Optimizing antimicrobial drug utilization

Studies and interventions in a university hospital

Inge C. Gyssens

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INGEBORG CARLA JORINA GYSSENS
geboren op 29 maart 1953
te Antwerpen, België

Promotor: Prof. dr. JWM van der Meer

Co-promotor: Dr. YA Hekster

Manuscriptcommissie: Prof. dr. F. Gribnau
Prof. dr. JAA Hoogkamp-Korstanje
Prof. dr. HA Verbrugh (E.U.R.)

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voor papa

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Introduction

The main reasons for control of antimicrobial drugs are to improve medical care, to limit the emergence and spread of resistant strains, and to contain costs.
In developed countries, 30% of all patients receive one or more antimicrobial drugs during their hospital stay. Antimicrobial drug sales in the U.S. rose from $ 3.7 billion in 1988 to $ 5.6 billion in 1993. Although there is some evidence that the magnitude of overuse of antimicrobial drugs is larger in developing countries, there have been very few studies (1). Antimicrobial drugs account for the largest proportion of all drugs, ranging from 13 to 37% of these purchases by hospitals in Europe (2). In the Netherlands, national expenses for antimicrobial drugs amounted to Dfl 180 million in 1990.
In the seventies, Kunin identified the new cephalosporins as "drugs of fear", which means: potent drugs with little toxicity being given to any patient with fever (3). For the past seven years, the quinolones have been (mis)used to a similar exent (4, 5). Reports of overuse and misuse of antimicrobial drugs have been published from all over the world for more than thirty years (1, 3, 5-8).
Microbial resistance to antimicrobial drugs has been increasing since the first years of their clinical use. In 1941 virtually all Staphylococcus aureus (SA) strains were susceptible to penicillin G, whereas today 80 to 95% of strains are penicillin resistant. Moreover, after the successful development of penicillinase-resistant penicillins, methicillin-resistant SA (MRSA) resistant to all beta-lactams emerged. Remaining MRSA-free is at present an increasing challenge to many hospitals in the Netherlands. In other countries, due to a high prevalence of MRSA, empiric therapy for severe SA infection is limited to less active, potentially toxic and expensive drugs. Bacteria have become resistant to antimicrobial drugs as a result of chromosomal changes or the exchange of genetic material via plasmids and transposons. Resistant genes can be transferred from commensals to pathogenic bacteria. For the last forty years, researchers and the pharmaceutical industry have fought back by developing

and promoting more than one hundred and fifty new broad-spectrum antimicrobial drugs. Many of these promising compounds, however, have become ineffective by now.

Several types of evidence link antimicrobial use to microbial resistance (9). In the community, geographical differences in patterns of antimicrobial drug use correlate with the distribution of resistant strains: for example, the relatively high resistance to macrolides of streptococci in France is explained by the country's extensive use of oral macrolides in the past. In hospitals, a series of studies have shown a relationship between hospital antimicrobial drug consumption and the frequency of microbial resistance (10-12). Within hospitals, a higher frequency of resistance is found in areas of high consumption such as Intensive Care Units (ICU). Selective Decontamination of the Digestive tract (SDD), although still controversial, was quickly adopted by many ICU's. At present there is strong suspicion that SDD leads to colonization with resistant gram-negative bacteria and/or gram-positive pathogens such as enterococci, MRSA and Staphylococcus epidermidis (13, 14). Resistant strains in the ICU constitute a reservoir that is spread to step-down units in the hospital. In nursing homes, newly admitted elderly are colonized with resistant flora from referring hospitals. In addition, at community level, antimicrobial drug use in the veterinary sector has become of particular concern. In the Netherlands, the rapid emergence of quinolone resistance in Campylobacter jejuni strains isolated from poultry products and human stools was traced to the extensive use of enrofloxacin in the poultry industry (15). Recently, the worldwide problem of widespread antimicrobial resistance has received the attention of scientific journals (16) and made scientists send out alarming messages into the world community (17). Magazine articles (18) have depicted the downfall of the miracle drugs in a war report style.

Appropriate use of antimicrobial drugs in humans and control of veterinary antimicrobial drug use are believed to delay and prevent bacterial resistance. In several hospitals, reduction of the use of an antimicrobial drug resulted in the decrease of resistant strains (10, 19, 20).

In the future the threat of microbial resistance will become the major tool of the infectious diseases community to implement antimicrobial drug policies. In the eighties, the introduction of budget systems in the United States - and to a lesser extent in some European countries - has been the major incentive to the development of antimicrobial drug policies (21). There are numerous reports in the literature indicating that intensifying antimicrobial drug policies results in cost containment. This is mainly due to the lower cost of directed therapy with narrow spectrum antimicrobial drugs and to the shorter duration of perioperative prophylaxis.

In the Netherlands, before the start of this study, there had been a limited number of studies on the quality of use of antimicrobial drugs and on the effect of antimicrobial drug policies. Ten years earlier, Hekster had studied quantitative utilization in defined daily doses (DDD) in a department of urology and presented general guidelines (22). Using this DDD methodology, a comparison of quantitative use between Dutch, Swedish and a Belgian university hospital was performed (23). Other authors studied compliance with guidelines (24, 25). Consultant microbiologists had focused on hospital antimicrobial drug use and the relation to bacterial resistance (11, 26). The national situation of the use of hospital formularies was studied by van Everdingen in 1988. Although we knew from the European study on the use of aminoglycosides (27) that consumption and resistance in Dutch hospitals compared favourably with other countries, we were not confident about the quality of antimicrobial drug prescribing. In the University Hospital of Nijmegen, the costs of antimicrobial drug consumption had doubled from Dfl. 1.5 million in 1982 to 3.0 million in 1988. This was the major reason for the board of the hospital to become interested in cost containment for these drugs. A proposal from our side to investigate antimicrobial drug prescribing was granted, so that we could start the investigations in October 1989. The results of these studies are presented in this thesis.

We addressed the following questions:

1. Is it possible to measure antimicrobial drug consumption in terms of

quality, quantity (DDDs), and costs in the main departments of a university hospital? In chapter I, an educational description of the principles of antimicrobial therapy that form the basis of the quality evaluation is given. Chapter II describes the method of quality evaluation based on established criteria, and chapter III the cost calculation method, both of which were developed for the study. The quality of antimicrobial therapy is dependent on the quality of microbiological diagnosis. We developed an analoguous quality evaluation method in order to analyse the appropriateness of the requests sent to the microbiology laboratory by clinicians; it was applied in a surgical department (Chapter V).

2. Is it possible to improve quality of use by a number of interventions tailored on the different specialties (surgery, internal medicine) and targeted to the type of inappropriate use identified (prophylaxis or therapy)? Three chapters deal with the study in surgical departments. In chapter IV we describe the results of the intervention study in the departments of surgery, gynaecology and orthopaedics. In chapter VI the crucial role of the anaesthetist in prophylaxis is stressed, and in chapter VII we describe the impact of the intervention on the timing of surgical prophylaxis.

   The intervention study in internal medicine is dealt with in chapters VIII and IX. In chapter VIII the effect of an educational programme and order form in this department are described. and in chapter IX the feasibility of the antibiotic order is analysed.

3. Does optimization of quality result in cost containment? In chapter IV, the cost savings obtained in surgical departments are analysed. Chapter VIII deals with the cost aspects in internal medicine.

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SECTION A **Background and methodology**

CHAPTER I

The principles of antimicrobial therapy.

IC Gyssens and JWM van der Meer

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Abstract

Antimicrobial therapy is causal therapy directed against microorganisms. For the decision to start antimicrobial therapy we should know whether the patient has indeed an infection and if so, whether it is wise to treat him with antimicrobial drugs. The complex interactions between pathogen and host, between pathogen and the commensal flora, and between antimicrobial drug and micro-organisms are reviewed. The activity of antimicrobial drugs and the resistance of the microorganisms result in either susceptibility or non-susceptibility of the microorganisms. When antimicrobial therapy is initiated, the spectrum of the antimicrobial drug chosen should be broad enough to cover the possible causative organisms associated with the clinical picture. This is called empiric or provisional therapy. After preliminary microbiology results become known, the therapy can be progressively adjusted to antimicrobial drugs that have a less broad spectrum. The final adaptation occurs when all culture results are known. This is called definitive or directed therapy. The process is described as "streamlining". The motives for combination of antimicrobial drugs are discussed. The rapidity of response is dependent on the causative microorganism, on host defense factors, and on the therapy chosen. The duration of treatment can be determined with parameters of response, and is mostly based on clinical experience with similar infections. Every physician should be aware that antimicrobial treatment has immediate implications for the commensal flora, and that, even if he prescribes antimicrobial drugs appropriately, he contributes to induction of resistance. Prudence in prescribing is essential.

Introduction

Antimicrobial therapy is causal therapy directed against microorganisms. For the decision to start antimicrobial therapy we should answer the following questions:

1. Are the signs and symptoms due to an infection? We need the patient's history, physical examination and the results of additional investigations.

2. What are the most likely causative organisms? Based on knowledge of infectious diseases it is possible to list organisms, factors such as symptomatology, organ localization and whether the infection is community or hospital acquired. The next step is to decide whether microbiological investigations should be carried out. For severe infections (hospitalized patients) this is the rule. The Gram stain of an appropriately taken specimen can provide preliminary identification of etiologic microorganisms while awaiting culture results.

3. Can the causative organism be treated with antimicrobial drugs? The infection may be at a site where no active concentrations of the drug can be achieved (for example an infected joint prosthesis); surgical intervention is indicated in such cases. In rare cases, total antimicrobial resistance may make therapy impossible.

4. Is it necessary to combat the causative organisms with antimicrobial drugs? (in other words: what is the rationale for treatment?) Some bacterial infections like impetigo, furunculosis and secondary infected decubital ulcers are not necessarily treated with antibiotics.

5. Which drug do we choose, which dosage regimen, which route of administration? If it is highly likely that the symptomatology is due to a bacterial infection which needs antimicrobial treatment, a choice should be made from the vast armamentary of antimicrobial drugs. The choice of initial therapy is determined by the most likely microorganisms that cause the infection. In practice, the choice should already be limited by the formulary list of the hospital. Dosage regimens are based on pharmacodynamic characteristics of the drugs.

6. How are we going to judge the effect of therapy, and how long are we going

to treat the patient? There are few hard data on the optimal duration of antimicrobial drug treatment. As for the judgement of effect, duration is mostly based on clinical experience with similar infections.

Before discussing choice, dosage regimen and duration of treatment, one should take in to consideration the large number of interactions between therapy, the host (the patient), the causative organism (the pathogen) and the commensal flora. These interactions can be depicted as the pyramid of infectious diseases (figure 1).

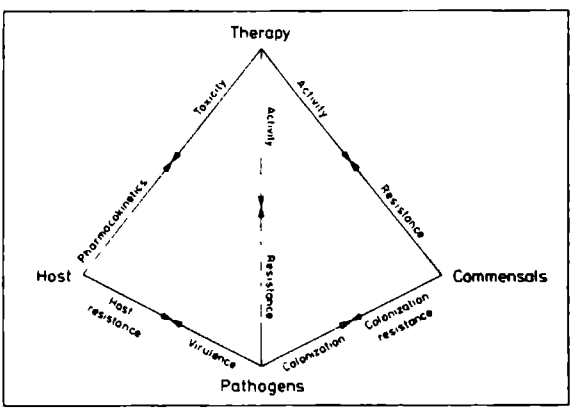

Figure 1 - The pyramid of infectious diseases

The interactions between pathogen and host

One important interaction between pathogen and host is virulence, which may be defined as the capacity of an organism to compete with surrounding flora, to damage tissues and to withstand host defense mechanisms. Virulence determines not only the number of individuals that become ill after exposure to the pathogen, but also the severity of disease. If host defense mechanisms are defective, pathogens of low virulence may cause disease.

An intact surface of skin and mucous membranes, as well as the humoral and cellular defense mechanisms form together the normal resistance to infection (1). In patients with impaired host defense, infections usually run a more severe

course. This has consequences for the selection of an antimicrobial drug, dosage regimen and duration of therapy, because the drugs have to compensate for the defects in host defense. For example, aminoglycosides alone are not very effective in granulocytopenic patients with Gram-negative infections (2). Higher dosages and different dosage regimens are necessary for a therapeutic effect in neutropenic animals (3).

For the choice of the initial antimicrobial therapy it is good to realize that certain defects in host defense will predispose to certain infections (1).

The pathogen and the commensal flora

The interactions between pathogenic and commensal flora can be described as colonization and colonization resistance. To be able to colonize, microorganisms need a series of properties. In recent years the understanding of these properties has increased and therapeutic modalities to interfere with such mechanisms have been investigated.

Colonization resistance (or microbial antagonism) (4) can be defined as the capacity of commensal microorganisms to limit colonization and outgrowth of other, potentially pathogenic microorganisms. An example of colonization resistance is found in the gastrointestinal tract, where the anaerobes grow out to concentrations of 10^{11}/g of faeces and do not allow the aerobes to grow out to more than 10^{7}-10^{8}/g. This antagonism is probably due to a competition for nutrients. Anaerobes limit the outgrowth of the aerobes; if we eliminate the anaerobes by means of antibiotics, the aerobes will grow out to 10^{11}/g. When both anaerobes and aerobes are suppressed by antibiotics, drug-resistant aerobes from the food will colonize and grow. Thus, antimicrobial therapy may produce dramatic changes in the colonizing microflora. Studies by Vollaard et al (5), have demonstrated that almost any antimicrobial drug will affect colonization resistance. For certain patients, such as neutropenic patients, it seems that secondary infections are prevented if the effects of both prophylactic and therapeutic antibiotics on colonization resistance are taken into account.

It is unknown to what extent colonization resistance plays a role in the

emergence of resistant microorganisms in the hospital.

The interaction between the antimicrobial drug and microorganisms

The activity of antimicrobial drugs and the resistance of the microorganisms result in either susceptibility or non-susceptibility of the microorganisms.

Culture results and *in vitro* susceptibility tests will be used for guidance. However, the results of susceptibility testing cannot be translated to the *in vivo* situation in an unrestricted fashion. The data on effective concentrations of antimicrobial drugs *in vivo* are very limited and more studies in this particular area are needed. Nevertheless, *in vitro* data are clinically useful. Moreover, antimicrobial therapy is the only form of treatment in which we can make a reasonable *in vitro* prediction of the *in vivo* effect.

In recent years, our insight in the pharmacodynamic aspects of antimicrobial treatment (e.g., the *in vivo* effect of the drug on its target, the microorganism) has increased considerably. For ß-lactam antibiotics we now know that the antimicrobial effect is mainly time-dependent and not very much dose-dependent (prolonged exposure to these drugs is necessary). Moreover, when antimicrobial concentrations become very low, bacterial regrowth occurs immediately: there is no "postantibiotic effect" (6). Aminoglycosides however, have a concentration-dependent and not time-dependent antimicrobial effect, and a strong "postantibiotic effect" (6), i.e. the microorganisms do not immediately regrow after elimination of the drug. Consequently, we tend to give more frequent dosages of ß-lactam antibiotics, rather than higher dosages, in infections that are difficult to treat; and less frequent, higher dosages of aminoglycosides are chosen (see also below the paragraphs dealing with toxicity).

Many mechanisms of antimicrobial resistance have been elucidated in recent years (table 1). The relative contribution of the various mechanisms for in-hospital situations as well as in the individual patient is not known, but studies have demonstrated that there is a direct relationship between the total amount of a certain antibiotic used in a particular hospital during a certain period and the amount of resistant strains that emerge (7, 8).

Therefore, it is no surprise that restrictive use of antibiotics in hospitals and nursing homes leads to a reduction in resistance. In our opinion, limitation of veterinary use of antibiotics is also an important issue (9,10). International concern about emergence of resistance has led to the foundation of the Alliance for the Prudent Use of Antibiotics (APUA).

Initial therapy and adaptation to definitive therapy

When antimicrobial therapy is initiated, the etiologic microorganism is generally unknown. The spectrum of the antibiotic chosen should be broad enough to cover the possible causative organisms associated with the clinical picture. This is called empiric or provisional therapy. After preliminary microbiology results become known, the therapy can be progressively adjusted to antimicrobial drugs that have a less broad spectrum. The final adaptation occurs when all culture results are known. This is called definitive or directed therapy. This process is described as "streamlining" in the literature (11). There is not only a change from broad spectrum to narrow spectrum, but also from combination therapy to single drug therapy, and from newer to older drugs. This strategy generally results in cost containment. Additional advantages of streamlining are:

Table 1 - Origins of resistant microorganisms

Resistant microorganisms:
1. were already resistant before treatment
2. became resistant during therapy due to:
a. enzyme induction
b. mutation
c. adaptation
d. chromosomal transfer of resistance
e. extrachromosomal transfer of resistance
3. took the place of sensitive microorganisms during or after treatment

1. Large experience with older drugs for similar infections.
2. Prevention of resistance; by switching to a narrow spectrum antibiotic we decrease selection pressure, and by switching to a conventional ("old") drug, we limit exposure to new broad spectrum drugs, thereby preventing emergence of resistance to the latter drugs.

Table 2 - The choice of antimicrobial drugs for treatment

The optimal antimicrobial drug for treatment

1. is highly active against the (suspected) causative organism
2. reaches effective concentrations at the site of infection
3. has very little toxicity
4. does not lead to emergence of resistant microorganisms
   - in the patient
   - in the environment
5. can be administered via the desired route
6. is economic

Combination of antimicrobial drugs

Combination of antimicrobial drugs leads to a broadening of the antimicrobial spectrum, thereby increasing the selection pressure on the microflora.

Although antibiotics are often combined aiming for a synergistic (potentiating) effect, our knowledge of synergism and antagonism in vivo is very limited. Combining antimicrobial drugs generally does not lead to dose reduction, but to more toxicity and a greater difficulty in judging to which drug a certain side effect (e.g. a rash) has to be attributed.

There is however a limited number of indications for combined therapy:

1. Initial, "blind" (empiric) therapy. This broad spectrum combination should be streamlined as soon as possible.
2. Mixed infections. Infections caused by multiple organisms (e.g. aerobes and

anaerobes) may necessitate combination therapy to cover the whole spectrum.

3. Synergistic combination. Synergism is proven for the combination of a penicillin and an aminoglycoside in endocarditis caused by viridans streptococci and enterococci; the combination of trimethoprim with sulphamethoxazole (cotrimoxazole) against a variety of pathogens; the combination of amphotericin B and 5 flucytosine for the treatment of cryptococcal meningitis. Reduced dosages are used in the combinations cotrimoxazole and amphotericin B and 5 flucytosine.
4. Prevention of resistance of the causative microorganism during treatment. Resistance may occur because the microorganism is able to adapt to the drug (e.g. Mycobacterium tuberculosis) or because the drug readily induces resistance when used in monotherapy (e.g. rifampicin, trimethoprim, fusidic acid). By using combinations of drugs this problem may be circumvented.

Judging the effect of therapy

If the isolated microorganism is the cause of the infection and the results of the susceptibility testing are correct, we usually expect a favourable response to therapy within 1 to 3 days. The rapidity of response is dependent on the causative microorganism, host defense factors, and the therapy chosen. A patient with normal host defense mechanisms and a pneumococcal pneumonia should be expected to respond to penicillin treatment within 24 to 36 hours. In staphylococcal septicemia or typhoid fever a clinical response to therapy takes much longer. The parameters to assess the results of treatment differ in each patient, such as the subjective state of the patient, the clinical picture, the temperature, the erythrocyte sedimentation rate, the white blood cell count, the results of x-ray examination and or other imaging procedures, and microbiological investigations. If the results of treatment are not in agreement with the expectations, a number of possible reasons should be considered, as listed in table 3.

Duration of therapy

The duration of treatment can be determined with the parameters mentioned above, and based on clinical experience with similar infections. We rarely need guidance by advanced imaging techniques (e.g. scintigraphy, CT-scan). Over the last years, the recommended duration of treatment for a number of infections has decreased based on the results of clinical trials.

Table 3 - Reasons for insufficient response to treatment

1. The duration of treatment is still too short for a clinical effect.
2. The clinical or microbiological diagnosis is wrong.
3. Therapy is wrong:
   a. antibiotic is not active against the microorganism
   b. the infection is not reached adequately, because:
      - dosage is too low
      - oral resorption of the drug is poor
      - antibacterial concentrations at the site of infection are low because of:
         * poor vascularization
         * abscess or empyema
         * foreign body
         * infection at a site which is difficult too reach

Conclusions

The major difference between antimicrobial therapy and other therapies is that antimicrobial treatment has immediate implications for the commensal flora and the environmental flora. Every physician should be aware that, even if he prescribes antimicrobial drugs appropriately, he contributes to induction of resistance. Prudence in prescribing is essential. Finally, physicians should not feel "outdated" if they do not prescribe the latest antibiotics.

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CHAPTER II

Quality evaluation of antimicrobial therapy

IC Gyssens, PJ van den Broek, BJ Kullberg, YA Hekster, & JWM van der Meer.

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Abstract

For the quality-of-use evaluation of antimicrobial drugs (AD), definitions and criteria are needed. We propose a modification of the original criteria of Kunin with the objective to provide maximal educational feedback of the evaluation to prescribers. The resulting classification allows evaluation of each parameter of importance associated with use of AD. In an antimicrobial drug course, individual prescriptions are analysed separately. Prescriptions for therapy are divided in empiric or documented episodes. The value of "streamlining", i.e. adjustment of therapy is stressed. We developed a flow chart which facilitates the sorting of prescriptions into categories, systematizes and accelerates the review. The evaluation is performed by two independent reviewers qualified in infectious diseases, who formulate alternative agents in case of inappropriate antimicrobial drug use. This is illustrated by a clinical example which obviates the advantages of the present classification and shows cost savings with the alternative policy.

Introduction

The major reasons for monitoring antimicrobial drug usage are to limit the development and spread of resistant microorganisms and to contain costs (1). When we started to investigate quantity and quality of use of antimicrobial drugs in a prospective way in the principal services of the 911-bed University Hospital of Nijmegen we encountered difficulties using the existing evaluation categories. The most authoritative classification is the classification that Kunin et al developed in 1973 (table 1) (2). It has been recently adopted in its original form in Thailand (3).

Table 1 - Categories of judgment of antimicrobial drug use (Kunin et al, 1973)

I.	Agree with the use of antimicrobial therapy/prophylaxis, the program is appropriate.
II.	Agree with the use of antimicrobial therapy/prophylaxis, but a potentially fatal bacterial infection cannot be ruled out or prophylaxis is probably appropriate, advantages derived remain controversial.
III.	Agree with the use of antimicrobial therapy/prophylaxis, but a different (usually less expensive or toxic) antimicrobial is preferred.
IV.	Agree with the use of antimicrobial therapy/prophylaxis, but a modified dose is recommended.
V.	Disagree with the use of antimicrobial therapy/prophylaxis, administration is unjustified.

Categories I and II essentially indicate "appropriate" therapy, categories III-IV indicate that there was some major deficiency in the choice or use of antibiotics by the physician managing the problem.

However, over the past 17 years most authors on the subject of antimicrobial drug evaluation have modified those criteria to be suitable for use when

considering specific aspects of antimicrobial drug use: dosage interval (4, 5), loading dose (6), route (7), obtaining the necessary serum drug concentrations (6, 8), duration of treatment or prophylaxis (4-7, 9, 10), allergic responses (6, 7, 9, 10), cost separated from toxicity (6, 8), broadness of spectrum (7, 10), failure to modify therapy after culture results become known (7), records insufficient for categorization (4, 5, 9). The present paper describes the development of an evaluation system and its advantages compared to previous classifications.

Method

In the quality-of-use study, each antimicrobial drug course registration form is completed by one researcher internist with information from the medical record to allow subsequent evaluation by two independent experts in infectious diseases.

Criteria for evaluation and flow chart

We adapted the criteria of Kunin et al. in order to be able to evaluate each parameter of importance associated with antimicrobial drug use. The modified criteria for evaluation are listed in table 2. Several subcategories have been added to the original criteria shown in table 1.

To facilitate the selection into the numerous categories, we arranged them in a flow chart (figure 1). During the review, the experts use the flow chart for each individual prescription, so that none of the parameters is omitted.

Definitions

Most terms used in the evaluation categories are strictly defined, preferentially based on authoritative literature. We use the term "prescription" to indicate every time that an individual antimicrobial agent is prescribed. We use the term "course" to describe one episode of clinical or suspected infection or increased risk of infection, in which prescription(s), either consecutively or in combination, are written to treat or prevent this same infection (11).

Table 2 - Antimicrobial drug (AD) evaluation categories, present study

I. Agree with the use of antimicrobial therapy/prophylaxis, the prescription is definitely appropriate.

II. The AD prescription for therapy/prophylaxisis inappropriate due to :

a. improper dosage
b. improper dosage interval
c. improper route

III. The AD prescription for therapy/prophylaxis is inappropriate due to:

a. excessive length
b. duration too short

IV. The AD prescription for therapy/prophylaxis is inappropriate due to:

a. more effective alternative agent (Aa): specify
b. less toxic Aa: specify
c. less expensive Aa: specify
d. less broad spectrum Aa: specify

V. The AD prescription for therapy/prophylaxis is unjustified: use of any antimicrobial is not indicated.

VI. Records insufficient for categorization.

Prescriptions and courses are defined either as prophylactic or therapeutic. Antimicrobial therapy without clinical evidence of infection and without a statement in the medical record indicating a specific suspected infection is considered prophylaxis (7). Prescriptions for prophylaxis are labelled ADP. Optimal agents and modalities for prophylaxis are derived from the Medical Letter (12). Infections are defined using the "CDC criteria for nosocomial infections" (13). Prescriptions for empiric therapy (ADE) treat a presumed infection before culture results become available. Prescriptions for documented therapy (ADT) are directed to a known (cultured) pathogen, primary or after ADE. Continuing antimicrobial drug therapy beyond 72 hours in the presence

of a negative culture result or in the absence of cultures is defined as continued empiric therapy (ADET). To allow separate evaluation of empiric therapy and subsequent continuation of empiric therapy or documented therapy with the same drug, we split up prescriptions. After the culture results become known or after a maximum of 72 hours, empirically chosen drug prescriptions (ADE) are divided by us in continuation of empiric therapy (ADET) or documented therapy (ADT). Prophylactic and therapeutic prescriptions are numbered consecutively.

Evaluation procedure

For each prescription, the flow chart (figure 1) is read down from top to bottom, except if the records are insufficient for categorization (stop at category VI) or if the criteria for infection (13) are not met (stop at category V, unjustified). Intravenous prophylaxis begun too early (not within 2 hours of induction of anaesthesia) or prophylaxis begun postoperatively is considered useless, thus equally classified as unjustified (category V).

Antimicrobial drug prescriptions can be inappropriate for several reasons at the same time and therefore can be placed in more than one category or subcategory (categories IV down to II). Prescriptions for therapy are considered inappropriate if errors are made in dose (category IIa), interval (category IIb) or route (category IIc), violating established pharmacokinetic principles (14). As correct length of therapy is frequently arbitrarily established, a duration of treatment which largely differs from the duration which is proposed in a leading infectious diseases textbook (15) is considered either too long (category IIIa) or too short (category IIIb). The reviewers are asked to give an alternative agent (Aa) for reasons of optimal effectiveness (microbiological and pharmacodynamic grounds) (category IVa), less toxicity (category IVb), and less cost (category IVc) in case of equieffectivity (14, 15) of the antimicrobial drug. The strategy of "streamlining" is adopted, in which empirically given, multiple-drug, broad spectrum antimicrobial therapy is progressively replaced by narrow spectrum therapy as soon as possible after the culture results become known (16). This

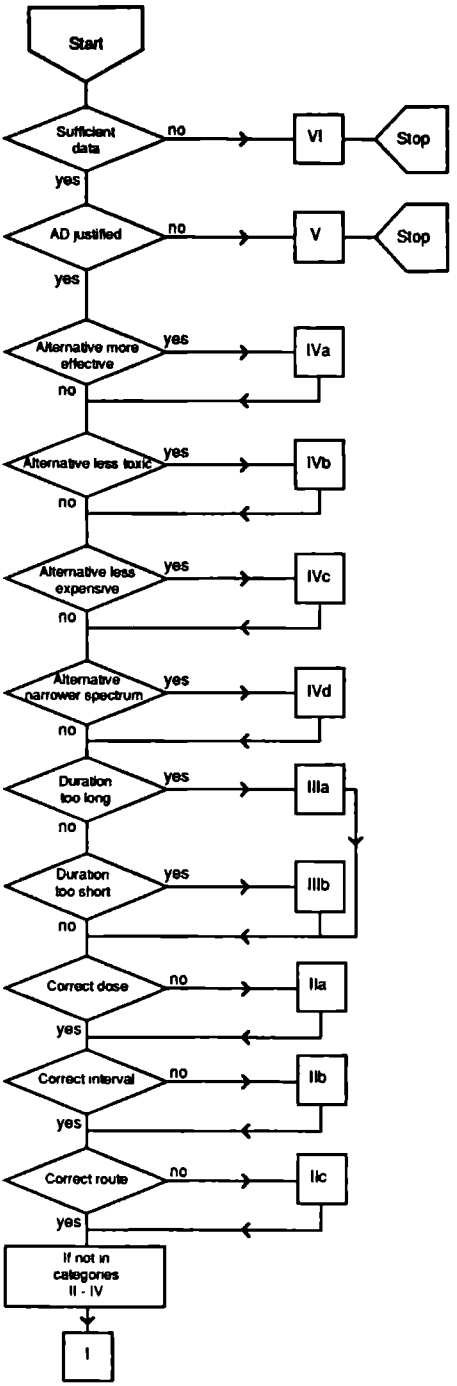

Figure 1 - Flow chart for quality-of-use evaluation of antimicrobial drug prescriptions.

often results in single drug therapy and cost containment. If there is an equieffective alternative drug which has a narrower spectrum, it is formulated (category IVd).

Cost calculation

After the reviewing process, cost comparison is made between the global cost of the given treatment and the global cost of the alternative regimen proposed by the reviewers. The method of global cost calculation which includes purchase costs, administration and monitoring costs is described elsewhere (17).

Data processing

The resulting categories of the evaluation are entered into a computer spreadsheet and database program.

Example

A clinical example is summarized in table 3. A 74-year-old man with diabetes mellitus is admitted with the clinical signs of septicaemia. His weight is 55 kg and serum creatinine is 120 mmol/l (estimated creatinine clearance 40 ml/min). Ceftazidime 1 g tid iv and gentamicin 80 mg tid iv are prescribed on August 7,1990 at 8 pm. Blood cultures are drawn before treatment. The suspected site of entry, a venous ulcer on his lower leg yielded *Pseudomonas aeruginosa*, sensitive to ceftazidime and gentamicin, 2 days earlier. On August 9 all 4 blood culture bottles grow Gram-positive cocci in clusters. The culture from the wound remains sterile. Gentamicin is withdrawn and vancomycin, 500 mg bid is added to the regimen. On August 10, the laboratory reports the growth of *Staphylococcus aureus*, sensitive to methicillin and resistant to penicillin, from the blood. The patient's condition is improving. Ceftazidime and vancomycin are continued until August, 12, when the attending physician stops the ceftazidime. Vancomycin is changed to flucloxacillin, 1 g qid when the microbiologist visits the ward on August, 13. Flucloxacillin is stopped on August, 16. By use of the flow chart, the reviewers made a classification into categories (table 3).

The empiric choice of ceftazidime (ADE1) was considered definitively appropriate in view of the previous cultures (category I); no alternative drug was proposed. Combination therapy with gentamicin (ADE2) was considered

Table 3 - Illustrative example of categorization of multiple prescriptions in an antimicrobial drug course with formulation of the alternative agent and global cost comparison

Indication*	Antimicrobial drug	Dosage iv	Start	Stop	No of doses	Category rev1/rev2	Cost (Dfl) actual	Aa
ADE1	ceftazidime	1 g tid	7/8/90 22 h	10/8/90 22 h	9	I	520	
Aa	id.	id.	id.	id.	9	-		520
ADE2	gentamicin	80 mg tid	7/8/90 22 h	9/8/90 22 h	7	IIb / V	179	
Aa	id. / -	80 mg bid	id.	id.	5	-		137
ADE3	vancomycin	500 mg bid	9/8/90 22 h	10/8/90 22 h	4	I / IVb,c,d	325	
Aa	id / flucloxacillin	id.	id.	id.	4	-		325
ADT1	ceftazidime	1 g tid	11/8/90 8 h	12/8/90 14 h	5	V	289	
Aa	none	-	-	-	0	-		0
ADT2	vancomycin	500 mg bid	11/8/90 10 h	13/8/90 22 h	5	IVb,c,d	406	
Aa	flucloxacillin	1 g qid	id.	id.	9	-		163
ADT3	flucloxacillin	1 g qid	13/8/90 22 h	16/8/90 8 h	13	IIIb	235	
Aa	id.	id.	id.	21/8/90 10 h	30	-		597
Total							1 954	1 742

* ADE, prescriptions for empiric therapy; ADT, prescriptions for documented therapy; Aa, alternative agent, rev, reviewer; id., identical

appropriate by reviewer 1. However, due to the impaired renal clearance the dose interval was considered too short (category IIb). Monotherapy with ceftazidime seemed sufficient to reviewer 2 (category V). The withdrawal of gentamicin and the addition of vancomycin (ADE3) was considered an acceptable change in view of the culture results. The dose reduction was this time according to the patient's renal function and reviewer 1 considered the prescription as definitely appropriate (category I). However, the other reviewer would have given flucloxacillin, because methicillin resistant *S. aureus* (MRSA) was considered unlikely on epidemiological grounds in this hospital (incidence MRSA <1%), and *Staphylococcus epidermidis* was not thought to be the causative organism on clinical grounds. Compared to vancomycin, flucloxacillin is a less toxic, less expensive and less broad spectrum drug and therefore ADE3 was labelled as category IVb,c,d. To continue ceftazidime (ADT1) for documented staphylococcal bacteraemia after August 10 was considered unjustified (category V). The continuation of vancomycin (ADT2) was then judged by both reviewers as category IVb,c,d: the causative organism was at that time known to be sensitive to flucloxacillin. The change to flucloxacillin (ADT3) on August 13 was right, but the duration of treatment (10 days) was considered too short for *S. aureus* septicaemia (category IIIb). The global cost of the illustrative course, i.e. the sum of empiric and documented therapy (ADE and ADT prescriptions), was Dfl. 1 954 (£ 576) (table 3, left cost column). The cost of the proposed treatment with alternative agents (Aa) formulated by reviewer 1 was Dfl 1742 (£ 514) (table 3, right cost column). Although the proposed duration of treatment was longer, savings of at least Dfl 212 or £ 62 (11%) were predicted for the alternative policy in this case.

Discussion

Using the original classification of Kunin (table 1), the illustrative case would have been difficult to classify. Our modified classification system allows separate evaluation of each individual drug according to well documented parameters of

antimicrobial therapy, whereas the original classification allocated courses in one of five broad categories, relying on the absolute authority of the infectious diseases specialist. Because opinions of experts may be different, we prefer review by two such specialists. The system visualizes well where the experts disagree, as illustrated in the clinical example. Credibility is increased by clearly defining terms, relying on authoritative literature (18). Many previous classifications consider courses instead of prescriptions and therefore do unjustice to prescribers: in a combination course, one prescription can be correct, the other a poor choice; the whole course is then considered inappropriate (2, 5, 7, 9). The value of streamlining antimicrobial drug therapy as an important tool in limiting the unnessecary use of broad spectrum antimicrobial drugs and in cost containment (7, 19) is stressed in our evaluation procedure. The drug may be well chosen as an empiric start, but the remainder of the treatment may be unjustified or the spectrum too broad after culture results are known (7). This problem of judgment is solved by dividing the prescription in empiric and documented therapy episodes. This technique artificially increases the total number of prescriptions, so total number of prescriptions should not be used for quantitative analysis of the review.

For prescriptions judged inappropriate, all alternative drug regimens can be fully formulated, thus constituting a comprehensible example of the alternative antibiotic policy for clinicians with their own patient material. Predicted savings can be calculated. Like most authors who have tried to deepen the classification of Kunin we had to add supplementary categories and/or subcategories. Some aspects of antimicrobial therapy categorized by others as described in the introduction were not included in new categories. "Allergic responses" is included in category IV b (less toxic alternative agent). "Loading dose" and "obtaining the necessary serum drug concentrations" are only required for a few antimicrobial drugs. We analysed those aspects separately in order to reduce the length of the category list. With the help of computer spreadsheet programs the the processing of numerous data is not a major problem. However, long lists of categories are difficult to handle during the review. Our flow chart systematizes

and accelerates the reviewing process. We conclude that the present modification of Kunin's criteria allows maximal educational feedback of the evaluation to prescribers.

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CHAPTER III

Global cost calculation of antimicrobial therapy.

IC Gyssens, CA Lennards, YA Hekster & JWM van der Meer

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Abstract

In the actual Dutch hospital budget system, inpatients' drug costs generate no revenue. Efforts to diminish drug costs result in financial benefit for the institution. This is also the case for antimicrobial drugs. To maximize cost containment, efforts are to be directed to all cost components : costs of acquisition, preparation and administration and monitoring of antimicrobial drugs. We describe the method of cost-identification analysis which was performed in our hospital during a review of antimicrobial drug usage evaluation. Purchase contract prices for antimicrobial drugs vary between hospitals and they are invariably lower than wholesale prices. However, to allow generalization of our calculation results to other Dutch general hospitals, we chose wholesale purchase prices of antimicrobial drugs and national prices for salaries and hospital costs. Global cost comparison points out the most cost-effective system of intravenous administration. Push injection is the most economic way to administer i.v. drugs which do not require dilution or prolonged infusion time. For stable solutions, such as metronidazole, ready-to-infuse bags are the most economic system. The global cost calculation is listed for commonly used antimicrobial drugs for inpatients. A cost comparison is given for vancomycin CP and teicoplanin, two antistaphylococcal drugs which are probably equieffective. The result of global cost comparison contributes to the decision to include new drugs in the hospital formulary or to replace older ones.

Introduction

The true cost of health care is what health care consumes of society's resources. Under a traditional medical system, hospital costs (i.e. consumption of hospital services such as those provided by the pharmacy and laboratory) are passed to the patient or third-party payers and generate revenues for the hospital, contributing to the inflationary spiral in health care costs. In general hospitals in the Netherlands, the current budget system was introduced in 1983 and university hospitals followed in 1984. These budgets are based on the hospital's consumption of resources during the year 1982 for general hospitals and 1983 for university hospitals. In this budget system, it becomes of primary importance to contain internal costs since the Government has limited hospital costs in an external budget. In 1988, a function-directed budget system was introduced for general hospitals (1). A significant portion of the total operating hospital budget is drug purchases. As in the prospective payment system which is used in the U.S. (i.e. reimbursment categorized according to Diagnosis-Related-Groups), drug costs for inpatients generate no revenues. Antimicrobial drugs account for the largest proportion of all drugs, ranging from 13 to 37% of these purchases by hospitals in a European study (2). However, the true cost of antimicrobial therapy for the institution involves considerably more than the purchase cost of the drug employed (3). The recognition that some drugs which are very inexpensive to purchase, are expensive to use, prompted the development of methods to estimate the global cost of antimicrobial chemotherapy (4-6). We performed a cost-identification analysis as described by Eisenberg (7), during a review of antimicrobial drug usage evaluation. We applied a method of global cost calculation which takes into account acquisition costs, administration and preparation costs, and monitoring costs in our hospital (8). We subsequently constructed a cost calculation system which quantifies the cost difference for each route and each intravenous system of antimicrobial drug administration. The method permits comparison of the cost of actual and alternative antimicrobial drug policies in the quality-of-use review.

Method

During a review of antimicrobial drug use evaluation in the 948-bed University Hospital of Nijmegen, cost parameters were determined for the following components of antimicrobial chemotherapy of inpatients: antimicrobial drug purchase costs, clerical costs, costs to prepare and administer the drugs and costs to monitor the drugs. The different cost components were arranged in a spreadsheet which permits calculation of the global cost per dose.

1. Purchase costs

The official wholesale price-list "Groothandelsprijslijst Courant Brocacef 1990" was chosen for acquisition cost of antimicrobial drugs, instead of contract prices of the hospital. Contract prices tend to vary between hospitals, reflecting the institution's antibiotic and purchase policy. The true acquisition costs of antimicrobial drugs in hospitals are generally below the wholesale price. However, the invoice prices of drugs include additional 6% taxes.

2. Clerical costs

Antimicrobial drugs listed in the hospital formulary are kept in stock in the wards. For formulary drugs, clerical costs per dose were determined by the labour time of nurses filling out the patient's medication sheet. In case of nonformulary drugs, extra time was needed to obtain individual receipts from the treating physician.

3. Costs to prepare and administer drugs

Only the time of nurses was taken into account, since pharmacists were not involved in the preparation of admixtures for injection, and formulary drugs were kept in stock in the wards.

Oral administration, i.v. push (bolus) injection, i.v. piggyback (quick, small-volume infusion) and intermittent i.v. infusion (large volumes up to 500 ml, requiring 30 minutes or more) were studied for cost comparison. Intramuscular injections were rarely used for antimicrobial drug administration in hospitalized patients. Most i.v. antimicrobial drugs had to be reconstituted with sterile water from powder vials as for cephalosporins and penicillins. Some manufacturers provide dilution fluid as for teicoplanin.

Table 1 - Costs of antimicrobial drugs in Dfl.

generic	brand	dosing schedule (mg)	route	wholesale cost/dose	admin. cost/dose	monitoring cost/dose	global cost/dose	global cost/day
benzylpenicillin	Natrium Pen G	1 MU/6h	i.v. push	1.30	5.80	0	7	28
benzylpenicillin	Natrium Pen G	1 MU/6h	i.v. infusion	1.30	8.80	0	10	40
cefazolin	Kefzol	o.r. 1x1000	i.v. push	15.02	1.90	0	17	17
cefazolin	Kefzol	o.r. 1x1000	i.v. infusion	15.02	5.80	0	21	21
cefazolin	Kefzol	1000/8h	i.v. push	15.02	5.80	0	21	62
cefazolin	Kefzol	1000/8h	i.v. infusion	15.02	8.80	0	24	71
ceftazidime	Fortum	1000/8h	i.v. push	48.60	7.00	0	56	167
ceftazidime	Fortum	1000/8h	i.v. infusion	48.60	10.00	0	59	176
clindamycin	Dalacin C	300/6h	i.v. infusion	12.10	9.40	0	22	86
clindamycin	Dalacin C	600/8h	i.v. infusion	24.20	10.60	0	35	104
gentamicin	Garamycin	120/12h,<72h	i.v. infusion	19.80	7.70	0	28	55
gentamicin	Garamycin	120/12h,>72h or *	i.v. infusion	19.80	7.70	6.30	34	68
metronidazole	Flagyl	2x250/8h	orally	1.20	0.60	0	2	5
metronidazole	metronidazole	o.r. 1x500	i.v. infusion	4.00	1.80	0	6	6
metronidazole	metronidazole	500/8h	i.v. infusion	4.00	3.60	0	8	23
piperacillin	Pipcil	o.r. 1x4000	i.v. infusion	46.55	5.80	0	52	52
ciprofloxacin	Ciproxin**	500/12h	orally	6.22	0.90	0	7	14
ciprofloxacin	Ciproxin**	200/12h	i.v. infusion	69.51	3.90	0	73	147

* renal function impairment; ** nonformulary drug; o.r. = operating room

Ampoules contain a high concentration of antibiotic solution as for gentamicin marketed as Garamycine®. Reconstituted vials were either injected with the help of a 20 ml syringe (push) into the tubing, were injected in a piggyback, or were injected into a large volume infusion bag for intermittent infusion when dilution was required, as for clindamycin marketed as Dalacin®. The direct costs associated with antimicrobial drug administration were broken down into personnel time and supplies. A questionnaire was given to the senior nurses of 2 different wards. They were asked to collect several (minimum three) time measurements from their staff for all the components of oral and i.v. antimicrobial drug administration. The nurses noted the time required with the help of a wristwatch. Subsequently, the senior nurses were interviewed. Surveillance time of the i.v. intermittent infusions was estimated for various duration of infusions (30, 60, 120 and 240 minutes). Both measurements and experience data were used to deduct mean administration time. Personnel time was multiplied by the average hourly salary rate of nurses to determine personnel costs.

System supply costs were also obtained from a wholesale price-list. Similarly, contract prices of supplies are usually lower as large quantities are purchased. Additional 18.5 % taxes are added in the invoice. Costs of personnel time and supplies were arranged in a separate spreadsheet to allow calculation of the administration costs per dose for each system of administration.

4. Monitoring costs

When an antimicrobial drug has a narrow therapy vs. toxicity range, additional laboratory tests are required to monitor drug concentrations in blood and organ function. For calculation of the monitoring costs of aminoglycosides, we assumed that no extra laboratory tests were required during the first 72 hours of treatment in patients with normal renal function in the absence of hemodynamic instability (9). However, patients presenting with unstable circulation due to Gram-negative septicemia, patients with burns, or patients who had impaired renal function required two extra measurements of creatinine and one set of aminoglycoside serum concentrations (peak and trough) per week for

monitoring. If treatment continued beyond 72 hours, even in patients with normal renal function, similar extra laboratory tests were needed. Since the real costs of laboratory tests are unknown on a national level, laboratory cost calculations were based on cost approximation by the Spaander points system. This system takes into account total laboratory operating costs (laboratory staff wages, supplies, equipment, energy etc). Each laboratory test is given a number of Spaander points which reflects the relative contribution of the test on workload and consumption of supplies. The total annual production by a laboratory is expressed in an amount of Spaander points. Dividing the total production by total operating costs results in a cost per Spaander point, which varies per laboratory. However, to allow cost comparison of laboratory tests on a national level, the average national cost per Spaander point, based on national guidelines was used for calculations (Centraal Orgaan Tarieven Gezondheidszorg, Richtlijnen Wijziging Declaratie Structuur 1988) (10).

Results

1. Purchase costs

The acquisition costs (wholesale price) per dose for commonly used antimicrobial drugs are listed in table 1, column 5.

2. Clerical costs

Nursing clerical time per dose was considered a question of seconds for formulary drugs, and not taken into account. However, nonformulary drugs took more time, i.e. an average of 0.5 min per dose.

3. *Costs to prepare and administer drugs*

The results of the nurse's average time needed to reconstitute, prepare and administer formulary drugs are shown in table 2. Oral doses (tablets or capsules) required 1 minute. Total time for i.v. push injections ranged from 4.5 minutes to 8.5 minutes, depending on the complexity of reconstitution. Reconstitution times varied from 1.5 to 4 minutes. For ease of calculations, we allocated the antimicrobial drugs to two groups: normal reconstitution (mean 2 min) and difficult reconstitution (mean 4 min). The average time required for injection into

Table 2 - Nurse's time needed for reconstitution, preparation and administration of one dose of an antimicrobial drug

Route of administration	Nurse's time (min)			Total time (min/dose)
	reconstitution	administration	surveillance*	
Oral	0	1	0	1
Intravenous	0	4.5	0	4.5
push	2 (normal)	4.5	0	6.5
	4 (difficult)	4.5	0	8.5
Intravenous	0	2	1 (15)	3
infusion			2 (30)	4
			4 (60)	6
	2 (normal)	2	1 (15)	5
			2 (30)	6
			4 (60)	8
			10 (240)	14
	4 (difficult)	2	1 (15)	7
			2 (30)	8
			4 (60)	10

* Infusion time in parentheses; 1 min surveillance time per 15 min infusion time up to 60 min, then 1 min surveillance time per 30 min infusion time

tubing (push) was 4.5 minutes. Suspending an infusion bag and connecting it to the patient's i.v. device (i.v. infusion tubing or heparin-lock catheter), averaged 2 minutes. All antimicrobial drug infusions were regulated with the help of a

Table 3 - Costs of intravenous supplies per dose (Dfl)

Supplies	Method of administration			
	push injection	infusion/ piggyback	infusion/ intermittent	infusion/ bag
Syringe 5 ml	0.32	0.32	0.32	-
Syringe 20 ml	0.69	-	-	-
Needles	0.32	0.32	0.32	-
Gauze, disinectant	0.07	0.06	0.06	0.10
Aqua destillata	0.50*/-	0.50*/-	-	-
Infusion bag (50-500ml)	-	2.90	2.90	-
Y site	-	1.70	1.70	1.70
Total	1.90*/1.40	5.80*/5.30	5.30	1.80

*Reconstitution fluid needed.

roller clamp. Total infusion times were according to the package insert. For surveillance of the infusion, one minute extra time was needed for 15 minutes infusion time, up to a total of 4 minutes for one hour infusion time. Intravenous antimicrobials which took 2 hours infusion time (vancomycin CP 1 g) and 4-6 hours infusion time (amphotericin B) scored 2 minutes/hour extra. The calculated cost of a nurse's minute was Dfl 0.60 in 1990, based upon factual nursing costs of this hospital. The supplies and associated cost (disinfection) needed for all procedures are listed in table 3.

As an illustrative example, the comparison between the costs to prepare and administer teicoplanin and vancomycin CP is shown in table 4. For teicoplanin and vancomycin CP, the exact measurements for preparation and administration time are used. Reconstitution of a single vial required 3 minutes for both drugs. Since teicoplanin was manufactured in vials of 200 mg, for the reconstitution of teicoplanin 400 mg, 6 minutes were needed. For injection of teicoplanin, 7.5 minutes were needed, due to the production of foam when nurses automatically shook the vial during the reconstitution process.

Since teicoplanin was manufactured in vials of 200 mg, for the reconstitution of teicoplanin 400 mg, 6 minutes were needed. For injection of teicoplanin, 7.5 minutes were needed, due to the production of foam when nurses automatically shaked the vial during the reconstitution process.

Table 4 - Costs to prepare and administer teicoplanin and vancomycin CP

Generic name	Route	Dosing schedule (mg)	Time (min)	Time* cost (Dfl)	Supplies cost (Dfl)	Administration cost/dose (Dfl)
Teicoplanin	i.v. push	400/24 h	13.50	8.10	1.40	9.50
Vancomycin CP	i.v. infusion	1000/12 h	11.00	6.60	5.80	12.40

* The cost of a nurse's minute is Dfl 0.60

4. *Monitoring costs*

Laboratory costs are listed in table 4. Monitoring aminoglycosides, as for

gentamicin, raised the weekly treatment costs by Dfl 88.40. This amount was due to serum creatinine measurement Dfl 6.80 twice weekly + one aminoglycoside serum peak and trough concentration Dfl 74.80. In a dosing schedule of gentamicin twice daily the additional monitoring cost/dose was Dfl 6.30. Similar monitoring of vancomycin CP amounted to Dfl 144 per week. When audiometry was performed, as advised in case of prolonged administration by the package insert, the weekly costs were Dfl 174 or Dfl 12.40 per dose (twice daily dosing). The package insert of teicoplanin advises to control renal and auditory function in patients with renal function impairment or prolonged administration, without measurement of serum concentrations. These costs amounted to Dfl 44 per week or Dfl 6 per dose. Serum (trough) concentrations were only considered meaningful for monitoring efficacy. The cost of a serum concentration of teicoplanin was Dfl 65.45. Laboratory costs per dose for vancomycin and teicoplanin are listed in table 6.

Table 5 - Costs of laboratory tests for antimicrobial drug monitoring in Dfl

Test	Spaander points *	Cost
leukocytes	2	2.72
creatinine	5	6.80
potassium	5	6.80
ASAT	8	10.88
serum concentration		
gentamicin	20	37.40
vancomycin	35	65.45

* Spaander point of the chemistry laboratory = 1.36 Dfl
Spaander point of the bacteriology laboratory = 1.87 Dfl

5. Global costs

The resulting global costs of common antimicrobial drugs are listed in table 1 (A complete list can be obtained from the authors upon request). As an illustrative example, global cost comparison between a formulary antimicrobial drugs (vancomycin CP) and a newly marketed antimicrobial drug with similar efficacy

(teicoplanin) is shown in table 6. For teicoplanin, at least one loading dose is needed to rapidly achieve steady state concentrations (11). For the first week of treatment with teicoplanin, the costs per week are the result of eight doses.

Table 6 - Cost comparison of vancomycin CP and teicoplanin (Dfl)

Generic name (Brand)	Dosing schedule (mg)	Route† i.v.	Wholesale cost/dose	Adminisration cost/dose	Monitoring cost/dose	Global cost/dose	Global cost/week
Teicoplanin (Targocid)	400/24 h*	push	250.02	9.50	0	259	2072
	400/24 h	push	250.02	9.50	6.00	265	1855
Vancomycin (Vancocin CP)	1000/12 h	infusion	119.06	12.40	0	131	1834
	1000/12 h	infusion	119.06	12.40	12.40	143	2007

*First week; including 1 loading dose, prolonged administration
† i.v.: intravenous

Discussion

In this paper we describe a cost-identification analysis of hospital antimicrobial drug therapy. The computer spreadsheet technique permits quick calculation if values of the cost components change, as for purchase prices or nurse's wages. Since purchase contracts differ between hospitals due to competitive bidding or quantity of drug purchased, wholesale prices were preferred to allow objective comparison between drugs on a national level. The contract acquisition price of an antimicrobial drug which is commonly used in an institution can be as low as 25% of its official wholesale price. However, this situation is rather exceptional, and it only exists for a few older drugs. The acquisition cost of most antimicrobial drugs is about 10% lower than the official price, after taxes are included.

We did not take into account pharmacy handling costs. Pharmacy distribution costs vary with the logistical organization of drug distribution within the hospital. Steenhoek combined pharmacy and nurse handling costs in his cost comparison of antibiotic therapies (1).

The present cost calculation points out the most economic way and system to

administer i.v. antimicrobial drugs. Different cost components seem relatively important for different drugs. The administration costs of benzylpenicillin 1 MU i.v. represent 83% to 88% of the global cost per dose and i.v. push injection is 30% less expensive than i.v. piggyback infusion (table 1). When the predominant cost element is the acquisition cost of the drug (vancomycin CP, teicoplanin), the proportional savings by changes in system of administration (i.v. push or intermittent infusion) and dosing schedule seem negligible (table 6). However, administration costs of i.v. piggyback (generally Dfl 8.80) are almost always larger than those of i.v. push injection (generally Dfl 5.80), as shown for benzylpenicillin and cefazolin in table 1. The infusion bag (50 to 500 ml) accounts for most of the cost difference between both systems. Thus, push injection invariably saves a fixed amount of money per dose of drug which does not require dilution or prolonged infusion. Although in some Dutch hospitals nurses are not authorized to perform injections into i.v. tubing or i.v. catheters, the reports of the committee on responsibility of nurses in general hospitals (VAR) advise the same code of authorization for the medical acts of intravenous infusion and intravenous injection (12, 13). Moreover, push injection has increased security since rapidly occuring side effects are noted faster. Thus, both for safety reasons as well as from a cost containment point of view, i.v. push injection (3-5 min) is preferable to short term (< 15 min) piggyback infusion. Intermittent infusion (large volumes, requiring more than 20 min) should be reserved for drugs that require dilution or a prolonged infusion time such as vancomycin or amphotericin B. For stable solutions, ready-to-infuse bags are the most economic system for intermittent administration (metronidazole, table 1). The concept of continuous (24 h) i.v. infusion, based on pharmacodynamic properties of some antimicrobial drugs, is not discussed here.

Teicoplanin has the advantage over vancomycin CP that it can be administered by push injection. However, by inadvertence, the production of foam during reconstitution can add several minutes to the subsequent injection and savings are less than one would expect (table 4).

Another strategy of antimicrobial drug administration which can save time of

nurses and supplies is illustrated in surgical prophylaxis. All anaesthesiologists in our hospital preferred to administer cefazolin by push injection (see Chapter VI). On the other hand, nurses in surgical wards almost invariably administered cefazolin in piggyback. The cost of one dose of cefazolin for peri-operative prophylaxis given by the anaesthesiologist in the operating theatre is Dfl 17. The same dose administered preoperatively on the ward by a nurse amounts to Dfl 23. Both calculations are shown in table 1.

The cost of aminoglycosides rises by Dfl 6.30 per dose (twice daily dosing) after 72 hours when monitoring becomes necessary. Aminoglycosides are much less expensive when used in empiric therapy for synergy and broadening of the spectrum during the first days before culture results become known. Monitoring costs can be avoided by replacing empirically given aminoglycosides by less toxic antimicrobial drugs in subsequent documented therapy.

From table 1 it is clear that single-dose prophylaxis with a combination of antimicrobial drugs is not always more expensive than prophylaxis with one drug; for example, peri-operative prophylaxis with one dose of piperacillin (Dfl 52) is more than twice as expensive as the combination of cefazolin with metronidazole (Dfl 23).

The global cost per day (table 1) or per week (table 6) should be considered for cost comparison between drugs, as the daily cost of antimicrobial therapy can be largely influenced by differences in dosing schedules and monitoring.

We did not include complication costs in our calculation system. To our knowledge, there are no European data on the subject. Figures from the United States are irrelevant for the European situation because they are largely influenced by litigation costs. Still, we feel that for antimicrobial drugs with established renal and otovestibular toxicity, such as aminoglycosides, a certain amount of money has to be added to obtain the true global cost of these drugs. This is a reason to try and replace toxic antimicrobial drugs from the formulary by less toxic, equieffective ones. Global cost considerations should guide decisions to introduce new drugs for the hospital formulary rather than purchase

costs of antimicrobial drugs.

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SECTION B **Surveys in surgical departments**

CHAPTER IV

Antimicrobial prophylaxis and therapy in surgery, gynaecology and orthopaedics.

IC Gyssens, IEJ Geerligs, JMJ Dony, JA van der Vliet, A. van Kampen, PJ van den Broek, YA Hekster* & JWM van der Meer.

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Abstract

Following a one-month prospective study of all antimicrobial drug use in surgical departments, new guidelines were implemented. The review was repeated after 2 years. Total number of patients (766 vs 744) and operations (542 vs 522) were similar. In both study periods, one third of the patients were prescribed antimicrobial drugs. Prophylactic drug consumption decreased from 0.75 to 0.53 DDD/operation. Compliance with guidelines improved from 32% to 79%. Duration of prophylaxis > 24 hours decreased from 21% to 8%. Single dose prophylaxis increased from 34% to 80%. Quality of the prophylactic courses improved, as evaluated by experts using established criteria. For prophylaxis, cost savings amounted to 57%. Better quality of therapeutic courses was associated with a cost increase of 15%. Indicators of satisfactory outcome with the new policy were a stable median length of stay (5.5 days in the first review and 5.0 days after intervention) and a reduction in the number of nosocomial infections/100 bed days treated with antimicrobial drugs (1.0 before intervention vs 0.77 after intervention).

Introduction

Antimicrobial drugs account for 13 to 37 % of the drug budget in European hospitals (1); between 30 and 60% of the courses are for prophylactic use (2, 3). The main reasons for monitoring antimicrobial drug use are to optimize medical care, to limit and reduce the spread of resistant microorganisms and to contain costs. In the U.S., the pressure to contain costs imposed by diagnosis-related group (DRG) prospective reimbursement has greatly influenced antimicrobial drug control (4). In Europe, the pressure to reduce costs is still increasing in countries with budgeting systems such as in the Netherlands. Parallel to a concern about increasing costs of antimicrobial drugs, many authors have described inappropriate use (5, 6). Surgical prophylaxis with antimicrobial drugs is long recognised as an area where overuse is often found and where it is also the easiest to correct (7, 8). Many antimicrobial drug intervention strategies are described to optimize quality at lower cost, including education, the development of protocols, targeting on specific drugs (9). A number of criteria for optimal therapy and prophylaxis are well established (10, 11). A widely accepted regimen of preoperative prophylaxis is 1 g of the first generation cephalosporin cefazolin, given within an optimal period of 30 min before incision, and repeated if the operation lasts for more than 3 h (12, 13). We conducted a prospective intervention study in three surgical departments in a large university hospital : 1) to define antimicrobial drug use (prophylaxis and therapy) in terms of quality and costs 2) to measure the effect of interventions to improve the quality of antimicrobial drug courses.

Patients and Methods

Setting

The University Hospital Nijmegen is a 948-bed teaching hospital with 344 surgical beds, and ± 1600 operations/month on inpatients. The study took place in the departments of gynaecology and obstetrics, surgery, and orthopaedics, hereafter named G, S and O. The hospital formulary listed 20 parenteral and 26

oral antimicrobial drugs at the start of the study. In the previous year, antimicrobial drugs accounted for 22% of the hospital drug budget of Dfl 14 million ($ 8.1 million). The Antibiotics Committee had issued a new edition of an antimicrobial drug formulary with guidelines for surgical prophylaxis and therapy. In addition, some departments had their own treatment protocols which contained detailed guidelines for antimicrobial use by staff and residents. We will refer to both as "guidelines". A classification of surgical procedures was used based on the original classification of Cruse and Foord adapted with newer guidelines (12, 14). Length of stay was calculated as follows: number of in-hospital days of patients included in the study/ number of patients included in the study.

Antimicrobial Drug Use Review

The first review took place during separate one-month study periods in 1990. Antimicrobial drug consumption was prospectively reviewed in 766 consecutive surgical patients. After a period of intervention, a similar review of 744 consecutive patients was repeated in 1992. The quality-of-use studies were performed by an infectious diseases physician and junior clinical pharmacists, who visited the wards and collected data on all patients receiving antimicrobial drugs on a daily basis. Abstracts were made of each antimicrobial drug course. A course was defined as an episode of clinical or suspected infection or increased risk of infection, in which prescription(s), either consecutively or in combination, were written to treat or prevent this particular infection. Clinical information was retrieved from the patient's record. Infections were defined according to CDC definitions for nosocomial infections (15). Nosocomial infection was defined as active infection that was not present or incubating at the time of admission. Microbiology results were obtained directly from the laboratory of medical microbiology. The schedule of systemic antimicrobial drug was copied from the patient's medication chart (Kardex®) and from the anaesthesia record. Antimicrobial drug use was converted in Defined Daily Doses (DDD). The Defined Daily Dose (DDD) represents the average therapeutical dose for an adult for the standard indication (16). Quantitative use in DDD of a drug/100

bed days can give an indication of the number of patients treated with the drug (17). Quantitative use was analysed by comparing the number of courses in the population at risk in the study periods (courses/100 bed days, incidence rate) and by comparing DDD/100 bed days. The DDD /100 bed days has been chosen by the WHO Drug Utilization Research Group as a unit of comparison between hospitals. Direct and indirect costs were calculated in Dutch guilders (1 Dfl= 0.65 $) by a method for global drug cost calculation, which includes costs of drug administration and costs of monitoring (18). Qualitative use was analysed in two ways. First, compliance with existing hospital guidelines was checked at the time of the initial review, and compliance with the department's new protocol after the intervention. Second, two independent experts in infectious diseases (named reviewer 1 and reviewer 2) evaluated quality in the following way: prescriptions were assessed using 6 categories of good antimicrobial use by means of established criteria arranged in a flow chart. The method is based on the original criteria of Kunin (10) and is described previously (11). In short, prescriptions can be definitely appropriate (category I), unjustified (category V) or the records insufficient for categorization (category VI). The other prescriptions are placed in categories of inappropriate use II, III, and IV. Inappropriate prescriptions can be allocated to several categories at the same time: incorrect dose (IIa), interval (IIb) or route (IIc), duration too long (IIIa) or too short (IIIb). If relevant, the experts cite a better alternative agent due to higher efficacy (IVa), lower toxicity (category IVb), lower cost (category IVc) and less broad spectrum (IVd). Global costs of actual and alternative policies (in this study the alternative policy proposed by reviewer 1) are compared to project savings by changes in policy.

Intervention

After the first review, a report of each department was sent to their chiefs of staff. The report was accompanied by recommendations for the alternative antibiotic policy of reviewer 1, a policy in concordance with the hospital's antimicrobial drug policy. The principal goal was to introduce a universal surgical prophylaxis standard of single-dose cefazolin at incision (with

metronidazole where an anaerobic spectrum was needed). The report and recommendations were discussed by the surgical staff. The recommendations were adapted to new protocols for prophylaxis and therapy with the help of a surgical staff member. After approval by the Antibiotic Committee, a presentation of the report and the protocol was held in the departments, in part by the surgical staff member. In most departments, the first dose of surgical antimicrobial prophylaxis was given by the anaesthetist in the operating room. Because anaesthesias were performed by a rotating pool of 40 anaesthetists (staff members and residents), the department of anaesthesiology was interviewed by means of a questionnaire. The inquiry showed deficient communication between anaesthetists and surgeons on the subject of administration and timing of prophylaxis (see chapter VI). In the intervention period, the results of the inquiry were used in an educational setting. The implementation of the protocols was assisted by the department of clinical pharmacy. Junior pharmacists organized briefings for nurses in the operating departments and in the wards, and the standardized prophylaxis guidelines were visualized in the wards and the operating rooms. Operating room drug stocks were reorganized. In departments S and O, pharmacy technicians discussed protocol violations with prescribers and nurses on their twice weekly visits to the wards, as a long term surveillance.

Generally, χ^2 tests were applied to establish systematic differences. The Wilcoxon's test was used for the comparison of length of hospital stay. The Fisher's exact test was used to compare duration of prophylaxis. Agreement between the experts was assessed by κ coefficients.

Results

Quantitative use

Table 1 shows the demographic characteristics of the study populations in the first and second study period for the three departments. The number of patients hospitalized, mean age, and the number of operations performed in the study months was similar in both reviews. The proportion of patients with

Table 1 - Demographic characteristics of three surgical departments and antimicrobial drug use (one-month reviews)

review	before intervention				after intervention			
department	G	S	O	Total	G	S	O	Total
patients	n=331	n=286	n=149	n=766	n=282	n=302	n=160	n=744
mean age, years	34.1	49.3	39.7	40.9	35.1	51.7	42.0	43.3
age range, years	15-82	11-88	2-87	2-88	20-85	14-94	0-92	0-94
number of operations	150	258	134	542	144	245	133	522
clean	104	112	73	289	94	115	84	293
clean/ prostheses	-	46	51	97	-	46	43	89
contaminated	46	47	-	93	50	52	-	102
dirty	-	53	10	63	-	32	6	38
patients with antimicrobial drugs *(%)*	76 *(23)*	110 *(38)*	71 *(48)*	257 *(34)*	60 *(21)*	128 *(42)*	59 *(37)*	247 *(33)*
patients with therapy *(%)*	30 *(9)*	51 *(18)*	24 *(16)*	105 *(14)*	15 *(5)*	53 *(18)*	18 *(11)*	86 *(12)*
patients with prophylaxis (%)	50 *(15)*	78 *(27)*	55 *(37)*	183 *(24)*	53 *(19)*	93 *(31)*	53 *(33)*	199 *(27)*
median length of stay, days (range)	2.5(1-42)	7.5(1-232)	9(1-92)*	5.5(1-232)	2.5(1-52)	7(1-172)	6(1-60)*	5(1-172)

* p= 0.005, Wilcoxon's test

Table 2 - Quantitative use of antimicrobial drugs in three surgical departments (one-month reviews)

review	before intervention				after intervention			
department	G	S	O	Total	G	S	O	Total
total number of courses	82	129	79	290	68	149	71	288
bed days	1586	2292	1199	5077	1284	2373	1085	4742
total courses/100 bed days	5.2	5.6	6.6	5.7	5.3	6.3	6.5	6.1
total consumption, DDD	352	655	320	1,327	340	835	574	1,749
parenteral DDD (%)	157(*45*)	493(*75*)	178(*56*)	828(*62*)	227(*67*)	705(*84*)	463(*81*)	1,395(*80*)
prophylactic courses (%)	52(*63*)	78(*61*)	55(*70*)	185 (*64*)	53(*78*)	96(*64*)	53(*75*)	202 (*70*)
prophylactic courses/100 operations	35	30	41	34	37	39	40	39
prophylactic consumption, DDD (%)	136(*39*)	168(*26*)	102(*32*)	406(*31*)	113(*33*)	110(*13*)	54(*9*)	277(*16*)
prophylactic DDD/ operation	0.91	0.65	0.76	0.75	0.78	0.45	0.41	0.53
therapeutic courses (%)	30(*37*)	51(*39*)	24(*30*)	105(*36*)	15(*22*)	53(*36*)	18(*25*)	86(*30*)
therapeutic courses/100 bed days	1.9	2.2	2.0	2.1	1.2	2.2	1.7	1.8
therapeutic consumption, DDD (%)	216(*61*)	487(*74*)	218(*68*)	921(*69*)	227(*67*)	725(*87*)	520(*91*)	1472(*84*)
therapeutic DDD/100 bed days	13.6	20.9	18.2	18.1	17.7	30.6	47.9	31.0
therapeutic DDD/course	7.2	9.5	9.1	8.8	15.1	13.7	28.9	17.1

antimicrobial drugs was also similar. The median length of hospital stay in both study periods was not statistically different in departments G and S. In department O, the median length of stay had decreased significantly (p=0.005). The distribution of the type of operations was also similar in the two study periods.

Quantitative consumption data before and after the intervention are presented in table 2. The proportion of parenteral DDDs increased in all departments. The shift from oral to parenteral route was most striking in department O. Quantitative data were analysed in detail according to prophylaxis and therapy.

Prophylaxis

Slightly more operations were performed under antimicrobial prophylaxis in the second review (table 2). However, the consumption of prophylactic antimicrobial drugs expressed in DDD/operation decreased. After the intervention, only 16% of total consumption (in DDDs) was for prophylactic use, compared with 31% in the first review. In the first review, a variety of antimicrobial drugs were used for prophylaxis in 24h-regimens (figure 1). An oral regimen that combined neomycin and bacitracin (Nebacetine forte^{R}) was used for large bowel surgery in department S and cefalexin was mainly prescribed in department G. Furthermore, when the medication order on the anaesthesia record mentioned "24 h", some nurses in the wards did not take into account the dose given by the anaesthetist in the operating room. This practice resulted in an extra dose in half of the 24h- prophylactic prescriptions in department S and in 10% of the 24h-prophylactic prescriptions in department O. After the intervention, the variety of regimens was mostly replaced by single dose cefazolin (plus metronidazole). Amoxicillin plus gentamicin was used for the prophylaxis of endocarditis (figure 1).

Therapy

Slightly less patients were treated therapeutically in the second review period (table 1). Also, therapeutic courses/100 beddays slightly decreased (table 2). Abdominal and pelvic infections were the most frequent type of infections

treated with antibiotics in both reviews, 37% and 40% respectively. Urinary tract infections accounted for 23% and 24% respectively. The number of nosocomial infections treated with antimicrobial drugs/100 bed days was 1.0 before intervention and 0.77 after intervention.

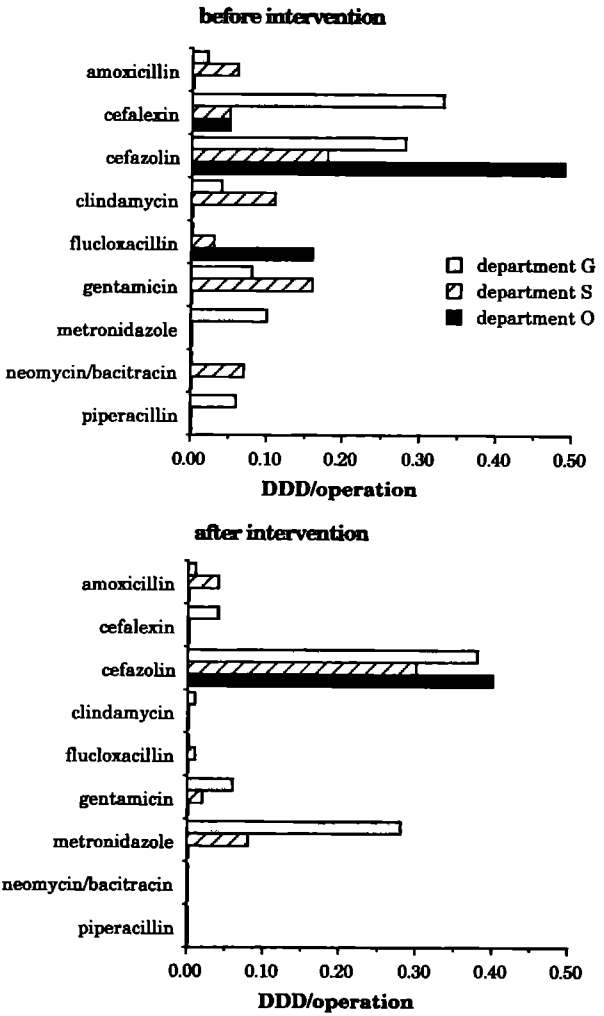

Figure 1 - Consumption of antimicrobial drugs for surgical prophylaxis in three departments of a university hospital before and after an intervention, one-month reviews.

In all departments, therapeutic consumption (expressed in therapeutic DDD/100 bed days) increased due to an increase of DDD/therapeutic course (table 2). Two reasons could be found for the increase: first, the new protocols advised to treat severe infections such as osteomyelitis with higher doses and for longer periods than usual; second, narrow spectrum penicillins (penicillin G, flucloxacillin) were preferred in directed therapy. For the treatment of osteomyelitis with benzylpenicillin 6 million units daily, the prescribed daily dose was 3 times the DDD (PDD/DDD ratio =3).

The major changes in the types of therapeutic antimicrobial drugs are presented in table 3. Penicillin use increased fourfold and i.v. cephalosporins increased by half. Part of the changes in drug use were not foreseen. Amoxicillin-clavulanate had been introduced in the hospital formulary in december 1990. The new treatment protocol advised use of the drug only for the treatment of postpartum endometritis. In the second review, amoxicillin-clavulanate consumption amounted to 6.9 DDD/100 bed days in department G, which represented 86% of its penicillin use, and 39% of the departments' total therapeutic use (table 3). Amoxicillin-clavulanate was not mentioned in the new protocols of departments S and O. In those departments, amoxicillin-clavulanate consumption remained low, 4% and 8% respectively. Ciprofloxacin, added to the formulary in september 1991, but not introduced in the treatment protocols, was not or still minimally used in the three departments during the second review.

Costs.

Cost figures (in Dfl) are presented in table 4. Overall, cost savings amounted to 11%. Projected annual savings for the three departments amounted to Dfl 49,800.

Prophylaxis

Figure 2 presents the total distribution of costs of prophylaxis by antimicrobial drug group before and after the intervention in the three departments. Piperacillin was only used in department G. Before the intervention, piperacillin, that accounted for 7% of the department's consumption, accounted for 34% of

Table 3 - Consumption of antimicrobial drugs for therapy in DDD/100 bed days by three surgical department (one-month reviews)

review	before intervention				after intervention			
department	G	S	O	Total (%)	G	S	O	Total (%)
penicillins	2.8	6.6	1.4	4.2 (*23*)	8.0	13.5	39.4	18.0 (*58*)
cephalosporins	1.6	2.3	8.3	3.5 (*19*)	2.3	7.4	3.8	5.2 (*17*)
gentamicin	0.4	3.0	-	1.5 (*8*)	-	2.1	-	1.1 (*3*)
clindamycin	-	1.7	2.3	1.3 (*7*)	-	-	0.9	0.2 (*1*)
doxycyclin	4.0	-	0.3	1.3 (*7*)	1.6	-	-	0.4 (*1*)
metronidazole	4.0	2.4	-	2.4 (*13*)	3.5	3.0	-	2.5 (*8*)
co-trimoxazole	-	2.9	1.9	1.8 (*10*)	1.2	2.7	1.4	2.0 (*6*)
ciprofloxacin	-	-	-	-	-	0.6	0.2	0.3 (*1*)
miscellaneous	0.8	2.3	3.8	2.2 (*12*)	1.1	1.3	2.2	1.4 (*5*)
Total	13.6	21.2	18.2	18.1 (*100*)	17.7	30.6	47.9	31.0 (*100*)

Table 4 - Global cost in Dfl* of antimicrobial drug use in three surgical departments (one-month reviews)

review	before intervention				after intervention			
department	G	S	O	Total	G	S	O	Total
total cost	5,808	23,124	8,516	37,448	4,208	19,648	9,442	33,298
total cost/bed day	2.4	10.1	7.1	6.3	2.2	8.3	8.7	6.4
cost of prophylaxis	3,790	7,413	2,173	13,376	2,355	2,209	1,161	5,725
prophylactic cost/operation	1.5	3.2	1.8	2.2	1.4	0.9	1.1	1.1
cost of therapy	2,018	15,711	6,343	24,072	1,853	17,439	8,281	27,573
cost of therapy/bed day	1.3	6.9	5.3	4.7	1.4	7.4	7.6	5.8
cost/therapeutic DDD	9.3	32.3	29.1	26.1	8.2	24.1	15.9	18.7

* 1 Dfl = $ 0.65

costs. In department S, clindamycin, that accounted for 16% of total consumption, accounted for 48% of costs. Potential savings in prophylaxis, calculated by the experts after the first review, were estimated at 83%. The savings realized in the second review amounted to 57% (table 4). Prophylactic cost/operation was halved. Savings were merely realized by replacing the broad spectrum agent piperacillin (Dfl 44.9/single dose) and the regimen of gentamicin with clindamycin (Dfl 107.6/24h course) by cefazolin (Dfl 6.3/single dose) with or without metronidazole (Dfl 6.1/single dose).

Therapy

The cost estimate of the alternative policy of reviewer 1 predicted 34% savings.

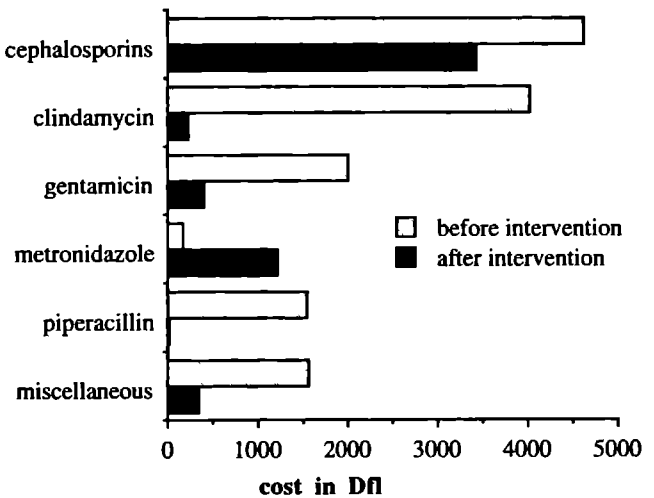

Figure 2. - Costs in Dfl (1Dfl. = $ 0.65) of antimicrobial drugs for surgical prophylaxis in three departments of a university hospital before and after an intervention, one-month reviews.

However, after the intervention, overall costs of therapy increased by 15% (table 4). This increase was due merely to higher dosage and longer duration of treatment, as the drugs for therapy of the new protocol were often cheaper. After the intervention, the cost/ therapeutic DDD was lower than before. However, part of the costs were still due to unjustified or inappropriate prescriptions.

Qualitative aspects.

Prophylaxis

After the intervention, there was a higher overall compliance with the new protocols than with the old guidelines ($p<0.0001$) (table 5). The difference was significant in the three departments. Parameters of quality for prophylaxis improved: the probability of a prophylactic course for more than 24 h decreased significantly in department S ($p<0.0001$, Fisher's exact test), but not in department G ($p=0.16$) and department O. Single dose prophylaxis increased ($p<0.0001$). The difference was significant in the three departments. The intervention also corrected timing, (administration within 1h before surgical incision), which was documented in departments S and O (see chapter VII).

Agreement (ignoring category VI) between the two experts who assessed quality of prophylaxis before and after intervention was very good in both reviews ($\kappa = 0.80$). Therefore, only the assessment of one expert, reviewer 1, is discussed here and presented in table 5. There were significant differences in quality before and after the intervention in department G ($p<0.0001$), department S ($p<0.0001$) and department O ($p=0.004$).

Table 6 shows most frequent type of errors (evaluation categories II to V) by prophylactic drug in the first review. Oral cefalexin prophylaxis started postoperatively and continued for 5 days was considered unjustified (category V). Oral prophylaxis with neomycin/bacitracin was followed by intravenous gentamicin plus clindamycin at induction of anaesthesia in 15 out of 28 courses.

Table 5 - Quality parameters of antimicrobial drug prophylaxis in three surgical departments (one-month reviews)

review	before intervention				after intervention			
department	G	S	O	Total	G	S	O	Total
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
prophylactic courses	52	78	55	185	53	96	53	202
according to guidelines	8 (*15*)	25 (*32*)	26 (*47*)	59 (*32*)*	35 (*66*)	86 (*90*)	39 (*74*)	160 (*79*)*
duration >24h	14 (*27*)	18 (*23*)‡	6 (*11*)	38 (*21*)	8 (*15*)	3 (*3*)‡	5 (*9*)	16 (*8*)
single dose	30 (*58*)	16 (*21*)	17 (*31*)	63 (*34*)*	41 (*77*)	75 (*78*)	45 (*85*)	161 (*80*)*
evaluation by reviewer 1								
prophylactic prescriptions	91	113	61	265	110	141	52	303
definitely appropriate (cat I)	1 (*1*)	12 (*10*)	26 (*43*)	39 (*15*)	65 (*59*)	103 (*73*)	38 (*73*)	206 (*68*)
unjustified (cat V)	57 (*63*)	25 (*22*)	22 (*36*)	104 (*39*)	23 (*21*)	6 (*4*)	5 (*10*)	34 (*11*)
inappropriate (cat II-III-IV)	33 (*36*)	72 (*64*)	13 (*21*)	118 (*44*)	20 (*18*)	31 (*22*)	8 (*15*)	59 (*20*)
unevaluable (cat VI)	0 (*0*)	4 (*4*)	0 (*0*)	4 (*2*)	2 (*2*)	1 (*1*)	1 (*2*)	4 (*1*)

* $p < 0.0001$, χ^2 test, , ‡ $p<0.0001$, Fisher's exact test,

Table 6 - Quality evaluation of 265 prophylactic prescriptions in three surgical departments (one-month review before intervention)

prophylactic drug	number of prescriptions n	total cost Dfl	most frequent type of error*	unjustified (catV) prescriptions n (%)	cost avoidance Dfl (%)
cefalexin	17	364	V	15 (*88*)	307 (*84*)
cefazolin	88	3,401	V, IIIa	35 (*40*)	1,028 (*30*)
cefuroxime	9	203	V	3 (*33*)	58 (*29*)
clindamycin	26	4,247	IVc, IIIa	3 (*12*)	496 (*12*)
gentamicin	33	1,757	IVa,b,c, IIIa	7 (*21*)	196 (*11*)
metronidazole	9	265	V, IIIa	4 (*44*)	152 (*57*)
neomycin/bacitracin	28	610	V, IIb, IVa	15 (*54*)	331 (*54*)
piperacillin	31	1,392	IVc,d	14 (*45*)	628 (*45*)
miscellaneous	24	1,138	V	8 (*33*)	519 (*46*)
Total	265	13,377		104 (*39*)	3,715 (*28*)

* category IIb = incorrect dosage frequency, category IIIa = too long, category IVa = alternative agent more effective, category IVb = alternative agent less toxic, category IVc = alternative agent less expensive, category IVd = alternative agent less broad spectrum, category V = unjustified.

The oral prescriptions were judged unnecessary (category V). Moreover, the review revealed some erroneous prophylactic practices. In department S, nurses administered neomycin/bacitracin to all patients undergoing a bowel rinsing procedure, including those patients undergoing mechanical rinsing for anorectal operations (category V). Most oral prophylaxis (double or postoperative) were abandoned after the intervention. Prophylaxis with piperacillin was found too broad and expensive (category IV c,d). Overall, 39% of prophylactic prescriptions were judged to be unjustified. Their cost represented 28% of total prophylactic cost (table 6) and 66% of the predicted cost savings with the alternative policy proposed by the reviewer 1.

Therapy

Overall agreement between the two reviewers was much lower for therapy. This was true before intervention ($\kappa = 0.37$), and after intervention ($\kappa = 0.30$). Figure 3 illustrates as an example, the comparison of detailed categories of evaluation of therapeutic prescriptions by the two reviewers before and after intervention in department S. It is noted that categories II, III and IV can be assigned simultaneously to a prescription. In department S, surgical peritonitis was treated by clindamycin and gentamicin in combination. Reviewer 1 considered cefuroxime with metronidazole a better alternative to this regimen. He thought it to be more effective, less toxic, and less expensive (category IV a,b,c). Gentamicin dosage was 80 mg 3 times daily in 17 out of 21 courses, with a median duration of 4.3 days. The majority of these courses were allocated to category II a/b (inappropriate dose/ interval) by both reviewers. Although in 17 courses gentamicin was given for more than 72 h, serum concentrations were only measured in 3 courses. Because of the overall inappropriate use of gentamicin, it was decided in the new protocol to reserve aminoglycosides for the treatment of severe sepsis only. In the second review, gentamicin courses had decreased by 68%.

The new protocols had been based on the alternative policy of reviewer 1.

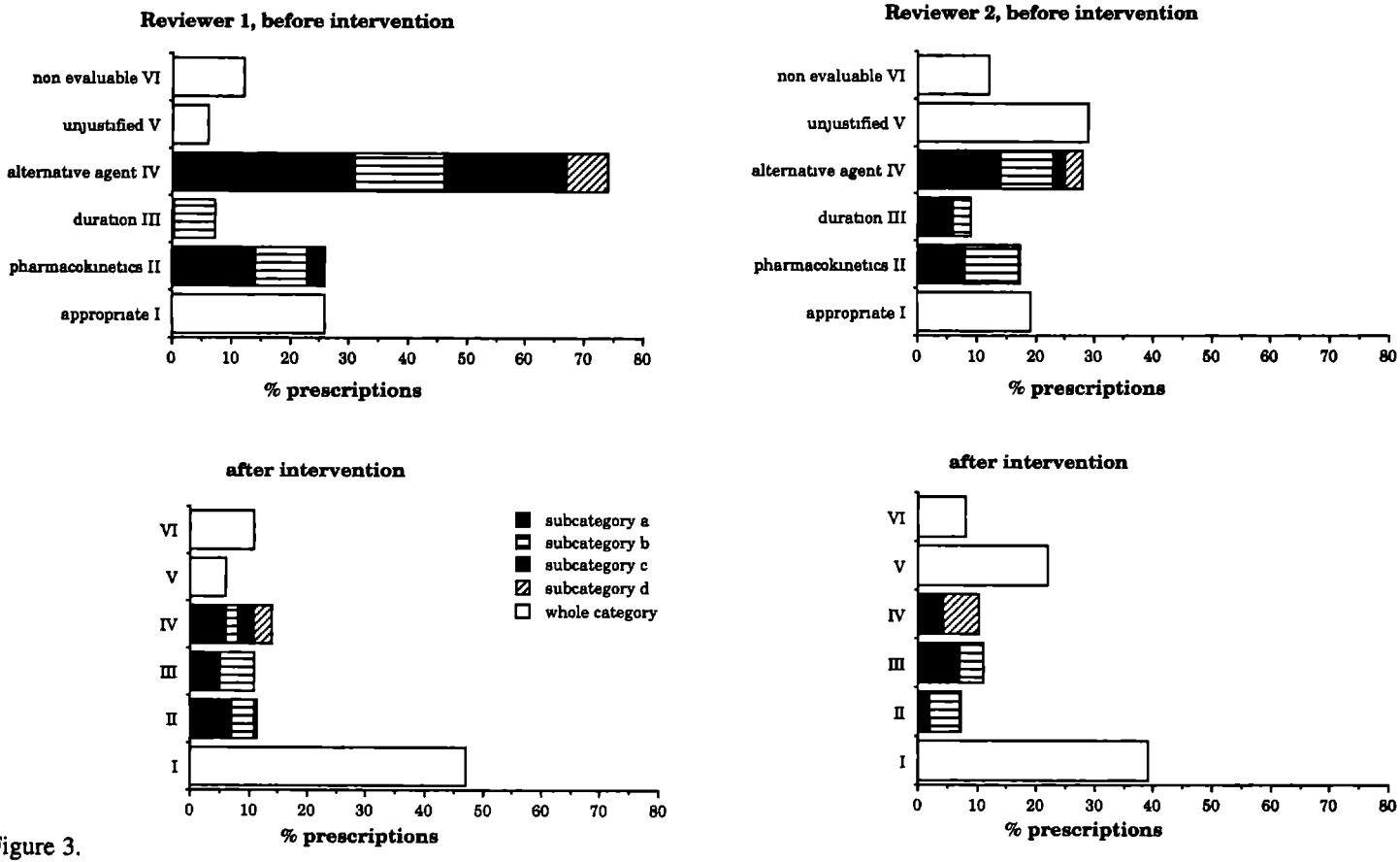

Figure 3.

Evaluation of therapeutic prescriptions in department S by two reviewers before (n= 99) and after (n= 96) intervention. Left: reviewer 1. Right: reviewer 2. Categories of evaluation: I = definitely appropriate, IIa = incorrect dose, IIb = incorrect dosage frequency, IIc = incorrect route, IIIa = too long, III b = too short, IVa = alternative agent more effective, IVb = alternative agent less toxic, IVc = alternative agent less expensive, IVd = alternative agent less broad spectrum, V = unjustified.

Considering the overall evaluation of 224 and 169 therapeutic prescriptions of the three departments, respectively before and after the intervention by reviewer 1, the proportion of prescriptions that were considered definitely appropriate (category I) increased from 70 (31%) to 80 (47%). No indication for therapy (category V) decreased from 35 (16%) to 14 (8%). Inappropriate prescriptions accounted for 100 (45%) and 61 (36%) respectively. The changes were statistically significant (p=0.007).

Discussion

From the initial quality-of-use review we concluded that antimicrobial drug use in the surgical departments could be improved in terms of quality and costs. In our hospital, major misuse such as prophylaxis > 48 h, or a combination of more than three drugs, as cited by Kunin (10) were seldom encountered. Noncompliant physicians were rare.

Prophylaxis

The intervention succeeded in implementing a widely accepted standard of single dose cefazolin and metronidazole (if needed) for surgical prophylaxis. This type of intervention has been successful in departments of gynaecology and obstetrics (7, 19). The contribution of parenteral clindamycin to costs is known to be considerable (20). Replacement of clindamycin by metronidazole is known to be cost containing (21). We implemented the regimen in several surgical specialties for all procedures where prophylaxis was deemed appropriate. The intervention included the education of anaesthetists and nurses as well as the surgeons. The preparation and acceptance of the new guidelines took several months. At implementation however, the effect was sometimes immediate, for example, the day after the pharmacy removed piperacillin from one operating room drug stock. The standard regimen replaced a variety of broad spectrum antimicrobial drugs, previously chosen on the basis of personal preferences and possibly the result of promotional efforts of the pharmaceutical companies. The new prophylactic regimen was less costly. It was cheaper even in combination with metronidazole (18). Cost containment was also obtained by

shortening the duration of prophylaxis. Halving of the prophylactic cost/operation was obtained by improving quality. Compliance with guidelines improved, as did the result of the evaluation by the experts. Both reviewers agreed to a high degree upon the improvement of quality of the courses.

Therapy

In therapy, improvement of quality was less striking, and it was achieved at a higher cost. Correction of undertreatment (underuse) of severe infections (described above) towards higher doses, parenteral route and longer duration, was mainly responsible for the cost increase. There was only partial agreement between the two experts concerning the quality of surgical therapy. Reviewer 2 judged less therapeutic prescriptions appropriate and more prescriptions unjustified than reviewer 1 in all departments, before and after the intervention. However, his assessment also changed significantly after the intervention (data not given). One reason for the differences in judgment could be due to personal factors, reviewer 2 being more strict. Another reason could be that the new protocols were based on the alternative policy of reviewer 1.

Method

Reviews of this type are time consuming. However, the in-depth analysis detected many logistic problems which solving seemed crucial for the success of adequate prophylaxis. In prophylaxis, organizational aspects are of major importance, as others described recently in the U.K. (22). The in depth analysis also detected problems with specific drugs. The frequency in which aminoglycoside assays were performed in this review compared unfavourably with the data of another review (18% vs 78%) (23). Although amoxicillin-clavulanate was introduced in the new protocol for one indication only, surgeons started to use it instead of older drugs for various other indications. The addition of a drug to the hospital formulary did not lead to consumption of the drug in surgical departments where it was not introduced in the new protocol (e.g, ciprofloxacin).

We used defined daily doses (DDDs) as a unit of measurement to allow international comparison of the utilization data. The review showed that in

hospitalized patients, the Prescribed Daily Dose (PDD) for certain drugs can be quite different from the DDD, depending on the indication. When DDDs are used as a unit of measurement for single dose surgical prophylaxis, the PDD/DDD ratio should be given to estimate the number of patients treated with the drug. An extreme example is piperacillin which has a DDD of 14 g. In single dose prophylaxis with piperacillin (4 g), the PDD/DDD ratio = 0.3. Thus, for single dose prophylaxis, the DDD/100 bed days underestimates the population exposed. In severe infections, the number of patients treated with an antimicrobial drug can be overestimated using DDD/100 bed days as a unit of measurement, if the PDD/DDD ratio is not known.

In all surgical departments, due to previous underuse, therapeutic use in DDDs increased while the same proportion of patients were treated with antimicrobial drugs. The overall proportion of patients receiving prophylaxis increased slightly (24 to 27%), but more of these prescriptions were judged appropriate.

We conclude that this intervention resulted in optimizing the quality of prophylactic and therapeutic antimicrobial drug courses in surgical departments at a lower cost. Indicators of satisfactory outcome with the new policy were a stable median length of hospital stay and a reduction in the number of nosocomial infections/100 bed days treated with antimicrobial drugs.

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CHAPTER V

The diagnosis of infection in orthopaedic surgery. Analysis of microbiology laboratory utilization.

IC Gyssens, C Smits-Caris, MVM Stolk-Engelaar, TJJH Slooff & JAA Hoogkamp-Korstanje.

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Abstract

Surgical specimens for microbiological analysis are precious because they may have been obtained at considerable expense to the patient, and they may not easily be collected again. One hundred and seventeen consecutive requests for microbiological analysis by a department of orthopaedic surgery were audited. These requests were prospectively obtained during 55 clinical episodes, 39 of which were of (presumed) infection and 16 of surveillance. The main sites sampled were joint tissue, -fluid or -bone: 28 (51%) and extraarticular bone or tissue: 6 (11%). Of 98 surgical specimens, 20 (20%) yielded a relevant microorganism. In a formal evaluation performed by 2 consultant microbiologists, the requests were classified as definitely appropriate in 67% and 85% of episodes, respectively. Collection, handling and transport were categorized as definitely appropriate in 56% and 73% of requests by the 2 consultants. No request was considered unjustified. Major problems were underutilization in about 10% of episodes. Inappropriate sampling for anaerobic culture was seen in 1/4 of specimens and a prolonged transport time to the laboratory in 1/3. Analysis of compliance with an existing protocol for prosthetic joint revision revealed similar errors. We conclude that audits of this type can give invaluable information about the no man's land between the clinician and the laboratory and can identify appropriate measures for corrective action.

Introduction

Surgical tissue specimens or puncture aspirates are precious because they may have been obtained at considerable expense to the patient, and they may not easily be collected again. Microbiological analysis of surgical specimens should be optimal for establishing the right diagnosis, knowledge of a pathogen and choice of the right antimicrobial therapy. Culture of deep tissue (for example of bone in osteomyelitis) often provides the only definitive information on the etiology of the infection (1). Isolation of the pathogen permits streamlining of empirically chosen antimicrobial drug therapy towards the optimal antimicrobial agent in terms of activity, spectrum, cost and side effects. These features, although relevant for all surgical specimens, are particularly important in revision operations for loosening of a prosthetic joint, i.e. to differentiate mechanical loosening from infection (2, 3).

In order to study the quality of the entire spectrum of activity related to laboratory testing, the process can be divided in 6 steps: 1. ordering of the test, 2. collection of the specimen, 3. transport to the laboratory, 4. analysis, 5. reporting and interpretation of the results and 6. impact on diagnosis and treatment (4). In the limited number of published audits of microbiological laboratory testing, steps 2 and 3 are not adressed. Some authors have audited all types of specimens, (5, 6), or cultures of urine (7), blood (8), cerebrospinal fluid (9) and stools (10). We are not aware of studies on surgical specimens. We describe an audit of microbiology laboratory use patterns in a department of orthopaedic surgery, with special attention to ordering, collection and transport of surgical specimens.

Method and patient population

The department of orthopaedic surgery in the University Hospital Nijmegen has 50 beds, and approximately 1700 operations are performed annually on

inpatients. All consecutive requests by this department (operating room and wards) were prospectively gathered over 6 weeks in the microbiology laboratory by a technician.

The types of orthopaedic procedures performed included arthroscopies, biopsies, procedures of osteosynthesis and insertion of prosthetic material.

Data sources

Procedures

Requests for microbiological tests were accompanied by a form on which the clinician had to fill in 1) his/her name, 2) adequate clinical information and the use of antimicrobial drugs, 3) the nature of the specimen and ordered test, 4) date and time of collection. The form had to be labelled with stickers containing patient name, identification number, date of birth, department, ward or outpatient clinic. The department of orthopaedic surgery had developed a protocol for handling material from loose prostheses according to relevant literature (2, 11). The protocol included the following procedures: 4 or more specimens from distinct sites of the joint (synovial fluid, capsule, femur interface, acetabulum or tibia interface) had to be taken. For each specimen, the surgeon had to use sterile, not previously used forceps. Joint aspirate had to be injected in 2 blood culture bottles and in 1 sterile dry tube. Tissue or bone biopsies of $1 cm^2$ were to be collected in sterile containers. A transport box was provided for all containers, tubes and bottles of a single procedure. Transit time had to be less than 30 min. Each specimen had to be cultured for aerobes and anaerobes. For each type of culture (aerobic, anaerobic), a different specimen and/or request card had to be provided. Antimicrobial drugs had to be administered after the collection of specimens.

For other materials, standard instructions for sampling and transport were used (12). Some of the standard instructions are cited below

- Collection of tissue or fluid from a site presumed to be involved on

clinical grounds is always superior to swabs (13).

- Large-volume fluid specimens should be inoculated in blood-culture bottles to enhance recovery of microorganisms (14).
- Collection of specimens for presumed infection should preferentially precede treatment, as the relation between time of collection and start of antibiotics may have an impact on the result. (3).
- Transit time of tissue specimens should not exceed 1h, as after 1 h recovery of anaerobes may be impaired. For urine specimens, refrigeration up to 8 h is considered acceptable (4).

Clinical information

Clinical information on the cases for whom tests were ordered was available in abstract form from a concurrent study of antimicrobial use (see chapter IV). The information was retrieved from medical records and operating room schedules and contained type, date and time of surgical procedures and the clinical presentation of infection. It also contained the antibiotic regimen for therapy or prophylaxis (including start and stop time) which was copied from anaesthesia records and medication charts (Kardex^R).

Evaluation

At arrival in the laboratory a technician noted the time of receipt and the type of containers submitted. Transit time was calculated by: time of receipt in the laboratory minus time of collection.

Combining the data from request cards and the data from abstracts allowed the allocation of multiple requests to a single clinically relevant episode of (presumed) infection or surveillance.

Two consultant microbiologists performed the evaluation independently. Ordering was evaluated per clinical episode of (presumed) infection or surveillance. Collection, handling and transport were evaluated per individual

request. Clinical episodes were assessed using the categories presented in table 1, by means of evaluation criteria based on the guidelines for microbiology laboratory testing (12) and the advice of experts (11). Ordering practices could be definitely appropriate, inappropriate , unjustified, or the data could be insufficient for categorization. Ordering was judged inappropriate if insufficient clinical information was given to the laboratory, and/or if additional specimens or additional requests were considered necessary to establish the diagnosis. The evaluation categories of collection, handling and transport on the individual requests are presented in table 2. Requests were considered definitely appropriate, inappropriate, unjustified or records could be insufficient for categorization. Requests could also be judged inappropriate for several reasons at the same time: inappropriate way of collection, incorrect container or transport medium, prolonged transit time, or incorrect timing of collection vs start of antimicrobial treatment. For both evaluations, agreement between the 2 reviewers was assessed by kappa coefficients.

Results

One hundred and ninety-seven orthopaedic patients were hospitalised during the study period. One hundred and sixty-six operations were performed. Forty-six patients (23%) had specimens sent by 8 physicians. Four physicians were responsible for 77 % of requests. On 1 request, the name of the physician was missing. The surgeons wrote themselves the requests in the operating room before the start of the operation. One hundred and thirty-seven requests for analysis were collected in the microbiology laboratory. Twenty requests of bone specimens, harvested for the bone bank, were excluded from the analysis. Items on the card such as type of specimen and ward were filled in properly in more than 95%. In 19 out of 137 requests (14%), the time of collection was missing. Other sources permitted calculation of transit time in all but 3 requests.

Evaluation of ordering.

All clinical episodes

With the help of the clinical information, the 117 requests for clinical specimens could be allocated to 55 clinical episodes. Thirty-nine (71%) were episodes of (presumed) infection (including 8 episodes of prosthetic joint revision), 7 (13%) episodes had infection included in the differential diagnosis and 9 (16%) episodes consisted of surveillance cultures. In 13 out of the 39 episodes of presumed infection (33%), patients were already taking antimicrobial drugs prophylactically (4 patients) or empirically (9 patients) before the collection was done.

The surgical sites sampled were: joint (tissue, fluid, bone) 28 (51%), extra articular bone or tissue 6 (11%), wound 6 (11%). Other sampling sites were urinary tract 11 (20%), respiratory tract and skin 4 (7%). The reviewers considered the information provided by the abstract of the medical record insufficient to perform quality evaluation in 4 clinical episodes (table 1). Both reviewers agreed that there was no unjustified microbiological testing ($\kappa = 1$). Concerning the appropriateness of the remaining 51 episodes, there was only partial agreement between the 2 reviewers ($\kappa = 0.32$). In 10 episodes, reviewer 1 would have preferred more information than was provided. Reviewer 1 found underutilization (missing specimens or requests) in approximately 1/10 of episodes: in 5 episodes, another specimen of the site should have been sampled, and in 4 episodes, other specific tests such as tuberculosis, anaerobic culture, cultures for yeast or fungi should have been ordered. The ordering practice was judged definitely appropriate in 67% of the episodes by reviewer 1 and in 85% by reviewer 2.

Prosthetic joint revision

Eight clinical episodes for prosthetic joint revision were recorded. In 6 revisions the indication was loosening of the prosthesis, in 2 revisions the operation was done for dysfunction of the prosthesis e.c.i.. Only 3 of the 8 episodes were handled without protocol violations.

Table 1 - Quality evaluation of ordering microbiology laboratory tests in 55 clinical episodes by two independent reviewers.

evaluation categories	**number of episodes classified in corresponding category** by Reviewer 1* n (%)	by Reviewer 2* n (%)
- not evaluable due to insufficient information in the record	4 (*7*)	4 (*7*)
- microbiological testing unjustified	0 (*0*)	0 (*0*)
- ordering practice inappropriate	14 (*25*)	4 (*7*)
due to:		
- insufficient clinical information provided to the laboratory	10	3
- additional specimen of other body site wanted	0	0
- additional specimen of same body site wanted	5	2
- additional request wanted for same specimen	4	0
- ordering practice definitely appropriate	37 (*67*)	47 (*85*)

* coefficient of agreement $\kappa = 0.32$

Evaluation of collection, handling and transport of specimens

Surgical specimens

Of a total of 98 clinical surgical specimens, 26 (27%) consisted of fluid (23 synovial fluid), 41 (42%) of tissue, 22 (22%) of bone; 5 (5%) were wound swabs, 4 (4%) consisted of pus. In 72 (73%) requests, specimens consisted of the tissue proper, 26 (27%) specimens were sent as swabs. Twenty-five out of 31 surgical specimens of which anaerobic culture was ordered were sent in anaerobic transport medium. The laboratory performed an anaerobic culture of 3 tissue or fluid specimens, for which a single request for aerobic culture was provided. Thirty-four requests out of 98 were sampled during revision operations and were analysed separately. The remaining 64 miscellaneous surgical specimens consisted of 28 specimens sampled for presumed infection, 17 specimens for surveillance and 19 specimens of which infection was included in the differential diagnosis. There was no growth in 57 (89%). Eight (29%) of the specimens cultured for presumed infection yielded a relevant microorganism. None of the surveillance cultures and none of the cultures where infection was included in the differential diagnosis were positive. However, all surveillance specimens and 2 out of 7 specimens of the latter group were taken after the administration of prophylactic antibiotics.

The evaluation of 117 requests for clinical specimens is presented in table 2. The evaluation of the requests of surgical specimens was not very different from the total evaluation. Both reviewers judged all requests justified ($\kappa = 1$). Agreement on the other categories was also partial ($\kappa = 0.43$). All 24 inappropriately collected specimens were surgical specimens, as were 22 out of the 29 specimens which had a prolonged transit time. Median transit time of all surgical specimens was 2 h (range 30 min - 19 h). Fifty-two (53%) surgical specimens had a transit time of more than 2 h and for 18 (18%) surgical specimens, transit time exceeded 4 h.

Table 2 - Quality evaluation of collection, handling and transport of 117 specimens for microbiological diagnosis by two independent reviewers.

evaluation categories	**number of requests classified in corresponding category** by Reviewer 1* n (%)	by Reviewer 2* n (%)
- not evaluable due to insufficient data	4 (*3*)	4 (*3*)
- request unjustified	0 (*0*)	0 (*0*)
- request inappropriate	47 (*40*)	28 (*24*)
due to:		
- inappropriate way of collection	24	13
- incorrect container/transport medium	1	0
- prolonged transit time	29	13
- incorrect timing of sampling vs start of antimicrobial treatment	1	2
- request definitely appropriate	66 (*56*)	85 (*73*)

* coefficient of agreement $\kappa = 0.43$

Specimens for prosthetic joint revision

Thirty-four specimens were sent in. In 12 (35%) there was growth of a relevant microorganism. Again, most frequent errors were the inappropriate way of collecting specimens for anaerobic culture (swabs in a transport medium instead of tissue) and a prolonged transit time. None of the revision specimens had a transit time of less than 1 h. Median transit time was 3h (range: 55 min- 19 h 30 min). On 1 request the time of collection was missing. One set of 6 specimens was received the morning after the intervention: the bone and tissue specimens were kept in a refrigerator.

Other specimens

The non-surgical specimens consisted of 15 (13%) urines, 2 sputa and 2 throat swabs. (3%). Thirteen out of the 15 urine cultures were positive, although in 2 there was growth of $< 10^5$ microorganisms/ml, possibly due to previous administration of antibiotics. The other specimens yielded non pathogenic bacteria. There were no blood or stool culture requests during the study period. Half of the requests containing insufficient clinical information were for urine cultures. Median transit time was 4 h 30 min (range 30 min- 16 h 30 min). Five specimens of secondary importance (swabs, urine) collected on pediatric wards had the shortest transit time (less than 1 h).

Discussion

We concluded that the department of orthopaedic surgery had an acceptable quality level of microbiology laboratory utilization. From our previous quality-of-use studies in surgical departments (see chapter IV), we suspected that other departments in our hospital were performing less well. However, we preferred an approach of continuous improvement (15), by auditing a department which had an established diagnostic protocol, instead of identifying at random such

errors in daily practice.

Although the 2 reviewers agreed that there was no unjustified testing, there was only partial agreement concerning the definite appropriateness of ordering, collection and transport. Part of the discrepancy in the evaluation was due to different handling of the criteria. Reviewer 1 applied the criteria from the literature rather strictly, while reviewer 2 had a more balanced view, based on personal experience.

No data from other audits are available for comparison. There are a few reasons for the lack of studies. Examination of the rationale behind laboratory utilization is not often done by consultant microbiologists, because the necessary clinical information for evaluation is often lacking. On the other hand, clinicians consider that their responsibility ends with the verbal ordering of the test (4). Furthermore, in large hospitals, between the operating room or the bedside where the decision to perform diagnostic tests is made and the laboratory where the specimen will be analysed, there is a wide no man's land of ward desks, window sills, nurse's utility rooms, corridors, dark storage places and, last but not least, refrigerators.

Audits of the last 3 steps in the process of laboratory testing, (from laboratory analysis to interpretation of the report) have more often been done (5, 6, 16, 17). According to reviewer 1, the department had a certain degree of underutilization of the microbiology laboratory, as in 1 out of 10 episodes another specimen or request seemed necessary. Underutilization has been reported before from surgical departments (5). The practice of taking surveillance cultures during insertion of prosthetic material was considered appropriate, although the usefulness of this sampling after the administration of prophylactic antibiotics remains unclear (18). Only a few reports have been published on tests that are not useful in other settings: for example the routine CSF culture for mycobacteria (9) or urinary cultures in uncatheterized patients

receiving antibiotics (7). The optimal number of deep specimens from a prosthetic joint is determined as 3 to 5 (11). For blood cultures the optimal number of specimens is also known (8), and single sets of blood cultures have been proposed as indicator of unwanted outcome (19).

The major problems revealed by the audit were improper sampling for anaerobic culture and prolonged transit time of surgical specimens. In a way, both errors may have been related. The transit time of less than 30 min stated by the revision protocol was practically impossible to realise, as the time between collection of the first and last specimen of the procedure averaged more than 1 h. Unable to solve the logistic problem caused by the distance between operating rooms or wards and the laboratory and the lack of extra personnel for transport, the surgeons tried to overcome this problem by sending the anaerobic specimens as swabs in transport medium. Although this strategy may enhance survival of anaerobes, swabs of specimens should be discouraged when surgical specimens are available. Specimens with the shortest transit time came from wards located near the microbiology laboratory, regardless of the nature of the specimen. In the future, mailing by vacuum tube system might solve the problem of prolonged transit time from remote areas.

The process components associated with ordering, collection and transport are thought to influence outcome more than the components of the internal laboratory process (step 4), for which quality control is mandatory in most countries (4). Audits of this type, conducted jointly by clinicians and laboratory physicians, can give invaluable information about the no man's land between the ward and the laboratory and can identify appropriate measures for corrective action.

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CHAPTER VI

The anaesthetist as determinant factor of quality of surgical antimicrobial prophylaxis.

IC Gyssens, JTA Knape, G Van Hal & JWM van der Meer.

Submitted for publication

Abstract

A staff of 44 anaesthetists was interviewed by means of a questionnaire about the practice of surgical prophylaxis in a university hospital. Response rate was 36/44 (82%). The anaesthetists' way of administering surgical prophylaxis was rather uniform and economic: cephalosporins were almost exclusively administered by bolus method. The main reason was that infusion was more cumbersome (range 77-85%). Communication between surgeon and anaesthetist was reported to be poor, and in two out of six operating departments, orders of prophylaxis transmitted at or after induction accounted for more than 80%. Seventy seven percent of the responders asked the surgeon if prophylaxis was necessary if they were in doubt; 20% responded that they checked it systematically. There was an association between poor communication reported by the anaesthetists and the late administration (after incision) of prophylactic antibiotics. The inquiry proved useful in the process of optimizing surgical prophylaxis in our hospital.

Introduction

Antimicrobial drugs account for 13-37% of the drug budget in European hospitals; 30% is used for prophylaxis (1). Misuse is most frequently described with prophylactic drugs for various aspects as indication and duration (2). The timing of surgical prophylaxis and its organisational aspects have rarely been analysed. Recently, suboptimal timing of antibiotic prophylaxis was found to be associated with a significant higher rate of wound infections in a large series (3). Intravenous administration of the drug during induction of anaesthesia within 30 minutes before incision is a generally accepted standard (4). In this situation, anaesthetists play an executive role in surgical antimicrobial drug prophylaxis.

In the University Hospital of Nijmegen, ± 20 000 operations were performed in 1990. An estimated 30% of patients were receiving perioperative prophylaxis with antimicrobial drugs. Prophylaxis was almost exclusively started in the operating room. However, it was suspected that the timing of prophylaxis varied between surgical departments. By means of an inquiry we studied the anaesthetists' perception of the organisation of prophylaxis in the different surgical departments and their views on optimizing prophylaxis.

Another reason to optimize antimicrobial prophylaxis is to reduce unnecessary costs. As we planned to implement the most economical way of administration of beta-lactam antibiotics (bolus injection in 3- to 5-min) (5), we also asked the anaesthetists about their usual ways of administration of those antibiotics and the reasons for their choice.

Methods

All 44 staff members (seniors and residents) of the department of anaesthesiology who were performing anaesthesias were sent a pre-numbered questionnaire by internal mail in May, 1990. In our hospital, all anaesthetists rotated in a working schedule in all operating departments. The forms were

distributed and collected by JTA K, a senior staff member of the department of anaesthesiology, who added an introductory letter, and urged on nonresponders for three weeks. The forms were then returned so that anonymity was preserved to IC G. Thirty-nine (87%) staff members returned the form. Three returned the form blank. Thirty-six forms of responders (82 %) were used for analysis.

The form contained three blocks of precoded questions on four pages. To fill in the form, only a few minutes were required. Anaesthetists were asked for their usual ways of administration of intravenous antimicrobial drugs for prophylaxis i.e. by bolus injection over 3- to 5 min or i.v. infusion over 15- to 30 min, and the reasons for their choice in terms of safety, time, habit and cost. They were asked questions about the transmission of the antibiotic order by the surgeon and its relation to the timing of the operation in the various operating departments of the hospital, both for scheduled and emergency procedures. Space was allowed for comments. Finally, they were asked for their attitude towards measures to improve the organisation of antimicrobial preoperative prophylaxis.

Absolute and relative frequencies of responses to the questionnaire were tabulated. The chi-square test was used for statistical analysis.

Results

Thirty-six anaesthetists out of 44 responded. Considering the age classes younger than 35 years (n= 24, mostly residents), 35 -45 years (n= 14, mostly staff members) and older than 45 years (n=6, senior staff members), no difference in age could be found (p= 0.88) between responders and non-responders.

Way of administration

All anaesthetists but one administered prophylactic cefazolin and penicillins only by bolus injection (97%) (table 1). Gentamicin was administered only by bolus injection in 62 %.

The main reasons for this choice seemed to be practicality (range 77-85%) and

Table 1 - Usual way of administration of prophylactic antibiotics by anaesthetists

	Frequency distribution (%) of replies				
	ampicillin	flucloxacillin	cefazolin	cefuroxime	gentamicin
	n=35	n=33	n=35	n=34	n=34
bolus injection	34 (97)	32 (97)	34 (97)	27 (79)	21 (62)
i.v. infusion	0	0	0	4 (12)	10 (29)
both methods	1 (3)	1 (3)	1 (3)	3 (9)	3 (9)

Table 2 - Reasons for choice of i.v. administration by anaesthetists

	Frequency distribution (%) of replies				
	ampicillin	flucloxacillin	cefazolin	cefuroxime	gentamicin
safety (n=33)					
i.v. bolus safer	0	0	0	0	0
i.v. infusion safer	3 (9)	2 (6)	4 (12)	6 (18)	16 (49)
no difference	20 (61)	21 (64)	19 (58)	17 (52)	9 (27)
no opinion	10 (30)	10 (30)	10 (30)	10 (30)	8 (24)
time (n=30)					
i.v. infusion more cumbersome	25 (85)	23 (77)	23 (77)	23 (77)	23 (77)
bolus more cumbersome	0	0	2 (6)	1 (3)	0
no difference	5 15)	7 (23)	5 (17)	6 (20)	7 (23)
habit (n=32)					
always bolus method	30 (94)	26 (81)	28 (88)	25 (78)	21 (65)
always i.v. infusion	0	0	2 (6)	2 (6)	6 (19)
varying methods	2 (6)	2 (6)	2 (6)	4 (13)	4 (13)
no opinion	0	4 (13)	0	1 (3)	1 (3)
cost (n=32)					
bolus is more expensive	0	0	1 (3)	0	0
i.v. infusion is more expensive	8 (25)	8 (25)	7 (22)	7 (22)	8 (25)
no difference	10 (31)	11 (34)	10 (31)	12 (37)	11 (34)
no opinion	14 (44)	13 (41)	14 (44)	13 (41)	13 (41)

habit (range 65-94%) (table 2). Although 48% considered i.v. infusion safer for gentamicin, this view did not always determine their choice of administration: 29% gave gentamicin solely by i.v. infusion (table 1). A difference in cost was not a major issue; on the average, 33% thought there was no difference and 42% had no opinion on the subject.

Communication of prophylactic orders

The different ways in which the anaesthetist was informed about the need for administration of preoperative antibiotics are given in table 3. The questionnaire gave five possible kinds of communications, and one "unknown". Also multiple replies were given. In the operating departments of surgery (SU) and gynaecology (GY), replies indicated that the majority of orders were transmitted at the earliest, at or after induction: 27.5/31 (89%) and 26.5/31 (85%) respectively. In the operating departments of orthopaedic surgery (OS) and urology (UR), about half the replies indicated late communication. In the operating department of otorhinolaryngology (ORL), 29.5/32 (92%), and of neurology (N), 18/26 (69%) of the replies indicated that the drug was sent with the patient.

The question on communication between the surgeon and the anaesthetist was repeated for emergency (unscheduled) operations (table 4). The overwhelming majority of orders was transmitted at the earliest, at- or after induction of anaesthesia: in this situation not much difference was observed between the operating departments.

Contribution to quality

Seven out of 35 (20%) anaesthetists who replied to this part of the questionnaire would ask the surgeon systematically at induction about the need for prophylactic antimicrobial drugs. Eleven assumed that no prophylaxis was necessary if the surgeon did not inform them. Nevertheless, 27/35 (77%) would ask him if in doubt.

Table 3 - Communication between surgeon and anaesthetist concerning antimicrobial prophylaxis scheduled operations

operating department	SU	OS	ORL	GY	UR	N
number of anaesthetists responding	33	32	34	33	33	32
Replies of early communication						
a. antimicrobial drug sent with the patient to the operating room	0	4	24	1	12	16
b. order preoperatively written in medical chart	0	0	0	0	0	1
c. order transmitted orally before the patient is in the o.r.	2	9	0	1	1	1
combinations of a, b or c	1	4	5	2	3	2
Replies of late communication						
d. order transmitted orally at induction of anaesthesia	10	9	1	16	5	4
e. asked for by the anaesthetist at/after induction	9	1	1	7	5	2
combinations of d and e	8	1	0	3	4	0
other combinations	1	2	1	1	0	0
f. unknown	2	2	2	2	3	6

SU = Surgery, OS = Orthopedic Surgery, ORL = Otorhinolaryngology, GY= Gynaecology, UR = Urology, N = Neurology

Table 4 - Communication between surgeon and anaesthetist concerning antimicrobial prophylaxis emergency operations

operating department	SU	OS	ORL	GY	UR	N
number of anaesthetists responding	29	29	28	29	29	28
Replies of early communication						
a. antimicrobial drug sent with the patient to the operating room	0	0	5	0	1	2
b. order preoperatively written in medical chart 0	1	0	0	0	0	
c. order transmitted orally before the patient is in the o.r.	2	5	2	2	1	2
combinations of a or b with c	4	2	2	4	4	3
Replies of late communication						
d. order transmitted orally at induction of anaesthesia	6	11	3	10	8	5
e. asked for by the anaesthetist at/after induction	13	6	7	9	11	9
combinations of d and e	2	0	1	2	0	1
f. unknown	2	4	8	2	4	6

SU = Surgery, OS = Orthopedic Surgery, ORL = Otorhinolaryngology, GY= Gynaecology, UR = Urology, N = Neurology

Standardizing measures

Thirty one out of 34 (91%) responding anaesthetists agreed that written information was necessary for the individual patient. Three thought that oral information would suffice. Five anaesthetists (three staff members, two residents) wrote comments on the deficient communication and two suggested that the policy of operating department ORL (preoperatively written order) be adopted.

Discussion

Although anaesthetists play a crucial role in the execution of antimicrobial drug prophylaxis in surgery in most hospitals, no studies have been performed on organisational aspects of that matter. The present inquiry helped us to identify operating departments where communication between surgeon and anaesthetist on antimicrobial drug prophylaxis was good and others where it was particularly poor. In operating departments SU, OS and ORL the timing of surgical antimicrobial prophylaxis was analysed in a quality-of-use review (see Chapter IV). There was an association between the relative frequencies of replies of "late" communication for the operating departments SU, OS and ORL in the inquiry and the delayed administration (after surgical incision) in those departments.

Anaesthetists seemed to play an important role in reminding the surgeon of prophylaxis, as almost three quarters stated that they checked it if in doubt. However, such reminders occurred late in or after induction of anaesthesia, again resulting in a delay of prophylaxis. The variety of replies concerning communication of prophylaxis within some operating departments probably reflect a diversity of practices. For the unit ORL which sent the prophylactic antibiotic with the patient, replies were rather uniform, suggesting that the unit had a standardized policy. This was confirmed by the audit. The diversity of practices in the other departments was identified as a negative critical factor

impeding quality. We advocated a hospital-wide uniformity in the administration procedure of surgical antimicrobial prophylaxis. Almost all anaesthetists had a favourable reaction to the policy of preoperatively written drug orders by the surgeon. We subsequently implemented a pre-operative patient checklist that included the need for antimicrobial prophylaxis.

The inquiry informed us that our plans to implement the least expensive way of administration of prophylactic antibiotics corresponded with the actual practice of the anaesthetists. Although cost factors were not perceived by the majority of the responding anaesthetists, we learned that other motives such as practicality made bolus injection already the preferred way of administration for prophylactic penicillins and cephalosporins. Concerning gentamicin there was a common but erroneous belief that slow i.v. infusion would reduce the risk for toxicity. However, gentamicin can be safely injected over 3- to 5 min (6), and, both from a pharmacodynamic and pharmacokinetic point of view, there are indications that high initial peak concentrations are most effective and not associated with higher toxicity (7).

The results of this inquiry were used in an educational setting. We successfully intervened in the departments of surgery and orthopaedic surgery where poor timing was recorded, and optimized preoperative antimicrobial prophylaxis in these departments (see Chapter IV). In our hospital, this inquiry helped us to detect problem areas rapidly and provided us with useful information on practices of numerous staff.

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CHAPTER VII

The timing of antimicrobial prophylaxis in surgery.

IC Gyssens, IEJ Geerligs, MG Nannini-Bergman, JTA Knape, YA Hekster, & JWM van der Meer

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Abstract

The timing of surgical antimicrobial prophylaxis was measured before and after an intervention. The intervention consisted of the education of surgeons, anaesthetists and nurses on the subject of antimicrobial drug prophylaxis and the subsequent implementation of new protocols of single dose prophylaxis administered within one hour before incision. This prospective study was performed in three surgical departments of a university hospital. For comparison, the timing of prophylaxis was also measured in an operating department of a community hospital. The timing improved considerably in the departments of the university hospital where the intervention was carried out: optimal timing of the first dose administration of the first dose within one hour before incision increased from 39% to 69% in department A and from 64% to 80% in department B. Before the intervention, seven out of 16 prophylactic doses were given after inflation of the tourniquet. After the intervention all doses of prophylactic antibiotics were administered before inflation of the tourniquet. Initially, the intervals of multidose prophylaxis varied widely. In the second review, single dose prophylaxis increased from 21% to 78% in department A and from 31% to 85% in department B. We conclude that the intervention succeeded in improving the quality of surgical prophylaxis.

Introduction

Timing of intravenous antimicrobial drug prophylaxis in surgery is considered to be optimal about 30 minutes before incision, i.e. at induction of anaesthesia (1). For commonly administered antimicrobial drugs, adequate concentrations are present in the tissues at incision and two hours thereafter (2). The rationale for optimal timing of prophylaxis is found in the experimental work of Burke and the clinical trials of Stone (3, 4). The protective effect against infection is maximal when the antibiotic is in the tissues before microbial inoculation occurs in the wound. The optimal interval is now clearly delimited to one hour before the incision: administration more than one hour preoperatively resulted in a higher rate of infectious complications (5). Recently, significantly less wound infections were noted in those patients to whom the drug was given preoperatively instead of peroperatively (i.e. within two hours after incision) (6). In distal limb orthopaedic surgery, the antibiotic should be injected before the application of the tourniquet to reach protective concentrations in the limb (7). Whether one or more additional postoperative doses offer any benefit is unlikely (8).We assessed the effect of implementing accepted guidelines for specific surgical procedures (1) on the quality of timing of surgical antimicrobial drug prophylaxis.

Materials and methods

Setting and patient population

This prospective study was conducted in three separate operating departments: surgery (A), orthopaedic surgery (B) and otorhinolaryngology (C), of the 948-bed University Hospital Nijmegen. The operating departments were staffed by a rotating pool of 40 anaesthetists. The timing of antimicrobial prophylaxis was registered as part of a general quality-of-use review of antimicrobial drug use in these departments (see chapter IV). During one month, all consecutive operations were reviewed; the first review was conducted in 1990, the second in 1992. In a 326-bed community hospital, an infection control nurse (MN) collected data on the administration of antimicrobial prophylaxis of 500

consecutive operations by three anaesthetists. She used an identical method.

Method of the review

Time recordings of the injection of the antibiotic by the anaesthetist, of the induction of anaesthesia, incision and end of the operation were copied from the anaesthesia record after the return of the patient from the operating room. The anaesthesia record, (partially) computerized, allowed time recording with an error of at most five minutes. In the university hospital, for multidose prophylactic regimens lasting 24 hours or more, the times of second and third injections of antibiotics were copied from the patient medication sheet in the ward.

Intervention

After the first review, a report of each department was sent to their chiefs of staff. The report was accompanied by recommendations for an alternative antibiotic policy. The principal goal was to introduce a universal surgical prophylaxis standard of a single-dose cephalosporin for all but dirty procedures (2), with a second injection during the procedure for interventions lasting more than three hours. Cefazolin was to be given at incision (with metronidazole where an anaerobic spectrum was needed). The reports were discussed by the surgical staff, and the recommendations were formulated into new protocols for prophylaxis. After approval by the Antibiotic Committee, a presentation of the report and the protocol was held in the departments. In most departments, the first dose of surgical antimicrobial prophylaxis was given by the anaesthetist in the operating room. An inquiry (questionnaire by mail) in the department of anaesthesia showed deficient communication between anaesthetists and surgeons on the subject of administration and timing of prophylaxis and the wish of the anaesthetists to standardise prophylaxis (see chapter VI). The results of the inquiry were presented at the time of introduction of the protocols. The whole intervention took more than one year. The implementation of the protocols was assisted by junior pharmacists who organized briefings for nurses in the operating departments and in the wards. The standardized prophylaxis

guidelines were visualized in the wards and the operating rooms. Operating room drug stocks were reorganized.

Outcome measures

Two years after the first review, an identical review was performed. The effect of the intervention was measured in operating departments A and B, where the timing was found to be inadequate. The number of nosocomial infections (defined as active infections not present or incubating at the time of admission) per 100 bed days treated with antibiotics is given as an indicator of the effect of prophylaxis.

Generally, chi-square tests were applied to establish systematic differences. The Fisher's exact test was used to compare the timing in relation to tourniquet application, and variance ratio F-tests for comparing variations in dosage intervals.

Results

Timing of the first dose in the university hospital

In the first review, the timing of 276 intravenous prophylactic prescriptions was studied in operating department A, B and C of the university hospital. Thirty nine (14%) prescriptions were excluded from the analysis, because the timing of the first antibiotic dose was not noted or the anaesthesia record was missing. Prophylactic injections were divided in three groups: injections given more than one hour before incision, within one hour before incision, and after incision. There was a significant difference in the frequency distribution of the injections between the departments A, B and C ($p<0.001$). The frequency distribution of the injections in the departments A and B is shown in figure 1.

The number of injections given within one hour before incision and those given after incision differed widely between the three departments. In department A, 32 (39%) of the total number of injections were given within one hour before incision, in department B this amounted to 32 (64%) and in department C to 65 (78%). Almost all surgical prophylaxis was administered by the anaesthetist in

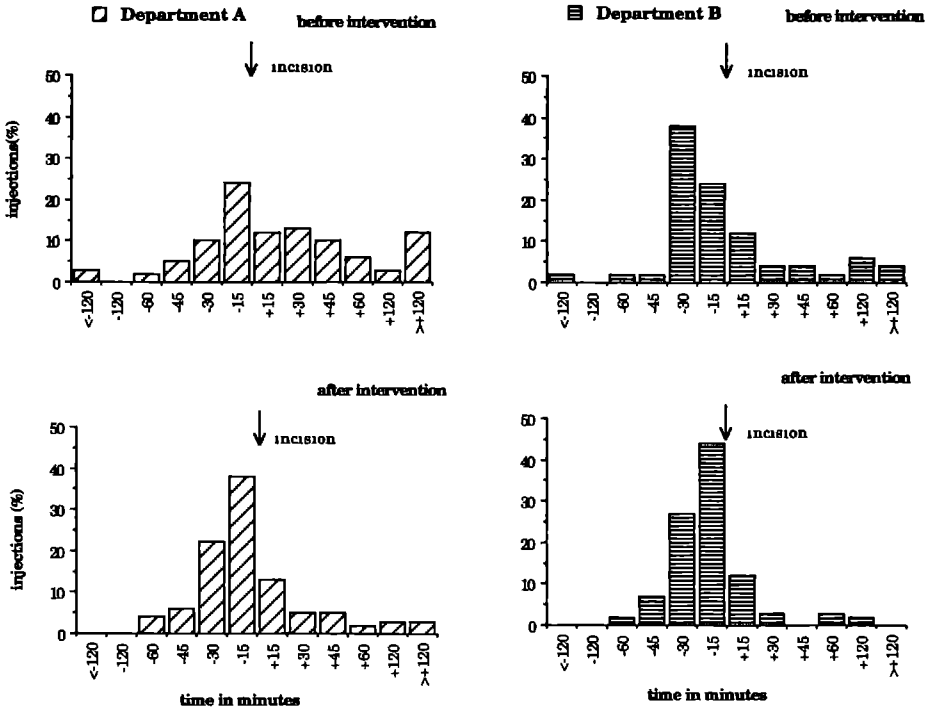

Figure 1 - Timing of antimicrobial drug prophylactic injections in surgical departments before (A: n=104 and B: n=50) and after intervention (A: n=120 and B: n=41). Time=0 is the time of incision.

the operating room. Only the prophylactic antimicrobial drugs against endocarditis were administered by the nurses in the wards at 8h (i.e. often more than one hour before incision). Therefore, the number of injections given more than one hour before incision was low for all departments: 3 (3%) in department A, 2 (4%) in department B and 1 (1%) in department C.

In department A we looked at the differences between scheduled (n=63) and emergency (n=41) procedures. The timing data were not statistically different between both types of procedures (p= 0.94).

In the second review, 161 prophylactic injections were studied in department A

and B. The timing of prophylaxis in departments A and B after intervention is also shown in Figure 1. In department A, the frequency distribution of injections was significantly different from the first review ($p<0.001$). In department B, no significant changes were obtained ($p=0.15$). After the intervention, almost 70% (A) and 80% (B) were given within one hour before incision and no injection was given for more than one hour preoperatively.

Timing of the first dose in the community hospital

In the community hospital, intravenous prophylaxis was given in 128 out of 500 operations (26%). In 12 (9%), the time recordings of induction and/or intravenous administration were missing. The timing of prophylaxis was studied for 116 procedures. Anaesthetists administered the prophylactic drugs in the operating room. However, the first scheduled patient of the day was given the prophylactic drug by the ward nurse. Although 81 (70%) injections were given before the incision, 30 (26%) injections were given more than one hour preoperatively. Overall, there was suboptimal dosing in 56% of the procedures.

Tourniquet Use

In the first review, 16 procedures in the university hospital were performed under tourniquet control (Figure 2). In seven procedures, prophylaxis was given after inflation of the tourniquet. In the second review, all of eight prophylactic doses were administered within 30 minutes before inflation of the tourniquet ($p= 0.054$).

Dosage Interval

At the first review in the university hospital, we studied 100 antimicrobial drug regimens that were started in the operating room as prophylaxis or therapy and were continued postoperatively. The intervals between the first and subsequent doses were measured. In the wards, intravenous antibiotics were administered by nurses in fixed schedules of six- or eight-hourly administrations. In department A, patients returning from the recovery room were shifted into the fixed schedules without taking into account the doses given in the operating room. In department B, nurses calculated the correct interval by checking the time of the first dose on the anaesthesia record. There were 40 three times a day

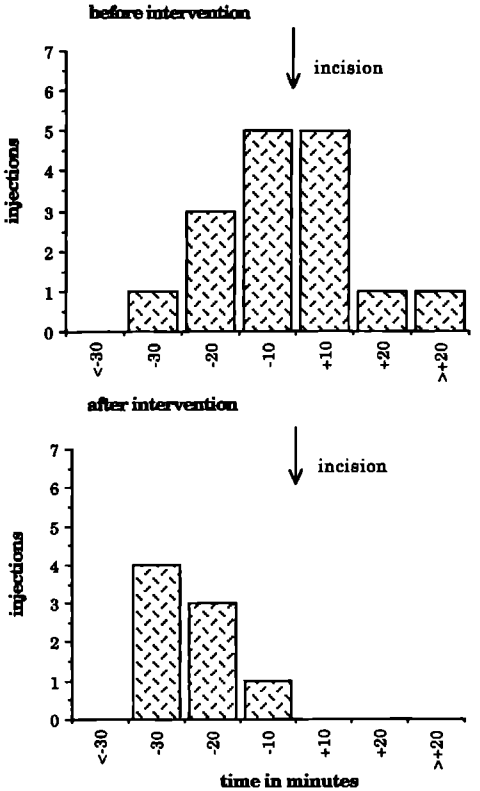

Figure 2. - Timing of antimicrobial drug prophylaxis in surgery of the limb, before intervention n=16 and after intervention n=8. Time=0 is the inflation of the tourniquet.

regimens in department A and 29 in department B. The distribution of the intervals for A and B is shown in Figure 3.

The average interval between first and second dose was 7 h 40 min (range 0 h 30 min - 13 h 30 min) for A and 7 h 30 min (range 1h 10 min - 11 h) for B. A significantly higher standard deviation was found for department A compared with B ($p=0.01$). The average interval between the second and third dose in ward A was 7h 45 min (range 4 to 11 hours). The standard deviation was significantly smaller compared with that of the first interval in A ($p<0.001$).

We did not study dosage intervals in the second review as, after the introduction of single dose prophylaxis, only a small number of postoperative doses were recorded.

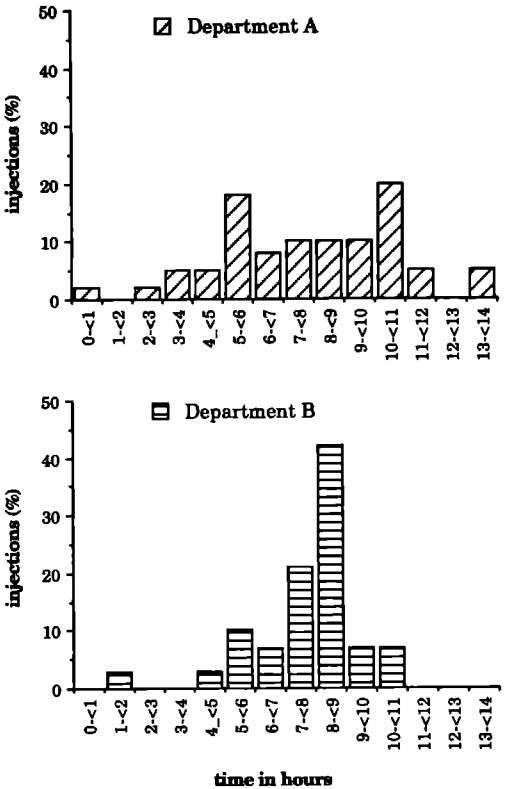

Figure 3 - Interval between first antimicrobial drug dose in the operating room and second postoperative dose for n=40 three times a day regimens in ward A and n=29 three times a day regimens in ward B (before intervention).

Single dose prophylaxis

Single dose prophylaxis increased from 21% to 78% ($p<0.001$) in department A and from 31% to 85%($p<0.001$) in department B. In department A, two thirds of multiple dosing (24h) regimens were due to noncompliance with the protocol. One third consisted of antimicrobial use for dirty procedures. In department B, all multiple dosing (24h) regimens were due to noncompliance with the protocol.

Discussion

Although the optimal timing of administration of surgical prophylaxis has been

established a long time ago, our study shows that in daily practice, the timing does not seem too adequate. Suboptimal timing was recorded in a university hospital and a community hospital. For many patients the administration of the antibiotic was delayed until late in the course of the procedure. The prophylaxis timing data of distal limb surgery were particularly shocking, since it has been shown in an animal model that no adequate drug concentrations can be attained in the distal tissues after inflation of the tourniquet (7). Our intervention started with the reporting of the data to the surgeons and anaesthetists. The review reports, several meetings with the staff and finally, the implementation of new guidelines succeeded in optimizing the timing of the first dose. In the second review, the tourniquet control timing data were all within the correct range.

The inquiry in the department of anaesthesiology showed the importance of communication between the surgeon and the anaesthetist. In the departments A and B where the anaesthetist was informed by the surgeon about the need for prophylactic drugs after the induction of anaesthesia (see chapter VI), the percentage of injections of prophylactic drugs after surgical incision was high. Delayed administration of prophylaxis was found not only in the large-scale setting of the university hospital, but also in the community hospital, suggesting that this might be a general problem. The administration of prophylactic drugs when the patient is called to the operating room and is given premedication - as happened in the community hospital -, often resulted in doses given for more than one hour preoperatively. Department C, where the prophylactic drug was sent with the patient to the operating room, seemed to score best for the timing of the first dose. This strategy was applied in department B after intervention, but did not result in significant improvement.

Our data in department A showed widely varying intervals between the first and second prophylactic dose and therefore resulted in weird pharmacokinetics and probably inadequate prophylaxis. Patients returning at irregular time points from the operating room to the wards were administered the second dose following the fixed medication times - for example 6h-14h-22h - in eight-hourly regimens. Once the patient remained in the ward, the regular time schedule of the nursing

staff provided good quality of prescribing, as was described by others (9).

In 1990, many surgeons adhered to 24 hours prophylaxis regimens, because they felt it to be unsafe to switch to a single dose regimen. The inconsistency of the 24-hours prophylaxis practices revealed by the review helped us to convince the staff to implement protocols of single dose regimens. In the second review, all surgeons used single dose prophylaxis, although some of them continued to use 24h prophylaxis in selected cases.

Optimizing of the timing results in a reduction of wound infection rates as shown by Classen (6). In our study, not only the timing, but also the choice of drug and duration of prophylaxis changed after the intervention, following the guidelines for optimal prophylaxis (1). Although we did not prospectively study the incidence of postoperative wound infections during the study periods, there are some indicators that the new policy improved the quality of prophylaxis. The number of nosocomial infections treated with antibiotics /100 beddays was 1.38 in the first study period and 0.90 in the second. The average length of stay, as an indicator of postoperative infectious complications, has continued to decrease since 1986.

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SECTION C **Surveys in internal medicine**

CHAPTER VIII

Antimicrobial therapy in internal medicine.

IC Gyssens, WL Blok, PJ van den Broek, YA Hekster, & JWM van der Meer.

Submitted for publication

Abstract

Antimicrobial drug use was prospectively analysed in the department of internal medicine of a 948-bed university hospital. Following an initial quality-of use review of all consecutive antimicrobial drug courses during four weeks, an educational programme was conducted. In search for an appropriate surveillance method, an antibiotic order form was introduced. Four years after the first surveillance, an identical review was done. Quality was evaluated using established criteria.

In the first review, 109/347 (31%) of the patients were prescribed antimicrobial drugs, 94% of which were for therapy. The quality of only 40% of the prescriptions was definitely appropriate, and 13% were considered unjustified. There was a certain degree of underutilization, and only 67% of clinical isolates were susceptible to empirical therapy.

In the review after intervention, 164/796 (21%) patients were treated with antimicrobial drugs, of which 83% was for therapy. There was an increase in DDD/100 bed days from 59.8 to 72.6 between the two reviews. The consumption of antiviral and antifungal drugs doubled. Fifty three percent of the prescriptions were judged optimal, and only 9% were judged unjustified. Ninety percent of the clinical isolates were susceptible to empirical therapy. One year after introduction, the compliance with the antibiotic order forms on voluntary basis in two units was 77% and 50 % respectively. As correctly predicted by our first evaluation, improvement in quality resulted in an increase in antimicrobial drug consumption for fewer patients and a higher total cost per bed day. Thus, our study shows that combined interventions lead to improved quality. The antibiotic order form proves useful for antimicrobial drug surveillance in European hospitals, provided logistic support of the pharmacy.

Introduction

Increasing costs of antimicrobial drug consumption, reports on inappropriate use of antimicrobial drugs (1, 2) and the worldwide increase in resistance (3) are the main incentives for antibiotic policy measures of the nineties. Recently, national antimicrobial drug consumption data from European hospitals have been published by Janknegt (4). Dutch university hospitals seemed to have a rather low consumption of antimicrobial drugs (44.3-46.6 DDD/ 100 bed days) compared with German and Belgian hospitals and this seems to be reflected by lower resistance rates in the Netherlands. However, little is known about the quality of use.

Criteria for evaluation of therapy and prophylaxis with antimicrobial drugs are well established (5, 6). Many strategies to improve the quality of prescribing have been described. Education as single intervention strategy to improve quality has not always been successful (7). Antibiotic order forms filled in by prescribers have been used to monitor use and to influence prescribing habits in the U.S. (8, 9), but the experiences in Europe are very limited and unpublished.

We studied the use of antimicrobial drugs in the department of internal medicine of a large university hospital. The intervention study was designed: 1) to define the patterns of antimicrobial drug use in terms of quality and costs 2) to measure the effect of an educational programme and 3) to measure the value of an antibiotic order form.

Patients and Methods

Study population, study period and trends

The University Hospital Nijmegen is a 948-bed teaching hospital. The department of internal medicine counts 183 beds in several subunits (table 1). Some of these subunits were highly specialised, such as the units of haematology and nephrology, where organ transplants were performed, and

most patients were taking immunosuppressive drugs and/or corticosteroids. There was also a large unit of general internal medicine with an older patient population. The study started with an antimicrobial drug use review in October 1989. In October 1993 a similar review was performed. Between the two reviews, the number of beds had remained unchanged. The number of kidney and allogeneic bone marrow grafts had increased from 90 and 26 in the first study year to 111 and 38 in 1993 respectively.

Utilization reviews and antimicrobial drug supply

In the first review, performed over four weeks, all the units of internal medicine were studied (table 1). The second review was conducted over six weeks in three selected units. The units I (general internal medicine) and N (nephrology) were selected to measure the effect of an educational programme and antibiotic order form, while the unit of pulmonary diseases (P), where no order form had been used, was studied as a control.

At the time of the first review, the hospital formulary listed 20 parenteral and 26 oral antimicrobial drugs. In that year, antimicrobial drugs accounted for 22% of the total drug budget of Dfl 14 million. Hospital formulary drugs were kept in ward-based stocks. Pharmacy technicians supplied the drugs to the wards on a twice-weekly basis. Non formulary drugs had to be ordered from the pharmacy on special orders for individual patients. Computerized consumption figures were available for different wards, but not for individual patients. Between the two reviews, an update of the antimicrobial drug formulary was issued, and five antimicrobial drugs were added to the formulary: amoxicillin-clavulanate, ciprofloxacin, trimethoprim, fluconazole and itraconazole. Five older drugs were removed.

Method of the review

Prospective quality-of-use studies were performed by an infectious diseases

physician and junior clinical pharmacists, who visited the wards and collected data on all patients receiving antimicrobial drugs on a daily basis. The first review was conducted over four weeks, the second review over six weeks. Abstracts were made of each consecutive antimicrobial drug course. A course was defined as an episode of clinical or suspected infection or increased risk of infection, in which prescription(s), either consecutively or in combination, were written to treat or prevent this particular infection. Clinical information was retrieved from the patient's record. Infections were defined according to CDC (10). Nosocomial infection was defined as active infection that was not present or incubating at the time of admission. The schedule of systemic drug therapy was copied from the patients' medication chart (Kardex®). Antimicrobial drug use was analysed quantitatively, and converted in defined daily doses (DDD). The DDD represents the average therapeutical dose for an adult for the standard indication (11). Quantitative use of a drug in DDD /100 bed days has been chosen by the WHO drug utilization group to compare use in hospitals (12). Costs were calculated in guilders (Dfl) by a method for global drug cost calculation, which includes costs of administration and monitoring (13). Microbiology results (culture reports and serum antibiotic concentrations) were obtained directly from the department of medical microbiology.

A quality evaluation of individual prescriptions was performed by two independent experts in infectious diseases. The method is based on the original criteria of Kunin (5) and is described previously (6). In short, prescriptions can be categorized as definitely appropriate (category I), unjustified (category V) or the records can be insufficient for categorization (category VI). The other prescriptions are placed in categories of inappropriate use II, III, and IV. Inappropriate prescriptions can be allocated to several categories at the same time: incorrect dose (IIa), interval (IIb) or route (IIc), duration too long (IIIa) or too short (IIIb). If relevant, the reviewers cite a better alternative agent due to

higher efficacy (IVa), lower toxicity (category IVb), lower cost (category IVc) and less broad spectrum (IVd). Global costs of actual and alternative policies are compared to project savings by changes in policy. Because only one expert, reviewer 1, was involved in the education and policy changes during the intervention, detailed evaluation results will be presented of reviewer 1 only.

A few parameters of quality were recorded separately: mentioning in the medical record of the suspected microorganism in empirical therapy, and the monitoring of potentially toxic antimicrobial drugs. We equally checked if the isolated microorganism was susceptible to the empirically started drug, and if streamlining was done after microbiology results became available.

Intervention strategies: education and an antibiotic order form

The principal goal of the interventions was to improve quality of use. Sessions of clinical case reviews were organised on a weekly basis from 1989 through 1992 and could be attended by all residents in internal medicine. In addition to the educational programme, an antibiotic order form was introduced in units I and N in 1992 (see chapter IX). On the order form, the physicians were asked to categorize prescriptions as prophylaxis, empiric therapy or directed therapy. They had to state the (presumed) site of infection, (presumed) causative microorganism, planned duration of the course and parameters such as weight, serum creatinin and presence of allergy. A limited number of formulary antimicrobial drugs and dosage regimens was printed on the form and could be ticked off.

Generally, χ^2 tests were applied to establish systematic differences. Agreement between the experts was assessed by κ coefficients.

Results

First review

- **all units of the department of internal medicine**

Overall, 173/569 (30%) patients received antimicrobial drugs (table 1). Antimicrobial drug use varied considerably and ranged from 9% of the patients in the unit of cardiology to 86% of the patients in the unit of haematology. Table 1(left) shows the proportion of the patients treated with antimicrobial drugs for 7 units, and the proportion for a subpopulation of patients > 70 years old. In the units of haematology and nephrology, none of the patients were older than 70 years. In the 5 remaining units, 22% of the patients were older than 70 years. In these units, a higher proportion of the older patient group received antimicrobial drugs compared with the younger group, 30% vs 20% (p=0.02). Patients > 70 years were almost exclusively prescribed formulary drugs (99%), compared with the younger population, for whom 85% of the antimicrobial drugs were formulary drugs (Fisher's exact test, p=0.001).

Seventy-eight DDD/100 bed days were prescribed in the entire department. The unit of haematology was the largest consumer with 437 DDD/100 bed days. The mean consumption of the other units was 49 DDD/100 bed days. The majority of antimicrobial use was categorized as therapy, except in the unit of haematology, where 35/68 (51%) of the courses were categorized as prophylactic. This prophylaxis was administered to neutropenic patients according to standardised protocols.

The overall most frequent type of infection treated with antimicrobial drugs was respiratory tract infection (34% of the courses). The range for the different units was 27-78%). In the units of oncology and nephrology urinary tract infections were most frequent, 3/10 (30%) and 12/37 (32%) respectively, and in haematology courses in patients with neutropenia and fever accounted for 13/33 (39%). Overall cost/bed day was Dfl 24.4. In the units of haematology and nephrology, antiviral and antifungal agents contributed to 42% of all antimicrobial drug costs, compared with 5% in the other units.

Table 1 - Antimicrobial drug consumption in internal medicine. Comparison of the total population and the elderly.

review	before intervention†						after intervention††					
	all patients	patients with AD		patients >70 years		patients >70 years with AD*	all patients	patients with AD		patients >70 years		patients >70 years with AD*
	n (%)	n (%)		n (%)		n (%)	n (%)	n (%)		n (%)		n (%)
general internal medicine (I)	253	57	(23)	62	(25)	18 (29)	576	85	(15)	119	(21)	24 (20)
cardiology	85	8	(9)	26	(31)	6 (23)	-	-		-		-
oncology	58	11	(19)	2	(3)	0 (0)	-	-		-		-
rheumatology	36	8	(22)	5	(14)	1 (20)	-	-		-		-
pulmonary diseases (P)	42	22	(52)	10	(24)	7 (70)	82	34	(41)	20	(24)	10 (50)
haematology	43	37	(86)	0	(0)	0 (0)	-	-		-		-
nephrology (N)	52	30	(58)	0	(0)	0 (0)	138	45	(33)	9	(7)	1 (11)
total	569	173	(30)	105	(18)	32 (30)	796	164	(21)	148	(19)	35 (24)

* AD = Antimicrobial Drugs, † one-month review †† six-weeks review

- **selected units I, N and P**

Detailed analysis of the data from the selected units: general internal medicine (I), nephrology (N) and pulmonary diseases (P), is presented in table 2 to 6 to allow comparison with the data of the second review.

Quantitative use

In the first review in the selected units, 109/347 (31%) of the patients were administered antimicrobial drugs (table 1). There was a large difference in consumption between unit I and both units N and P, where more than half of the patients were treated with antimicrobial drugs. Overall concomitant use of corticosteroid drugs was 45%, and use of immunosuppressive drugs amounted to 27%. The patients in unit N had the highest consumption in terms of courses/100 bed days, but due to renal function impairment, most patients had dose reductions which resulted in a relatively low consumption expressed in DDD/100 bed days (table 2). Unit P had the highest consumption in DDD/100 bed days, and more than three quarters of the drugs were administered orally, whereas in the other units, the majority of the drugs were given parenterally.

Indication

The courses were almost exclusively categorized as therapy (table 2).The types of infections treated with antimicrobial drugs are presented in table 3.

Respiratory tract infections were the most frequent type of infections treated with antimicrobial drugs (39%). Thirty-three percent of all infections treated could be classified as nosocomial. The consumption of therapeutic antimicrobial drugs, divided in major groups and expressed in DDD/ 100 bed days, is presented in table 4. Penicillins accounted for half of the overall consumption. Antifungal and antiviral drugs accounted for 16%.

Costs.

Cost figures are presented in table 5. There were large differences in the

Table 2 - Quantitative use of antimicrobial drugs in three units of the department of internal medicine

review unit	before intervention* I	N	P	Total	after intervention† I	N	P	Total
bed days	2 200	430	379	3 009	2 372	626	326	3 324
total number of courses	73	39	23	135	98	72	38	208
prophylactic courses (%)	6 (*8*)	2 (*5*)	0 (*0*)	8 (*6*)	4 (*4*)	27 (*38*)	4 (*11*)	35 (*17*)
therapeutic courses (%)	67 (*92*)	37 (*95*)	23 (*100*)	127 (*94*)	94 (*96*)	45 (*62*)	34 (*89*)	173 (*83*)
courses in combination (%)	19 (*26*)	8 (*21*)	5 (*22*)	32 (*24*)	15 (*15*)	7 (*10*)	4 (*11*)	26 (*13*)
total courses/100 bed days	3.3	9.1	6.1	4.5	4.1	11.5	11.7	6.3
total consumption, DDD	1231	252	315	1798	1394	672	413	2413
parenteral DDD (%)	824 (*67*)	105 (*42*)	68 (*22*)	997 (*55*)	965 (*69*)	128 (*19*)	116 (*28*)	1209 (*50*)
DDD/100 bed days	56.0	58.6	83.1	59.8	58.8	107.3	126.7	72.6
DDD/course	16.9	6.5	13.7	13.3	14.2	9.3	10.9	11.6

* one-month review ,† six-weeks review

I= general internal medicine, endocrinology and gastro-enterology; N= nephrology; P= pulmonary medicine

Table 3 - Types of infections treated with antimicrobial drugs in three units of the department of internal medicine

review	before intervention*				after intervention†			
unit	I	N	P	Total	I	N	P	Total
therapeutic courses	n=67	n=37	n=23	n=127	n=94	n=45	n=34	n=173
sites	%	%	%	%	%	%	%	%
respiratory tract	30	32	78	39	24	22	82	35
urinary tract	9	32	0	14	9	29	6	13
fever	1	0	4	2	4	0	0	2
septicemia	21	8	0	13	13	13	3	11
abdominal	12	3	0	7	17	0	0	9
skin	9	5	4	7	14	7	0	9
miscellaneous/unknown	18	19	13	17	19	29	9	20

* one-month review, † six-weeks review

I= general internal medicine, endocrinology and gastro-enterology; N= nephrology; P= pulmonary medicine

Table 4 - Consumption of antimicrobial drugs for therapy in DDD/100 bed days by three units of the department of internal medicine

review	before intervention*				after intervention †			
unit	I	N	P	Total (%)	I	N	P	Total (%)
penicillins	34.3	10.5	35.4	31.0 (52)	26.6	21.9	61.5	29.1 (39)
cephalosporins	2.6	11.5	6.1	4.3 (7)	3.4	3.1	5.6	3.6 (5)
aminoglycosides	1.9	0.8	4.1	2.0 (3)	1.5	0.0	17.5	2.8 (4)
trim/sulfa combinations	3.5	2.8	14.0	4.7 (8)	2.4	26.5	14.4	8.1 (11)
miscell. antibacterial	4.6	8.2	2.7	4.9 (8)	5.6	21.1	14.7	9.4 (13)
antiviral	0.4	5.3	6.8	1.9 (3)	2.3	12.8	0.0	4.0 (5)
antifungal	8.1	12.2	3.0	8.0 (13)	15.5	17.6	6.4	15.0 (20)
Total	55.9	58.7	83.1	59.7 (100)	58.8	107.4	126.6	74.6(100)

* one-month review, † six-weeks review

I= general internal medicine, endocrinology and gastro-enterology; N= nephrology; P= pulmonary medicine

Table 5 - Global cost in Dfl of antimicrobial drug use in three units of the department of internal medicine

review	before intervention*				after intervention†			
unit	I	N	P	Total	I	N	P	Total
total cost	18 966	10 874	9 773	39 613	35 720	17 338	13 219	66 277
cost of prophylaxis	422	10	0	432	135	2 416	79	2 630
cost of therapy	18 544	10 864	9 773	39 181	35 585	14 922	13 140	63 647
total cost/bed day	8.6	25.3	25.8	13.2	15.1	27.7	40.6	19.9
total cost/ DDD	15.4	43.9	31.0	22.1	25.6	25.9	32.0	26.8
total cost/ course	259.8	278.8	424.9	293.4	364.1	242.1	336.1	316.8

* one-month review, † six-weeks review

I= general internal medicine, endocrinology and gastro-enterology; N= nephrology; P= pulmonary medicine

cost/bed day. Although unit N used expensive drugs, total cost/bed day and cost/course was relatively low due to previously mentioned dose adaptations for impaired renal function. One course cost on average Dfl 293. The cost distribution of antimicrobial drugs of unit I, N and P is given in figure 1. More than half of the costs were made for cephalosporins and penicillins.

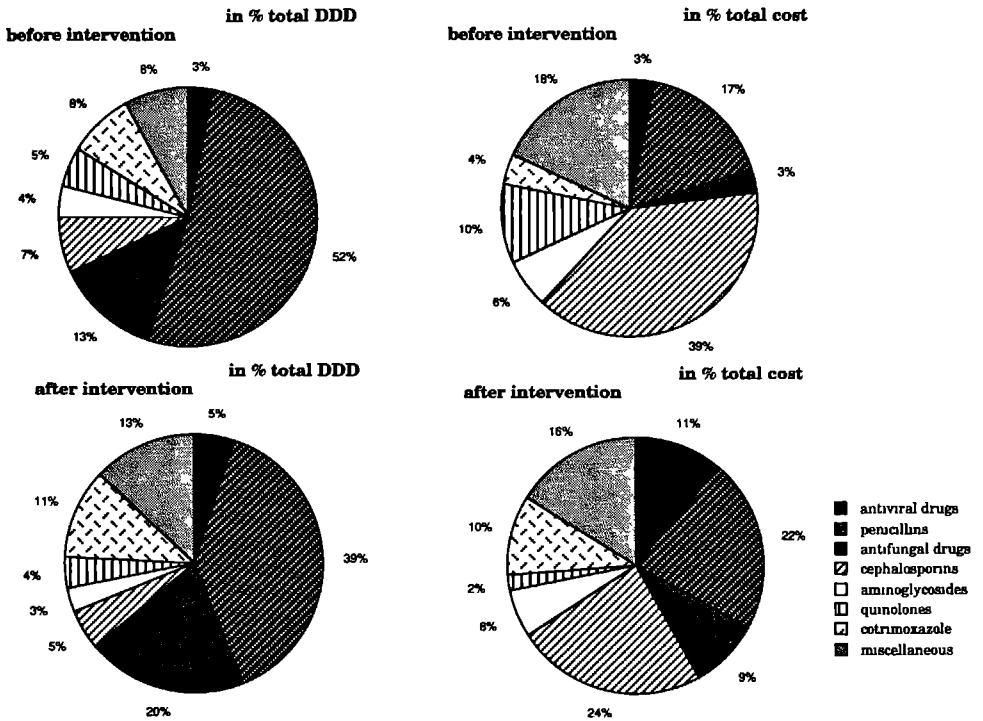

Figure 1 - Distribution of antimicrobial drug consumption in the department of internal medicine before and after intervention. Left: distribution in % total DDD. Right: distribution in % total cost.

Qualitative aspects.

Causative organisms

The most frequently isolated microorganisms were *Escherichia coli* and Klebsiella spp. (20%), and staphylococci (*Staphylococcus aureus* 6% and *Staphylococcus epidermidis* 6%). In figure 2 the relationship between

antimicrobial drug prescribing and microbiology laboratory utilization is drawn. Microbiology laboratory testing could be studied in 123/127 therapeutic courses of which the site of infection was known. In three quarters of these courses microbiology tests were performed. The tests yielded a relevant microorganism in 69%. Only 67% of these microorganisms were susceptible to the empirically started drugs. In less than half of the courses where the microorganism was not susceptible, therapy was changed to an adequate spectrum. Streamlining of empirical therapy was done in 46%.

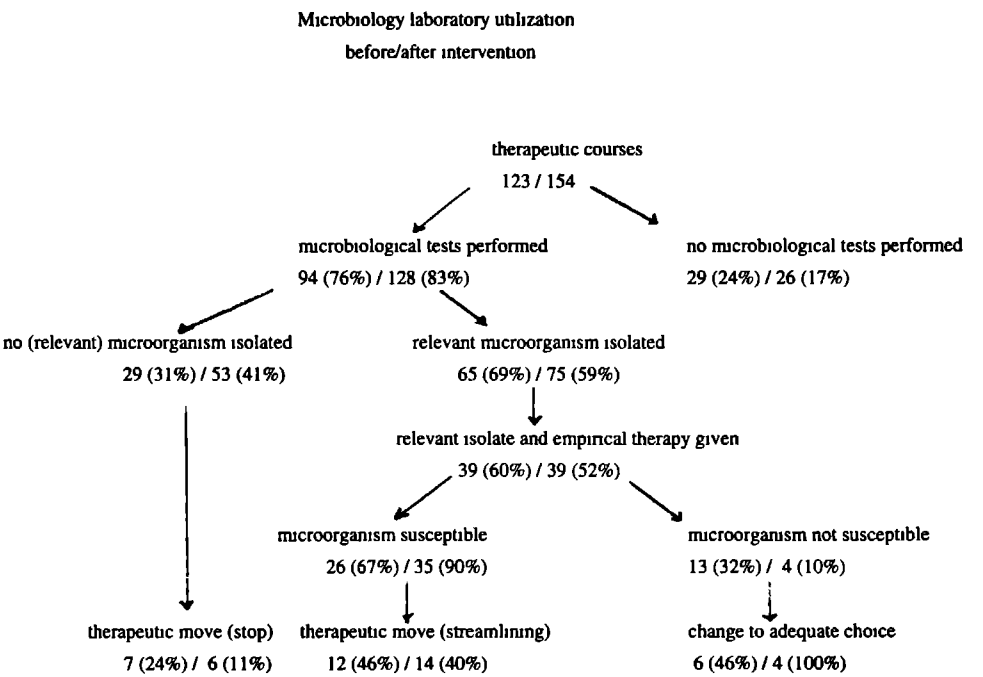

Figure 2 - Microbiology laboratory utilization by the department of internal medicine and the impact of the laboratory results on prescribing. Only therapeutic antimicrobial drug courses were studied; n=123 before intervention, n= 154 after intervention.

Quality evaluation of individual prescriptions

Figure 3 summarizes detailed categories of evaluation of all prescriptions by the two reviewers. Two hundred and fifty-nine prescriptions could be evaluated. It is noted that categories II, III and IV can be assigned simultaneously to a prescription. There was only moderate agreement (ignoring category VI) between the reviewers (κ=0.40). Agreement was higher when only categories I (definitely appropriate) and V (unjustified) were considered (κ=0.56). Reviewer 2 judged more prescriptions unjustified than reviewer 1, and this was true for the three units. He also judged less prescriptions definitely appropriate.

Table 6 shows the results of the evaluation by reviewer 1 for the three units. Less than half of the prescriptions were definitely appropriate (category I), and 13% were judged unjustified (category V). Thirty-seven percent of prescriptions could be optimized (category II-IV).

Cost projections were made. Elimination of prescriptions judged as unjustified by reviewer 1 would result in savings of only 8%. The low frequency of less costly alternatives (category IVc) 5 %, or alternative with less broad spectrum (category IV d) 3%, did predict minor savings. Moreover, because duration of therapy was almost never considered too long (category IIIa) and was even judged too short (category III b) in 2 %, no savings were expected by an improvement in prescribing. Finally, the combination of category II a (incorrect dose, mostly too low) 15%, category IV a (more effective alternative wanted) 19%, and only 68% of microorganisms susceptible to empirically started drugs, suggested the need for higher doses of drugs with a broader spectrum. It was anticipated that implementing the policy of reviewer 1 would result in cost increase.

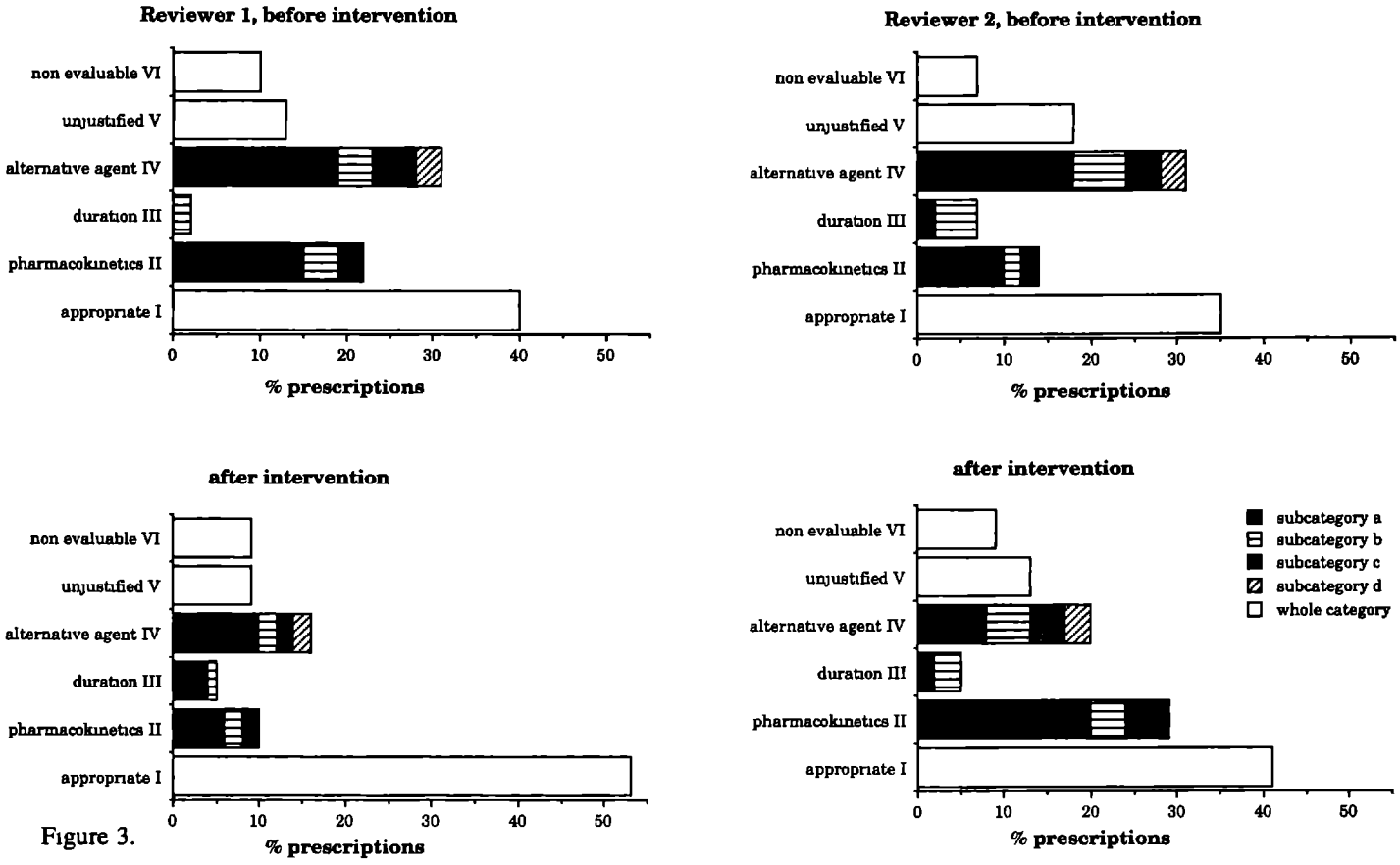

Figure 3.

Quality evaluation of antimicrobial drug prescriptions in the department of internal medicine by two reviewers before (n= 259) and after (n=332) intervention. Left: reviewer 1. Right: reviewer 2. Categories of evaluation: I = definitely appropriate, IIa = incorrect dose, IIb = incorrect dosage frequency, IIc = incorrect route, IIIa = too long, III b too short, IVa = alternative agent more effective, IVb = alternative agent less toxic, IVc = alternative agent less expensive, IVd = alternative agent less broad spectrum, V = unjustified

Table 6 - Quality evaluation of antimicrobial drug use in three units of the department of internal medicine by reviewer 1.

review	before intervention				after intervention			
unit	I	N	P	Total	I	N	P	Total
prescriptions	n=143	n=71	n=45	n=259	n=162	n=121	n=49	n=332
	%	%	%	%	%	%	%	%
definitely appropriate (cat I)	41	30	56	40	59	47	47	53
unjustified (cat V)	11	13	18	13	12	2	18	9
inappropriate (cat II-III-IV)	35	48	24	37	23	37	24	29
unevaluable (cat VI)	13	10	2	10	6	14	10	9

Other quality parameters

In 16/70 (23%) of empirical courses the suspected microorganism was mentioned in the medical record. Unit P scored best with 6/16 (38%). Formulary drugs were used in 86% (88% in unit I, 76% in unit N, 93% in unit P). In all 12 courses of gentamicin lasting >72h, serum concentrations were measured. Courses were given as three times daily regimens. In 4/12 a peak concentration <5 mg/l was measured (considered too low) and in 4/12 a trough concentration of >1mg/l (considered too high). In all courses the dose and/or frequency was adapted. In 3 courses the second peak concentration was still below 5mg/l.

Intervention and surveillance over the years 1990-1992

Surveillance data of the pharmacy showed that expenses for antimicrobial drugs had remained stable in 1990, but had increased by 35% in 1991 and 45% in 1992 in the units I and N. In those units, the average length of stay had decreased by one day between 1989 to 1993.

The purchase cost of most antimicrobial drugs decreased between the two reviews. The cost of cephalosporins decreased by 10 % and the cost of ciprofloxacin and vancomycin by 25%. The antifungal drugs fluconazole and itraconazole that were used on compassionate use basis in the first review, became part of the hospital formulary, resulting in a cost increase for antifungal drugs. To analyse the consequences of those complex cost changes, a second in-depth review was done.

Changes in the second review

Quantitative use

Comparing the units I, N and P in which both reviews were held, there was a reduction in the overall proportion of patients receiving antimicrobial drugs, from 31% to 21% (table 1). The difference was significant in unit I (p=0.006)

and unit N (p=0.002), but not in unit P (p=0.25). Overall concomitant use of corticosteroid drugs was 48%, and use of immunosuppressive drugs amounted to 23%. Table 2 shows the comparison of quantitative data. Overall consumption increased, both in terms of courses/100 bed days and in terms of DDD/ 100 bed days. The proportion of parenterally administered drugs decreased only in unit N. Part of these quantitative changes could be explained by a policy change in unit N (as discussed below).

Indication

Six percent of the courses was intended for prophylaxis in the first review and 17% after intervention (table 2). This consumption increased mainly because the department of nephrology started post transplantation prophylaxis with cotrimoxazole against Pneumocystis carinii. Eighteen percent of the patients in unit N were on prophylaxis with cotrimoxazole.

Respiratory tract infections were still the most frequent type of infections treated with antibiotics (table 3), and the sites of infection were very similar. The consumption of penicillins, cephalosporins and aminoglycosides remained stable (table 4). There was an increase in the use of combinations of trimethoprim with sulfonamides in unit N. Antiviral and antifungal drug consumption doubled and the remaining increase was merely due to slight changes in a variety of antimicrobial agents. The consumption of amoxicillin-clavulanic acid, and ciprofloxacin, drugs that were added to the formulary in 1991, did not increase. Combinations of two or more antimicrobial drugs were less frequently seen in the second review (table 2).

Costs.

Comparison of the cost distribution of antimicrobial agents before and after intervention is shown in figure 1. The increase in prophylaxis had only minor influence on the cost, as the drugs used were oral and of low cost (approximately 4% of total cost). Comparison of cost parameters before and

after the intervention is shown in table 5. The total cost/bed day increased from Dfl 13.2 to 19.9. The increase in cost/bed day was seen in each of the three units, although most pronounced in unit I and unit P. A higher cost/DDD, representing the use of more expensive drugs, and a higher cost/course were noted in unit I only.

Validation of the antibiotic order form

During the second review, the data on the antibiotic order forms of units I and N were compared with the data collected by the in-depth method.

Defining compliance as the total number of antibiotic order forms collected/ total number of prescriptions, compliance was 77% in unit I and 50% in unit N. In 98/170 (58%) courses, at least one order form was filled in. At least one form was filled in for 39% of prophylactic courses and for 61% of therapeutic courses. In unit I, 86% of total antimicrobial drug costs were documented by order forms. In unit N, this only amounted to 41%. Categorization in prophylaxis or therapy and site of infection were well documented in 98% in unit I and in 90% in unit N. In empirically started therapy, a suspected agent was mentioned in 70% and 62% respectively. However, some items were regularly omitted. History of allergy was most frequently left blank (44%), followed by weight 41%, and creatinin 31%. Only 33% of forms were filled in without blanks. In 98% of the forms, the formulary drugs preprinted on the form were chosen. In unit I, on 80% of the forms, preprinted doses and dosage intervals were ticked off. In unit N, only 33% of the preprinted regimens were used. This was probably due to dose and/or dosing interval adaptations for impaired renal function, although this reason was only mentioned on half of those forms.

Quality

Causative microorganisms

The utilization of microbiological tests in therapeutic courses increased from 76% to 83% in the second review (Figure 2). The yield of relevant

microorganisms was lower in the second review (59% versus 69%). After the intervention, 90% of the isolates were susceptible to the empirical therapy, compared with 67% before intervention. All empirical therapy was changed to an adequate spectrum after culture results were known.

Quality evaluation of individual prescriptions

Three hundred and thirty-two prescriptions could be presented for evaluation. Figure 3 allows comparison of detailed categories of evaluation of all prescriptions by the two reviewers before and after intervention. After the intervention, agreement (ignoring category VI) between the reviewers was only partial (κ=0.27). Again, reviewer 2 considered more prescriptions unjustified than reviewer 1. He also judged less prescriptions definitely appropriate, and this was true for the three units.

Comparison of the quality evaluation for the three units by reviewer 1 before and after the intervention is shown in table 6. According to reviewer 1, the overall proportion of prescriptions that were considered definitely appropriate (category I) increased from 40% to 53%. Unjustified prescriptions (category V) decreased from 13% to 9%. There were relatively less prescriptions classified in categories II to IV (inappropriate). The differences were statistically significant for the total prescriptions (p=0.01). There were also significant differences in quality before and after the intervention in unit I (p=0.003) and unit N (p=0.002), but not in unit P (p=0.91), where no order form was used. According to reviewer 2, there were significant differences in quality before and after the intervention in unit N only (data not given).

After the intervention, 96% of the antimicrobial drug prescriptions were formulary drugs in unit I and N. In unit P this amounted to 89%.

Discussion

The first analysis of antimicrobial drug use in this department of internal

medicine showed that, although there was no major misuse, quality could be optimized. We projected that, due to a certain degree of underutilization, implementing a policy to improve quality would result in cost increase. Although quantitative use in terms of DDD/100 bed days increased after the intervention, the proportion of patients who were receiving antimicrobial drugs was lower than before. This can be explained by the use of higher dosages and/or longer duration of treatment restricted to patients with proven infections, and the shorter length of stay. Total cost/bed day increased for the same reason, and also due to the use of drugs with a broader spectrum (thus more expensive, and increase in cost/DDD). The higher proportion of older patients receiving antimicrobial drugs was consistent with the finding of Moss et al. (14). However, in contrast to what was found in the British study, there was a more prudent use. There was only partial agreement between the two experts who evaluated quality of use. Personal factors (reviewer 2 was more strict for all units) may have played a role, but also the fact that reviewer 1 was involved in the development of the new policy.

To the best of our knowledge, this is the first report in the English language literature on the use of antibiotic order forms in Europe. Quality improved in units N and I where the antibiotic order form was used. As we combined several intervention strategies (education, update of the formulary, antibiotic order forms), it was not possible to estimate the effect of each intervention separately. The effect of a compulsory formulary must on its own be considerable. Even before the introduction of the order form, a separate order had to be sent to the pharmacy for non formulary drugs. This resulted in a very high compliance with the formulary of 86% before the use of the order form, and also in unit P in the second review. The order form was successful in stimulating wanted dosing frequencies as was found in unit I. This effect of the order form has been described by others (9). Another advantage of the form is that the suspected

causative microorganism has to be explicitely mentioned on the form. Without an order form it is otherwise not clear if the prescriber does not know the suspected agent or fails to mention it in the record, unless the prescriber is interviewed.

The order form may thus have had an effect on quality, but its main purpose was surveillance. The in-depth reviews were very time-consuming. The order form was generally well accepted by prescribers. In terms of surveillance, the form was successful in unit I with a high voluntary compliance of more than 75% and a coverage of more than 80% of antimicrobial drug costs. Compliance with the form can probably be improved by making the form mandatory and controlled by the pharmacy (15).

When antimicrobial drug use is expressed in DDD, comparisons can be made between hospitals (4, 16), but also within hospitals and in the same department over time, regardless of the types of antimicrobial drugs used. In our hospital, consumption was higher in internal medicine than in the department of surgery, where consumption was 31 DDD/100 bed days for therapeutic courses (see chapter IV).

Our method of quality evaluation, although time-consuming, proved effective for an initial review. Furthermore, the method could predict the effect of policy changes on costs. The antibiotic order form was only partially successful on a voluntary basis, although well accepted by physicians. With support of the hospital pharmacy, i.e. by making the form mandatory and by taking actions in case of noncompliance, the form could be a useful tool for antimicrobial drug surveillance in European hospitals in the future.

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CHAPTER IX

Feasibility of an antibiotic order form in internal medicine.

WL Blok, IC Gyssens, YA Hekster, PP Koopmans and JWM van der Meer.

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Abstract

Inadequate control of antimicrobial drug use may lead to excessive expenditure for antimicrobial drugs and improper prescribing. It may also result in the emergence of multiresistant bacteria. An antibiotic order form may improve the quality of prescriptions by increasing the awareness of the physician of the antimicrobial spectrum needed (i.e. which microorganism is expected in a given patient), the desired duration of treatment, the potential need to adjust dosage, and the potential allergy of the patient to the drug. Furthermore, such an antibiotic order form facilitates prospective evaluation of both the quantity and the quality of prescribing practice. However, the introduction of yet another form to fill in may meet with opposition from prescribers. We have developed an easy-to-use antibiotic order form that incorporated the conventional medication order that was already in use in our hospital. Compliance (percentage of antimicrobial drug prescriptions for which an order form was used) rose from 58% in the first two weeks after introduction to 76% over the following half year. Data retrieved from the antibiotic order forms could be used for surveillance. We conclude that this antibiotic order form was feasible in a large department of internal medicine of a university hospital. Future usefulness will depend on compliance and on personnel support for data processing and intervention.

Introduction

Inadequate control of antimicrobial drug use may lead to excessive expenditure for antimicrobial drugs and improper prescribing. It may also result in the emergence of multiresistant bacteria that threaten both the patient receiving the antimicrobial drug and other patients in the hospital (1, 2). Education and guidelines or restrictions on the availability of antimicrobial drugs may improve the quality of prescribing (3).

Durbin et al. were the first to introduce an antibiotic order form. The order form was designed to encourage the physician to review basic clinical and laboratory information and to categorize antimicrobial drug use as prophylactic, empirical (culture results not available), and therapeutic (4). Use of the order form was mandatory, i.e. antibiotics were delivered to the patient only if the form was completed. Furthermore, antibiotics were automatically discontinued by the pharmacy after a predetermined number of days depending on the indication. Over the past ten years, further experience with the form was reported from several US hospitals (5-12). An antibiotic order form may improve the quality of prescriptions by increasing the awareness of the physician of the desired antimicrobial spectrum, i.e. which microorganism is suspected in a given patient, the desired duration of treatment, the potential need to adjust dosage, and potential allergy of the patient to the drug (7, 9, 13, 14). By filling in the antibiotic order form, the prescriber provides himself the data for drug utilization surveillance. In return, the antibiotic order form facilitates prescribing by providing information on the formulary drugs and preferred dosing regimens at the time of prescription. However, the introduction of uniform prescription guidelines and yet another form to fill in may meet with opposition from prescribers. Therefore, we investigated physician's acceptance of and compliance with an antibiotic order form. In addition, an attempt is made to evaluate the quality of antimicrobial drug prescriptions with help of the antibiotic order forms.

Methods

Setting.

The order form was introduced in the departments of general internal medicine, gastroenterology, nephrology, and endocrinology of the 948-bed University Hospital Nijmegen, in the course of an intensified education program on the use of antimicrobial drugs. Total number of beds in these wards was 100. Most of the prescriptions were written by nine residents, who were supervised by six internists. Data are presented on the first seven months following the introduction of the antibiotic order form.

Drug supply and antibiotic order form.

In the University Hospital Nijmegen, the pharmacy delivered formulary drugs for inpatients to the wards on a twice-weekly basis. Computerized drug consumption data were available per ward level, but not for individual patients. Formulary drugs were kept in ward stocks, that were managed by nurses. Non formulary drugs had to be ordered on individual prescriptions and were directly controlled by the pharmacy. Formulary drugs for individual patients were prescribed on medication orders consisting of a strip of paper and duplicate sticker that was pasted on the patient's Kardex medication card. The strips were kept in the patient's nursing record, and the stickered Kardex cards were sent to the pharmacy after discharge of the patient. So far, Kardex cards were the only resource for antimicrobial drug surveillance on individual patient level. In this drug delivery system, a conventional antibiotic order form could not be used, because the nurses, not the pharmacy technicians, were dispensing the majority of the drugs out of a stock. Therefore, an adapted antibiotic order form was developed (figure 1). Although it was not only introduced for antibacterial drugs, but also for antiviral and antifungal drugs, we preferred to keep the name "antibiotic order form" (7), used in the original description.

The lower part of the antibiotic order form was similar to the original medication order strip. After filling in the order on the sheet, the duplicate sticker could be pasted on the Kardex card. The text on the order form stickers was printed in blue instead of black ink, and therefore the sticker could easily be identified

sticker met patiëntgegevens

Academisch Ziekenhuis Nijmegen
St Radboud

Antibiotica formulier *mei 1992*
na invullen retour apotheek

datum: _____

Vul in van A tot E welk antibioticum u nu wilt voorschrijven:

arts: _____ afd: _____

A ☐ nieuw voorschrift ☐ verlenging ☐ verandering van dosis of route: ga naar D

B INDICATIE DUUR (planning)

☐ PROFYLAXE ☐ chirurgische ingreep: _____ ☐ < 24 u

☐ andere: _____ _____ dgn

☐ empirische THERAPIE, vermoedelijke verwekker: _____ ☐ 3-5 d

☐ gerichte THERAPIE, aangetoonde verwekker: _____ _____ dgn

LOKALISATIE

☐ bloed ☐ urinewegen ☐ luchtwegen ☐ centraal zenuwstelsel

☐ maagdarmkanaal ☐ huid/weke delen ☐ bot/gewrichten ☐ andere: _____

C gewicht: _____ serumcreatinine: _____ allergie: ☐ nee ☐ ja, voor: _____

D

MIDDEL	aanbevolen bij normale nierfunctie									
	route	dosis			frequentie	route	dosis			frequentie	
feneticilline	PO ☐	500mg	☐ 1g		☐ 4dd						
penicilline G						IV ☐	0,5 MIE	☐ 1 MIE	☐ 2 MIE	☐ 4dd	☐ 6dd
amoxicilline	PO ☐	500mg	☐ 1g		☐ 3dd	IV ☐	1g	☐ 2g		☐ 4dd	☐ 6dd
amoxi/clav	PO ☐	625mg	☐ 1,2g		☐ 3dd	IV ☐	1,2g			☐ 3dd	
flucloxacilline	PO ☐	500mg	☐ 1g		☐ 4dd	IV ☐	1g	☐ 2g		☐ 4dd	☐ 6dd
piperacilline						IV ☐	2g	☐ 4g		☐ 3dd	
cefazoline						IV ☐	1g				☐ 3dd
cefuroxim						IV ☐	750mg	☐ 1,5g			☐ 3dd
ceftazidim						IV ☐	1g	☐ 2g			☐ 3dd
gentamicine						IV ☐	___ mg				☐ 2dd
ciprofloxacine	PO ☐	500mg	☐ 750mg		☐ 2dd	IV ☐	200mg	☐			☐ 2dd
clindamycine	PO ☐	150mg	☐ 300mg		☐ 4dd	IV ☐	300mg	☐ 600mg			☐ 4dd
colistine	PO ☐	100mg			☐ 4dd						
doxycycline *	PO ☐	100mg			☐ 1dd	IV ☐	100mg				☐ 1dd
erytromycine	PO ☐	500mg	☐ 1g		☐ 4dd	IV ☐	500mg	☐ 1g			☐ 4dd
metronidazol	PO ☐	500mg			☐ 3dd	IV ☐	500mg				☐ 3dd
nitrofurantoïne	PO ☐	50mg			☐ 4dd						
trimethoprim	PO ☐	300mg			☐ 1dd						
trimeth/sulfa	PO ☐	960mg	☐ ___ mg		☐ 2dd	IV ☐	960mg	☐ ___ mg			☐ 2dd
vancomycine						IV ☐	500mg				☐ 4dd
aciclovir	PO ☐	200mg	☐ 800mg		☐ 5dd	IV ☐	250mg	☐ 500mg	☐ 750mg		☐ 3dd
ganciclovir						IV ☐	___ mg				☐ 2dd
amfotericine B	PO ☐	10mg	☐ 100mg		☐ 4dd	IV ☐	___ mg **				☐ 1dd
flucytosine	PO ☐	___ mg			☐ 4dd	IV ☐	___ mg				☐ 4dd
ketoconazol	PO ☐	200mg			☐ 1dd						
fluconazol *	PO ☐	100mg	☐ 200mg		☐ 1dd	IV ☐	200mg				☐ 1dd
miconazol gel	PO ☐	5ml			☐ 4dd						

* *met oplaaddosis* ** *proefdosis, oplaadschema*

E **ANDER MIDDEL** reden voor andere keuze: _____

begindat.	geneesmiddel en sterkte	or.	im.	rect.	iv.	dosis	tijd
stopdat.	___ x per dag ___						
kamer.		par.arts					
begindat.	geneesmiddel en sterkte	or.	im.	rect.	iv.	dosis	tijd
stopdat.	___ x per dag ___						
kamer	naam	par.arts					

Figure 1
Antibiotic order form with conventional medication order strip.

when checking the cards. The order forms were gathered by the ward clerk and processed for surveillance by the first author. Prescribers were asked to categorize all their prescriptions of antimicrobial drugs as prophylaxis, empirical therapy, or directed therapy. For empirical prescriptions, they were asked to state the suspected causative microorganism; for directed therapy, they were asked for the isolated pathogen. Empirical therapy had to be streamlined to directed therapy after 72 hours, and documented by another form.

Further items to be filled in included patient data, date of prescription, site of infection, weight, serum creatinine, and a history of allergy. A limited number of formulary antimicrobial drugs and dosage regimens were printed on the form and could be ticked off. The prescriber was asked to state his/her reasons to deviate from the preprinted antimicrobial drugs and/or dosing regimens. Use of the form was voluntary, i.e. delivery of the antimicrobial drugs to the patients was not dependent on completion of the form.

Compliance.

Compliance (percentage of prescriptions for which an order form was used) was measured by checking the Kardex cards as described above. Pharmacy technicians identified the patients to whom antimicrobial drugs were prescribed on their twice weekly visits to the wards. They scored the total number of antimicrobial drug prescriptions and these figures were compared with the antibiotic order forms received. When order forms were missing, no further action was undertaken. Newsletters provided the physicians with feedback about their actual compliance.

Quantity of use.

The number of prescriptions is an incomplete estimate of the quantity of antimicrobial drug use, as duration of treatment may vary. Therefore, an estimate of the prevalence of antimicrobial drug use was made. Twice a week, pharmacy technicians scored the number of patients that actually received antimicrobial

therapy. The score of one month was related to the number of bed days of that month. Thus, the estimate of the prevalence presented is the twice-weekly-scored number of patients receiving an antimicrobial drug/100 bed days over a month. Prescriptions on the forms were quantified according to patient age. The distribution of the types of antimicrobial drugs prescribed on the forms was calculated.

Quality of use.

Data extracted from the antibiotic order forms were used to quantify the sites of infection, the microorganisms suspected or isolated, and the reasons to deviate from the antimicrobial drugs or the dosages indicated on the form. Prescriptions that were categorized as empirical therapy were evaluated separately for adequacy of microbiological spectrum, i.e. if the isolated pathogen was susceptible to the drug. No attempt was made to evaluate microbiological efficacy, i.e. the actual cure rate of infections.

Results

Compliance. Acceptance of the antibiotic order form by physicians was high. Compliance rose from 58% in the first two weeks after introduction to 76% from week five on. However, many forms were not filled in completely. Localisation of infection was indicated on 84% forms, and on 73% of those forms, a suspected or isolated pathogen was indicated.

Quantity of use.

Six hundred and fifty-eight forms with new therapeutic antibiotic prescriptions were collected over seven months. The number of patients on antimicrobial drugs/100 beddays as scored by the pharmacy technicians was 9.0, 9.8, 8.6, 9.8, 8.8, 10.6 and 12.8. The number of prescriptions/ 100 bed days according to age is given in table 1.

Table 1 - Distribution of 564 new prescriptions on antibiotic order forms according to age

age (years) classes	prescriptions n (%)	prescriptions /100 beddays
11-20	17 (3)	4.4
21-30	46 (8)	2.4
31-40	67 (12)	3.1
41-50	95 (17)	2.9
51-60	92 (16)	3.2
61-70	136 (24)	4.1
>70	111 (20)	2.7

The frequency distribution of the types of antimicrobial drugs prescribed is given in figure 2.

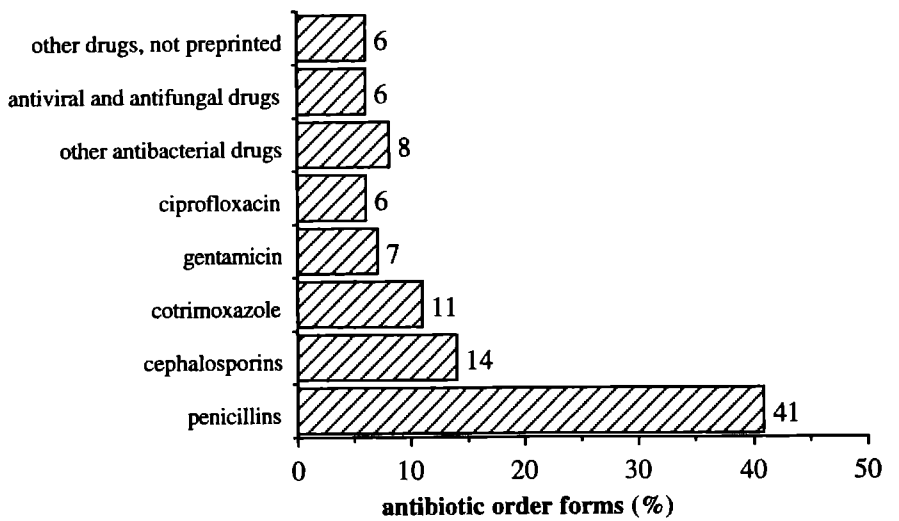

Figure 2 - Frequency distribution of antimicrobial drug types prescribed on 658 new order forms.

Penicillins were the most frequently prescribed drugs (41%), followed by cephalosporins (14%) and cotrimoxazole (11%).

Quality of use.

In 108 (16%) out of 658 forms the localisation was left blank and they were excluded from the analysis. Localisation of the infection and the mentioning of a (suspected) pathogen are analysed in the remaining 550 forms (table 2). Of the 403 forms that showed both localisation of the infection and (suspected) pathogen, 51% were categorized as empirical therapy and 49% as directed therapy. Fifty-three percent of all 550 prescriptions were made for the treatment of respiratory tract infections and urinary tract infections.

Table 3 shows, as an example, 97 suspected and 37 isolated pathogens cited on 103 forms to treat respiratory tract infections.

The prescribers deviated from the proposed antimicrobial drugs in 6% only. Overall, alternative drugs and/or alternative dosing regimens were prescribed in 22%. In the department of nephrology, dosing adaptations amounted to 38%, mostly due to renal function impairment.

Table 2 - Localisation of infections and categorization of 550 new antibiotic order forms

site of infection	forms n (%)	suspected* pathogen n (%)	isolated† pathogen n (%)	no pathogen mentioned n (%)
respiratory tract	158 (29)	70 (35)	33 (16)	55 (37)
urinary tract	133 (24)	38 (19)	69 (35)	26 (18)
blood	85 (15)	23 (11)	43 (22)	19 (13)
skin /soft tissue	57 (10)	29 (14)	22 (11)	6 (4)
abdominal	63 (12)	22 (11)	18 (9)	23 (16)
bone and joint	7 (1)	5 (3)	0 (0)	2 (1)
central nervous system	6 (1)	1 (0)	5 (3)	0 (0)
other site	41 (8)	15 (7)	10 (5)	16 (11)
Total	550 (100)	203 (100)	200 (100)	147 (100)

* categorized as empirical therapy, † categorized as directed therapy

A subgroup of 68 consecutive empirical prescriptions was analysed in detail. Isolated microorganisms were susceptible to the empirically chosen drug in 23/31 (74%). The probability that the isolated pathogen was susceptible to the empirically started drug was higher when the prescribing physican cited a suspected pathogen on the form: Odds ratio 3.1 (95% confidence interval: 0.6-16.6). However, according to Fisher's exact test, the difference was not significant (p=0.23).

Table 3 - Pathogens (n= 134) as mentioned on 103 antibiotic order forms for respiratory tract infections.

pathogen	suspected n (%)	isolated n (%)
pneumococci	24 (25)	6 (16)
H. influenzae	22 (23)	5 (14)
Gram-negative bacteria	13 (13)	3 (8)
Gram-positive bacteria	7 (7)	2 (5)
anaerobes	5 (5)	-
Legionella	4 (4)	1 (3)
Klebsiella	3 (3)	-
Proteus	-	1 (3)
meningococci	-	1 (3)
Aspergillus	3 (3)	-
streptococci	4 (4)	1* (3)
staphylococci	3 (3)	5† (14)
Pneumocystis	2 (2)	5 (14)
M. catharrhalis	2 (2)	2 (5)
M. tuberculosis	-	2 (5)
miscellaneous	5†† (5)	3# (8)
Total	97 (100)	37 (100)

* group A; † S. aureus 3x; †† Chlamydia psittaci 2x, Mycoplasma pneumoniae 2x, Herpes simplex; # Citrobacter, E. coli, Herpes simplex.

Discussion

Over the first half year after the introduction of the order form, surveillance of limited parameters of antimicrobial drug use could be done. According to the prescribing physicians, incorporation of the conventional medication order in the antibiotic order form facilitated its use. The collection and the analysis of the data on the forms was much less time consuming for the researchers than former analysis by reviews of medical records (see chapter VIII).

As delivery of antimicrobial drug therapy to the patient was not dependent upon the completion of the antibiotic order form, compliance was limited. Higher compliance rates may be achieved when use of the form is mandatory (15). Nevertheless, with a compliance of 76%, we consider the data extracted from the forms as representative for the half year studied.

The scores of the pharmacy technicians, used as an estimate of the prevalence of antimicrobial drug use, allowed for monthly comparisons. There was no decrease in consumption over the first seven months. Comparison with consumption data before the introduction of the form is more difficult. In a one-month review performed two years earlier in the same department, antimicrobial drug consumption was accurately quantified with the help of the medication sheets (Kardex®). The incidence rate was 4.2 therapeutic courses/ 100 bed days (see chapter VIII). The decrease in consumption following use of the form described in US hospitals, was probably achieved by the automatic stop of drug delivery by the pharmacy after 72 hours for empirical therapy or after the planned duration of directed therapy had expired (7). In our setting, the planned duration filled in on the forms had no consequences for the actual delivery of the drugs to the patient.

This relatively high compliance with the form on voluntary basis may have served the purpose of enhancing quality of prescription. The prescribers used almost exclusively the proposed drugs on the form (94%). Moreover, half of the other prescriptions were for tuberculostatic drugs, that had been omitted from the form. In addition, the order form reminded the prescriber to think of a suspected microorganism. It is thought that there is a relationship between the

quality of prescribing antimicrobial drugs and the knowledge of a (suspected) pathogen (16). The degree of appropriateness of empirical therapy of 74% compared favorably with the figures of the previous antimicrobial drug review before the implementation of the order form. At that time, 67% of the isolated pathogens were susceptible to the drug chosen. A suspected microorganism was spontaneously mentioned in the medical record in 20 % of empirical courses (see chapter VIII). Again, data before and after the introduction of the form are not entirely comparable, as, without a form, prescribers were not asked for the (suspected) pathogen. Analysing the prescribing practices after introduction of the antibiotic order form by the in-depth method used in the review before introduction, may provide a better evaluation of the effectiveness of the form.
We conclude that surveillance of antimicrobial drug use by an order form was feasible in this large department of internal medicine. Future usefulness of the form will depend on the level of compliance and the availability of personnel and support for data processing and intervention.

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General Discussion

We measured quantitative use, qualitative use and costs of antimicrobial drugs in the main medical and surgical departments of a university hospital between 1989 and 1993. These departments should be representative for the overall use in the hospital. After doubling between 1982 and 1988 (see introduction, p.7), hospital antimicrobial drug costs have remained on a fairly constant level over the following four years (figure 1).

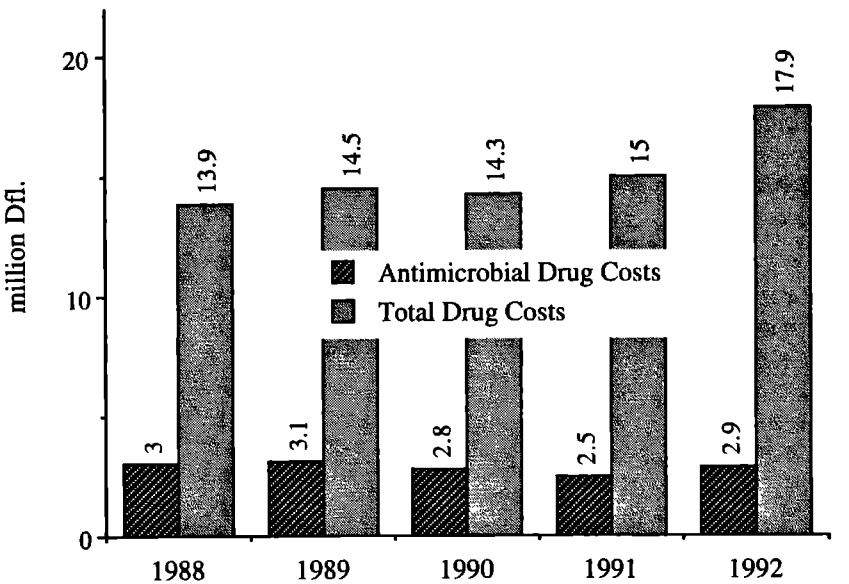

Figure 1 - Drug consumption in the University Hospital Nijmegen

The relative contribution of antimicrobial drugs in the total hospital drug budget decreased from 22% in 1989 to 16% in 1992. Total patient days varied less than 2% per year.

The in-depth method of the utilization reviews (chapters II, IV and VIII) was very time-consuming, partly due to the lack of computerized pharmacy data on individual patients. However, the first review yielded invaluable information on logistic pitfalls in prescribing and on psychological motives of doctors, nurses

and clerk personnel. We believe that this in-depth approach contributed to the successful implementation of the protocols in the departments of surgery. Although conducted prospectively, a shortcoming of this type of review is the incomplete information provided by the medical record in order to evaluate the appropriateness of antimicrobial drug use. Interviewing the prescriber (1) would certainly give more information on the rationale behind prescribing. However, this approach is even more time consuming, and the review may have in itself an effect on prescribing (2). In search of a more economic personnel distribution, the reviews were performed with the help of hospital pharmacists in training and pharmacy technicians (chapter VIII). The analysis learned that clinical data for our evaluation of therapy could only be recorded satisfactorily by a clinician. Most other aspects of these studies, on the edge of clinical medicine, microbiology, pharmacy, epidemiology, hospital hygiene, management and economics could not have been performed without the help of a multidisciplinary team. In addition, most skills required for the intervention studies had nothing to do with clinical internal medicine. To perform audits of this type, the doctor should resemble the ideal infection control doctor described by Daschner (3).

Use of an antibiotic order form can solve part of the personnel support problem (4). However, within the Dutch university hospital drug supply system, the antibiotic order form was of limited success (chapter VIII-IX). In the future, surveillance by order form will be possible if compliance is sufficient (at least 75%) and if the data on the form are processed regularly. Therefore, logistic support of the pharmacy of a form which is made mandatory, is recommended. Targeted interventions on duration of empiric therapy or on the use of specific drugs will then become possible.

The consumption figures were lower than those found in the U.S., although comparison is often difficult, due to the variety of measurement units employed in U.S. studies. Recently, the outcome of the consumption analysis comparing hospitals in the Netherlands with neighboring countries was favorable (5). We have tried to provide standardized quantitative data by using the unit of defined

daily doses/ 100 bed days, as proposed by the WHO Drug Utilization group. Even this approach does not give comparable consumption data over time, as lists of DDDs are regularly updated. Lists of DDD are published regularly in the Nordic Statistics on Drugs (6). An example illustrates this problem. The DDD for parenteral quinolones, cephalosporins and even benzylpenicillin have been adapted between 1985 and 1995. For a few drugs, we had to use 2 different DDDs for the studies in surgery and internal medicine.

In internal medicine, we saw that due to tertiairy care, the contribution of antiviral and antifungal drugs to the total antimicrobial drug consumption and costs is considerable.

The cost of antimicrobial drugs involves considerably more than the purchase of the drug. We performed a global cost calculation (true cost calculation) for antimicrobial drugs tailored to the Dutch hospital situation (chapter III). Cost comparisons and cost savings calculations were all done by taking into account the extra costs of administering and monitoring (chapters IV and VIII).

In surgery, 30% of consumption was for prophylaxis and the first review showed that, for prophylaxis, the indication, the timing and the duration were not up-to date. Suboptimal timing was confirmed in a peripheral hospital. Organizational aspects seemed of primary importance. The implementation of protocols was very effective. Different parameters of quality improved and consumption decreased.

As correctly predicted by our first evaluation, improvement in the quality of therapeutic courses resulted in an increase in antimicrobial drug consumption for fewer patients, both in surgical and medical departments, and therefore in a higher total cost per bed day.

In internal medicine, we also found suboptimal quality. There was a certain degree of underutilization in severe infections: empiric therapy was not effective against all cultured pathogens, the dosage was often too low, the duration of therapy too short. On the other hand, many short courses with oral drugs were judged unnecessary. We intervened with educational programs and an antibiotic order form. These combined strategies resulted in an improvement in

quality. Less patients were prescribed antimicrobial drugs. Patients with severe infections were treated with drugs with a broader spectrum, higher doses and a longer duration of therapy. This intervention resulted in higher expenses for antimicrobial drugs.

The effect of an antibiotic policy according to the principles of "good antimicrobial drug prescribing" (chapter I) on patient care is not easily measured. As in comparative clinical trials of antimicrobial drug therapy that use clinical outcome of infectious diseases as a measure of effect, large numbers of patients are needed to show a difference in outcome. An example is the reduction of postoperative wound infections as an effect of optimizing the timing of antimicrobial drug prophylaxis (7). However, if the hospital has no systematic and computerized registration of wound infections, these data are lacking. An indirect measure of the improved quality is the trend over time of the median length of hospital stay in surgical departments with a constant pattern of surgical procedures. Another indicator can be the number of nosocomial infections that need to be treated with antimicrobial drugs. In our opinion, there is no need to prove in every hospital that the application of the principles of good antimicrobial drug prescribing results in a better outcome for the individual patient.

The studies in the present thesis have been done against a background of strong national policy and tradition of prudent antimicrobial drug use. In the Netherlands, socio-economic and marketing pressures which lead to inappropriate use are controlled and physicians are educated in this tradition. This has been recently documented in several studies. Stobberingh studied Dutch guidelines for prescription (8). From the study of Janknegt we know that Dutch university hospitals have a low consumption of antimicrobial drugs compared with German and Belgian hospitals. From the EPIIC study (9) we know that bacterial resistance in ICU's in the Netherlands compares favourably with other European countries. It has been suggested that strong policies are the cause of the low rates of resistance (10).

Recommendations

Guidelines to improve the use of antimicrobial drugs in hospitals developed by the Infectious Diseases Society of America (11) are still applicable. Every hospital should have its antibiotic committee. Formularies should be adapted to the local antibiotic susceptibility data. The formularies should be stringent so that newly marketed drugs are automatically restricted. Utilization reviews and interventions have to be done by multidisciplinary teams. Antimicrobial drug reviews in referal hospitals should include antiviral and antifungal drugs. Each hospital should chose the appropriate control method(s) available (12). Full support of the hospital board is a prerequisite for success. Until now, the most powerful tool for a change in policy has been the prediction of antimicrobial drug cost reduction in the presence of budget exceedings.

Drug utilization reviews and intervention methods in surgery

Protocols are the most successful method of intervention in surgery if prepared with the co-operation of the surgical staff. Prophylaxis guidelines should be clear and regularly updated. With the help of computer software, prophylaxis can be monitored at pharmacy level. The program used in the studies of this thesis was originally developed for Apple Macintosh computers by the authors; a revised version has been developed for use under Ms-Windows by BJ Kullberg & M Roomer of Nestor BV, The Netherlands, on behalf of a working party of hospital pharmacists, infectious disease physicians and consultant microbiologists.

For a utilization review of antimicrobial prophylaxis, a suitable sample size should be chosen, depending on local situation. In general surgery, actually 30% to 40% of all operations can be allocated to categories for which prophylaxis is deemed appropriate. Thus, to gather enough data on the presciptions of 100 prophylactic courses, a consecutive sample of 250 to 300 operations is needed. Collection of the data can be done by a well-trained

pharmacy technician or infection control nurse. The evaluation of antimicrobial prophylaxis for surgical procedures can be performed by the hospital pharmacist using the flow chart (chapter II). The help of a surgery staff member is advisable to classify the procedures into the correct categories (i.e. clean, contaminated..) in order to judge appropriateness of prophylaxis and compliance with guidelines.

After an initial review indicates that prophylaxis can be optimized, alternative regimens should be proposed. Projected cost savings can be calculated. The new protocols have to be implemented. The result of these interventions should be evaluated in a repeated survey. Pharmacy technicians can detect protocol violations during their routine work on the wards and correct and/or report them as a continuous surveillance, or collect the data on prescriptions in the computer database for later evaluation.

Utilization reviews and intervention methods in internal medicine

Education of physicians in the matter of infectious diseases and antimicrobial therapy, and peer reviews are the best accepted methods of intervention in internal medicine. However, education as sole intervention has not always been successful (13). An antibiotic order form will have a high compliance if it is made mandatory and controlled by the pharmacy. It will be more effective if computerized pharmacy data allow for targeted interventions. At that time, automatic stop orders can be applied, controlling for the duration of empiric therapy and for streamlining of therapy. In referal and training hospitals with complicated cases, a structured consultancy service of infectious diseases specialists and consultant microbiologists is probably the best tool to optimize the quality of antimicrobial drug courses.

It would be a challenge to try the interventions used in this thesis in hospitals with major antimicrobial resistance and/or hospitals where overconsumption of antimicrobial drugs is still a problem. If developing countries strengthen their policies to allow the application of these methods, it is anticipated that major cost savings and reduction in resistance will ensue.

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Summary

This thesis is composed of studies on the use of antimicrobial drugs in a Dutch University Hospital. Most of the descriptive studies have been followed by an intervention to improve quality of use, and a second review has been performed to measure the effect of the intervention in terms of quantity, quality and costs of antimicrobial drug courses.

SECTION A **Background and methodology**

Chapter I gives as an introductory background the principles of good antimicrobial drug use. How antimicrobial drug therapy differs from other kinds of drug therapy and what physicians should consider before starting a treatment.

Chapter II describes the method that has been developed in order to evaluate quality of use of antimicrobial drugs, based on established criteria. The method allows for evaluation of each individual parameter associated with antimicrobial drug use. We developed a flow chart which facilitates the sorting of prescriptions into categories, systematizes and accelerates the review. The evaluation is performed by two independent reviewers qualified in infectious diseases, who formulate alternative agents in case of inappropriate antimicrobial drug use.

Chapter III deals with the method of cost-identification analysis which was used in the quality-of-use studies. To maximize cost containment, efforts to obtain cost savings have to be directed to the following cost components : costs of acquisition, costs of preparation and administration, and costs of monitoring of antimicrobial drugs. Purchase contract prices for antimicrobial drugs vary between hospitals and they are invariably lower than wholesale

prices. However, to allow generalization of our calculation results to other Dutch hospitals, we chose wholesale purchase prices of antimicrobial drugs and national prices for salaries and hospital costs. The result of global cost comparison contributes to the decision to include new drugs into the hospital formulary or to replace older ones.

SECTION B **Surveys in surgical departments**

In **chapter IV** we describe how new guidelines were implemented in surgical departments, following a one-month prospective review of consecutive antimicrobial drug use. The review was repeated after 2 years. Total number of patients (766 vs 744) and operations (542 vs 522) were similar. In both study periods, one third of the patients were prescribed antimicrobial drugs. Prophylactic drug consumption decreased from 0.75 to 0.53 DDD/operation. Compliance with guidelines improved from 32% to 79%. Duration of prophylaxis > 24 hours decreased from 21% to 8%. Quality of prescribing improved, as evaluated by the method described in Chapter II. For prophylaxis, cost savings amounted to 57%. Better quality of therapeutic courses was associated with a cost increase of 15%. Indicators of satisfactory outcome with the new policy were a stable median length of stay and a reduction in the number of nosocomial infections/100 bed days treated with antimicrobial drugs.

Chapter V is a prospectively conducted audit of consecutive requests for microbiological analysis sent to the laboratory by a department of orthopaedic surgery during a six weeks period. The majority of the specimens were surgical. The microbiology analysis of these specimens is crucial in order to establish the correct diagnosis and appropriate choice of antimicrobial drugs. In a formal evaluation performed by 2 consultant microbiologists, the majority of the requests were classified as definitely appropriate. Collection, handling and transport was not optimal. No request was considered unjustified. A certain degree of underutilization, inappropriate sampling for anaerobic culture and a

prolonged transport time to the laboratory were found. Analysis of compliance with an existing protocol for prosthetic joint revision revealed similar problems.

Chapter VI shows how the anaesthetist plays a key role in surgical antimicrobial prophylaxis. The staff of 44 anaesthetists and residents was interviewed by means of a questionnaire about the practice of surgical prophylaxis. Response rate was 82%. The anaesthetists' way of administering surgical prophylaxis was rather uniform and economic. Communication between surgeon and anaesthetist on the subject of prophylaxis was reported to be poor. In two out of six operating departments, orders of prophylaxis transmitted at or after induction accounted for more than 80%. Seventy seven percent of the responders asked the surgeon if prophylaxis was necessary if they were in doubt; 20% responded that they checked it systematically. There was an association between poor communication reported by the anaesthetists and the late administration (after incision) of prophylactic antibiotics. The inquiry proved useful in the process of optimizing surgical prophylaxis in our hospital.

Chapter VII describes the considerable improvement of the timing of prophylaxis in the surgical departments of the university hospital where the intervention (described in chapter IV) was carried out. Optimal timing (administration within one hour before incision) increased. Before the intervention, seven out of 16 prophylactic doses were given after inflation of the tourniquet. After the intervention all doses of prophylactic antibiotics were administered before inflation of the tourniquet. Initially, the intervals of multidose prophylaxis varied widely. Single dose prophylaxis increased from 21% to 78% in department A and from 31% to 85% in department B.

SECTION C **Surveys in internal medicine**

Chapter VIII

Following an initial prospective quality-of-use review of all consecutive antimicrobial drug courses in the department of internal medicine during four weeks, an educational programme was conducted and an update of the formulary was issued. In search for an appropriate surveillance method, an antibiotic order form was introduced in two out of three units. Four years after the first review, an identical survey was done. Quality was evaluated using the method described in chapter II. As correctly predicted by our first evaluation, improvement in quality resulted in an increase in antimicrobial drug consumption for fewer patients (21% vs. 31%), and a higher total cost per bed day. One year after introduction, the compliance with the antibiotic order forms on voluntary basis in two units was 77% and 50% respectively. With support of the hospital pharmacy, i.e. by making the form mandatory and by taking actions in case of noncompliance, the form could be a useful tool for antimicrobial drug surveillance in European hospitals in the future.

Chapter IX describes in detail the easy-to-use antimicrobial ordering sheet (antibiotic order form) that was introduced in the department of internal medicine (chapter VIII). An antibiotic order form may improve the quality of prescriptions by increasing the awareness of the physician of the antimicrobial spectrum needed (i.e. which microorganism is expected in a given patient), the desired duration of treatment, the potential need to adjust dosage, and the potential allergy of the patient to the drug. Furthermore, such an antibiotic order form facilitates prospective evaluation of both the quantity and the quality of prescribing practice. An overall compliance on voluntary basis of 76% was reached in the first seven months. Data retrieved from the antibiotic order forms could be used for surveillance. We concluded that this antibiotic order form was feasible in a large department of a university hospital.

Samenvatting

Dit proefschrift is samengesteld uit studies naar het gebruik van antimicrobiële middelen in een academisch ziekenhuis in Nederland. De meeste descriptieve studies werden gevolgd door een interventie die tot doel had de kwaliteit van het gebruik te bevorderen. Daarna werd een tweede registratie uitgevoerd om het effect van de interventie te meten.

DEEL A Achtergrond en methoden

Hoofdstuk I schetst als inleidende achtergrond de principes van goed gebruik van antimicrobiële middelen. Hoe de behandeling met antimicrobiële middelen verschilt van andere vormen van farmacotherapie en waaraan artsen moeten denken voor zij deze middelen voorschrijven.

Hoofdstuk II beschrijft de methode die werd ontwikkeld om de kwaliteit van het gebruik van antimicrobiële middelen te beoordelen. Deze methode is gebaseerd op gevestigde criteria. De methode laat toe elke parameter die van belang is voor antimicrobiële therapie afzonderlijk te evalueren. Er werd een stroomdiagram ontwikkeld, dat het sorteren in categorieën van goed gebruik vergemakkelijkt. Het stroomdiagram brengt systematiek in de beoordeling en versnelt het evaluatieproces. De beoordeling wordt uitgevoerd door twee onafhankelijke experts op het terrein van infectieziekten. In die behandelingen waar het gebruik als suboptimaal wordt ervaren, moeten zij alternatieve behandelingsschema's voorstellen.

Hoofdstuk III beschrijft de methode van kosten-identificatie die toegepast werd in de gebruiksstudies. Om tot een maximale kostenbesparing te komen, moeten de inspanningen gericht zijn tegen alle componenten van een integrale kostenberekening. Het betreft de aankoopkosten, de kosten van klaarmaken

en toedienen, en de kosten van monitoring van toxiciteit. Aankoopprijzen via contracten variëren sterk tussen de verschillende ziekenhuizen, en zijn meestal lager dan de groothandelsprijzen. Om vergelijking met andere Nederlandse ziekenhuizen mogelijk te maken, hebben wij als aankoopprijs de groothandelsprijzen Brocacef gehanteerd, en nationale cijfers gebruikt voor de salarissen en ziekenhuiskosten. Het resultaat van de integrale kosten berekening kan de beslissing om nieuwe geneesmiddelen in het ziekenhuisformularium op te nemen, of om oudere middelen te vervangen, beinvloeden.

DEEL B Studies in de chirurgische afdelingen

In **hoofdstuk IV** beschrijven we hoe na de rapportage van een eerste prospectieve gebruiksstudie, nieuwe richtlijnen geimplementeerd werden in chirurgische afdelingen. De registratie van het gebruik werd na 2 jaar herhaald. Het totale aantal patiënten (766 vs 744) en het aantal ingrepen (542 vs 522) van beide metingen was vergelijkbaar. In beide onderzoeksperioden van een maand werd aan een derde van de patiënten antimicrobiële middelen voorgeschreven. Het gebruik van profylaxe daalde van 0.75 tot 0.53 DDD/ingreep. Na de interventie hield men zich ook beter aan de richtlijnen, in 79% versus 32% voor de interventie. Profylaxe langer dan 24 uur werd in 8% toegepast, terwijl dat in het eerste onderzoek 21% bedroeg. Ook volgens de beoordelaars die de methode uit hoofdstuk II hanteerden, was de kwaliteit van voorschrijven verbeterd. In de profylaxe werd een kostenbesparing van 57% gerealiseerd. De betere kwaliteit van de therapeutische behandelingen ging echter gepaard met een kostenstijging van 15%. Indicatoren van een bevredigend klinisch resultaat met het nieuwe beleid waren een stabiele mediane ligduur en een daling van het aantal nosocomiale infecties/100 beddagen dat behandeld moest worden met antimicrobiële middelen.

Hoofdstuk V is een prospectieve audit van opeenvolgende aanvragen voor

microbiologisch onderzoek ingezonden door een afdeling orthopaedie, en dit over een periode van 6 weken. Het betrof in de meerderheid chirurgisch verkregen monsters. De microbiologische analyse van deze monsters is essentieel om de correcte diagnose te stellen en de adekwate therapie te kiezen. In een gestandaardiseerde evaluatie door 2 artsen-microbioloog werd de meerderheid van de aanvragen als volledig juist geclassificeerd. Geen enkele aanvraag werd als overbodig geclassificeerd. Onvoldoende benutten van de diagnostische mogelijkheden van het laboratorium, een niet optimale bemonstering voor anaerobe kweken en een te lange transporttijd naar het laboratorium waren de resterende problemen. Analyse van de compliance met een bestaand protocol voor revisie van gewrichtsprothesen toonde dezelfde tekortkomingen als bij de niet protocollaire aanvragen.

Hoofdstuk VI toont hoe de anaesthesioloog een sleutelpositie heeft in de chirurgische antimicrobiële profylaxe. Een schriftelijke enquête bij 44 stafleden en assistenten van een afdeling anesthesiologie had een respons van 82%. De toedieningswijze van keuze voor de profylaxe bleek éénvormig en economisch. De communicatie tussen de chirurg en de anaesthesioloog over de profylaxe werd door de anesthesiologen als onvoldoende ervaren. In 2 op 6 operatiekamers werden de instructies voor profyaxe in meer dan 80% pas gegeven op het ogenblik van de inleiding van de anaesthesie of nog later. Zevenenzeventig percent van de responders vroegen de chirurg of profylaxe nodig was als ze zelf twijfelden; 20% antwoordde dat ze er systematisch om vroegen. Er was een verband tussen de gebrekkige communicatie in sommige operatiekamers zoals die gerapporteerd werd door de anaesthesiologen, en de laattijdige toediening (na de incisie) van de profylactische antibiotica bij metingen in diezelfde operatiekamers (hoofdstuk VII). De enquête leverde snel een goed inzicht in de opinies en het medisch handelen van deze grote groep artsen. De resultaten werden gebruikt bij het reorganiseren van de profylaxe.

Hoofdstuk VII beschrijft de belangrijke verbetering van de timing van de

profylaxe in de operatiekamers van het academisch ziekenhuis waar de interventie (beschreven in hoofdstuk IV) uitgevoerd werd. De antimicrobiële middelen werden vaker in de optimale periode (binnen een uur voor incisie) toegediend. Vóór de interventie waren 7 op 16 profylactische doses pas toegediend na het aanleggen van de bloedleegte. Na de interventie werden alle injecties voor profylaxe toegediend voor het opblazen van de bloedleegteband. Bij de eerste registratie bestond er een grote variatie in de intervallen van de injecties bij profylaxe met meerdere doses. Vóór de interventie werden eenmalige doseringsschema's voor profylaxe slechts in 21% (afdeling A) en 31% (afdeling B) toegepast. In het naonderzoek was dit toegenomen tot respectievelijk 78% en 85% .

DEEL C Studies in de interne geneeskunde

Hoofdstuk VIII

In de interne geneeskunde werd ook gestart met een registratie van alle opeenvolgende behandelingen met antimicrobiële middelen gedurende vier weken. De interventies bestonden uit een vernieuwing van het formularium, een educatief programma in de vorm van wekelijkse casusbesprekingen, en een antibioticaformulier dat slechts in twee op drie afdelingen werd geintroduceerd. Vier jaar na het eerste onderzoek werd een identieke registratie uitgevoerd. De kwaliteit werd door de twee experts beoordeeld volgens de methode beschreven in hoofdstuk II. Zoals de eerste evaluatie kon voorspellen, resulteerde een verbetering in de kwaliteit in een toename van het gebruik van antimicrobiële middelen voor een kleiner aantal patiënten (21% versus 31%), en in hogere kosten per beddag. Een jaar na introductie van het antibioticaformulier was de compliance op vrijwillige basis in de twee afdelingen respectievelijk 77% en 50%. Met de logistieke steun van de ziekenhuisapotheek, bv. door het formulier verplicht te maken en door acties te voeren in het geval van niet invullen van het formulier, kan het antibioticaformulier bruikbaar zijn voor continue registratie van het gebruik

van antimicrobiële middelen in Europese ziekenhuizen.

Hoofdstuk IX beschrijft in detail het antibioticaformulier dat gebruikt werd in de afdelingen van interne geneeskunde (hoofdstuk VIII). Een antibioticaformulier kan de kwaliteit van het voorschrijfgedrag beinvloeden door de voorschrijver te vragen om een vermoedelijke verwekker te noemen en hem zo te doen nadenken over het benodigde spectrum van het antimicrobieel middel. Verder verhoogt het de alertheid op de mogelijke noodzaak om de dosering aan te passen en op mogelijke allergieën. Het vraagt de arts meteen een plan op te maken over de vereiste therapieduur. Het formulier vergemakkelijkt de prospectieve registratie van zowel kwantitatieve als kwalitatieve aspecten van het gebruik van antimicrobiële middelen. In de eerste zeven maanden werd een compliance op vrijwillige basis van 76% bereikt. De gegevens van de formulieren waren bruikbaar voor continue registratie. Het gebruik van het antibioticaformulier was haalbaar in deze grote afdeling in een academisch ziekenhuis.

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Curriculum vitae

Inge Gyssens werd geboren op 29 maart 1953 te Antwerpen. In 1970 behaalde zij het diploma van de Latijn-Griekse humaniora aan het Instituut van de Heilige Familie te Berchem. Zij studeerde geneeskunde aan de Rijksuniversiteit Antwerpen (kandidaturen 1971-1974) en aan de Universitaire Instelling Antwerpen (doctoraten 1975-1978), met onderscheiding. In 1979 behaalde zij aan het Prins Leopold Instituut voor Tropische Geneeskunde te Antwerpen het diploma in de Tropische Geneeskunde met grote onderscheiding. Zij werkte vervolgens als tropenarts in Niger, NW Afrika, in een project van de Belgische Ontwikkelingssamenwerking (ABOS) van 1979 tot 1984.

Aansluitend was zij als internist in opleiding werkzaam in het Sint Vincentiusziekenhuis te Antwerpen en in het Universitair Ziekenhuis te Antwerpen van 1984 tot 1989. In 1987-1988 werkte zij een half jaar in de afdeling infectieziekten van het Academisch Ziekenhuis Leiden (hoofd: Prof. dr. R van Furth) met een beurs van de Belgische Rotary. Van 1989 tot 1992 werkte zij als internist-onderzoeker in de afdeling algemene interne geneeskunde van het Academisch Ziekenhuis Nijmegen (hoofd: Prof. dr. A van 't Laar). Het onderzoek in het AZN, onder leiding van Prof. dr. JWM van der Meer, resulteerde in dit proefschrift.

Sinds 1992 is zij aangesteld als internist-infectioloog in de afdeling klinische microbiologie en de afdeling interne geneeskunde II van het Academisch Ziekenhuis Rotterdam.

STELLINGEN

behorend bij het proefschrift

Optimizing antimicrobial drug utilization.
Studies and interventions in a university hospital.

Nijmegen, 28 mei 1996

Inge C. Gyssens

1. De wetenschappelijke basis voor een optimale chirurgische antibioticaprofylaxe is al dertig jaar bekend; dit wil niet zeggen dat ze optimaal wordt uitgevoerd (dit proefschrift).

2. De antibioticacommissie dient overleg te plegen met de anesthesiologen bij het opstellen en implementeren van richtlijnen voor chirurgische profylaxe (dit proefschrift).

3. Het Antibioticaformulier zal in een Nederlands academisch ziekenhuis pas een maximum compliantie bereiken als het beheerd en gecontroleerd wordt door de apotheek (dit proefschrift).

4. Bij onderzoek naar het gebruik van antimicrobiële middelen in academische ziekenhuizen moet men het gebruik van antivirale en antifungale middelen in het onderzoek betrekken (dit proefschrift).

5. Het verbeteren van de kwaliteit van het gebruik van antimicrobiële middelen leidt niet tot kostenbesparing indien er sprake is van onderbehandeling van ernstige infecties (dit proefschrift).

6. De Verenigde Staten zouden op gebied van antibioticabeleid veel kunnen leren van landen waar de resistentie tegen antimicrobiële middelen beperkt is (*JWM van der Meer & EH van de Lisdonk. CID 1995;21:1069*). Een commentaar op hoofdstuk IV van dit proefschrift als: "The manuscript suffers from the following shortcoming: the study was carried out in a hospital in the Netherlands", door een referee van het tijdschrift *Clinical Infectious Diseases*, stemt niet tot optimisme.

7. It is possible for women to combine motherhood with a fulfilling career in academic medicine, but it is difficult, and most such women believe that motherhood slows the progress of their careers. (*W Levinson, SW Tolle & C Lewis. Women in academic medicine. N Engl J Med 1989; 321: 1511-7).*

8. Een vrouw die in deze westerse samenleving wil slagen in een carrière heeft enkele troeven nodig: organisatievermogen, flexibiliteit, en een geëmancipeerde man.

9. Het definitief van de weg halen en tot schroot verwerken van een miljoen personenwagens zal meer bijdragen tot de volksgezondheid dan het afslachten van een miljoen Britse koeien.


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