Improving the Quality of Use of Antimicrobial Drugs

Assessments and Interventions

Stephanie Natsch

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CONTENTS

INTRODUCTION 7

CHAPTER I

Use of amoxicillin-clavulanate and resistance in Escherichia coli over a four-year period
Infect Control Hosp Epidemiol 1998;19:653-656. 11

CHAPTER II

Application of the ATC/DDD Methodology to Monitor Antibiotic Drug Use
Eur. J. Clin. Microbiol. Infect. Dis. 1998;17:20-24. 25

CHAPTER III

Use of fluconazole in daily practice: still room for improvement
J. Antimicr. Chemother. 2001;48:303-310. 39

CHAPTER IV

Delay in Administering First Dose of Antibiotics in Patients Admitted to General Internal Medicine with Serious Infections
Eur. J. Clin. Microbiol. Infect. Dis. 1998;17:681-684. 55

CHAPTER V

Earlier Initiation of Antibiotic Treatment for Severe Infections After Interventions to Improve the Organization and Specific Guidelines in the Emergency Department
Arch Intern Med. 2000;160:1317-1320. 65

CHAPTER VI

Outcomes in Studies Aimed at Improving Rational Use of Antibiotics
Submitted 77

GENERAL DISCUSSION 89

SUMMARY 93

SAMENVATTING 97

ZUSAMMENFASSUNG 101

CURRICULUM VITAE 105

LIST OF PUBLICATIONS 107

DANKWOORD 111

INTRODUCTION

Despite many efforts to improve the quality of use of antimicrobials in daily clinical practice, the spread of microbes resistant to antimicrobial agents is more extensive and faster than ever before. (1) Antimicrobial resistance results in increased morbidity, mortality, and rising costs of health care. (2,3) Multiple factors play a role in the development of resistance, but selective pressure caused by inappropriate and widespread use of antimicrobial drugs is considered one of the major factors. (4) The introduction of new antimicrobial drugs into practice will give some relief but is by no means a solution of the problem. (5) On the contrary, the increase of the number of severely immunocompromised patients and of patients with more severe illnesses will further increase the use of newer antibiotics. This calls for the development of sophisticated strategies to delay or reverse the trend toward increased antibiotic resistance. (6) Optimal use of antimicrobial drugs must be promoted and implemented in daily clinical practice. (7) Historically, the high costs of antimicrobial therapy had been of major concern, particularly in terms of inappropriate use. (8) Later on, the focus changed to concerns about the impact on the development of resistance. (9) Only recently, the many aspects of what comprises optimal antimicrobial use have been reviewed. (10) Sound methods are needed for the assessment of the use and resistance patterns and the evaluation of treatment strategies and protocols. (6) Multifaceted interventions are needed to implement good clinical practice with regard to the prescription and administration of antimicrobial drugs. (11) The involvement of every member of the health-care team is essential. (10) Interdisciplinary collaboration among physicians, clinical pharmacists, the microbiology laboratory, infection control practitioners and nurses will improve the quality of care substantially. Pharmacists have a broad education and are well trained to take a leading role in the coordination of projects and interventions. Care has to be taken however, that these efforts are accepted in an institution and are not only based on personal and tailor-made advice concerning the treatment of individual patients. (12) Rather, comprehensive recommendations and guidelines are required for every health-care setting. (6) All aspects of the use of antimicrobial drugs -- the choice, the dosage, the duration, the route of administration as well as the timing of initiation of treatment -- all these have to be critically reviewed and optimised.

The results of a series of studies addressing several aspects of the quality of use of antimicrobial drugs and assessing the implementation of interventions to improve the quality are presented in this thesis.

In chapter I, we describe the results of an intervention study with the aim of reducing the use of amoxicillin-clavulanate after high resistance rates in Escherichia coli were detected. The study was performed at an acute-care hospital in Switzerland, including the four major departments of surgery, internal medicine, obstetrics-gynaecology and the interdisciplinary intensive-care unit. In this study, the amount of antibiotics consumed was measured in grams of substance and in number of treatment courses. These are useful parameters when comparisons within institutions are done. But for the comparison of drug consumption data between different institutions, within regions, countries or even internationally, a system that is independent of package size, sales prices or local dosage recommendations is needed. For these purposes, the World Health Organisation (WHO) developed the Anatomical Therapeutical Chemical Classification/ Defined Daily Doses (ATC/DDD) system. (13) In chapter II, the application of this methodology to monitor antibiotic drug use is described. As an illustration, the pattern of quinolone use in the general population, in long-term care facilities, and within a single institution was analysed. These kinds of studies allow researchers to discover possible areas of concern such as disproportionally high use of a specific drug in a particular institution. For a closer look at the prescribing habits in an institution, medication use evaluations and target drug programs are necessary. They should focus on inappropriate drug use, drug use problems, optimizing use of drugs and improving the level of patient care. (14) In chapter III, we describe the performance of a comprehensive evaluation of the use of fluconazole, one of the best-tolerated and effective antifungal drugs available. Because we were concerned that suboptimal use of this valuable drug would limit its future usefulness, the aim of the study was to assess the prescribing patterns in daily clinical practice. A prospective audit of the use of fluconazole was undertaken in two different hospitals, a university and a non-university hospital in The Netherlands.

Beside the choice of the appropriate antimicrobial drug, and the right dosage and duration of the treatment, other aspects can be crucial in the process of care for the optimal use of antimicrobials. In chapter IV, the evaluation of the timeliness of initiation of antibiotic therapy in patients presenting with a serious infectious disease in the emergency room is presented. The results led to the

analysis of the barriers to change and in chapter V, the results of a series of educational and organizational interventions to change the performance of the health care practitioners concerning the timing of antimicrobial drugs in serious infections are presented. The studies presented in chapter IV and V led to considerations of what are appropriate outcomes and outcome measures in studies aimed at improving the use of antimicrobials and in the evaluation of the effectiveness of policies and guidelines put in place. Several aspects are discussed in more depth in chapter VI. A general discussion and summary are given at the end.

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CHAPTER I

Use of amoxicillin-clavulanate and resistance in Escherichia coli over a four-year period

S. Natsch, C. Conrad, C. Hartmeier, B. Schmid

Infect Control Hosp Epidemiol 1998;19:653-656.

Abstract

Objective: To reduce the use of amoxicillin-clavulanate after high resistance rates in Escherichia coli were detected.

Design: Intervention study; the interventions were introduced successively over a four-year period while closely monitoring the resistance patterns.

Setting: A 260-bed acute care hospital in Switzerland.

Interventions: Introduction of therapeutic guidelines for specific departments or indications, which proposed alternative antibiotics to amoxicillin-clavulanate. The perioperative prophylactic use of amoxicillin-clavulanate was eliminated completely.

Results: The absolute amount of amoxicillin-clavulanate consumed decreased by 23% from 24.8 g per 100 patient days in 1992 to 18.5 g per 100 patient days in 1995. The number of courses, a parameter that takes the prophylactic use into account, decreased by 62% from 2.3 per 100 patient days in 1992 to 0.9 per 100 patient days in 1995. The percentage of sensitive strains increased from 54.9% (n=512) in 1992 and 54.0% (n=506) in 1993 to 72.1% (n=546) in 1994 and 83.1% (n=668) in 1995. No major changes were detected for other antimicrobials, such as cotrimoxazole, tetracycline or cefuroxime, used in this 4-year period.

Conclusions: A decrease in the use of amoxicillin-clavulanate was followed by an increase in susceptibility of E coli to it. It was not possible to prove a causative relationship. Only a temporal association was discovered. The reduction of the use of amoxicillin-clavulanate was achieved through the implementation of treatment guidelines, facilitated through a close collaboration among the clinical pharmacists, the infection control practitioner, the microbiology laboratory, and the physicians in charge of the respective departments.

Introduction

Several articles have been published that show a connection between the use of antimicrobials and the development of resistance. In 1979, Buckwold and Ronald (1) discussed this issue and proposed improved medical education, the adaptation of a policy of restricting the use of specific antimicrobial agents, the introduction of guidelines, and a close collaboration among hospital infection and pharmacy committees and the clinical microbiology laboratories. Hollmann (2) analyzed data on antimicrobial consumption and resistance patterns in 1980 and discovered a correlation. In 1983, Daschner et al. (3) stated that the restriction of the use of antimicrobials often leads to a decrease in resistance rates. In 1983, McGowan (4) compiled a review of studies performed between 1950 to 1980, which showed a relationship between antibiotic use and resistance. In 1987, (5) he assumed that epidemiological criteria for a causal relationship between antibiotic use and resistance of hospital organisms was supported by new data despite confounding variables inherent in the studies. In 1994, McGowan stated that the temporal association between resistance and use already asked for the development of appropriate measures such as education of prescribers, the implementation of restrictions, and intensive control programs. (6) Several authors published data that compared specific antimicrobials with specific species of bacteria. Ma et al. reported a substantial decrease in cephalosporin resistance in gram-negative bacilli after a marked decrease in prescribing of these drugs. (7) Data on antibiotic purchases and bacterial susceptibilities in 18 hospitals in the United States revealed a statistically significant correlation between increasing ceftazidime use and increasing Enterobacter cloacae resistance. (8) Richard et al. reported the results of a case-control study and found that treatment with fluoroquinolones was an independent risk factor for nosocomial infections caused by fluoroquinolone-resistant gram-negative bacilli. (9)

Sanders and Sanders (10) published a review of resistance to β-lactam-antibiotics in gram-negative rods. There are several possible factors determining resistance to amoxicillin-clavulanate in Escherichia coli. One is TEM-1 β-lactamase hyperproduction. (11-13) Another mechanism of resistance may be an altered permeability of the outer cell membrane. (14) Others described mutations in the genes encoding for TEM-1 β-lactamases. (15-17) Published data on the rate of resistance to amoxicillin-clavulanate in E coli vary considerably. In France, isolates from urine in 1993 showed 25% of

strains were resistant, and 15% were intermediate. (11) On the other hand, a survey of isolates from six intensive-care units in Switzerland in 1994 showed 93% of strains were sensitive. (18) Kastanakis et al. from Crete reported that 18% of strains in urine and 30% of strains from other sources were resistant, (19) whereas Kouppari et al (20) reported less than 2% of strains isolated from neonates in the Children's Hospital in Athens were resistant.

Methods

Setting

The present study was conducted at a 260-bed acute-care hospital in Schaffhausen, Switzerland. The data from the four major departments (surgery, internal medicine, obstetrics-gynecology and the interdisciplinary intensive-care unit) have been analyzed, amounting to approximately 65,000 to 70,000 patient-days per year.

Antibiotic Consumption

The hospital pharmacy's annual analysis of the amount of antimicrobials delivered to all of the departments in the hospital has been calculated in two different ways:

a) In gram of substance; this parameter showed the total amount of the drugs used in the hospital.

b) In number of courses; this parameter indicated, how many times the decision to use amoxicillin-clavulanate was made. This was of particular interest because the interventions taken concerned the prophylactic use of the drug, as well as the dosages. The following assumptions have been made: (1) the quantities of prophylactic courses were known from a survey of all surgical patients in 1993 and from the number of hysterectomies and cesarean sections performed in the hospital; (2) for therapeutic use, an average duration of treatment of 7 days has been assumed for the ward and 3 days for the intensive-care unit (according to the average length of stay in that unit).

Surveillance of Resistance

Data from routine resistance testing in the microbiology laboratory were analyzed using a computer program (ResiMed, written by M. L. Mueller and C. Conrad (21)). The system eliminated duplicate specimens if the isolates came from the same patient in the same material and with the same resistance

pattern. The fact that isolates from multiple sites from the same patient are included in the analysis did not have any influence on the results.

Routine resistance testing was performed by the disc diffusion method 22 using culture media from Bio-Life (Milan, Italy) and antibiotic discs from Becton Dickinson Europe (Meylan, France).

Control of the Resistance Testing

Between November 1994 and February 1995, 30 consecutive isolates determined by routine testing to be intermediately sensitive to amoxicillin-clavulanate were collected. Their susceptibility was tested again using materials from different manufacturers. For the disc diffusion method, (22) antibiotic discs from Becton Dickinson, as well as from Sanofi (Sanofi Diagnostics Pasteur, Marnes La Coquette, France) were used. To determine the minimum inhibitory concentrations, E-Test-strips (AB Biodisk, Solna, Sweden) were used. Both methods were performed on culture media from Bio-Life, as well as from Sanofi. The interpretation of the results was made according to the guidelines of the National Committee for Clinical Laboratory Standards. (22)

Interventions

To influence the use of amoxicillin-clavulanate, the following interventions were undertaken:

- In the guidelines for the prophylactic and therapeutic use of antimicrobials in the department of gynecology and obstetrics, implemented at the beginning of 1993, the use of amoxicillin-clavulanate was abandoned completely. For prophylaxis, amoxicillin was substituted alone, because these patients usually come directly from home and are not expected to carry nosocomial pathogens. For treatment, cefuroxime was introduced instead.

- In the guidelines for treatment of urinary tract infections, introduced in all departments in October 1994, cefuroxime replaced amoxicillin-clavulanate for the indications "pyelonephritis" and "urosepsis".

- In the guidelines for perioperative antimicrobial prophylaxis in the department of surgery, introduced at the beginning of 1995, amoxicillin-clavulanate was replaced by cefoxitin.

- For the treatment of infections caused by Staphylococcus aureus and for soft tissue infections, it was proposed that flucloxacillin be used whenever possible.
- Furthermore, it was advised that amoxicillin-clavulanate be used in a very restricted manner in the intensive care unit.

All of these changes were made in close interdisciplinary collaboration among the physicians, the clinical pharmacist, and the infection control practitioner and on the basis of comprehensive surveillance data. The implementations consisted of oral presentations of the new guidelines, information for all prescribing physicians, and the introduction of the guidelines in the handbooks of the departments. Beginning in 1993, all physicians new at the hospital were trained by the infection control practitioner and the clinical pharmacist about the local situation concerning resistance problems and guidelines for use. Additionally, a consultation service running during working hours and daily ward rounds of the infection control practitioner and the clinical pharmacist were implemented.

Results

Use of Amoxicillin-Clavulanate

The total amount of amoxicillin-clavulanate used decreased over the period of 4 years by 23%, from 24.8 g per 100 patient days in 1992 to 18.5 g per 100 patient days in 1995. The number of courses over the same period dropped by almost 62%, from 2.3 per 100 patient days in 1992 to 0.9 per 100 patient days in 1995. Detailed data are shown in Table 1.

Development of Resistance

There was a continuous increase in the susceptibility in E coli to amoxicillin-clavulanate since 1994. In 1992, 54.9% of the 512 strains isolated were sensitive, and in 1993, 54% of 506 strains were sensitive. But this percentage increased in 1994 to 72.1% (n=546), and in 1995 to 83.1% (n=668). Surprisingly, in 1992 a high percentage of intermediate strains were isolated, 27.9%, which decreased to 11.2% in 1995. In 1992, 17.2% of strains were resistant, and this figure decreased to 5.7% in 1995. The detailed data are summarized in Table 2.

Table 1: Consumption of amoxicillin-clavulanate by service and year

	Use per 100 Patient Days									
	Surgery		Internal Medicine		Obstetrics-Gynecology		Intensive-Care Unit		Total	
Year	Grams	Courses	Grams	Courses	Grams	Courses	Grams	Courses	Grams	Courses
1992	22.0	2.4	23.3	1.4	23.7	3.6	98.8	6.8	24.8	2.3
1993	22.5	2.2	27.9	1.3	2.3	0.2	70.1	4.0	22.5	1.5
1994	19.9	2.0	21.5	1.0	1.1	0.1	53.3	3.0	18.2	1.3
1995	17.3	0.8	24.2	1.1	2.7	0.2	52.7	3.3	18.5	0.9
1995 vs. 1992	-21.4%	-65.5%	+3.8%	-24.3%	-88.6%	-95.2%	-46.6%	-51.3%	-23.0%	-61.8%

Table 2: Resistance in Escherichia coli to amoxicillin-clavulanate by service and year

	Percentage of Strains Categorized as (R)esistant, (I)ntermediate, and (S)ensitive														
	Surgery			Internal Medicine			Obstetrics-Gynecology			Intensive-Care Unit			Total		
Year	R	I	S	R	I	S	R	I	S	R	I	S	R	I	S
1992	32.4	23.4	44.2	14.7	30.7	54.6	6.8	39.0	54.2	34.9	30.2	24.9	17.2	27.9	54.9
1993	23.0	21.2	55.8	16.7	31.0	52.3	14.5	26.1	49.4	29.3	27.6	43.1	16.8	29.2	54.0
1994	24.7	25.3	50.0	2.9	21.4	75.7	0	17.0	83.0	36.2	24.6	39.1	9.2	18.7	72.1
1995	5.1	11.3	83.6	7.9	13.0	79.1	7.7	13.9	78.4	6.3	12.5	81.3	5.7	11.2	83.1

Use and Resistance of Other Antimicrobials

Three other antimicrobials used over the 4-year period from 1992 to 1995 were evaluated: cotrimoxazole, tetracycline and cefuroxime. No major changes in susceptibility could be detected. The susceptibility of E coli remained stable to cotrimoxazole and tetracycline with 80.7% to 87.6% and 68.3% to 75.7%, respectively, and even increased to cefuroxime from 87.4% to 96.8%. The amount of the drug used varied for cotrimoxazole, doubled for tetracycline and increased 10-fold for cefuroxime (Table 3).

The use of broad-spectrum antimicrobials increased from 1992 to 1995, but no changes were detected in the resistance pattern of E coli. Because these substances were not in use during the entire 4-year period, the data are not shown in detail.

Table 3: Consumption and resistance patterns of other antimicrobials from 1992 to 1995 (all departments)

	Use in Grams per 100 Patient Days (% Sensitive)			
Antibiotic	**1992**	**1993**	**1994**	**1995**
Cotrimoxazole	4.8 (86.1)	10.5 (87.6)	5.4 (80.7)	3.3 (84.1)
Tetracycline	0.0 (71.4)	0.1 (68.3)	0.1 (69.5)	0.1 (75.7)
Cefuroxime	0.4 (87.4)	0.8 (94.6)	0.9 (95.4)	3.7 (96.8)

Validation of the Routine Resistance Testing

Control assays of intermediate strains from the routing testing yielded homogeneous results. For the agar disc diffusion tests, the diameters measured lay between 11 and 21 mm and their averages between 14.5 and 16.6 mm, depending on the materials used. Determination of the minimum inhibitory concentration by E-test resulted in values from 4 to 16 μg/ml, with averages between 10.3 and 11.8 μg/ml. The different test media yielded the same results.

Cross-Resistance

E coli strains with decreased susceptibility to amoxicillin-clavulanate also had decreased susceptibility to first-generation cephalosporins, cotrimoxazole, and tetracycline, and, to a lesser extent, to second- and third-generation cephalosporins (Table 4). There were only a few strains intermediately sensitive or resistant to tobramycin, imipenem, or piperacillin-tazobactam.

Table 4: Cross-resistance in E Coli in 1992 and in 1995, isolates of all departments

	1992			1995		
Resistant to:	**AMC-sensitive**	**AMC-intermediate**	**AMC-resistant**	**AMC-sensitive**	**AMC-intermediate**	**AMC-resistant**
Ceph-1	61.2%	97.9%	95.3%	20.7%	85.3%	79.0%
Ceph-2	0%	3.4%	24.7%	1.2%	8.0%	21.1%
Ceph-3	0%	0%	4.7%	0.2%	0%	2.6%
Tetracycline	18.3%	41.2%	56.4%	18.1%	54.6%	52.7%
Cotrimoxazole	2.9%	21.0%	27.1%	10.9%	38.6%	44.7%

Abbreviations: AMC, amoxicillin-clavulanate; ceph-1, first-generation cephalosporin; ceph-2, second-generation cephalosporin; ceph-3, third-generation cephalosporin

Discussion

In the present study, a decrease in the use of amoxicillin-clavulanate was followed by an increase in susceptibility of E coli to it. The reduction in the amount of amoxicillin-clavulanate use was achieved mainly through the introduction of treatment guidelines into daily clinical practice, in which alternative antibiotics were suggested whenever possible.

It is not possible to show a causative relationship between these two parameters, but there was a clear temporal association between antibiotic-use restriction and resistance patterns.

During the study period, a dramatic increase in the use of cefuroxime occurred. Thus far, this has not had any adverse effect on resistance rates. However, use and susceptibility must be monitored closely in the future, because follow-up monitoring of the present study was short, with only 4 years' worth of data.

The high percentage of intermediate strains in E coli raised doubts as to the appropriateness of the routine-testing. However, control tests performed with materials from different manufacturers yielded the same results and thus confirmed the data.

The mechanism of resistance was not proven, but analysis of the pattern of cross-resistance could imply that the cause of resistance may be overproduction of TEM-1 β-lactamases, as described in the introduction.

An important aspect of the present study was that all actions were taken in close collaboration with the clinical pharmacists, the infection control practitioner, the microbiology laboratory, and the physicians in charge of the respective departments. This interdisciplinary approach facilitated the implementation of the necessary measures. Ongoing surveillance of the development of resistance, as well as the use of antibiotics in a specific setting, are an important procedural basis from which to detect any adverse events as soon as possible and to take appropriate measures. This procedure will allow control over, and will restrict the use of, antibiotics, as well as the development of resistance.

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CHAPTER II

Application of the ATC/DDD methodology to monitor antibiotic drug use

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Eur. J. Clin. Microbiol. Infect. Dis. 1998;17:20-24.

Abstract

Objective: In order to monitor the use of antibiotics, it is essential to have comprehensive data on drug consumption. The findings of drug utilisation studies can serve to describe the pattern of drug use in a particular population, to detect areas of concern, and to evaluate the impact of interventions taken to influence the use of drugs.

Methods: Application of the Anatomical Therapeutical Chemical Classification/Defined Daily Doses (ATC/DDD) system developed by the World Health Organisation. The system measures the amount of drug used independent on package sizes and sales price, which allows comparisons not only within an institution but also within a region, a country or even internationally. To illustrate the method, the pattern of quinolone use in the general population, in long term care facilitites and within a single institution was analysed.

Results: Quinolones were widely used in long-term care facilities in the Nijmegen region of The Netherlands, accounting for about 30% of the antibiotics used in these settings, whereas in the general population as well as in the University Hospital Nijmegen, these drugs constitute only about 6% of the total antibiotics used.

Conclusions: These differences are large enough to warrant closer analysis of patterns of antibiotic usage in different settings to identify the reasons for the use of quinolones and to identify measures that might be taken to rationalise the prescription of these drugs.

Introduction

The monitoring of patterns of antibiotic use is very important because of the development of resistance worldwide (1-4) and because of the growing costs of these expensive groups of drugs. (5-7) Reliable data on drug consumption are, therefore, crucial and should ideally be based on the treatment of individual patients. However, as such data are seldom readily available, drug utilisation studies are performed to analyse management data (8-10) obtained over a certain period of time or to evaluate the effects achieved by therapeutic interventions. (11-13) Moreover, the patterns of use in different settings or by different prescribers need to be compared in order to obtain the information necessary to devise and update prescribing policies as well as to provide proper feedback to the prescribers. (14,15)

A methodology that is independent of sales prices and package size is preferable in order to obtain reliable and useful data on drug consumption. The Anatomical Therapeutical Chemical Classification/Defined Daily Doses (ATC/DDD) system developed by the World Health Organisation (WHO) (16) is one such approach widely used in northern Europe. It provides a convenient tool (17-20) that allows comparisons between different settings, regions or even countries. The quality of the results is completely dependent upon strict adherence to the method, but we have noted variations in its application. Therefore, we assessed the advantages and disadvantages of the system by examining the use of quinolones in different settings, as these drugs are often used improperly (21,22) and because serious concerns have been raised about the development of resistance. (23-27)

Materials and Methods

The Anatomical Therapeutical Chemical Classification/ Defined Daily Doses system

The ATC/DDD-system was developed by the Drug Utilization Research Group of the WHO as a tool for pharmacoepidemiology to measure, analyse, and influence the use of drugs and to detect changes over time. To this end, a comprehensive and logical classification system was developed to categorise drug substances, which were divided into different groups according to the organ or system on which they act (anatomic), and then according to their therapeutic, pharmacological and chemical characteristics. This is illustrated in Table 1 by the complete ATC classification of ciprofloxacin.

Table 1: The Anatomical Therapeutical Chemical (ATC) classification of ciprofloxacin (adapted according to the WHO guidelines)

ATC code	ATC level	Description
J	Main anatomic group	general anti-infective agents for systemic use
J01	Therapeutic group	antibacterial agents for systemic use
J01M	Pharmacological group	quinolone antibacterial agents
J01MA	Pharmacological subgroup	fluoroquinolones
J01MA02	Chemical substance	ciprofloxacin

The amount of a substance used also must be measured in order to enable comparisons in drug utilisation studies. This led to the assignment of defined daily doses (DDD) to every substance used. This is a technical unit of measurement and does not necessarily reflect the recommended or actual dose used. Rather, it should be considered as an international compromise based on a review of the available data at a particular point in time. Usually it is based on the average dosage for the main indication in adults with normal organ function and related to the population analysed. The number of DDDs per 1000 persons per day is usually used for studies performed in the general population, whereas the number of DDDs per 100 bed-days is preferred for inpatients. These figures allow drug use to be compared in different countries, regions, hospitals, or hospital wards.

Sources of information

We chose to illustrate the method by examining the use of quinolones in comparison to the total use of antibiotics in different populations in the Netherlands. The information on drug use in the general population was obtained from the PHARMO RLS database, established by a specialist group in pharmaco-epidemiology and pharmacotherapy based at the Faculty of Pharmacy in Utrecht, (28) which now contains the complete medication histories of more than 500,000 patients in six cities in the Netherlands.

The data for inpatients was collated from the pharmacy statistics collected in the University Hospital Nijmegen and was based on the amount of drugs delivered to the wards over a single year.

Results

Use of Antibiotics in the General Population

An average of 8.3 DDD/1000 persons/day of antibiotic was consumed in the general population of the Netherlands in 1994 (Table 2). This increased from 6.6 DDD/1000 persons/day for people younger than 44 years to 19.0 DDD/1000 persons/day for those older than 75 years of age. Men younger than 44 years consumed 5.5 DDD/1000 persons/day and those older than 75 years of age 23.0 DDD/1000 persons/day. The respective figures for women were 7.6 DDD/1000 persons/day and 16.9 DDD/1000 persons/day. The consumption of quinolones was 0.5 DDD/1000 persons/day, and made up an average of 6% of the total use of antibiotics, with 2.7% being consumed by those younger than 44 years and 13.9% by those above 75 years of age; there was no difference in use between men and women.

Use of Antibiotics in Long-Term Care Facilities

The amount of antibiotics used in 1995 in long-term care facilities depended largely on the category of patients admitted (Table 3). Drug use in five institutions varied between 6 and 10 DDD per 100 bed-days, whereas the amount was much lower in the only psychiatric institution (no. 5 in Table 3), in which 2.3 DDD per 100 bed-days were consumed. Quinolones accounted for 24 to 38% of the total antibiotics used; this was again lower in the psychiatric institution, where they accounted for only 16% of the total.

Use of Antibiotics in the University Hospital Nijmegen

The average use of antibiotics in the University Hospital Nijmegen amounted to 47.3 DDD/100 bed-days and varied between 22.2 DDD/100 bed-days for the combined department of neurology, psychiatry and geriatrics to 169.0 DDD/100 bed-days for the department of anaesthesiology and intensive care (Table 4). Overall, quinolones accounted for 3.1 DDD/100 bed-days or 6.6% of the total antbiotics used. The use of quinolones as a percentage of total antibiotics used varied from 2.3% in the combined departments of dermatology and ear, nose, and throat to 10.9% in the department of internal medicine.

A wide range of results can be found within a specific department, so closer analysis of the Department of General Internal Medicine was undertaken. and showed that the haematology and oncology wards used the largest amount of

Table 2: Data from the PHARMO-RLS database of the University of Utrecht for 1994

User group	No. of persons	DDD/1000 persons/day					
		All antibiotics			Quinolones		
		Men+ Women	Men	Women	Men+ Women	Men	Women
Age 0-44 years	250,147	6.6	5.5	7.6	0.2	0.2	0.2
Age 45-59 years	63,523	8.9	7.9	10.1	0.6	0.6	0.6
Age 60-74 years	41,347	13.1	14.5	11.9	1.4	1.7	1.1
Age >75 years	16,824	19.0	23.0	16.9	2.7	3.2	2.4
All ages combined	371,841	8.3	7.4	9.1	0.5	0.5	0.5

Table 3: Use of antibiotics in long-term care facilities in the Nijmegen region in 1995

Institution no.*	No. of beds	Total DDD per 100 bed-days (all antibiotics)	Quinolones	
			DDD per 100 bed-days	Percentage of total
1	250	6.7	1.9	27.5
2	100	9.7	2.8	29.1
3	198	9.3	2.7	28.5
4	150	6.1	2.3	38.5
5	180	2.6	0.4	16.7
6	234	6.6	1.6	24.0

* Nr. 1 is a psycho-geriatric nursing home, Nr. 5 is a psychatric institute, the others are general nursing homes for patients > 65 years of age.

antibiotics, accounting for 126.0 DDD/100 bed-days, with quinolones accounting for 36.6 DDD/100 bed-days, or 29.1% (Table 5).

Discussion

In the ATC-classification, substances are classified according to their main therapeutic use. The coding is important for obtaining accurate information in epidemiologic studies. (29) The five different levels allow comparisons to be made at various levels according to the purpose of a study. For antimicrobial agents, the J group as a whole indicates the systemic use of antimicrobials. More distinct analysis can be performed for the antibiotics, group J01, or, at lower levels, group J01M for all quinolones, for example. Even though the system has some drawbacks (30) and alternatives have been proposed, (29, 31) it seems to be quite consistent.

The DDD-system was developed as a technical unit of measurement in order to enable epidemiological comparisons of drug consumption that were independent of differences in price or package size. It is especially useful in long-term studies in which trends are tracked and for making comparisons between different regions, countries, or settings. (19, 20) Therefore, the system must be used without any adaptations. If more detailed information is required

Table 4: Use of antibiotics in the University Hospital Nijmegen in 1995

Ward	No. of bed-days	Total DDD per 100 bed-days (all antibiotics)	Quinolones	
			DDD per 100 bed-days	Percentage of total
All wards combined	238,201	48.0*	3.2*	6.6
Anaesthesiology/ICU	10,505	169.0	7.0	4.1
Paediatrics	32,139	27.0	0.9	3.4
ENT and dermatology	25,971	36.9	0.8	2.3
Internal medicine	58,880	72.3	7.9	10.9
Surgery 1	35,284	31.7	1.2	3.9
Surgery 2	34,373	42.5	1.5	3.6
Neurology/psychiatry/geriatrics	41,049	22.2	1.3	5.6

* Values represent averages for all wards combined. ENT, ear, nose and throat; ICU, inensive care unit.

Table 5: Use of antibiotics in the Department of Internal Medicine of the University Hospital Nijmegen in 1995

Ward	No. of bed-days	Total DDD per 100 bed-days (all antibiotics)	Quinolones	
			DDD per 100 bed-days	Percentage of total
All wards combined	58,880	72.3*	7.9*	10.9
Haematology and oncology	7,727	126.0	36.6	29.0
Gastroenterology and nephrology	10,350	48.3	3.8	7.9
Cardiology	8,771	70.8	0.7	1.0
Rheumatology	6,470	43.7	2.6	5.9
Other departments with mixed pathology	25,562	69.7	4.2	6.0

* Values represent averages for all internal medicine departments combined.

on the indications for the prescribing, the variations in individual dose, and the therapeutic outcome, it must be sought separately. (18, 30) When problem areas are detected, more elaborate studies, such as prospective surveillance, can then be conducted to provide the detailed information necessary for a clinical judgement of therapeutic quality. (32) The method is not without some disadvantages. First, DDDs have not been established for some types of drugs (e.g. preparations for topical use, sera and vaccines, antineoplastic drugs, anaesthetics or contrast media). Second, the therapeutic maintenance dosage for an adult person of 70 kg of bodyweight and normal organ function is usually taken as a basis, making it impossible to draw any conclusions on the use in children or in patients with renal failure. Lastly, the prophylactic use of a given substance is not reflected in these data making target studies on drug utilisation necessary.

In our practical example, we showed that quinolones account for about 6% of the total amount of antibiotics used in the total population of the Netherlands as well as in the acute care setting of a university hospital. From the available data, it can be seen that relatively more quinolones are prescribed for elderly people than for younger people. Within the hospital, this value varies considerably, depending on the department, i. e., the patient population. Not surprisingly, the highest amount is used in the department of internal medicine and, more specifically, within the haematology and oncology wards. This is related primarily to the prophylactic use in neutropenic patients. (33)

A completely different picture becomes apparent from the analysis of the use in long-term care facilities, where quinolones accounted for a surprisingly high average of around 30% of the antibiotics used. This was unexpected, considering the many warnings about the use of quinolones and the development of resistance; it warrants further analysis to determine whether this is a general pattern in these facilities. If so, then the indications for the use of these drugs in this setting should be more clearly defined. It should also be established whether patients in long-term care facilities are suffering from recurrent infections with resistant organisms or whether they receive these drugs prophylactically in association with bladder catheterisation. Finally, the implications of this pattern of use for the development of resistance should be determined. Once identified, the indications should be compared with those employed in the general population. Last, but not least, an analysis of the pattern of resistance in microorganisms isolated from the respective populations should be undertaken.

Comprehensive analysis of data on the use of antibiotics can provide a clear indication of the actual pattern of use, which may allow areas of concern to be defined and appropriate measures to be developed and implemented in order to influence the use of antibiotics. (34) This is especially important, given the many problems related to antibiotic use, such as the development of resistance, relatively high costs, and the incidence of adverse reactions. Furthermore, such analysis may lead to better use of antibiotics in the population at large.

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CHAPTER III

Use of fluconazole in daily practice: still room for improvement

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Abstract

Objective: To perform a comprehensive evaluation of the use of fluconazole, in order to assess the prescribing practices in daily clinical practice.

Methods: One hundred courses of fluconazole treatment in a university hospital and 81 courses in a non-university teaching hospital have been analysed in a prospective audit. The quality of treatments was assessed by an infectious disease specialist and a pharmacist according to standard guidelines.

Results: In the non-university hospital, prescribed dosages were lower than in the university hospital, and often below the recommended dose. Mean duration of treatment for oesophageal candidosis and disseminated infections was considerably shorter in the non-university hospital compared with the university hospital, and often judged too short. Microbiological samples were examined in 75% of the cases in both hospitals. The expert reviewers agreed with the indication to use fluconazole in 58%-100% of cases in the university hospital and 42%-80% in the non-university hospital, depending on the type of infection.

Conclusions: There did not appear to be a major problem with inappropriate use of fluconazole. However, important issues for improvement could be identified, such as increasing the dosage and duration of treatment in cases of serious infections, and withholding treatment from patients with colonisation rather than infection.

Introduction

World-wide, there is an increasing incidence of fungal infections. (1) This may be owing to a growing number of immunocompromised hosts, such as granulocytopenic cancer patients, (2) organ transplant recipients and AIDS patients, as well as to the escalating use of broad-spectrum antibiotics in patients in haematology wards and intensive care units. (3) Fluconazole is one of the best tolerated antifungal drugs available, with good activity against most yeast species. It has favourable pharmacokinetic properties with an oral bioavailability of >90%, a half-life of approximately 30 h and good penetration into tissues. (4) Furthermore, the drug has a wide therapeutic range, with little toxicity. (5) These properties inherently lead to a low threshold of prescribing, which gives rise to concerns about the quality of use. It has been suggested that the increasing use of fluconazole has concurred with a rising incidence of Candida non-albicans strains that have a reduced susceptibility for fluconazole. (6-12) Although the proof of a causative role has been lacking, fluconazole should be prescribed with caution and on strict indications to reduce the potential development of resistance. In addition, administration may induce drug interactions thereby influencing the effect of other prescribed drugs. The aim of this study was to perform a comprehensive evaluation of the use of fluconazole, in order to assess the prescribing practices in daily clinical practice. A prospective audit of the use of fluconazole was undertaken in two different hospitals, a university and a non-university hospital in The Netherlands.

Materials and Methods

The study was performed in two hospitals, a 980-bed university hospital (hospital A) and an 820-bed non-university teaching hospital (hospital B), for 9 and 12 month periods, respectively. Consecutive adult patients receiving a prescription for fluconazole were included in the study. Patients in the haematology department receiving fluconazole as part of a standard prophylaxis protocol were excluded. The clinical notes and drug charts were reviewed. The reason for initiation of fluconazole, the underlying disease, the dosage, means of administration and duration of therapy, previous and concomitant treatment with antibiotics or other antifungals, and outcome of the treatment were recorded on data collection sheets. Results of microbiological tests were obtained from the computer databases of the microbiology departments.

Assessment of therapy

Each course of fluconazole treatment was assessed by B.J.K. (infectious diseases specialist) and S.N. (pharmacist) on the basis of current guidelines employed in the hospitals and national and international recommendations. Recently published comprehensive guidelines were in press at the time of the evaluation, (13, 14) but there was agreement among experts on principles of antifungal treatment and several recommendations and reviews on the subject had been published in The Netherlands. (9, 15, 16) Table I is a compilation of these and represents the guidelines applied to this evaluation.

The percentage agreement with indication, dosage and duration of treatment was determined using a standardized method for antimicrobial drug use evaluation, developed by Gyssens et al. (17) The indications were subdivided into superficial infections (oral and vaginal candidosis and skin infections), oesophageal candidosis, disseminated infections (catheter-related infections, bloodstream infections, presumed systemic fungal infection), deep localised infections (pneumonia, urinary tract infections, peritonitis, meningitis) and prophylactic treatments.

Laboratory investigations

Blood (at least 15 ml) was cultured aerobically with using the Bactec 9240 (Becton-Dickinson, Woerden, The Netherlands) in hospital A and with the BacT/Alert (Organon Teknika, Boxtel, The Netherlands) automated system in hospital B.

In hospital A, Candida isolates were processed in the local specialist mycology laboratory. In hospital B, isolates were processed in the general microbiology laboratory.

Candida albicans was identified by germ tube and chlamydospore formation. Suspected Candida dubliniensis or germ tube negative isolates were further identified with the Auxacolor commercial yeast identification system (Biorad, Marnes-La-Coquette, France). Yeast susceptibility testing was performed by broth dilution according to the NCCLS. (18) Interpretative breakpoints of fluconazole were applied as proposed by Rex et al. (19)

Table I: Treatment recommendations for Candida infection (modified according to ref 9,13-16)

Indication	Recommended therapy	Dosage of fluconazole
Superficial infection		
Oropharyngeal infection	Oral azoles[a], oral polyenes[b], iv amphotericine B if refractory	100mg/day for 7-14 days
Vaginal infection	Topical[c] or oral azoles	150mg single dose
Skin infection	Topical or oral azoles	100mg/day
Oesophageal candidosis	Oral azoles, iv amphotericin B if refractory	100-200mg/day for 14-21 days
Disseminated infection	Iv amphotericin B, oral or iv fluconazole, comb. with flucytosine may be considered	400mg/day until 2-4 weeks after last positive blood culture
Deep localized infections		
Pneumonia	Iv amphotericin B or fluconzole	400mg/day
Intra-abdominal infection	Iv amphotericin B, oral or iv fluconazole	400mg/day for 2–3 weeks
Meningitis	Iv amphotericin B, flucytosine may be added, iv fluconazole	Until 4 weeks after resolution of all symptoms
Urinary tract infection	Oral or iv fluconazole, iv amphotericin B, oral flucytosine	200mg/day for 7-14 days
Prophylaxis		
AIDS and cancer patients	Oral fluconazole or itraconazole	100mg/day
Neutropenic patients and solid-organ transplantation	Oral or iv fluconazole, iv amphotericin B, oral itraconazole	150-400mg/day

[a]Oral azoles: fluconazole, ketoconazole, itraconazole; [b]Oral polyenes: nystatin, ampohtericin B susp.; [c]Topical azoles: clotrimazole, miconazole and others

Table II: Indications for which fluconazole was prescribed and the microorganisms isolated

Indication	Hospital A	Hospital B
Total	100	81
Superficial infections	33	23
Oropharyngeal	31	19
Vaginal	2	3
Skin	--	1
Oesophageal candidosis	13	18
Disseminated infection	28	21
With positive blood cultures	15	2
Positive cultures from other sites	13	19
Deep localized infections	15	12
Pneumonia	--	6
Intraabdominal infection	4	1
Meningitis	4	--
Urinary tract infection	5	4
Parotitis	1	--
Pleural infection	1	--
Dysbacteriosis of the gut	--	1
Prophylaxis	11	5
Not documented	--	2
Micro-organism isolated	63	53
Candida albicans	46 (73%)	46 (87%)
Candida glabrata	11 (17%)	4 (7.5%)
Candida tropicalis	2	1
Candida krusei	1	1
Candida parapsilosis	--	1
Cryptococcus neoformans	2	--
Sporobolomyces spp.	1	--

Results

One hundred consecutive courses of fluconazole in 88 patients in hospital A and 81 courses in 81 patients in hospital B were included in the study. The distribution of the various indications is shown in table II. For the two hospitals, expert reviewers agreed with the indications in 72% and 63%, respectively.

Prescribed dosages

On average, higher dosages were prescribed in hospital A compared to hospital B. (Figure 1) The evaluation revealed least agreement with the dosage in cases of oesophageal candidosis, because of rather low dosages prescribed in both hospitals, in disagreement with the guidelines. In hospital B in particular, prescribed dosages for all indications often tended to be lower than those recommended.

Duration of treatment

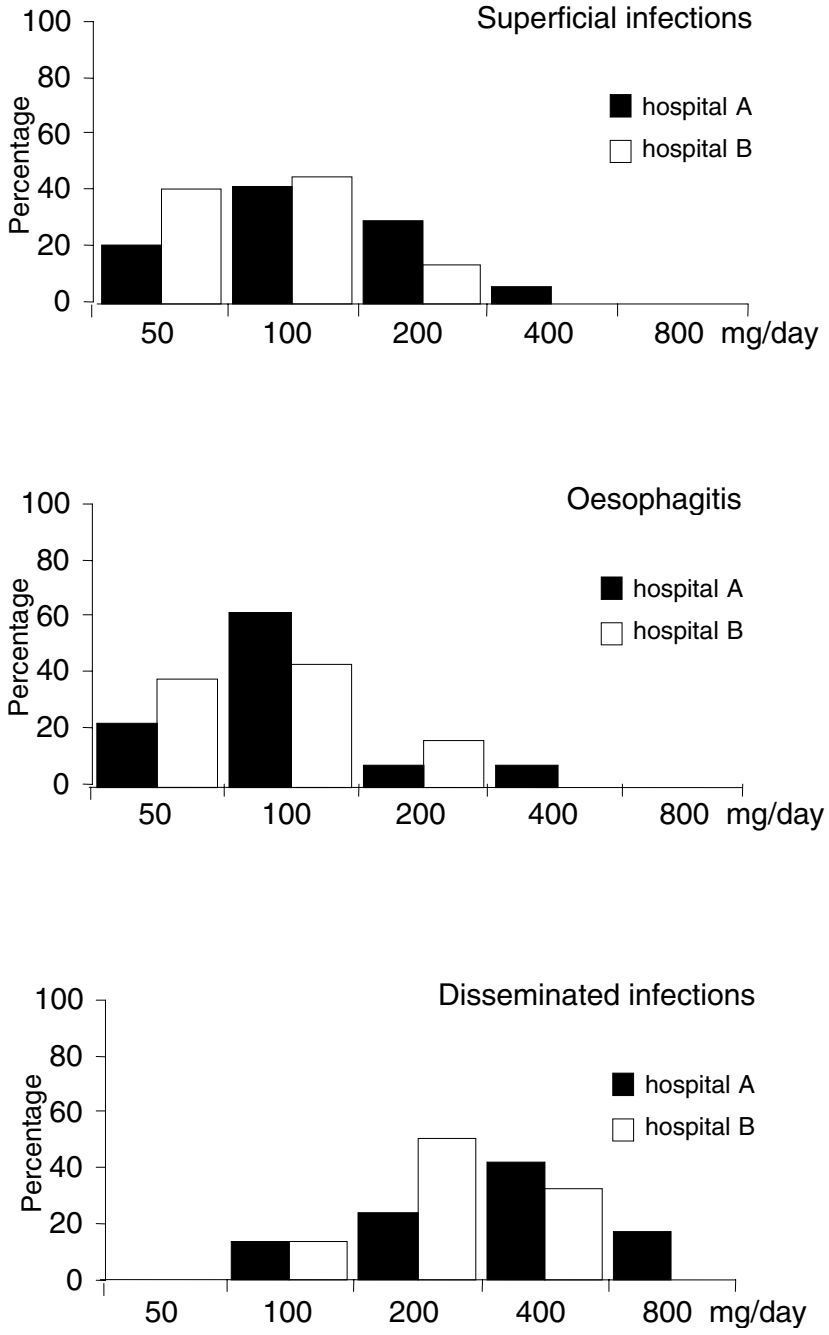
Patients who died during treatment or who were switched to another antifungal treatment, were excluded from the evaluation of duration of treatment (Figure 2). The mean duration of treatment for oesophageal candidosis and disseminated infections was considerably longer in hospital A than in hospital B ($P=0.03$ and $P=0.006$ respectively). The reviewers agreed with the duration of treatment in only 40-50% of cases of oesophageal candidosis, mainly because the prescribed courses of treatment were considered to be too short. Also for disseminated infections, duration of treatment was considered too short in 60% of cases in hospital B.

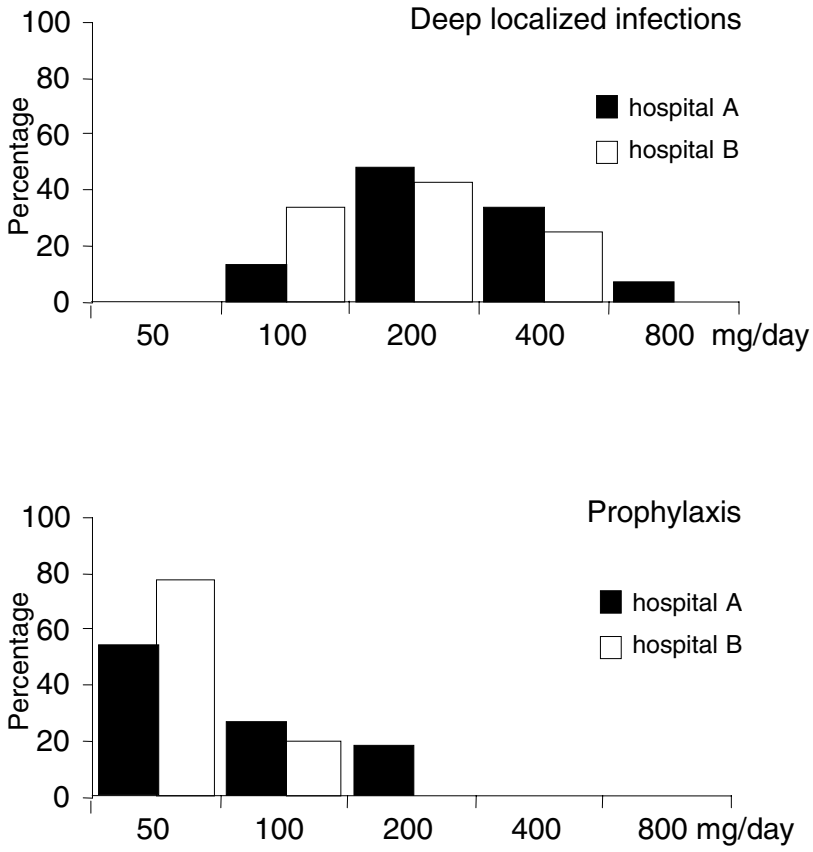
Microbiological results

Culture results were available in 75% of the cases. In 84% and 87% of these cases from hospital A and B, respectively, the isolate was identified. In hospital A, Candida albicans was found in 73% of the cases and Candida glabrata in 17%. In hospital B, C. albicans was isolated in 87% and C. glabrata in only 8% (table II).

Susceptibility to antifungal agents was determined for 18 Candida isolates in hospital A and six isolates in hospital B. All isolates of C. albicans tested were susceptible to fluconazole (MIC $\leq$ 4 mg/l). Four of the 15 isolates of C.

Figure 1. Percentage of patients receiving each dosage of fluconazole for different indications





glabrata were resistant (MIC ≥ 64 mg/l), one isolate was susceptible-dose dependent (MIC 16 mg/l), six were susceptible (MIC ≤ 8mg/l), and for four isolates, resistance was not determined. In three patients with resistant C. glabrata isolates, treatment was changed to itraconazole after obtaining the in vitro susceptibility results, and in one patient, the dose of fluconazole was increased to 800 mg/day. The patient with the susceptible dose-dependent isolate first received higher doses of fluconazole and was later switched to amphotericine B. Of the four patients of whom the susceptibility of the isolate was not known, one was switched to itraconazole, one suffered from a urinary tract infection, which was successfully treated with a single dose of 400 mg of fluconazole and two died of other medical complications of their underlying disease within 2 and 40 days, respectively, after initiation of fluconazole treatment.

Superficial infections

The reviewers disagreed with the indication in 40% of the cases of presumed superficial candidosis in both hospitals. Reasons for disagreement were lack of culture results after failure of another antifungal treatment, or negative culture results. Seventeen patients in hospital A and six patients in hospital B had received prior antifungal therapy. Agreement with the prescribed dosage was 82% in hospital A and 56% in hospital B. In hospital A, disagreement was due to the administration of higher than recommended dosages, while in hospital B the prescribed dosages were too low. There was agreement with the duration of treatment for 82% of cases in both hospitals.

Oesophageal candidosis

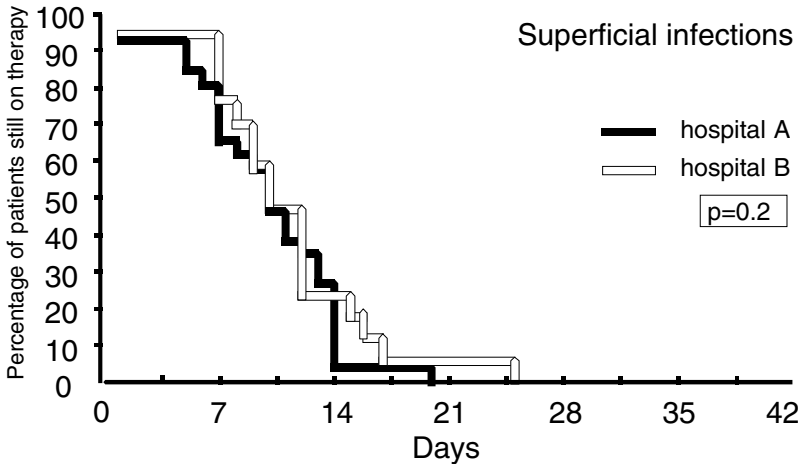
Endoscopy was performed in 61% of patients with oesophageal candidosis in both hospitals. In hospital A, culture samples were taken in 75% of these, while in hospital B, this was the case in only one patient.

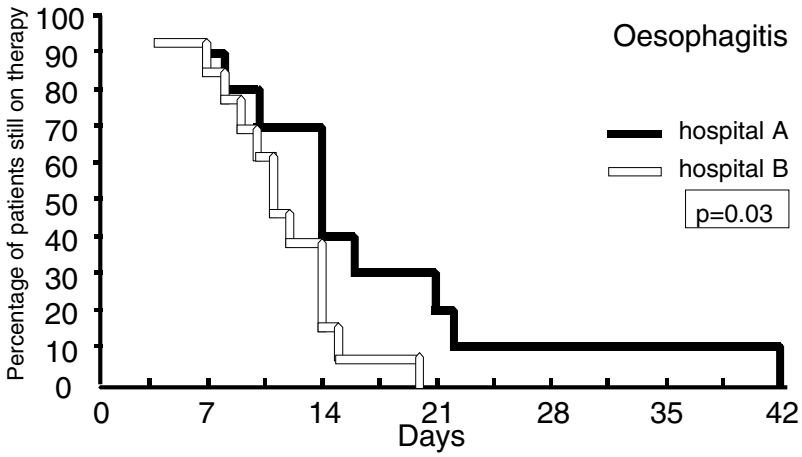
There was agreement with the indication to use fluconazole in 77% of the cases of oesophageal candidosis in both hospitals. Agreement with dosage was 62% in hospital A but only 39% in hospital B largely because of low prescribed dosages. Also, the duration of treatment was judged too short in 46% in hospital A and 61% in hospital B.

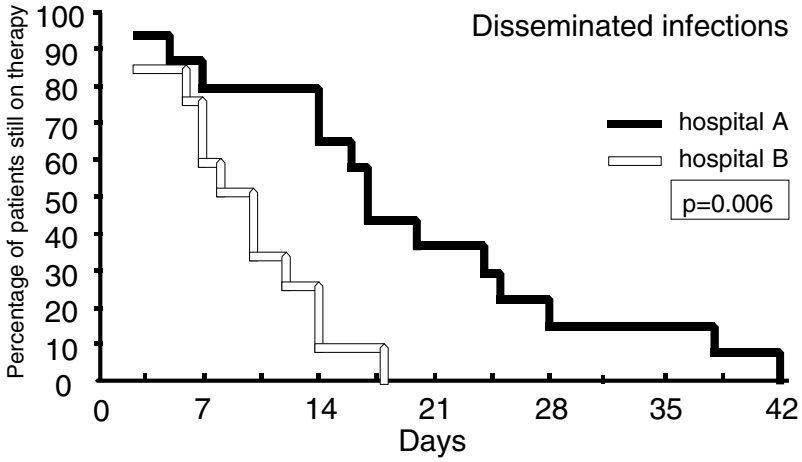
Disseminated infections

Of the 28 patients with disseminated candidosis in hospital A, 15 had positive blood cultures and 13 had negative blood cultures but were presumed to have disseminated infections on the basis of positive cultures from multiple, normally sterile, sites. Treatment of all cases with positive blood cultures was judged adequate, whereas of the cases with negative blood cultures, only six treatments were judged as definitely justified and three as probably justified. In the remaining four cases the indication was not justified, as the culture results were felt to reflect colonization rather than disseminated infection. The prescribed dosage was adequate in those cases in which the indication was thought to be justified, but inadequate if there was disagreement with the indication, in which cases the dose was judged too low for presumed systemic infection.

Figure 2: Duration of treatment with fluconazole







Of the 21 patients diagnosed with disseminated infections in hospital B, only two had positive blood cultures. Four patients had positive cultures of the catheter tip and the insertion site, and were presumed to have a catheter-related infection. Treatment of all of these six cases was considered justified. In 15 patients, presumed disseminated candidosis was diagnosed because of several positive culture results from other specimens. Treatment of seven of these cases was judged appropriate since positive cultures had been obtained from normally sterile sites and the clinical course was compatible with disseminated candidosis (13,20) In the remaining eight cases, the diagnosis of disseminated candidosis was considered inappropriate, since positive cultures were obtained from colonized surfaces only (e.g. bronchus or skin wound), without further clinical signs of invasive infection. Follow up blood cultures during antifungal therapy were not performed routinely in neither hospital.

Deep localized infections

In hospital A, the indication for treatment was considered appropriate in 93% of the cases of deep localized infection, dosage was adequate in 80% and the duration of treatment was adequate in 87% of the cases. In hospital B, the expert reviewers agreed with the indication in only 42% of the cases, mainly because of disagreement with the diagnosis "pneumonia", which had been made on the basis of positive tracheal aspirates or sputum cultures without further signs of invasive infection. Dosage was considered adequate in 83% of the cases, but the duration of treatment was appropriate in only 50% of the cases.

Prophylaxis

Prophylactic use of fluconazole outside standard protocols accounted for only 11% of the indications in hospital A and 6% in hospital B. In these cases, the reviewers agreed with the prophylaxis in 100% and 80% of the cases in hospital A and B, respectively.

Discussion

The general conclusion from this study is that fluconazole is being appropriately prescribed in daily practice. However, there are points that need improvement, especially in the non-university hospital (hospital B). First of all, even though samples for culture have been obtained in many cases, the quality of microbiological examinations could be improved. Cultures should be obtained from all patients with presumed oropharyngeal or oesophageal

candidosis, who are switched to fluconazole after treatment with another antifungal drug has failed. Because of the increasing incidence of Candida spp. other than C. albicans, all Candida isolates should be speciated, especially as some species have very predictable susceptibility profiles, and speciating may therefore guide the choice of antifungal therapy. Susceptibility testing should be performed and reported of all clinically relevant isolates, especially in those cases that are at an increased risk of resistance to fluconazole.

In the non-university hospital (hospital B), the dosage and duration of treatment needs to be addressed. Especially for the treatment of oesophageal and disseminated candidosis, low dosages were prescribed for a rather short duration, which does not follow the current treatment guidelines.(13)

Another point of concern is the use of fluconazole in cases of colonisation rather than true infection. This is the case in the patients diagnosed as suffering from "Candida pneumonia", which is based solely on isolation of Candida from bronchial secretions. (21) Also in the case of presumed disseminated infections, diagnosis was based on positive cultures from sites indicative of colonisation leading to disagreement with the indication in this situation.

The study was performed in two different hospitals, a university and a non-university hospital. The most important differences detected were the lower dosages and the shorter duration of treatment prescribed in the non-university hospital. Another interesting difference was the lower prevalence of disseminated infections with positive blood cultures in the non-university hospital, which is probably due to a patient population that is less severely ill or the fact that blood cultures are less likely to be taken in this setting. Finally, the use of fluconazole in cases of colonisation was more prevalent in the non-university hospital, as was reflected by the observation that Candida pneumonia was diagnosed six times during our study, whereas none of these diagnoses could be substantiated.

There are very few data in the literature to compare with the current study. An audit on antifungal drugs by Gutierrez et al (22) revealed 58% of the regimens to be compliant with a predefined standard. In their study, fluconazole was the drug most often used for non-approved indications, mostly for superficial infection in non-neutropenic patients. In only 20 of the 74 patients studied, were microbiological results known.

Overall, in our drug use evaluation study, we could not detect major inappropriate use of fluconazole. However, it did highlight important issues

and areas for improvement could be identified. Discussion of these issues with the hospital staff, and refinement of local guidelines should result in improved use. Direct feedback of the results of a comprehensive audit of prescribing habits is one of the most successful means of influencing physicians' performance, especially when feedback is supported by a chart review, as we did in our study. (23,24)

Acknowledgement

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CHAPTER IV

Delay in administering first dose of antibiotics in patients admitted to general internal medicine with serious infections

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Eur. J. Clin. Microbiol. Infect. Dis. 1998;17:681-684.

Abstract

Objective: The interval from the time of admission to the emergency room until the administration of antibiotics in patients presenting with a serious infectious disease was analysed.

Methods: Fifty patients presumptively diagnosed in the emergency room as having a serious infection (respiratory tract, urinary tract, erysipelas, fever with neutropenia or bacteremia) needing immediate empirical antibiotic treatment were enrolled in the study.

Results: A median interval from time of admission to administration of antibiotics of 5 hours was determined (range 0.6-3.3 h). The interval was significantly shorter in patients admitted at night than in patients admitted during office hours (3.7 vs. 6.0 h, $P<0.05$). There was no difference with respect to the presenting features, body temperature, laboratory values at presentation or number of cultures performed. In 41 of the 50 patients blood samples were taken for culture. More than 80% of the patients received an antibiotic chosen in accordance with hospital guidelines.

Conclusions: The analysis revealed that the median delay of 5 hours before patients received their initial antibiotic depended on several factors. Attempts to provide optimal antimicrobial therapy should thus concentrate not only on the correct choice and dosage of a drug but also on prompt institution of therapy.

Introduction

Consensus exists among experts that patients suspected of having serious infections such as bacterial meningitis should receive antibiotic therapy as early as possible. However, there are grounds for concern over delay in administration of the first dose of antibiotics in patients admitted to hospital with suspected serious infections. The study of Meadow et al. (1) revealed a median delay of 2 h in children with meningitis. Furthermore, a significant difference was found between the actual interval in daily practice and what medical experts expect it to be. In the literature, the intervals reported between admission and administration of antibiotics range from 2.1 to 8h. (2-7) Talan and Zibulewsky (8) attempted to demonstrate an association between clinical presentation and the time of institution of antibiotic therapy in patients with suspected bacterial meningitis. Although certain clinical factors were shown to be associated with a lesser delay in starting antibiotic therapy, management practices appeared to be of greater importance, representing an area of potentially avoidable delay. In another study of Talan et al. (5), clinical presentation was not shown to be a notable factor accounting for delay in the start of therapy, the most important factor being the location of the patient when antibiotic therapy was initiated, namely the emergency room or the ward. Rollins et al. (7) discovered a delay of nearly 7 h before patients with pneumonia received their first dose of antibiotics. In a quality improvement project with a multidisciplinary approach, they where able to reduce this delay by about 3 h.

In this study we analysed the interval from the time of admission to the emergency room until the administration of antibiotics in patients suspected of having a serious infection needing immediate empirical antibiotic treatment, and attempted to identify any existing clinical management problems.

Patients and Methods

A prospective survey of medical records and prescription charts was carried out at the Division of General Internal Medicine of the University Hospital Nijmegen. Between February and August 1997, a total of 50 patients (28 female, 22 male) admitted to the emergency room and presumptively diagnosed as having a serious infection needing immediate empirical antibiotic treatment were recruited for the study. The mean age was 64 years (range 27-92), with 60% of the patients being over 60 years of age. The presumptive

diagnoses comprised respiratory tract infections (n=18), urinary tract infections (n=12), erysipelas (n=8), fever with neutropenia (n=2) or suspected bacteremia (n=10).

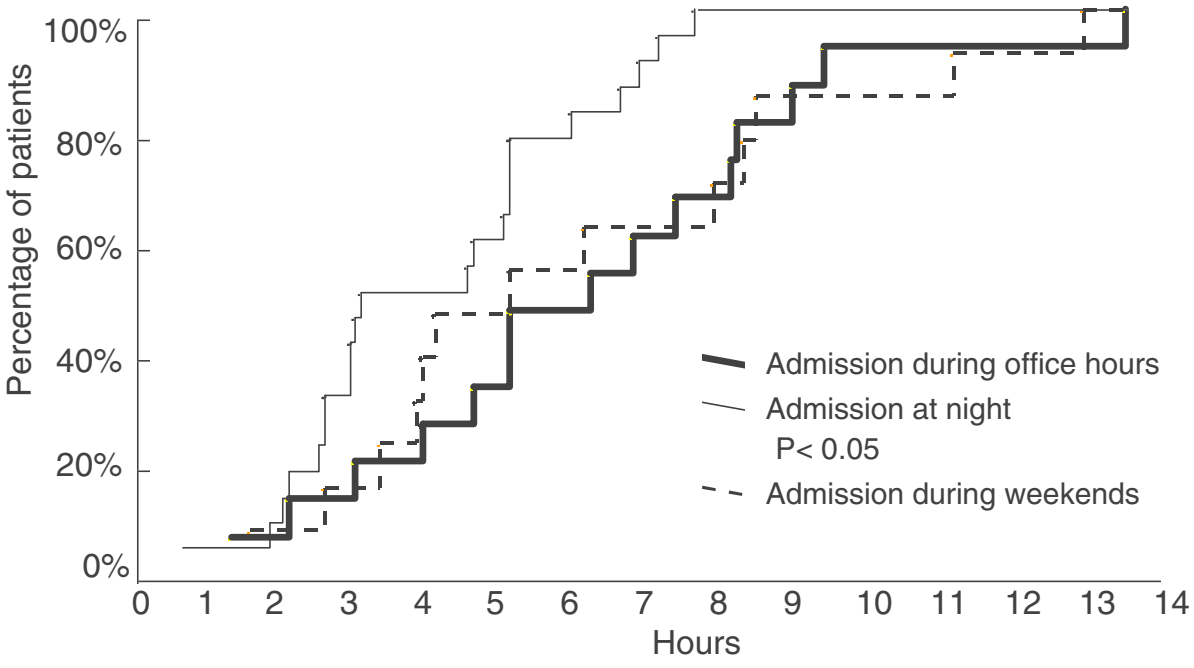
The interval from presentation to the emergency room until the administration of antibiotics and, if possible, the time of taking samples for microbiological investigations were determined. Furthermore, the number of cultures made, the body temperature, the leukocyte count and the ESR at admission were documented.

The Mann-Whitney U test was used to compare the different subgroups of patients.

Results

Overall, the median interval from admission to administration of antibiotics was 5 h, (range 0.6-13.3 h). The interval was significantly shorter in patients admitted at night than in patients admitted during office hours (3.7 vs. 6.0 h, P<0.05). Cumulative histograms for the various times of admission are shown in Figure 1. As shown in Table 1, the nature of the suspected infection did not influence the interval until antibiotic administration.

Figure 1: Interval from time of admission to time of administration of first dose of antibiotics



No correlation could be detected between this interval and the body temperature, leukocyte count, ESR at admission or the number of samples taken for culture before starting therapy (data not shown).

The time of admission of the patients was randomly distributed between 9 a.m. and 11 p.m. However, there was some clustering of the time of administration of antibiotics, 54% of the patients receiving the antibiotic at routinely scheduled application times fixed by the nursing staff, mainly 6 p.m. and 12 p.m.

Table 1: Time between admission and administration of the first dose of antibiotics in patients suspected of having serious bacterial infections

	Median time to administration (hours)
All patients studied	4.96
Admission during office hours	6.08
Admission at night	3.71
Admission at weekends	5.00
Diagnosis of respiratory tract infection	4.96
Diagnosis of urinary tract infection	4.46
Diagnosis of erysipelas	5.41

In 41 of the 50 patients blood samples were taken for aerobic and anaerobic blood culture (in 19 one set, in 16 two sets and in 6 three sets). In 5 of the 18 patients diagnosed as having a respiratory tract infection, a sputum sample was collected before the administration of antibiotics. In 6 of the 12 patients diagnosed as having a urinary tract infection, a urine sample was collected. In 24 patients the time of taking samples for cultures was recorded exactly, the first sample being taken at a median of 1.9 h after admission. After taking the last sample for culture a further median 1.4 h elapsed before antibiotic therapy was started. The median interval between collecting the first and the last sample was 1.2 h.

In only 8 of 50 (16%) patients was the choice of empirical antibiotic therapy not in accordance with hospital guidelines. One patient could not be evaluated, and in 41 patients the choice was considered appropriate.

Discussion

From the findings of this study, an important problem becomes apparent: patients admitted with suspected severe infection experienced often considerable delay, on average 5 h, before receiving their initial antibiotic dose. It should be pointed out that only patients for whom there was a clear and urgent indication for antibiotic therapy were included in this study. Patients not diagnosed in the emergency room as suffering from a bacterial infection were not included.

This delay seemed to depend on several factors, although some of the obvious explanations do not seem to apply. Thus, there was no correlation with the clinical presentation or the type of infection the patient presented with. Also, the time required for the collection of culture samples did not cause any real delay, as these were collected within a median of 1.2 h. It is generally accepted that culture samples should be taken before starting antibiotic therapy; however, this practice need not delay starting antibiotics in severely ill patients. Several techniques are available for making specific bacteriological diagnosis after the start of antibiotic therapy such as antigen detection and culture of samples from remote foci of infection. In those cases where it is essential to obtain culture samples before initiating antibiotic therapy, a written protocol for the procedure might help reduce any delay.

However, other causes of delay in administering antibiotics seem to play a greater role. A step-by-step analysis reveals that patients admitted to the emergency room are first seen by the medical officer on duty. He or she tends to analyse fully the problems a patient presents with and to order the first diagnostic procedures before consulting a senior doctor. As as result of this consultation, supplementary diagnostic measures are often ordered and time is lost waiting for the results; once they are available there is a reevaluation of the patient. Only then is therapy prescribed. By this time, the patients are considered fully evaluated as far as the emergency room is concerned and are transferred to the wards. There, patients are seen by other doctors who tend to reevaluate the situation and delay therapeutic decisions until they have reached their own conclusions. Even when written orders have been given in the emergency room, nurses await orders from doctors on the ward and tend to administer the drugs at the scheduled times. Thus, more than half of the patients in this study received their first dose at scheduled times after transfer to the ward. A number of steps can be taken to help overcome these problems. Firstly, instructions should be given to medical officers on duty that in cases of

suspected serious infections, cultures and other diagnostic measures should be ordered immediately and antibiotics prescribed before full evaluation of the patient. Medical officers should know that antibiotics are stocked in the emergency room and should be administered before transfer of the patient to the ward. Secondly, doctors on the wards should be aware that therapeutic decisions made in the emergency room should be carried out before they have reevaluated the patient themselves. Finally, nurses on the wards must be instructed that if transferred patients have still not received the prescribed antibiotics, they should be administered immediately.

There are two possible explanations as to why patients admitted at night received their first dose of antibiotics more rapidly. One explanation is that at night less people are involved in the management of a patient and decisions are taken more quickly. Another explanation is that patients admitted at night are more seriously ill than patients admitted during the day and the need for immediate treatment is more obvious.

The influence of a delay in the start of antibiotic therapy on the outcome of infection in patients in this study is difficult to estimate. However, studies in patients with meningococcal disease show a reduction in morbidity and mortality when antibiotics are given earlier in the course of the disease. (9, 10) Another study showed an association between an earlier start of therapy and a decrease in the morbidity and length of stay in patients with sepsis. (11) Chattopadhyay and Al-Zahawi (12) reported a highly significant difference in the overall mortality of bacteremia between patients over 60 years of age versus patients below 60 years (5% vs. 36.6%). Most of the patients who died, succumbed within 24 to 48 hours of admission. This authors argue that the most important therapeutic measure is to start antibiotic therapy as soon as possible. In the present study, 60% of the patients were also over 60 years of age.

In our study, the choice of antibiotic therapy did not cause problems as comprehensive hospital guidelines are in force. However, the study showed that medical officers need to take a more active role in initiating antibiotic therapy and that antibiotics should be administered in the emergency room. Furthermore, administrative reasons for delay should be addressed.

Acknowledgement

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CHAPTER V

Earlier initiation of antibiotic treatment for severe infections after interventions to improve the organization and specific guidelines in the emergency department

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Arch Intern Med. 2000;160:1317-1320.

Abstract

Objective: To examine whether combined interventions improve the timely administration of antibiotic therapy and acquisition of material for culture from patients admitted to the emergency department with a serious infectious disease.

Methods: Guidelines and educational programs were developed to facilitate timely antibiotic administration: guidelines on handling patients with serious infections and on ordering immediate treatment, guidelines on obtaining culture samples, lectures to medical and nursing staff, improvement of availability of antibiotics in the emergency department, and removal of financial restraints on stocking and ordering of antibiotics. Fifty consecutive patients were evaluated after this series of interventions and compared with the results in 50 patients evaluated before the interventions. The interval from presentation to the emergency department until the administration of antibiotics, number of samples taken for microbiological investigations, and number of patients receiving a first dose of antibiotic at routinely scheduled drug distribution rounds were evaluated.

Results: The median time to the initial dose of antibiotics administered decreased from 5.0 hours to 3.2 hours (P=.04). The number of blood cultures obtained did not change. The percentage of sputum cultures obtained increased from 28% to 50%, and the percentage of urine cultures obtained increased from 50% to 100%. The percentage of patients whose first dose of antibiotic was delayed until a routinely scheduled drug distribution round decreased from 54% to 32% (P=.03).

Conclusions: Combined interventions to expedite diagnostic and therapeutic actions through directed clinical practice guidelines and organizational measures are successful. This may lead to a substantial quality improvement in the process of care.

Introduction

The acquisition of material for culture and the timely administration of effective antibiotic therapy are widely viewed as basic to the treatment of patients with serious infections. However, with the exception of studies in patients presenting with bacterial meningitis, few data are available that describe these processes.(1, 2)

In a previous study, we analyzed the interval from the time of admission to the emergency department (ED) until the administration of antibiotics in patients suspected of having a serious infection needing immediate empirical antibiotic treatment.(3) We found a median delay of 5.0 hours (range, 0.6-13.3 hours) before patients received their first dose of antibiotics. A step-by-step analysis revealed that this delay depended on several factors.

Whereas the clinical presentation, the type of infection, or the collection of cultures did not influence the delay in the start of therapy, we found that extensive evaluation of the patient by residents and senior staff was a main cause for delay.(3) In addition, the transfer of the patient from the ED to the ward often leads to repeated diagnostic procedures and delay of therapeutic measures. Finally, despite written orders to start antibiotic therapy, nurses tended to delay the administration of antibiotics until routinely scheduled drug distribution rounds fixed by the nursing staff, mainly at 6 PM and 12 PM.(3)

The objective of the present study was to conduct a series of educational and organizational interventions, and to reevaluate the management of patients admitted to the hospital with serious infections, after implementing these interventions designed to improve the process of care. A combined approach was chosen to analyze the barriers to change and implement multiple interventions to change the performance of the health care practitioners. In previous studies it has been shown that a combination of guidelines, formal educational methods, and changes in organization and logistics are successful in changing behavior to improve process outcome and patient care. Methods that are practice based rather than didactic and address the factors that influence practice are more successful in changing professional behavior.(4-8)

Patients and Methods

Statement of the problem

In our previous study we identified a number of causes for the delay in administering antibiotics to patients with serious infections.(3) Obstacles were the belief that patients should be fully evaluated before taking any action, the belief that blood cultures should only be taken with a body temperature above 38.5°C, and that antibiotics were not readily accessible in the ED; hence, patients were transferred to the ward before starting treatment. On the ward, nurses often thought they could wait until the next scheduled drug distribution round for administration of the prescribed antibiotic.

Data Collection

A prospective survey of medical records and prescription charts was performed at the Division of General Internal Medicine of the University Hospital Nijmegen, the Netherlands. Fifty patients admitted to the ED and presumptively diagnosed as having a serious infection that required immediate empirical antibiotic treatment were recruited for the study, as described previously.(3) After analysis of the barriers to change and subsequent intervention, another 50 patients consecutively admitted to the ED with a presumptive diagnosis of serious infection were analyzed.

Interventions

On the basis of the analysis, guidelines and educational programs were developed to facilitate timely antibiotic administration. The interventions performed are summarized below.

- Newsletter to the medical staff informing about the observed delay
- Guidelines on managing patients with presumed serious infections and on ordering immediate treatment
- Guidelines on obtaining cultures for microbiological analysis
- Lectures to the medical staff
- Lectures to the nursing staff
- Improvement of the availability of antibiotics in the ED in a readily accessible place

- Removal of financial restraints on stocking and ordering antibiotics in the ED

The guidelines determine that antibiotics are administered in the ED immediately after taking cultures, not waiting for the next routinely scheduled drug distribution round. Two sets of blood cultures should be taken irrespective of the patient's body temperature. A urine sample and/or a sputum sample, if necessary after induction of sputum with isotonic sodium chloride solution should be collected, where appropriate. The collection of cultures may not delay the administration of antibiotics.

In educational sessions, the guidelines were introduced to all medical officers of the department. The nurses of the infectious diseases ward were taught about the measures.

In discussions with the head of the ED various organizational problems concerning the administration of antibiotics were solved such as the funding of the antibiotics needed, the stocking in a readily accessible place, and the ordering process from the pharmacy.

Outcomes

The outcomes measured were variables to define the appropriateness of the procedure of initiating antibiotic treatment and to assess the quality of the provided health care services; the interval from presentation to the ED until the administration of antibiotics, subdivided into day, night, or weekend shift; the source and number of samples taken for microbiological investigations; the relation between body temperature at admission and collection of culture samples; and the number of patients receiving their first dose of antibiotic at routinely scheduled drug distribution rounds. Furthermore, length of stay and in-hospital mortality was assessed.

Statistical Analysis

$P \leq .05$ was considered statistically significant. The Mann-Whitney U test was used to compare the time intervals between the 2 groups of patients. The χ^2 test was used to test categorical variables. Where indicated, data are given as mean ±SD.

Results

The patient characteristics are summarized in Table 1. There was no difference between the groups studied before and after the interventions with regard to baseline characteristics.

The median time from admission to the initial administration of antibiotics was 5.0 hours (range, 0.6 to 13.3 hours) for all 50 patients before the interventions. This decreased significantly to 3.2 hours (range, 0.6 to 10.5 hours; P=.04) after the interventions (Table 2). Whereas before the interventions the interval was significantly longer in patients admitted during office hours than in patients admitted at night (6.1 ± 3.2 hours vs 3.7 ± 1.9 hours; P=.03), this difference was no longer significant after the interventions (3.3 ± 2.8 hours vs 2.8 ± 1.9 hours; P=.39). The percentage of patients whose first dose of antibiotic was delayed to a routinely scheduled drug distribution round decreased from 54% to 32% (P=.03; Table 2).

No differences were found in the total number of blood cultures taken before or after the interventions. However, of the patients presenting with a respiratory tract infection, a sputum culture before starting antibiotic treatment was obtained from 5 (28%) of 18 before and 12 (50%) of 24 patients after the interventions (P=.15). In the case of presumed urinary tract infection, a urine culture was obtained from 6 (50%) of 12 patients before the interventions and in 100% of the patients after the interventions (P=.16).

Table 1: Patient Characteristics

Characteristic	Before Interventions (n=50)	After Interventions (n=50)	*P*
Sex, M/F	22/28	30/20	0.11
Age, mean ± SD, y	64±19	63±19	0.25
Aged >60 y, No. (%)	30 (60)	34 (68)	0.40
Diagnosis, No. of patients:			
Respiratory tract infection	18	24	0.22
Urinary tract infection	12	5	0.06
Erysipelas	8	3	0.11
Fever and neutropenia	2	3	1.00
Septicemia	10	15	0.25

Table 2: Administration of Antibiotics

	Before Interventions	After Interventions	*P*
Delay between admission and antibiotics, median ± SD, h			
Total	5.0±2.9	3.2±2.5	.04
During office hours	6.1±3.2 (n=15)	3.3±2.8 (n=23)	.06
At night	3.7±1.9 (n=22)	2.8±1.9 (n=17)	.22
During weekends	5.0±3.4 (n=13)	4.5±2.3 (n=10)	.49
Antibiotics delayed until routine drug rounds, No. (%) of patients	27 (54)	16 (32)	.03

More blood cultures were obtained from patients with a high temperature at admission. Before the interventions, the peak temperature of patients with 2 or more blood cultures was 38.8°C ± 1.0°C compared with 37.8°C ± 1.2°C for those with none or 1 set of blood cultures (P=.002). After the interventions, the same pattern existed (38.9°C ± 1.2°C vs 38.2°C ± 0.9°C; P=.03). The mean length of stay decreased from 19.1 ± 17.2 days before the interventions to 14.7 ± 12.4 days after the interventions (P=.05). The in-hospital mortality (4%) did not change after the interventions.

Comment

In the present study we have shown that interventions to expedite the timely performance of key diagnostic and therapeutic actions through directed clinical practice guidelines are successful. Efforts to identify and minimize common barriers significantly improved the timing of antibiotic administration. A combination of written and oral interventions was performed to educate the medical and nursing staff involved in the treatment of these patients.

The findings of the present study are in agreement with a vast body of research on medical education strategies. Whereas interventions and conventional medical education programs have little effect, multifaceted interventions have been shown to be particularly effective. Such strategies should concentrate on already developed and generally approved guidelines, and be targeted at specific behaviors identified by a gap analysis and audit addressing specific shortcomings and barriers to change.(4-9) The present study has specifically

focused on these types of intervention, which may have contributed to the favorable outcome.

The interventions in this study have improved the percentage of patients who had urine or sputum cultures taken when the focus of infection was thought to be the urinary or respiratory tract.

The practice of obtaining blood cultures could not be changed with the present interventions. The preconception that blood cultures are only of value if the patient presents with a body temperature above 38.5°C still appears to be widespread. This observation should lead to a further intervention, since it has been shown that there is little correlation between the presence of fever at admission and culture-proven septicemia.(10)

Limited data are available in the literature describing these types of interventions. Guidelines on initial antibiotic treatment only incidentally contain advice on the timing of treatment.(11-13)

Reports of delays in administering antibiotics vary considerably between 3.5 hours and 12.8 hours.(14-18) Blood cultures have been taken in 34% to 81% of the patients(14, 16-18) and sputum cultures in 22% to 70%.(14, 16, 18)

Only a few published studies have shown an improvement of the variables studied after interventions. One study reports a reduction of the interval between admission and administration of antibiotics by about 3 hours.(19) Other authors report that more patients received the antibiotic within 4 hours (20) or that more patients received antibiotics in the ED after intervention.(21) In a study on the reduction in mortality from pneumonia, a series of interventions consisting of written and oral information on the performance of the therapeutic interventions in the ED led to an increase in the percentage of patients receiving their first dose of antibiotic within 4 hours of admission from 42% to 87% and reduction of the mortality rate from 10.2% to 6.8%.(22) In one retrospective study of patients with urinary tract infections,(23) a significant reduction in the mean length of stay was seen comparing patients whose antibiotics were administered within 4 hours of admission vs those whose antibiotics were administered outside the 4-hour frame.

The present study was aimed at behavioral change rather than assessing patient outcome, and although there was a trend toward shorter hospital stay after the interventions, the number of patients is not appropriate to statistically evaluate such effects. Nevertheless, the significant improvement in the process of care is considered crucial in improving outcome.(22, 23) Attention to the process of

care, in addition to its content, is important in assessing the need for formulation of institutional practice guidelines. Coordination of care in the ED and on the inpatient ward with contributions from the pharmacy and the laboratory is necessary to modify key aspects of management, such as reducing the time to initiate antibiotic treatment. This may lead to a substantial improvement of quality in patient care.

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CHAPTER VI

Outcomes in studies aimed at improving rational use of antibiotics

Practical considerations

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Introduction

Already in the early days of the application of antimicrobial drugs, overuse and misuse of these valuable drugs has been reported. (1) With the introduction of many different antimicrobial drugs, they soon became a sizeable part of the drug budget. The main concerns were directed at the drug quantities used and the costs involved. Almost at the same time, the development of resistance related to the use of antimicrobials became an even greater concern. (1)

Meanwhile, it has become clear that there are more parameters involved that define optimal use of antimicrobials. (2) The prescription and administration of an antimicrobial drug to a patient is the result of a complex process, which comprises many steps that are undertaken in the care for a patient. Studies addressing antimicrobial drug use may address specific factors of such a process, and the results of this process are measured as the outcome of the study. In a broad sense, an outcome is any consequence of health care. A clear distinction is needed between clinical outcomes and process outcomes. Clinical outcomes encompass the improvement in health state achieved in a patient. Process outcomes are indicators of how well care is delivered to a patient. This makes clear that the term "outcome measure" should not be confused with the term "outcome of treatment".

Careful attention must be paid to the selection of appropriate outcome measures. Clear definitions are needed for the different outcomes of studies. In the field of antimicrobials, the reduction of use, reduction of costs, influence on resistance patterns, or influence on process parameters such as timing, dosing, route of administration are suitable examples of process outcome measures.

In this report, we will discuss in more depth a few characteristics of outcomes: how to identify and select possible outcomes best suiting the purpose of the study intended to perform, how to best measure outcomes, how to validate the results and how to assess the link between process outcomes and clinical outcomes.

Identification and Selection of Possible Outcomes

When designing studies on optimal use of antimicrobial drugs, it is important to define in an early stage, which parameters are suitable to measure optimal use or optimal care.

A step-by-step analysis of the process can lead to the identification of possible outcome parameters. First, there are clinical outcomes, which may be strong parameters such as rate of morbidity and mortality, or clinical and microbiological cure or improvement. More indirect or surrogate parameters are biochemical, functional or anatomical changes, such as decrease in body temperature or changes in leukocyte count. These are all intra-patient variables that are measured over time within the same patient. Examples of between-group parameters of outcome are microbiological outcomes, such as changes in resistance rates or the species isolated in different study groups. (3) Also, assessment of costs or amount of antimicrobials used are between-group parameters. (4)

Furthermore, process parameters can be chosen as outcomes. From the point of view of the patient, these are more indirect parameters. From the perspective of the process of health care delivery however, these are direct outcomes to assess the success or failure of a particular process. The process of care consists of many different steps. An analysis of this process is needed to identify possible barriers in the delivery of optimal care. These processes comprise two aspects, the technical competence to carry them out, consisting of knowledge, skills and judgement of the health care practitioner, and the humanistic aspects of attitude and behaviour of the provider of the service in question. Both aspects – technical and humanistic – can be defined, observed and measured, and hence both types of process parameters may be suitable outcomes in a given study. (5)

Finally, the processes are carried out within given structures of an organisation, with the goal to achieve a desired outcome. Also, characteristics of this structure have to be analysed to identify possible barriers.

In medical sciences, primarily the clinical outcome is measured. Even though reduction in morbidity and mortality is the final goal of any clinical intervention, often these are not suitable outcomes, because of the time frame of the study, the number of individuals included in the study, or other parameters of influence. Morbidity and mortality are general measures, which mostly reflect the coordinate efforts of a multidisciplinary health care team. (6)

As an example, an intervention is performed aiming at increasing the percentage of patients switched from parenteral to oral treatment with antibiotics; and differences in length of stay are measured as an outcome of the study. Length of stay, however, is a rather general parameter, influenced by

many other factors in the course of a patient's recovery or the hospital organisation and therefore too general to be directly linked to the intervention. Also, interventions directed at specific indications with measurement of the total use of antibiotics as outcome are too general to prove a causal relationship. (7) Changes in other treatment strategies or in patient population can greatly influence this parameter, besides the actual intervention.

It is thus important to select an outcome that is directly linked to the process of care under study. (8) Such an outcome must be specific to identify changes that occurred. (9) Global variables may be influenced by many other factors, and are therefore too far removed from the process performed.

An example of a study aimed at analysing the process of care is our study on the delay of administration of the first dose of antibiotics to patients admitted to the emergency department with serious infections. (10) This delay seemed to depend on several factors in the process of care, such as full evaluation of patients before taking any action, waiting for results from the laboratory, delays in obtaining cultures, and delay of administration until the next scheduled drug distribution round. Also, barriers in the structure such as less than optimal access to antimicrobial drugs in the emergency department and financial restraints could be identified. Outcomes were the interval from presentation of the patient to the emergency department until administration of antibiotics, the source and number of samples taken for microbiological investigations, and the number of patients receiving their first dose of antibiotic immediately, rather than at the next scheduled drug distribution round. In an intervention study, (11) the causes of delay were addressed, and after implementation of the intervention through guidelines and educational programs, the same outcomes were measured again. Length of stay and mortality were assessed but did not show any change after intervention. However, more direct outcome measures of the process of care, such as the time interval from admission to administration of antibiotics or the number of patients receiving their first dose before rather than during the routinely scheduled drug distribution rounds changed significantly, indicating a considerable improvement of the delivery of care to this group of patients. (11)

Also, the target drug program on use of fluconazole is an example of a program that allows to identify possible outcomes. (12) The comparison of the prescribing habits in two hospitals revealed that the dosing and duration of fluconazole treatment often were not in agreement with the current guidelines

in one of the two hospitals. Thus, dosage and duration of treatment can now be used as an outcome.

Measurement and Validation of Outcomes

After the identification of a suitable outcome, the outcome measures must be selected, i.e. the variables that can be measured. This is required in order to be able to observe in some systematic and objective way the change in delivery of care. (8,13)

Many different tools can be chosen to actually measure an outcome. (14) Categorical measurement scales can be chosen if clear-cut dichotomous categories of patient outcomes can be defined, for example the number of patients switched from parenteral to oral treatment. In many cases, more subtle interval scales should be applied to measure changes, (15) and changes in the distribution of scores should then be assessed. An example is the timing of initiation of antimicrobial treatment after admission to the hospital. A categorical assessment may split the patients into a group started less than 4 hours after admission versus a group started later, (16) and changes in the size of these two groups are assessed. However, the sensitivity to record changes in outcome is greatly increased using a more subtle analysis that assesses the actual time of administration of the drug and performs a survival or trend analysis to assess changes. (10,11)

The amount of antimicrobials used can also be measured in many different ways. If an overall analysis of the use in different settings is needed, the application of the Anatomical Therapeutical Chemical Classification/Defined Daily Doses (ATC/DDD) methodology is useful to generate comparable data. (4) The system measures the amount of drug used independent on package sizes and sales price, which allows comparisons within institutions, regions, countries or even internationally. The DDD is a technical unit of measurement and does not necessarily reflect the recommended or actual dose used. However, if a closer analysis on the patterns of prescribing is desired, precise data on the use in individual patients is needed, such as the actually prescribed dosage and duration of a treatment. This is the case in target drug programs (17) or in prospective audits to evaluate prescribing practices. (10,12)

Attention must be paid to the statistical methods to be applied to the evaluation of outcomes. The most traditional way is the intention-to-treat analysis, thus a dichotomous analysis. This will lead to a net estimate of treatment effects.

However, if the goal is to explain how and why certain effects were achieved, more differentiated statistical methods are necessary. (18) For instance, survival analysis helps to estimate relative group differences. (19) When studying the duration of treatment, this kind of analysis helps to discover subtle differences between groups of patients. (12) When assessing the degree of delay of initiation of treatment, differences in the behaviour of different groups of prescribers could be detected. (10)

An essential point is that the quality of the measurements performed must be considered. (8) The validity of an outcome measure must be adequate for detecting any change. (20) Outcome measures must also be sufficiently distinctive to indicate important changes, and must be sensitive enough to differences occurring between two study groups. (7,14) The failure to find hypothesised differences between study groups may reflect the inability of the measure to accurately detect any change, and may not necessarily indicate that no change occurred. (8,20)

An outcome measure must also be reliable. That means that given measures produce the same results when the same cases are assessed more than once. (5,20) Reliability reflects the precision of a measure.

Also the timeframe chosen for the performance of a study should be validated. Is the outcome measured likely to change during the study period chosen? (6)

Many examples have already been published, and it is advisable to search the existing literature to identify outcome measures used in earlier studies, which showed to be valid and reliable to detect a change.

The Causal Link between Outcomes

Measuring and monitoring process outcomes may not be sufficient to show that the process rather than other influences has caused the changes observed. The challenge is to be able to show a sound link between the process and the desired final outcome. There must be a causal relationship between the process and the outcome, which must be established beforehand. It is an issue of probability that can vary widely, but the strength of causality determines the validity and usefulness of parameters as outcome measures. (6)

An example is the timing of surgical antibiotic prophylaxis. The causal relationship between timely administration of antibiotics before start of surgery and the prevention of wound infections has been established in an

experimental study. (21) Intervention studies aiming at implementing these experimental findings into daily clinical practice may now focus only on the timing itself, without assessing the rate of wound infections again. (22,23) Therefore, measuring the time interval between administration of antibiotics and surgery should be an adequate outcome of such a study.

These types of relationships must be identified for every study planned. Such knowledge serves to interpret the effects of an intervention, as well as the results measured in an evaluation, even without intervention, like in audits of prescribing or target drug programs. (10,12,17)

Conclusions

The discussion whether process parameters or clinical outcomes of care are to be preferred as outcome measures is unproductive. (5) Different outcomes have a value in different settings and for different purposes. (6) The essential point is to choose the appropriate outcome measure for the goals of the desired study design. The trend goes into the direction of greater integration of additional variables into experimental designs in order to acquire more data about factors that might explain the variability of outcomes. Much attention must be given to the selection of the outcome measures included in such analysis, and a better understanding is needed on the link between processes and outcomes. (18)

The many pitfalls that are encountered with the choice of outcomes and outcome measures lead to the recognition that assessment of the process of care is essential. This requires assessment of the structure of an organisation and the evaluation of the processes of care, as well as evaluation of outcome measures associated with effective service delivery. Attention must be paid to the influence of the external context in which a study is to be performed. (18) This will ensure the quality of the structure and the process, rather than just the desired clinical outcomes, and in this sense, process parameters as outcome measures obtain a role in quality assessment and quality assurance. (6)

Choosing appropriate, valid and reliable individual outcome measures will be essential in order to make sure the planned study will lead to the desired results and will have the intended impact on the daily clinical practice. Care should be taken about which outcomes to choose, about the desired level of change that should be achieved, and which outcome measures to be applied to measure the

desired change. Also, the statistical methods that will be applied to evaluate the results should be carefully selected.

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GENERAL DISCUSSION

In a series of studies addressing specific topics within the broad subject of the quality of use of antimicrobial drugs, different methods of surveillance have been applied to clinical practice. Monitoring both the amount of use of antimicrobial drugs in a particular patient-population and the rate of resistance of specific microorganisms against certain antimicrobials is important to discovering possible areas of concern (chapter I). (1,2) The results presented in Chapter I showed that more sophisticated methods for the evaluation of these data are necessary. For the comparison of data on the total use of antimicrobials in different populations, a methodology that is independent of sales prices or package sizes or other local factors is needed. This has led to the application of the Anatomical Therapeutical Chemical Classification/ Defined Daily Doses (ATC/DDD) system developed by the World Health Organisation (WHO) (3) to evaluate the use of quinolones in an acute care hospital, long-term care facilities and the general population (chapter II). On the other hand, specific target drug programmes are needed if the evaluation of prescribing habits in daily practice are to be assessed (chapter III and IV). (4)

Using hospital-wide data to monitor susceptibility changes can obscure significant changes in specific patient-care areas. (5) Higher rates of resistance are often discovered in intensive-care units compared to general patient-care areas. The discovery of the development of resistance in association with specific patient populations is important. On the other hand, hospital wards are not closed systems and resistant strains can rather easily be spread through an institution. Changes in some areas of a health-care setting can have profound influence on other areas and groups of patients (chapter I). The same holds true for consumption data in the general population. Global figures may obscure disproportionally high use in a small but important group of patients (chapter II).

It is difficult to prove a causal relationship between the use of antimicrobial drugs and the development of resistance. This is true because of many possible factors of influence such as a more intense study of outbreaks with resistant strains, the performance of more intense microbiological analysis in the case of resistance, the lack of control for confounders and insufficient power of studies because of small sample sizes, variations in drug use and introduction of

multiple control measures at the same time as well as a publication bias as studies showing a relationship are probably more likely to be published. (6) Nevertheless, many studies have shown a consistent association and concomitant variation as well as a dose-effect relationship between the use of antimicrobials and changes in resistance rates of microorganisms, such as the one presented in chapter I.

Monitoring of the use of antimicrobials and prescribing habits serves as an important basis to discover possible problematic areas and to analyse barriers to change among the health care practitioners. These evaluations support the formulation of interventions aimed at improving the process of care in daily clinical care and hence improving the quality of use of antimicrobials (chapter I and V).

The target drug program presented in chapter III points to problems when generally published practice guidelines are adapted in daily routine. The information may not be easily accessible to the health care practitioners, or current hospital policies may not be in accordance with "state of the art" publications. This observation leads to the recognition that the development of guidelines and the implementation of interventions aimed at changing the performance of health care practitioners in daily clinical care need careful attention. They must be developed on a local level, taking care of specific characteristics of the local setting, based on sound scientific knowledge about the topic in question. (7-10) The implementation needs to be addressed at various levels within an organization, and all members of the health care team have to be actively involved into every process of change. (11) Multifaceted interventions carried out by an interdisciplinary team have the greatest chance for success. (12-14) As shown in chapter I, this approach allowed the reversal of the development of resistance in Escherichia coli to amoxicillin-clavulanate gradually over a 4-year period through close collaboration of the clinical pharmacists, the infection control practitioner, the microbiology laboratory, and the physicians in charge of the respective departments. In chapter V, another aspect of the process of care is shown to be improvable with a similar approach. As the timing of the initiation of the antimicrobial treatment was addressed, it was important to involve the nursing staff closely in the implementation phase of the intervention. They are important in deciding when to administer a drug to a patient. If a prescriber is unaware of the fact that writing a prescription is no guarantee that the patient readily receives the prescribed drug, the whole process of care may be insufficient just because of a

lack of communication between the different health care professionals involved in the care of an individual patient. A significant improvement in the process of care, considered crucial in improving the outcome, was achieved through coordination of care with contributions from the pharmacy and the laboratory. Attention to the process of care, in addition to its content, is important in assessing the need for formulation of institutional practice guidelines.

After the formulation and implementation of interventions into clinical practice, the evaluation of the effects achieved is necessary. To do so, clearly defined outcomes are necessary. This must not be confused with the evaluation of the clinical outcome of treatment. (15) The many pitfalls encountered with the choice of outcomes lead to the recognition that assessment of the process of care is essential. (16) This requires assessment of the structure of an organisation and the evaluation of the processes of care, as well as evaluation of outcome measures associated with effective service delivery. In future studies, the selection of appropriate, valid and reliable individual outcome measures will be essential in order to make sure the planned study will lead to the desired results and have the intended impact on the daily clinical practice.

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SUMMARY

In a series of studies, specific topics concerning the quality of use of antimicrobial drugs have been addressed. Several methods of assessment have been applied to clinical practice. And in two studies, the implementation of interventions to improve the quality is assessed.

In **chapter I**, the results are presented of a study aimed at reducing the use of amoxicillin-clavulanate, after high-resistance rates in Escherichia coli were detected. The study was carried out at a 260-bed acute-care hospital in Switzerland. The antibiotic consumption and resistance data of four major hospital departments were evaluated over a 4-year period. During this period, a series of interventions was successively introduced while the resistance patterns were closely monitored. The interventions consisted of the introduction of therapeutic guidelines for specific departments or indications, which proposed alternative antibiotics to amoxicillin-clavulanate. The perioperative prophylactic use of amoxicillin-clavulanate was eliminated completely. The implementation of the treatment guidelines was facilitated through a close collaboration among the clinical pharmacists, the infection control practitioner, the microbiology laboratory, and the physicians in charge of the respective departments. The absolute amount of use of amoxicillin-clavulanate decreased by 23% and the number of courses prescribed decreased by 62%. This was followed by an increase in susceptibility of E coli to it from 55% sensitive strains in 1992 to 83% sensitive strains in 1995. No major changes were detected for other antimicrobials used in the same period.

In **chapter II**, a comparison of the use of quinolones in different patient populations is presented. To do so, the Anatomical Therapeutical Chemical Classification/Defined Daily Doses (ATC/DDD) system developed by the World Health Organisation was applied. The system measures the amount of drug used independent of package size and sales price. The DDDs are a technical unit of measurement and do not necessarily reflect the recommended or actual dose used. But this standard unit of measurement enables comparisons not only within an institution but also within a region, a country,

or even internationally. Quinolones were widely used in long-term care facilities in the Nijmegen region of the Netherlands, accounting for about 30% of the antibiotics used in these settings, whereas, in the general population as well as in the University Hospital Nijmegen, these drugs constitute only about 6% of the total antibiotics used.

In **chapter III**, the results of a target drug program are presented. One hundred courses of fluconazole treatment in a university hospital and 81 courses in a non-university teaching hospital are analysed in a prospective audit to evaluate prescribing practices. Fluconazole should be prescribed with caution and on strict indications to prevent the development of resistance. The quality of treatments was assessed by an infectious disease specialist and a pharmacist according to standard guidelines. There did not appear to be a major problem with inappropriate use of fluconazole. However, important issues for improvement could be identified, such as increasing the dosage and duration of treatment in cases of serious infections, and withholding treatment from patients with colonisation rather than infection. Cultures should be obtained from all patients with presumed oropharyngeal or oesophageal candidosis who are switched to fluconazole after treatment with another antifungal drug has failed. Isolates should be speciated and susceptibility testing should be performed and reported on all clinically relevant isolates.

In **chapter IV**, the analysis of a process of care is presented: the interval from the time of admission to the emergency room until the administration of antibiotics in 50 patients presenting with a serious infectious disease is analysed. A median interval from time of admission to administration of antibiotics of 5 hours was determined (range 0.6-13.3 h) but this was significantly shorter in patients admitted at night than in patients admitted during office hours (3.7 vs. 6.0 h, $P<0.05$). There was no difference with respect to the presenting features, body temperature, laboratory values at presentation or number of cultures performed. However, other causes of delay in administering antibiotics seem to play a greater role. Obstacles were the belief that patients should be fully evaluated before taking any action, the belief that blood cultures should only be taken with a body temperature above 38.5°C, and that antibiotics were not readily accessible in the emergency room. On the ward, nurses often thought they could wait until the next scheduled drug distribution round for

administration of the prescribed antibiotic. As more than 80% of the patients received an antibiotic chosen in accordance with hospital guidelines, the choice of antibiotic therapy did not cause problems. However, the study showed that medical officers need to take a more active role in initiating antibiotic therapy and that antibiotics should be administered in the emergency room. Furthermore, administrative reasons for delay should be addressed.

In **chapter V**, the results of the implementation of a series of educational and organisational interventions designed to improve the process of care as described in chapter IV are presented. Guidelines and educational programs were developed to facilitate timely antibiotic administration: guidelines on handling patients with serious infections and on ordering immediate treatment, guidelines on obtaining culture samples, lectures to medical and nursing staff, improvement of availability of antibiotics in the emergency department, and removal of financial restraints on stocking and ordering of antibiotics. The median time to the initial dose of antibiotics administered decreased from 5.0 hours to 3.2 hours (P=.04). The percentage of patients whose first dose of antibiotic was delayed until a routinely scheduled drug distribution round decreased from 54% to 32% (P=.03). Combined interventions to expedite diagnostic and therapeutic actions through directed clinical practice guidelines and organisational measures are successful. Efforts to identify and minimise common barriers significantly improved the timing of antibiotic administration. This has been achieved through multifaceted interventions and may lead to a substantial quality improvement in the process of care.

From the studies presented in chapters I through V, it has become clear that well defined outcomes and outcome measures are necessary. Additional implications drawn from these studies are discussed in **chapter VI**. Carefully designed intervention studies are needed to achieve changes in the patterns of prescription of antimicrobial drugs as well as changes in the process of care of administration of antimicrobials. Choosing appropriate, valid and reliable individual outcome measures will be essential in order to make sure the planned study will lead to the desired results and have the intended impact on the daily clinical practice. This must not be confused with the evaluation of the clinical outcome of treatment. In future studies, the assessment of the structure of an organisation and the evaluation of the processes of care as well as

evaluation of outcome measures associated with effective service delivery is required.

SAMENVATTING

Dit proefschrift is samengesteld uit een aantal onderzoeken naar de kwaliteit van het gebruik van antimicrobiële middelen. Meerdere methoden voor surveillance zijn in de klinische praktijk toegepast. In twee onderzoeken werd de implementatie van interventies ter verbetering van de kwaliteit van het gebruik geëvalueerd.

In **hoofdstuk I** worden de resultaten gepresenteerd van een onderzoek naar het verminderen van het verbruik van amoxicilline/clavulaanzuur nadat grote resistentie tegen Escherichia coli werd vastgesteld. Het onderzoek werd uitgevoerd in een perifeer ziekenhuis met 260 bedden in Zwitserland. Het antibiotica-verbruik en de resistentiegegevens van de vier belangrijkste afdelingen van het ziekenhuis werden gedurende vier jaar geëvalueerd. In deze periode werden een aantal interventies geïntroduceerd terwijl de resistentiegegevens nauwkeurig gevolgd werden. De interventies bestonden uit de introductie van behandelprotocollen voor bepaalde afdelingen of indicaties, waarin alternatieve antibiotica in plaats van amoxicilline/clavulaanzuur waren opgenomen. Het perioperatieve gebruik van amoxicilline/clavulaanzuur werd volledig geëlimineerd. De implementatie van de protocollen werd ondersteund door een nauwe samenwerking tussen de klinische farmacie, de infectie preventie consulent, het microbiologische laboratorium en de verantwoordelijke artsen. Het totale verbruik van amoxicilline/clavulaanzuur daalde met 23% en het aantal voorschriften verminderde met 62%. Deze reductie werd gevolgd door een toename aan voor amoxicilline/clavulaanzuur gevoelige stammen van E. coli van 55% in 1992 naar 83% in 1995. Er werden geen grote veranderingen vastgesteld in het resistentiepatroon van andere antibiotica die in dezelfde periode werden voorgeschreven.

In **hoofdstuk II** wordt een vergelijking van het verbruik van chinolonen in verschillende patiënten-groepen gepresenteerd. Daarvoor werd gebruik gemaakt van het ATC/DDD-systeem (Anatomical Therapeutical Chemical Classification/Defined Daily Doses) dat door de Wereld Gezondheidsorganisatie werd ontwikkeld. Dit systeem meet het verbruik van

geneesmiddelen onafhankelijk van verpakkingsgrootte of inkoopprijzen. DDD's zijn een technische eenheid en geven niet per se de therapeutische doseringen weer. Het systeem maakt vergelijkingen mogelijk niet alleen binnen één ziekenhuis maar ook binnen een regio, een land of zelfs internationaal. Chinolonen werden vaak gebruikt in verpleeghuizen in de regio Nijmegen, tot 30% van het totale verbruik aan antibiotica in deze instellingen, terwijl in de totale bevolking als ook in het Academisch Ziekenhuis Nijmegen chinolonen maar 6% van het totale antibioticaverbruik uitmaakten.

In **hoofdstuk III** worden de resultaten van een "target-drug" programma gepresenteerd. Honderd voorschriften voor fluconazol in een academisch ziekenhuis en 81 voorschriften in een perifeer ziekenhuis werden geanalyseerd in een prospectieve audit met het doel het voorschrijfgedrag te evalueren. Ter voorkoming van resistentie moet fluconazol terughoudend en alleen op strikte indicatie voorgeschreven worden. De kwaliteit van de voorschriften werd door een infectioloog en een apotheker beoordeeld op basis van standaard richtlijnen. In het algemeen wordt fluconazol op de juiste wijze voorgeschreven. Maar er blijven een aantal punten voor verbetering vatbaar zoals verhogen van dosis en duur van de behandeling van ernstige infecties en aan de andere kant eliminatie van behandeling van patiënten met alleen kolonisatie. Kweken moeten worden afgenomen bij alle patiënten met vermoeden op orofaryngeale candidiasis of oesofagitis die omgezet werden op fluconazol nadat behandeling met een ander antimycoticum gefaald heeft. Isolaten van schimmels moeten gespecificeerd en gevoeligheidsbepalingen uitgevoerd worden voor alle klinisch relevante isolaten.

In **hoofdstuk IV** wordt een procesanalyse gepresenteerd: het interval tussen het tijdstip van opname op de spoedeisende hulp en de eerste toediening van antibiotica werd geanalyseerd bij 50 patiënten die zich met een ernstige infectie presenteerden. Een mediaan interval van 5 uur werd vastgesteld (spreiding 0.6-13.3 uur) maar dit was significant korter bij patiënten die 's nachts werden opgenomen ten opzichte van patiënten die tijdens kantooruren werden opgenomen (3.7 vs. 6.0 uur, $P<0.05$). Er was geen verschil met betrekking tot de klinische symptomen, lichaamstemperatuur, laboratoriumuitslagen bij opname of afgenomen kweken. Andere oorzaken voor de vertraging in het starten met antibiotica blijken een grotere rol te spelen. Knelpunten waren de

veronderstelling dat eerst een volledige anamnese en lichamelijk onderzoek uitgevoerd moest worden voor dat enige actie werd genomen, de veronderstelling dat bloedkweken pas bij een temperatuur boven de 38.5°C afgenomen moesten worden en dat antibiotica niet beschikbaar waren op de spoedeisende hulp. Op de afdeling dachten de verpleegkundigen dat ze met de toediening konden wachten tot de volgende medicatieronde. De keuze van het voor te schrijven antibioticum veroorzaakt geen problemen, gezien het feit dat meer dan 80% van de patiënten een antibioticum overeenkomstig met de ziekenhuisrichtlijnen voorgeschreven kreeg. Het onderzoek laat echter zien dat de artsen een actievere rol moeten spelen bij het starten van een antibiotische therapie en dat de antibiotica reeds op de spoedeisende hulp toegediend moeten worden. Verder moeten administratieve knelpunten die een mogelijke vertraging kunnen veroorzaken, opgelost worden.

In **hoofdstuk V** worden de resultaten gepresenteerd van de implementatie van een aantal educatieve en organisatorische interventies met het doel, het proces zoals beschreven in hoofdstuk IV te verbeteren. Richtlijnen en educatieve programma's werden ontwikkeld ter bevordering van het eerder toedienen van antibiotica: richtlijnen voor het behandelen van patiënten met ernstige infecties, richtlijnen voor het op tijd voorschrijven van antibiotische behandeling, richtlijnen voor het afnemen van kweken, lezingen voor het medische en verpleegkundige personeel, verbetering van de beschikbaarheid van antibiotica op de spoedeisende hulp, en oplossen van financiële knelpunten. Het mediane interval tussen opname en de eerste dosis antibiotica verminderde van 5.0 uur naar 3.2 uur (P=.04). Het aantal patiënten dat hun eerste dosis pas bij de volgende medicatieronde kreeg toegediend daalde van 54% naar 32% (P=.03). Gecombineerde interventies ter verbetering van diagnostiek en therapie middels praktijkrichtlijnen en organisatorische maatregelen zijn succesvol. De inspanningen om knelpunten op te sporen en op te lossen leidden tot een significante verbetering van het starten van antibiotica. Dit werd bereikt door middel van interventies op meerdere onderwerpen en kan bijdragen aan een substantiële verbetering van de kwaliteit van zorg.

Uit de onderzoeken zoals gepresenteerd in hoofdstuk I tot en met V werd duidelijk dat precies gedefinieerde uitkomsten en uitkomstmaten nodig zijn. In **hoofdstuk VI** wordt een aantal punten hieromtrent besproken. Goed

georganiseerde interventiestudies zijn nodig om veranderingen in voorschrijfpatronen voor antimicrobiële middelen als ook veranderingen in het zorgproces te bereiken. De keuze van passende, valide en betrouwbare uitkomstmaten is essentieel wil men ervan verzekerd zijn dat de geplande onderzoeken tot de gewenste resultaten leiden en de gewenste invloed hebben op de dagelijkse praktijk. Dit moet niet worden verwisseld met de evaluatie van klinische uitkomsten van een behandeling. In toekomstige studies zal de evaluatie van de structuur van een organisatie en van de zorgprocessen alsmede de evaluatie van de uitkomstmaten van effectieve zorgverlening noodzakelijk zijn.

ZUSAMMENFASSUNG

In einer Reihe von Studien wurden spezifische Aspekte der Qualität des Antibiotikaeinsatzes untersucht. Mehrere Methoden der Beobachtung wurden dabei in der klinischen Praxis eingesetzt. In zwei Studien wurde zudem die Einführung von Interventionen zur Verbesserung der Qualität evaluiert.

Im ersten Teil werden die Resultate einer Studie präsentiert, die zum Ziel hatte, den Verbrauch von Amoxicillin/Clavulansäure zu vermindern nachdem hohe Resistenzraten bei Escherichia coli entdeckt wurden. Die Studie wurde an einem Schweizer Akutspital mit 260 Betten durchgeführt. Der Antibiotikaverbrauch und die Daten der Resistenzstatistik der vier grössten Abteilungen des Spitals wurden während vier Jahren ausgewertet. In dieser Periode wurde eine Reihe von Interventionen schrittweise eingeführt während die Resistenzlage genau überwacht wurde. Diese Massnahmen bestanden aus der Einführung von Therapierichtlinien für einige Abteilungen oder Indikationen, in denen Alternativen zu Amoxicillin/Clavulansäure vorgeschlagen wurden. Der perioperative Einsatz von Amoxicillin/Clavulansäure wurde vollständig vermieden. Die Einführung der Therapierichtlinien wurde durch die enge Zusammenarbeit zwischen den klinischen Pharmazeuten, dem Spitalhygieniker, dem mikrobiologischen Labor und den verantwortlichen Ärzten der jeweiligen Abteilungen unterstützt. Der totale Verbrauch von Amoxicillin/Clavulansäure verringerte sich um 23% und die Anzahl Verschreibungen für Amoxicillin/Clavulansäure wurde um 62% reduziert. Danach stieg die Sensibilität von E.coli gegen Amoxicillin/Clavulansäure von 55% empfindlicher Stämme im Jahr 1992 auf 83% empfindlicher Stämme in 1995. Dabei wurden keine relevanten Veränderungen bei der Resistenz anderer Antibiotika festgestellt, die im selben Zeitraum eingesetzt wurden.

Im zweiten Teil wird eine Studie zum Einsatz von Chinolonen bei verschiedenen Patientengruppen vorgestellt. Dabei wurde das ATC/DDD System (Anatomical Therapeutical Chemical Classification/ Defined Daily Doses) der Weltgesundheits-organisation eingesetzt. Mit diesem System kann

der Antibiotikaverbrauch unabhängig von Packungsgrösse oder Preisen gemessen werden. DDD's sind eine technische Messgrösse die nicht direkt die empfohlenen oder aktuellen Dosierungen repräsentieren. Damit ist es aber möglich, Vergleiche nicht nur innerhalb eines Spitals, sondern auch in einer Region, landesweit oder sogar international durchzuführen. Chinolone wurden im grossen Stil eingesetzt in Pflegeheimen in der Region Nijmegen in den Niederlanden, mit circa 30% des totalen Antibiotikaeinsatzes in diesen Heimen, während in der Gesamtbevölkerung wie auch im Universitätsspital Nijmegen nur circa 6% der verwendeten Antibiotika Chinolone sind.

Im dritten Teil werden die Resultate eines „Target-drug" Programms vorgestellt. 100 Verordnungen für Fluconazol in einem Universitätsspital und 81 Verordnungen in einem regionalen Spital wurden in einer prospektiven Studie zur Evaluation von Verordnungen in der Praxis analysiert. Fluconazol sollte vorsichtig und mit strenger Indikationsstellung verschrieben werden um Resistenzentwicklung zu verhindern. Die Qualität der Behandlungen wurde durch einen Infektiologen und einen Apotheker nach Standardrichtlinien beurteilt. Dabei konnten keine grösseren Probleme im Einsatz von Fluconazol festgestellt werden. Trotzdem wurden einige Aspekte identifiziert, die verbessert werden können wie einerseits höhere Dosierungen und längere Therapiedauer bei schweren Infektionen und andererseits Unterlassen der Behandlung bei reiner Kolonisation von Patienten ohne Infektion. Proben zur mikrobiologischen Analyse sollten bei allen Patienten mit oropharyngealer Candidiasis oder Oesophagitis gewonnen werden, denen Fluconazol verschrieben wird nachdem die Behandlung mit einem anderen Antimycotikum erfolglos war. Bei allen klinisch relevanten Isolaten sollten die Keime identifiziert und deren Empfindlichkeit getestet werden.

Im vierten Teil wird die Analyse eines Pflegeprozesses vorgestellt: Das Zeitinterval zwischen der Aufnahme auf der Notfallstation und der Gabe der ersten Dosis eines Antibiotikums wurde bei 50 Patienten, die sich mit einer schweren Infektion präsentierten, gemessen. Ein Interval mit einem Median von 5 Stunden (range 0.6-13.3 h) wurde festgestellt. Dieses war jedoch signifikant kürzer bei Patienten, die in der Nacht aufgenommen wurden im Vergleich zu Patienten, die während Normalarbeitszeiten aufgenommen wurden (3.7 vs. 6.0 h, $P<0.05$). Dabei war kein Unterschied festzustellen im

Bezug auf klinische Symptome, Körpertemperatur, Laborwerte bei Aufnahme oder Anzahl mikrobiologischer Proben, die abgenommen wurden. Andere Gründe scheinen eine wichtigere Rolle zu spielen als Ursache für diese Verzögerung. Dazu gehören die Auffassung, dass ein Patient erst vollständig untersucht werden muss, bevor weitere Schritte unternommen werden, die Auffassung, dass Blutkulturen erst bei Fieber über 38.5°C abgenommen werden sollten, und dass Antibiotika auf der Notfallaufnahme nicht direkt zur Verfügung standen. Auf der Pflegeabteilung dachte das Pflegepersonal oft, dass mit der Verabreichung bis zur nächsten Medikamenten-Runde gewartet werden könnte. Da mehr als 80% der Patienten ein Antibiotikum gemäss den spitalinternen Richtlinien verschrieben wurde, scheint die Wahl eines Antibiotikums keine Probleme zu verursachen. Die Studie zeigt aber, dass die Ärzte eine aktivere Rolle spielen sollten beim Starten einer Antibiotikatherapie und dass die erste Antibiotikadosis bereits auf der Notfallstation verabreicht werden sollte. Im weiteren müssen administrative Hürden vermindert werden.

Im fünften Teil werden die Resultate einiger Massnahmen vorgestellt, die zum Ziel hatten, den Pflegeprozess wie er im vierten Teil beschrieben wurde zu verbessern. Richtlinien, Weiterbildungen und andere Massnahmen wurden entwickelt, um die rechtzeitige Gabe von Antibiotika zu unterstützen: Richtlinien zur Evaluierung von Patienten, die sich mit einer schweren Infektion präsentieren, sowie zur schnellen Verordnung einer Behandlung, Richtlinien zur Materialgewinnung, Präsentationen an die Ärzte sowie ans Pflegepersonal, und die Verbesserung der Logistik rund um Antibiotika auf der Notfallstation. Der Median des Zeitintervals bis zur ersten Dosis verringerte sich von 5 Stunden auf 3.2 Stunden (P=.04). Der Anteil der Patienten, denen die erste Dosis erst während der erstfolgenden Medikamenten-Runde verabreicht wurde, verminderte sich von 54% auf 32% (P=.03). Die Kombination von Massnahmen zur Beschleunigung von diagnostischen und therapeutischen Schritten mit Hilfe von praktischen Therapierichtlinien sowie logistischen Verbesserungen war erfolgreich. Die Anstrengungen zur Identifikation und Verringerung von Hindernissen verbesserten die rechtzeitige Verabreichung von Antibiotika signifikant. Dies wurde mittels vielschichtiger Interventionen erreicht und kann damit zu einer substantiellen Qualitätsverbesserung im Pflegeprozess führen.

Bei der Ausführung der Studien, wie sie in den ersten fünf Teilen beschrieben werden, wurde deutlich, dass genau definierte Endpunkte wesentlich sind. Im sechsten Teil werden weitere Aspekte dieses Themas erläutert. Sorgfältig geplante Interventionsstudien sind nötig, um Veränderungen im Verordnungsverhalten im Bereich der Antibiotika wie auch Veränderungen im Pflegeprozess bei der Verabreichung dieser Medikamente feststellen zu können. Die Wahl von adäquaten, validen und zuverlässigen individuellen Endpunkten ist essentiell, will man sicherstellen, dass eine geplante Studie auch zum gewünschten Resultat führt und den gewünschten Effekt in der täglichen Routine hat. Dies darf man jedoch keinesfalls mit der Evaluation der klinischen Effektivität verwechseln. In zukünftigen Studien wird sowohl die Evaluation der Struktur einer Organisation und der Pflegeprozesse wie auch die Evaluation der Endpunkte, die damit zusammenhangen, notwendig sein.

CURRICULUM VITAE

Stephanie Natsch graduated with a degree in pharmacy from the Swiss Federal Institute of Technology in Zurich in 1991. From 1992 to 1996, she worked as a hospital pharmacist at a district hospital in Switzerland. In 1996, she got a PhD degree in pharmacy at the University of Berne on the topic of implementation of antibiotic guidelines in the hospital. In 1996, she moved to the Netherlands, to pursue her research project on quality of use of antimicrobial drugs at the department of internal medicine of the University Medical Center in Nijmegen in close collaboration with the department of clinical pharmacy. In 1997/1998, she had an appointment at the European Society of Clinical Pharmacy as interim-director of the International office. In 1998/1999, she worked for the Netherlands Pharmacovigilance Foundation. From 1999 until 2001, she completed the specialist training in hospital pharmacy at the department of clinical pharmacy at the University Medical Center in Nijmegen in order to be registered as hospital pharmacist in the Netherlands. She is now continuing her specialist training at the University Medical Center Nijmegen to get a degree in clinical pharmacology.

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