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Review

Antibiotic stewardship: does it work in hospital practice? A review of the evidence base

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ABSTRACT

Background: Guidelines for developing and implementing stewardship programmes include recommendations on appropriate antibiotic use to guide the stewardship team's choice of potential stewardship objectives. They also include recommendations on behavioural change interventions to guide the team's choice of potential interventions to ensure that professionals actually use antibiotics appropriately in daily practice.
Aims: To summarize the evidence base of both appropriate antibiotic use recommendations (the 'what') and behavioural change interventions (the 'how') in hospital practice.
Sources: Published systematic reviews/Medline.
Content: The literature shows low-quality evidence of the positive effects of appropriate antibiotic use in hospital patients. The literature shows that any behavioural change intervention might work to ensure that professionals actually perform appropriate antibiotic use recommendations in daily practice. Although effects were overall positive, there were large differences in improvement between studies that tested similar change interventions.
Implications: The literature showed a clear need for studies that apply appropriate study designs—(randomized) controlled designs—to test the effectiveness of appropriate antibiotic use on achieving meaningful outcomes. Most current studies used designs prone to confounding by indication. In the process of selecting behavioural change interventions that might work best in a chosen setting, much should be learned from behavioural sciences. The challenge for stewardship teams lies in selecting change interventions on the careful assessment of barriers and facilitators, and on a theoretical base while linking determinants to change interventions. Future studies should apply more robust designs and evaluations when assessing behavioural change interventions. **M.E.J.L. Hulscher, Clin Microbiol Infect 2017;23:799**

Introduction

To help curbing antibiotic resistance in hospitals, better use of current agents is warranted (https://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf). Antibiotic stewardship programmes are developed to optimize antibiotic use while striking a balance between the potent ability of antibiotics and their potentially hazardous effects for the collective of present and future patients [1].

Antibiotic stewardship can be seen as 'a coherent set of actions designed to use antimicrobials in ways that ensure sustainable access to effective therapy for all who need them' [2].

Guidelines and policy statements for developing and implementing stewardship programmes include recommendations on appropriate structural or system preconditions that should be met when embarking on stewardship (http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-stewardship/resource-materials/ and http://www.nice.org.uk/guidance/ng15) [3–7]. These include, for example, the establishment of a multidisciplinary antibiotic stewardship team that includes specified and compensated core members; an administratively supported, necessary infrastructure to track

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antibiotic use; and availability of local guidance, i.e. local diagnostic and therapeutic antibiotic guidelines or a list of restricted antibiotics.

Guidelines and policy statements also include recommendations to guide the activities of the established stewardship team. These recommendations encompass two intrinsically different aspects of stewardship: the 'what' and the 'how.' A first set of stewardship recommendations guides the team's choice of potential stewardship objectives ('what to aim for?'). These recommendations describe appropriate antibiotic use in hospital inpatients regarding indication, choice of drug, dose, route or duration of treatment. Examples of such appropriate antibiotic use in individual patients are provided in Table 1.

Unfortunately, literature on the performance of recommended care in daily practice consistently shows the failure to translate evidence into practice [8]. This is also true for the performance of appropriate antibiotic use. For example, a cross-sectional point-prevalence study in 22 Dutch hospitals (1890 patients treated with antibiotics for a suspected bacterial infection) showed that in 50% of patients, empirical therapy was changed to pathogen-directed therapy after culture results became available (streamlining); therapy was correctly switched from iv to oral therapy in 32% [9]. To successfully bridge this evidence-to-practice gap, a second set of stewardship recommendations guides the team's choice of potential interventions to ensure that professionals actually use antibiotics appropriately in daily practice. In other words, these recommendations provide advice on how to change the behaviour of individual prescribers so that patients, throughout their hospital stay, actually receive—if indicated and at any moment—appropriate antibiotic treatment. These are the behavioural change interventions that either directly or indirectly (i.e. by changing the system or organization) target the professional and overall restrict or guide the more effective use of antibiotics (Table 1).

Here we aim to summarize the current literature on the evidence base of both appropriate antibiotic use recommendations (the 'what') and behavioural change interventions (the 'how') in hospital practice (Fig. 1).

Appropriate antibiotic use

Guidelines are important tools in defining appropriate patient care. They reflect the current state of knowledge and provide recommendations for clinical practice. The Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases are, for example, important professional societies that develop guidelines for various infectious diseases (http://www.idsociety.org/IDSA_Practice_Guidelines/ and https://www.escmid.org/escmid_library/medical_guidelines/escmid_guidelines/). The key recommendations within guidelines can be translated into so-called quality indicators (QIs) to measure whether antibiotics are used appropriately in daily patient care. QIs are 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality, and hence change in the quality, of care provided' [10]. QIs can refer to recommended structures, processes or outcomes of care.

Table 1
Examples of recommendations to guide activities of stewardship team [7]

Recommended appropriate antibiotic use
• Streamlining or de-escalation of therapy.
• Parenteral to oral conversion.
• Dose optimization.
Recommended behavioural change interventions
• Prospective audit with intervention and feedback.
• Education.
• Antimicrobial order forms.

During the past decade, many governmental and professional associations have developed QIs for various healthcare settings to measure and compare the appropriateness of patient care [11,12]. We recently published a systematic literature review of published QIs describing appropriate antibiotic use in hospitalized adult patients. In addition, we described the methodologic approaches used to develop and validate the QIs [13]. Fourteen studies were included, in which 200 QIs were described: 17 structure and 183 process indicators. In almost 60% of these studies a Delphi procedure was performed to reach consensus on appropriate use among a multidisciplinary team of experts. The most frequently mentioned indicator (in 71% of the included studies) concerned prescribing guideline-concordant empirical antibiotic therapy, followed by a timely switch from iv to oral therapy (64%), drawing at least two sets of blood cultures (57%) and change to pathogen-directed therapy after culture results become available (57%). Most QIs were disease specific: they were developed for lower respiratory tract infection, urinary tract infection or sepsis. Only five studies (36%) tested the clinimetric properties (e.g. measurability, reliability, case-mix stability) of the QIs; 65% of the tested QIs were considered valid. One QI set was designed for hospitalized children and neonates [14]. The QI set developed by the Drive AB group is the most comprehensive (http://drive-ab.eu/wp-content/uploads/2014/09/WP1A_Final-QMs-QIs_final.pdf). Validation of these QIs is, however, necessary before using them in daily practice. Van den Bosch *et al.* [9,15] developed and subsequently validated a QI set that can be generically used to measure whether antibiotics are used appropriately in the treatment of all bacterial infections in hospitalized adult patients.

Does appropriate antibiotic use work?

To assess whether appropriate antibiotic use impacts patient outcomes (e.g. mortality, length of stay), adverse events, costs and bacterial resistance rates, we previously published a systematic review of the evidence base of 14 QIs defining appropriate antibiotic use (Table 2) [16].

We identified 145 studies with data on nine of the 14 selected QIs [16]. Overall, the quality of evidence was low, and heterogeneity between studies was moderate to high. Low-quality evidence showed significant benefits for one or more of the four outcomes selected, for six QIs: empirical therapy according to guidelines, de-escalation of therapy, switch from iv to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics and bedside consultation [16]. For example, following guideline recommendations in the administration of empiric antibiotics appeared to be associated with improved clinical outcomes as well as reduced costs, frequency of adverse events and mortality (40 articles included). Evidence of effects was less clear for three QIs: adjusting therapy according to renal function, discontinuing therapy on the basis of lack of clinical or microbiologic evidence of infection and having a local antibiotic guide. We did not find articles for the remaining QIs [16].

In this review, the impact of appropriate use was assessed for 14 QIs separately. In practice, several care recommendations are usually performed simultaneously (care bundle). The combined effect of performing various appropriate use recommendations together could therefore be larger than performing a single recommendation [17].

The literature shows that there is a clear need for studies that apply appropriate study designs to test the effectiveness of appropriate antibiotic use on achieving meaningful outcomes. A minority of studies currently included in the literature applied a (randomized) controlled design. Most studies used a case–control study or cohort design. Such studies are prone to confounding by