Development of quality indicators for appropriate antibiotic use in daily hospital practice
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Chapter 7

General Discussion
Many interventions and programs have been developed to improve appropriate antibiotic use in terms of choice of antibiotics, dosing, timing, de-escalation and duration. These programs are collectively known as antibiotic stewardship programs. Their objective is to optimize clinical outcome while minimizing unintended consequences of antibiotic use, including the emergence of resistance. An essential tool for an effective stewardship program in order to set priorities and focus improvement is the ability to reliably measure the appropriateness of hospital antibiotic use. This thesis focused on the development and validation of quality indicators for appropriate antibiotic use.

**MAIN FINDINGS**

**Comprehensiveness and compliance of local guidelines**

A local, evidence-based hospital antimicrobial guide is an essential element of a successful stewardship program. In chapter 2 we studied the local antimicrobial guides in use in Dutch hospitals. These local guides are either based on the national antimicrobial guide (SWAB-ID), customized to local resistance patterns, or they are locally developed (non-SWAB-ID). In this chapter we compared the local SWAB-ID based with the non-SWAB-ID based antimicrobial guides for comprehensiveness and compliance with the national treatment guidelines. Fifty antimicrobial guides, covering nearly every hospital in the Netherlands, were scored on 199 pre-specified items to measure comprehensiveness (e.g. presence of recommendations for prophylaxis or the empirical treatment of cholangitis) and on 35 items to measure compliance with the national guidelines (e.g. the recommendation for empirical treatment of diverticulitis). The non-SWAB-ID based local antimicrobial guides (n=27) were significantly less comprehensive (p < 0.001) and less guideline-compliant (p < 0.001) than the SWAB-ID based local antimicrobial guides (n=23). In conclusion, the use of a local version of the national SWAB-ID antimicrobial guide significantly increased comprehensiveness and guideline-compliance of the local antimicrobial policy and the recommendations more often trace back to evidence-based guidelines. A comprehensive national guideline like SWAB-ID with customized local versions may therefore help to improve the quality of local antimicrobial policy.

**Development of quality indicators**

In 2010 SWAB published a guideline regarding antimicrobial use in hospitalized patients with sepsis. Sepsis is a common reason for clinicians to start with antibiotics, and severe sepsis or septic shock is a frequent cause of in-hospital mortality. In chapter 3 we utilized this guideline to develop a concise set of QIs to assess the appropriateness of antimicrobial use in hospitalized adult patients with sepsis, using the RAND-modified Delphi method. A Dutch multidisciplinary panel of 14 experts appraised and prioritized 40 key recommendations derived from the SWAB Sepsis guideline during two rounds of questionnaires with an in-between face-to-face consensus meeting. This systematic, stepwise method, which combined evidence with expert opinion, led to a concise and therefore feasible set of 5 QIs. The final set comprised the following QIs: obtain cultures; prescribe empirical antimicrobial therapy according to the national guideline; start intravenous drug therapy; start antimicrobial treatment within one hour; and streamline antimicrobial therapy.

The aim of the study described in chapter 4 was to develop generic quality indicators which can be used to measure the appropriateness of antibiotic use in the treatment of all bacterial infections in hospitalized non-ICU adult patients. The RAND-modified Delphi consensus method was once again used, after potential QIs were retrieved from the literature. An international multidisciplinary expert panel (17 experts) appraised and prioritized 24 potential QIs in two questionnaire mailings with an in-between face-to-face consensus meeting. Eleven QIs were selected. Nine QIs described recommended care at the patient level (i.e. process indicators): (1) take at least two sets of blood cultures before starting systemic antibiotic therapy, (2) take cultures from suspected sites of infection before starting systemic antibiotic therapy, (3) prescribe empirical antibiotic therapy according to the local guideline, (4) change empirical to pathogen-directed therapy as soon as culture results become available, (5) adapt dose and dosing interval of systemic antibiotics to renal function, (6) switch systemic antibiotic therapy from intravenous to oral antibiotic therapy after 48 -72 hours on the basis of the clinical condition and when oral treatment is adequate, (7) document antibiotic plan in the case notes at the start of systemic antibiotic treatment, (8) perform therapeutic drug monitoring, and (9) discontinue antibiotic therapy if infection is not confirmed. Two structure QIs describing recommended care at the hospital...
level were: (10) a local antibiotic guideline should be present in the hospital, and (11) these local guidelines should correspond to the national antibiotic guidelines. Both sets of QIs (sepsis and generic) can be used in antibiotic stewardship programs to determine for which aspects of antibiotic use there is room for improvement.

**Quality indicators in daily hospital care**

After developing QIs, assessing their feasibility in daily practice is essential before using them to measure the quality of antibiotic use. This was done in chapter 5 by testing important clinimetric characteristics. An observational multicenter study was conducted and during a point prevalence measurement in 22 hospitals in the Netherlands on non-Intensive Care Unit departments, 1890 patients treated with antibiotics for a suspected bacterial infection were included. In this cohort we tested the measurability, applicability, reliability, room for improvement and case mix stability of the generic QIs. Low applicability (≤ 10%) was found for the QIs ‘perform therapeutic drug monitoring’, ‘adapt antibiotic dosage to renal function’ and ‘discontinue empirical therapy in case of lack of clinical and/or microbiological evidence of infection’. For the latter, we also found a low inter-observer agreement (kappa < 0.4). The QI ‘a local antibiotic guideline should be present’ showed a low improvement potential. In conclusion, seven of the eleven QIs (i.e. six process indicators and one structure indicator) had sound clinimetric properties. Case-mix correction was necessary for most process QIs. For all QIs, we found ample room for improvement and large variation between hospitals.

**Quality indicators and outcome**

Chapter 6 addresses the impact of appropriate antibiotic use on length of hospital stay (LOS). Data from the previously described observational multicenter study in 1890 patients using antibiotics for a suspected bacterial infection were used. Appropriate antibiotic use in hospitalized patients was defined by the previous six process QIs with sound clinimetric properties. From the patients’ medical charts data were retrieved to determine QI performance scores and LOS. Performance scores were calculated for all QIs separately (appropriate =1 and inappropriate =0) in a patient, divided by the number of QIs that applied to that specific patient. We divided the sum scores into two groups: low sum scores (0 – 49%) versus high scores (50 – 100%). LOS was log-transformed before analyses were done, to satisfy normality assumptions, and afterwards LOS was back-transformed for presentation as geometric mean (95% confidence interval). Multilevel mixed model analyses, correcting for confounders, were used to correlate QI performance (single and combined) with LOS. Sub-analyses were conducted for patients with community-acquired versus hospital-acquired infections. The geometric mean for LOS was 10.2 days form community acquired infections and 11.9 days for hospital-acquired infections. An association was demonstrated between an early i.v.-oral switch and a shorter LOS (geometric mean 6.5 vs. 11.2 days; P <0.001), also in both subgroups separately. Similarly, a high sum score was associated with a shorter LOS (geometric mean 10.1 vs. 11.2 days; P = 0.002), this also applied to the subgroup community-acquired infections (geometric mean 9.7 vs. 10.9 days; P = 0.007). The subgroup hospital-acquired infections (geometric mean 11.6 vs. 12.2 days; P = 0.08) was smaller and although patients with a high sum score had a shorter length of hospital stay, the difference was not significant. In conclusion, appropriate antibiotic use, defined by validated process QIs in hospitalized patients with a suspected bacterial infection, seems to reduce length of stay with one day and therefore positively contributes to patient outcome and healthcare costs.

**IMPLICATIONS FOR PRACTICE**

**Using guidelines as a starting point for quality measurement**

In this thesis guidelines play an important role as starting point for defining and measuring appropriate antibiotic use. In chapter 2 we measured comprehensiveness and guideline-compliance of the Dutch local hospital antibiotic guides. The use of an online, locally customized version of the national SWAB-ID antimicrobial guide significantly increased comprehensiveness and compliance with the national guidelines of the local antimicrobial policy. Studies show that developing trustworthy evidence-based clinical practice guidelines requires considerable expertise, time and financial support, which are mostly not available at the local level. It takes specific
national or local contexts into account, for example the local resistance patterns of causative microorganisms of common bacterial infections, while limiting unnecessary duplication. The national antibiotic guide SWAB-ID, which can be locally customized, is a good example of this concept, and the fact that the local version is web-based makes it easy to update the guide when for instance resistance rates are changing. Therefore, we concluded that a comprehensive national guideline like SWAB-ID with customized local versions may be an effective way to improve the quality of local antimicrobial policy.

Clinical practice guidelines are thought to be a cornerstone of evidence-based medicine and the international interest in clinical practice guidelines seems to increase, but the development of guidelines is not without problems. Scientific evidence for recommendations is sometimes lacking, misleading or misinterpreted, and guidelines do not always meet the basic quality requirements. Therefore, rigorous methods for developing trustworthy evidence-based guidelines have been proposed, but less attention has been paid to the updating of a guideline or the development of guideline-based quality indicators. A previous study by our group showed that two years after publication of a national guideline for complicated urinary tract infections, relatively high inadequate coverage rates of many guideline recommended empiric treatment options were found. This was probably because of continuously changing resistance rates and differences between the epidemiology of uropathogens assumed in the guideline and those in real-life. Even when recommendations are based on a low level of evidence, antibiotic guideline adherence has been shown to be associated with a decreased mortality, a lower admission rate to the intensive care unit (ICU) and a shorter length of hospital stay. In addition, we previously also showed that guideline adherence seems to increase coverage rates without prescribing unnecessary broad regimens. This is an important finding, because decreasing the use of broad-spectrum antimicrobial therapy is an important strategy to contain the emergence of resistant pathogens.

**Delphi procedure**

Guidelines and international literature are used to systematically develop QIs. In a systematic review regarding the Delphi method, Boulkedid et al. concluded that a systematic and well-designed procedure increases the reliability and rigorousness of the QIs, and they created a practical guidance with recommendations for planning, using and reporting the Delphi procedure. In chapter 3 and 4 we developed indicators using an international, multidisciplinary panel of experts, with discussion of the indicators in a face-to-face meeting, in accordance with the recommendations of Boulkedid et al.

When raising the question “what is appropriate care?” the answer will often be “it depends”. It depends on which clinicians are asked, where they live and work, what weight is given to different types of evidence and endpoints, and whether one considers the preferences of patients and families and level of resources in a given health system. Therefore, consensus methods are used to define appropriate care and these are important when assessing many aspects of performance in which evidence alone is insufficient to support recommendations. The RAND modified Delphi procedure is well-known and valuable for achieving consensus about issues or potential QIs when no QIs existed previously. However, the reproducibility of the Delphi procedure is not perfect; it varied from good to only moderate agreement, although the reliability of panels rating the same set of QIs was generally regarded as acceptable. Ayanian et al. showed that over a 1000 surveyed physicians agreed for most indications with the Delphi expert panel about the appropriateness of coronary angiography after myocardial infarction, concluding that well-designed expert panels can closely reflect the views of practicing physicians. Experts contribute to the content validity of indicators, because they interpret potential QIs and integrate results from studies with information from daily clinical practice. We carefully planned the Delphi procedures and the expert panel: an international multidisciplinary panel in which all the main specialism’s involved in antibiotic treatment were represented. This was important, because studies have shown that panel composition influences ratings, and heterogeneity in a panel contributes to different point of views about quality of care, which improves the result of the Delphi procedure.

Hutchings et al. evaluated the differences between a consensus procedure with or without a face-to-face meeting. They found that indeed opinions of experts are more likely to shift when groups meet. Discussion resulted in more complete or revised indicators that incorporated the views of multiple experts.
Generic Quality Indicators in Clinical Practice

In chapter 4 and 5 we developed a valid set of generic QIs that can be used to measure, on the patient level, the various steps in the process of antibiotic use along the entire antibiotic pathway. An important strength of these indicators is that they are generic indicators, and therefore enable comparison of antibiotic use between different infectious diseases across hospitals. Instead of developing sets for each infectious disease, one set can be used to measure the appropriateness of antibiotic use in all infectious diseases. Moreover, it creates opportunities to measure the appropriateness of antibiotic use for more rare infectious diseases or when there are two possible diagnoses. Another potential benefit is that generic indicators are less susceptible to change, because they contain little detailed information.

To test the QIs in daily clinical practice, we collected data by means of a point prevalence measurements and a retrospective chart review. Subsequently, to calculate the QI scores, data were inserted into constructed algorithms which captured the denominator and numerator of the QIs, to minimize variation when interpreting appropriateness of antibiotic use. This was a major strength of this study and can possibly also explain the high inter-observer reliability. Although these algorithms have been rigorously constructed, disadvantages of the method we used are that the assessment was retrospective, and potentially justified deviations from the guideline may have been disregarded, because not all data that influenced the physicians’ choices may have been documented properly, especially in complex treatment decisions. Collecting the data prospectively might have diminished this problem.

Generic Quality Indicators and antibiotic stewardship programs

These QIs can potentially represent “Antibiotic Stewardship QIs”, which can be used by inpatient treatment facilities and governmental agencies for the purposes of estimating appropriate antibiotic use in acute care hospitals. There is a great need for such reliable process indicators for acute care hospitals throughout the world, because stewardship programs have been implemented at many hospitals in Europe and the United States, but assessing the true effect of these programs remains challenging and their impact has been difficult to measure. Measures to evaluate antimicrobial stewardship can be split up in four main categories: patient outcomes, unintended consequences, antimicrobial utilization and costs, and process measures.

Antimicrobial utilization and costs are frequently used to assess stewardship programs, among others because this type of data is easy to collect and this measure is of great interest for administrators to justify these programs. Generally there is a great interest in outcome measures, because they reflect multiple aspects of appropriate care and improving outcome is the ultimate goal of the intervention. Only, evaluating patient outcome data without some quantification of associated stewardship process strategies is not useful. So none of these measures is on its own adequate enough to assess the overall effect of stewardship programs. The combination of both process QIs and related patient-specific outcomes seem to be the most effective way to measure appropriate antibiotic care.

Therefore in chapter 6 we addressed the impact of appropriate antibiotic use, defined by process QIs, on length of hospital stay (LOS). Controlling for multiple confounders, appropriate antibiotic use, defined by the sum score of these process QIs, was associated with a reduction in length of stay with one day.

It seems obvious that appropriate antibiotic use improves clinical outcome. However, measuring clinical outcome is challenging, since a large sample size is needed to find clinically meaningful and significant differences in outcome measures like mortality, ICU admission or readmission rate. Furthermore, outcomes like clinical response, LOS or mortality depend on various aspects of care and not only on the quality of antibiotic care. Controlling for confounding factors is essential and can be difficult.

IMPLICATIONS FOR FUTURE RESEARCH

Measuring appropriate antibiotic use

In this thesis, the method of using generic quality indicators (QIs) for measuring appropriateness of antibiotic use has been validated. An important limitation of this measurement method was that the used method, retrospectively hand searching medical charts, was very resource- and labor intensive. To enhance future use of the QIs, we evaluated possibilities for data reduction. First, we examined the relationship between the various process QIs, with the ultimate aim of reducing the number of QIs, and therefore the data collection necessary to assess ‘appropriate antibiotic use’. Since no correlation was found, this was not possible. Second, we explored what the consequences would be when
certain patient characteristics (allergies, pregnancy, and previous ESBL infection) were not taken into account when computing the algorithm of the QI ‘prescribe empirical antibiotic therapy according to the guideline’. We found that excluding allergies, pregnancy and previous ESBL infection changed the mean performance rate by only 1.1%. Omitting these parameters when assessing this QI could be considered, however still many patient parameters are needed when assessing appropriate antibiotic use. In conclusion, major data reduction to assess ‘appropriate antibiotic use’ using quality indicator performance was not possible and so this method is still very labour intensive. Therefore, it is important to consider other methods.

Various methods can be used to evaluate the quality of antibiotic use in hospitals, ranging from continuously monitoring overall antibiotic use at an institutional- or organizational level, to performing point prevalence studies in which appropriate use is assessed in individual patients, like was done in this thesis. These methods have never been compared and at present, the (cost) effectiveness of these various options in measuring and providing feedback information on antibiotic use is unknown. Future research should evaluate whether monitoring of overall antibiotic use suffices, or whether labor-intensive and costly point prevalence studies are cost-effective when evaluating appropriateness of antibiotic use. At present, a multicenter study is being performed in 21 hospitals in the Netherlands, comparing the (cost) effectiveness of the various approaches (the "IMPACT"-study, funded by ZonMw).

Improving appropriateness of antibiotic use

Only a few studies, including ours, have been performed to examine the relationship between multiple care processes and the clinical outcome of hospitalized patients treated with antibiotics for a suspected bacterial infection. For patients with lower respiratory tract infections (LRTI), complicated urinary tract infections (UTI) or sepsis, guideline-concordant empirical therapy has been associated with a lower mortality rate, a decreased admission rate to the intensive care unit (ICU) and a decreased length of hospital stay. However, the most important conclusion of chapter 6 was that not adherence to one single QI, but that adherence to a combination of concomitant processes of care resulted in a decreased duration of hospital stay.

These findings show resemblance with the concept of ‘care bundles’: a small set of practices (usually three to six elements), that, when implemented together, are expected to result in better outcome than when implemented individually. Care bundles should be delivered by one healthcare team at one point in time. An example is the bundle for the management of severe sepsis and septic shock. Extensive guidelines for these diseases have been summarized into the ‘Surviving Sepsis Campaign (SSC) care bundles’, including a bundle that should be completed within 3 hours and another bundle that must be done within 6 hours. Using the SSC bundle led to sustained quality improvement in sepsis care and was associated with reduced mortality. Also checklists have been shown to increase patient safety and patient outcome. The reasoning behind a checklist is the same as a bundle. For example, in general surgery, implementation of a comprehensive multidisciplinary SURGical Patient Safety System (SURPASS) was associated with an absolute reduction in surgical complications of 10.6 percentage points and a decrease of the mortality rate of 0.7 percentage points. Similarly, the introduction of a checklist to improve patient care among gynecologic oncology patients resulted into a decreased length of stay of one day.

The next step, after developing and validating generic QIs, is the embedding of appropriate antibiotic use in daily clinical practice. The development of an antibiotic checklist can be a tool for this implementation. The construction of the antibiotic checklist can be based on the generic quality indicators. Translating the QIs into checklist items would mean separating the QIs into two bundles: an early checklist (day 0) with the QIs ‘perform blood cultures’, ‘perform culture from suspected site of infection’, ‘prescribe empirical therapy in accordance with the national guideline’, ‘documentation of antibiotic plan’, followed by a checklist on day 3 with the QIs ‘switch from intravenous to oral treatment’ and ‘adapt empirical to pathogen-directed antibiotic therapy as soon as culture results become available’. At present, a cluster-randomized multicenter trial has started in the Netherlands to analyse the effect of the introduction of this antibiotic checklist on intensive care unit (ICU)- and hospital stay, adequate treatment, mortality rates, total antibiotic use, and costs (funded by ZonMw).
In conclusion, this thesis provides a reliable set of generic QIs which can be used to measure and improve the various steps in the process of antibiotic use in the hospital, by identifying for which step along the antibiotic pathway there is room for improvement. In particular adherence to a combination of generic process QIs, rather than just one QI, seems to decrease the duration of hospital stay. Prospective studies are needed to determine whether interventions that improve compliance with these validated generic QIs, could improve patient outcome and reduces length of stay.

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