Improving the prescription of antibiotics: focus on surgical prophylaxis

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Improving the prescription of antibiotics: focus on surgical prophylaxis

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op het gebied van de Medische Wetenschappen

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Doe wat je denkt niet te kunnen

Eleanor Roosevelt

Voor mezelf

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Introduction

Introduction

The discovery and development of antimicrobial drugs was a major step forward in medical history. With the increasing use of these drugs however, the antimicrobial resistance started to develop and nowadays, this is a global problem in the battle against infectious diseases.[1-3] Although many mechanisms are responsible for the development of antimicrobial resistance, overconsumption and inappropriate use of antibiotics is the main driving force.[4,5] The development of new antimicrobial drugs is not keeping pace and able to tackle the problem of antimicrobial resistance. In addition, new antimicrobials only give temporarily relief.[6,7] This gradually led to the global awareness that controll of the use of antibiotics is concern for health care authorities, and national and international initiatives were launched to provide recommendations for antibiotic use.[8]

The Netherlands has a tradition of prudent use of antibiotics which until now has resulted in a low incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant pneumococci.[9]

To formalize and advocate the prudent use of antibiotics in the Netherlands, the Dutch Working Party on Antibiotic Policy (SWAB) was established in 1996 by the Dutch Society of Infectious Diseases (VIZ), the Dutch Society of Medical Microbiology (NVMM), and the Dutch Society of Hospital Pharmacists (NVZA). One of the spearheads of the SWAB was to promote the optimal antibiotic use by guideline development for antimicrobial treatment and prophylaxis. Regarding optimal use, antibiotic choice, duration and timing are essential elements of quality improvement. In case of antibiotic choice, the primary goal is to choose an antibiotic which is effective against the presumed causative pathogen and at the same time avoid an unnecessary broad spectrum to prevent selective pressure as much as possible. Drugs with low toxicity profiles are preferred. Regarding the duration of treatment, treatment must be long enough to guarantee a good clinical outcome but in the mean time be as short as possible to avoid unnecessary toxicity, development of resistance and high costs. Proper timing of administration of antibiotics is a keystone of antibiotic management in prophylaxis as well as in therapy. It improves morbidity and mortality as well as length of stay of patients with community-acquired pneumonia and sepsis.[10,11] In surgical prophylaxis, correct timing proved to be essential for its efficacy.[12,13] In addition to these factors, issues of dosage adjustment to renal function, streamlining, and switching from the intravenous to the oral route need to be addressed in a good antibiotic policy.

Data from an intervention study conducted in a large University hospital in the Netherlands in 1992 showed that there was still room for improvement in prophylaxis as well as in therapy.[14,15] This conclusion was in line with many other studies in the international literature.[16-19] In the Dutch study, the implementation of new guidelines for surgical antimicrobial prophylaxis and improvement of logistics resulted in a reduction in the use of broad-spectrum antibiotics, a shorter duration of prophylaxis, an improvement of timing and in cost-savings.[15,20]
Unfortunately, only a few intervention studies have focused on patient outcome, and opponents fear that reducing the use of antibiotics in prophylaxis could lead to decreased efficacy, resulting in a higher incidence of surgical site infections. Therefore, there was a need for studies not only taking into account process outcome but also patient outcome.
In 1996, the National Institute for Public Health and the Environment (RIVM) and the Dutch Institute for Healthcare Improvement (CBO) had started a national surveillance program of surgical site infection, PREZIES, that could serve as a basis for intervention studies.[21] In 1998, the SWAB initiated the development of national guidelines for surgical prophylaxis, which were released in 2001. A joint application of researchers at SWAB , RIVM and CBO resulted in a grant awarded by the Prevention program of The Netherlands Organization for Health Research and Development (ZonMw). Thus the Surgical Prophylaxis and Surveillance of Wound Infections project (Chirurgische profylaxe en Postoperatieve wondinfecties, CHIPS) could be started in 1999. The aim of the CHIPS project, a multi-center intervention project, was to improve the quality of prophylaxis in Dutch hospitals and to promote prudent use while maintaining or improving the efficacy of prophylaxis in reducing surgical site infections (SSI). This would be achieved by implementing the SWAB guideline for surgical prophylaxis and using audit and feedback as implementation methods and monitoring patient outcome by recording the incidence of surgical site infections before and after the intervention. The results of these studies are presented in this thesis.

Chapter 1.1 describes the methodology of the CHIPS study and the process of hospital recruitment. In Chapter 1.2, the SWAB guideline for surgical prophylaxis that served as the basis for implementation of recommendations in the CHIPS study is presented.

Chapter 2 reports on the presence and use of local guidelines for surgical prophylaxis in the participating hospitals prior to the intervention and asks the question how healthcare workers adhere to them. In this analysis the question is investigated what potential barriers to guideline adherence are.

Chapter 3 deals with the question what the effect of implementation of the SWAB guideline for surgical prophylaxis on the quality of prophylaxis is in the participating hospitals. Antibiotic choice, duration and timing of antibiotic use before and after an intervention were investigated by using time-series analysis.

Chapter 4 reports on the effect of the intervention on the incidence of surgical site infections and addresses the question whether a prudent antibiotic policy does or does not have a detrimental effect on the antibiotic efficacy.

Chapter 5 describes the relationship between several aspects of surgical prophylaxis and patient outcome in terms of incidence of surgical site infections following total hip implant surgery. Special attention is paid to timing of the first dose of prophylaxis.

Chapter 6 addresses the effect of the implementation of recommendations on antibiotic therapy, in an University Hospital. The study focuses on timely administration of antibiotics next to dosage adjustment to renal function, antibiotic streamlining and intraveneus to oral switch therapy.

Chapter 7 is an inventory of the barriers to change that were encountered in the CHIPS prophylaxis study and their correlation to the process outcome. Here, we explored whether general recommendations can be formulated that can predict the success of implementation.

In the general discussion, the results of the study are put into perspective, and recommendations for the future are discussed.

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Chapter 1.1

The set up of a multi-center intervention study to improve the quality of surgical prophylaxis using a national surveillance network

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Introduction

The aim of the CHIPS multi-center intervention project (Surgical prophylaxis and surveillance), was to improve the quality of prophylaxis in Dutch hospitals and to promote prudent use while maintaining or improving the efficacy of prophylaxis in reducing SSI. This was intended by implementing a framework of national guidelines on surgical prophylaxis of the Dutch Working Party on Antibiotic policy (SWAB). The study was conducted within the PREZIES-surveillance network.

The PREZIES surveillance system of SSI in The Netherlands

The PREZIES national surveillance network of nosocomial infections is an initiative of the Dutch Institute for Healthcare Improvement and the Centre for Infectious Disease Epidemiology of the National Institute for Public Health and the Environment (RIVM). It is funded by the Ministry of Health, Welfare and Sports.[1] Within this network, surveillance of surgical site infections has been operational since 1996 and contact between the network's coordination center and the hospitals is maintained through the hospital infection control committees. Members of these committees are infection control practitioners (ICPs), medical microbiologists, clinicians and pharmacists.

In the Netherlands, every hospital employs one ICP per 250 beds. These ICPs have a background as a nurse or as a medical laboratory technician and 1.5-year's training at accredited infection prevention schools. Most ICPs are supported by medical microbiologists [2] although ICPs often operate independently. ICPs occupy an unique position in the hospital by having access to various patient data and having contacts with many different medical disciplines. Although the assessment of SSI is also done by physicians, the final responsibility for the surveillance in the PREZIES surveillance network lies with the ICP.[1] The PREZIES coordination center supports ICPs through a telephone-helpline, workshops and occasional visits.

Study design of the CHIPS-project

The CHIPS-project was a prospective multi-center intervention study with a before-and-after design without a control group.

The study consisted of five parts with the following time schedule:
- Recruitment and enrollment of hospitals, preparation of data collection (6 months).
- Pre-intervention study (6 months).
- Educational intervention (6 months).
- Post-intervention study, identical to the pre-intervention study (6 months).
- Data analysis (12 months).

Recruitment of hospitals and local setup

As a representation of the 135 Dutch hospitals, a minimal sample of eight hospitals was considered for the CHIPS study. These were geographically spread over the country and included small and large hospitals as well as teaching and non-teaching hospitals. The hospitals had to commit themselves to perform surveillance of SSI according to the PREZIES-protocol including post discharge surveillance (PDS).[1] Since CHIPS could not provide any financial support, the motivation of hospitals to participate was of utmost importance. Hospital staff had to be convinced of the value of the study for their own quality program and hospitals were expected to facilitate data collection and to create a climate for intervention.
At the time of the grant application, the infection control committees of the PREZIES hospital network were approached for their interest in the study. In order to recruit a maximum number of hospitals, the following strategy was designed at the start of the CHIPS-project:
- A letter containing a synopsis of the protocol was sent to the infection control committees of all Dutch hospitals. Hospitals could obtain the complete study protocol on request.
- Hospitals of the PREZIES-network that did not respond to this letter but had expressed an earlier interest in the study, were contacted by telephone.
- A workshop was organized for potential participants. ICPs, microbiologists, and members of infection control committees from all hospitals that had showed an interest in the study were invited to attend.
- The CHIPS study group established a multidisciplinary advisory committee, comprising academic opinion leaders from different universities (a surgeon, an anesthetist, a medical microbiologist, a pharmacist and an infection control specialist), which was invited to participate in the workshop.

- At the workshop, both scientific and practical aspects of the study were discussed and hospital representatives had the opportunity to sign up for the study.
- Principal responsibility in each hospital was assigned to an appointed specialist. This specialist, along with the CHIPS researchers and the ICP, organized meetings within the hospitals. At these meetings, written information about the CHIPS-study and the method of data collection was to be distributed among anesthetists, surgeons, nurses and pharmacists.
- After approval by the clinicians and the hospital management, contracts for participation were signed.
- Special local conferences were organized for surgeons and anesthetists since their role during the intervention was considered crucial.
- Confidentiality was secured at patient level.
- Approval of the hospital medical ethics committee was not considered mandatory since the study would be part of the hospital's quality improvement program.

Out of the 58 PREZIES hospitals that were contacted in 1998, initially 32 (55%) had been interested in participating in an intervention study on prophylaxis (Figure 1). However, in 1999 when the grant for the CHIPS-study had been obtained, there was a very low response from the correspondence sent to all 135 hospitals in the Netherlands. Eighteen hospitals answered favorably (13%) of which only two were PREZIES hospitals that had been interested in 1998. Of these hospitals only those performing post-discharge surveillance (PDS) were consulted by telephone (28 hospitals), and thereafter another eight of these (29 %) reconsidered participation (Figure 1). The other 20 PREZIES-hospitals declined participation for various reasons: no priority issue (nine hospitals), lack of time of the local ICP (four hospitals), vacancy for ICPs (two hospitals) and not specified (five hospitals). A total of 26 hospitals requested the complete studyprotocol.

In July 1999, the infection control teams from the 26 hospitals that had requested the protocol were invited to the organized study workshop. Fourteen teams attended the workshop. The teams consisted mainly of ICPs (n=11/14) and medical microbiologists (n=3/14), one pharmacist and two medical specialists (one surgeon and one infectious diseases specialist). The complete CHIPS study team and four out of the five advisory committee members were present at the workshop.

Due to logistics in the hospitals and the absence of hospital staff during summer holidays, the approval by the clinicians and the hospital management took several months. By the end of 1999, 6 months behind schedule, 13 hospitals actually

started the study, of whom only four had attended the workshop. Ten hospitals withdrew due to the anticipated extra workload for the local ICP, four were unable to start due to ICP-vacancies or sick leave of the local ICP. One hospital, that had declined to participate in 1999, joined the study after a new ICP was appointed.
Ten of the 13 hospitals that participated in the study had previous experience with surveillance in the PREZIES-network. There were four small hospitals (<400 beds), six medium size hospitals (400-800 beds) and three large hospitals of more than 800 beds, including two university hospitals. The 13 participating hospitals were geographically spread throughout the country.
In eight hospitals, the local conferences for the medical specialists were coordinated by the investigator and the ICP of the project. In five hospitals, the local ICPs preferred to inform the specialists themselves.

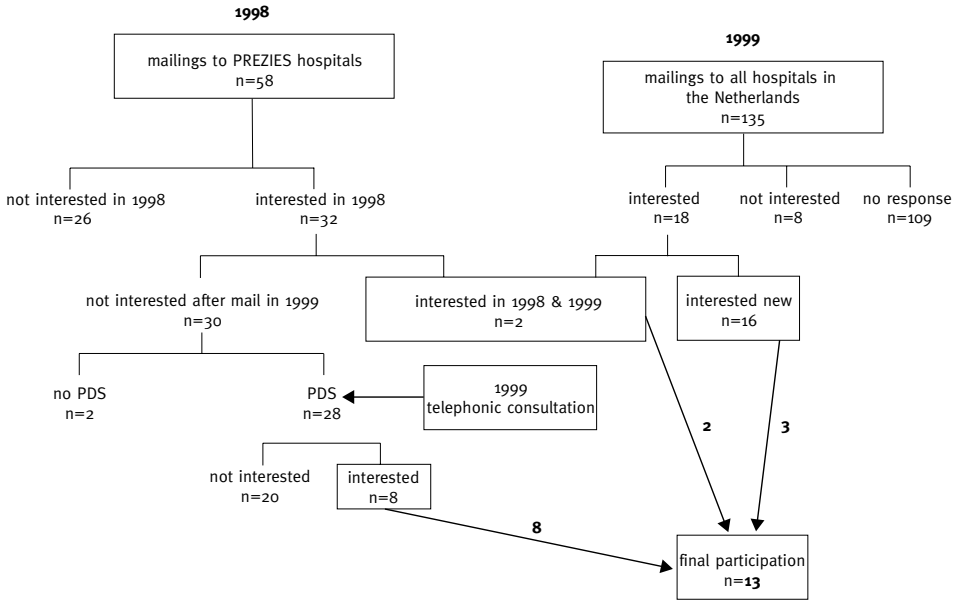

Figure 1. Recruitment of hospitals for the CHIPS project

Response to inquiries requesting willingness to participate in the CHIPS-study. In 1998 letters were sent to hospitals participating in the PREZIES-SSI-network. In 1999 an outline of the CHIPS study was sent to all hospitals in the Netherlands (including hospitals of the PREZIES-network). Hospitals of the PREZIES-network that performed post-discharge surveillance (PDS) but that did not respond to the inquiry were approached by phone. Those without post-discharge surveillance were not contacted.

Selection criteria for surgical procedures

Frequently performed procedures in four major medical disciplines were selected. (Table 1). To avoid disagreement regarding indication for prophylaxis, procedures were selected for which antibiotic prophylaxis is generally recommended in the international literature.[3-5] To ensure that prophylaxis was recorded and not antibiotic therapy, procedures with suspected or established infection prior or during surgery were excluded. Non-elective procedures were also excluded.
To facilitate the evaluation of the quality of surgical prophylaxis broken down by medical discipline or by hospital, a minimum number of 20 procedures per discipline was aimed at before and after intervention in each hospital.
Hospitals were free to choose which of the selected procedures they included in the study. During the study it became clear that orthopaedic procedures were overrepresented. The minimum number of 20 procedures required per discipline was attained in all but one hospital (vascular surgery).

Table 1. Selected procedures according to estimated wound class (Altemeier) [26] for inclusion in the CHIPS-study.

Clean	Clean-contaminated
Total hip replacement	Vaginal hysterectomy (with or without vaginal repair)
Femoral hemiprosthesis	Abdominal hysterectomy*
Reconstruction of the aorta	Colon resection
Femoropopliteal bypass	Anterior resection of the recto-sigmoid
Femorotibial bypass	Abdominoperineal resection of the sigmoid

* depending on the procedure; supravaginal or not, this procedure can be classified as clean or clean-contaminated.

Data collection, data sources and data sets

Data collection of SSI was performed by the local ICPs in each hospital according to the PREZIES protocol.[1] The surgical departments were visited at least twice weekly and this included inspection of the surgical wounds of patients in the wards. SSI were diagnosed according to the criteria of the Centers for Disease Control translated into a Dutch guideline.[6,7] PDS was done until 30 days after discharge,

except for implant surgery for which the PDS surveillance period was extended to one year. Data collection on surgical prophylaxis was performed by the local ICP (10 hospitals) or by the ICP of the project (3 hospitals).
Table 2 shows the set of data collected on SSI. The ICPs entered these data into the standard software program that they used for the ongoing PREZIES surveillance. The parameters that were collected on antimicrobial prophylaxis for the CHIPS study were recorded manually on separate record forms (Table 3).
Source documents were defined as medical records, nursing and anesthetic records, operation protocols and medication charts. In the surgical suite, only drugs that were written down in the anesthetic records were considered to be administered. In the ward, only prescriptions initialed by the nurse were assumed as being administered.
In every hospital a pilot study of five random procedures was conducted. In these pilot studies, the availability and quality of the data collection was evaluated by the investigators. If necessary, the method of data collection was improved.

Table 2. Collected parameters in the CHIPS study concerning SSI

Demography	**Surgery**	**SSI**	**in case of SSI**
Hospital code	date of procedure	Y/N	pus Y/N
date of birth	COTG code of procedure*		wound explored Y/N
gender	type of procedure		superficial or deep
date of admission	duration of procedure		diagnosis surgeon Y/N
date of discharge	surgical wound class		abscess Y/N
ASA-score	antibiotic prophylaxis Y/N elective/urgent code of surgeon *code of resident*		microbiological test performed Y/N *specimen* *isolated micro-organisms* *antibiotic sensitivity of isolates*

* COTG code is a financial administration code of the Dutch Central Organization for Charges in Healthcare in the Netherlands. The code is based on anatomy and surgical maneuvers. Items in italics are optional.

Table 3. Collected parameters concerning antibiotic prophylaxis in the CHIPS study

Demography	procedure	antibiotic prophylaxis
CHIPS code *	date of surgery	generic name of antibiotic(s)
date of birth	COTG-code of procedure	dose
gender	description of procedure	time of administration of antibiotic doses
date of admission	duration of procedure	mode of administration B / I **
date of discharge	elective procedure Y/N	total number of doses
ASA-score	surgical wound class 1-4 antibiotic prophylaxis administered Y/N suspected infection at surgical site prior to surgery Y/N suspected infection at surgical site during surgery Y/N time of induction of anesthesia time of first incision	number of units of an antibiotic per dose allergy to antibiotics Y/N, name of antibiotic topical prophylaxis Y/N

* unique code for every procedure in the study, including a specific hospital code.

** B = bolus, I = infusion

Validation of the data collection

To validate the data collected on SSI, the national validation team of PREZIES visited the participating hospitals once during the study period. A visit lasted one day and consisted of a process and outcome validation. During the validation process, the procedure of inclusion, the method to detect SSI, the handling of criteria for the assessment of SSI and the feedback of surveillance results were evaluated.[8] The outcome validation was carried out as a prevalence-study assessing the 20 most recent cases of patients with a SSI. In addition, five random cases could be submitted to the validation team for discussion. During the validation visits, a very good conformity was found with the collection of SSI data. In two hospitals minor flaws were observed and corrected.

To validate the data collection on antimicrobial surgical prophylaxis, either the investigator (MvK) or the ICP of the CHIPS-study (MR) visited the hospitals every 6-8 weeks. The case record forms were compared with the source documents. At the first visit, a minimum of 25% of the procedures was checked. In the case of

discrepancies, the method of data collection and SSI assessment were discussed and optimized if necessary. During the next validation visit, again 25% of the cases were evaluated. If there were no discrepancies, the outcome of a minimum of 10% of the recorded procedures was validated at subsequent visits. There was a very good conformity on the outcome after two visits in each hospital.

Data processing

The local ICPs sent the SSI data on diskette to the PREZIES-center for checks on data integrity and completeness, and for aggregation. The NNIS risk index, developed by the Centers for Disease Control, was calculated. A wound class of 3 or 4, an ASA score of 3 or more and a duration of surgery longer than the 75th percentile of all procedures in a given category, each added a value of 1 to the NNIS index which could vary from 0 to 3.[9] Data on antibiotic prophylaxis were sent on the record forms to the investigator who entered them in a spreadsheet and checked for consistency.

Data assessment

Process outcome: qualitative and quantitative evaluation of prescription at the patient level including costs.

The investigator performed the evaluation of the quality-of-use of antimicrobial prophylaxis by two methods: comparison with the local hospital guideline and comparison with the SWAB-guideline. To determine the evaluation of adherence to hospital guidelines, the most recent version of local guidelines for surgical prophylaxis, issued by the committees for antibiotic policy, was requested from each hospital. Criteria for this evaluation of adherence are described elsewhere.[10]

To evaluate quality-of-use according to the SWAB-guideline, a modification of the method that has been previously described [11] was sed. Every parameter of prophylaxis, i.e. antibiotic choice, duration, dose, interval and timing, was evaluated separately.

The amount of antibiotics used per hospital was expressed in DDD/ 100 bed-days [12] and DDD/operation.[13] Purchase costs (wholesale) of antibiotics and costs for administration (materials and personnel) were calculated and expressed in Euro. Some

parameters, e.g. timing and duration of prophylaxis, were analyzed quantitatively. The adherence to the local and SWAB -guidelines was analyzed using SPSS for Windows (release 10.0).

Patient outcome: incidence of surgical site infections.
It was hypothesised that improvement in the quality of surgical prophylaxis would result in a similar or reduced incidence of SSI than before the intervention. A power calculation was carried out with a two-sided significance level of 0.05 and a power of 80%. Based on SSI rates of the PREZIES-network for the selected procedures, it was estimated that the mean initial SSI rate would be 7.5 %. At the start of the study it was assumed that the mix of surgical procedures in the pre- and post-intervention study would be similar, that all disciplines would be equally represented and that data from different hospitals could be aggregated. A sample size of 1600 surgical procedures would be needed in the pre- and post-intervention period to detect a statistical significant decrease in SSI rate of 7.5 % to 5.0 %.
To study the relation between the quality-of-use of surgical prophylaxis and the incidence of SSI, the aggregated data of SSI and surgical prophylaxis were analyzed in SAS for Windows (release 8.1; SAS Institute, Cary NC). The databases were aggregated by matching the procedures based on date of birth of the patient, date of admission, date of procedure and date of discharge.

Discussion

The CHIPS-study shows that a national surveillance network for nosocomial infections can serve as an infrastructure to set up an intervention study on the quality of care. There are however pro's and cons of the set-up which are in part related to this network. The collaboration between research groups from medical universities and the national surveillance network on nosocomial infections led to stimulating multidisciplinary team work. On the one hand, the medical research groups had crucial scientific and practical experience with antibiotic intervention policies [13-16] which might have motivated hospitals to participate in this study. On the other hand, the national surveillance network provided a number of hospitals already involved in collaborative efforts with existing systems for recruitment, data collection and data assessment.[1] The involvement of hospital ICPs enabled the study to be performed without extra funding for data managers. The performance of ICPs as

data managers was excellent. The experience of the ICPs in performing surveillance guaranteed the quality of the data collection, as shown by the validation of both the surveillance of SSI and of antimicrobial prophylaxis. ICPs also played a key-role in the recruitment of hospitals which was initiated through the surveillance network and its contacts. A major strength of this study was the multi-center approach of both measurement of the effect on process outcome (quantity and quality of surgical prophylaxis) and on patient outcome (SSI). Most other recent intervention studies on surgical prophylaxis have been performed in a single hospital.[17] [18-21] Only a few studies have been performed in multiple centers, [22,23] or have focused on the correlation between surgical prophylaxis and the incidence of SSI.[24,25]

The study set-up suffered however from several shortcomings. First, because of the lack of funds to support hospitals for the data collection, the CHIPS-team was dependent on the time that the local ICPs could make available to perform the data collection. Vacancies for ICPs and an already high workload in the hospitals was probably the main reason for a relatively low number of participating hospitals after an initial favorable response. Financial support for participating hospitals may therefore be warranted to motivate hospital staff to continue data collection during a relatively long follow-up period. Second, because the recruitment of hospitals was done through the PREZIES network, the primary contacts of the CHIPS team were with ICPs and medical microbiologists. There was no direct communication of the CHIPS-team with surgeons to discuss participation. Although the multidisciplinary advisory committee was present at the first workshop, hardly no surgeons visited this workshop and therefore were not reached at a primary stage of the study. In future studies on prophylaxis, professional societies of surgeons should be approached at an early stage and invited to act as facilitators for recruitment for such a study. They could assign local opinion leaders and launch such a project through their members.

Third, because participation in the study was on a voluntary basis, a selection bias cannot be excluded. Nevertheless, the included hospitals seemed to represent in-patient care in the Netherlands since the number of procedures finally recorded in the recruited hospitals was quite large, different disciplines were represented in different types of hospitals and there was a wide geographic distribution of the hospitals. Fourth, the time-schedule of the study turned out to be too optimistic. Recruitment of hospitals took much more time than was foreseen and also the time needed to obtain approval of all participating medical specialists and the hospital management was much longer. Once the data collection had started, the time

needed to include the required minimum number of 1600 procedures appeared longer than the originally planned six months due to a relatively low incidence of performed procedures in some hospitals. Due to an over-representation of clean procedures (which reflected the PREZIES network) the true SSI incidence in the preintervention period was lower than the estimated incidence used for the power calculation. Therefore the number of recorded procedures had to be increased and the periods of data collection had to be extended. More attempts to increase the inclusion of procedures with a relatively high intrinsic rate of SSI, e.g. intestinal procedures, might have prevented this.
In conclusion, a national SSI surveillance network provided a valuable framework for hospital recruitment, data collection and data management for intervention strategies on surgical antibiotic prophylaxis. However these activities are time-consuming and, without extra financial support for hospitals, are only possible by a strong commitment by all participants. To enhance commitment for such a study, it could be helpful to involve professional associations of surgeons at an early stage.

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Chapter 1.2

Optimization of the antibiotic policy in the Netherlands. SWAB guidelines for perioperative antibiotic prophylaxis

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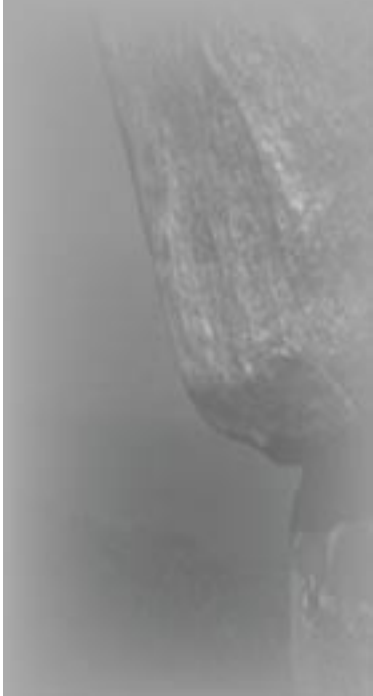

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Abstract

The Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibioticabeleid SWAB) has developed guidelines for perioperative antibiotic prophylaxis in Dutch hospitals.
Prophylaxis is not indicated for all procedures. In particular, patients should be considered for perioperative antibiotic prophylaxis when the procedure is associated with a relatively high risk for surgical site infections or if the development of such an infection would have very serious consequences.
Studies have demonstrated that prophylaxis administered within 2 hours of the start of the procedure is most effective. Short-term, preferably single-dose, prophylaxis was found to be just as effective for most procedures as multiple-dose regimens; the former is to be preferred from the standpoint of cost management and prevention of the development of resistance.
The antibiotic of first choice for perioperative prophylaxis is preferably not an important therapeutic drug, is as selectively active as possible against mircoorganisms expected to cause a surgical site infection and has a half-life which is long enough to make one preoperative dose of the drug to be sufficient.
For the above reasons, cefazolin is often administered as perioperative prophylaxis.

Introduction

The Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibioticabeleid SWAB) develops guidelines for the use of antibiotics in hospitals, with the aim to optimize antibiotic policies and thus to contribute to the control of the development of resistance.[1]
The SWAB guidelines described here for perioperative antibiotic prophylaxis for adults are meant as a framework for the Antibiotic Policy Committees in diverse hospitals. For guidelines for children, see "Blueprint for paediatric antimicrobial therapy".[2]
The guidelines are based on the following important criteria for the use of antibiotics:

1. The indication for prescription of the antibiotic must be correct,
2. The antibiotic must be directed against the expected causative microorganisms,

3. The antibiotic must be administered at the correct time and administration should not last longer than necessary, the spectrum must be as narrow as possible, the antibiotic must be as safe and inexpensive as possible, and it must be possible to administer it via the desired route. At the end of this article there is a list of recommended literature.[3-32]

Definition of perioperative antibiotic prophylaxis

"Perioperative antibiotic prophylaxis" is the administration of an antibiotic for a surgical procedure within a short period of time to prevent postoperative infections at the surgical site (SSI). These SWAB guidelines do not cover all surgical procedures in detail but focus on those which are performed relatively often, those with a relatively high percentage of wound infections, those for which the consequences of a wound infection would be severe and those for which the benefit of prophylaxis has been studied extensively. These guidelines therefore are not presumed to be complete. However on the basis of the general principles outlined in this guideline every hospital can draw up detailed guidelines which are tailored to the local situation. Prophylaxis which is administered as part of a diagnostic procedure falls outside the scope of this guideline.

The use of antibiotics to prevent postoperative infections at the surgical site is generally accepted nowadays. It represents however only a small part of the strategy to prevent these infections. Antibiotics do not compensate for inadequate perioperative care and/or poor surgical techniques. In addition the benefit of perioperative prophylaxis has not been established for all procedures.

Postoperative wounds are classified into different classes according to the system of Mayhall (Table 1). The relevance of this classification system is that there is a difference between classes in the risk that a postoperative infection will develop at the surgical site. The indication for perioperative prophylaxis is determined to a large extent by this risk. That is why wound classification is estimated before surgery: the prophylactic plan is based on this classification.

Table 1. Surgical wound classification (according to Mayhall).[6,32]

Wound Class	Description of the wound
Clean	Elective surgery, primarily closed without drains* Non traumatic, not infected Good asepsis Respiratory, digestive of urogenital tract not opened
Clean-contaminated	Respiratory, digestive or urogenital tract opened under controlled conditions and without unusual contamination Oropharynx opened Vagina opened Genitourinary tract opened in the absence of positive culture of urine Biliary tract opened without suspicion of cholangitis
Contaminated	Open, fresh (less than 6 hours old) traumatic wound Visible spill of faecal material from gastrointestinal tract Opening of urogenital tract in presence of positive culture of urine Opening or perforation of biliairy tract in case of suspected cholangitis Surgery in acute non-purulent inflammated area
Dirty-infected	Traumatic wounds with necrotic material or traumatic wound with corpus alienum Delayed surgery of traumatic wound Perforated organ, faecal contamination Acute inflammation with pus

* The SWAB considers that a wound with a drain left in place for a short time (1-2 days) for drainage of blood or fluid can still be classified as a "clean" wound. This is for example the case for total hip arthroplasty with a so-called Redon drain.

Indications for prophylaxis

Clean wounds

In general prophylaxis is not indicated for procedures where a clean wound is expected (postoperative risk of infection less than 2-5% under normal conditions) (Figure 1). Examples are most procedures in Plastic surgery, Vascular surgery without implant of synthetic materials and without an incision in the groin, and procedures of the ear or nose (without implants).

Despite the low percentage of SSI, there are clean procedures for which a SSI can have such severe consequences that prophylaxis is indicated. This applies for a large number of procedures involving implantation of synthetic materials (Table 2). Implantation of synthetic mesh is as yet not considered by SWAB to be a procedure for which prophylaxis is indicated.

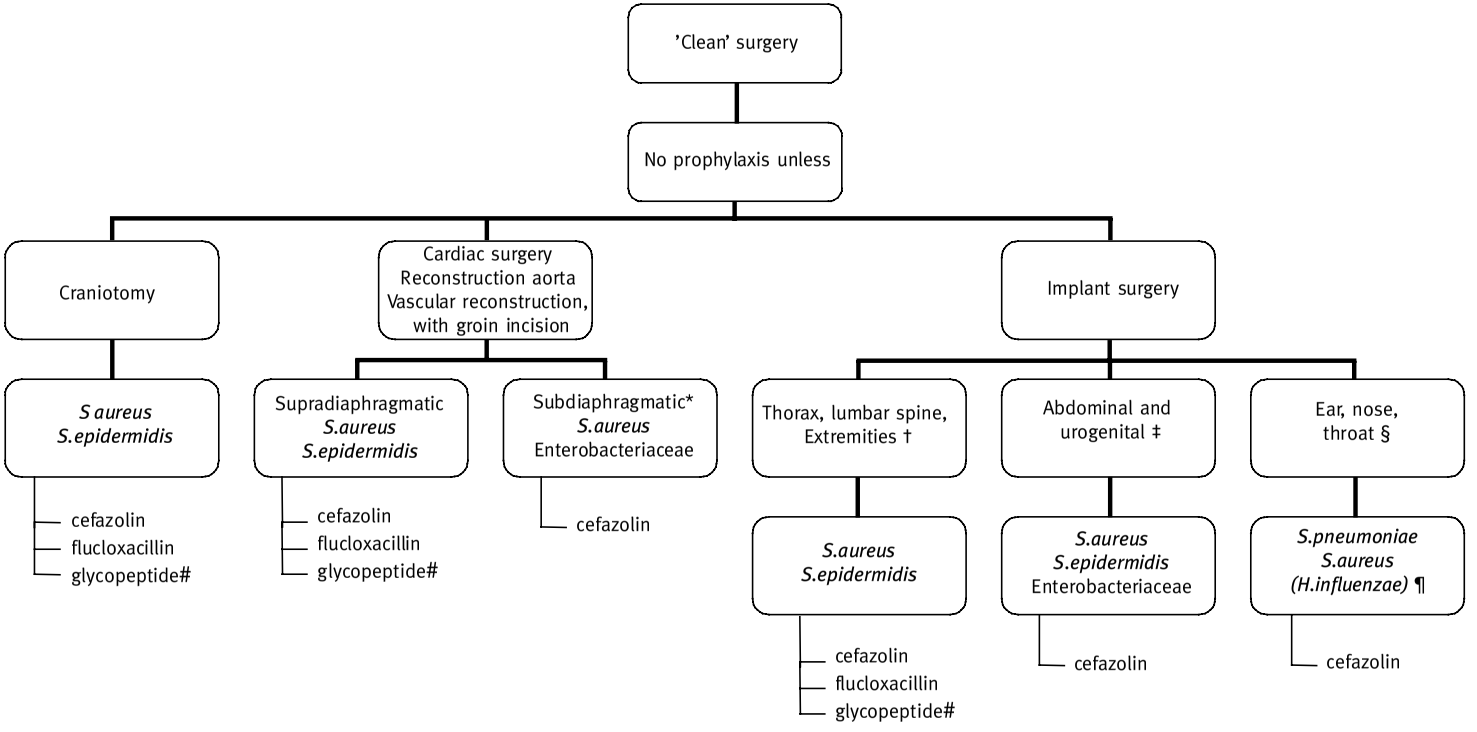

Figure 1. Flow diagram for the decision to administer perioperative antibiotic prophylaxis for a surgically "clean" wound (for an explanation of "clean", see table 1); * this includes amputation in ischaemic tissue; † examples are osteosynthesis and the implantation of joint prostheses and vascular implants; ‡ an example is introduction of a penile prosthesis; implantation of synthetic mesh is not included; § examples are stapedectomy, introduction of a cochlear or nasal implant; # only in the case of frequent occurrence of SSI caused by meticillin-resistant staphylococci; ¶ robust data on microorganisms that cause postoperative infections are missing; in hospitals where infections due to *Haemophilus influenzae* are frequent, a second-generation cephalosporin can be chosen.

Table 2. Procedures for which, according to general consensus, perioperative antibiotic prophylaxis is indicated.

Wound Classification Clean	
Ear Nose Throat	– Stapedectomy – Implant surgery, bone transplant
Neurosurgery	– Craniotomy
Vascular surgery	– Implant surgery / synthetic material – Aorta reconstruction and vascular surgery with groin incision
Cardiovascular	– Open-heart surgery including coronary bypass surgery and implantation of artificial valve
Orthopaedic / bone surgery	– Implant joint prothesis – Osteosynthesis – Amputation in ischaemic area
Wound Classification Clean-contaminated/ contaminated	
Head Neck Surgery	– Opening oral cavity / pharynx or oesophagus
Neurosurgery	– Procedures by naso- of oropharyngeal route
Thoracic surgery	– Lobectomy and pneumectomy
Surgery digestive tract	– Gastric and duodenal surgery in patients with hypochlorhydria, disturbed gastric motility or in extremely obese patients – Biliary tract surgery in patients with cholangitis, stone in common bile duct, obstructive icterus or in patients >70 years old – Colo-rectal surgery – Appendectomy without appendicitis
Surgery urogenital tract	– Surgery of urinary tract with non-sterile urine – Vaginal / abdominal hysterectomy – Secondary caesarean section – Manual removal of placenta – Abortion in 2nd trimester or after pelvic inflammatory disease in 1st trimester – Vulvectomy
Trauma	– Open fracture – Penetrating abdominal or thoracic trauma, <6 hours old

For a number of procedures with a presumed clean wound, such as craniotomy and coronary bypass surgery, it has appeared that in fact the risk of wound infection is clearly higher than 5%, i.e. 8-20% according to various studies. This is probably

attributable to the prolonged duration of the procedure. Prophylaxis for these procedures has indeed been found to be beneficial.
Recently a number of studies have been performed concerning the effectiveness of prophylaxis in clean non-implant surgery. For mastectomy and herniorraphy prophylaxis significantly reduced the incidence of SSI.[25] The absolute risk of SSI was however low and one must administer antibiotic prophylaxis to a very large number of patients undergoing such surgery in order to prevent one SSI. SWAB considers this undesirable in view of the possible induction of resistance and therefore believes that the advantages of prophylaxis for these procedures do not outweigh the disadvantages and therefore does not advise prophylaxis for these procedures.

Clean-contaminated/contaminated wounds

For procedures for which a so-called clean-contaminated or contaminated wound is expected, the risk of a SSI increases to 10 and 20%, respectively. Thus the advantages of prophylaxis do outweigh the possible disadvantages. The most important measures for prevention of SSI of contaminated wounds are incidentally local management of the wound and leaving the wound open. For exploration of open traumatic wounds (except bite wounds), antibiotic prophylaxis can often be excluded from the list of measures to be taken. Table 2 presents a survey of a large number of procedures for which the indication for perioperative prophylaxis is generally accepted. For procedures involving some organs, perioperative prophylaxis is essential only under certain circumstances or for a certain group of patients. The method of surgery, i.e. conventional or laparoscopic, does not appear to be a determining factor.
For two procedures in Table 2, abdominal hysterectomy and pulmonary surgery, the benefit of prophylaxis is somewhat controversial according to the literature. Many studies have been published on the effectiveness of prophylaxis for abdominal hysterectomy but in general they were without sufficient statistical support. Furthermore in a number of studies, the prevention of both a SSI and, for example, infection of the urinary tract served as an outcome measure of the success of prophylaxis. Several studies showed the advantage of prophylaxis for specific risk categories, such as obese patients. According to several meta-analyses however prophylaxis is beneficial in abdominal hysterectomy and therefore the majority of the consultants of SWAB agreed with prophylaxis in both vaginal and abdominal uterus extirpation.

For pulmonary surgery only a few placebo-controlled studies have been carried out with relatively small numbers of patients. The results of these studies are controversial and the success of prophylaxis is evaluated on the basis of several outcomes (superficial SSI alone or together with postoperative pneumonia). In an American guideline, published in the Medical Letter of 1997, prophylaxis is recommended for pneumonectomy and lobectomy,[3] and in view of the positive results with prophylaxis in a number of recent studies, SWAB supports this standpoint.

Environmental and patient-related factors

In addition to the nature of the procedure, environmental and patient-related factors can contribute to the risk of infection (Table 3). Patients with these risk factors have a greater chance of SSI than those without these risk factors. However, as yet controlled studies have not been able to show that the risk of SSI decreases when patients with one of these risk factors receive prophylaxis for a procedure for which prophylaxis is not generally indicated. Furthermore there are no official guidelines in which the presence of these risk factors has played a role in the decision to administer prophylaxis. In general it is accepted that if there is no consensus about the effectiveness of prophylaxis it is better not to administer it.

For procedures at an infected site, administration of antibiotics is therapeutic instead of prophylactic and the administration of the antibiotic is usually continued until several days after surgery. This subject falls outside of the scope of this guideline.

Microorganisms that cause surgical site infections

The most common causative microorganism of SSI is *Staphylococcus aureus*. In addition, *Staphylococcus epidermidis* (especially infections of joint prostheses and artificial valves), streptococci and, in a limited number of cases, enterobacteriaceae and Pseudomonas species are important. This applies mainly for colorectal procedures and surgery involving infected bile ducts or an infected genitourinary tract. Patients with a malignancy in the oral pharyngeal region regularly carry enterobacteriaceae, especially if they have received radiotherapy. The role of these enterobacteriaceae however in the development of SSI is controversial. Although enterococci are often isolated from superficial and deep wounds after surgery involving the digestive tract, the clinical relevance of the presence of these micro-

organisms is not completely clear. In the case of a procedure involving the digestive tract, the pharynx or the genitourinary tract, not only aerobic but also anaerobic bacteria play a role.

Antibiotic choice for prophylaxis

Antibiotic prophylaxis represents a substantial proportion of the total use of antibiotics in the hospital and therefore contributes to the problem of selectivity of hospital flora and the normal flora of the patient. For this reason it is important to choose drugs for perioperative prophylaxis which are selectively active against the expected microorganisms and which preferably are not an important part of the therapeutic arsenal of the hospital. In addition safety, a favourable dosage profile and limited costs are important. Studies in which several antibiotics (usually different cephalosporins) were compared show few differences in efficacy. However most studies have insufficient statistical power to be able to demonstrate these differences. In Figures 1 and 2, the drugs which can be considered for perioperative prophylaxis, according to SWAB, are listed for different procedures.

Cefazolin

Considerable experience has been collected with the first-generation cephalosporins, in particular cefazolin. It meets the criteria listed and offers good protection against the most common facultative aerobic microorganisms that cause SSI (this applies for a patient who has not had extensive prior treatment with antibiotics and has not been hospitalized for a prolonged period). The spectrum of cefazolin includes streptococci, staphylococci (with the exception of the methicillin-resistant staphylococci) and a limited number of enterobacteriaceae. Anaerobic intestinal bacteria are not susceptible, as are enterococci. After intravenous administration high serum concentrations are achieved and despite strong protein binding the concentration of cefazolin in surgical wounds is more than sufficient. The half-life of cefazolin with respect to that of other first and second-generation cephalosporins is relatively long, i.e. 1.5 – 2 hours. For a procedure that lasts no longer than 4 hours, one dose is sufficient.

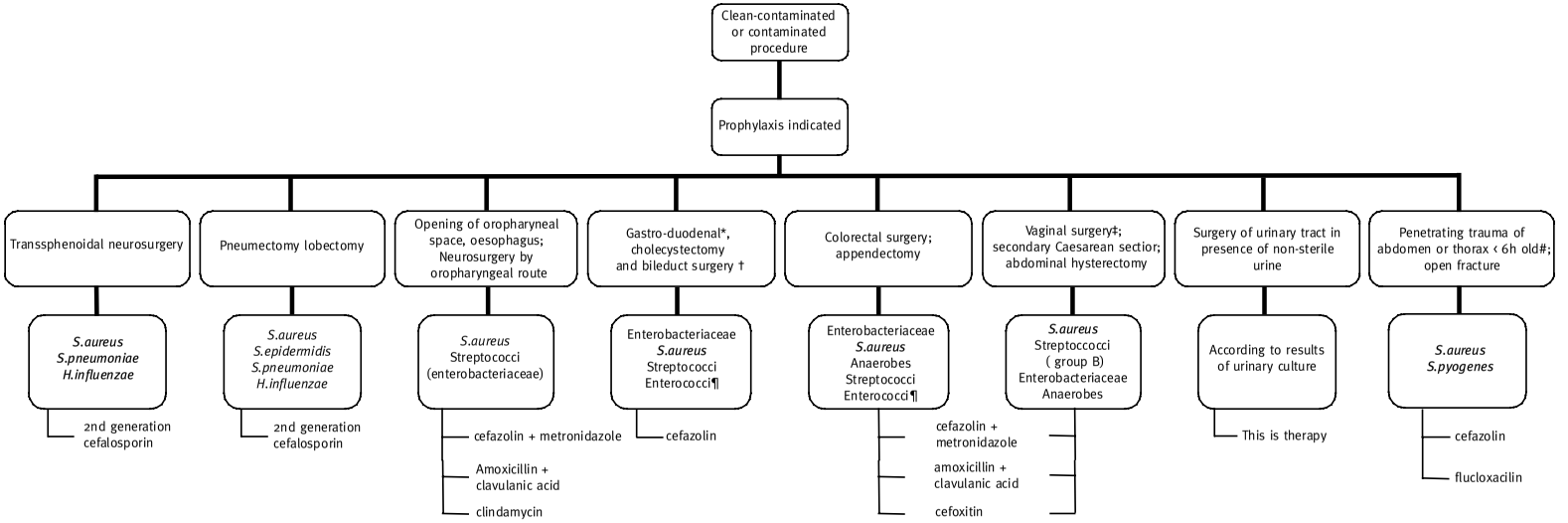

Figure 2. Flow diagram for the decision to apply perioperative antibiotic prophylaxis for a surgical "clean/contaminated" or "contaminated" wound (for an explanation of the wound classification, see Table 1);* this applies only in the case of decreased gastric acidity, disturbed motility or morbid obesity;† this applies only for acute cholecystitis, obstructive icterus, stones in the biliary tract, or age >70 years;‡ this applies only for vaginal hysterectomy, vulvectomy, abortion in the 2nd trimester, abortion after PID and manual expulsion of the placenta; § in the event of sterile urine, prophylaxis is not indicated, for non-sterile urine, preoperative treatment is required and an elective procedure must be postponed; # this applies if there are no visceral lesions; in the case of a lesion of the colon or rectum the recommendations for colorectal surgery apply;¶ the role of enterococci in the development of SSI - without coinfection with enterobacteriaceae – is subject of controversy; therefore in general, prophylaxis is not targeted at this microorganism.

On the basis of the excellent results of clinical studies, SWAB concludes that cefazolin can play an important role in perioperative prophylaxis. Cephalosporins of the second or third-generation do not offer any advantages with respect to effectiveness and due to the broader spectrum probably lead to more intense selective pressure and the risk of the development of resistance. In general they must therefore be avoided. On the other hand they should be administered when *Haemophilus influenzae* is the cause of a SSI, such as after lobectomy whereby a postoperative pneumonia due to *H. influenzae* must be considered as a deep SSI.

Metronidazole

When an anaerobic flora is expected, it is recommended that intravenous metronidazole be added to cefazolin. An alternative is intravenous amoxicillin with clavulanic acid. However, in hospitals in which amoxicillin clavulanic acid plays a prominent role in therapy, this drug should not be administered as prophylaxis. Cefoxitin, a second-generation cephalosporin with a spectrum which covers aerobic and anaerobic causative microorganisms, is a less attractive alternative because of its high cost. In addition it has a short half-life (40-60 minutes) so multiple doses are often required.

Although the combination of oral neomycin and erythromycin is effective as prophylaxis for colon surgery, this approach is fairly time-consuming and expensive. One must start administration 18 hours before the start of the procedure and mistakes are easily made. SWAB therefore prefers the above-mentioned intravenous alternatives.

Part of the anaerobic oral flora is not sensitive to first-generation cephalosporins. For this reason in major surgery of the head-neck region whereby the oral cavity or pharynx is opened, in particular, metronidazole is added. Although amoxicillin with clavulanic acid is an alternatve, this combination is preferably reserved for therapeutic purposes. A controversial point is whether, for procedures involving the head-neck area, antimicrobial drugs without activity against enterobacteriaceae can be used. As far as perioperative prophylaxis is concerned, good results have been reported for clindamycin alone as well as in combination with aminoglycosides.

For surgical procedures which are associated predominantly with SSI caused by staphylococci such as neurosurgical procedures, flucloxacillin can also be used for prophylaxis. Flucloxacillin is however usually reserved for therapeutic purposes in most hospitals. Moreover the half-life of flucloxacillin is relatively short. In the case of a neurosurgical procedure which usually is quite prolonged, repeated doses

will be required which increases the chance of errors. Clindamycin could be an alternative drug but it is more expensive and is better reserved for patients with a penicillin allergy.
Because glycopeptides are the only effective drug against a number of micro-organisms and because large-scale use leads to resistance, glycopeptides should only be administered for antibiotic prophylaxis when SSIs are caused regularly by meticillin-resistant staphylococci. In such cases prophylaxis with a first-generation cephalosporin or flucloxacillin is no longer sufficient. Obviously in the event of infections with meticillin-resistant *S. aureus* extensive hospital hygienic measures are required.

Topical prophylaxis
In a number of cases topical prophylaxis can (also) be applied. Examples are antibiotic eye drops for ophtalmologic surgery and gentamicin bone cement for orthopaedic procedures. The application of mupirocin or chlorhexidine nose ointment before vascular thoracic surgery is also considered topical prophylaxis. This ointment is applied from day 1 before the operation to 5 days after surgery in order to eliminate the possibility of becoming a carrier of staphylococci. Although a number of studies have demonstrated that this is an effective method to decrease the number of SSI with staphylococci, SWAB considers further research necessary before mupirocin nose ointment can in general be recommended for vascular thoracic surgery.

Timing of antibiotic prophylaxis

For optimal efficacy of prophylaxis it is essential that an adequate concentration of the antibiotic be present at the site of the wound from the time of the first incision to time of closure of the wound. If prophylaxis is administered approximately 30 minutes before the first incision or before inflation of the tourniquet, then for most antibiotics an adequate tissue concentration will be achieved at the time of the incision. Studies on the optimal time for administration show that prophylaxis administered within 2 hours of the start of the procedure is most effective. Studies of surgical practice reveal that for timing of prophylaxis there is still much room for improvement. Intravenous administration of prophylaxis by the anaesthetist at induction of anaesthesia offers the best condition for correct timing.

Duration of prophylaxis

Prophylaxis which lasts longer than 24 hours is not beneficial and can lead to unnecessary disturbance of the microbial flora. Comparative studies have shown that one single dose of an antibiotic with a half-life of at least 1-1.5 hours, is just as effective as multiple doses over 24 hours For this reason SWAB prefers one single preoperative dose. If the procedure lasts longer than 3 times the half-life of the administered antibiotic, or in case of considerable blood loss (more than 2 litres) or extracorporeal circulation, administration of the antibiotic must be repeated.

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Chapter 2

Adherence to local hospital guidelines for surgical antimicrobial prophylaxis. A multicentre audit in Dutch hospitals

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Abstract

Objective: To study the adherence to local hospital guidelines for antimicrobial prophylaxis in surgery and explore reasons for non-adherence.
Methods: A prospective multicentre audit of elective procedures, without prior suspicion of infection, was carried out in 13 Dutch hospitals. By reviewing medical anaesthetic and nursing records, and medication charts, the prescription of antibiotics was compared with the local hospital guideline on antibiotic choice, duration of prophylaxis, dose, dosing interval and timing of the first dose.
Results: Between January 2000 and January 2001, 1763 procedures were studied. Antibiotic choice, duration, dose, dosing interval and timing of the first dose were concordant with the hospital guideline in 92 %, 82 %, 89 %, 43 % and 50 % respectively. Overall adherence to all aspects of the guideline, however, was achieved in only 28 %. The most important barriers to local guideline adherence were lack of awareness due to ineffective distribution of the most recent version of the guidelines, lack of agreement of surgeons with the local hospital guidelines, and environmental factors such as organisational constraints in the surgical suite and in the ward.
Conclusion: This study shows that, although adherence to separate aspects of local hospital guidelines for surgical prophylaxis in the Netherlands is favourable, overall adherence to all parameters is hard to achieve. Adherence to guidelines on dosing interval and timing needs improvement, in particular. To increase the quality of antimicrobial prophylaxis in surgery, effort should be put into developing guidelines acceptable to surgeons, in adequately distributing the guidelines and to facilitating logistics. Audits of surgical prophylaxis may help hospitals to identify barriers to guideline adherence.

Introduction

The use of antimicrobial prophylaxis for selected surgical procedures is one of the measures used to prevent the development of a surgical site infection (SSI).[1] In past decades, many papers have described optimal prophylaxis, and guidelines for surgical prophylaxis have been developed.[1-6] Despite the availability of these guidelines, recent studies assessing the current practice of prophylaxis throughout the world have shown that over-consumption of antimicrobial drugs and inappropriate timing

remain a problem in surgical prophylaxis.[7-14] Historically, the Netherlands has a restrictive antibiotic policy.[15] Nevertheless, misuse of antibiotics has been reported in Dutch hospitals. An intervention study, which analysed antibiotic utilization in surgical departments of a single university hospital in the Netherlands between 1990 and 1992, showed that over-consumption and suboptimal timing of antibiotics for surgical prophylaxis was found in up to 66 % and 56 % of the procedures, respectively.[16,17]

Since the early 1990's, most hospitals in the Netherlands have developed local hospital guidelines to improve the quality of prophylaxis. However, quality improvement is not confined to guideline development. Facilitation of adherence to these guidelines and their effective implementation, are as important.[18] Since the latter is often underestimated, many guidelines are abandoned in daily practice. In 1999, the CHIPS (surgical prophylaxis and surveillance) project, an audit and improvement programme looking at the quality of surgical prophylaxis related to SSI, was started in the Netherlands. Part of this project was to study the adherence to local hospital guidelines for prophylaxis and to explore reasons for non-adherence. The results are presented in this paper.

Methods

Frequently performed surgical techniques, for which the efficacy of antibiotic prophylaxis has been researched extensively in well-conducted trials, were selected for this prospective multicentre study. To observe normal daily routine, only elective procedures were included. Four major surgical disciplines were audited, and techniques with a differing intrinsic risk for SSI were selected. In orthopaedic surgery and vascular surgery, procedures classified as "clean" [19] included total hip implant, femoral hemiprosthesis, grafting of the aorta and femoropopliteal and femorotibial bypass. In gynaecological and intestinal surgery, approaches classified as "clean-contaminated" [19] included abdominal and vaginal hysterectomy with or without vaginal repair and various colorectal procedures. To avoid difficulties in discriminating prolonged prophylaxis from post-operative therapy, procedures with suspected or established infection during surgery were excluded. The study was conducted in 13 hospitals participating in a national survey of SSI, the PREZIES-project.[20] The hospitals represented inpatient care in the Netherlands, since university, non-university teaching and non-teaching hospitals were included.

Between January 2000 and January 2001, the adherence to local guidelines for antimicrobial surgical prophylaxis in these hospitals was reviewed. The study period per hospital varied between 6-10 months depending on the incidence of the selected procedures in the hospitals. The following aspects of antimicrobial prophylaxis were audited: antibiotic choice, duration, dose, interval between doses, timing of first dose, and antibiotic choice in case of allergy. Wound-class,[19] physical condition of the patient according to the classification of the American Society of Anesthesiologists (ASA-score),[21] time of induction of anaesthesia, the time of the first incision, and the duration of the procedure, were recorded. Data were collected by infection control practitioners from medical, anaesthetic and nursing records, and medication charts. Before the start of the project, as well as during the study, data collection was validated at regular intervals (M.E.E. van Kasteren, A.S. de Boer, M. Ridderhof – van 't Veer, J. Mannien, J. Wille, B.J. Kullberg & I.C.Gyssens, unpublished data). Each hospital was requested to provide their most recent version of local guidelines for prescription of surgical prophylaxis. Only guidelines composed by the committees for antibiotic policy of the participating hospitals, printed in an official hospital guide for antibiotic prescription, were considered. The prophylaxis actually given was assessed according to these guidelines by the same investigator for all procedures. A modificied standardized qualitative method for evaluation was used.[22] The criteria for evaluation of adherence are summarized in table 1.

Courses of antimicrobial drugs were evaluated. If more than one drug was prescribed for a single procedure, all parameters were evaluated separately for each drug. Subsequently, a final assessment of the antibiotic course was composed by combining these separate drug evaluations. Any divergence from the guideline in the prescription of one of the drugs led to a final assessment of the prophylactic course as discordant with the guideline. If no antibiotic prescriptions had been recorded, it was assumed that antibiotics were not given. If data on a certain parameter of the antibiotic prescription were lacking, this was classified as missing data on this parameter only. If an antibiotic was given while it was not indicated, the parameters of antibiotic choice, duration, dose, dosing interval and timing were not evaluated.

The infection control practitioners collected data prospectively using standardized forms. These data were entered in a database, double-checked by the investigator and infection control practitioner of the project, and analysed using SPSS 10.0.

Table 1. Criteria for assessment of adherence to local guidelines

Parameter	Discordant if
Antibiotic choice	Agent differed from recommendation
Duration	Duration differed from recommendation
Dose (all agents except gentamicin)	Dose differed from recommendation
Dose of gentamicin	Dose deviated >20 mg from recommended dose
Dosing interval during surgery	Dosing interval exceeded the guideline by >30 min
Dosing interval on the ward	Dosing interval deviated from the guideline by >60 min
Timing of first dose at fixed time before incision	Timing of fist dose deviated >15 min from the recommended time
Timing of first dose within fixed time-range	Timing of first dose was outside the recommended time-range
Timing of first dose before incision	Timing of first dose was at or after the incision

Results

Between January 2000 and January 2001, 1763 surgical procedures were recorded in 13 Dutch hospitals. Table 2 shows the demographic data of the patients and the distribution of the procedures according to surgical specialty and wound class. Not every hospital performed all types of procedures. Almost two-thirds of the procedures were clean, and the majority were orthopaedic. The main features of the guidelines obtained from the participating hospitals are summarised in Table 3.

Overall assessment of all parameters

In 1598 out of 1763 procedures (91%), data on all parameters of prophylaxis were available and a complete evaluation of the prophylaxis could be performed. In 439 procedures (28 %), there was full adherence to local guidelines for all parameters. Without including the dosing interval for antibiotics given in the ward or in the operating theatre, prophylaxis was completely concordant with the guidelines in 543 cases (34 %). Parameters were also evaluated separately, so that missing data of one parameter did not preclude assessment of the other.

Table 2. Demographic data

Characteristics	**Number (%)**
Number of patients	1763
Sex male / female	524 / 1239
Age (years) median	67
range	19-93
ASA-score	
1	561 (*32*)
2	860 (*49*)
3	274 (*16*)
4	26 (*2*)
5	1
Unknown	41 (*2*)
Procedure	
Orthopaedic	
wound class clean [a]	942 (*53*)
Gynaecological	
wound class clean-contaminated [a]	398 (*23*)
Vascular	
wound class clean [a]	171 (*10*)
wound class clean-contaminated [a]	1 (<1)
Intestinal	
wound class clean-contaminated [a]	244 (*14*)
wound class contaminated [a]	7 (*<1*)

[a] wound-classification according to Altemaier et al.[19]

Indication

Procedures for which antibiotics are generally indicated were selected, although, one hospital's local guidelines recommended no prophylaxis for abdominal hysterectomy (unless performed for carcinoma). According to the hospital guidelines, antibiotics were indicated in 1737 procedures. In 33 procedures (2 %), no prophylaxis was given and in 17 procedures (1 %), one out of two drugs was omitted.

Antibiotics were administered in 1712 procedures. In eight of these procedures, no antibiotics were recommended. These were all abdominal hysterectomies performed in the one hospital that did not recommend prophylaxis. In 11 cases, two types of antibiotics were administered whereas only one was indicated. In one case, three types of antibiotic were administered whereas only two were indicated. So in the 1704 procedures, at least one antibiotic was indicated and, when available, data on antibiotic choice, duration, dose, dosing interval and timing were evaluated (Table 4).

Table 3. Local hospital guidelines for surgical prophylaxis in the participating hospitals.

Surgical specialty	Hospital	Antibiotic choice and dose	Duration	Repeated dose in the theatre b	Dosing Interval in the ward f	Timing of first dose (min) g ¤	Latest revised version (year) h	Recommended drug in case of allergy
Gynaecological surgery	A	Amoxicillin 2000 mg + metronidazole 500 mg	single [a]	-	-	30 min PI	2000	genta + metro [i]
	B	Cefuroxime 750 mg + metronidazole 500 mg	single [a]	>4h [c]	-	PI	2000	-
	C	Amoxicillin -clavulanic acid 2200 mg	single [a]	>6h	-	within 60 min PI	1999	-
	F	Amoxicillin -clavulanic acid 1200 mg	single [a]	-	-	PI	2000	-
	J	Cefuroxime 1500 mg + metronidazole 500 mg [d]	single [a]	>3h [c]	-	30 min PI	1998	-
Orthopaedic surgery	B	Cefuroxime 750 mg	single [a]	>4h	-	PI	2000	-
	C	Cefuroxime 1500 mg	single [a]	>6h	-	within 60 min PI	1999	-
	D	Cefuroxime 1500 mg (750 mg [e])	24 h	>4h	8h	within 30-15 min PI	1998	-
	E	Cefamandol 1000 mg	single [a]	>3h	-	within 30 min PI	1997	clindamycin
	F	Cefazolin 1000 mg	24 h	-	6h	PI	2000	-
	G	Cefuroxime 1500 mg (750 mg [e])	24 h	>4h	8h	within 30-15 min PI	1998	-
	H	Cefazolin 1000 mg	24 h	-	8h	within 30 min PI	1998	-
	I	Flucloxacillin 2000 mg (1000 mg [e])	24 h	-	6h	PI	1997	-
	J	Cefuroxime 1500 mg	single [a]	>3h	-	30 min PI	1998	-
	K	Cefuroxime 1500 mg (750 mg [e])	24 h	>4h	8h	within 30-15 min PI	1998	-
	L	Cefuroxime 1500 mg	single [a]	>3h	-	within 30 min PI	1998	clinda + genta [i]

Surgical specialty	Hospital	Antibiotic choice and dose	Duration	Repeated dose in the theatre b	Dosing Interval in the ward f	Timing of first dose (min) g ¤	Latest revised version (year) h	Recommended drug in case of allergy
Intestinal Surgery	B	Cefuroxime 750 mg + metronidazole 500 mg	single [a]	>4h [c]	-	PI	2000	-
	E	Cefamandol 1000 mg + metronidazole 500 mg	single [a]	>3h [c]	-	within 30 min PI	1997	clinda + genta [i]
	H	Amoxicillin-clavulanic acid 2200 mg (1200 mg [e])	24 h	-	8h	within 30 min PI	1998	- o
	J	Tobramycin 4 mg/kg + metronidazole 500 mg	single [a]	-	-	30 min PI	1999	-
	L	Cefuroxime 1500 mg + metronidazole 500 mg	single [a]	>3h [c]	-	within 30 min PI	1998	-
	M	Cefuroxime 1500 mg + metronidazole 500 mg	single [a]	>4h [c]		within 30 min PI	1994	genta + metro [i]
Vascular Surgery	B	Cefuroxime 750 mg	single [a]	>4h	-	PI	2000	-
	E	Cefamandole 1000 mg	single [a]	>3h	-	within 30 min PI	1997	clindamycin
	L	Cefuroxime 1500 mg	single [a]	>3h	-	within 30 min PI	1998	erythro + genta [i]
	M	Cefuroxime 1500 mg	single [a]	>4h	-	within 30 min PI	1994	-

[a] single dose prophylaxis, to be repeated during surgery in case the procedure is prolonged or when blood loss exceeds 2 L. [b] duration of the procedure after which a repeated dose is recommended in the theatre; [c] for cephalosporin only; [d] no prophylaxis recommended for abdominal hysterectomy; [e] dose of repeated antibiotic prescription in the ward; [f] dosing interval of repeated prescription in the ward; [g] timing of the first dose expressed in number of minutes prior to the first incision (PI) ; [h] Year of publication of the hospital guide including the most recent version of the local guidelines; [i] genta, gentamicin; clinda, clindamycin; metro, metronidazole; erythro, erythromyin.

Table 4. Non-adherence to local guidelines for prophylaxis according to the assessment defined in table 1.

Parameter	Nonadherence Number of procedures (%)	
	N	%
Antibiotic choice	129	(8)
Duration	299	(18)
too short	42	(3)
too long	257	(15)
Dose	175	(11)
too high	123	(8)
too low	15	(1)
combined error [a]	37	(2)
Interval	457	(57)
Timing	810	(50)
too early	358	(22)
too late	448	(28)
combined error [b]	4	(<1)

[a] combined error indicates: dose of one of the drugs too high and of the other too low

[b] combined error indicates: timing of one of the drugs too early and of the other too late

Antibiotic choice

In 1560 of 1689 evaluable procedures (92 %), antibiotic choice was concordant with the hospital guideline and discordant in 129 (8 %) (Table 4). More than 80 % of the discordant cases were reported in two hospitals (hospital F and H). In these hospitals, the antibiotic choice was discordant in more than 30 % of the procedures because the surgeons used a protocol that differed from the guideline issued by the hospital committee for antibiotic policy. The adherence of the surgeons to their own protocol was 100 %. The remaining errors were incidental and almost equally distributed over the hospitals. In many instances where an allergy to β-lactams was suspected, antibiotic choice was incorrect. In 15 cases, the antibiotic choice could not be evaluated because the hospital guideline did not provide an alternative for allergy to the primary drug of choice.

Duration

In 1389 of 1688 evaluable procedures (82 %), duration was concordant with the hospital guideline. In 257 procedures (15 %), duration was longer than recommended

and shorter in 42 (3 %) (Table 4), including eight procedures in which a second dose was not administered during prolonged surgery. In three hospitals (C, H and L), more than 25 % of the prescriptions were continued longer than recommended (range 25-50 %). In hospital C, the prolonged use was fully attributable to orthopaedic surgeons, who followed their own protocol rather than the hospital guideline. Adherence to this protocol was almost 100 %. In hospital H, deviation from the hospital guideline was unintentional, and the result of inaccurate "stop" orders for antibiotics in the ward. In hospital L, local hospital guidelines were violated because some surgeons felt insecure about the length of prophylaxis recommended by these guidelines.
In 16 cases (1%) duration could not be evaluated because medication charts were incomplete.

Dose

In 1461 of 1636 evaluable procedures (89 %), the dose was concordant with the local hospital guidelines. In 15 procedures (1 %) the dose was lower, and in 123 procedures (8 %) the dose was higher than recommended (Table 4). Higher doses were mainly recorded in one hospital (F), in all participating specialties. In 37 procedures (2 %), performed in hospital J, the dose of one of the agents was too high and of the other too low. Reasons for incorrect dosing were: application of outdated guidelines instead of the most recent version in hospital F and J, and deliberate use by orthopaedic surgeons in hospital F of higher doses than recommended in the hospital guidelines. In 68 of 1704 procedures (4 %), data on dosing were missing or the hospital recommendation was incomplete. In almost half of the hospitals that provided guidelines of what to administer in case of allergy to the primary drug of choice, dosing recommendations for these alternative drugs were lacking.

Dosing interval

In 835 of 1704 procedures (49 %), more than one dose was administered. Of these, the dosing interval of antibiotics repeated during surgery or on the ward, could be calculated in 802 procedures. In 345 procedures (43 %) dosing intervals were concordant with the guidelines and discordant in 457 (57 %) (Table 4). In seven hospitals, more than 50 % of the dosing intervals were discordant with the guideline, and in four hospitals (G, H, I, L) almost all intervals were incorrect. Most errors were because of administration of antibiotics by nurses on the ward at fixed clock rounds, instead of adjusting this to the time of the previous dose.

In 55 of the evaluable cases, antibiotic doses were repeated during surgery. In six cases (11 %) the interval exceeded the recommended interval.

Timing

In 809 of 1619 evaluable procedures (50 %), timing was concordant with the hospital guideline. Timing was earlier than recommended in 358 (22 %) procedures and later in 448 (28 %) (Table 4). In four procedures, timing of one of the drugs was too early and of the other too late.

In three hospitals (B F, and I), an assessment of "timing too early" could not be made, since specific recommendations for the timing of the first dose other than "before the incision", were not given (Table 3). In three hospitals (G, H, and K), prophylaxis was administered earlier than recommended in more than 80 % of the cases. In eight hospitals, prophylaxis was administered later than recommended in more than 25 % of the procedures. There was a striking difference in timing per specialty. In general, timing in orthopaedic procedures was earlier than recommended. However, in intestinal surgery and gynaecological surgery, timing of the first dose was later than recommended in more than 50 % of the cases. This pattern was observed in almost all hospitals. Errors in timing were mainly due to logistics in the surgical suite and not because of deliberate deviation from the guidelines. The time of arrival at the operating complex and the type of anaesthesia, epidural or general anaesthesia, was an important determinant for timing of the first dose. In one hospital (H), timing was too early for almost all procedures because the first dose of prophylaxis was given in the ward instead of in the operating theatre. In 85 of 1704 procedures (5 %), data on timing were missing because the moment of the first incision, or the moment of the administration of the first antimicrobial dose, could not be retrieved from the records.

Discussion

The present study demonstrates that, although in the Netherlands adherence to separate aspects of prophylaxis was favourable, adherence to all aspects of a guideline for surgical prophylaxis was difficult. It is noteworthy that the criteria for assessment of adherence were strict and that the guidelines recommended a prudent use of antibiotics. Taking into account the adherence in some hospitals to non-official hospital guidelines drawn up by surgeons, it can be concluded that

the willingness to adhere to guidelines in general is good. Hardly any variation in antibiotic choice, dose and duration were observed that were based on individual decisions of surgeons. In only one hospital (L), did surgeons decide individually to extend the duration of prophylaxis. A study by Motola et al. showed that in Italy the willingness to adhere to guidelines is disappointing.[14]

In contrast to the present study, most studies in other countries have assessed the quality of prophylaxis according to an international or a national standard. Only a few have studied the adherence to local guidelines.[23-25] One report from a tertiary teaching hospital in Brazil,[23] showed that in only 3 % of the procedures prophylaxis was given according to hospital guidelines in terms of antibiotic choice, duration, dose and timing. In the present study, concordance with local guidelines on antibiotic choice, duration, dose and timing was 34 %. In the study of Finkelstein et al.,[25] performed in Israel, adherence to duration and timing was comparable to the present study. In the study by Vaisbrud et al,[24] also performed in Israel, the adherence was slightly better, especially for timing of the first dose.

Guideline adherence can be hindered by various barriers.[26,27] In exploring these barriers in the present report, the process of guideline development and distribution was studied. With a few exceptions, guidelines were revised regularly (Table 3), but revised versions did not always reach the people that had to use them. In some hospitals, several revised versions of a guideline were distributed within a short time, leading to confusion about which one to apply. Sometimes, a revised version of the hospital guideline was printed in the antimicrobial hospital guide without changing local protocols in the ward or without updating reminders in the operating theatre. This lack of awareness of the appropriate guideline was the main barrier to guideline adherence regarding antimicrobial choice and dose. Acquaintance may be improved by electronic distribution of the guidelines and by pre-printing sections of the guideline on prescription charts.

Some hospital committees continued to produce guidelines with which they knew surgeons disagreed. In two hospitals, lack of agreement of the orthopaedic surgeons with the recommended duration of prophylaxis was the most important barrier to adherence to the local hospital guideline. Testing the feasibility and acceptance of clinical guidelines among the target group is important for effective implementation.[18,28,29] It is just as important to ensure that recommendations in the guideline agree with the current evidence base and that links between recommendations and scientific evidence are made explicit.[30] Therefore, more effort should be put into providing surgeons with evidence of the content of the guideline

and in trying to achieve consensus, before implementing new guidelines. Finally, antibiotic policy makers are often unaware of logistic problems in the surgical suite or in the ward. Logistical constraints were the most important barriers to adherence to guidelines for timing and dosing intervals. The difference in time of arrival at the operating complex could have been responsible for most variations in timing of the first antibiotic dose between orthopaedic surgery versus gynaecological and intestinal surgery. Studying these logistic constraints in more detail can help to create conditions that facilitate guideline adoption.

Our study has several limitations. First, the hospitals participating in this study, comprised only 10% of the hospitals of the Netherlands. However, the selection seems to represent daily practice since the number of procedures recorded was large, different specialties were represented in different types of hospitals, and the geographic distribution of the hospitals was wide. Nevertheless, since participation was voluntarily, it is possible that we have included a favourable selection of hospitals, and that adherence to local guidelines in other Dutch hospitals may be poorer in comparison. Second, adherence to guidelines does not automatically imply that the quality of surgical prophylaxis is optimal and inappropriate guidelines may explain some of the deviation in practice from guidance. To evaluate this, a critical appraisal of the content of the guidelines is needed. However, focussing only on the content of guidelines, without paying attention to their adoption, is a main reason for the failure of guidelines as an instrument for quality improvement, and therefore both processes are needed.[18] For most hospitals in this study, several problems of adherence to guidelines in this study were similar, and therefore this study might provide general information for those involved in quality improvement of surgical prophylaxis. Other problems seemed specific for the local situation. For this reason and for constant reinforcement of guidelines, repetitive audits of surgical prophylaxis are recommended. Since these studies are time-consuming, adequate financial resources are required.

In conclusion, this study shows that in the Netherlands, the willingness to adhere to guidelines for surgical prophylaxis is good. To achieve optimal adherence, antibiotic policy makers should develop evidence-based guidelines in unison with surgeons, need to guarantee an effective distribution of the guidelines, and facilitate situations to make them more applicable.

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Chapter 3

Quality improvement of surgical prophylaxis in Dutch hospitals: evaluation of a multi-site intervention by time series analysis

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Abstract

Objectives: Misuse of antibiotics in surgical prophylaxis is still quite common. The objectives of this study were to reduce the quantity and improve the quality of surgical prophylaxis and to reduce costs.
Methods: Prospective multi-site study of elective procedures in 13 Dutch hospitals. The quality of prophylaxis was audited before and after an intervention consisting of performance feedback and implementation of national clinical practice guidelines. Process outcome parameters were antibiotic choice, duration, timing, antibiotic volume and costs. Segmented regression analysis was used to estimate the effect size of the intervention. Patient outcome was documented by the incidence of surgical site infections (SSI).
Results. Before the intervention, 1763 procedures were recorded and 2050 thereafter. Antimicrobial use decreased from 121 to 79 DDD (defined daily doses) /100 procedures and costs reduced by 25 % per procedure. After the intervention, antibiotic choice was inappropriate in only 37.5% of the cases instead of in 93.5% expected cases had the intervention not occurred. Prolonged prophylaxis was observed in 31.4 % instead of 46.8 % expected cases and inappropriate timing in 39.4 % instead of the expected 51.8%. Time series analysis showed that all improvements were statistically significant ($P<0.01$) and that they could be fully attributed to the intervention. The overall SSI rates before and after intervention were 5.4% (95% CI: 4.3-6.5) and 4.6% (95% CI: 3.6-5.4) respectively.
Conclusion: The intervention led to improved quality of surgical prophylaxis and to reduced antibiotic use and costs without impairment of patient outcome.

Introduction

Surgical site infections (SSI) are the most common nosocomial infections in surgical patients and lead to prolonged hospital stay,[1] readmissions to the hospital, and increased morbidity and mortality. For many procedures, perioperative antimicrobial prophylaxis has proven to be effective in reducing the incidence of SSI.[2] However, inappropriate use of surgical antimicrobial prophylaxis, in terms of prolonged duration and use of broad-spectrum antibiotics, can select for resistant microorganisms and leads to high costs.[3] Moreover, incorrect timing of prophylaxis reduces its efficacy.[4] Therefore, the quality of prophylaxis has been the subject of many audits [5-9] and

intervention studies [10-17] and national guidelines have been developed to support its correct use.[18-21]
In the Surgical Prophylaxis and Surveillance project (CHIPS) we studied the adherence to local hospital guidelines for surgical prophylaxis in Dutch hospitals [22] and implemented a national guideline issued by the Dutch Working Party on Antibiotic Policy (SWAB).[19] The effect of the intervention on process outcome parameters (administration of prophylactic antibiotics) and patient outcome (incidence of surgical site infections) was studied and is presented in this article.

Materials and methods

Setting

This prospective multi-site intervention study, with a before and after design, was performed in 13 different hospitals throughout the Netherlands that were participating in the national surveillance network of nosocomial infections, PREZIES.[1] Elective procedures for which antibiotic prophylaxis is generally accepted in the literature [18,23] were studied. These procedures were distributed among four surgical disciplines: orthopaedic surgery, vascular surgery, gynaecological surgery and intestinal surgery. The following procedures were included: total hip arthroplasty, hemiarthroplasty, grafting of the aorta, femoropopliteal and femorotibial bypass, abdominal and vaginal hysterectomy with or without vaginal repair and various colorectal procedures.
Although this was a before and after intervention study of which the main objective was to improve process outcome, i.e. the quality of prophylaxis, the study was also powered to observe an improvement in patient outcome, i.e. a decrease in the overall SSI rate. The required sample size was calculated using the following assumptions: overall risk of SSI before the intervention of 7.5% and an estimated achievable decrease in SSI rate to 5% after intervention. The figure of 7.5 % was based upon PREZIES data for the selected procedures in previous years and assumed an equal distribution of the selected procedures (orthopaedic, gynaecological, vascular and bowel surgery) in the CHIPS study. With a significance level of 5% and a power of 80%, 1600 surgical procedures before and 1600 after intervention would suffice to demonstrate a decrease in SSI incidence to 5.1% or less, or increase to at least 10.3%.

Data collection

During the pre-intervention and post-intervention periods, all consecutive procedures meeting the inclusion criteria were recorded by the local infection control practitioner (ICP) of each hospital. Data were extracted from medical, anaesthetic and nursing records and medication charts. Hospitals participating in the study contributed data for all types of procedures studied or for only a selection of procedures. ICPs collected the following patient and procedure characteristics: gender, date of birth, dates of admission, surgery and discharge, ASA score,[24] wound contamination class [25] and data on allergy for antibiotics. For patients receiving antibiotics, the choice of the antibiotic, unit doses, number of post-operative doses, time of administration of first dose and subsequent doses, time of anaesthesia and time of first incision were recorded. The duration of prophylaxis was derived from the number of post-operative doses and the timing of subsequent doses. The ICP performed surveillance of SSI, including post-discharge surveillance, according to the PREZIES-protocol using the criteria of the Centers for Disease Control and Prevention.[1,23] Superficial SSI was defined as an infection which occurs within 30 days after the operative procedure and which involves only the skin or subcutaneous tissue. Deep SSI was defined as an infection that appears to be related to the operative procedure and occurs within 30 days of surgery, or within one year in case of implant (non-human vascular graft or prosthesis) surgery, and involves deep soft tissues, organ or spaces which have been opened or manipulated during surgery. The duration of the pre- and post- intervention period of data collection depended on the incidence of the procedures in each hospital and therefore varied between hospitals. To obtain a balanced distribution of the selected procedures, i.e. a similar case-mix between the hospitals, it was aimed to record within each hospital a minimum of 20 procedures per surgical specialty in the period before and after the intervention. However, the CHIPS study was dependent on the PREZIES network protocol, according to which hospitals were free to select the procedures for surveillance.

Data assessment

Antimicrobial use was analyzed quantitatively by calculating the defined daily doses (DDD) per 100 procedures. DDDs were obtained from the ATC/DDD Index 2003 of the WHO Collaborating Centre for Drugs Statistics Methodology.[26] Total costs of antibiotics were calculated by adding purchase costs to indirect costs of personnel and supplies for administration of the antibiotics. The lowest price for generic drugs from the Royal Dutch Pharmaceutical Society price list (G-standard, Z-index, July

2003) was used for calculation. Wholesale discounts for individual hospitals were not taken into account.

The first author (MvK) performed an audit to measure the adherence to the SWAB-guideline for surgical prophylaxis [19] according to a standardized method.[27] Review criteria derived from the key recommendations in the guideline are presented in Table 1.

Table 1. Criteria for evaluation of prophylaxis according to the SWAB guidelinea for antimicrobial prophylaxis.

Parameter of prophylaxis	Criteria for evaluation
Antibiotic choice	
efficacy	Inappropriate if agent is less effective than agent recommended in SWAB guideline [b]
toxicity	Inappropriate if agent is more toxic than agent recommended in SWAB guideline [c]
antibiotic spectrum	Inappropriate if agent has a broader spectrum than agent recommended in SWAB guideline
costs	Inappropriate if agent is more expensive than agent recommended in SWAB guideline [d]
therapeutic use	Inappropriate if agent is more frequently used in therapeutic setting than agent recommended in SWAB-guideline
Duration of prophylaxis	Inappropriate if prophylaxis is prolonged after the end of surgery (=postoperative dosing)
Timing of prophylaxis	Inappropriate if prophylaxis is administered more than 30 minutes before the first incision or after the first incision

[a] The SWAB-guideline [19] recommends single dose prophylaxis with a first-generation cephalosporin, preferably cefazolin (with metronidazole in case of need for anaerobic coverage), administered within 30 minutes before the first incision or tourniquet. During surgery, prophylaxis has to be repeated when the procedure exceeds three times the half-life of the administered drug or when blood loss is extensive (>2L).

[b] An agent was classified as less effective if the antibiotic did not cover the spectrum of the most frequent causative microorganisms causing SSI after that particular procedure.

[c] An agent was classified as more toxic when more allergic reactions were reported in the literature than with the use of the agent in the SWAB-guideline (i.e. penicillins, vancomycin) or when more nephrotoxicity was reported with that drug.(i.e. aminoglycosides).

[d] An agent was classified as more expensive based upon costs of one pre-operative dose using the lowest price for generic drugs from the Royal Dutch Pharmaceutical Society price list (G-standard, Z-index, July 2003), including costs of administration by bolus injection or infusion.

The SWAB guideline recommends intravenous single dose prophylaxis of an inexpensive non-toxic antibiotic with a limited spectrum, which is not used extensively in therapy, administered within 30 minutes before the first incision. Cefazolin (combined with metronidazole if activity against anaerobic microorganisms is needed) is the drug of first choice, since it meets many of the above characteristics. Repeated dosing is recommended when blood loss during the procedure exceeds 2 L or when surgery is prolonged beyond three times the half-life of the administered antibiotic.

Courses of antimicrobial drugs were audited for antibiotic choice, dosage, duration and timing of prophylaxis. If more than one drug was prescribed for a single procedure all parameters were evaluated separately for each drug. Subsequently, assessment of the complete antibiotic course was composed by combining these separate drug evaluations. Divergences from the SWAB guideline in the prescription of one of the drugs lead to a final assessment of the prophylactic course as discordant with the SWAB guideline. If no antibiotic prescriptions were recorded, it was assumed that antibiotics had not been administered. If data on a certain parameter of the antibiotic prescription were lacking, these were classified as missing data on this parameter only.

Intervention

After the pre-intervention period, every hospital received feedback of its own data on antibiotic prophylaxis. The hospitals' auditing report and the SWAB-guideline were discussed with surgeons, anaesthetists, pharmacists, microbiologists, nurses and the local antibiotic policy committee. The CHIPS study group formulated recommendations for local improvement in each hospital and discussed them with the participants. In addition, educational meetings were organized for medical specialists and nurses. Depending on the results of the audit, the intervention focused on modification of the local guidelines, guideline adherence or both. The day of the first feedback was considered as the start of the intervention period in each hospital. The intervention period varied between 2-9 months (median 6 months) depending on the number of activities and the time needed to achieve approval on updated guidelines.

The post-intervention data collection started immediately after all the intervention activities had ended and, if necessary, after a new antibiotic policy was implemented. An assessment identical with the pre-intervention period was performed for the prophylaxis and the data on surgical site infections. Finally, the effect of the

intervention on all aspects of the use of antibiotic prophylaxis and the occurrence of SSI was evaluated.

Statistical analysis

The graphs of the different outcome parameters over calendar time were visually inspected. The length of data collection for the different hospitals ranged between 6 and 13 months although all hospitals had data for at least 6 months before and 6 months after the intervention. For clarity, only data for the means of these 12 months are shown. The figures were not corrected for procedure mix.

In order to assess the effect of the intervention, we estimated the expected number of inappropriate cases if no intervention had taken place taking into account changes in mixes and differences in follow-up period of the different hospitals. To estimate these expected numbers, time series segmented regression analysis was used which includes changes in level and trend, as recommended by The Cochrane Effective Practice and Organisation of Care Group (EPOC).[28] In this study, data were collected on an individual patient level. As the interventions were targeted at hospitals with different mixes of surgical specialties, a hierarchical structure had to be taken into account in the analyses. Most response variables were binary (i.e. appropriate versus inappropriate prophylaxis). For these variables, a non-linear mixed model, SAS PROC NLMIXED (release 8.2; SAS Institute Inc. Cary, NC, USA) was used. For the continuous response variables duration and antibiotic use, SAS PROC MIXED was used. In the models, the hospital was treated as a random variable while surgical specialty and calendar time of the pre-intervention, intervention and post-intervention period were treated as co-variables. In this way, the model corrected for unequal distribution of procedures in the pre- and post-intervention period, for unequal distribution within surgical specialties and hospitals as well as for differences in length of registration and intervention periods. The model did not correct for seasonal trends.

A conservative model was chosen to ensure that the effect of the intervention was not overestimated. In this model, a trend in the pre-intervention period towards an increase in inappropriate prophylaxis was ignored while a trend towards a decrease in inappropriate prophylaxis was included in the analyses. For each parameter, the following outcome measurements were generated: mean level in the pre- and post-intervention period, change in level immediately after the intervention and the pre- and post-intervention slope. In the results section, only the *P* values of these outcome measurements are shown since the quantitative outcome values do not

represent the absolute change in outcome on a numeric scale. The observed and expected numbers of inappropriate prophylaxis were tested using the cumulative binomial distribution with the zero-hypothesis of no impact of the intervention. In this test, the hierarchical structure was not taken into account.

Results

Data were collected between January 2000 and January 2001 (pre-intervention period) and between July 2001 and October 2002 (post-intervention period). Before the intervention, 1763 procedures were recorded compared with 2050 after the intervention. The length of both pre- and post-intervention period varied between 6 and 13 calendar months per hospital depending on the incidence of the recorded procedures in the participating hospitals. Table 2 shows the distribution of the procedures in each period according to hospital and surgical specialty. In the pre- and post-intervention period, the overall number of procedures that were needed to assess the effect of the intervention on the incidence of SSI was met.

Indication

After the intervention, the observed number of cases for which prophylaxis was indicated but not administered was significantly lower than expected; 26 versus 55 (Table 3). Time series analysis showed that this effect was sustained during the post-intervention period ($P<0.02$ for change in level, $P=0.25$ for post-intervention slope).

Table 2. Distribution of procedures (n=3813) before and after intervention according to hospital and surgical specialty.

	Orthopaedic surgery		Vascular surgery		Gynaecological surgery		Intestinal surgery		Total			
Hospital	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**	**Before n (%)**		**After n (%)**	
A					63	60			63	(3.6)	60	(2.9)
B	32	50	47	46	63	71	37	46	179	(10.2)	213	(10.4)
C	142	135			137	175			279	(15.8)	310	(15.1)
D	220	256							220	(12.5)	256	(12.5)
E	49	55	9	5			41	26	99	(5.6)	86	(4.2)
F	67	91			68	90			135	(7.7)	181	(8.8)
G	41	80							41	(2.3)	80	(3.9)
H	74	82					40	49	114	(6.5)	131	(6.4)
I	50	48							50	(2.8)	48	(2.3)
J	59	70			67	70	39	43	165	(9.4)	183	(8.9)
K	94	109							94	(5.3)	109	(5.3)
L	114	179	23	18			45	45	182	(10.3)	242	(11.8)
M			93	103			49	48	142	(8.1)	151	(7.4)
total	**942**	**1155**	**172**	**172**	**398**	**466**	**251**	**257**	**1763**		**2050**	

Table 3. Observed and expected outcomes of quality parameters before and after the intervention.

Parameter of antibiotic prophylaxis	Observed before intervention No. inappropriate (total)		%	Observed after intervention No. inappropriate (total)		%	Expected after intervention No. inappropriate (total)		%	p-value observed-expected
Indicated but not administered	51	(1763)	2.9	26	(2050)	1.3	55	(2050)	2.7	<0.01
Antibiotic less effective	88	(1712)	5.1	36	(2024)	1.8	64	(2024)	3.2	<0.01
Antibiotic more toxic	327	(1712)	19.1	241	(2024)	11.9	387	(2024)	19.1	<0.01
Antibiotic more expensive	1275	(1712)	74.5	454	(2024)	22.4	1550	(2024)	76.6	<0.01
Antibiotic broader spectrum	1458	(1712)	85.2	688	(2024)	34.0	1751	(2024)	86.5	<0.01
Antibiotic in therapeutic use	1295	(1712)	75.6	686	(2024)	33.9	1579	(2024)	78.0	<0.01
Antibiotic choice not cefazolin	1646	(1712)	96.1	758	(2024)	37.5	1893	(2024)	93.5	<0.01
Duration exceeding single dose	779	(1699)	44.2	631	(2015)	31.4	944	(2015)	46.8	<0.01
Timing first dose inappropriate	822	(1627)	50.5	779	(1976)	39.4	1024	(1976)	51.8	<0.01

Antimicrobial use

Figure 1 shows the antimicrobial use over time. There was a significant decrease in antibiotic use immediately after the intervention (P<0.01 for change in level). This use further decreased during the post-intervention period (P<0.01 for post-intervention slope). The number of DDD per 100 procedures decreased from 121 before to 79 after the intervention. The antibiotic costs per procedure decreased by 25 % from EUR 10.96 to EUR 8.24.

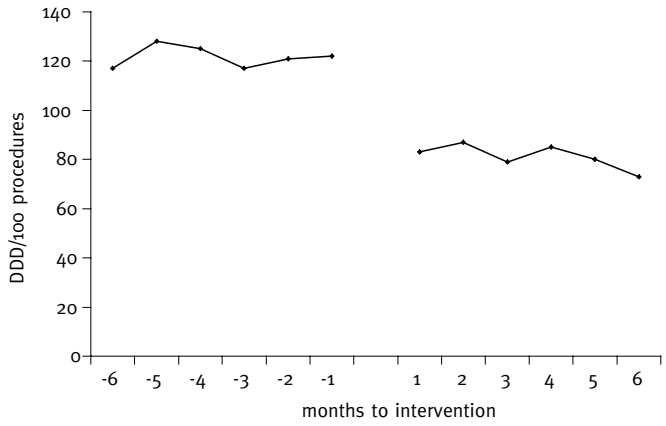

Figure 1. Antimicrobial use in 13 hospitals before and after the intervention. The horizontal axis shows the time in months to the intervention. The length of both registration periods to the intervention differed per hospital from 6 to 13 months, but all hospitals registered at least 6 months before and after the intervention. To be representative for all hospitals, only these 6 months are illustrated in the figure.

Antibiotic choice

The antimicrobial drugs used over time are shown in Figure 2. For each parameter of antibiotic choice, the observed number of inappropriate cases after the intervention was significantly lower than the expected number of cases had the intervention not occurred (P<0.01, Table 3). Immediately after the intervention, the use of the first generation cephalosporin cefazolin increased significantly (P<0.01 for change in level). This increase continued during the post-intervention period (P<0.01 for post intervention slope). After the intervention, the observed number of cases not using cefazolin was significantly lower than expected, 758 instead of 1893 (P<0.01, Table 3).

For the qualitative parameters of antibiotic choice, i.e. efficacy, spectrum, toxicity, costs and use in therapy, there was a significant decrease in the number of cases with inappropriate prophylaxis immediately after the intervention ($P<0.05$ for change in level) which paralleled the increased use of cefazolin. For the parameters spectrum, toxicity, costs and use in therapy, this effect was sustained or even improved during the post-intervention period. For the parameter efficacy, there was a significant trend towards an increase in inappropriate prophylactic drugs ($P<0.02$ for post intervention slope). This was almost completely attributable to the use of drugs which were alternatives in cases of an allergy to β-lactam antibiotics but that did not cover the most frequent causative microorganisms of SSI of that particular procedure, e.g. erythromycin for bowel surgery.

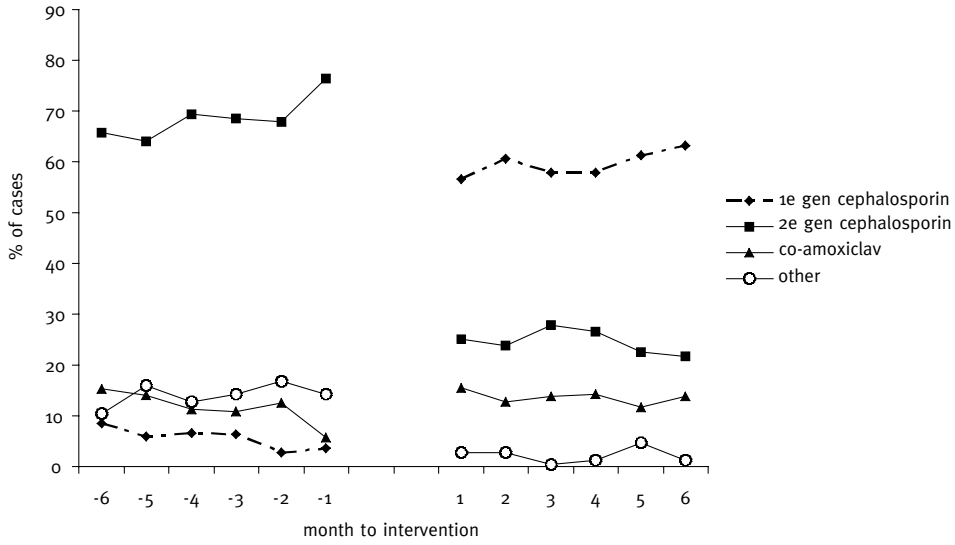

Figure 2. Antibiotic choice before and after the intervention in 13 hospitals. The horizontal axis shows the time in months to the intervention. The length of the registration periods to the intervention differed per hospital from 6 to 13 months but all hospitals registered at least 6 months. To be representative for all hospitals, only these 6 months are illustrated in the figure. Abbreviations: 1st gen, first-generation; 2nd gen, second-generation.

Duration of prophylaxis

The duration of prophylaxis before and after the intervention, expressed as number of post-operative doses, is shown in Figure 3. The observed number of cases with prolonged prophylaxis after the intervention was significantly lower than expected: 631 instead of 944 (P<0.01, Table 3). Immediately after the intervention, there was a significant decrease in the number of cases with prolonged prophylaxis (P<0.01 for change in level). This effect was sustained in the post-intervention period (P=0.50 for post-intervention slope). The median time between the first dose at the surgical suite and the last dose at the ward decreased from 16 h (range 1.5 h - 5 days) before the intervention to 12 h (range 8 h - 2.5 days) after the intervention. There was a marked difference in duration of prophylaxis between surgical specialties (Figure 4). Extended prophylaxis was mainly recorded in orthopaedic departments.

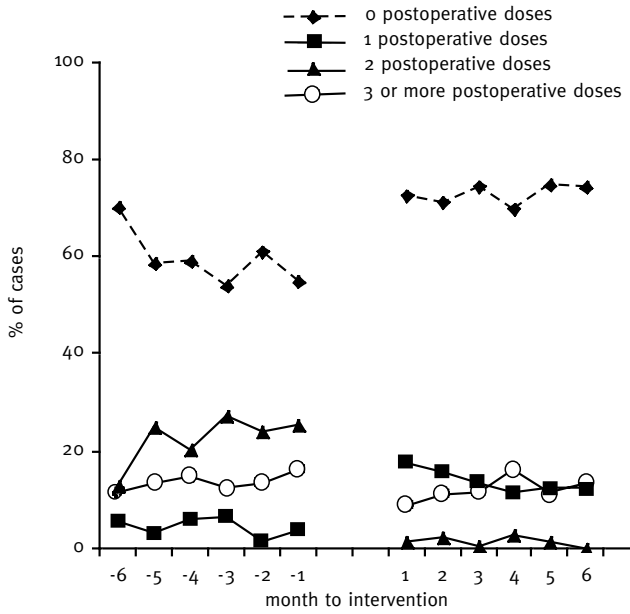

Figure 3. Duration of prophylaxis before and after the intervention in 13 hospitals. The horizontal axis shows the time in months to the intervention. The length of the registration periods to the intervention differed per hospital from 6 to 13 months, but all hospitals registered at least 6 months. To be representative for all hospitals, only these 6 months are illustrated in the figure.

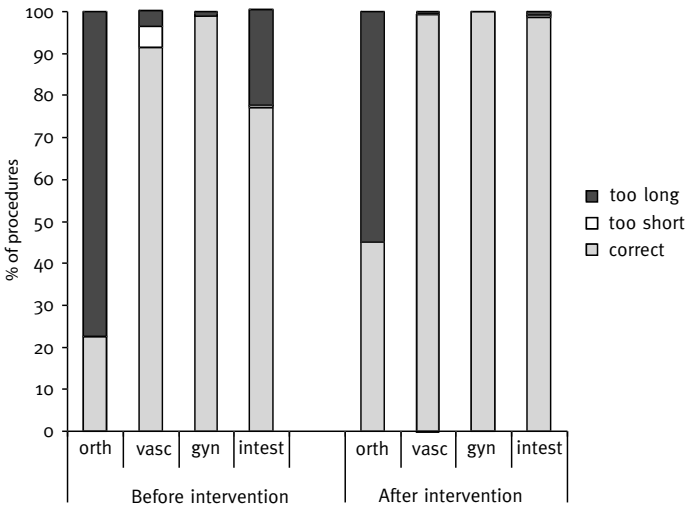

Figure 4. Duration of prophylaxis according to surgical specialty in 13 hospitals. For each surgical specialty, the percentage of procedures with an appropriate, prolonged or too short duration of prophylaxis is shown before and after the intervention. Orth, orthopaedic surgery; vasc, vascular surgery; gyn, gynaecological surgery; intest, intestinal surgery. Too short means that a repeat dose of the prophylactic antibiotic was omitted during surgery, although surgery exceeded more than three times the half-life of the administered drug.

Timing of prophylaxis

The timing of prophylaxis before and after the intervention is shown in Figure 5. The intervention resulted in a slight decrease in the number of cases with inappropriate timing (P=0.07 for change in level). However, during the post-intervention period, there was a significant trend towards a further decrease in the number of cases with inappropriate timing (P<0.01 for post-intervention slope). This resulted in a significant difference between the observed and expected cases with inappropriate timing after the intervention, 779 instead of 1024 (P<0.01, Table 3). The total number of cases that received prophylaxis at an optimal timing, within 30 minutes before the first incision, improved from 805 cases before (50%) to 1197 cases (61%) after the intervention.

In general, timing of prophylaxis in orthopaedic surgery was much earlier than in intestinal surgery and gynaecological surgery (Figure 6). Although the number of procedures in intestinal surgery with a timing of the first dose after the incision decreased, the difference in timing between the surgical specialties remained.

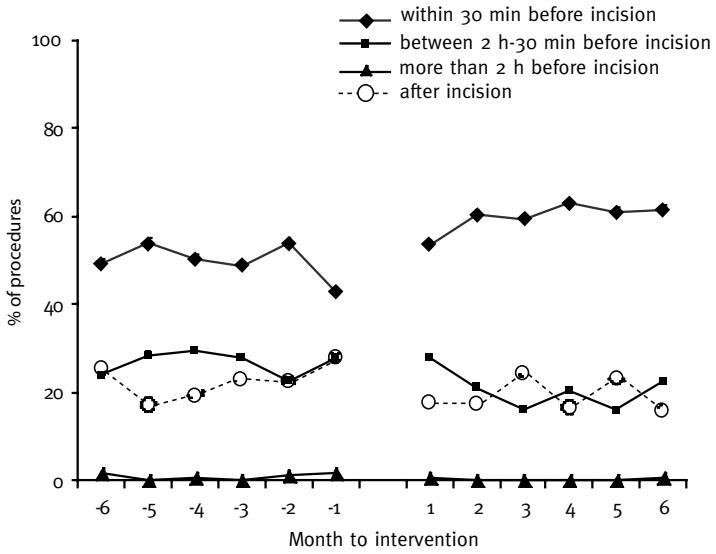

Figure 5. Timing of prophylaxis before and after the intervention in 13 hospitals. The horizontal axis shows the time in months to the intervention. The length of the registration periods to the intervention differed per hospital from 6 to 13 months, but all hospitals registered at least 6 months. To be representative for all hospitals, only these 6 months are illustrated in the figure.

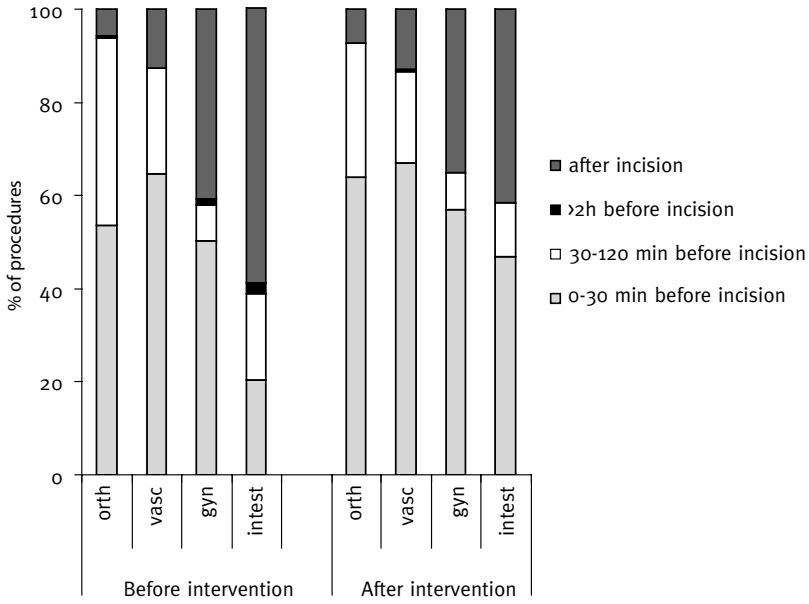

Figure 6. Timing before and after the intervention according to surgical specialty in 13 hospitals. Orth, orthopaedic surgery; vasc, vascular surgery; gyn, gynaecological surgery; intest, intestinal surgery

Overall quality

Prophylaxis was completely administered according to the recommendations of the SWAB guideline in only 6 of 1615 (0.4%) cases before the intervention and in 494 of 1967 (25%) cases after the intervention. Time series analysis could not be performed because the number of adherent cases before the intervention was too small to run the model.

Surgical site infection

The incidence of surgical site infections could be evaluated in 12 out of 13 hospitals. One hospital could not provide data on SSI because of lack of personnel to perform the data collection in 63 procedures before and 60 procedures after the intervention. The data on the quality of prophylaxis were linked to the PREZIES database of surgical site infections by matching date of birth, date of admission and date of surgery. This linkage failed 27 times before and 22 times after the intervention due to missing data or errors in the data entry. Therefore, data on SSI were available of 1673 patients before the intervention and of 1968 patients after the intervention. The overall SSI rate decreased from 5.4% (95% CI: 4.3-6.5) to 4.6% (95% CI: 3.6-5.4), a difference which was not statistically significant. Time series analysis showed that there were no significant trends in SSI rate during the pre- and post-intervention periods. The SSI rates before and after the intervention in the four categories of surgical specialty are shown in Table 4.

Table 4. SSI rates in the four categories of surgical specialties before and after the intervention.

	Before intervention			**After intervention**		
	no.	SSI rate, %	95 % CI	no.	SSI rate, %	95 % CI
Vascular surgery	165	9.1	4.7-13.5	152	12.5	7.2-17.8
Intestinal surgery	250	14.8	10.4-19.2	257	10.9	7.1-14.7
Gynaecological surgery	328	1.5	0.2-2.9	402	1.5	0.3-2.7
Orthopaedic surgery	925	3.6	2.4-4.8	1142	3.1	2.1-4.1

Discussion

This study shows that the implementation of a national guideline for peri-operative prophylaxis improves the quality of prophylaxis and significantly decreases antibiotic use. The remarkable decrease in antibiotic use and costs per procedure was due to a reduction in the number of postoperative doses, the use of less costly antibiotics and, to a small extent, to the use of lower dosages (data not shown).

The magnitude of quality improvement between the different parameters differed remarkably. Changing the antibiotic choice proved to be relatively easy and the use of a low-cost non-toxic antibiotic of limited spectrum, not extensively used in therapy, increased significantly. The use of cefazolin for surgical prophylaxis is justified in the Netherlands because the prevalence of methicilline-resistant *Staphylococcus aureus* is very low, (<1% data from NethMap) [29] as is the percentage of cefazolin resistant *Escherichia coli* in patients on admission and in the community.[30] The duration of prophylaxis after the intervention was shortened but several orthopaedic surgeons were still reluctant to use single dose prophylaxis. They based their opinion on the results of a Dutch study of 2651 hip replacements [31] in which the incidence of SSI tended to be lower in the 24 h prophylaxis group than in the single dose group. Although this difference was not significant, the study may not have had the power to detect small potential benefits of prolonged prophylaxis. For this reason, some orthopaedic surgeons still favoured 24 h prophylaxis whereas antibiotic policymakers used the results of this study to recommend single dose prophylaxis.[19,20] In this study, the timing of surgical prophylaxis improved only to a limited extent and the absolute number of cases with optimal timing in the post-intervention period was still disappointing. These results are comparable to the studies by Welch *et al.*[13] and Schell *et al.*[14] in which the percentage of procedures with appropriate timing of prophylaxis improved from 46 tot 67% and 42 to 52 %, respectively. In our study, the targets of improvement were more ambitious than in other studies, e.g., duration shortened to single dose instead of 24 h and timing within 30 min before incision instead of within 1 or 2 h before the incision. These more ambitious goals could explain why improvement in duration and timing of prophylaxis was harder to achieve. On theoretical grounds and based on earlier studies,[4,32,33] the most optimal timing seems to be as near as possible to the incision. One might argue, that aiming at a timing within 1 h before incision would already be a qualitative improvement and more feasible to adhere to in daily practice.

The low figure of overall adherence to the national guideline after implementation

in 25% of cases is thus explained by the use of very strict criteria. According to the recent advisory statement of the National Surgical Infection Prevention Project,[21] many antibiotics are considered appropriate, a duration of 24 h or even 48 h is accepted and timing is considered appropriate within 60 min before incision. When applying this broader timing criterion to the CHIPS data, 80 % of the cases would be considered appropriate in the post-intervention period instead of 61%. This quality level is similar to findings in the second quarter of the continuous quality improvement program in US hospitals (80%).[34]

The difference in success rates of quality improvement between the parameters of prophylaxis may partially be explained by the nature of the changes that had to be brought about to achieve improvement. Barriers to implementation of guidelines and guideline adherence are various [35] and some are easier to overcome than others. The fact that the sudden change in appropriate timing of prophylaxis after the intervention was limited while the timing gradually improved over time, suggests that changing the timing is a logistical process with a continuous learning curve. In contrast, changing the antibiotic choice has been described as an on-off phenomenon.[10,11]

Audits of antimicrobial use have shown that the quality of surgical prophylaxis varies greatly among hospitals around the world but improvement is almost universally desirable.[5-7,9] However, only few studies have reported the results of interventions to achieve improvement. Most of these studies were performed in one hospital,[10-13,15,17] regarding one type of surgery [10,14,16] or focusing at a single aspect of prophylaxis (e.g. timing).[13,16] We are aware of only one other intervention study that mirrored the real-life implementation of surgical prophylaxis guidelines in a variety of hospitals, the recently published report on the National Surgical Infection Prevention Collaborative.[34] Our study was performed simultaneously in many different hospitals, covering different surgical specialties and intervening on different aspects of prophylaxis. The methodology of surveillance and the qualitative assessment were highly standardized using a national protocol and strict criteria for assessment. This renders these data reliable and reproducible. By using segmented regression analysis with an interrupted time series design, it could be excluded that the improvement had been the result of a gradual change over time not related to the intervention and that the results are robust. Recently, Ramsay *et al*. critically reviewed the literature to evaluate the methodology of studies on improving antibiotic prescribing.[36] Most studies have only reported the mean numbers with appropriate prophylaxis before and after an intervention and

did not correct for secular trends. With the use of at least 5 to 12 time points before and after the intervention (number varying per hospital), our study meets the criteria of the Cochrane EPOC Data Collection Checklist for correct interrupted time series analysis.[28] Although seasonal variation was not taken into account, it is not expected to be an important issue in surgical prophylaxis.

A limitation of this intervention study is the lack of control groups. The changes in antibiotic prophylaxis could have been due to local initiatives rather than being the result of the intervention by the study group. However, when a control group is lacking, interrupted time series analysis is the strongest quasi-experimental approach to evaluate longitudinal effects of intervention.[37]

This quality intervention study did not only evaluate the process outcome, but also the patient outcome, i.e. the incidence of SSI. Because the overall SSI rate and the SSI rates in the four surgical specialties were generated from a specific case-mix, they can only be compared within the study and not with SSI rates from other published studies. We hypothesised that changing the prophylactic drugs to a single dose first-generation cephalosporin would be non-inferior to actual practices, but that improving the timing would result in a decrease of the SSI rate. The study was powered to demonstrate a decrease in SSI rate from 7.5% to about 5%. The actual SSI rate before intervention however was lower, 5.4%, mainly due to overrepresentation of orthopaedic procedures in the study. On the other hand, more evaluable procedures were included in the study than we had anticipated (1673 before and 1968 after intervention). With this sample size and pre-intervention SSI rate, the study had enough power to demonstrate an improved outcome at post-intervention SSI rates of 3.4% or beyond, or poorer outcome at rates of at least 7.7%. However, we observed no change in SSI rate before and after intervention, as the difference between rate estimates was minor, with largely overlapping 95% confidence intervals.

In conclusion, this study shows that an intervention using audit and feedback as an instrument for change can improve the quality of prophylaxis and can decrease the antibiotic use with sustained efficacy in preventing SSI.

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Chapter 4

Effect of optimized antibiotic prophylaxis on the incidence of surgical site infection

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Abstract

Objective: To compare the rate of surgical site infection (SSI) before and after an intervention period in which an optimized policy for antibiotic prophylaxis was implemented. To demonstrate that a more prudent, restrictive policy would not have a detrimental effect on patient outcomes.

Design: Before-after trial with prospective SSI surveillance in the Dutch nosocomial surveillance network (Preventie Ziekenhuisinfecties door Surveillance [PREZIES]), using the criteria of the Centers for Disease Control, including postdischarge surveillance for up to 1 year.

Methods: During a preintervention period and a postintervention period (both 6-13 months), 12 Dutch hospitals collected data on antimicrobial prophylaxis and SSI rates. The study was limited to commonly performed surgical procedures in 4 specialties: vascular, intestinal, gynecological and orthopedic surgery. Selected risk factors for analysis were sex, age, American Society of Anesthesiologists classification, wound contamination class, duration of surgery, length of hospital stay before surgery, and urgency of surgery (elective or acute).

Results: A total of 3,621 procedures were included in the study, of which 1,668 were performed before the intervention and 1,953 after. The overall SSI rate decreased from 5.4% to 4.5% (P=0.22). Among the procedures included in the study, the largest proportion (55%) were total hip arthroplasty, and the smallest proportion (2%) were replacement of the head of the femur. SSI rates varied from 0% for vaginal hysterectomy to 21.1% for femoropopliteal or femorotibial bypass surgery. Crude and adjusted odds ratios showed that there were no significant changes in procedure-specific SSI rates after the intervention (P>0.1).

Conclusions: An optimized and restrictive prophylactic antibiotic policy had no detrimental effect on the outcome of clean and clean contaminated surgery, as measured by SSI rate.

Introduction

Surgical site infections (SSIs) account for 38% of surgical infections and 17% of all nosocomial infections.[1,2] In the United States in the 1990s, SSIs prolonged hospital stay by an average of 6.5 days, doubled the risk of death, and were associated with a risk of readmission to the hospital 5 times that for patients without SSI.[3] In the

Netherlands, the mean postoperative length of stay for patients with an SSI is 8.2 days longer than for patients without an SSI.[4]

Decades ago, the effectiveness of antimicrobial prophylaxis in reducing SSI rates was demonstrated in randomized clinical trials.[5-10] For optimal prophylaxis, an antibiotic with a targeted spectrum should be administered at sufficiently high concentration in the serum, tissue, and the surgical wound during the entire time that the incision is open and at risk of bacterial contamination.[11] In the United States, the Surgical Infection Prevention Guideline Writers Workgroup (SIPGWW) reached a consensus that infusion of the first dose of antimicrobial should begin within 60 minutes before surgical incision and that antimicrobial prophylaxis should be discontinued within 24 hours after the end of surgery.[12] Studies showed that the prolonged use of antibiotic prophylaxis leads to emergence of bacterial resistance [13-15] and high costs,[16,17] and inappropriate timing of the administration leads to decreased efficacy.[18,19]

As part of the prospective, multisite, Surgical Prophylaxis and Surveillance (CHIPS) project, an optimized and restrictive antibiotic policy based on the national guideline was implemented in The Netherlands.[20] This guideline recommends prophylaxis with a single dose of antimicrobial administered intravenously within 30 minutes before the first incision. In view of the very low incidence of infection with methicillin-resistant *Staphylococcus aureus* in The Netherlands (less than 1% of all *S. aureus* infections), cefazolin (combined with metronidazole, if coverage for anaerobic pathogens is needed) is recommended.

The goal of the study intervention was to slow down the development of antibiotic resistance and reduce the costs of antimicrobial prophylaxis without decreasing the efficacy of prophylaxis, as measured by a higher SSI incidence.

In the present report, the patient outcome of this optimized and restrictive antimicrobial prophylaxis policy is assessed by comparing the SSI rate before and after the intervention.

Methods

Setting

The CHIPS project was a prospective intervention study conducted at 13 Dutch hospitals, which participated voluntarily. These hospitals give a representative picture of inpatient care in The Netherlands, since they were geographically spread

over the country, according to the population density (Figure 1), and various types of hospitals (small, large, university and general hospitals) were included. At 1 of the 13 hospitals, data on SSIs could not be recorded because of the sudden absence of the infection control professional (ICP).

Figure 1. Location of participating hospitals (*filled circles)* in The Netherlands (population, 16 million; area, 41,526 km^2)

Data on antimicrobial prophylaxis and SSIs were collected in these 12 hospitals between January 2000 and November 2001 (the preintervention period) and between July 2001 and November 2002 (the postintervention period). The duration of these periods in each hospital ranged from 6 to 13 months, depending on how often the selected procedures were performed. During the intervention period, which lasted 2-9 months, a restrictive antibiotic-use policy was implemented. The policy was based on the national guideline for surgical prophylaxis issued by the Dutch Working Party on Antibiotic Policy (SWAB).[21]

Four major surgical specialties were selected for this study: vascular, intestinal, gynecological and orthopedic surgery. The study was limited to frequently performed procedures for which antimicrobial prophylaxis is generally recommended [21,22]: grafting of the aorta, femoropopliteal or femorotibial bypass, various colorectal procedures, abdominal and vaginal hysterectomy with or without vaginal repair, total hip arthroplasty and replacement of the head of the femur.

Only elective procedures were included, so that the normal daily routine of administering antimicrobial prophylaxis would be observed. To avoid assessment of procedures in which antibiotics were given for therapeutic reasons rather than prophylactic reasons, procedures with a dirty or infected wound (ie, wound contamination class 4) [1,23] were excluded.

Data collection

The methods used to collect data on antimicrobial prophylaxis have been described elsewhere.[20,24] Data were collected prospectively by infection control professionals from medical, nursing, anesthesia, and medication records. Before the start of the project, as well as during the study, the collection of data on antimicrobial prophylaxis was validated at regular intervals through on-site review of the 20 most recently recorded patient files.

All CHIPS hospitals participated in the module "Surgical site infections" of the Dutch national nosocomial infections surveillance network (Preventie Ziekenhuisinfecties door Surveillance; PREZIES;[4] general information is available at the network's Web site, http://www.prezies.nl). From 1996 to 2003 within the PREZIES network, 62 of the 98 Dutch hospitals participated and collected SSI data on 129,142 procedures. According to the PREZIES protocol, infection control professionals collected information on the demographic characteristics of patients and on the surgical procedure, risk factors for SSI, and incidence of SSI. The selection of risk factors was based on the literature and included the patient's sex, age, and physical condition (American Society of Anesthesiologists classification);[25] wound contamination class; duration of surgery; preoperative length of hospital stay; and whether surgery was elective or acute.[26-29] The criteria of the Centers for Disease Control and Prevention were used for the assessment of SSIs.[22,30] If an SSI occurred in a patient, the surveillance staff recorded the day the SSI became manifest, whether it was a superficial or deep SSI, and which microorganisms were isolated. Deep incisional SSIs and organ/space SSIs were combined and termed deep SSIs. All patients were followed up to 30 days postoperatively; in case of insertion of a prosthetic implant the duration of follow-up was 1 year. To monitor the quality and reliability of the surveillance data used in this study, SSI surveillance was validated in each participating hospital.

To achieve a significance level of 5% and a power of 80%, the required sample size for observing a change in the SSI rate was 1,600 surgical procedures before the intervention and 1,600 after. This was calculated using the assumptions that

the overall risk of SSI before the intervention was 7.5% and that the estimated achievable SSI rate after the intervention was 5%. The figure of 7.5% was based upon PREZIES data for the selected procedures in previous years and assumed an equal distribution of the selected procedures (orthopedic, gynecological, vascular and bowel surgery) in the CHIPS study. However, the CHIPS study was dependent on the PREZIES protocol, according to which hospitals were free to choose the type of procedures for surveillance.

Data analysis

The X^2 test or Student *t* test was used to screen potential risk factors for SSI. Variables with a *P* value of less than .2 for their univariate association with SSI were candidates for multivariable analysis. Logistic regression analysis was used to calculate odds ratios (ORs) for SSI after the intervention compared with before the intervention, according to the type of surgical procedure, and after adjusted for procedure-specific confounders. The best model was selected by considering the -2 log likelihood as well as the c-index. The c-index is a measure of predictive performance and represents the proportion of instances in which a patient who develops an SSI is assigned a higher probability of SSI than a patient who does not develop an SSI.[31]

As recommended by the Cochrane Effective Practice and Organization of Care Group (EPOC),[32] we used segmented time series analysis, which includes changes in level and in trend, to estimate the effect size of the intervention. Data were collected on individual patient level, whereas the interventions were targeted towards hospitals with different mixes of surgical procedures. Therefore, the resulting hierarchical structure was taken into account in the analyses. As the response variable was binary (SSI present or absent), a non-linear mixed model analysis was applied using SAS Proc NLmixed, version 8.2 (SAS Institute). In the model, the hospital where the procedure was performed was treated as a random variable, and surgical procedure and calendar time of the preintervention, intervention and postintervention periods were treated as covariables. In this way, the model corrected for unequal distribution of procedures in the preintervention and postintervention periods, for unequal distribution within hospitals, and for differences in length of registration and intervention periods. The following outcome measurements were generated: mean SSI rates in the preintervention and postintervention periods, change in SSI rate immediately after the intervention, and the slopes of the curve of the SSI rates before and after the intervention.

All analyses were performed in SAS for Windows, release 8.2 (SAS Institute). A *P* level of less than 0.05 was considered statistically significant.

Results

Overall results of the optimized antibiotic policy

The optimized antibiotic policies led to a decrease of 35% in the use of prophylactic antibiotics (calculated as the number of defined daily doses (DDD) per procedure) and a decrease of 25% in the costs per procedure, mainly as a result of a shorter period of administration of prophylaxis.[20] After the intervention, antibiotics were administered inappropriately in 37.5% of the procedures, instead of the expected 93.5% had the intervention not occurred. Administration of doses after closure of the wound, instead of the recommended single dose before the first incision (with a second dose if there is major blood loss or the procedure has a long duration), was observed in 31.4% of procedures instead of the expected in 46.8%. Inappropriate timing of antibiotic administration (ie, not within 30 minutes before the first incision) was observed in 39.4% of procedures, instead of the expected 51.8%. Time series analysis showed that these improvements were statistically significant ($P<0.01$) and that they could be fully attributed to the intervention.[20] The percentage of procedures in which antimicrobial prophylaxis was administered within 1 hour before the first incision changed only slightly, from 72% to 79%.[20]

SSI results before and after the intervention

The results described here are for a total of 3,621 procedures, of which 1,668 were performed before the intervention and 1,953 after. The overall SSI rate decreased from 5.4% (95% confidence interval [CI]: 4.3%–6.5%) before to 4.5% (95% CI, 3.6%-5.4%) after the intervention ($P=0.22$).

Table 1 summarizes the characteristics of each participating hospital. Three of the 12 hospitals had fewer than 400 beds, and 3 hospitals had more than 800 beds. There were 5 teaching hospitals, of which 2 were university hospitals. The total recorded number of surgical procedures at each hospital varied from 97 to 581. Vascular procedures were recorded at 4 hospitals, intestinal procedures at 6 hospitals, gynecological procedures at 4 hospitals, and orthopedic procedures at 11 hospitals.

Table 1. Characteristics of the 12 study hospitals and number of surgical procedures performed during the 2 study periods

			No. of procedures recorded before and after intervention									
			Total		Vascular surgery		Intestinal surgery		Gynecological surgery		Orthopedic surgery	
Hospital	No. of beds	Type of hospital	Before	After	Before	After	Before	After	Before	After	Before	After
A	>800	Teaching	271	310	-	-	-	-	131	175	140	135
B	400-800	General	206	254	-	-	-	-	-	-	206	254
C	400-800	General	94	103	-	-	-	-	-	-	94	103
D	<400	General	114	131	-	-	40	49	-	-	74	82
E	>800	University	165	181	-	-	39	43	67	70	59	68
F	400-800	Teaching	136	135	87	87	49	48	-	-	-	-
G	400-800	General	41	80	-	-	-	-	-	-	41	80
H	<400	Teaching	134	178	-	-	-	-	68	88	66	90
I	400-800	General	50	47	-	-	-	-	-	-	50	47
J	<400	General	99	86	9	5	41	26	-	-	49	55
K	400-800	General	182	238	23	15	45	45	-	-	114	178
L	>800	University	176	210	46	45	36	46	62	69	32	50

The distribution of risk factors before and after the intervention is shown in Table 2. More than half of the patients were over 65 years old, 31% of the patients were male, and less than 20% of the patients had an American Society of Anesthesiologists classification of 3 or higher; 66% of the procedures were classified as clean procedures. Twenty percent of the recorded procedures were performed in university hospitals and 32% in other teaching hospitals. There were no significant differences in the distribution of the risk factors before and after the intervention ($P \geq 0.3$).

Table 3 shows PREZIES SSI rates [4] and SSI rates before and after the intervention in the present CHIPS study, according to the type of surgical procedure. The distribution of the surgical procedures was fairly similar before and after the intervention. However, the recorded number of femoropopliteal or femorotibial bypasses decreased significantly ($P=0.04$).

For 4 procedures the SSI rate decreased after the intervention, and for 3 procedures the SSI rate increased after the intervention. Table 4 shows the crude and adjusted ORs, according to the type of procedure, for the comparison of the SSI rate after the intervention with the rate before the intervention, adjusted for procedure-specific confounders. These ORs did not differ significantly from 1, indicating that the SSI rates had not changed remarkably during the intervention.

Table 2. Comparison of risk factors before and after the intervention

	Percentage of procedures with risk factor present		
Risk factor	**Before intervention (*n*=1,668)**	**After intervention (*n*=1,953)**	***P***
Age >65 years	56.4	58.1	0.30
Male sex	30.9	30.4	0.76
ASA classification ≥3	17.7	17.6	0.89
Wound class ≥2	34.7	33.7	0.54
Duration of surgery >*P*75	24.6	24.1	0.76
Teaching hospital	48.9	47.3	0.33
University hospital	20.4	20.0	0.75

Note. ASA, American Society of Anesthesiologists, *P*75, 75th percentile

Table 3. Surgical Site Infection (SSI) Rates in the Dutch National Preventie Ziekenhuisinfecties door Surveillance (PREZIES) Network and in the Surgical Prophylaxis and Surveillance (CHIPS) project

		CHIPS			
	PREZIES*:	**Before intervention**		**After intervention**	
Surgical procedure	SSI rate, % (95% CI)	n	SSI rate, % (95 % CI)	n	SSI rate, % (95 % CI)
Reconstruction of the aorta	1.9 (0.4-3.5)	95	5.3 (0.8-9.8)	95	7.4 (2.1-12.6)
Femoropopliteal or femorotibial bypass	6.3 (3.7-8.9)	70	14.3 (6.1-22.5)	57	21.1 (10.5-31.6)
Colorectal surgery	7.3 (5.6-9.0)	250	14.8 (10.4-19.2)	257	10.9 (7.1-14.7)
Abdominal hysterectomy	1.6 (0.6-2.5)	205	2.4 (0.3-4.6)	239	1.7 (0.0-3.3)
Vaginal hysterectomy	0.3 (0.0-0.8)	123	0	163	1.2 (0.0-2.9)
Replacement of the head of the femur	3.5 (2.5-4.5)	25	20.0 (4.3-35.7)	42	11.9 (2.1-21.7)
Total hip arthroplasty	2.8 (2.4-3.2)	900	3.1 (2.0-4.2)	1,100	2.7 (1.8-3.7)

Note. CI, confidence interval. * PREZIES data from 2000-2002, without the CHIPS data

Table 4. Crude odds ratio (OR) and Adjusted OR of the Surgical Site Infection rate after the intervention compared with before the intervention

Procedure	**Crude OR (95 % CI)**	**Adjusted OR (95% CI)**	**Variables adjusted for:**
Reconstruction of the aorta	1.4 (0.4-4.7)	1.4 (0.4-4.6)	Sex
Femoropopliteal or femorotibial bypass	1.6 (0.6-4.0)	1.1 (0.4-3.1)	Age (≥65 years), university hospital
Colorectal surgery	0.7 (0.4-1.2)	0.7 (0.4-1.1)	Age (≥65 years)
Abdominal hysterectomy	0.7 (0.2-2.6)	0.6 (0.2-2.4)	Duration of surgery (>*P*75)
Vaginal hysterectomy	Not calculable	Not calculable	
Replacement of the head of the femur	0.5 (0.1-2.1)	0.6 (0.1-2.6)	Age (continuous), duration of surgery (>*P*75)
Total hip arthroplasty	0.9 (0.5-1.5)	0.9 (0.5-1.5)	Age (≥75 years), ASA classfication (≥3), duration of surgery (>*P*75)

Note. ASA, American Society of Anesthesiologists; CI, 95% confidence interval; *P*75, 75th percentile.

Time series analysis that took into account possible changes over time in hospitals concerning unmeasured factors confirmed that the optimized and more-restrictive administration of antibiotic prophylaxis did not have a significant impact on the SSI rate (*P*=0.99) and that there were no significant trends in SSI rates during the preintervention and postintervention periods. Specific changes in different aspects of prophylaxis (e.g. choice, timing, and duration of antibiotic prophylaxis) after the intervention are described elsewhere.[20]

Discussion

Our results demonstrate that implementing an optimized and more-prudent antibiotic policy in hospitals did not change the risk of SSI. Our findings are in line with the results of studies that have shown that narrow-spectrum antimicrobials are as effective as broad-spectrum antimicrobials for preventing SSIs [33-35] and that single-dose prophylaxis is as effective as multiple-dose prophylaxis.[34-39] Furthermore, Classen et al.[18] have demonstrated that the SSI incidence is lower if antimicrobial prophylaxis is administered within 2 hours before the first surgical incision, compared with administration earlier or later. Despite the evidence, surgeons are still reluctant to follow guidelines that advocate use of narrow-spectrum antibiotics and single-dose prophylaxis, because they fear an increase in the incidence of SSI. Many guidelines, therefore, have not found their way into daily practice. However, in the present study, implementation of these recommendations was successful, and the improvement in quality resulted in less use and improved use of antibiotics,[20] and the effectiveness of the antibiotics for SSI prevention did not diminish. Since the timing of prophylaxis only slightly improved after the intervention, the positive effect of this improvement on the incidence of SSI might have been limited, although pharmacokinetic data indicate the desirability of administration as close as possible to the time of the first incision.[40,41]

The CHIPS multiple-site study was unique in several aspects. It involved 12 hospitals; measured SSIs as patient outcomes, in addition to the process-outcome parameters; and considered various common procedures in 4 surgical specialties. Of the many studies that have tried to implement an improved antibiotic prophylaxis policy, only a few considered an outcome parameter. A study by Gyssens et al. [17,42] recorded the number of nosocomial infections per 100 bed days. Two other implementation studies recorded the SSI rate but included only 2 hospitals [43] and 6 hospitals.[44]

Schell et al. [43] focused solely on bowel surgery, and Weinberg et al. [44] focused on cesarean section. The present CHIPS study was conducted within PREZIES. Therefore, SSI surveillance was performed according to a standardized protocol, which included postdischarge surveillance and validation of the data collection in the hospitals, which yielded reliable data on SSIs.

A limitation of our study is the lack of a control group. However, it did not seem feasible to include a control group of hospitals that would be motivated to invest a lot of effort in the data collection without the possibility of implementing the national guideline and improving the overall quality of antimicrobial prophylaxis. The participating hospitals had agreed not to introduce any other intervention during this study. Consequently, there was no change in surgical personnel, surgical methods, operating room protocols, or postoperative wound care in the participating hospitals. Despite this agreement, changes in SSI rates could still have been the result of a gradual change in practices not related to the study intervention. However, by using segmented time series analysis, trends over time not related to the intervention could be excluded.

Another limitation might be that the preintervention SSI rate was 5.4%, mainly because of overrepresentation of orthopedic procedures in the study, which is less than the 7.5% on which the power calculation was based. However, more procedures were included in the study than we had anticipated: 1,668 before and 1,953 after intervention, instead of 1,600. With this sample size and given the preintervention SSI rate, the study had enough power to demonstrate a decrease in the overall SSI rate to 3.4% or lower or an increase to 7.7% or higher. However, we observed no change in overall SSI rate before and after intervention; the observed difference was minor, with overlapping 95% CIs. Unfortunately, this study had not enough power to demonstrate a significant change in SSI rate according to the type of procedure.

In this study, no data on antibiotic resistance were collected. Therefore, we were not able to investigate how antibiotic resistance was affected by the decreased use of antibiotics (from 121 to 79 defined daily doses per 100 procedures) and the decreased use of agents with a broader spectrum than cefazolin (from 85% to 34% of procedures).[20] However, it might be expected that the restricted antibiotic use that was achieved in this study will contribute to a decrease in antimicrobial selective pressure.[13]

Most aggregated procedure-specific SSI rates reported in the present CHIPS study were higher than the national SSI rates from PREZIES. It appeared that the national

rates during the CHIPS study (during 2000-2002) were, by coincidence, lower than the average infection rates during the total national surveillance period of 1996-2004. A possible explanation for the higher rates in the CHIPS hospitals might be that the SSI surveillance during the CHIPS study was performed more accurately and thoroughly, resulting in a higher proportion of SSIs detected. Another explanation could be that not all hospitals participating in PREZIES performed postdischarge surveillance, whereas all CHIPS hospitals did perform postdischarge surveillance. However, when only SSIs that developed during hospitalization were considered, the trend of higher SSI rates in the CHIPS study was still apparent. The difference in SSI rates might also be caused by differences in present risk factors between the CHIPS and PREZIES study population, since only the crude infection rates were compared.

In conclusion, this study shows that the implementation of an optimized and restrictive antibiotic policy had no detrimental effect on the outcome of clean and clean-contaminated surgery, as measured by SSI rate.

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Chapter 5

Antibiotic prophylaxis and the risk for surgical site infections following total hip arthroplasty. Timely administration is the most important factor

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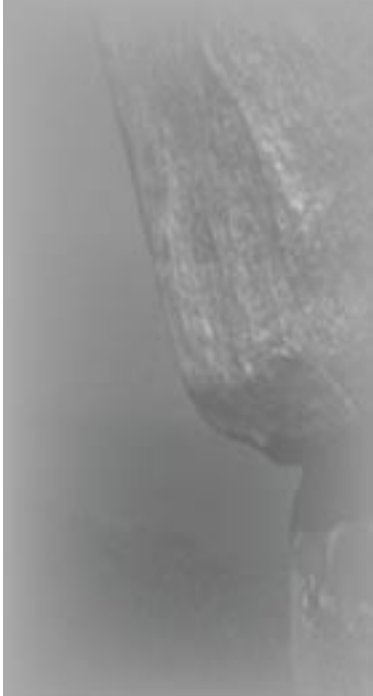

Abstract

Background: Surgical site infections (SSIs) following total hip arthroplasty can lead to prolonged hospitalization, increased morbidity and mortality, and high costs. This article analyzes the effect of various parameters of surgical antibiotic prophylaxis on the risk of SSI following total hip arthroplasty.

Methods: Data about SSI, and potential prophylaxis- patient- and procedure-related risk factors were prospectively collected for 1922 patients who underwent elective total hip arthroplasty in 11 hospitals that participated in the Dutch intervention project, Surgical Prophylaxis and Surveillance. Multivariate logistic regression analysis was performed to correct for random variation among hospitals.

Results: SSIs (superficial and deep) occurred in 50 patients (2.6 %). The highest odds ratios for SSI were found in patients who received prophylaxis after incision (2.8, 95% confidence interval [CI], 0.9-8.6; *P*=0.07), had an American Society of Anesthesiologists score that was >2 (2.8, 95% CI, 0.8-9.2; *P*=0.09), and experienced a duration of surgery that was >75th percentile (2.5; 95% CI, 1.1-5.8; *P*=0.04). Prolonged prophylaxis after the end of surgery and the use of antibiotic-impregnated cement did not contribute to fewer SSIs in this study.

Conclusion: This study suggests that intervention programs in search of amendable factors to prevent SSI should focus on timely administration of antibiotic prophylaxis.

Introduction

Surgical site infection (SSI) following total hip arthroplasty (THA) can lead to prolonged hospitalization, increased morbidity and mortality, and high costs.[1,2] The health and economic burdens of SSI are not restricted to patients' hospital stay.[3] Deep- implant SSI following THA is almost always diagnosed after discharge. Deep-implant SSIs following THA occur infrequently (0.3 -1.3 %) [4-6] but can lead to severe incapacitation.[7] Known risk factors for SSI are related to the environment, surgeon, and patient.[8] Some of these factors are amenable to intervention (e.g., conditions in the operating room). Other factors, such as advanced age and diabetes mellitus, are intrinsic patient risks and cannot be modified.[9] Antimicrobial prophylaxis contributes to the reduction in incidence of SSI and is standard practice for THA. Specific recommendations are available regarding the choice of the antibiotic, duration of prophylaxis, and timing of the first dose.[8,10-12] The cephalosporins cefazolin and

cefuroxime are considered to have equal prophylactic efficacy. Available evidence suggests that administration of the first dose as near to the incision time as possible, will achieve a decreased likelihood of SSI. However, controversy exists regarding the optimal duration of prophylaxis in connection with THA. The US advisory statement recommends that antimicrobial prophylaxis be administered within 1 h before incision and discontinued within 24 h after the end of the operation.[12] However, European guidelines recommend a single dose within 30 min before the incision.[11,13] In addition, despite the potential benefits of antibiotic-impregnated bone cement for joint arthroplasty, controversies remain regarding its use.[12]

Most studies that have analyzed risk factors for SSI following THA have mainly focused on patient, procedure, or hospital characteristics.[4,14-16] However, prospective studies of the contribution of the qualitative aspects of surgical prophylaxis to the prevention of SSI following THA are scarce. We conducted a prospective, multisite intervention study (the Surgical Prophylaxis and Surveillance [CHIPS] project) to research the quality of surgical prophylaxis in the Netherlands and documented patient outcome by surveillance of SSI.[17-19] This project aimed at narrowing the spectrum, shorten the duration, and optimizing the time of administration of prophylactic antibiotics without increasing the incidence of SSI by implementing the national guidelines for surgical prophylaxis. These guidelines, developed by the Dutch Working Party on Antibiotic Policy (SWAB), recommend intravenous single-dose cefazolin administered within 30 min before the first incision for THA.[13] Here, we explore the contribution of the parameters of the prophylaxis process to the incidence of SSI for the population undergoing THA, with an emphasis on the timing of administration of prophylaxis.

Methods

During 2000 - 2002, 11 of the 13 Dutch hospitals of the CHIPS project provided data on elective, primary THA before and after the implementation of the national guidelines for surgical prophylaxis. Procedures for revision of a hip prosthesis were excluded.

Data collection

All hospitals participated in the national surveillance network PREZIES (Preventie van Ziekenhuis Infecties door Surveillance)(www.prezies.nl). Data about the surgical procedure, potential SSI risk factors, and infections for patients who developed SSI were collected according to the PREZIES protocol,[20] using the criteria of the US

Centers for Disease Control and Prevention.[21] Local infection-control professionals prospectively collected the data and identified cases of SSI. SSIs following THA were categorized as superficial (involving skin or subcutaneous tissue) or deep (involving fascia, muscle and joint space). Postdischarge surveillance was performed for all patients. Surgeons were requested to describe clinical symptoms and whether a patient had developed a SSI on a registration card that was added to the outpatient medical record. The records were reviewed by the local infection-control professional at 30 days and 1 year after discharge.[15] Data about the quality of prophylaxis were collected from medical, anesthetic and nursing records and medication charts.
The method of prophylaxis data collection and validation are described elsewhere.[17] The choice of the antibiotic, number of doses, time of administration of the first dose and subsequent doses, use of antibiotic-impregnated bone cement, time of induction of anesthesia, and the time of incision and closure of the wound were recorded.

Prophylaxis- , patient-, and procedure-related risk factors

Duration of prophylaxis was divided into 3 categories: single dose (1 or, in case of prolonged surgery, as recommended by the national guidelines), 24 h (postoperative dosing for 24 h), and >24 h (postoperative dosing for >24 h). Timing of administration of prophylaxis was assessed as the interval (in minutes) between the administration of the first dose and the incision. If prophylaxis was administered by intravenous infusion, the point at which one-half of the infusate had been administered was noted as the time of administration. Timing of administration was divided in 4 categories: within 30 min before incision (as recommended by the national guidelines), 31- 60 min before incision, >60 min before incision, and during or after incision. The use of antibiotic-impregnated bone cement was considered a potential confounder of the effect of systemic prophylaxis.
The selection of potential patient- and procedure-related risk factors for SSI included in the national PREZIES surveillance was based on the literature to allow comparison with data generated by surveillance systems of other countries and was limited by feasibility.[20,22] The factors included sex, age, physical condition of the patient according to the American Society of Anesthesiologists [ASA] score,[23] wound class, duration of surgery >75th percentile, National Nosocomial Infections Surveillance (NNSI) score [24] and duration of preoperative of hospital stay (Table 1). The annual volume of surgery and the teaching status of the hospital, which were recently described as important risk factors for THA,[15] were also considered as possible confounders. Data about the quality of prophylaxis were linked to the PREZIES SSI database by matching date of birth, admission and surgery.

Table 1. Univariate analysis: association of selected variables with surgical site infection (SSI) following THA.

	SSI (N=50)	No SSI (N=1872)	Odds ratio (95% CI)	p-value [a]
Antibiotic prophylaxis variables				
Duration of prophylaxis				
single dose [b]	16 (33)	633 (34)	reference	
multiple postoperative doses for ≤24 h	26 (54)	782 (42)	1.4 (0.7-2.5)	0.29
multiple postoperative doses for >24 h	6 (13)	427 (23)	0.6 (0.2-1.4)	0.22
Timing of administration of first dose				
>60 min. before incision	5 (10)	110 (6)	2.0 (0.8-5.4)	0.16
31-60 min. before incision	14 (28)	524 (28)	1.2 (0.6-2.3)	0.60
1-30 min. before incision	25 (50)	1118 (60)	reference	
during or after incision	6 (12)	120 (6)	2.2 (0.9-5.6)	0.08
Use of antibiotic-impregnated bone cement	25 (50)	732 (39)	1.5 (0.9-2.7)	0.14
Patient and procedure related variables				
Age, mean years ± SD [c]	72 ± 10	68 ± 11	1.5 (1.1-2.0)	0.014
Female sex	40 (80)	594 (68)	1.9 (0.9-3.7)	0.08
ASA score [23] [d]				
1	8 (16)	507 (27)	reference	
2	29 (59)	1130 (61)	1.6 (0.7-3.6)	0.23
3+	12 (24)	217 (12)	3.5 (1.4-8.7)	0.007
NNIS-score [24] [e]				
0	22 (46)	1267 (69)	reference	
1	20 (42)	516 (28)	2.2 (1.2-4.1)	0.010
2	6 (13)	65 (4)	5.3 (2.1-13.6)	<0.001
Duration of preoperative hospital stay, days				
0-1 days	47 (94)	1766 (94)	reference	
≥2	3 (6)	106 (6)	1.1 (0.3-3.5)	0.92
Duration of surgery >75th percentile	20 (41)	435 (23)	2.3 (1.3-4.1)	0.006

Note. Data are no. (%) of patients, unless otherwise indicated. ASA, American Society of Anesthesiology; NNIS-score, National Nosocomial Infection Surveillance, surgical wound infection risk index.

[a] Univariate analysis $X2$ square and Student's t-test.; [b] Zero postoperative doses; [c] Per 10 years increase; [d] 1, healthy; 2 mild systemic disorder; ≥3 severe systemic disorder; [e] Includes the following elements: ASA-score, wound contamination class, and duration of surgery.

The CHIPS prophylaxis database contained 2031 consecutive patients who inderwent elective primary THA. Linkage with the SSI database of PREZIES was successful for 1999 procedures. For 1922 (96%), the data on the timing of antibiotic administration were complete. This data`set was considered appropriate for analysis. Missing data for ASA score (n=19), duration of surgical procedure (n=7), and duration of surgical prophylaxis (n=32) were adjusted using the missing value indicator method.[25]

Statistical analysis

Statistical analysis was performed using SAS Software, release 9.1 (SAS Institute). The correlation between antibiotic prophylaxis parameters and potential patient and procedure related risk factors for SSI was tested univariately with the X^2 test or Student's *t* test. Pearson's correlation coefficient was used to assess the correlation between the annual number of arthroplasties performed per hospital and the incidence of SSI. Multivariable regression analysis was performed to account for these possibly confounding risk factors. According to our hypothesis, the variables duration and timing of prophylaxis and the use of antibiotic-impregnated bone cement were forced into the multivariable model. The patient- and procedure-related risk factors for SSI, with a threshold of statistical significance of P<0.1 in crude analyses, were included in the model. The NNIS-score was not included in the multivariate analysis because all procedures were clean (value, 0), and its other components (the ASA score and duration of surgery >75th percentile) were already included in the model.

In the present multicenter study, patients were clustered by hospital. This level of hierarchy can introduce additional sources of variability and correlation (e.g., by hospital-specific treatment policies, risk factors, and the diagnostic accuracy of the infection-control professional). Therefore, a random coefficient model (procedure NLMIXED in SAS) was used to adjust the risk estimates for random variation among hospitals. In this model, both fixed and random effects can be entered nonlinearly. This model is basically a logistic regression model, supplemented with an extra term in the equation for the random effects associated with differences in infection risk among hospitals. Because regular logistic regression models do not take into account interhospital variability, they might overestimate the contribution of patient- and prophylaxis-related factors.

The final multivariate model was used to calculate the predicted probability of developing an SSI for each patient. These probabilities were averaged separately for patients with and for those without an SSI. The mean predicted probability for patients with an SSI was divided by the mean predicted probability for patients

without an SSI. This ratio represents a measure of the goodness of fit of the model, with a ratio of 1 indicating that the risk factors in the model do not contribute to the prediction of developing an SSI. Adjusted odds ratios were expressed with 95% CIs. $P<0.05$ was considered to be statistically significant.

Results

All 11 hospitals had operating rooms with laminar air-flow conditions. Drains were routinely used in all hospitals. The annual number of THAs per hospital varied from 47 to 249. Of the 1922 patients included in the analysis, 69 % were female, with a mean age (±SD) of 68.8 ± 10.8 years. The ASA score was >2 for 12% of patients. The mean duration of preoperative stay (±SD) was 1.2 ± 2.1 days, the mean duration of the procedure (±SD) was 78.6 ± 35.3 min, and the mean duration of postoperative stay (±SD) was 8.8 ± 5.6 days. All patients received antimicrobial prophylaxis. The antibiotics that were administered were classified according to the Dutch Working Party on Antibiotic Policy guidelines as effective with a narrow spectrum (cefazolin [*n*=947], flucloxacillin [*n*=48], and erythromycin [*n*=8] or clindamycin [*n*=1] (in cases of allergy) or with a broader spectrum (cefamandole [*n*=39], cefuroxime [*n*=873], amoxicillin plus netilmicin [*n*=1] and clindamycin plus gentamicin [*n*=1]. No antibiotic with a very short half-life (e.g, cephalothin; half-life, 0.5 h) was used. For the 2 patients receiving >1 prophylactic antibiotic, the combination was assessed as a single course. In 49% of the procedures, the antibiotic choice was completely according to the guideline. Prophylaxis with an antibiotic of a broader spectrum was not associated with fewer SSIs than prophylaxis with an antibiotic with a more narrow spectrum (OR, 0.7 ; 95% CI, 0.5-1.4; *P*=0.43). Prophylaxis with an antibtiotic with a longer half-life (erythromycin [half-life, 1.75 h] and cefazolin [half-life, 2 h]) was not associated with fewer SSIs than prophylaxis with an antibiotic with a shorter half-life (flucloxacillin and cefamandole [half-lives, 0.75 h]) and cefuroxime [half-life,1 h]; OR, 1.1; 95% CI, 0.5-2.3; *P*=0.75. For 34% of the procedures, no postoperative doses were administered, and for 59%, the first dose was administered within 30 min before incision, according to the guidelines. Antibiotic-impregnated bone cement was used in 757 cases (39%). SSI occurred in 50 patients (2.6%). Of these infections, 40 were superficial (2.1%), and 10 (0.5%) were deep (including prosthesis-related). The average duration of stay (±SD) for patients without SSI was 9.9 ± 6.0 days, compared with 14.1 ± 12.0 days for patients with SSI.

Univariate analysis

The crude association of the selected prophylaxis-, patient-, and procedure-related variables with SSI is presented in table 1. Administration of the first dose of prophylactic antibiotics after incision was associated with an increased (although statistically nonsignificant) incidence of SSI. Dividing the timing of prophylaxis into 3 categories; within 60 min before incision, >60 min before incision, and during or after incision, did not change the results (OR for timing during or after incision, 2.9; *P*=0.06). Postoperative antibiotic doses and the use of antibiotic-impregnated bone cement were not inversely associated with SSI risk. Older age, comorbidity expressed by ASA score of >2, and prolonged surgery were associated with a higher rate of SSI. Undergoing surgery in a teaching hospital did not affect the risk of a SSI (*P*=0.30, by X^2 for risk). The incidence of SSI per hospital was not correlated with the annual volume of total hip procedures (Pearson *R*=-0.19, *P*=0.58). Rates of SSI according to the time of administration of the first dose are shown in Figure 1.

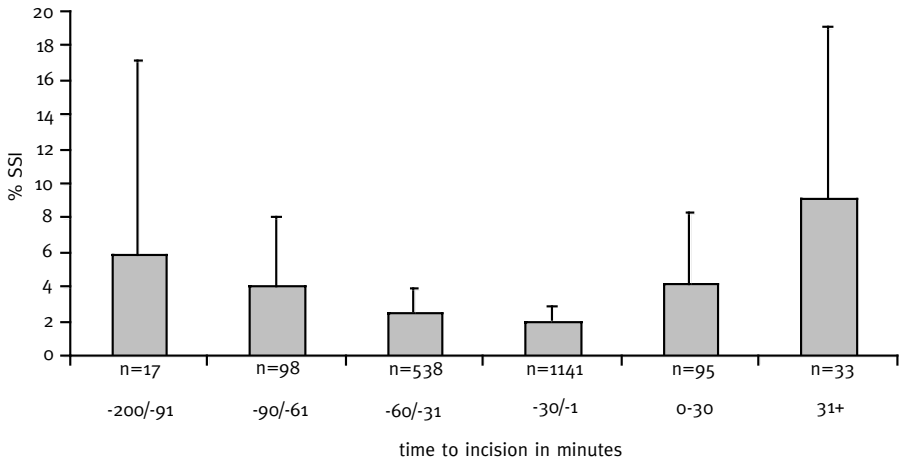

Figure 1. Association between the timing of prophylaxis and the incidence of SSI in total hip arthroplasty. SSI; surgical site infection

Multivariate logistic regression analysis

The multivariable analysis confirmed that multiple-dose postoperative prophylaxis and the use of antibiotic-impregnated bone cement were not inversely associated with the rate of SSI. Of the 4 potential patient- and procedure-related risk factors that reached the threshold of statistical significance and therefore were included

in the model, only duration of surgery >75th percentile was independently and significantly associated with SSI (OR, 2.5; 95% CI, 1.1-5.8) (Table 2). Relatively high ORs could be calculated for the independent associations of rate of SSI with ASA score of >2 (OR, 2.8; 95% CI, 0.8-9.2) and with timing of administration of prophylaxis after incision (OR, 2.8; 95% CI, 0.9-8.6).
The mean predicted probability of the model was 0.076 for patients with an SSI and 0.024 for patients without an SSI. The ratio of the means was 3.2, which indicates that according to the model, the likelihood of developing an SSI was 3.2 times higher for patients with the selected risk factors than for patients without the risk factors.

Table 2. Multivariate analysis of risk factors for SSI following total hip arthroplasty corrected for clustering of effects within hospitals.

	OR	95% CI	p-value [a]
Antibiotic prophylaxis variables			
Duration of prophylaxis			
single dose [b]	Reference		
multiple postoperative doses for ≤24 h	2.0	(0.6-7.0)	0.26
multiple postoperative doses for >24 h	1.4	(0.2-9.2)	0.69
Timing of prophylaxis			
>60 minutes before incision	1.3	(0.4-4.4)	0.68
31-60 minutes before incision	0.9	(0.4-2.1)	0.82
1-30 minutes before incision	Reference		
during or after incision	2.8	(0.9-8.6)	0.07
Use of antibiotic-impregnated bone cement	0.8	(0.3-1.9)	0.57
Patient- and procedure- related variables			
Age, years [c]	1.4	(1.0-2.1)	0.08
Female sex	1.7	(0.7-3.9)	0.19
ASA score [23] [d]			
1	Reference		
2	1.5	(0.6-3.8)	0.39
3+	2.8	(0.8-9.2)	0.09
Duration of surgery (>75th percentile)	2.5	(1.1-5.8)	0.04

Note. ASA, American Society of Anesthesiology score. [a] Random coefficient model procedure NL MIXED in SAS software (SAS Institute); [b] Zero postoperative doses; [c] Per 10-years increase; [d] 1, healthy; 2 mild systemic disease; ≥3, severe systemic disorder.

Discussion

In this multivariable analysis of prophylaxis-, patient-, and procedure-related risk factors for SSI following THA, prolonged duration of surgery (>75th percentile) was the only independent and statistically significant confounding risk factor. Although it did not reach statistical significance, failure to administer the first dose of antibiotic before incision seemed the most important prophylaxis-related factor for increasing the risk of SSI. These findings are important for clinical practice. Although several other studies have made risk assessments for SSI in orthopedic surgery,[4,14,15,26] this is, to our knowledge, the first study to have evaluated the association of SSI with duration of surgery, timing of administration of prophylaxis, and the use of antibiotic cement. In addition, by excluding emergencies and revisions, the findings indicate the net effect of antibiotic prophylaxis on incidence of SSI in patients undergoing primary elective THA; previous studies included both emergency and elective surgery.[14,15,26] In our surveillance, postdischarge surveillance was performed until 1 year after surgery, and therefore, the incidence of SSI might be higher than in other studies that did not perform postdischarge surveillance. Yet, the SSI incidence of 2.6 % is comparable with incidence rates found in other surveillance studies of THA.[4,27]

Although not significant, the OR for timing of administration of prophylaxis after incision suggests that the relative risk of SSI increases in the presence of this factor. The number of patients in some timing categories was too small to draw firm conclusions about the optimal preincisional timing period. Previous studies of general and colorectal surgery also found that administering prophylaxis after incision had a detrimental effect on the incidence of SSI.[28,29]

Previous experimental studies have shown the importance of the presence of antibiotics in the tissue at the moment of potential contamination.[30,31] In another,[32] injection of antibiotics as an intravenous bolus immediately prior to incision resulted in adequate antibiotic levels in the tissue levels at the start of surgery. During orthopedic surgery, administration of cephalosporins during incision resulted in sufficiently high concentration in bone at the moment of removal of the femoral head.[33,34] An advantage of the administration of antibiotics shortly before the incision is that, in most procedures, the concentration of the antibiotic will still be high enough to prevent infection at the end of the procedure, and repeated dosing during prolonged surgery is less often required. The importance of a sufficient concentration of an antibiotic at the time of closure of the wound on SSI rate was recently established for gentamicin in colorectal surgery.[35]

In the present analysis, duration of prophylaxis was not correlated with the rate of SSI. In a report that included data from 22,000 THA procedures in the Norwegian Arthroplasty Register (during 1987-2001), the incidence of SSI in the group who received single-dose prophylaxis was equal to that in the group who received 4 doses. However, the incidence of aseptic loosening of the joint was higher in the single-dose group.[36] Unfortunately, the authors did not provide data on dosing intervals and timing of administration of the first and subsequent doses, which may have confounded the effect on outcome in this long-term cohort. This is especially important because, in the majority of the cases, cephalothin was used _which has a very short half-life_ and consequently, tissue concentrations quickly decrease.[37] It is likely that the use of cephalothin has confounded the results. Cefazolin, which has a much longer half-life and is recommended by many guidelines,[11,13] is likely to negate the use of repeated dosing, as was convincingly demonstrated in our study.

The duration of surgery, identified in our study as the most important risk factor for SSI, could be potentially confounded by other unmeasured factors. Detailed data about complications that could affect duration of surgery (e.g, bleeding, resulting in low antibiotic concentrations) were not collected in our study. Furthermore, duration of surgery seems not readily amenable to change by an intervention. The unchangeable patient risk factors of older age and higher ASA score also resulted in higher ORs for SSI. These risk factors are also described in other studies.[4,26,29] In contrast to findings by others, the duration of preoperative hospital stay could not be identified as a risk factor in our study. This discrepancy was probably because of the fact that almost 95 % of the patients in our study had a preoperative hospital stay of ≤1 day.

Apart from patient- or procedure- related risk factors, hospital-related factors (e.g.surgical technique) can influence the incidence of SSI. By using the procedure NLMIXED in SAS with hospital as a level, we took the hierarchical structure of the data into account and thereby corrected for possible random variation among hospitals.

Our study does have some limitations. First, the number of risk factors included in our study was limited to those reported within the PREZIES network. Although diabetes mellitus, malignancy, and corticosteroid use are reflected in the ASA-score, separate reporting of these known risk factors might have rendered risk assessment more precise. Other risk factors that are not reflected in the ASA-score (e.g., obesity, perioperative body temperature, and oxygenation) were shown to be relevant in other studies.[38-40] Another limitation of our analysis was the relatively low number

of SSIs (n=50), which was the dependent outcome variable of our analysis. Of the 77 patients from the CHIPS database to whom prophylaxis was administered but who were excluded from this analysis because information on timing was not known, 8 patients (10.3%) developed an SSI, compared with 50 (2.6%) of 1922 patients who were included in our analysis (P<0.0003). This difference could be because of the characteristics of these patients or could imply that reporting the time of administration of prophylaxis is in itself a marker of correct performance. Finally, the fact that the postdischarge surveillance depended on reporting by the surgeons could have resulted in the underreporting of SSI.
In conclusion, prolonged duration of surgery was the only significant risk factor for SSI following THA. Although it did not reach statistical significance, the timing of the administration of the first dose of an antibiotic after incision seems to be the most important prophylaxis parameter. Multiple postoperative dosing did not contribute to reduction of the incidence of SSI. We strongly recommend that intervention programs on surgical prophylaxis focus on timely administration of the prophylactic antibiotic.

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Potential conflict of interest

All authors: no conflicts

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Chapter 6

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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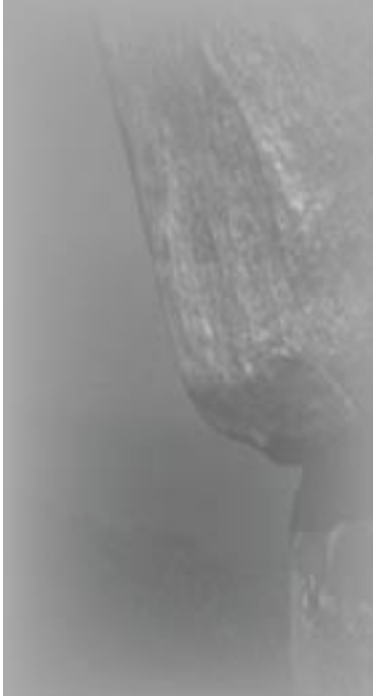

Abstract

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 parameters, 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=0.003). Dosage adjustment to renal function remained unchanged at 45% vs 52% (P=0.09) of cases where necessary. Switching of therapy from intravenous to oral improved from 46% to 62% (P=0.03) and was performed a mean of 1.6 days earlier (P=0.002). 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.

Introduction

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.[1] Up to the present, guidelines in antimicrobial therapy have mainly focused on the choice of the 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.[2]

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.[3-6] 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.[7, 8] 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.[9] 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,[10] adverse drug reactions,[11] 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,[12-16] and it has been shown to save costs, shorten length of hospital stay, and decrease adverse reactions of IV administration, with equal therapeutic outcome. Conceptually, streamlining of antibiotics (i.e, adjustment to narrow-spectrum therapy, guided by culture reports) can contribute to the prevention of antimicrobial resistance,[2, 17] and an adequate system of reporting culture reports 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.

Patients and 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 included. An antibiotic course was defined as therapy with one 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 to 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.[18] A table for dosage adjustment to renal function, based on generally accepted data,[19] 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 [14-16, 20-26] 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.

Table 1. Guidelines for switching from intravenous to oral administration of therapy.

Basic criteria	Not eligible	Sometimes eligible*
Significant clinical improvement	*Staphylococcus aureus* bacteremia	Immunosuppressive therapy
Hemodynamic stability	Endocarditis	Immunodeficiency
Evident normalizing body temperature	Meningitis or cerebral abscesses	Neutropenia
Normalizing leukocyte count	Undrained abscesses, empyemas, mediastinitis	Severe sorft tissue infections
Good patient compliance	Intravascular infection (ie, infected valve or vascular prothesia, infected thrombus	*Pseudomonas* bacteremia
No signs of malabsorption		Exacerbation of cystic fibrosis
Ability to take oral medication		Severe intra-abdominal infection or endometritis
Good pharmacokinetics of oral antibiotic		Liver abscesses, drained abscesses and empyemas, osteomyelitis, and arthritis can sometimes be switched after 2 wk of IV therapy
Suitable oral alternative for IV medication available		

Abbreviation: IV, intravenous. * Indicates infectious disease consultation required

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).[1, 27-29] No specific advice was given at the individual prescription level.

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=0.05). By considering that 10% of the initial prescriptions are given orally, a total of 250 patients was needed in every group. In the case of timing, 50 patients in each group proved enough statistical power in a previous study of our hospital.[8]

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 χ^2 test. A *P* value less than 0.05 was considered statistically significant.

Results

Pre-intervention results

During the pre-intervention 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 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).

Table 2. Demographic characteristics*

	Preintervention (*n*=247)	**Postintervention (*n*=250)**
Wards, No. of patients		
Internal medicine	166	165
Surgery	56	60
Neurology	25	25
Sex, M/F	123/124	110/140†
Mean age, y	58.4	58.9
No.of courses	298	299
No. of prescriptions	563	598
Urinary tract infections	80	52‡
Respiratory infections	65	91‡
Abdominal infections	48	56
Sepsis without definite focus/ intravascular infection	20	28
Skin/wound infections	24	26
Fever and neutropenia	20	11
Fever without definite focus	13	11
Abscess/empyema/osteomyelitis/arthritis	11	8
Miscellaneous	17	16
Positive blood-culture findings	57	52

* Unless otherwise indicated, data are expressed as number of courses. † $P<0.05$. ‡ $P<0.01$

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 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 1.13 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 one 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).

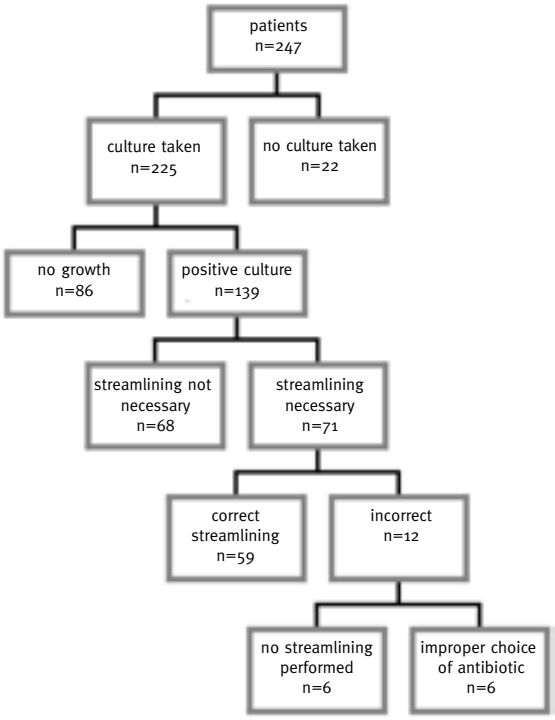

Figure 1. Profile of patients included in analysis of antibiotic streamlining. Appropriateness of streamlining can only be assessed in case of cultures with positive results.

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.

Table 3. Barriers to change

Timing	Order to nurse unclear Urgency of antibiotic therapy not known Time-consuming decision making Postponement of first dose to regular medication round Waiting for obtainment of cultures Intravenous access not yet available Antibiotics not immediately available at the ward Transfer from emergency room to ward
Dosing intervals	Administration of oral antibiotics with meals No administration of drugs at nighttime
Dose adjustment to renal function	Underestimation of the prevalence of renal insufficiency Serum creatinine <1.6 mg/dl (<140 µmol/l) considered as safe, especially in elderly patients Failure to calculate creatinine clearance
Switch	Unawareness of the concept of switching therapy

Administration schedules used by nurses for orally administered antibiotics were not ideal for two main reasons. First, oral antibiotics were often given during the meals. Second, the dosing interval during the night was often prolonged for logistical reasons. Reasons for omitting dosage adjustment to renal function were underestimation of the prevalence of renal insufficiency; considering 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 feed back 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's formula on the desktop (Excel spreadsheet, Microsoft 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 as well as possible oral alternatives to IV therapy (Table 1) to be pasted into their antibiotic guidelines booklet. Nurses were instructed to remind physicians to the possibility of switch after two days of IV therapy.

Post-intervention results

The number 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=0.003) for all cases and from 2.7 to 1.7 hours in potentially severe cases (Figure 2a; P=0.003). The number of first administrations in the wards within 2 hours in potentially severe cases increased from 60% to 76% (P=0.02). For mild infections, the mean delay in the wards decreased from 8.0 to 4.1 hours (Figure 2b; P=0.006). 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 the first dose decreased from 4.2 to 3.9 hours (Figure 2c; P=0.30). The number of first doses administered in the emergency department increased from 19% to 27% (P=0.13).

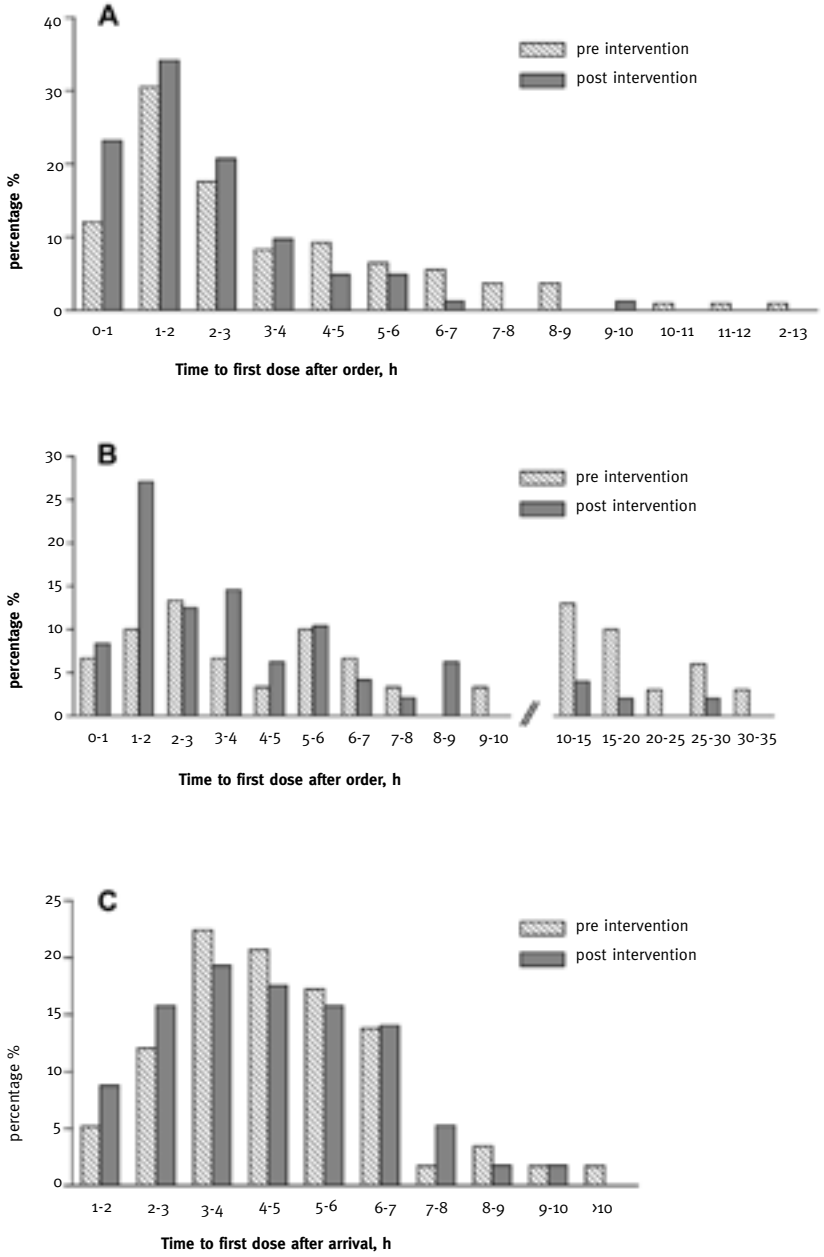

Figure 2. Timing of administration of the first dose of antibiotics, including time from the order to the first dose during the preintervention and postintervention periods at the wards in potentially severe cases (A) and mild cases (B), and time from arrival at the emergency department to the first dose in potentially severe cases (C).

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*=0.045). For oral administration, deviations from more than one third of the interval improved from 21% to 14% (*P*=0.056).

In the postintervention period, creatinine clearance was less than 50 ml/min in 68 (30%) of 224 patients for whom renal function could be calculated. Dosage adjustment was necessary in 129 of 171 antibiotic prescriptions. The number of correct prescriptions improved from 45% to 52% (*P*=0.09).

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*=0.03). The switch was performed 1.6 days earlier with a mean of 0.7 days after the per-protocol moment (*P*=0.002). In three 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.

Discussion

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 has 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.[30] 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 the 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 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.[14, 31, 32] 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 room [7,8] 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 the area of administration of antibiotics.

Acknowledgements

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Chapter 7

Implementing a national guideline for perioperative prophylaxis in Dutch hospitals: barriers to change and process evaluation of the intervention

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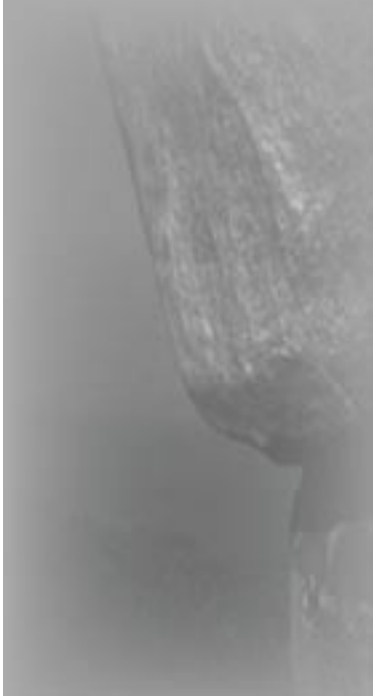
submitted



Abstract

Objective: to study the barriers to change for implementation of a guideline for surgical prophylaxis.
Methods: Questionnaire, audits and on site visits in 13 Dutch hospitals participating in the Surgical Prophylaxis and Surveillance Study (CHIPS).
Results: To achieve a change in antibiotic choice, the chairman of the antibiotic policy committee was the key player, and barriers for change were lack of agreement with antibiotic choice. To optimize the duration of prophylaxis, key players for change were the surgeons, and barriers were lack of agreement – especially in orthopaedic surgery –, and lack of outcome expectancy. Regarding timing of administration, the anaesthetists and, importantly, anaesthesiology nurses were the key players for improvement, whereas organisational constraints; for example time of arrival at the surgical suite and time spent in holding area, test-dose before actual administration and infusion instead of bolus injection, were the most important barriers to change. The nature of these organisational constraints differed per surgical specialty and per hospital.
Conclusion: Barriers to change involved in the implementation of a guideline for surgical prophylaxis differ per parameter of prophylaxis, between surgical specialties and within hospitals. Therefore, identification of the specific, local barriers to change, as well as identifying and working with the key players for change in the local setting is essential for the successful implementation of antibiotic policy.

Introduction

The administration of perioperative antibiotics is one of the tools used to reduce the incidence of surgical site infections (SSI).[1] Misuse of antibiotics for prophylaxis however is quite common.[2-5] In general, prolonged use of antibiotics and the use of broad spectrum antibiotics have been shown not to improve the efficacy of surgical prophylaxis [6-10] but rather lead to higher costs and increased risk of development of resistance.[11] Inappropriate timing however, is associated with decreased efficacy.[12,13] Therefore, the Dutch Working Party on Antibiotic Policy (SWAB) has issued guidelines for surgical prophylaxis in the Netherlands, advocating prudent use of antibiotics in terms of single dose prophylaxis with the narrow spectrum antibiotic within 30 minutes before incision. In this guideline, cefazolin is the recommended drug, supplemented

by metronidazole for surgery at sites with a prevalence of anaerobic bacteria.[14] Many guidelines however are abandoned in daily practice, and various implementation strategies have been used with mixed success.[15,16] There is no magic implementation strategy, and a successful strategy in one setting can be totally ineffective in the other.[17] Adherence to clinical guidelines may be hindered by a variety of barriers, which can be highly situational and depend upon the various health-care providers involved.[18,19] In surgical prophylaxis, the stakeholders are antibiotic committees and infection control committees, in which surgeons, pharmacists, anaesthetists and microbiologists are represented, as well as the anaesthesiology nurses and nurses on the ward. Identification of barriers to change in these groups can help to target interventions and thereby facilitate the process of guideline implementation.
The multisite intervention project CHIPS (Dutch acronym for Surgical Prophylaxis and Surveillance of Infection) was conducted from 2000 to 2002 in 13 Dutch hospitals to implement the national SWAB guidelines on surgical prophylaxis.[20] The present article describes the barriers to change that were encountered during the implementation and their impact on the effect of the intervention at the various sites.

Methods

Design of the intervention study

The present intervention study aimed at optimizing antibiotic prophylaxis in terms of antibiotic choice, duration and timing by promoting single dose prophylaxis with cefazolin within 30 minutes before the surgical incision.[14]
The study was conducted in the surgical departments of 13 Dutch hospitals participating in the CHIPS study.[20] Between January 2000 and October 2002, the quality of prophylaxis was audited before and after an intervention. A total number of 2097 orthopaedic, 344 vascular, 864 gynaecological and 508 intestinal procedures were investigated.

Method of intervention, process evaluation and inventory of barriers to change

The CHIPS intervention team consisted of an infectious disease physician and an infection control professional (ICP). This team was supported by two senior infectious disease physicians, an epidemiologist, and a consultant of the Quality Institute CBO. Opinion leaders from the surgical specialties involved served as an advisory committee.

Audit and feedback was used as the main intervention strategy to make participating hospitals aware of the local situation and to motivate them for change.
A step-wise approach was followed:
Step one: Hospital specific audit data of the pre-intervention period were fed back as a written report, and specific recommendations for improvement were given to individual hospitals depending on the outcome of the audit.
Step two: The national guideline for surgical prophylaxis was distributed among surgeons, anaesthetists, pharmacists, microbiologists, the committee on antibiotic policy and the infection control committee. A questionnaire was sent to the chairpersons of the antibiotic policy committees of the participating hospitals to evaluate their opinion about the national guideline.
Step three: On site, meetings were organised with medical microbiologists, members of the antibiotic policy committee, surgeons, anaesthetists and anaesthesiology nurses to discuss the data, and to define, per parameter of prophylaxis, the key players for improvement as well as to make an inventory of barriers to change. Barriers to change were grouped according to the classification by Cabana [19,21] whether they affect internal barriers, such as knowledge (lack of awareness or lack of familiarity) or attitude (lack of agreement, lack of self-efficacy, lack of outcome expectancy, inertia of previous practice) or external barriers, i.e., organisational constraints.
Step four: Depending on the results of the barriers to change, local implementation strategies were formulated and a local intervention team was formed.
Step five: Implementation of revised guidelines by local intervention teams was facilitated by the CHIPS team by organising educational meetings and by providing plasticized reminder cards which could be pasted on the wall of the operating theatre.
Step six: Audit of prophylaxis after intervention, evaluation of success, identification of features to failure or success.

Results

Thirteen hospitals were included in the study, 5 teaching hospitals, including two university hospitals, and 8 community hospitals. The chairpersons of the antibiotic policy committees (9 microbiologists, 3 hospital pharmacists, 1 infectious diseases physician) from all 13 hospitals returned the questionnaire.

Antibiotic choice

The audit revealed that in 12 of the 13 hospitals, independent of surgical specialty, the administered antibiotic was not cefazolin but mostly a second generation cephalosporin. In 11 of these 12 hospitals, the local guidelines did not recommend cefazolin and needed to be updated.

Inventory of barriers to change

The questionnaire showed that the antibiotic policy committee chairperson agreed on cefazolin as the first choice agent in 10 out of 12 hospitals.

During discussions of the results of the audit with the physicians, it became clear that surgeons generally follow the recommendations of the antibiotic policy committee (APC) regarding the antibiotic choice. For the intervention team, this meant that key players for improvement of antibiotic choice in these hospitals should be the members of the APC. Results of the discussions with APC representatives showed only minimal barriers to antibiotic change at this level. Only in two hospitals the APC disagreed with the choice of cefazolin, which confirmed the results of the questionnaire. This barrier was classified as *lack of agreement* (Table 1).

In two other hospitals, there were barriers affecting behaviour. In these hospitals, the APC experienced *organisational constraints*, (Table 1) as they preferred simultaneous hospital-wide implementation of a new antibiotic choice, rather than in those specialties involved in the present study only. This hospital-wide implementation was considered not feasible within the time schedule of the study. Therefore, guideline changes in these hospitals were postponed. In one hospital, where the guideline recommended cefazolin, an additional barrier affecting knowledge was identified: a *lack of awareness* of orthopaedic surgeons with a recent APC guideline change favouring cefazolin.

Implementation and evaluation

The representatives of the APCs of 8 hospitals prepared guideline changes by organising local consensus meetings with all members of the APCs and the surgeons. After reaching consensus, updated prophylaxis guidelines were disseminated on paper and presented at local educational meetings. The hospital pharmacists made sure that cefazolin was in stock at the theatres and that other prophylactic antibiotics were removed. The role of the CHIPS team was mainly one of support, e.g., by giving oral presentations or by providing hospitals with reminder cards which could be pasted on the wall of the theatres.

Table 1. General overview of barriers to change encountered during the CHIPS intervention study on surgical prophylaxis

Experienced barrier for change	**Antibitoic choice**		**duration**		**timing**	
	Barrier present	**Successful implemetation**	**Barrier present**	**Successful implemetation**	**Barrier present**	**Successful implemetation**
Internal barriers knowledge						
Lack of awareness	1(F)	1(F)	-	-	-	-
Internal barriers attitude						
Lack of agreement	2 (B,F)	0	7 (C,D,F,G,I,K)	2 (G,I)	-	-
Lack of outcome expectancy	-	-	5 (C,D,F,K,L)	0	1 (M)	0
Lack of motivation	-	-	-	-	1 (D)	0
External barriers						
Environmental factors, organisational constraints	2 (C,M)	0	1 (H)	1 (H)	11 (A,B,C,E,F G,H,I,J,K,L)	4 (G,H,J,K)

A-l = individual hospital code

When guidelines were updated by the local APCs, surgeons confined themselves to these guidelines, and a significant improvement in antibiotic choice was achieved (Table 2); In hospital F, increased awareness of the original APC guideline after the intervention led to a major increase of cefazolin prophylaxis in orthopaedic surgery.

Table 2. Determinants of timing of prophylaxis

Determinants	Effect on timing of administration	Suggestions for improvement in case of incorrect timing
More time spend at holding area prior to surgery	Earlier	In case of general surgery; timing mostly too late: earlier arrival at holding area. In case of othopaedic surgery; timing mostly too early: delay administration untill transfer to operating theatre.
Intubation before administration of antibiotics	Later	Administration of antibiotic before intubation
Test dose before administration of full dose of antibiotic	Later	Only test dose in case of presumed allergy
Mode of administration of antibiotic as infusate	Later	If possible, administer antibiotic as push
Indication for prophylaxis written down in record	Earlier	Provide written instruction in medical record

Duration of prophylaxis

As was assessed in the audit, prolonged administration of prophylactic antibiotics after surgery was extended at the ward in 8 hospitals. There were large differences between surgical specialties. Extended prophylaxis was a problem almost exclusively encountered in orthopaedic surgery, except for one hospital where general surgeons also continued the prophylactic antibiotics postoperatively. In total, six hospitals recommended a duration of 24 hours of prophylaxis in their local guideline (D,F,G,H,I,K).

Inventory of barriers to change

The questionnaire showed that the chairperson of the APC of all 8 hospitals agreed on single dose prophylaxis.

After discussing the results with the microbiologists and the orthopaedic surgeons during on-site meetings, it became clear that the APCs had aimed to change the

local guidelines in the past, but orthopaedic surgeons were not convinced about the efficacy of single-dose prophylaxis. Although antibiotic policymakers [14,22] refer to a Dutch study of prophylaxis in 2651 hip replacements [23] to support single dose prophylaxis, orthopaedic surgeons referred to the same study to favour 24 h prophylaxis. After discussions with the orthopaedic surgeons, the barriers to change affecting attitude, i.e., *lack of agreement* and a *lack of outcome expectancy* with single dose prophylaxis, remained in 5 hospitals. (Table 1). Thus, the inventory of barriers identified orthopaedic surgeons as key players for improvement, and convincing these surgeons of the efficacy of single dose prophylaxis was necessary before implementing new guidelines.

In hospital H, the general surgeons were motivated for a change to single dose prophylaxis in bowel surgery. The major barrier for prolonged administration of prophylaxis in this hospital was an inadequate stop order at the ward, a barrier of *organisational constraint* (Table 1).

Implementation and evaluation

In order to convince orthopaedic surgeons to switch to single dose prophylaxis, the CHIPS team presented the audit reports containing discussions of the literature in the various hospitals. Because no consensus could be obtained, the primary author of the aforementioned Dutch trial on duration of prophylaxis in orthopaedic surgery, who was asked to act as opinion leader, wrote a personal comment on his own study supporting the use of single dose prophylaxis. This comment was sent to all orthopaedic surgeons involved.

Ultimately, single dose recommendations were accepted by the orthopaedic surgeons in only two hospitals (G,I). In these hospitals, a significant increase in single dose administration was achieved. In hospital H, were the lack of clear stop orders resulted in prolonged administration, the nurses were requested to check whether administration of the prophylactic antibiotic was stopped after surgery. This resulted in a significant shortening of the duration of prophylaxis in intestinal surgery.

Timing of antibiotic administration

According to the audit results, timing of the first dose was not within 30 minutes before the surgical incision in at least 28% of the surgical procedures in all participating hospitals. In some hospitals, this occurred in up to 80 % of the procedures. In four hospitals, the local guidelines recommended to administer the

first dose before the incision, but there was no exact recommendation for the appropriate timing. Marked differences between surgical specialties in the way timing was discordant with the SWAB-guideline were observed in all hospitals. The moment of administration of the first dose was significantly earlier in orthopaedic surgery than in intestinal and gynaecological surgery. In orthopaedic surgery, the first dose was most often administered between 30 and 60 minutes before the incision instead of within 30 min. as recommended in the guideline. In most gynaecological and intestinal procedures however, the antibiotic was administered after the incision. In one hospital (H), the first dose was administered at the ward before the operative procedure in more than half of the patients. This led to too early administration of prophylaxis in orthopaedic as well as intestinal surgery.

Inventory of barriers to change

The questionnaire showed that the chairperson of the APC of 13 hospitals agreed on optimal timing within 30 minutes prior to the incision.

In all hospitals, anaesthetists and local ICPs attended the on-site meetings. In half of the hospitals, the anaesthesiology nurses could also be interviewed. In 12 out of 13 hospitals, administration of the antibiotics was the anaesthetist's duty, most often delegated to the anaesthesiology nurse. The intervention team should therefore focus on the anaesthetist and anaesthesiology nurses as key players of improvement. Not all anaesthetists considered timing within 30 minutes before incision a high priority, and there were barriers affecting attitude, such as *lack of motivation to change* or a *lack of outcome expectancy* (Table 1). In discussing the process of preparing the patient for surgery, the anaesthetists and anaesthesiology nurses pointed out several determinants of the timing of the administration of the first dose of prophylaxis that could be identified as *organisational constraints*. These determinants are time of arrival at the surgical suite and time spend in the holding area, the need of a test dose before the actual administration of the full dose of the antibiotic, delaying administration after intubation, administration as infusion in stead of bolus injection and a written order for prophylaxis in stead of the need to wait for instructions (Table 2). The way these factors influenced the timing could differ per surgical specialty. For example, in orthopaedic surgery, which is often performed under loco-regional anaesthesia, the patient usually arrives amply before the start of surgery, which enables the anaesthetist to administer prophylaxis early. Intestinal and gynaecological surgery however, are generally performed under general anaesthesia, and the interval between time of arrival

at the operating theatre and start of surgery is much shorter, which leaves less time for the proceedings of the anaesthetist and can result in administration of prophylactic antibiotics after the incision. In intestinal surgery, metronidazole has to be administered as an infusion, which takes more time than push administration of cefazolin.
Several anaesthesists argued that postponing the administration of antibiotics until after intubation was preferred, to have airway access in case of anaphylaxis. As most antibiotics in intramural and extramural health care are administered without prior intubation, it may be argued that this notion is debatable.

Implementation and evaluation
The CHIPS team initiated educational meetings with anaesthesiology nurses and gave suggestions to remove the barriers to change (Table 2).
In general, improvement of the timing was a difficult process, and changing logistics was not easy. In particular, the unpredictable time of arrival of the patient at the surgical suite was a structural problem that could not be solved easily in most hospitals.
Only in those hospitals in which both the anaesthetists considered timing to be a priority issue and a special meeting was organised for the anaesthesiology nurses, the organisational constraints could be overcome and improvement in timing could be achieved (Table 3). The timing in hospital E showed no improvement, and it even deteriorated in hospital F. In that hospital, timing had improved in gynaecological surgery, i.e., the number of patients for whom timing was too late did decrease. On the other hand, in orthopaedic surgery, prophylaxis was administered more than 30 minutes before the incision, i.e., too early, for significantly more patients, as a result of implementing new hospital-wide guidelines for administration of prophylaxis in the holding area. This example underscores the notion that specific strategies to improve timing have to be developed for each specialty. In orthopaedic surgery, too early administration may be prevented by withholding the administration of the antibiotic until patient is transferred from the holding area to the theatre. In intestinal surgery however, timing can be improved when antibiotics are administered earlier, that is in the holding area, instead of waiting until the surgeon arrives in the theatre to approve on administration. This is particularly important for antibiotics that have to be administered as an infusion and thus require additional time to reach adequate tissue concentrations.

Table 3. Effect of implementation on improvement of timing in relation to meetings with anaesthesiology nurses

Hospital	Meeting with anaesthesiology nurses	Facilitators involved in meeting	before % within 30 min to incision	after % change to within 30 min
G	yes	no	20	+71
H	yes	yes	13	+54
K	yes	no	16	+45
J	yes	no	35	+28
E	yes	yes	61	+13
M	no	no	49	+ 11
C	no	no	57	+10
L	no	no	37	+7
B	no	no	49	+3
A	no	no	72	-3
F *	yes	yes	62	-6
D	no	no	72	-12
I	no	no	72	-12

* in this hospital timing after the intervention improved in gynaecological but detoriated in orthopedic surgery.

Discussion

This study shows that an identical set of interventions to implement a national guideline in hospitals, i.e., audit and feedback, dissemination and update of guidelines, and use of opinion leaders, can have variable process outcome results when used at different sites. There is a lack of evidence on which implementation methods are most effective. In most studies, audit and feedback showed modest effects with mixed results [15,16,24] and little is known about how and when it works best.[25,26] Dissemination of printed material is considered to be less efficacious. Reminders and educational outreach perform best, but these strategies are very costly and time-consuming. In the present study, resources for implementation were limited, and the funding was used to appoint one infectious diseases specialist and

one coordinating ICP for 13 sites. They could therefore only serve as moderators of local initiatives. Within this setting, audit and feedback was considered the most feasible method.

Whatever implementation method is used, an inventory of barriers to change is essential to develop local strategies to facilitate guideline adherence.[18] The existence of local barriers is one of the main reasons why the same implementation strategy shows divergent results in different settings. Identification of, and access to the key players for improvement was essential for successful implementation and this differed per hospital but also per item that had to be changed. Our inventory of barriers to change showed that when evidence for the guideline was weak, e.g., in case of duration of prophylaxis, the success of the implementation was limited. This is in line with results from previous studies on guideline adherence.[19,27]

In case of changing the timing of prophylaxis, our study showed that organisational constraints played a central role. A recent study by Tan e.a, exploring obstacels for proper timing, also pointed out that the issue of workflow was a main reason for inappropriate timing.[28] To overcome these barriers our study showed that those who were directly involved in patient care, were to be reached.

In conclusion, this study shows that an implementation method of audit and feedback can yield divergent results when applied in different hospitals, in different surgical specialties, and even according to the item that one wants to change. Barriers to change involved in a specific aspect of a guideline may be different between hospitals, even in a homogenous set of hospitals within one country, and thus should be assessed locally. Identifying and getting access to the key players for change is essential for success as well as identification of barriers to change.

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General discussion and recommendations

General discussion

In this thesis, the results of studies aimed at improving the quality of antibiotic use in prophylaxis as well as in therapy are presented. The major part of the thesis concentrates on the CHIPS project, which aimed at improving surgical prophylaxis and measured both process and patient outcome. Our study proved that, even in a country with a history of prudent antibiotic use, important improvements in quality of surgical prophylaxis may be achieved, and cost savings could be obtained while maintaining efficacy in terms of prevention of surgical site infections. Timely administration of antibiotics in prophylaxis as well as in therapy is appreciated in the literature as a factor that determines patient outcome.
Our study has shown that, even though influencing the process of timing of antibiotic administration may be complicated, improvements can be achieved.

Methods of the CHIPS study
By using the operational national surveillance network of PREZIES, patient outcome data could be collected and correlated to process outcome, which made the CHIPS study unique. Due to the extensive experience of local infection control professionals (ICPs), the quality of the data collection was excellent. In Chapter 1.2 we showed however that recruitment of hospitals for such a large study without any prospect of financial compensation was cumbersome. Data collection and processing were very time-consuming. Auditing and intervention projects could not always be prioritized, due to vacancies for ICPs in the hospitals.
In the early days of the study, the established contacts of PREZIES acted as the hospital contacts for the CHIPS study, i.e., mainly ICPs and chairpersons of infection control and antibiotic policy committees, of which the majority were medical microbiologists or hospital pharmacists. Promotion of prudent use of antimicrobial drugs appealed to these professionals, as was their awareness of the problem of antimicrobial resistance. At a later stage of the study, surgeons were involved in most hospitals, who feel safer with maximal prophylaxis rather than a prudent and cost-effective regimen, and tend to administer prophylaxis a little longer rather than for a short period. In discussing the targets of the CHIPS study, surgeons were better motivated for prophylaxis changes that would reduce the incidence of SSI rather than for prudent use of antibiotics without an increase in SSI.

Auditing adherence to local guidelines for prophylaxis

The inventory of the local guidelines for surgical prophylaxis (Chapter 2) showed that, compared to other countries, local antibiotic policies on duration and timing of surgical prophylaxis in the Netherlands were already relatively strict before the intervention.[1,2] The majority of the hospital policies recommended single dose prophylaxis, or a duration of no more than 24 hours. The adherence to these local guidelines in terms of antibiotic choice and duration was high, again reflecting the general pattern of prudent antibiotic use in the Netherlands.[3] Reasons for not following local guidelines were lack of awareness, due to ineffective distribution of the most recent version of the guidelines, or lack of agreement by surgeons with the guidelines established by the antibiotic policy committee. As an example, in some hospitals orthopaedic surgeons did not agree with hospital guidelines advocating single dose prophylaxis, and had developed their own guidelines recommending 24h prophylaxis, subsequently fully adhering to their revised guidelines. Although antibiotic policy committees prefer to develop local guidelines that are in line with national and international guidelines, issuing guidelines with which the stakeholders disagree is known to lead to poor adherence.[4] The compliance with local guidelines for timing of administration was much lower. This has been described earlier in the international literature.[5,6]

Intervention on the quality of surgical prophylaxis; process outcome

In Chapter 3, the effect of an intervention on the quality of surgical prophylaxis was assessed. The intervention was aimed at implementation of the national SWAB guideline, which promotes prophylaxis with a single i.v. dose of cefazolin (plus metronidazole if coverage of anaerobic bacteria is warranted) within 30 minutes before the incision. The intervention by the CHIPS team resulted in important improvements of all aspects of prophylaxis and showed that, even in a country with a tradition of prudent use, antibiotic cost savings could be made while containing efficacy in terms of prevention of SSI. By using segmented regression analysis with an interrupted time series design, our study met the criteria for a proper intervention study as recommended by The Cochrane Effective Practice and Organisation of Care Group (EPOC). The possibility that the improvement had been the result of a gradual change over time not related to the intervention could be excluded. This is in contrast to a variety of other recently published implementation studies with a suboptimal design, where confounding by changes over time has not been taken into account.[1,7-9]

It may be argued that any national clinical guideline should be easily applicable in everyday clinical work. From this point of view, it is alarming that only every fourth patient received completely appropriate prophylaxis despite our intervention. Although the intervention resulted in improvement on all three parameters – choice, duration, and timing of prophylaxis –, establishing a change in timing of the first dose and in duration of prophylaxis was more difficult than antibiotic choice. Recent surveillance data from the Surgical Infection Prevention Project from the US showed that, even when goals were less ambitious, i.e. aiming at a duration no longer than 24 hours or timing of administration within 60 minutes before the incision, adherence to that guideline after two years of surveillance and intervention only improved from 40.7 to 52.9%.[10] Timing improved from 47.6% to 69.7% concordant cases. Adherence to antibiotic choice, however, was correct in 92.2% after intervention.

Intervention on quality of surgical prophylaxis; patient outcome

Our study was unique as it did not only provide data on process outcome but also on patient outcome. As shown in Chapter 4, the more prudent use of antibiotics as established by implementation of the guideline did not have any detrimental effect on the rate of surgical site infections (SSI). Due to the overrepresentation of clean procedures, the actual SSI rate (5.4% before intervention) was lower than expected (7.5%). Therefore, although we included more procedures than the number that was originally required by the power calculations, i.e. 1668 before and 1953 after the intervention, the power of the study may have been suboptimal to detect small differences. The confidence intervals of the SSI rates before and after intervention, however, were narrow: the SSI rate before intervention was 5.4% (95% CI: 4.3–6.5) and the SSI rate after intervention 4.5% (95% CI: 3.6-5.4).

Timing of antibiotic administration; an important amenable factor for intervention in prophylaxis as well as in therapy

The extensive data collection on all parameters of prophylaxis and on patient outcome in the CHIPS study made it possible to study the correlation between these parameters and the rate of SSI. For this purpose, data were selected from the largest subgroup, comprising patients with total hip arthroplasty. The effect of timing of prophylaxis in this patient group has been described in Chapter 5. In the multivariate analysis of patient characteristics, procedures and accuracy of prophylaxis, the duration of surgery was the only independent significant risk factor for development of SSI. Of the factors amenable for intervention, failure to administer the first dose

of the antibiotic before the moment of incision was most important (OR 2.8; 95% CI 0.9-8.6). Timing within 30 minutes before the incision seemed most favourable for preventing SSI, and this finding is in agreement with the landmark study by Classen et al.[11] Although experimental studies have shown that antibiotics administered close to, or at the moment of incision were most effective,[12] the optimal timing in surgery remains unclear. Most international guidelines recommend administration of the antibiotic within 60 or within 30 minutes before the incision.[13-17] In addition, it has been demonstrated that, for efficacy of prophylaxis, it is essential that antibiotics still be present at a substantial level at the time of closure of the wound.[18] Administration as close as possible to the moment of incision decreases the need for repeated dosing in case of prolonged surgery.

Interestingly, in our prospective cohort of 1922 patients undergoing total hip arthroplasty, the rate of SSI was not correlated with the total duration of prophylaxis. This finding is in disagreement with the retrospective analysis of data from the Norwegian cohort of 22000 total hip arthroplasties performed between 1987 and 2001. That study has suggested a higher incidence of loosening of the prosthesis during a 0 to 14 years follow up in patients who had received a single-dose prophylaxis. However, these data should be interpreted with caution. Firstly, cephalothin, a drug with a short half life, was used in the majority of cases in that cohort.[19] Because of its short half life, the use of cephalothin is not recommended by most international guidelines.[15-17,20] It is not surprising that repeated administration of a short-acting drug may be required, whereas this is not the case for an antibiotic with prolonged activity, such as cefazolin. Secondly, no data on timing of prophylaxis were collected in that study, and timing may have been inappropriate in patients that subsequently experienced prosthesis failure. In particular, the use of a short-acting drug may have impacted the deleterious effect of too early administration of a single dose.

Correct timing of antibiotic administration was a main goal of our intervention study on quality of antibiotic therapy performed in a single University Hospital. In Chapter 6, the implementation of guidelines on timing, dosage adjustment to renal function and i.v. to oral switch therapy are described. The intervention was most successful in improving the optimal timing of administration at the wards. After the intervention, the median delay from order to administration of the first dose of antibiotics decreased from 4.1 to 2.6 hours (P=0.003) for all prescriptions, and from 2.7 to 1.7 hours (P=0.003) in patients with severe infections. This finding is highly relevant for clinical practice, as multiple studies have recently demonstrated the benefit of timely administration of the antibiotic on patient outcome.[21-23]

Barriers to change

In Chapter 7, an analysis of the barriers to change the process of antibiotic prophylaxis in the CHIPS study is presented. Several important observations were made in this study. Firstly, regarding the choice of the antibiotic agent for prophylaxis, surgeons follow the recommendations of antibiotic policy committees. Restricting the antibiotics in stock in the surgical suite to the recommended drug will automatically lead to adherence to the recommendation. Regarding duration of prophylaxis, however, orthopaedic surgeons were particularly reluctant to switch to single-dose prophylaxis. The barrier they experienced was a lack of agreement with the guideline. Existing evidence from the literature, in particular a prospective trial of 1 versus 3 doses of cefazolin for arthroplasty [24] was interpreted differently by antibiotic policy makers [16,17] and orthopaedic surgeons;[25] the latter did argue that the study may have been underpowered to reveal a benefit of multiple-dose prophylaxis. It is however very unlikely that a prospective study with a greater statistical power will ever be performed to definitively answer this question.

Although observational data from large cohorts, such as the American Surgical Intervention Project (SIP) [10] may provide additional insights, such cohort studies must be interpreted cautiously, as retrospective, non-randomised studies may suffer from multiple confounders. This was exemplified by the Norwegian cohort study on total hip arthroplasty, as described earlier.[19] As for our own prospective study, a detailed analysis of the 1922 patients undergoing total hip arthroplasty (THA) showed that duration of prophylaxis, either single dose or for 24 hours, was not correlated with the incidence of SSI (Chapter 4). In a large intervention study in a tertiary hospital implementing single-dose prophylaxis in orthopaedic surgery, Fonseca et al. compared over 1600 procedures before and after intervention and reported no increase in SSI.[8] A limitation of that study was that post-discharge surveillance was only achieved in 50 % of the patients. In case of total hip arthroplasty, post-discharge surveillance, as was performed in our study, is mandatory, as a recent study has shown that this has a large impact on the rate of SSI detected.[26]

The inventory of barriers to change revealed that multiple logistical problems had to be overcome in the process of improving timing of administration. The issues varied greatly dependant of the local situation and of the surgical specialty involved. Important determinants influencing appropriate timing in our study were the presence of a written order, the time the patient spent in the holding area before surgery, and the administration of the drug as a bolus injection or intravenous infusion. Organisational constraints was also found to be a major obstacle in proper

antibiotic timing in a recent study by Tan et al,[27] and a written order for prophylaxis was recently found to be a positive predictive factor for a timely first dose by Turnbull et al.[28]

Importantly, a logistical change to improve the timing could have opposite effects in various patient groups. For example, the recommendation to administer prophylaxis in the holding area led to improvement in gynaecological surgery in one hospital, i.e., the number of patients for whom timing was too late did decrease. In orthopaedic surgery however, more patients received prophylaxis more than 30 minutes before the incision, i.e., too early, as a result of the new policy (Chapter 6). This example underscores the notion that specific strategies to improve timing have to be developed for each specialty and setting.

Not all anaesthetists were convinced of the importance of appropriate timing as recommended in the SWAB guideline. After consensus on the appropriateness of the guidelines had been reached, the anaesthetists and, most importantly, anaesthesiology nurses were the key players for implementation of timely administration of prophylaxis.

In conclusion, the prudent use of antibiotics is the cornerstone of good clinical practice in combating infectious diseases, in order to limit the spread of resistance and to contain costs. Although the field of surgical prophylaxis may be easier to address compared to changing behaviour in therapeutic use of antimicrobial therapy, the present study has emphasized that there is no universal general improvement strategy. Audits remain an important instrument to assess the problem and to get healthcare workers involved and motivated for change. An inventory of barriers is essential to identify key players and achieve their involvement in the implementation process, especially when working attitudes have to be changed. Strategies that are effective in one situation may not necessarily work in other situations. In addition, changing behaviour is a continuous process that needs reflection and repetition.

Future prospects

Several issues remain to be addressed in the area of surgical prophylaxis. Our studies have identified the need for better data on the efficacy of single-dose versus prolonged prophylaxis in patients undergoing hip arthroplasty. In view of the questions remaining after publication of the randomised study by Wymenga et al.,[24] a larger and sufficiently powered randomised controlled trial is warranted. Only additional scientific evidence will lead to consensus between orthopaedic surgeons and antibiotic policy makers on this subject.

In addition, the question on the optimal timing of the first dose of prophylaxis to prevent SSI has not been conclusively answered. Potential advantages of keeping strict timing intervals, e.g., 60-30 min., 30-15 min., or 15-0 min. before incision, have not been investigated in sufficient detail. Data from our study suggest that it may be worthwhile to compare these timing intervals in a prospective randomised controlled trial.

After completion of the CHIPS study, several steps have been taken to further implement strategies to optimise surgical prophylaxis, as recommended by our studies. First, the Dutch Institute for Healthcare Improvement (CBO) has been using the results of our study to highlight the importance of a correct timing of prophylaxis in their "Doorbraak" project, a multidisciplinary national quality improvement project to decrease the number of SSI in Dutch hospitals.

Second, the recommendation that awareness and accessibility of evidence-based guidelines is crucial to improve adherence, has contributed to the ongoing process at the Dutch Working Party on Antibiotic Policy (SWAB) aimed at improving the development and implementation of their guidelines. SWAB develops guidelines according to the recommendations for evidence-based guideline development (EBRO)[29] and the AGREE instrument (www. agreecollaboration.org). All members of the professional societies involved are now consulted during guideline development, using a web-based module. In addition, SWAB has been developing a National Antibiotic Guide, based on evidence-based guidelines and expert opinion, which is available both online and as downloadable PDA application. Local antibiotic committees are encouraged to adopt these guidelines, and to create a version adapted to local resistance patterns and policies, which will be accessible online and as a PDA application using the SWAB server and software. These types of collaboration between national and local policy makers will facilitate the dissemination and credibility of guidelines among healthcare workers, addressing a key issue revealed by our studies.

In addition, a series of recommendations for clinicians and investigators has resulted from our studies:

Recommendations for the clinician

- Surgeons should perform surveillance of SSI, and should take the opportunity to participate in national surveillance networks.
- Communications between surgeons and anaesthetists about surgical prophylaxis should be clear, and make use of written orders.

– Prudent use of antibiotics preserves the therapeutic armamentarium for the future without affecting outcome in the present.

Recommendations for the investigator

– Audits and intervention studies should provide financial compensation for local professionals performing the surveillance and interventions.
– Surgeons should be actively involved at an early stage of implementation studies on surgical prophylaxis, as they act as facilitators.
– Intervention studies to improve processes should also measure patient outcome, as this provides assurance to safety concerns of the individual physician. The more robust the evidence on favourable patient outcomes, the more chance for success.
– Intervention studies should use time-series analysis to evaluate the effect of the intervention. When a control group is lacking, interrupted time series analysis is the strongest quasi-experimental approach to evaluate longitudinal effects of an intervention.[30]

Recommendations for the policy makers

– Hospitals should invest in infection control practitioners, as they are indispensable for performing audits as an important basis for quality interventions.
– National guideline committees on surgical prophylaxis should put more effort into recruiting surgeons as participants in quality improvement projects.
– The knowledge that prudent antibiotic use for prophylaxis is safe should be disseminated among surgeons and, importantly, surgical residents.
– National and international guidelines should serve as basis for locally-developed guidelines. In addition, consensus among the users of the guideline is crucial for proper implementation.
– Timely administration of prophylaxis should be part of every program aimed at reducing the incidence of SSI, and should also play a crucial role in intervention studies on antibiotic therapy.
– Recommendations on improving timing in prophylaxis should be tailored to the local situation and the specific surgical specialty.

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Summary

Summary

This thesis comprises several studies on implementation of guidelines for antimicrobial use in prophylaxis as well as in therapy. The main part focuses on the data of the CHIPS-study; a quality improvement project of surgical prophylaxis in the Netherlands.

Chapter 1.1. In this Chapter, the recruitment for and the methodology of the CHIPS study (Surgical Prophylaxis and Surveillance Study) is described. The aim of the CHIPS study was to improve the quality of prophylaxis in Dutch hospitals, and to promote prudent use while maintaining or improving the efficacy of prophylaxis in reducing surgical site infections (SSI). This would be achieved by implementing the SWAB guideline for surgical prophylaxis, using audit and feedback as intervention method, and monitoring patient outcome by recording the quality of surgical prophylaxis and the incidence of surgical site infections before and after the intervention. The PREZIES (Preventie van Ziekenhuisinfecties door Surveillance) national surveillance network for nosocomial infections served as a basis for recruitment of the hospitals for the CHIPS study. The study was supported by a grant from The Netherlands Organization for Health Research and Development (ZonMw), but there was no additional funding for the hospitals to support the data collection. Infection control practitioners of the participating hospitals played a central role in the data collection and implementation process. Thirteen out of 135 Dutch hospitals, were recruited for the study. Ten of these hospitals had participated in the PREZIES–surveillance network before the start of the study. The hospitals collected data on process outcome, i.e., qualitative parameters of antimicrobial use, and patient outcome, i.e., surgical site infections (SSI), including post-discharge surveillance, in a preintervention and a postintervention period.

Chapter 1.2 describes the guidelines for perioperative antimicrobial prophylaxis issued by the Dutch Working Party on Antibiotic Policy (SWAB), which were implemented in the CHIPS study. SWAB promotes the use of single-dose prophylaxis with cefazolin (plus metronidazole in cases where anaerobic flora is expected), to be administered within 30 minutes before the incision.

In **Chapter 2,** the adherence to the local guidelines for surgical prophylaxis that had been established by the Antibiotic Policy Committee (APC) of the participating hospitals is described. Overall, the willingness to adhere to local guidelines was

high. Adherence to guidelines for antibiotic choice was 92%, for duration 82%, for dosage 89%, but for timing 50% only. When surgeons had developed their own guidelines, for example, guidelines on duration of prophylaxis in orthopaedic surgery, the compliance with these guidelines was 100%.
The most important barriers to local guideline adherence were lack of awareness. due to ineffective distribution of the most recent version of the guidelines, lack of agreement of surgeons with the local hospital guidelines established by the APC, and environmental factors, such as organisational constraints in the surgical suite and in the ward.

In **Chapter 3,** the results on the process outcome, i.e., the quality of surgical prophylaxis after implementing the SWAB guideline in the hospitals participating in the CHIPS study are described. The parameters antibiotic choice, duration, timing, volume, and costs were assessed in four surgical disciplines; orthopaedic, gynaecological, vascular and intestinal surgery. Only elective procedures were included in the study. Segmented regression analysis was used to estimate the effect size of the intervention. Patient outcome was documented by the incidence of surgical site infections. Before the intervention, 1763 procedures were recorded, and 2050 after intervention. Antimicrobial use decreased from 121 to 79 Defined Daily Doses (DDD) /100 procedures, and costs decreased by 25 % per procedure. After the intervention, antibiotics were administered inappropriately in 37.5% of the cases, compared to 93.5% expected cases had the intervention not occurred. Prolonged prophylaxis was observed in 31.4 % compared to 46.8 % expected cases and inappropriate timing in 39.4 % compared to the expected 51.8%. There was a marked difference between surgical specialties. Extended prophylaxis was mainly recorded in orthopaedic departments. As for inappropriate timing, in orthopaedic and vascular surgery, administration was too early in the majority of the cases, and too late in intestinal and gynaecological surgery. Time series analysis showed that all improvements after the intervention were statistically significant ($P<0.01$) and that they could be fully attributed to the intervention. The intervention led to improved quality of surgical prophylaxis. Although in The Netherlands prudent use of antibiotics is custom, volume and costs could still be reduced by the intervention.

In **Chapter 4,** the results of the implementation of the SWAB guideline on the incidence of SSI in elective procedures in four surgical disciplines are described. Included procedures were total hip arthroplasty, femoral hemiprosthesis, abdominal

and vaginal hysterectomy, colorectal surgery, reconstruction of the aorta, and femoropopliteal and femorotibial bypass. Data on SSI were recorded before and after the intervention, using the criteria of the Centers for Disease Control, including postdischarge surveillance. For vascular implant surgery and for total hip arthroplasty, the period of postdischarge surveillance was one year.
Data on 1668 procedures before and 1953 after the intervention could be analysed. The analysis included the risk factors sex, age, ASA-score, wound contamination class, duration of surgery and length of hospital stay before surgery. The overall SSI rate decreased from 5.4 % to 4.5 % (*P*=0.22). Crude and adjusted odds ratios showed that there were no significant changes in procedure-specific SSI rates after the intervention. The study showed that, for the selected procedures, a prudent use of antimicrobial prophylaxis had no detrimental effect on the incidence of SSI.

In **Chapter 5,** the correlation between parameters of surgical prophylaxis and the incidence of SSI is described for total hip arthroplasty (THP), which was the main surgical procedure recorded in the CHIPS-study. In 1922 elective THP procedures, potential prophylaxis-, patient-, and procedure-related risk factors were collected and multivariate logistic regression analysis, correcting for random variation among hospitals, was performed. SSI (superficial and deep) occurred in 50 patients (2.6%). The highest odds ratios for SSI were found in patients who received prophylaxis after incision (2.8, 95% CI 0.9-8.6, *P*=0.07), had an American Society for Anesthesiologists score >2 (2.8, 95% CI 0.8-9.2, *P*=0.09), or experienced a duration of surgery that was >75th percentile (2.5, 95% CI 1.1-5.8, *P*=0.04). Prolonged prophylaxis after the end of surgery and the use of antibiotic impregnated cement did not contribute to fewer SSIs in this study. The results of the study suggest that intervention programs in search of amendable factors to prevent SSI should focus on timely administration of antibiotic prophylaxis.

In **Chapter 6,** the results of a quality improvement program of antibiotic therapy in various departments of a University are described, reporting process outcomes before and after an intervention program that focussed on timely administration of the first dose, dosage adjustment to renal function, switch from intravenous to oral administration, and streamlining. After a preintervention period, in which data that were collected on all these parameters were fed back to the clinicians, an inventory of barriers to change was made, and a tailored set of interventions was used for improvement. After the intervention, the mean time from the order of the

first dose at the wards improved from 2.7 to 1.7 hours in potentially severe cases (*P*=0.003). Switching therapy from intravenous to the oral route improved from 46% to 62% (*P*=0.03). Dosage adjustment to renal function showed no improvement, and streamlining was already performed correctly in most cases before the intervention.

Chapter 7 describes the results of an inventory of the barriers to change encountered during the implementation of the SWAB guideline for surgical prophylaxis in the hospitals participating in the CHIPS study.
In order to achieve a change in antibiotic choice, the chairman of the antibiotic policy committee was a key player for improvement. The main barrier to change was lack of agreement with antibiotic choice.
Regarding the duration of prophylaxis, key players for change were the surgeons, and barriers were lack of agreement – especially in orthopaedic surgery –, and lack of outcome expectancy. Evidence from the literature was interpreted differently by orthopaedic surgeons and antibiotic policy makers.
Regarding the timing of administration, the anaesthetists and, importantly, anaesthesiology nurses were the key players for improvement. Organisational constraints (for example time of arrival at the surgical suite and time spent in the holding area, administering a test dose before actual administration, and infusion instead of bolus injection) were the most important barriers to change.
The barriers to change differed per surgical specialty and per hospital. Therefore, identification of the specific local barriers to change, as well as identifying and working with the key players for change in the local setting is essential to achieve improvements.

An important conclusion of this thesis is that, even in a country with a history of prudent antibiotic use, important improvements in quality of surgical prophylaxis could be achieved, and cost savings could be obtained while maintaining efficacy in terms of prevention of surgical site infections. Our study showed that timely administration of antibiotics is an important parameter that improves patient outcome, i.e. the incidence of SSI. Finally, we found that there is no general improvement strategy that is applicable to all surgical specialties. Audits and inventories of barriers are important instruments to assess the problem, to identify key players, and to get healthcare workers involved and motivated for change. Strategies that are effective in one situation may not necessarily work in other situations, and local, tailor-made interventions may be the best approach to improve the quality of antibiotic use in hospitals.

Samenvatting

Samenvatting

In dit proefschrift worden diverse studies besproken die betrekking hebben op de implementatie van richtlijnen voor antibioticagebruik in zowel profylaxe als therapie. Een belangrijk deel van het proefschrift beschrijft de resultaten van het Chirurgische Profylaxe en Surveillance project (CHIPS), een interventiestudie op het gebied van peri-operatieve antimicrobiële profylaxe in Nederland.

Hoofdstuk 1.1. In dit hoofdstuk wordt beschreven hoe de ziekenhuizen voor het CHIPS–project werden gerekruteerd en wordt de methodologie van de studie besproken. Het doel van de CHIPS-studie was om de kwaliteit van de perioperatieve antimicrobiële profylaxe in de Nederlandse ziekenhuizen te verbeteren en om een restrictief antibiotica beleid te bevorderen met behoud van of misschien zelfs met verbetering van de effectiviteit ten aanzien van het voorkomen van postoperatieve wondinfecties (POWI). Om dit te bereiken werd de richtlijn perioperatieve antimicrobiële profylaxe van de Stichting Werkgroep Antibioticabeleid (SWAB) geïmplementeerd en werden gegevens over de kwaliteit van de chirurgische profylaxe en de incidentie van postoperatieve wondinfecties voor en na de interventie geregistreerd. Door terugkoppeling van de gegevens uit de voorregistratie werd het interventieproces op gang gebracht. Het nationale surveillance netwerk voor nosocomiale infecties, Preventie van Ziekenhuisinfecties door Surveillance (PREZIES), diende als basis voor inclusie van de ziekenhuizen. De studie werd gesubsidieerd door de Nederlandse organisatie voor Gezondheidsonderzoek en Zorginnovatie (ZonMw), maar er waren geen financiële middelen beschikbaar om de ziekenhuizen te ondersteunen bij de dataverzameling. De ziekenhuishygiënisten van de deelnemende ziekenhuizen speelden een centrale rol in de dataverzameling en in het implementatieproces. Van de 135 Nederlandse ziekenhuizen namen er 13 deel aan de studie. Tien van hen hadden eerder deelgenomen aan PREZIES. Voor en na de interventie werden van opeenvolgende ingrepen data verzameld over de procesuitkomst, de kwaliteit van de profylaxe, en van de zorguitkomst, het aantal POWI's geregistreerd tijdens opname maar ook na ontslag.

Hoofdstuk 1.2 beschrijft de door de SWAB ontwikkelde richtlijnen voor perioperatieve antimicrobiële profylaxe, die werden geïmplementeerd in de CHIPS-studie. De SWAB adviseert een éénmalige dosis van cefazolin (in combinatie met metronidazol indien anaërobe flora verwacht wordt), toe te dienen binnen 30 minuten voor de incisie.

In **Hoofdstuk 2** wordt beschreven hoe men zich in de deelnemende ziekenhuizen hield aan de lokale richtlijnen voor perioperatieve profylaxe zoals die waren opgesteld door de antibioticacommissies van de ziekenhuizen. Over het algemeen was de bereidheid in de deelnemende ziekenhuizen om lokale richtlijnen te volgen groot. Aangaande de keuze van het antibioticum volgde men in 92 % van de gevallen de richtlijnen, aangaande de duur van de profylaxe in 82%, aangaande de dosis in 89 %, maar aangaande het tijdstip van toedienen van de eerste dosis slechts in 50 % van de gevallen. Indien chirurgen, bijvoorbeeld orthopeden, zelf richtlijnen hadden ontwikkeld in plaats van of naast de algemene ziekenhuisrichtlijn, dan volgden zij deze eigen richtlijnen in 100 % van de gevallen op.
De belangrijkste belemmerde factoren voor het opvolgen van de lokale richtlijnen waren onvoldoende kennis over het bestaan ervan door inadequate verspreiding van de meest recente richtlijnen, gebrek aan instemming met de inhoud, en organisatorische zaken die te maken hadden met de werkwijze in de operatiekamer of op de verpleegafdeling.

In **Hoofdstuk 3** worden de effecten beschreven van de implementatie van de SWAB-richtlijnen op de kwaliteit van de perioperatieve profylaxe in de aan de CHIPS studie deelnemende ziekenhuizen. In 4 snijdende specialismen; orthopedische chirurgie, gynaecologische chirurgie, vaatchirurgie en gastro-intestinale chirurgie, werden van de volgende procesindicatoren gegevens verzameld: de antibioticumkeuze, de duur van de profylaxe, het tijdstip van toedienen, de hoeveelheid toegediende antibiotica en de kosten. Alleen electieve ingrepen werden geïncludeerd. Gesegmenteerde regressie-analyse werd gebruikt om de grootte van het effect van de interventie te kunnen schatten. Als maat voor de zorguitkomst werd de incidentie van de postoperatieve wondinfecties geregistreerd.
Er werden 1763 ingrepen voor en 2050 ingrepen na de interventie geregistreerd. Het gebruik van antibiotica nam af van 121 naar 79 Defined Daily Doses (DDD) / 100 ingrepen, en de kosten namen af met 25 % per ingreep. Na de interventie was de keuze van het antibioticum in slechts 37.5 % van de gevallen incorrect, terwijl berekend werd dat 93.5 % van de gevallen incorrect zouden zijn geweest als de interventie niet had plaatsgevonden. De profylaxe werd na de ingreep in 31.4 % van de gevallen ten onrechte te lang voortgezet, in plaats van 46.8 % verwachte gevallen van de langdurige profylaxe. Het toedienen van de eerste dosis op een incorrect tijdstip gebeurde in 39.4 % van de gevallen in plaats van de te verwachten 51.8%.

Er was een duidelijk verschil tussen de diverse specialismen. Te langdurige profylaxe vond vooral plaats op de orthopedische afdelingen. Te vroege toediening van de eerste dosis van de profylaxe werd vooral gezien bij orthopedische en vasculaire chirurgie, en te late toediening vooral bij gynaecologische en gastrointestinale chirurgie. Uit de time-series analyse kwam naar voren dat alle verbeteringen na de interventie statistisch significant waren en dat zij volledig toegeschreven konden worden aan de interventie zelf. Hoewel er in Nederland al een restrictief antibioticagebruik is, konden door de interventie toch de hoeveelheid voorgeschreven antibiotica en de kosten verminderd worden.

In **Hoofdstuk 4** wordt het effect van de implementatie van de SWAB-richtlijnen op de incidentie van het aantal POWI's in 4 snijdende specialismen beschreven. De volgende ingrepen werden onderzocht: implantatie van totale heup prothese, plaatsen kop/hals prothese, abdominale en vaginale uterusextirpatie, reconstructie van de aorta, femoropopliteale en femorotibiale bypass en diverse colorectale ingrepen. Voor en na de interventie, werden data betreffende POWI's verzameld volgens de criteria van de Centers for Disease Control, inclusief surveillance na ontslag (SNO). Voor vaatreconstructies met kunstmateriaal en implantaten van de heup, bedroeg de periode van SNO 1 jaar.
Uiteindelijk konden de gegevens van 1668 ingrepen voor en 1953 na de interventie worden geanalyseerd. De volgende risicofactoren werden hierbij in het model meegenomen: geslacht, leeftijd, American Society of Anesthesiologists (ASA)-score, wondklasse, duur van de ingreep, en preoperatieve opnameduur. Het totale percentage wondinfecties daalde na de interventie van 5.4 % naar 4.5 % (P=0.22). De ongecorrigeerde en gecorrigeerde odds ratios per ingreep lieten geen significante veranderingen zien in de incidentie van POWI's na de interventie. De studie liet zien dat, voor de geselecteerde ingrepen, een restrictief antibioticumbeleid geen nadelig effect had op de uitkomst maat in de zin van de incidentie van POWI's.

In **Hoofdstuk 5** wordt de relatie tussen de diverse parameters van perioperatieve profylaxe en de incidentie van POWI's bij totale heupprothese (THP) operaties beschreven. In 1922 electieve THP operaties werden potentiële profylaxe-, patiënt- en procedure-gerelateerde risicofactoren verzameld en geanalyseerd middels een multivariate logistische regressie, waarbij gecorrigeerd werd voor de variatie tussen de ziekenhuizen. Bij 50 patiënten trad een POWI op (2.6%; oppervlakkig en diep). De hoogste odds ratios voor POWI werd gevonden bij patiënten die de eerste

profylactische dosis na de incisie kregen toegediend (2.8, 95% CI 0.9-8.6, *P*=0.07), bij hen die een ASA –score >2 hadden (2.8, 95% CI 0.8-9.2, *P*=0.09) en bij patiënten met een operatieduur boven de 75e percentiel (2.5, 95% CI 1.1-5.8, *P*=0.04). In deze studie droegen verlengde profylaxe na de ingreep en het gebruik van met antibiotica geïmpregneerd cement niet bij aan een vermindering van het aantal wondinfecties. De resultaten van deze studie suggereren dat interventieprogramma's die op zoek zijn naar beïnvloedbare factoren om het ontstaan van wondinfecties te beperken, zich zouden moeten richten op het tijdig toedienen van de profylaxe.

In **Hoofdstuk 6** worden de resultaten besproken van een interventieprogramma in een academisch ziekenhuis dat gericht was op kwaliteitsverbetering van antibiotische therapie. Dit interventieprogramma werd uitgevoerd op diverse afdelingen en richtte zich op: het tijdig toedienen van de eerste dosis van het antibioticum, dosis aanpassing aan de nierfunctie, switch therapie van de intraveneuze naar de orale toedieningsvorm, en op stroomlijnen, d.w.z. aanpassen van de therapie op geleide van kweekresultaten. Data van de audit in de pre-interventie fase betreffende genoemde parameters werden teruggekoppeld naar de artsen. Na een inventarisatie van eventuele belemmerende factoren voor verandering werden diverse interventies gedaan om verbetering te bewerkstelligen. Na de interventies verbeterde op de afdelingen, in potentieel ernstige gevallen, de gemiddelde tijd tussen order en de daadwerkelijke toediening van de eerste gift van het antibioticum van 2.7 naar 1.7 uur. (*P*=0.003). Switch therapie van de intraveneuze naar de orale route nam toe van 46 % naar 62 % (*P*=0.03). Dosisaanpassing aan de nierfunctie verbeterde niet en stroomlijnen gebeurde al correct in een zeer groot aantal gevallen voor de interventie.

In **Hoofdstuk 7** worden de resultaten beschreven van een inventarisatie van de belemmerende factoren voor verandering die tijdens de implementatie van de SWAB-richtlijnen voor perioperatieve profylaxe in de CHIPS-studie werden ervaren. Ten aanzien van het veranderen van de keuze van het antibioticum bleek de voorzitter van de antibioticumcommissie een belangrijke sleutelfiguur. De belangrijkste hindernis die werd ervaren was gebrek aan consensus over de antibioticumkeuze die door de SWAB-richtlijn werd voorgesteld. Ten aanzien van de duur van de profylaxe bleken de chirurgen de sleutelfiguren. Vooral sommige orthopeden waren het niet eens met de richtlijn en twijfelden aan de effectiviteit hiervan. De beschikbare data uit de literatuur werden anders geïnterpreteerd door

de orthopeden dan door antibioticabeleidsmakers. Ten aanzien van het tijdstip van toedienen van de profylaxe waren de anesthesisten en zeker ook de anesthesie-verpleegkundigen de sleutelfiguren. Organisatorische zaken, zoals het moment van arriveren van de patiënt in de operatiekamer en in de voorbereidingsruimte, het toedienen van een testdosis voor de uiteindelijke toediening van het antibioticum, en het toedienen per infuus in plaats van als bolus injectie, bleken de belangrijkste belemmerende factoren voor een correct tijdstip van toedienen.
De aard van de belemmerende factoren verschilde per snijdend specialisme en per ziekenhuis. Het is daarom essentieel dat men, om veranderingen te kunnen bewerkstelligen, zich eerst op de hoogte stelt van deze locaal aanwezige barrières.

Een belangrijke conclusie van de dit proefschrift is dat, in een land met een historie van een restrictief antibioticumbeleid, duidelijke verbeteringen in de kwaliteit van perioperatieve chirurgische profylaxe konden worden bewerkstelligd en dat kosten konden worden gereduceerd met behoud van effectiviteit in termen van preventie van postoperatieve wondinfecties. In onze studie werd aangetoond dat het tijdig toedienen van antibiotica een belangrijke parameter is die de zorguitkomst, c.q. de incidentie van postoperatieve wondinfecties, verbetert.
Tenslotte vonden we dat er geen algemene verbeterstrategie is, die toepasbaar is bij alle chirurgische disciplines. Audits en inventarisaties van belemmerende factoren voor verandering zijn belangrijke instrumenten om de aard van het probleem helder te krijgen, om sleutelfiguren voor het veranderingsproces te identificeren, en om te zorgen dat gezondheidswerkers betrokken en gemotiveerd raken om te veranderen. Strategieën die in de ene situatie effectief blijken, hoeven dit niet automatisch te zijn in andere situaties, en lokale op de werkvloer afgestemde interventies lijken de beste benadering om de kwaliteit van antibioticagebruik te verbeteren in ziekenhuizen.

List of publications

List of publications

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Dankwoord

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Curriculum vitae

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De auteur van dit proefschrift werd op 13 juni 1962 geboren te Goirle. Na het behalen van het Gymnasium-β diploma aan het Theresialyceum te Tilburg, volgde zij de opleiding tot fysiotherapeut te Breda, alwaar zij in 1984 afstudeerde. Aansluitend studeerde zij Geneeskunde aan de Katholieke Universiteit Nijmegen (doctoraal examen 1988, artsexamen in 1991 (beiden cum-laude). In 1991 begon zij met de opleiding tot internist in het St Elisabeth ziekenhuis te Tilburg (opleider Dr C. van der Heul) en in 1994 werd de opleiding voortgezet in het Universitair Medisch Centrum St. Radboud te Nijmegen (opleider Prof.dr. J.W.M. van der Meer). Zij onderbrak in 1997 voor 1 jaar haar opleiding om te werken aan de ontwikkeling van richtlijnen voor de Stichting Werkgroep Antibioticabeleid (SWAB), waarbij 1 van deze richtlijnen de basis vormde voor dit proefschrift. In oktober 1998 werd zij geregistreerd als internist om vervolgens begin 1999 zowel te starten met de opleiding tot internist-infectioloog (opleider Prof dr. Kullberg) als met het onderzoek dat vermeld staat in dit proefschrift. Zij werd in oktober 2002 geregistreerd als internist-infectioloog en is als zodanig sinds juli 2003 werkzaam in het St. Elisabethziekenhuis te Tilburg. Zij is de moeder van een zoon, Koen.