antibiotics, despite no changes in infection control practices [8].

3. What are the main components of an antimicrobial stewardship programme in hospitals?

The main components that should be considered for developing an effective and functional ASP are summarised in Table 1. Many of these will be briefly discussed.

There are two major approaches to AMS in hospitals. (a) A pre-prescription or 'front-end' strategy includes the restricted availability of certain drugs and the need for pre-authorisation of some antimicrobials. However, it requires a trained AMS team continuously available and easy to reach. This strategy has shown significant improvements in antimicrobial use [8,24] but tends to generate greater opposition of prescribers compared with the 'back-end' approach. In one study [25], the proportion of prescriptions of restricted (vs. non-restricted) agents was higher in the hour after the ASP approval requirement ended (22:00–22:59 h) compared with the mean of other hours (57.0% vs. 49.9%; $P = 0.02$). There was a borderline significant trend for patients with orders placed during this hour not to have continuation of any antimicrobials.

Another pitfall to the pre-authorisation approach is the risk of increasing resistance to essential drugs (i.e. carbapenems). One study showed that cephalosporin restriction resulted in a 44% reduction in the incidence of ceftazidime-resistant *Klebsiella*