Improving the Process of Antibiotic Therapy in Daily Practice

Interventions to Optimize Timing, Dosage Adjustment to Renal Function, and Switch Therapy

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Background: Timely administration of the first dose, dosage adjustment to renal function, switch from intravenous to oral administration, and streamlining are important aspects of rational antibiotic prescription. The goals of this study were to investigate all of these variables, compare them with predefined quality standards, and implement improvement with specific interventions.

Methods: At the departments of internal medicine, surgery, and neurology and the emergency department of a tertiary referral university medical center, all consecutive patients receiving therapeutic antibiotics were enrolled. Dosages, timing of first doses, dosing intervals, administration routes, and adjustment of the chosen drug to clinical data were investigated. After the preintervention period, barriers to change were identified, followed by specific interventions and a postintervention measurement.

Results: In the preintervention and postintervention periods, 247 and 250 patients were enrolled, receiving 563 and 598 antibiotic prescriptions, respectively. The mean time from the order to first dose at the wards improved from 2.7 to 1.7 hours in potentially severe cases (P= .003). Dosage adjustment to renal function remained unchanged at 45% vs 52% (P=.09) of cases where necessary. Switching of therapy from intravenous to oral improved from 46% to 62% (P=.03) and was performed a mean of 1.6 days earlier (P=.002). Streamlining was performed correctly in most cases, and thus no interventions were necessary.

Conclusions: Timing of antibiotic therapy and switch therapy may be improved with a combination of interventions. To improve poor adjustment of dosing to renal function, other strategies are needed. In our setting, streamlining was already correct in most cases.

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Evidence-based medicine is the driving force behind the development of practice guidelines. However, introduction of such guidelines does not automatically lead to changes in clinical behavior. Up to the present, guidelines in antimicrobial therapy have mainly focused on the choice of antibiotic. However, many other steps in the process of administration are important to guarantee optimal use of a drug, including the right drug at the right moment at the right dosage for the right patient. Timely administration of the first dose, dosage adjustment to renal function, switch from intravenous (IV) to oral administration, and streamlining to narrow-spectrum antibiotics are important aspects of antibiotic use. Prompt administration of antibiotics improves morbidity, mortality, and length of hospital stay. A previous study in our hospital showed that a median delay of 5 hours after presentation of a patient with a severe infection to the emergency department could be improved to 3 hours. To our knowledge, timely administration of antibiotics has not been studied at sites other than the emergency department. Beside the timing of the first dose, administration of antibiotics in proper intervals across 24 hours is important, especially for drugs with a short half-life. Dosage adjustment of antibiotics to renal function is recommended for many antibiotics that are eliminated by the kidney. Avoiding dose adjustment to renal function leads to unnecessarily high plasma concentrations, adverse drug reactions, unnecessary costs, and an increased workload for nurses. Actual dose adjustment of antibiotics to renal function has, until recently, been neglected in quality assessment studies. Switch therapy, the change from IV to oral treatment, has been studied by several investigators in the past few years, and it has been shown to save costs, shorten length of hospital stay, and decrease adverse reactions of IV administration, with equal therapeutic out-
come. Conceptually, streamlining of antibiotics (ie, adjustment to narrow-spectrum therapy, guided by culture reports) can contribute to the prevention of antimicrobial resistance, and an adequate system of reporting culture results can support this process.

The goal of our study was to investigate all aforementioned key variables of the administration of antibiotics. On the basis of this investigation, key processes amenable for improvement were identified, and an intervention for optimization was designed and performed.

**METHODS**

**STUDY DESIGN**

The study was performed at a tertiary referral, university hospital (953 beds). All antibiotic prescriptions at the wards of internal medicine (general internal medicine, nephrology, gastroenterology, endocrinology, and oncology), surgery, and neurology (a total of 234 beds) were investigated during 2 separate periods. A total of 248 nurses, 92 residents, and 95 specialists were involved in the study. The study was performed with the permission of the hospital’s ethics committee.

Data were collected in a preintervention and a postintervention period of 3 months each. We aimed to enroll 250 patients in each period.

**DATA COLLECTION**

Patients eligible for inclusion were identified by checking all antibiotic prescriptions in the prescription charts of all admitted patients. The case records of patients to whom antibiotics were prescribed were investigated, and the prescribing resident was interviewed. All consecutive patients with a first prescription of antibiotics were included. Patients who started antibiotic therapy at wards that did not participate in the study, outside the hospital, or for prophylactic reasons were excluded. At the surgical ward, patients who started antibiotic therapy in the intensive care unit and in the operating room were also excluded. An antibiotic course was defined as therapy with 1 or more antibiotics.

Timely administration of the first dose was investigated in the emergency department as well as at the wards. The time of first administration and the administration schedule were obtained from the prescription chart. If the order for antibiotic therapy was given in the emergency department, the time of arrival in the emergency department was used to calculate the delay of initiation of therapy. If the order was given at the wards, the time at which the physician gave the order was obtained by searching the records or asking the prescribing physician. A maximum delay of 4 hours between arrival and administration in the emergency department and a maximum delay of 2 hours between order and administration at the wards were accepted as allowable. Indications for antimicrobial therapy were divided into a requirement for immediate administration (ie, potentially severe infections) and a less urgent start of administration (ie, mild infections). Cases were defined as mild if there was no fever, hypotension, tachypnea, or tachycardia and if the leukocyte count was within the reference range. All other cases were considered potentially severe.

The ideal dosing interval was defined as 24 hours divided by the number of daily doses. The actual dosing intervals were compared with this ideal interval, and the largest deviation per prescription was expressed as a percentage of the ideal interval.

Renal function was calculated according to the formula of Cockroft and Gault. A table for dosage adjustment to renal function, based on generally accepted data, was available for prescribers in the antibiotic guidelines booklet of the hospital. The prescribed dosage was compared with this guideline.

Criteria for switch from IV to oral therapy that were based on the literature were proposed. These criteria were discussed with the infectious diseases specialists, microbiologists, and pharmacists of the hospital. The basic consensus criteria used in this study are given in Table 1. The day the patient fitted these criteria was defined as the per-protocol moment to switch from IV to oral therapy.

To study the correctness of streamlining, culture reports were collected, and advice given by microbiologists or infectious diseases physicians were recorded. These were compared with the spectrum of the antibiotic actually prescribed at the moment all of the above information was available to the prescriber.

**INTERVENTION STRATEGY**

After the first registration period, barriers to change were identified and, with the support of key persons in the process, strategies to solve these problems were designed. Implementation strategies for improvement consisted of audit and feedback for all physicians and nurses in peer discussions, combined with mailings; stickers providing additional recommendations to be inserted into all antibiotic guidelines booklets; adjustment of computers; and presentations by a local opinion leader (continuous medical education strategy). No specific advice was given at the individual prescription level.
Table 2. Demographic Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Preintervention (n = 247)</th>
<th>Postintervention (n = 256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wards, No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal medicine</td>
<td>166</td>
<td>165</td>
</tr>
<tr>
<td>Surgery</td>
<td>56</td>
<td>60</td>
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<tr>
<td>Neurology</td>
<td>25</td>
<td>25</td>
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<tr>
<td>Sex, M/F</td>
<td>123/124</td>
<td>110/140†</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>58.4</td>
<td>58.9</td>
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<tr>
<td>No. of courses</td>
<td>298</td>
<td>299</td>
</tr>
<tr>
<td>No. of prescriptions</td>
<td>563</td>
<td>598</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>80</td>
<td>52‡</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>65</td>
<td>91‡</td>
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<tr>
<td>Abdominal infections</td>
<td>48</td>
<td>56</td>
</tr>
<tr>
<td>Sepsis without definite focus/intravascular infection</td>
<td>20</td>
<td>28</td>
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<tr>
<td>Skin/wound infections</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Fever and neutropenia</td>
<td>20</td>
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<tr>
<td>Fever without definite focus</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Abscess/empyema/osteomyelitis/ arthritis</td>
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<tr>
<td>Miscellaneous</td>
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<td>16</td>
</tr>
<tr>
<td>Positive blood culture findings</td>
<td>57</td>
<td>52</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are expressed as number of courses.
†P < .05.
‡P < .01.

STATISTICS

Previous studies have shown that of all patients starting with IV antibiotics, approximately 40% were eligible for switch therapy.14,15 To reach a statistical power of 80%, a total of 90 patients eligible for switch therapy was necessary to prove a 20% increase in correct use (α = .05). By considering that 10% of the initial prescriptions are given orally, a total of 230 patients was needed in every group. In the case of timing, 50 patients in each group proved enough statistical power in a previous study from our hospital.6

Time intervals were tested nonparametrically with the Mann-Whitney test. Standard errors of the mean are displayed unless stated otherwise. Categorical variables were tested with the χ² test. A P value less than .05 was considered statistically significant.

RESULTS

PREINTERVENTION RESULTS

During the preintervention period, 247 patients were included who received 298 courses of antibiotics, consisting of a total of 563 antibiotic prescriptions. The distribution across the wards is given in Table 2. Two hundred seventeen orders for antibiotic courses were given at the wards; 62 were given in the emergency department, 11 in the operating room, and 8 in the intensive care unit.

The mean time from arrival in the emergency department to administration of the first dose of antibiotics was 4.2 ± 0.3 hours. Of these 58 patients, 33 (57%) received their first dose within 4 hours after arrival and 11 (19%) received their first dose in the emergency department.

At the wards, the interval between the physician’s order to the first administration of antibiotics was measured. Exact prescription and administration times were known for 151 courses. The mean delay between the order and administration of first dose of antibiotics at the wards was 4.1 ± 0.5 hours. Of 113 potentially severe cases, therapy was started in 66 (58%) within 2 hours of prescription (mean, 2.8 ± 0.3 hours).

Exact administration schedules were known for 498 prescriptions. A maximum deviation of more than 50% of the ideal interval was found in 39 cases (8%). In 57 prescriptions (11%), this deviation was more than 33%. For oral administration, 37 (21%) of 180 were found to deviate by more than 33% and 26 (14.4%) were found to deviate by more than 50% of the ideal interval.

Renal function could be calculated for 225 of the 247 patients. A renal clearance rate less than 50 mL/min, at which most antibiotics require dosage adjustment, was present in 69 (31%) of 225 patients. These patients received 168 antibiotic prescriptions, of which 129 required dosage adjustment according to the antibiotic guidelines. The antibiotic dosage was adjusted in 58 (45%) of 129 cases. The risk for nonadjustment in elderly patients with an impaired renal function was high; the odds ratio for nonadjustment was 3.1 in patients older than 65 years and 2.9 in those older than 75 years. The finding of a serum creatinine level less than 1.13 mg/dL (<100 µmol/L) may have masked an impaired renal function in elderly patients with low body weight. The odds ratio for nonadjustment of the antibiotic dose in patients with a creatinine clearance less than 50 mL/min and a serum creatinine level less than 1.1 mg/dL (<100 µmol/L) was 3.7. The percentage of failures in adjusting the dosage did not differ significantly between the specialties studied.

Antibiotic therapy was started intravenously in 184 of 247 first courses. Of these, 98 were eligible for switch to oral administration. This procedure was actually performed in 45 cases (46%), with a mean delay of 2.3 days after the per-protocol moment. Unjustified switch therapy was performed in 1 case.

One or more culture specimens were taken in 225 (91%) of 247 cases. Streamlining of antibiotic therapy was considered necessary in 71 (51%) of 139 cases with positive culture results. It was not performed in 6 cases (8%), and it was performed improperly in 6 cases (8%). In 59 cases (83%), streamlining was performed correctly (Figure 1).

BARRIERS TO CHANGE

After the first registration period, the barriers to change were identified, in cooperation with all departments involved (Table 3). Barriers to change timely administration were several. At the wards, misinterpretation of the urgency of the order by nurses was often a serious cause of delay. In addition, time-consuming diagnostic procedures and decision making may have given nurses the unjustified feeling of nonurgent therapy. Transfer from the emergency department to the wards was an important cause of delay, if the patient had not received the first dose at the emergency department.

Administration schedules used by nurses for orally administered antibiotics were not ideal for 2 main reasons. First, oral antibiotics were often given during the meals. Second, the dosing interval during the night was
with positive results. Appropriateness of streamlining can only be assessed in case of cultures.

Consideration of a serum creatinine value less than 1.6 mg/dL (140 µmol/L) as safe, no application of the formula of Cockroft and Gault, and no easy access to this formula. The most important factor for not switching from IV to oral therapy was the unawareness of the principles of switch therapy. In most cases, streamlining was optimal, and no barriers to change could be defined.

INTERVENTIONS

To address the identified barriers to change, all physicians and nurses were approached by a direct mailing, and the residents in internal medicine were addressed regularly during weekly courses in infectious diseases. Discussions with peers were held, and audit and feedback of the findings were performed for all physicians and nurses in attendance of a local opinion leader. In addition, the following specific interventions were made.

- To improve timely administration, several antibiotics were made more easily available at the wards.
- To improve dosage adjustment to renal function, all computers on the wards were equipped with the Cockroft and Gault formula on the desktop (Excel spreadsheet, 1997; Microsoft Corp, Redmond, Wash). Surgeons received a sticker with a table containing estimated renal function, which could be pasted into their antibiotic guidelines booklet.
- To improve switch therapy, all physicians received stickers with switch criteria and possible oral alternatives to IV therapy (Table 1) to be pasted into their antibiotic guidelines booklet. Nurses were instructed to remind physicians of the possibility of switch after 2 days of IV therapy.

POSTINTERVENTION RESULTS

The numbers of patients, courses, and prescriptions and the distribution across the wards were similar to those of the preintervention period. Only the male-female distribution was significantly different. The basic demographic data of both periods are given in Table 2.

The mean delay from the order to first dose in the wards decreased from 4.1 to 2.6 hours (P = .003) for all cases and from 2.7 to 1.7 hours in potentially severe cases (Figure 2A; P = .003). The number of first administrations in the wards within 2 hours in potentially severe cases increased from 60% to 76% (P = .02). For mild infections, the mean delay in the wards decreased from 8.0 to 4.1 hours (Figure 2B; P = .006). The number of first administrations that were postponed until the next day decreased from 9 to 3 cases.

The mean time from arrival in the emergency department to first dose decreased from 4.2 to 3.9 hours (Figure 2C; P = .30). The number of first doses administered in the emergency department increased from 19% to 27% (P = .13).

Exact administration schedules were known for 549 prescriptions in the postintervention period. A maximum deviation of more than 33% of the ideal administration interval decreased from 11% to 8% of the prescriptions (P = .045). For oral administration, deviations from more than one third of the interval improved from 21% to 14% (P = .056).

In the postintervention period, creatinine clearance was less than 50 mL/min in 68 (30%) of 224 pa-
Dosage adjustment was necessary in 129 of 171 antibiotic prescriptions. The number of correct prescriptions improved from 45% to 52% ($P = .09$).

Of 180 first courses that were started as IV therapy in the postintervention period, 97 were eligible for switch therapy. The amount of IV courses with appropriate switch to oral administration increased from 46% to 62% ($P = .03$). The switch was performed 1.6 days earlier, with a mean of 0.7 days after the per-protocol moment ($P = .002$). In 3 cases, a switch back to IV therapy had to be performed, in one case because of noncompliance, in another because of clinical deterioration on the day of the switch, and in another because the choice of drug was not adequate.

**COMMENT**

The present study shows that timely administration of the first dose, dosing intervals, dosage adjustment to renal function, and switch to oral administration of antibiotics are amenable for improvement in a hospital setting. By using a combination of audit and feedback, peer discussions, continuous medical education, stickers to
be pasted into the antibiotic guidelines booklets, and provision of computer programs, the timing of first dose, dosing intervals, and switch therapy could be improved. However, dosage adjustment to renal function and timely initiation of therapy in the emergency department showed a small, nonsignificant improvement. Remarkably, streamlining was already performed correctly in most cases, and the number of failures was too small to achieve improvement.

An evident improvement was achieved in the delay to first dose administration at the wards. In contrast to our emergency department, no previous intervention had been performed on this subject at the wards. The delay to administration of the first dose in cases of a mild infection decreased by almost 50%. First doses postponed until the next day were less frequent, as a sign of rising awareness of the importance of antibiotic timing.

The increasing tendency to switch from IV to oral administration underscores the requirement of correct dosing intervals of orally administered antibiotics. In the Netherlands, drug orders are usually given as number of doses per day, rather than in terms of a fixed dosing interval. In most cases, the actual times of administration are chosen by the nurse, rather than by the physician. Nurses often try to give medication with meals to avoid inconvenient hours. The huge deviations from the ideal interval that may arise are especially undesirable in drugs with short serum half-lives. This problem improved significantly in our postintervention period.

The prevalence of patients with a severely impaired renal function was very high in the present study. Thus, a large number of prescriptions required dosage adjustment, but we were not yet successful at improving actual dose adjustment with our interventions. Especially in elderly patients with serum creatinine levels in the reference range, renal function is erroneously considered normal, and overdosing of antibiotics occurs. Correct dosing will decrease adverse reactions, the workload for nurses, and antibiotic selection pressure, and will save money. The presence of a pharmacokinetics service, which monitors dosing of selected drugs on request, apparently does not prevent erroneous dosing in a large number of cases. Computerized support systems linking patient data and laboratory results to prescriptions may help to solve the problem.

In most studies on switch therapy, an infectious diseases consultation at the individual patient level governs the decision to switch to oral treatment. This is considered the most effective method to implement switch therapy. However, this method is costly and time-consuming, and not all patients who receive antibiotics may be traced and covered. Therefore, we implemented a stringent protocol aimed at the attending physician, without infectious diseases consultation unless in cases of doubt. In the present study, the percentage of patients eligible for switch therapy was slightly higher than in other studies, probably because not all of the departments were involved in the study. With combined interventions, we could improve switch therapy to 63% of applicable cases, suggesting that significant improvement can be achieved with relatively cheap but multifaceted interventions.

The motto “never change a winning team” may lead to continuation of broad-spectrum antibiotic therapy, even when this is unnecessary with respect to the causative microorganism. However, in the present study, optimal streamlining was performed in most cases, and thus no intervention was found necessary. The adherence to streamlining rules most likely is the result of an active policy of unsolicited infectious diseases consultations in every case of positive blood culture results and to previous continuing education of residents.

Often the beneficial effects of educational campaigns are observed to be short-lived unless the intervention is continuously applied. However, during the 3-month postintervention period, there was no decrease in adherence to the various aspects of the intervention (data not shown). Since the previous intervention in the emergency department7,8 4 years earlier, the delay to first dose administration had increased slightly. Repeated measurements are required to monitor continued adherence in the future.

CONCLUSIONS

The present study demonstrates that interventions supported by a multidisciplinary team consisting of infectious diseases specialists, medical microbiologists, clinical pharmacists, nephrologists, and nurses leads to improvements of the process of care in administration of antibiotics.

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