Antibiotic stewardship

Measuring and improving antibiotic use in hospitals

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Summary in English

Since their discovery in the twentieth century, antibiotics have improved patient outcomes and provided health care opportunities. The effectiveness and easy availability of antibiotics, however, has led to overuse, causing bacteria to develop resistance against antibiotics. Along with the emergence of antibiotic resistance, the steady decline in the discovery of new antibiotics creates one of the greatest current threats to human health. Antibiotic Stewardship Programs (ASPs) have been designed to monitor and improve the appropriateness of antibiotic use, which has been shown to be beneficially associated with patient outcomes, adverse events, resistance rates and costs.

In **Chapter 1** we introduced the three building blocks for a successful ASP: stewardship prerequisites, stewardship objectives and improvement strategies. We emphasized the importance of proper monitoring of antibiotic use in hospitals and described different methods available to measure and feedback on in-hospital antibiotic use, ranging from continuously monitoring quantitative antibiotic use at an institutional level, to performing point-prevalence studies (PPS) on the appropriateness of antibiotic use in individual patients. In addition, we emphasized the importance of tailoring improvement activities based on local barriers, since performance might be hindered by a variety of barriers, and barriers in one setting may not be present in another. The chapter ends with an overview of research questions addressed in this thesis.

In **Chapter 2**, we systematically developed a survey based on the three building blocks for ASPs. The systematic literature search resulted in 57 potentially relevant articles and two additional checklists, from which a total of 955 survey questions were selected and categorized. The final survey consisted of 46 questions. Using this survey, we evaluated the current state of antibiotic stewardship in 80 Dutch acute care hospitals. The response rate was 80% (n=64), indicating a reliable reflection of the current situation in Dutch acute care hospitals. Ninety-four percent of hospitals had established an antibiotic stewardship team ("A-team"). Nine percent received dedicated IT support. Fifty-one percent of the teams were financially supported, with a median of 0.6 FTE per team (0.1 – 1.8). Each participating hospital carried out stewardship improvement strategies, but the level of activity differed. The majority of A-teams monitored the use of restricted agents (91%), therapeutic drug monitoring (TDM) (65%), bedside consultation (56%) and IV-to-oral switch (53%). Other stewardship objectives were monitored in only one third of the hospitals. Fifty-eight percent of the hospitals provided education to residents and 28% to specialists.

Similarly, **Chapter 3** describes the current state of ASP in acute care hospitals in four European countries: the Netherlands, Slovenia, France and Italy. Survey response rates were 80% (n= 64), 86% (n=25), 45% (n=97) and 66% (n=41), respectively. A formal ASP program was present mainly in the Netherlands (91%) and France (84%). Presence of a stewardship team ranged from 42% in France up to 94% in the Netherlands. Lack of salary support for stewardship teams was an issue in all four countries: salary was provided in 12% in Italy up to 68% in France, but often this was not sufficient to optimally develop and maintain ASPs. Furthermore, the countries varied substantially in the use of 'prospective monitoring and advice' as a strategy to improve stewardship objectives.

Overall, there was variation between and within countries in the prerequisites met, and the objectives and improvement strategies chosen. Despite the many efforts made in the last years to fight antibiotic resistance and implement antibiotic stewardship at the national and international level, our survey showed that there is room for improvement.

A requirement for an effective stewardship program is the ability to measure the appropriateness of antibiotic use in individual patients. An acknowledged method to measure the quality of antibiotic use is the use of quality indicators (QIs). QIs are measurable elements of practice performance which can be used to assess the quality of antibiotic care provided. In the past decade, many QIs have been designed to measure the quality of antibiotic care provided. In **Chapter 4** we performed a systematic review to assess the currently available QIs for appropriate antibiotic use in hospitalized adult patients. Fourteen studies were included in the literature review, describing a total of 200 QIs: 17 structure and 183 process indicators. The most frequently mentioned QIs concerned empirical antibiotic therapy according to the guideline (71% of studies), switch from IV to oral therapy (64% of studies), drawing at least two sets of blood cultures and change to pathogen-directed therapy based on culture results (57% of studies). Moreover, we assessed the development methodology and validation procedures of these QIs. A (RAND)-modified Delphi procedure was used in the majority of studies (57%). Six studies took outcome measures into consideration during the procedure. Only five out of fourteen studies (36%) tested the clinimetric properties of the QIs in practice; 41 of the 63 tested QIs (65%) were considered valid for use in the clinical setting. Overall, the set of QIs developed by the Drive AB group and the set of QIs developed by van den Bosch et al. were the most comprehensive, but only van den Bosch et al. had validated their QIs in a clinical setting. Therefore, we recommend in comparable settings to apply the set of QIs by van den Bosch et al. to measure and feedback on in-hospital antibiotic use.

Another acknowledged method to measure antibiotic use in ASPs is the use of quantitative data. In **Chapter 5** we performed a retrospective observational study, measuring overall systemic antibiotic use at specialty-level over a 1-year period in fourteen university and non-university hospitals in the Netherlands. For this purpose the most frequently used metrics to measure and benchmark antibiotic use were applied: defined daily dose (DDD) and days of therapy (DOT). We observed a large variation in antibiotic use between and within hospitals, and a low correlation between DDD and DOT as metrics of total antibiotic use in hospitalized adult patients. Likely, this was caused by differences in organisational factors, data sources, data registration and data extraction. In our opinion, a clear understanding of these factors, together with a uniform and transparent approach in defining organizational units within hospitals, and uniform data sources, registration and extraction procedures are necessary for reliable measurement and valid comparison of antibiotic use using quantitative data. Therefore, we provided a list with recommendations on how to reliably measure quantitative antibiotic use on a specialty level in order to support an ASP.

In **Chapter 6** we performed a cluster-randomized multicenter study to assess the difference in effect on length of hospital stay (LOS) and days of antibiotic therapy (DOT) between three recommended methods to measure and feedback information on hospital antibiotic use, when used as the first step of a stewardship intervention. The methods were: 1) measurement and feedback on quantity of antibiotic use (DDD, DOT) from past year's hospital pharmacy data versus feedback on performance scores from point prevalence studies using either 2) validated or 3) non-validated quality indicators (QIs). First, stewardship teams performed the measurements and received a feedback report for both clusters in their hospital. Second, teams were trained to apply a structured approach, using an implementation tool, to systematically develop and perform setting-specific stewardship improvement strategies based on the feedback reports. The geometric mean of LOS of the entire patient group, corrected for national secular trends, decreased from 9·5 days (95% CI 8·9 – 10·1, 4245 patients) at baseline to 9·0 days (95% CI 8·5 – 9·6, 4195 patients) after the intervention (p<0·001), but no significant differences were found between the three measurement and feedback methods. Similar results were found for total, IV and restricted DOT. Even though no difference in effect was found between the methods, the Overall use method was scored by the stewardship teams as least effective for ASP purposes, compared to the PPS-ECDC and PPS-QI. Apparently, information on quantitative data made it more difficult to select improvement targets. Importantly, more consistent use of the stewardship implementation tool resulted in a larger decrease in total DOT, IV DOT and restricted DOT, underlining the importance of a structured approach to stewardship.

Subsequently, in **Chapter 7,** we conducted a cost-benefit analysis alongside the cluster-randomized multicenter study, from a hospital perspective, to estimate the costs associated with the study intervention, specified for each of the three recommended methods to measure and feedback information on hospital antibiotic use, in relation to economic benefits of the intervention, in terms of reductions in LOS and DOT. Based on a model estimation the benefit-to-cost ratios for one cluster during a 20 month intervention period were estimated at 17.8 for the overall use method, 14.7 for the PPS-QI method and 17.1 for the PPS-ECDC method. We showed that structured stewardship interventions are potentially cost-beneficial, and that the type of measurement and feedback method had limited impact on the total costs, but rather the time investment in the development and performance of stewardship strategies.

In **Chapter 8** we applied a modified-RAND Delphi procedure to systematically develop a set of four actionable quality indicators and one quantity metric for appropriate antibiotic use in adult ICUs, including: 1) perform at least two sets of blood cultures before start of empirical systemic therapy; 2) perform therapeutic drug monitoring in patients treated with vancomycin or aminoglycosides; 3) perform surveillance cultures if selective digestive or oropharyngeal decontamination is applied at the ICU; 4) biannual face-to-face meetings between ICU and microbiology staff in which local resistance rates are discussed; and 5) quantitative antibiotic use at the ICU expressed in DOT. In addition, we developed an implementation toolbox, containing a list of 24 possible barriers that lead to poor performance on the selected indicators, and a list of 37 improvement strategies to overcome these specific barriers, with the aim to support stewardship actions aiming at increasing performance on antibiotic use. Clinimetric properties of the indicators and feasibility in daily practice of electronic data reuse from the EHR or PDMS will be tested during an evaluation study in the near future.

In **Chapter 9** we tested the appropriateness of antibiotic use with two sets of QIs at an ICU of a general teaching hospital in the Netherlands: 1) the set of QIs for appropriate antibiotic use at the ICU developed in Chapter 8, and 2) QIs on Selective Digestive tract Decontamination (SDD) based on recommendations by the Dutch Working Party on Antibiotic Policy (SWAB). We showed that, overall, patients received the recommended antibiotic care with regard to performing blood cultures, determining blood levels in time when indicated, obtaining surveillance and colonisation cultures, and stopping third generation cephalosporin therapy. However, there was considerable room for improvement in doubling the dose of SDD if required by protocol. The QIs can be used by hospital stewardship teams to determine where to set priorities to improve the appropriateness of antibiotic use and where to acknowledge successes in critically ill patients admitted at the ICU.

In **Chapter 10** we summarized our most relevant findings and discussed them against the background of current literature. Furthermore, we provided a general conclusion and recommendations for future research and extension of antibiotic stewardship programs.