The use of antibiotics in paediatrics and its possible consequences

The use of antibiotics in paediatrics and its possible consequences

Het gebruik van antibiotica in de kindergeneeskunde en de mogelijke gevolgen

(met een samenvatting in het Nederlands)

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Contents

General introduction

Since the introduction of penicillins in patient care in 1941 a dramatic improvement in the treatment of infectious diseases was achieved.[1] Antibiotics have considerably changed the epidemiology and prognosis of infectious diseases. Diseases like malaria, tuberculosis and rheumatic fever were no longer untreatable and the morbidity and mortality related to these diseases were reduced tremendously. Complications of frequent bacterial infections such as otitis media have become rare and the mortality and morbidity of severe infections as meningitis and osteomyelitis have been reduced. Antibiotics were considered miracle drugs during the second half of the previous century. The number of new agents developed in the decades following the discovery of penicillin is striking.
The development of newer generation antibiotics created a number of advantages in treatment of bacterial diseases like a better penetration, faster sterilisation of infected body sites, easier use and last but not least less toxicity. The treatment of bacterial meningitis over the past 35 years is exemplary for this evolution. Common childhood meningitis was treated with several antibiotics like sulphonamides or penicillins in the late 1940s, mostly in monotherapy or in combinations of sulphonamides, penicillin G and streptomycin. The introduction of chloramphenicol in the early 1950s resulted in the abandonment of the toxic streptomycin and increased the effectiveness of the treatment of meningitis by the most common pathogens *H. influenzae, N. meningitides and S. pneumoniae*. Treatment with a single drug was theoretically possible, however, "triple" therapy with penicillin, chloramphenicol and a sulphonamide continued to be widely employed except in developing countries where monotherapy with chloramphenicol is still used today.[2] Finally due to the availability of several suitable drugs of the cephalosporin

group, the current standard is monotherapy with a third generation cephalosporin. This treatment with a third generation cephalosporin is safe, probably effective even against ampicillin and chloramphenicol-resistant *H. influenzae*, and intermediate penicillin-resistant pneumococci and aminoglycoside resistant enterobacteria.[3] Newer drugs have not replaced older antibiotics but do provide the physician with a broader range of choices for the treatment of many infectious diseases, allowing more individualization of therapy.[3]

Two important events however occurred concurrently with the increased use of newer agents: expanding costs and development of resistance. Antibiotics account for a substantial proportion of the expenditure in pharmacies and hospitals. In children antibiotics are among the most commonly prescribed drugs.[4] Several studies at the end of the 1970s focusing on antibiotic prescribing attitudes in hospitalised children indicate that approximately 35% of admitted infants and children receive antibiotics.[4-8] In outpatient settings even higher percentages were found.[9] Moreover since the development and introduction of the first antibiotic, these powerful drugs have been overused and misused. Almost half of all antibiotic prescriptions were found to be inappropriate, based on clinical and financial criteria.[10,11]

Because of the rising costs in health care, lack of uniformity in prescribing attitudes and the emergence of antibiotic resistance, monitoring and controlling antibiotic use is needed.[12,13] Several Dutch persons were interested in these data and did some excellent research. Gysens described the use of antimicrobial drugs in a university hospital, measured by several cost-entered methods.[14] In the Netherlands, a strong national health policy against overuse of antibiotics and a tradition of prudent antimicrobial drug use has been institutionalised. Socio-economic factors and marketing pressures which lead to inappropriate use are thus controlled and physicians are educated likewise in this tradition. This has

been recently documented by Stobberingh who studied Dutch guidelines for prescription.[15] However, there is room for improvement. Janknegt described the antibiotic policy in Dutch hospitals by studying antibiotic formularies.[16] He demonstrated that the situation regarding the availability of antibiotic formularies in the Netherlands is not ideal and that an active policy in hospitals concerning the preparation of an antibiotic formulary is recommended.

Next to these data if we wanted to get more informed about the resistance pattern in the Netherlands several surveillance studies were performed. And collected data from eight laboratories, representing about 30% of the Dutch samples sent for culture, giving a detailed estimate of the antibiotic resistance in Gram-negative bacteria and Gram-positive bacteria in the Netherlands.[17-19] In addition continuous surveillance of antibiotic resistance in *Staphylococcus aureus* and coagulase-negative staphylococci is performed in nine Dutch public health laboratories.[20] Finally the susceptibility of strains of Methicillin Resistant *Staphylocoocus Aureus* (MRSA) from local laboratories to the National Institute of Public Health and Environmental Protection is continuously being analysed. In general these studies show that antibiotic resistance in the Netherlands is relatively low compared with other countries. This was confirmed in a clinical study on severe infections in hospitalised patients.[21] The surveillance of resistance of staphylococci by an electronic network over a 6 year period showed a very low percentage of methicillin resistance in *S.aureus*.[22]

From this data we know more in detail about the incidence of antibiotic resistance but the most important motivation for an optimal use of antimicrobial agents is the relationship between antibiotic use and antibiotic resistance. Several studies show a correlation between antibiotic resistance and antibiotic consumption.[23,24] Much of the attention on antimicrobial resistance has been focused on nosocomial or hospital-acquired infections.[25] Hospitals have experienced periodic

episodes of antimicrobial resistance affecting a variety of organisms, beginning with the emergence of penicillin-resistant staphylococci in the early 1950s. Subsequent nosocomial problems have included the emergence of various resistant Gram-negative organisms, methicillin-resistant staphylococci, and most recent vancomycin-resistant enterococci and multidrug-resistant *M.tuberculosis*. There are other organisms, such as multidrug-resistant Gram-negative bacilli, that produce important nosocomial problems. Likewise a number of community-acquired bacterial pathogens are developing increased antimicrobial resistance. Antimicrobial resistance in community-acquired organisms occurs when organisms are transmitted from hospitals or animal farms but also emerges within the community itself in response to selective pressure of antimicrobial use.[25] It is not only a problem on the national level but resistant organisms can also be transmitted between communities, making resistance a worldwide problem. Antimicrobial resistance increases the morbidity, mortality, and the costs associated with the disease of diseases. Various factors are involved in the development of resistance including microbial characteristics, environmental animal or human reservoirs in which resistant genes or resistant organisms can persist, patterns of antimicrobial use, and socio-economic and technologic changes that affect the transmission of organisms. Various combinations of these factors determine the frequency of occurrence of drug-resistant organisms.[25] Several strategies are available to counteract this public health emergency. A clear antibiotic policy is essential for preventing the rapid and wide-spread development of resistance, focused on empiric antibiotic therapy, prophylactic and long-term use of antibiotics.[25,26] To keep the resistance at a low level it is of paramount importance to limit the use of antibiotics. A positive correlation between the turnover of broad spectrum penicillins in various hospital departments and the incidence of resistant strains in patients in these departments could be found.[27] It has been shown that

increased bacterial resistance in a hospital department is reversible by discontinuation or reduction of antimicrobial therapy.[28-30] Periodic monitoring of resistance should be performed. At regular intervals surveillance studies should be performed in several places, preferably in urban communities and in areas with intensive live-stock farming. On the basis of these studies an estimate should be made of the prevalence of resistant strains. The results of these studies can be used to formulate guidelines for the use of antimicrobial drugs in human as well as in veterinary medicine. These guidelines can be modified, if necessary. Several professional societies have issued guidelines designed to reduce the use of antibiotics world-wide by means of various control strategies.[31-34] For example the impact of a clinical infectious disease task force with a clinician, medical microbiologist and a pharmacist will be of great importance to streamline the appropriateness of antimicrobial therapy.[35] This will also be a way to get more insight in the use of antibiotics and to try to define rules for a more rational and appropriate usage of antibiotics.

Although the above mentioned situation in the Netherlands is acceptable, we think it important to improve this situation and to get people aware of the consequences of antibiotic use. Until now there has been no research in general medicine nor in paediatrics to gain a better insight in the situation of antibiotic related costs and prescription patterns. Nor was there any research on the knowledge of doctors regarding antibiotics and the situation of resistance. Therefore we started a study in a paediatric university hospital concerning all these data as described in this thesis.

The study was started in August 1995 and focuses on analysing antibiotic prescribing trends in relation to costs and antibiotic resistance. The study consists of a number of phases, starting with an inventory of important variables (antibiotic expenditure, use of antibiotics in daily practice, uniformity in prescribing behaviour). During the next phase a project group was formed to reach a consensus or a solution for the

problems defined in the first phase. After this an implementation phase was started in which all the defined solutions were used in the daily practice of the hospital. Finally a continuous surveillance was performed in which all variables were analysed again and compared with the initial results. After a period of three years the study was concluded by formulating guidelines for the future. The above mentioned phases of the study were defined as aims of the study.

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Aims of the study

Analysing costs relating to prescription of antibiotics in a tertiary care paediatric department.

(chapter 2 and 5)

Analysing physicians' prescribing attitudes regarding antibiotics.

(chapter 3)

Studying the impact of a more rational usage of antibiotics on antibiotic-related costs.

(chapter 4)

Studying antibiotic use in a paediatric intensive care unit in relation to the development of sepsis with Gram-negative bacteria.

(chapter 6)

CHAPTER ONE

Antimicrobial practice and malpractice in paediatrics

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Abstract

Antibiotics are prescribed for a considerable proportion of paediatric patients, often on an empirical basis without appropriate proof or suspicion that a bacterial infection is present. This overuse and abuse has a significant impact on both health care expenditure and development of antibiotic resistance. However, little is known on the mechanisms underlying prescribing patterns by physicians. Pharmacoeconomic data on antibiotic use in paediatrics are lacking and the correlation between prescribing patterns and resistance development is only documented for a limited number of paediatric infectious diseases. Unfortunately this information is indispensable in order to design future strategies to control health care costs and curtail resistance development.

Introduction

Antimicrobial agents are among the most frequently prescribed drugs, in adults as well as in children.[1,2] Since their discovery antibiotics have changed considerably the epidemiology and prognosis of bacterial infectious diseases. Complications of frequent bacterial infections such as otitis media have become uncommon, and the mortality and morbidity of severe infections as meningitis and osteomyelitis have been reduced considerably. Antibiotics have been considered miracle drugs during the second half of this century and the number of new agents that were developed in the decades following the discovery of penicillin is striking. However, with an exhaustive list of antibiotics available in the therapeutic armamentarium of every physician, it becomes increasingly evident that in a considerable proportion of cases antibiotics are prescribed unnecessarily, an inappropriate agent is chosen, or the dose is incorrect.[3,4] In addition a tendency exists to prescribe newer, more expensive, broad-spectrum drugs.[5,6] Partly as a result of these prescribing patterns costs involved in antibiotic usage are exorbitantly high, especially when all related expenses are taken in consideration (purchase of the drug, preparation and administration by trained personnel).[7]

More important however is the relation between the use of antibiotics and the emergence of antimicrobial resistance. Although the development of resistance is enhanced by a number of factors including usage of antibiotics in animal husbandry and over the counter use by patients, prescribing patterns by physicians are probably a major determinant. Although there is extensive literature on antibiotic policy in adults, information concerning antibiotic use and its possible consequences in the paediatric setting is scant. The present review summarises the relevant literature on antibiotic prescribing policy in relation to health economics and development of resistance, with a focus on paediatric data.

Use, overuse and abuse of antibiotics

The first studies on antibiotic use were performed in adults admitted to general hospitals.[8-10] It was shown that one third of adults receive at least one course of antibiotics during one hospitalization. It became clear from later studies that antibiotic usage was even higher in paediatric and surgical services. Young age and admission on an intensive care unit were correlated with an increased tendency to receive antibiotics. [11-14] We showed recently that in a tertiary care hospital infants less than 2 years of age received significantly more often antibiotics than older children (25 *vs.* 11% of all admissions). Children admitted on neonatal or paediatric intensive care units received more often antibiotics than patients admitted on medium care wards (50 *vs.* 30%) as well as more different courses (2.6 *vs*. 1.9 per patient per hospitalization).[13] Penicillins were prescribed most commonly, followed by cephalosporins, aminoglycosides and macrolides. More recently data have become available on the use of antibiotics in the outpatient setting. Although antibiotics have little or no effect on viral conditions such as upper respiratory tract infections and bronchitis, more than half of adult patients suffering from these diseases are prescribed antibiotic treatment.[15] Another study showed that 25% of the population of France was treated with antibiotics in 1991 (as compared to 17% in 1980). In the meantime an increased prescription rate for presumed viral conditions was demonstrated.[16] Although the methods used in the studies mentioned above differ considerably. The conclusion is inevitable: antibiotics are prescribed on a large scale both for hospitalised individuals and out-patients.

The use of antibiotics in paediatrics has some peculiar aspects. Children are especially prone to severe infections by micro-organisms as *S. pneumoniae*, *N. meningitidis* and *Salmonella* species. In the meantime the clinical presentation of a severe bacterial infection can be misleading in the very young in

comparison with the clear-cut clinical picture in the older patient. This implicates that certain forms of empirical antibiotic therapy in unproven but suspected bacterial diseases in childhood is legitimate, e.g. in febrile infants less than 3 months old, or children with meningitis and a negative Gram stain of the cerebrospinal fluid.

However, we cannot deny an unwarranted large-scale use of antibiotics and a gradually increasing use of new, broad-spectrum and expensive agents, suggesting overuse and possibly abuse of these drugs.[5,12,14,17,18] This malpractice can take several forms (table 1). Treatment of non-bacterial or self-limiting bacterial infections is common. Two recent reports in the paediatric literature, using questionnaires mailed to general practitioners and paediatricians, show that between 25 and 75% of patients with mild, probably viral, respiratory infections receive antibiotics, especially if the course of the disease is protracted for 7-10 days.[6,19,20] Even so,non-infectious diseases as asthma are often treated with a course of beta-lactam or macrolide antibiotics.[21] Finally, self-limiting bacterial upper respiratory tract infections are often treated with prolonged and repeated courses of antimicrobials, where withholding antibiotics or using a shorter course might be an

TABLE 1. Forms of overuse or abuse of antibiotics in clinical practice

- Treatment of non-bacterial diseases
- Treatment of self-limiting bacterial diseases
- Inappropriate antibiotic prophylaxis
- Treatment of "suspected" rather than proven infections
- Errors in generic choice, dosing and duration of therapy
- Inappropriate combination therapy
- Parenteral rather than oral therapy

effective treatment option. Although it is clear that some cases of otitis media and sinusitis deserve antibiotic therapy, in order to prevent infectious complications this is clearly not applicable to all patients. The majority of paediatric patients with these diseases recover without antimicrobial treatment. Delineating the complication-prone group is difficult and guidelines on antibiotic treatment of these upper respiratory tract infections should incorporate these uncertainties.[22-24] More than half of the antibiotic courses prescribed for hospitalised children are given on empirical grounds i.e. without microbiologic or clinical proof of a bacterial infection before or after the start of the antimicrobial treatment.[13]

Errors in generic antibiotic choice, dosing and duration of therapy are unacceptably common. It has been estimated that errors in prescription could be detected in 30% of medical and 60% of surgical cases both in adults and children.[14,25] A questionnaire containing 13 clear-cut clinical cases was sent to paediatricians in the Netherlands and Belgium. Physicians were asked to choose a generic antibiotic, as well as the dose and duration of treatment. There was a complete lack of uniformity in the three parameters of the questionnaire as shown for one particular case (bacterial meningitis) in figure 1. Between 25 and 50% of dosages and durations of therapy for the various clinical conditions fell outside the range of appropriate treatment. [26] Finally, inappropriate combination therapy and parenteral rather than oral therapy induce overuse of antimicrobial agents.[27-29]

Several reasons can be proposed to explain this manifest overuse and abuse of antibiotics (table 2). Driven by previous experience or litigation issues, physicians prescribe antibiotics out of a feeling of insecurity, especially if the disease runs a protracted course.[20,21,30,31] Patients' expectations, often against a background of an established doctor-patient relationship, can induce a culture of prescribing antibiotics for unclear

indications.[32,33] Lack of in-depth knowledge of microbiologic aspects of infectious diseases and of pharmacodynamics and pharmacokinetics of antimicrobial medications induce a lack of uniformity of prescription, especially in the absence of clear local or international guidelines.[26] Finally the impact of recent trials in which the physician collaborated and aggressive marketing by pharmaceutical companies cannot be ignored.[34]

This overuse (and abuse) of antibiotics is responsible for a disproportionate expenditure of health care money in general

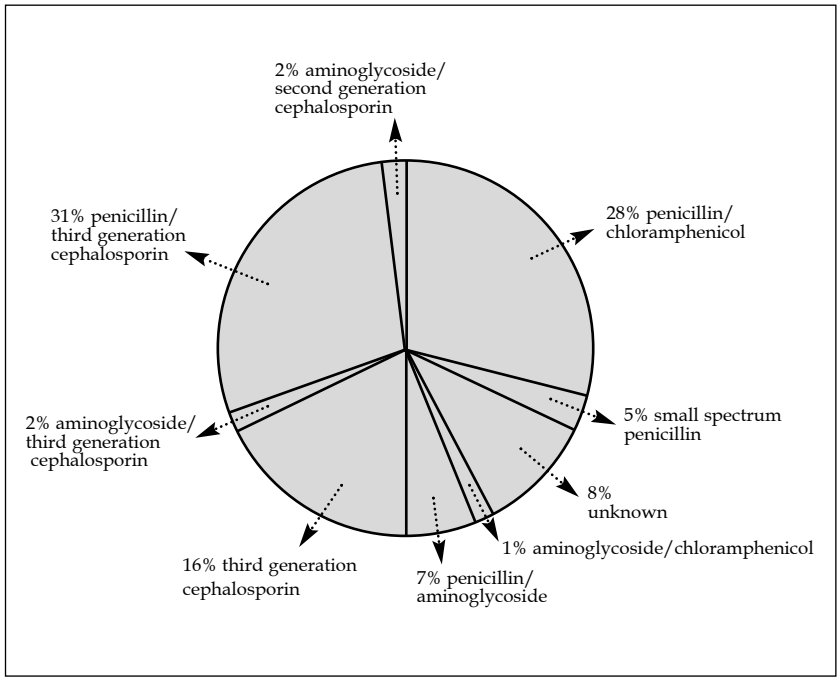

FIGURE 1. The antibiotic choice of paediatricians and residents for a child with bacterial meningitis. These results were part of a questionnaire, with 13 clear clinical cases, in which paediatricians and residents were asked for their generic antibiotic choice for each of the cases.

and hospital budgets in particular.[5] Unfortunately scientific literature on this correlation is almost non-existing.

Prescribing and resistance development

Widespread antimicrobial-drug resistance is one of the most important challenges in medicine at the turn of the century. Soon after the discovery and clinical application of antibiotics, resistance of both community- and hospital-acquired micro-organisms emerged. There is increasing doubt whether development of new drugs can keep pace with the ability of the bacteria to develop resistance. The mechanisms of resistance are reviewed in detail elsewhere.[35-37] For the paediatric population especially pneumococcal resistance against penicillin is cumbersome, as well as resistance of Gram-negative microorganisms against beta-lactam antibiotics.[38,39] Prior exposure of bacteria to antibiotics promotes the development of resistant mutants. In this regard the widespread use of antibiotics as growth-promoting agents in cattle and fowl is a definite determining factor.[40] A causal relationship between antibiotic usage in clinical medicine and development of resistance of microorganisms in hospitals has

TABLE 2. Reasons for overuse and abuse of antibiotics

- Feeling of insecurity (previous experience)
- Patients' expectations
- Doctor-patient relationship
- Aggressive marketing by pharmaceutical companies
- Lack of uniformity among physicians in the same organisation
- Lack of knowledge of microbiologic aspects of infectious diseases
- Lack of knowledge on pharmacodynamics and pharmacokinetics
- Impact of recent clinical trials ("seeding trials")

been suggested on the basis of consistent associations between the emergence of resistant strains and concurrent variations in antibiotic use in populations over time.[41] However, conclusions of the studies can not be generalised to all drugs and all patient populations because of the lack of uniformity in defining resistance, variations in susceptibility of test methods (and interpretation of the results), potential study selection biases, and failure to control for confounding variables, especially variations in infection control measures in the hospital or extended care setting.[42]

Nonetheless, there are sufficient reports of the association between antimicrobial usage both in the community and in hospitals, and the emergence of antimicrobial resistance to implicate prescription attitudes as a causal factor in antimicrobial resistance development.[43] A striking example was reported in Finland where the overall use of erythromycin nearly tripled from 1979 to 1989, followed by a rapid and substantial increase in resistance to erythromycin in group A streptococci.[44,45] A similar example constitutes the increased carriage rates of penicillin-resistant pneumococci following increased individual antibiotic use and total antimicrobial consumption in the population.[46] Several studies show a significant association between prior use of cephalosporins and the development of resistant Gram-negative micro-organisms which have become a major threat especially in intensive care units.[47-50] A survey of American hospitals reported by the Centers for Disease Control and Prevention indicated a linear increase in ceftazidime resistance among *Klebsiella* and *Enterobacter* isolates after the use of cephalosporins, particularly in intensive care units and teaching hospitals, between 1987 and 1991.[50] Also the use of the newer fluoroquinolones has been followed soon by fluoroquinolone resistance.[51]

Although these studies constitute only a few examples of the relation between antibiotic use and resistance development, they are illustrative for the magnitude of the problem and the necessity to take appropriate action on the local and global level.

Future strategies

The increasing costs accompanying overuse and abuse of antibiotics, as well as the problem of antibiotic resistance have made the necessity to design future strategies more urgent than ever. These strategies will have to be focused on all individuals involved in antibiotic consumption. Several national and international societies have recognised this challenge and taken action through the installation of task forces [52], and general as well as specific guidelines are proposed to control costs and slow down development of antimicrobial resistance.[43,53]

First, patients themselves need to understand what antibiotics can and cannot do. If antibiotics have been prescribed they should take the complete course as accurate as possible. Self-medication should be discouraged. Physicians and national authorities have the responsibility to educate the population about these issues, through mailings, symposia, broadcasting or direct individual argumentation.
Second, use of antibiotics as growth-promoting agents in animal husbandry should be discouraged and probably banned. In the absence of clear evidence for their effect as growth-stimulators and the global threat of resistance development, laws should be passed to prohibit this practice.

Third, pharmaceutical companies have the responsibility to concentrate on development of new agents rather than on aggressive marketing campaigns.[54] They should explore new targets for antibacterial drugs and in concert with the scientific community, design treatment strategies different from the classic pathogen-specific drugs.[55]
Fourth, national governments and international political and non-governmental organisations should stimulate research in the area of resistance control and support initiatives to implement stringent guidelines. Moreover, they should pass

laws and recommendations enforcing agreed-upon results of these initiatives to prevent overuse and abuse of drugs.

Fifth, physicians prescribing antibiotics, microbiologists engaged in hospital epidemiology and resistance surveillance, and hospital pharmacists evaluating the antibiotic-related costs, play an important role. Although the epidemic of antimicrobial resistance and the challenge of cost containment are global problems, monitoring and management need to be executed locally.[56] As shown by Seppälä et al., changing the prescription of macrolide antibiotics in Finland had a beneficial effect on the prevalence of macrolide resistant Group A streptococcal isolates.[44] Unfortunately, not all actions taken in this regard are as successful, as has been shown for changing prescription patterns of aminoglycosides.[57,58] Most probably, preventive strategies are more effective than actions taken after resistance has developed. [59,60] Several plans can be developed to streamline these preventive measures. Microbiologists and (paediatric) infectious disease specialists need to have a programmatic role in controlling antibiotic prescription guidelines.[61-63] Among the possibilities are strictly enforced antimicrobial formularies, specific antibiotic order forms [64,65], automated stop orders, computerised decision models for empiric antibiotic selection [66], top-down manipulation and enforcement of formularies [67], implementation of a "prior authorisation" model for selected drugs[68], general standardised antimicrobial prophylaxis guidelines [69], automated cost reports and individual feedback mechanisms controlled by the hospital pharmacy[70], and educational programs on the student and post-doctoral level. Each method itself has its own advantages and disadvantages and until now a study in which all these methods are compared has not been performed.

Conclusion

Antibiotic use, overuse and abuse for clinical and outpatient situations alike have driven antimicrobial-related costs to disproportionate levels and can be implicated as important promoters of development of antibiotic resistance. Since the majority of diseases of childhood has an infectious origin, paediatricians have contributed considerably to this threatening situation. Strategies to curtail these events need to be implemented soon in order to have a reasonable chance to slow the pace with which we are moving towards the post-antibiotic era.

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CHAPTER TWO

Shift in antibiotic prescribing patterns, in relation to antibiotic expenditure in paediatrics

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Abstract

Background • In paediatrics antibiotics are among the most commonly prescribed drugs. Because of an overall rise in health care costs, lack of uniformity in drug prescribing and the emergence of antibiotic resistance, monitoring and control of antibiotic use is of growing concern and strict antibiotic policies are warranted. Before such a policy can be implemented, detailed knowledge of antibiotic prescribing patterns and related costs is important. In this study a shift of antibiotic prescriptions patterns over time is described in relation to hospital antibiotic expenditure.

Methods • Over a 10-year period (1984 -1994) pharmacy surveys of antibiotic costs in relation to prescription patterns in a paediatric university hospital were analysed.

Results • In 1984 small- and broad-spectrum penicillins represented almost 50% of the total antibiotic expenditure, versus 7% in 1994. On the other hand, the use of third generation cephalosporins and vancomycin increased from 3.2% to 46.7% and 0.2% to 17.2% of the total antibiotic costs respectively. The reasons for this shift in prescribing pattern could only partially be explained by an increase in admissions of "high-use" patients or a shift in antibiotic resistance patterns. Moreover, monitoring the antibiotic costs is only of limited help in monitoring these prescription changes.

Conclusions • A considerable shift in prescription patterns towards more expensive and broader spectrum antibiotics occurs in paediatrics, carrying a risk for the development of antibiotic resistance among the most prevalent micro-organisms in this age group.

Keywords: children, antibiotics, drug expenditure, drug utilization, prescriptions.

Introduction

In children antibiotics are among the most commonly prescribed drugs.[1] Several studies focusing on antibiotic prescribing attitudes in hospitalised children indicate that approximately 35% of infants and children admitted to hospitals receive antibiotics.[2-5] Widespread misuse has been reported. Almost half of all antibiotic prescriptions have been found to be inappropriate, based on clinical and economical criteria.[6] Because of the rising costs in health care, lack of uniformity in prescribing attitudes and the emergence of antibiotic resistance, monitoring and controlling antibiotic use is of growing concern.[7-10] Several professional societies have issued urgent statements to reduce the use of antibiotics worldwide by means of strict local antibiotic policies.[7,10] Before such a policy can be implemented, detailed knowledge of antibiotic prescription patterns and related costs is important. Defined Daily Dose (DDD) can be used as a measure of drug utilization in adults.[11,12] Only one study described the use of DDD in children.[13] A combination of other, mostly indirect variables, as expenditure and number of prescriptions of antibiotics per patient or hospital day as well as recording all adverse reactions to drugs are used more often.[1-6,13]
In this study the use of antibiotics in a tertiary care paediatric university hospital over a 10-year period was evaluated, by analysing the prescription patterns in relation to the total antibiotic expenditure.

Methods

The study was performed in the Beatrix Children's Hospital, a Paediatric University Hospital in the Northern part of the Netherlands. The hospital is the only tertiary referral centre for a population of approximately 2.5 million. The number of beds increased during the study period from 80 to 103. A 23-bed

neonatal intensive care unit was built in 1984, followed by a 6-bed paediatric intensive care unit in 1986. Annually approximately 2000 patients are admitted for a mean duration of hospitalization of 13.9 days. Over a 10-year period (1984-1994) pharmacy surveys of antibiotic costs and prescriptions of all inpatients were analysed. Antibiotics used were classified according to the hospital formulary and the international Anatomical Therapeutical Chemical (ATC)-classification.[14] Additional information was collected from the financial records of the Children's Hospital. Total antibiotic expenditure for each antibiotic class, general prescription patterns, price changes and quantities of antibiotics used were investigated.

Results

During the study period the prescription patterns changed considerably. In 1984 penicillins represented almost 50% of the total antibiotic expenditure and the aminoglycosides 23.2%. In 1994 these percentages had decreased drastically to 7.0% and 9.0% respectively. On the other hand, the use of cephalosporins and vancomycin increased from 17.7% to 49.9% and 0.2% to 17.2% of the total antibiotic costs respectively (table 1).
The use of small- and broad-spectrum penicillins decreased from 47.8% in 1984 to 2.9% in 1994, while in the same period the use of combination penicillins (amoxicillin/ clavulanic acid) increased from 0.4% to 4.1%. Looking at the different generations of cephalosporins hardly any change was found for the first generation. The second generation decreased from 13.6% to 2.6%, but the third generation cephalosporins increased significantly during these 10 years, from 3.1% in 1984 to 46.7% in 1994. The antimycotic and antiviral drugs and quinolones were prescribed increasingly during the study period although changes were less dramatic. Other antibiotics as macrolides, tetracyclines, polypeptides, sulphonamides,

were responsible for less than 10% of total antibiotic expenditure and did not show a remarkable change during the study period. Although several reasons can be suggested for this shift in antibiotic expenditure, none of them is fully explanatory. Major changes in resistance patterns did not occur. Methicillin resistant *Staphylococcus aureus* and penicillin resistant *Streptococcus* necessitating empirical vancomycin use is an extremely rare event (less than 1%). Price fluctuations of

TABLE 1. Use of antibiotics as percentage of total antibiotic expenditure

Antibiotics	**1984**	**1985**	**1986**	**1987**	**1988**	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**
Penicillins											
small-spectrum	8.2	4.7	3.0	2.6	3.0	3.1	2.2	1.4	1.0	1.5	0.7
broad-spectrum	39.6	36.9	21.8	14.4	9.7	6.7	4.1	2.6	4.1	2.8	2.2
combination	0.4	0.6	0.4	0.2	1.9	0.9	1.8	0.6	1.1	3.5	4.1
Total	48.2	42.2	25.2	17.2	14.6	10.7	8.1	4.6	6.2	7.8	7.0
Cephalosporins											
first generation	0.9	0.5	0.7	0.3	0.4	0.5	0.2	0.2	0.3	0.4	0.3
second generation	13.6	11.4	5.7	9.2	9.4	10.7	16.0	11.3	11.1	5.9	2.6
third generation	3.2	15.0	40.0	33.0	26.5	23.2	18.0	21.7	23.0	42.6	46.7
Total	17.7	26.8	46.5	42.5	36.3	34.4	34.2	33.3	34.4	48.9	49.6
Vancomycin	0.2	1.5	2.2	4.8	7.0	10.1	20.0	19.4	21.1	15.0	17.2
Amino-glycosides	23.2	20.5	15.3	18.3	17.1	19.5	17.9	17.7	16.2	10.7	9.0
Antivirals	0.1	0.1	0.0	1.6	2.7	5.7	3.3	3.8	6.0	5.4	4.4
Antifungals	2.8	2.2	2.4	6.3	8.5	9.4	6.9	10.0	6.6	4.1	5.6
Quinolones	0.0	0.0	0.0	0.1	3.6	1.5	1.5	1.7	0.0	0.3	0.4
Others	7.8	6.6	8.4	9.1	10.1	8.7	8.1	9.5	9.5	7.8	6.8
Total (%)	100	100	100	100	100	100	100	100	100	100	100

antibiotics, used by pharmaceutical companies for marketing purposes as well as by hospital pharmacies to reduce drug costs, influence the crude expenditure figures considerably, as illustrated in table 2. When calculating an average price for prescribed antibiotics, the estimated antibiotic expenditure in 1994 would be nearly twice the expenditure in 1984 if the prices had not decreased over the years. Although prices and the number of prescription per patient decreased, the total expenditure remained constant, mainly because of the use of more expensive, broader spectrum drugs. If prices had not changed over the years the estimated expenditure would be doubled.

Discussion

Until now no study in literature could be found describing shifts in prescribing patterns of antibiotics in paediatrics. Over the study period a dramatic shift in antibiotic prescription patterns was observed, although the total antibiotic expenditure did not increase significantly. A remarkable shift occurred from the use of less expensive penicillins to newer,

TABLE 2. Estimation of expenditure in 1994 with constant number of prescribed units of antibiotics

Year	1984	1994
Total antibiotic expenditure (U.S.dollars)	278615.4	285031.4
Number of prescribed units antibiotics	46851	23598
Average price of antibiotics	5.9	11.9
Estimated expenditure with constant number of prescribed units antibiotics		557526.9
Estimated expenditure with constant price		140333.5

resistance inducing and more expensive cephalosporins and vancomycin.[15] This could not be explained by shifts in resistance patterns of isolated micro-organisms. A remarkable increase in the number of admissions or hospitalization days did not occur, although a shift to a higher intensity of medical care could not be ruled out. Over the study period a slight increase in number of admissions of "high-use" patients could be found. The number of patients admitted yearly to the neonatal intensive care unit increased gradually from 408 in 1984 to 604 patients in 1994. Of these admitted neonates the percentage of mechanically ventilated patients remained 50% over the years and the number of patients with an umbilical catheter which is a possible entrance for micro-organisms decreased from 50% in 1984 to less than 15%of all admitted patients in 1994. The number of patients admitted to the paediatric intensive care unit increased from 193 in 1986 to 289 patients in 1994. Next to these data an increase in the number of admitted oncology patients receiving antibiotics could be shown from 299 in 1984 to 367 patients in 1994. The influence of new antibiotic protocols is marginal and compensate each other mutually.
The total costs of antibiotics is often used by hospital boards to monitor budgets and motivate personnel for a change in prescribing attitudes. It is shown that due to several factors as marketing techniques and price cuts, this parameter is useless for monitoring antibiotic use in the hospital. It is necessary to study prescription patterns of antibiotics over several years, in order to study clinically, economically and microbiologically important shifts and relate these prescription patterns to shifts in the patient populations. More accurate indicators as DDD per 1000 hospital days should be used, but this parameter is only practical in adult medicine. To our knowledge no equivalent accurate parameter exists for children.

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CHAPTER THREE

Empiric antibiotic therapy: assessment of agreement between paediatricians

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Abstract

Background • Antibiotics are among the most commonly prescribed drugs in paediatrics. Most frequently antibiotics are started empirically. Lack of uniformity in prescribing attitudes causes uncontrollable expenses for antibiotic treatment and is at least partially responsible for the emergence of antibiotic resistance. The objective of this study was to assess the agreement on empiric antibiotic selection between paediatricians.

Materials and methods • A questionnaire including 13 hypothetical clinical cases was sent to all paediatricians and paediatric residents in the northern part of the Netherlands, and a random selection of paediatricians of Flanders, the northern part of Belgium. Their choice of antibiotic therapy (generic class, dose, duration) with regard to these cases was evaluated.

Results • One hundred and seven (68.6%) of 156 Dutch paediatricians and paediatric residents returned completed questionnaires. Thirty-six (36%) of 100 Belgian paediatricians returned completed questionnaires. A widespread variability in choice of antibiotic therapy was found, especially in the generic class of the antibiotic. A median of 17 and 11 different antibiotics for the Dutch and Belgian paediatricians respectively was found per clinical case. The greatest variability (32 and 17 different antibiotics for the Dutch and Belgian paediatricians respectively) was found for a premature infant with suspicion of bacteraemia. The lowest variability existed for cases with lower respiratory tract infections and otitis media (5 and 3 different antibiotics for the Dutch and Belgian paediatricians respectively). In addition the dose of the antibiotic and duration of treatment varied considerably. A disturbing proportion of doses was not in concert with commonly advised regimens.

Conclusion • Considerable variability was found in empiric antibiotic selection between paediatricians and paediatric residents in

The Netherlands and Flanders. In order to reduce antibiotic costs and limit antibiotic resistance development, one of the first goals will be to increase uniformity in antibiotic prescribing attitudes.

Introduction

In children antibiotics are among the most commonly prescribed drugs.[1] Several studies focusing on antibiotic prescribing attitudes in hospitalised children indicate that approximately 35% of infants and children admitted to hospitals receive antibiotics.[2-5] Most frequently antibiotics are started on an empirical basis, defined as treatment without clear clinical or microbiological evidence of infection.[6] Antibiotic selection has become more difficult with the recent release of many agents with various pharmacokinetic, antimicrobial and toxicological characteristics and the emergence of resistance to many traditional agents.[7] Widespread misuse of antibiotics has been reported. Almost half of all antibiotic prescriptions have been found to be inappropriate, based on clinical and economical criteria.[8] Serious consequences in terms of mortality and complications can result from inappropriate antibiotic therapy.[9] Because of the rising costs in health care, lack of uniformity in prescribing attitudes and the emergence of antibiotic resistance, monitoring and controlling antibiotic use is of growing concern.[10-13] Therefore worldwide attempts have been made to optimise the use of antibiotics. Several professional societies have issued urgent statements to reduce the use of antibiotics worldwide by means of strict local antibiotic policies.[12,13] In the Netherlands the "Health Council" stressed the importance of an optimal use of antibiotics based on data obtained by regular surveillance of bacterial resistance patterns.[14] In 1991 75% of the Dutch university hospitals and 53% of the hospitals with 500 beds or less had written guidelines, but these formularies require further improvement and need revision.[15] Since 1995 an independent formulary for paediatrics has been used most commonly for the treatment of infectious diseases in the Netherlands.[16] In order to implement an antibiotic policy it is important to determine the existence of uniformity in antibiotic prescribing attitudes for in- and outpatients. Although

consensus reports on the treatment of individual infectious diseases are available, large variability exists in therapeutic practice on the local, national and international level.[17-20] On the other hand it has been shown that compliance with a strictly enforced antibiotic regimen leads to reduction of costs and resistance development.[21,22] In order to study the degree of uniformity of empiric antibiotic therapy in paediatrics questionnaires with clinical cases was sent to all paediatricians and paediatric residents in the northern part of the Netherlands and Flanders.

Methods

Questionnaires were sent to all 156 paediatricians and paediatric residents in the northern part of the Netherlands and to 100 randomly selected paediatricians in Belgium. In the Netherlands sixty-seven are working in one university hospital, 89 divided over 25 regional hospitals. Each fifth paediatrician on an alphabetical list of all Flemish paediatricians was selected up to a total of 100 practising paediatricians. Initial non responders received up to two additional mailings of the same questionnaire. The questionnaire contained 13 clear clinical situations; a child of three weeks old with bacterial meningitis (1), a four year old girl with a clinically and radiologically proven bacterial pneumonia (2), a seven year old boy with sinusitis (3), a five year old girl with pyelonefritis (4), a four year old child with bilateral otitis media (5), a premature infant, with respiratory distress and sepsis (6), a twelve year old girl with high fever, hypotension, tachycardia and bloody diarrhoea (7), an eight year old boy with osteomyelitis of the ankle (8), an eight year old girl with atypical pneumonia (9), a three year old girl with bacterial meningitis (10), a four year old girl with endocarditis (11), a two year old girl with infected eczema (12) and a nine year old boy with septic arthritis (13). For each of these cases

an empirical antibiotic treatment was requested including generic name of the drugs, as well as dose and duration of treatment. Missing answers (because the respondent indicated he did not know the empirical treatment) were excluded from further analysis. Questionnaires were analysed for each case separately. For each case the number of different selected antibiotics (that means the number of generic groups and the number of antibiotics as part of the same generic group), as well as the variability in dose and duration of therapy was analysed. The degree of variability was empirically classified in three groups: greatest variability (< 2 doctors per choice), less variability (> 5 doctors per choice) and average variability (>2 and < 5 doctors per choice). Data were analysed for all paediatricians and for the Dutch paediatricians (in the university setting and regional setting) and Belgian paediatricians separately. The survey was conducted anonymously.

Results

In the Netherlands 30 paediatricians (71%) and 20 paediatric residents (80%) of the university hospital and 62 paediatricians (69.7%) of the community hospitals returned questionnaires, of which 107 (68.6%) were completed and 5 (3%) were returned without any answers. In Belgium 38 paediatricians (38%) returned questionnaires, of which 36 (36%) were completed and 2 (2%) were returned without any answers. A great variability in choice of antibiotic therapy was found, as shown in table 1 for each case. Looking at the different generic drugs even less uniformity in choice could be found (data not shown). For residents the greatest variability was found for the cases with central nervous system infections and endocarditis; for paediatricians in the university setting for the cases with suspicion of meningitis, pyelonefritis, and bacteraemia; for paediatricians in the regional setting for the child suspected of

endocarditis and for the Belgian paediatricians for the cases with suspicion of bacteraemia or endocarditis. The least variability was found for the residents for the cases with respiratory tract infections and pyelonefritis; for the

TABLE 1. Number of antibiotic classes chosen for each case
(The following antibiotic classes were defined: penicillins, cephalosporins, aminoglycosides, sulphonamides, vancomycin, quinolones, metronidazol or a combination of these antibiotics)
The chosen number of antibiotics / the exact number of respondents for each individual case. When the answer "unknown" was selected, this was considered a missing value and excluded for further analysis.

Case number	Residents University hospital (n = 20)	Paediatricians University hospital (n = 30)	Paediatricians Community hospital (n = 62)	Total Netherlands (n = 112)	Paediatricians Belgium (n = 36)
1.	5 / 19	4 / 26	4 / 59	5 / 104	6 / 34
2.	1 / 19	3 / 28	4 / 59	4 / 106	4 / 36
3.	2 / 17	2 / 27	4 / 59	4 / 103	3 / 36
4.	2 / 17	6 / 25	6 / 59	8 / 101	7 / 36
5.	2 / 19	2 / 28	3 / 59	3 / 106	5 / 36
6.	4 / 20	7 / 25	6 / 59	7 / 104	6 / 33
7.	8 / 15	11 / 21	11 / 53	15 / 99	10 / 34
8.	3 / 16	4 / 27	6 / 56	6 / 99	5 / 36
9.	2 / 17	3 / 26	4 / 56	5 / 99	5 / 36
10.	7 / 20	4 / 27	8 / 58	9 / 105	5 / 35
11.	5 / 13	5 / 18	6 / 38	8 / 68	7 / 25
12.	5 / 15	5 / 26	6 / 55	7 / 96	5 / 36
13.	3 / 13	4 / 23	4 / 52	4 / 88	4 / 31
mean:	3.8 ± 2.1	4.6 ± 2.4	5.5 ± 2.1	6.5 ± 3.1	5.5 ± 1.8
range:	1 – 8	2 - 11	3 - 11	3 - 15	3 - 10

paediatricians in the university setting for the cases with respiratory tract infections; for paediatricians in the regional setting for the children suspected of respiratory tract infections and for the Belgian paediatricians for the cases with respiratory tract infections. Average variability was found for all the rest of the cases. The dosage of the chosen therapy showed also a considerable variability and did not always comply with the literature or commonly used formularies[16,23] (table 2).

For both groups, the Dutch and Belgian paediatricians, greatest variability was found in the dosage of penicillins for central nervous system infections in a range between 13-500

TABLE 2. Dosage of antibiotic therapy (milligrams/kg)

Antibiotic (infectious diseases; case number)	**Dutch Paediatricians**		**Belgian Paediatricians**	
	range	**median**	**range**	**median**
Penicillins (central nervous system infections; 1 , 6, 7 and 10)	13 - 500	100	25 - 300	100
Penicillins (respiratory tract infections; 2, 3, 5 and 9)				
Oral	10 - 100	50	12.5 - 250	50
Intravenous	50 - 200	100	30 - 200	100
Cephalosporins (central nervous system infections; 1, 6, 7 and 10)				
Ceftriaxone	40 - 150	100	30 - 150	100
Ceftazidime/cefotaxime	50 - 300	100	50 – 200	100
Cephalosporins (pyelonefritis)	50 - 150	100	50 – 200	100
Aminoglycosides				
Gentamycin/netilmycin/tobramycin	2 - 10	5.0	3 - 8	6.0
Amikacin	5 - 20	10.0	5 - 20	15.0

milligrams/kg and 25-300 milligrams/kg respectively. Only 26% of the amoxicillin prescriptions were between the accepted range in dosage (200-400 milligrams/kg) as described in textbooks of paediatrics. In the Netherlands a child with suspicion of respiratory tract infections was treated intravenous or orally with a dosage of penicillins between 50 and 200 milligrams/kg and 10 and 100 milligrams/kg respectively. More than 75% was treated with a dosage as suggested in textbooks of paediatrics. In Belgium these data are comparable.
The dosage of the aminoglycosides netilmycin, gentamycin and tobramycin was too low or too high in 23% and 10% of prescriptions in the Netherlands and Flanders respectively. For

TABLE 3. Duration of therapy for each case

Case number	Dutch Paediatricians No. of days		Belgian Paediatricians No. of days	
	range	median	range	median
1.	7 - 21	14	3 - 21	10
2.	5 - 14	10	5 - 14	8
3.	5 - 14	7	5 - 21	10
4.	5 - 21	10	3 - 14	10
5.	5 - 10	7	5 - 14	8
6.	5 - 21	10	5 - 14	10
7.	5 - 14	10	5 - 10	7
8.	7 - 42	28	5 - 42	21
9.	3 - 14	10	3 - 21	10
10.	7 - 21	10	3 - 14	10
11.	10 - 42	42	6 - 42	28
12.	5 - 28	7	5 - 14	8
13.	3 - lifelong	-	1 - lifelong	-

central nervous system infections, 60% and 70% of all children were treated with a dosage of ceftriaxone according to the advised regimen in literature. Forty and thirty percent were treated with a low dosage. For ceftazidime and cefotaxime 90% and 52% respectively were treated with correct dosages. Finally the suggested duration of therapy showed a remarkable variability for both groups (table 3). Again generally accepted guidelines were breached in several occasions.

Discussion

Considerable variability was found in empiric antibiotic therapy between paediatricians and paediatric residents in the northern part of the Netherlands and part of Belgium. A slight difference exists between the choices of the paediatricians in the Netherlands and Flanders. The clinical relevance of these differences is not exactly clear, but the low response rate of the Belgian paediatricians could have accounted for part of the difference. This variability was evident for selected antibiotic groups, generic classes of antibiotics as well as for dose and duration of therapy. Although the data were derived from written case simulations, which are not always predicting physicians actual behaviour, the cases are clear, straightforward and common.[24] Highest variability was found for central nervous system infections and lowest variability for respiratory tract infections. This contrasts with the literature suggesting more agreement in the therapy of central nervous infections than for respiratory tract infections in children. For the purpose of this study we were more interested in the (lack of) agreement among doctors than in the scientifically correct choice of antibiotics. However for most infectious diseases a correct drug was chosen, the selected treatment was not often appropriate as far as duration of treatment or doses was concerned. In order to optimise patient care, to achieve a

reduction in health care costs and to reduce the emergence of drug resistance, antibiotics should be used rationally. Therefore an urgent need for a more appropriate selection and use of antibiotics exists.[11-13] In recent years treatment of numerous infectious diseases has undergone several changes and the question remains if there is a "best" antimicrobial therapy for each of these.[25] Both in the presence and absence of consensus reports on treatment of individual infectious diseases, considerable variability exists in therapeutic practice on the local, national and international level. [17-20] The duration of treatment of numerous infectious diseases is also controversial and no data from comparative studies are available to suggest the best duration of therapy. The 7-10-14 day rule has been followed for most cases.[19,20] Most clinicians want to safeguard their autonomy in antibiotic prescription and are only reluctantly willing to comply with strict guidelines, although these strictly enforced regimens may lead to a reduction of overall antibiotic use, costs as well as resistance development.[21,22] Best method to decrease antibiotic costs as well as development of antibiotic resistance will be to lower the use or prescription of antimicrobial drugs. Clear formularies are warranted for optimal clinical decision making, resulting hopefully in the choice of the best available product at an adequate dose for a reasonable period of time.[11-13] The formulary should be based on the knowledge of local trends in antimicrobial resistance. Enforcing the guidelines of the formulary should be accompanied by a continuous feedback for all prescribers, in which infectious disease specialists and hospital epidemiologists have a central role.

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CHAPTER FOUR

Antibiotic utilization for hospitalised paediatric patients

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Abstract

Background • Antibiotics are among the most commonly prescribed drugs in paediatrics. Because of an overall rise in health care costs, lack of uniformity in drug prescribing and the emergence of antibiotic resistance, monitoring and control of antibiotic use is of growing concern and strict antibiotic policies are warranted. Before such policy can be implemented, detailed knowledge of antibiotic prescribing patterns is important.

Methods • In this study the utilization of antibiotics in a paediatric university hospital over 3 consecutive years has been analysed. Over an 8-week period (1 november-22 december) in 1994, 1995 and 1996 patient charts were reviewed with regard to antibiotic prescription (generic class, dose, duration and indication).

Results • A total of 1120 patients were admitted during the study periods. Antibiotics were prescribed at least once for 36% of hospitalised children, although only 12.3% of the patients receiving antibiotics had a proven bacterial infection. Thirteen, 4.7, 2.6, and 2.7% of all children received 2, 3, 4 or more than 4 antibiotics respectively during a single hospitalization.
Infants less than 2 years are receiving more frequently antibiotics than the older children (25% and 11% respectively, $p = 0.0256$).
More children admitted to the intensive care unit received antibiotics compared to patients admitted on medium care. (49.7% and 29.3% respectively, $p < 0.0001$). Likewise they received more often several different antibiotic courses (2.6 courses per patient versus 1.9 courses per patient, $p < 0.0001$). These children also received more often intravenous compared with oral antibiotics ($p < 0.0001$).
Significant differences could be found between the generic classes of antibiotics prescribed to children admitted to the intensive care unit and the medium care. However high variability in dose and duration of antibiotic therapy for the same clinical indication was shown.

Conclusions • A high percentage of all hospitalised children received antibiotics. In most cases antibiotics are started on an empirical basis, without proof of a bacterial infection, nor before the start of therapy neither afterwards. The fact that especially children admitted to intensive care units and patients of younger age groups are at risk of receiving multiple courses of antibiotics, together with the knowledge that antibiotic resistance develops in the same setting, suggest that strategies to control antibiotic use should focus on these patient populations.

Keywords: children, antibiotics, drug utilization, and prescriptions.

Introduction

Antibiotics account for a substantial proportion of the expenditures in pharmacies and hospitals. In children antibiotics are among the most commonly prescribed drugs.[1] Several studies at the end of the 1970's focusing on antibiotic prescribing attitudes in hospitalised children, indicate that approximately 35% of admitted infants and children receive antibiotics.[1-6] Naqvi et al found a mean age of 5.6 years in their study among 295 patients receiving antibiotics.[1] Most studies showed a comparable mean age, only one study found the highest percentage of antibiotic prescription between 6 months and 1.5 years of age.[7] Widespread misuse has been reported. Almost half of all antibiotic prescriptions have been found to be inappropriate, based on clinical and economical criteria.[8,9] Because of the rising costs in health care, lack of uniformity in prescribing attitudes and the emergence of antibiotic resistance, monitoring and controlling antibiotic use is of growing concern.[10,11] Although there has been a tremendous increase of available products over the last 15 years, to our knowledge only one recent study has reported the antibiotic use in paediatric hospitalised patients.[7] On the contrary, several professional societies have issued guidelines designed urgent statements to reduce the use of antibiotics worldwide by means of various control strategies.[12-15] Before such policies and measures can be implemented, detailed knowledge of antibiotic prescription patterns is important. Defined Daily Dose (DDD) can be used as a measurement of drug utilization in adults.[16,17] Only one study described the use of DDD in children.[17] A combination of other mostly indirect variables, as expenditure and number of prescriptions of antibiotics per patient or hospi-tal day as well as recording all adverse reac-tions to drugs are used more often.[1-6] This study analysed the utilization of anti-biotics in a paediatric hospital over three consecutive years (1994-1996), with special regard to antibiotic prescription atti-tudes and patterns (generic class, dose, duration and indication).

Methods

This retro- and prospective study was performed in the Beatrix Children's Hospital, a Paediatric University Hospital in the northern part of the Netherlands. It is a hospital with 105 beds including 6 paediatric intensive care beds and 23 neonatal intensive care beds. It is the only tertiary referral centre for a population of approximately 2.5 million. Over an 8-week period (1 November - 22 December) in 1994, 1995 and 1996 all hospitalised patients were analysed for antibiotic use. Data were collected by using discharge letters, as well as daily visits of all paediatric services to screen patients for antibiotic use. Nursing and medical records were analysed for patient characteristics (age, gender, hospital department and number of hospital days), the number of antibiotics for each patient and the generic class, dose and duration of each antibiotic prescription. Most of the medical files could be used to obtain information on the indication of antibiotic prescription. Antibiotic therapy was defined to be prescribed for a definite infection, empiric without clinical or microbiological proof of infection or prophylaxis. An infection was considered definite when clinical signs (e.g. abscess), radiological evidence (e.g. infiltrate on chest X-ray, osteolytic lesion with systemic signs of infection) or microbiological tests (positive bacterial cultures of otherwise sterile body fluids) made infection most likely. Empiric therapy was defined as antibiotics administered in the presence of clinical features suggestive of infection but absence of localising signs or focus or microbiological confirmation. Prophylaxis was defined as the use of antibiotics for preventing infections e.g. before an operation or in certain immunocompromised patients. Data were collected and described for each year separately and for the 3 years together. To assess statistical significance between data Fisher's exact test and unpaired t-tests were used where appropriate. A p-value equal or less than 0.05 was considered significant.

Results

A total of 1120 patients was admitted during the study period, of which a mean of 36% received at least one course of antibiotics during their hospitalization. In 1994, 1995 and 1996 these percentages were 33.3%, 40.5% and 33.7% respectively. One hundred and eighty-three (49.7%) of 368 patients admitted on the intensive care unit received antibiotics versus 220 (29.3%) of 752 patients on medium care units. ($p < 0.0001$). The highest number of prescriptions was found in the youngest age group of the study population, of which a high proportion was admitted to the intensive care units. Infants less than 2 years are receiving more frequently antibiotics than the older children (25% and 11% respectively, $p = 0.0256$) Of the 403 patients receiving antibiotics 229 (56.8%) were boys and 174 (43.2%) girls. The median number of hospital days of children receiving antibiotics was 14 days (range 1-260 days) versus 13 days (range 1-377 days) for admitted patients not receiving any antibiotic. For all hospitalised patients receiving antibiotics no difference in number of prescribed antibiotics between the three consecutive years could be found, the

TABLE 1. The route of administration of prescribed antibiotics for children admitted to the intensive care unit and on the medium care in percentage of total antibiotic prescriptions on these departments
(The route of administration of 11 prescriptions was missing.)

	Intensive Care unit (n = 436)	**Medium Care unit (n = 409)**	
Oral	19 (2%)	185 (22%)	204 (24%)
Intravenous	417 (49%)	224 (27%)	641 (76%)
Total	436 (52%)	409 (48%)	845 (100%)

average number of antibiotics per admission in 1994, 1995, and 1996 was respectively 2.0, 2.4 and 2.1. Only 1 antibiotic course was prescribed in more than 35% of all prescriptions, 2 antibiotic courses were prescribed in 35% of all prescriptions, 3 antibiotic courses in 13% of all prescriptions, 4 antibiotic courses in almost 7% of all prescriptions and finally 5 or even more than 5 antibiotic courses were prescribed in about 8% of all prescriptions. There is a significant difference between the number of courses prescribed to children on the intensive care unit (2.6) and the number of courses prescribed to children on the medium care (1.9). ($p < 0.0001$) Also a significant difference could be found between the route of administration of antibiotics prescribed for children on the intensive care unit and children on the medium care shown in table 1,

TABLE 2. Generic classes of prescribed antibiotics for children admitted to the intensive care unit and on the medium care in percentage of total antibiotic prescriptions on these departments and the corresponding p-values between these percentages

Generic classes of prescribed antibiotics	Percentage of antibiotic prescriptions in percentage of all prescriptions		
	Intensive Care unit (n = 441)	Medium Care unit (n = 415)	p-value
Penicillins	33%	27%	p = 0.0546
Cephalosporins	16%	16%	N.S.
Aminoglycosides	31%*	11%	p < 0.0001
Macrolides	2%	7%*	p = 0.0005
Vancomycin	9%*	5%	p = 0.0106
Sulphonamides	1%	20%*	p < 0.0001
Others	8%	14%*	p = 0.0020

(* means a significant difference between the two percentages)

of 11 prescriptions the route of administration could not be found. ($p < 0.0001$) No significant difference in duration of oral prescribed antibiotics and intravenous prescribed antibiotics could be found. Many classes of antibiotics were prescribed as shown in table 2. A significant difference between most prescribed antibiotic classes on the intensive care unit and medium care could be found. Looking at the indication of prescribed antibiotic therapy, almost 60% of all prescriptions were started empirically, almost 30% as prophylaxis and only 12.3% of all prescriptions for a definite infection. Most commonly antibiotics were prescribed in case of a suspicion of bacteraemia, followed by the diagnoses of respiratory tract infections and neonatal infections or intrauterine infections. Inter-doctor variability existed for daily prescribed doses as well as for the duration of an antibiotic course. Table 3 illustrates the variability in daily prescribed doses of most frequently prescribed antibiotics. No difference in mean duration of prescribed antibiotics could be found between the

TABLE 3. The variation in prescribed dose of mostly prescribed antibiotics for several infectious diseases

Antibiotic	range (mgs/kg/day)	median (mgs/kg/day)
Penicillins (central nervous infections)	7.0 - 250	72.5
Penicillins (respiratory tract infections)		
Oral	10.7 - 111.1	48.0
Intravenous	42.9 - 205.1	100.0
Cephalosporins	19.5 - 200	107.1
Aminoglycosides		
Gentamicin/netilmicin/tobramycin	0.5 - 12.1	4.9
Amikacin	3.6 - 39.5	10.0
Vancomycin	5.0 - 74.3	40.3

intensive care unit and the medium care, (5.7 days (range 1-23) versus 5.9 days (range 1-57)).

Discussion

In this study a high percentage of all hospitalised children receive antibiotics. Over 50% of all antibiotic prescriptions were started on an empirical basis, without confirmation of a bacterial infection. Especially children admitted to intensive care units and young children are at risk of receiving multiple courses of antibiotics. Several methods are available to study antibiotic use in paediatric hospitals.[1-7,18] In this study attention was focused on the characteristics of the population receiving antibiotics. Moreover the indication of antibiotic prescription was studied. Our results are comparable with data found in studies reported in the literature, performed more than 15 years ago.[1-6] Until now no studies have been published on the difference of antibiotic prescriptions on different paediatric units. In our study a significant difference could be found in percentage of antibiotic prescriptions and the route of administration (more intravenous antibiotics in the Intensive Care unit) for children admitted to the intensive care unit compared with patients admitted on the medium care. ($p<0.0001$) Likewise a significant difference in number of antibiotic courses could be found between the former and latter group. ($p<0.0001$) The highest number of antibiotic prescriptions was made for children in the youngest age group (between 0 and 2 years). Most antibiotics were prescribed on an empirical basis. No uniformity in dose and duration of antibiotic therapy was found. In 1995 a general hospital formulary was introduced including the treatment of infectious diseases in children, but this was not used very often. More commonly old regimens have been followed. During the study period new guidelines for the treatment of neonatal sepsis and meningitis and new guidelines for

oncology patients with fever and neutropenia were introduced. Because of these a shift in the use of certain classes of antibiotics was observed. Overall we may conclude that over the study period a shift to the use of more expensive and broader spectrum antibiotics was seen for all groups. Nowadays we are dealing with large problems of rising health care costs and the emergence of antibiotic resistance.[10] Some recently performed studies showed an association between the prior use of antibiotics and the development of resistance.[19-22] Because of these emergent threats it is necessary to be informed continuously about the use of antibiotics in the hospital. Several professional organisations like the Infectious Disease Society of America or the American Medical Association stimulate or promote a more prudent use of antibiotics.[11,12,23] For example they recommended for each hospital a committee to monitor antibiotic use and it should provide guidance to the prescriber on good antibiotic practice.[24] The use of high-cost, specialized antimicrobial agents should be a privilege of infectious disease consultants and others trained in their use, just as performance of invasive procedures are limited to those who are qualified.[11] The infectious disease community must work in concert with the pharmaceutical industry to achieve a more optimal use of antibiotics. Methods should based on education about appropriate antibiotic use, hospital–based programmes, susceptibility testing and most important restricted use should be warranted.[11]

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CHAPTER FIVE

Changing prescribing behaviour after introduction of an antibiotic formulary

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Submitted

Abstract

Background • Antibiotics are among the most commonly prescribed drugs in children. Selection of the appropriate drug has become more difficult with the release of an increasing number of agents, causing a lack of uniformity in prescription attitudes of paediatricians. Unfortunately this prescription attitude probably facilitates the development of antibiotic resistance.
In this study an antibiotic formulary was introduced after intensive monitoring of antibiotic use in daily practice. The level of uniformity in empiric antibiotic therapy of paediatricians was analysed and compared with the level of uniformity reported in our earlier studies.[18,19] In addition, general knowledge about antibiotics was assessed.

Methods • The study was conducted in a tertiary paediatric teaching hospital. An authorised antibiotic formulary with empiric antibiotic therapy for most common diseases in paediatrics was introduced. Two months later a questionnaire including 13 hypothetical clinical cases was sent to all paediatricians and paediatric residents in the hospital. Their choice of antibiotic therapy (generic class, dose, duration) with regard to these cases was evaluated. Simultaneously the utilization of antibiotics in the hospital was analysed. Patient charts were reviewed with regard to antibiotic prescription (generic class, dose, duration and indication). Finally forty-five paediatricians were asked to participate in an interview. The interview consisted of an oral questionnaire focused on different characteristics of antibiotics.

Results • After the introduction of the formulary a significant improvement in uniformity in antibiotic choice for theoretical cases could be found compared with data found in our earlier studies. However such a shift could not be found in the actual use of antibiotics in daily practice. A high variability in chosen dosage and duration of antibiotic therapy could still be shown. The interview showed that the knowledge on the expected efficacy of an individual

agent for a particular disease ranged from 13 to 63% depending on the case. Most physicians (58%) could give a reasonable estimate of the price. The pharmaceutical manufacturer was not known by more than 80% of interviewees. Adverse reactions were known by 30% and 97% of interviewees, depending on the antibiotic. Only a few of the paediatricians could give a correct answer about the resistance pattern of the antibiotics.

Conclusions • A very high percentage of prescribing paediatricians was not familiar with characteristics of most commonly prescribed antibiotics in current practice. The introduction of an authorised antibiotic formulary solely is not enough to achieve a significant change in antibiotic prescribing behaviour in a hospital, although it can induce a learning effect.

Introduction

Antibiotics are among the most commonly prescribed drugs in paediatrics.[1] Several studies focusing on antibiotic use in hospitalised children indicate that approximately 35% of infants and children admitted to hospitals receive antibiotics.[2-5] Most frequently antibiotics are started on an empirical basis, defined as treatment without clear clinical or microbiological evidence of infection.[6] Antibiotic selection has become more difficult with the increasing release of many agents with various pharmacodynamic, antimicrobial and toxicological characteristics and the emergence of resistance to many agents.[7] Widespread misuse of antibiotics has been reported. Almost half of all antibiotic prescriptions have been found to be inappropriate, based on clinical and economical criteria.[8] Serious consequences in terms of mortality and complications can result from inappropriate antibiotic therapy.[9]
The appropriateness of treatment decisions of physicians is a recurrent issue in health care research.[10,11] It has been assumed that a lack of knowledge is the main determinant of suboptimal clinical decision making.[12] Many studies have shown that traditional continuing education programs in the usual lecture format do not result in long-term changes in knowledge, competence or quality of care.[13,14] Professional behaviour in delivering health care is influenced not only by knowledge but also by skills, attitudes, the health care system and the behaviour of patients. An improvement in physician prescribing behaviour could only be achieved by a combination of strategies as described by Plumridge.[15,16,17]
In this study an authorised antibiotic formulary was introduced. Soon after the introduction of this formulary a detailed study of the effect on uniformity in choice of empiric antibiotic therapy and the use of antibiotics in daily clinical practice was analysed. Finally we showed an analysis of the familiarity of paediatricians with most commonly prescribed antibiotics in daily practice.

Methods

The study was performed in the Beatrix Children's Hospital, a tertiary care paediatric department in the northern part of the Netherlands. At first an authorised antibiotic formulary was introduced including empiric antibiotic therapy for most common infectious diseases in children based on local sensitivity patterns.
Two months later the utilization of antibiotics was analysed. The method used was described before.[18] During an eight-week period patient charts were reviewed with regard to antibiotic prescription (generic class, dose, duration and indication). Simultaneously a questionnaire including 13 hypothetical clinical cases was sent to all paediatricians and paediatric residents in the hospital, as described in an earlier study. [19] Their choice of antibiotic therapy (generic class, dose, duration) with regard to these cases was evaluated. Both sets of data were analysed and compared with data found in earlier studies.[18,19] Special attention has been focused on the presence of uniformity in prescribing behaviour of paediatricians.
Finally forty-five paediatricians were invited to sit for an interview. The interview consisted of multiple-choice questions about efficacy, price, manufacturer, adverse reactions and development of resistance concerning 11 commonly prescribed antibiotics. These data were noted and prescribed in detail, for each above described item the percentage was calculated for the 11 antibiotics most commonly prescribed in daily practice. These data were compared with data found in the literature.

Results

Questionnaire with theoretical cases
Two months after the introduction of an authorised antibiotic formulary several data concerning uniformity in antibiotic

prescribing behaviour and actual prescribing behaviour as evident from the patient charts were collected. First the assessment of uniformity in prescribing antibiotics showed a significant shift towards more uniformity in comparison with an earlier study (table 1). Nineteen paediatricians (46%) and nine paediatric residents (38%) returned questionnaires, of which 24 (86%) were completed and four (14%) were returned without any answers. Greatest variability was found for the case with suspicion of Gram-negative bacteraemia or arthritis. Least variability could be shown for the respiratory tract infections. The dosage of the chosen therapy showed a considerable variability and did not always agree with the literature. The dosage of penicillins for central nervous system infections ranged from 75-200 milligrams/kg versus 13-500 milligrams/kg before the introduction of the antibiotic formulary. Only 6% of the amoxicillin prescriptions were within the accepted range in dosage) as described in various textbooks of paediatrics versus 26% before the introduction (200-400 milligrams/kg). For a child with suspicion of respiratory tract infections treated with intravenous or oral penicillins a dosage of penicillins between 30 and 100 milligrams/kg could be found. More than 95% versus 75% before the introduction were treated with a dosage as suggested in formularium or textbooks of paediatrics. The dosage of aminoglycosides varied between 2 and 8 milligrams/kg, in these cases only netilmycin was chosen. In 80% versus 23% aminoglycosides were dosed in a correct way. For central nervous system infections more than 85% versus 60% respondents would treat patients with a dosage of ceftriaxone according to the advised regimen in formularium. For ceftazidime and cefotaxime more than 95% versus 90% were treated with correct dosages. Finally the duration of therapy showed a less remarkable variability than in a study performed before introduction of the formulary. However, generally accepted guidelines were breached on several occasions.

TABLE 1. Number of chosen antibiotic classes for each case, with in parentheses, the number of respondents for the particular case

The first column was before introduction of the formulary, the next columns after introduction of the formulary. The following antibiotic classes were defined: penicillins, cephalosporins, aminoglycosides, sulphonamides, vancomycin, quinolones, metronidazole, and all different combinations of these individual classes. And the percentages of chosen therapy corresponding with the therapy named in the introduced formulary.

Case number and description	Paediatricians and residents		Same therapy as in formulary
	Before (n = 50)	After (n = 29)	After
1. a child of three weeks old with bacterial meningitis	15 (45)	4 (24)	71%
2. a four year old girl with a clinically and radiologically proven bacterial pneumonia	8 (47)	2 (22)	91%
3. a seven year old boy with sinusitis	5 (44)	2 (22)	86%
4. a five year old girl with pyelonefritis	12 (43)	3 (22)	86%
5. a four year old child with bilateral otitis media	3 (47)	3 (23)	61%
6. a premature infant, with respiratory distress and sepsis	20 (45)	3 (22)	82%
7. a twelve year old girl with high fever, hypotension, tachycardia and bloody diarrhoea	18 (36)	5 (16)	17%
8. an eight year old boy with osteomyelitis of the ankle	10 (43)	4 (21)	67%
9. an eight year old girl with atypical pneumonia	6 (43)	1 (23)	65%
10. a three year old girl with bacterial meningitis	12 (47)	2 (22)	86%
11. a four year old girl with endocarditis	17 (30)	2 (12)	92%
12. a two year old girl with infected eczema	8 (41)	3 (18)	33%
13. a nine year old boy with septic arthritis	10 (36)	4 (15)	7%

Chart review

During the eight-week period 311 courses of antibiotics were prescribed for 158 hospitalised patients. Of these 158 patients 99 were boys and 59 were girls. The age of the study population varied between 0 and 18 years, with a mean of 2.5 years. The median length of hospital stay was 10 days (range 1-164 days) for the children receiving antibiotics. Most antibiotics were prescribed for children in the neonatal intensive care unit (35%), followed by 83 patients (52%) admitted to the nursing departments. Only 13% of all patients were admitted to the paediatric intensive care unit with one or more antibiotic courses during their hospitalization. The average number of antibiotics prescribed was 2.0, comparable with data found in an earlier study over the years 1994, 1995 and 1996. [18] One single antibiotic course was prescribed in more than 25% of all cases, two antibiotic courses were prescribed in 55% of all cases, three antibiotic courses in 10% of all cases and finally four or even more than four antibiotic courses were prescribed in about 9% of all courses. There is a significant difference between the number of courses prescribed to children on the intensive care unit (2.3) and the number of courses prescribed to children on the medium care units (1.8). ($P < 0.0001$)

A significant difference could also be found between the route of administration of antibiotics prescribed for children on the intensive care unit and children on the medium care. ($P < 0.0001$) No significant difference in duration of oral and intravenous prescribed antibiotics could be found. Many classes of antibiotics were prescribed as shown in Table 2. A significant difference between the most prescribed antibiotic classes on the intensive care unit and medium care unit could be found. Comparing both periods, before and after the introduction of the antibiotic formulary, the number of prescribed antibiotics per patient were almost the same. But a shift in prescribing pattern from broader spectrum towards small spectrum antibiotics could be shown. For example after

the introduction of the formulary 42% of all antibiotic prescriptions in the Intensive Care Unit was made for penicillins versus 33% before the introduction. For cephalosporins and vancomycin a decrease in prescriptions in the Intensive Care Unit could be found. The group of others consisting of broad spectrum antibiotics like carbapenems or quinolones were also prescribed in a less percentage after the introduction of the formulary. Looking at the indication of prescribed antibiotic therapy, more than 60% of all prescriptions were started empirically, almost 30% as prophylaxis and only 10% of all prescriptions for a definite

TABLE 2. Generic classes of prescribed antibiotics for children admitted to the intensive care unit and on the medium care in percentage of total antibiotic prescriptions on these departments and the corresponding p-values between these percentages for the period before the introduction of the formulary and the period after the introduction of the formulary

Generic classes of prescribed antibiotics	Percentage of antibiotic prescriptions in percentage of all prescriptions			
	Before		After	
	Intensive Care unit (n = 441)	Medium Care unit (n = 415)	Intensive Care unit (n = 165)	Medium Care unit (n = 144)
Penicillins	33%	27%	42%	26%
Cephalosporins	16%	16%	8%	18%
Aminoglycosides	31%	11%	37%	17%
Macrolides	2%	7%	2%	3%
Vancomycin	9%	5%	6%	6%
Sulphonamides	1%	20%	1%	18%
Others	8%	14%	4%	12%

infection. Most commonly, antibiotics were prescribed in case of suspicion of bacteraemia, followed by the diagnosis of respiratory tract infections and neonatal or intrauterine infections. Inter-doctor variability exists for daily-prescribed doses as well as for the duration of an antibiotic course. Table 3 illustrates the variability in daily-prescribed doses of most frequently prescribed antibiotics. No difference in mean duration of prescribed antibiotics could be found between the intensive care unit and the medium care.

TABLE 3. The variation in prescribed dose of mostly prescribed antibiotics for several infectious diseases for the period before the introduction of the formulary and the period after the introduction of the formulary

Antibiotic	Before		After	
	range (mgs/kg/day)	median	range (mgs/kg/day)	median
Penicillins				
(central nervous infections)	7.0 - 250	72.5	26.6 - 120	75
Penicillins				
(respiratory tract infections)				
Oral	10.7 - 111.1	48.0	50 - 100	75
Intravenous	42.9 - 205.1	100.0	47.6 - 400	75
Cephalosporins	19.5 - 200	107.1	32.3 - 150	100
Aminoglycosides				
Gentamicin/netilmicin/				
tobramycin	0.5 - 12.1	4.9	0.95 - 50.8	4.8
Amikacin	3.6 - 39.5	10.0	not prescribed	
Vancomycin	5.0 - 74.3	40.3	17.1 - 76.9	36.1

Interviews

Finally in the last part of the study 30 paediatricians (67%) participated. Reasons for refusal were lack of time, or lack of daily practice in prescribing antibiotics. The gender of the respondents was fifteen men and fifteen women. The age of the doctors was between 32 and 57 years, with a mean age of 43 years. The years of experience varied for the general practice between 7 and 30 years, with a mean of 16 years. For practice in paediatrics the years of experience varied between 1 and 25 years, with a mean of 10 years. Most existing

TABLE 4. Familiarity of all 30 paediatricians with 11 most commonly prescribed antibiotics in current practice

	Range of efficacy	Price	Manu-facturer	Adverse reactions	Resistance
Ceftazidime	17 (57%)	12 (40%)	12 (40%)	14 (47%)	11 (37%)
Vancomycin	4 (13%)	15 (50%)	1 (3%)	25 (83%)	10 (33%)
Amoxicillin/ clavulanic acid	19 (63%)	20 (67%)	11 (37%)	29 (97%)	9 (30%)
Trimethoprim	4 (13%)	23 (77%)	6 (20%)	18 (60%)	11 (37%)
Co-trimoxazole	8 (27%)	20 (67%)	7 (23%)	23 (77%)	9 (30%)
Ciprofloxacin	6 (20%)	20 (67%)	2 (7%)	16 (53%)	7 (23%)
Cefuroxime	8 (27%)	23 (77%)	10 (33%)	20 (67%)	13 (43%)
Netilmicin	14 (47%)	7 (23%)	3 (10%)	29 (97%)	12 (40%)
Amoxicillin	13 (43%)	25 (83%)	14 (47%)	29 (97%)	26 (87%)
Imipenem	12 (40%)	15 (50%)	1 (3%)	11 (37%)	5 (17%)
Piperacillin	8 (27%)	11 (37%)	1 (3%)	9 (30%)	5 (17%)

Values are numbers (%) of paediatricians who gave correct answers. As answers could be correct or incorrect, and all data were complete, the complement of values provided are the numbers of paediatricians who gave wrong answers.

subspecialisms in paediatrics were presented between the respondents. Most physicians prescribed less than 5 courses of antibiotics each week. A few percentages of the paediatricians prescribed more than 10 antibiotics a week. The median number was five antibiotic prescriptions a week.
Study of the familiarity of paediatricians with antibiotics showed that the knowledge on the expected efficacy of an individual agent for a particular disease ranged between 13 and 63% depending on the case. As showed in table 4, questions on most used or prescribed antibiotics (e.g. ceftazidime) resulted in higher percentages of good answers in comparison with less used antibiotics (e.g. piperacillin). This could be found for all aspects of antibiotics that were asked for. Most physicians could give a reasonable estimate of the price especially of the most commonly prescribed antibiotics. More difficult were to answer the questions on the pharmaceutical manufacturers, which were not known in more than 80%. Adverse reactions were better known, especially of the most commonly used or prescribed antibiotics (e.g. amoxicillin/clavulanic acid, amoxicillin and netilmicin). Only a few of the paediatricians could give a correct answer about the resistance pattern of the antibiotics (table 4).

Discussion

Antibiotics are among the most commonly prescribed drugs in paediatrics. The appropriateness of the treatment decisions of physicians is a recurrent issue in health care research.[10,11] Almost half of all antibiotic prescriptions have been found to be inappropriate, based on clinical and economical criteria.[8] In addition serious consequences in terms of mortality and complications can result from inappropriate antibiotic therapy.[9] In general it is recognized that not much is known about these group of drugs.[12] This study tested first the acquaintance of physicians of most important items of the

11 most commonly used or prescribed antimicrobial drugs nowadays. It could be shown that most paediatricians did not know much about the range of efficacy, manufacturer, adverse reactions and the resistance of antimicrobial drugs. The knowledge of the price of each antibiotic was higher than expected and as was described in literature.[20] No difference could be found between paediatricians prescribing more or less antibiotics a week. No significant difference in gender or years of experience (general or paediatric) could be found for making the right or wrong diagnosis and for right or wrong choice of antibiotics. In order to improve the quality of prescribing antibiotics and health care several solutions are available.[12,21] Continuous education is one possibility, physicians should be continuously informed about the antibiotic policy of the hospital, about new antimicrobial drugs and all developments which are important to know. This study aimed to get information about the value of the introduction of an authorised antibiotic formulary in children's university hospital. Several professional organisations have tried to develop strategies to optimise the use of antibiotics in a hospital. As far as we know until now no study was performed concerning the implementation of an antibiotic formulary in a paediatrician's population. We analysed two kinds of variables. At first the presence of uniformity in empiric antibiotic therapy, followed by the use of antibiotics in daily practice. A significant shift towards more uniformity in empiric antibiotic choice could be observed. Almost all cases, described in the antibiotic formulary were answered with the correct antibiotic choice. Although the number of responding doctors was less than the first time a tendency towards more uniformity could be found for chosen class of antibiotics, as well as for the chosen dose and duration of the antibiotic therapy. Another bias of the study is the short time span between introduction of the formulary and the second measurement described in the present study.
The use of antibiotics in daily practice showed a total different

view. Almost the same data were found as established in an earlier performed study.[18] Highest percentage of antibiotic prescriptions could be observed in the intensive care unit and for the youngest part of the patient population. Looking at the generic classes of antibiotics, most prescriptions were made for penicillins and aminoglycosides. A shift towards use of less expensive and small spectrum drugs could be demonstrated. Although we found a significant change in empiric antibiotic choice in theory and in daily clinical practice a shift towards less broad spectrum antibiotics could be found. The introduction of an authorised antibiotic formulary solely is not enough to change the prescribing behaviour of doctors in a hospital. It should be accompanied by continuous education, feedback and monitoring of all variables.
Only when physicians get sufficient information it is possible to achieve a better antibiotic policy, resulting in more appropriate prescribing behaviour, a decrease in antibiotic costs and possible also a decrease in the emergence of resistance.

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CHAPTER SIX

Does the empirical use of vancomycin in paediatrics increase the risk for Gram-negative bacteraemia?

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Abstract

Background • Gram-negative bacteraemia in children, a major cause of morbidity and mortality, may in part be induced by intensive treatment procedures and unspecific use of antibiotics. Our primary objective was to study the causal relation between the use of vancomycin and Gram-negative bacteraemia, for which this antibiotic is not specifically indicated.

Methods • The study was conducted in a 105-bed tertiary care children's hospital in the period of 1994 to 1997. The study pertains to a cohort of children with suspected bacteraemia, in whom a blood culture was performed during hospital stay. Using the bacteriological laboratory registration system we selected all paediatric cases with bacteriologic proven Gram-negative bacteraemia (n=105), and a random sample of 225 paediatric controls with negative blood cultures. Using logistic regression analysis we examined associations between Gram-negative bacteraemia and the following factors: preceding use of antibiotics, antacids, corticosteroids, surgery, mechanical ventilation, parenteral nutrition, invasive instrumentation, and the intensity of care assessed with the Therapeutic Intensity Scoring System (TISS 28).

Results • Gram-negative bacteraemia was positively associated with the use of aminoglycosides, cephalosporins, surgical interventions, central venous catheters, parenteral nutrition, antacids, and dexamethasone. The strongest association was with the use of vancomycin (OR = 8.1, 95% CI: 3.1 to 20.9). In a multiple logistic regression model containing all above-mentioned variables, the use of vancomycin remained positively and strongly associated with Gram-negative bacteraemia (OR = 3.88, 95% CI: 1.34 to 11.21). Further adjustments and restrictions in the analysis did not materially change these findings concerning vancomycin.

Conclusions • Among children suspected of bacteraemia there are several drugs and clinical procedures influencing the risk for

Gram-negative bacteraemia. Empiric use of vancomycin is strongly and independently associated with Gram-negative bacteraemia. The safety of using vancomycin solely on the basis of suspicion of bacteraemia in children may not be warranted.

Introduction

Gram-negative organisms are common causes of bacteraemia. In children these organisms are responsible for more than 50% of all cases of bacteraemia and cause a significant morbidity and mortality.[1, 2] The extensive use of antibiotics in outpatient settings, increased use of neonatal and paediatric intensive care units and the prolonged use of central intravenous catheters, chemotherapy and corticosteroids make Gram-negative bacteraemia a significant problem in tertiary care paediatric hospitals.[1] In Gram-negative bacteraemia in childhood most frequently the enteric bacteria Escherichia coli, Enterobacter, Klebsiella and nonenteric bacteria, such as Pseudomonas are isolated.[1]
It is generally accepted that antecedent antibiotic exposure predisposes the individual patient to colonisation and infection with resistant microorganisms.[3,4] The widespread use of broad-spectrum antibiotics and inappropriate empiric antibiotic treatment result in increased mortality and the emergence of increasingly resistant microorganisms.[5,6] Early recognition and correct treatment of Gram-negative bacteraemia are of paramount importance to prevent morbidity and mortality.[1] The use of antibiotics and the intensity of care are possibly important risk factors for patients to develop Gram-negative bacteraemia. On the other hand intensive antibiotic use and other intensive treatments and procedures are also a reflection of disease severity; extensive antibiotic medication and invasive procedures are more frequently applied in the more severely ill children, particularly those with Gram-negative bacteraemia.

A challenge is therefore to discern between intensive use of antibiotics and means of care as actual predictors of Gram-negative bacteraemia or as consequences of serious disease from Gram-negative bacteraemia. Our primary objective was to quantify the risk of Gram-negative bacteraemia associated

with the empiric use of antibiotics and with indicators for intensity of care.

Methods

Patients

The study was performed at the Beatrix Children's Hospital, a paediatric university hospital in the northern part of the Netherlands. The hospital is the only tertiary referral center for a population of approximately 2.5 million. The study pertains to a cohort of children treated between 1994 and 1998 (from Jan.1, 1994 through Dec.31, 1997) in whom a blood culture was performed during hospital admission because of suspected bacteraemia. Using the record system of the Department of Microbiology and Epidemiology we selected from this period all 108 recorded positive blood cultures with Gram-negative microorganisms, and a random sample of 229 registered negative blood cultures. The concomitant resistance patterns of isolated micro-organisms were available for analysis. Seven patients were admitted twice. As we intended to study patients and not episodes we excluded each second admission thereby leaving 105 paediatric patients with proven Gram-negative bacteraemia (cases) and 225 patients with proven negative blood cultures (controls) for analysis. There were three sets of twins in the control group who were each included in all analyses.

Measurements

We retrieved information about risk indicators from the medical files pertaining to a period of maximally 10 days before the venipuncture for bloodculture was taken. We categorized the use of antibiotics by the following categories: penicillins, aminoglycosides, cephalosporins, vancomycin, and

other antibiotics. Additionally, we recorded the use of corticosteroids, selective bowel decontamination, and antacids. Furthermore, we recorded patient characteristics (age, gender, body weight), the number of attended hospitalization units during admission, the department attended at the time of risk indicator determination, the attending subspecialties, duration of hospitalization, surgical intervention, use of invasive instrumentation and type of intervention. The intensity of care was estimated by using the Therapeutic Intensity Scoring System TISS-28.[7,8]

Data analysis

Logistic regression analysis was used to assess odds ratio's for the univariate associations between the abovementioned measurements and the outcome, Gram-negative bacteraemia versus no bacteraemia. Data were entered into SPSS 9.0 release, 1998. Subsequently, multiple logistic regression was used to assess the extent to which associations found between antibiotics use and the outcome were independent of other risk indicators.[9]

Results

Table 1 shows general characteristics of cases and controls and clinical follow-up data. Compared with controls, cases were on average somewhat younger and had been more ill as indicated by a statistically significantly longer duration of hospitalization, higher TISS-score and higher mortality. The frequencies of Gram-negative bacteraemia were clearly dependent on diagnoses.
Table 2 shows univariate associations between various exposures and Gram-negative bacteraemia. The use of antibiotics such as aminoglycosides, cephalosporins,

vancomycin, other antibiotics, and other drugs such as antacids and dexamethasone were each risk indicators for Gram-negative bacteraemia. The same applied to invasive

TABLE 1. Baseline characteristics and clinical follow-up

	No bacteraemia		Gram-negative bacteraemia	
Number of patients	225		105	
Age (years)	0.3	[0 – 18.3]	0.3	[0 – 16.2]
Male/female	1.03		1.7	
Body weight (kg)	5.3	[0.7 – 99.0]	4.9	[0.6 - 69.5]
TISS-score*	13	[1 - 42]	19	[4 – 42]**
Clinical follow-up:				
Duration of admission (days)	12	[range 0 - 370]	27	[range 0 - 217]**
Primary diagnosis in:				
Infectiology	28		15	
Hematology/oncology	26		15	
Gastro-enterology	29		20	
Neonatology	59		39	
Nephrology			5	
Cardiology	21		3	
Pulmonology	33		1	
Congenital pathology	9		1	
Neurology	19		2	
Unspecified	1		4	
Died	19		34***	

Values are median [range], unless indicated otherwise.
* TISS-28: Therapeutic Intensity Scoring System, based on 28 items measuring the intensity of treatment.
** $p < 0.0001$ (Mann Whitney U test).
*** $p < 0.0001$ (Chi-square = 30.4 , df = 1).

TABLE 2. Results of univariate logistic regression with an indicator for presence of Gram-negative bacteraemia or no bacteraemia as dependent variable

Variable*	OR	95% CI
Continuous independent variables		
Age (months)	1.00	0.99 to 1.00
Body weight (kg)	0.99	0.97 to 1.01
TISS-28	1.06	1.03 to 1.09
Dichotomous independent variables		
Gender (male/female)	0.61	0.38 to 0.98
Use of antibiotics (yes/no)	2.16	1.34 to 3.46
Use of penicillins (yes/no)	1.59	0.94 to 2.69
Use of aminoglycosides (yes/no)	2.17	1.21 to 3.87
Use of cephalosporins (yes/no)	2.26	1.15 to 4.45
Use of vancomycin (yes/no)	8.06	3.12 to 20.87
Use of other antibiotics (yes/no)	3.82	1.96 to 7.46
Use of SDD** (yes/no)	4.42	0.80 to 24.50
Use of dexamethasone (yes/no)	3.19	1.73 to 5.88
Use of antacids (yes/no)	3.51	1.98 to 6.23
Surgical intervention (yes/no)	1.88	1.05 to 3.38
Abdominal surgery (yes/no)	2.52	1.19 to 5.31
Central venous catheter (yes/no)	2.24	1.40 to 3.60
Drain (yes/no)	0.63	0.29 to 1.39
Thoracal drain (yes/no)	1.77	0.68 to 4.63
Tracheostoma (yes/no)	0.01	Undefined
Urinary catheters (yes/no)	0.60	0.12 to 2.96
Mechanical ventilation (yes/no)	1.42	0.89 to 2.26
Parenteral nutrition (yes/no)	2.27	1.36 to 3.80

* The variables were measured up to 10 days before the blood culture was taken.
For all dichotomous variables non-users were the reference category
and for gender, females were the reference category.
** SDD is Selective Gastrointestinal Decontamination.

procedures such as surgical interventions, use of a central venous catheter and parenteral nutrition. These findings were also reflected in the association found with the TISS 28 score. The strongest univariate association, OR = 8.06, 95% CI: 3.12 to 20.87, was with empiric use of vancomycin. Vancomycin is specifically not indicated for Gram-negative bacteraemia, except *Flavobacterium* infection. We therefore further analysed the association between vancomycin and Gram-negative bacteraemia. First, we assessed the extent to which this association was dependent on other possibly confounding factors associated with Gram-negative bacteraemia. Second, we evaluated whether this association was due to the

TABLE 3. Results of bivariate logistic regression providing the risk for Gram-negative bacteraemia with the use of vancomycin combined with each of the given variables as independent variables

Use of vancomycin combined with	OR	95% CI
Gender (male/female)	8.50	3.25 to 22.24
Use of antibiotics (yes/no)	6.16	2.26 to 16.77
Use of aminoglycosides (yes/no)	7.36	2.82 to 19.21
Use of cephalosporins (yes/no)	7.09	2.64 to 19.03
Use of other antibiotics (yes/no)	5.94	2.22 to 15.90
Use of dexamethasone (yes/no)	7.29	2.77 to 19.17
Use of antacids (yes/no)	6.09	2.29 to 16.23
Surgical intervention (yes/no)	7.37	2.82 to 19.26
Abdominal surgery (yes/no)	7.42	2.84 to 19.37
Central venous catheter (yes/no)	7.16	2.73 to 18.96
Parenteral nutrition (yes/no)	7.81	2.98 to 20.44
TISS-28	8.14	3.10 to 21.38

The variables were measured up to 10 days before the blood culture was taken.

combined prescription of antibiotics and whether it persisted within subgroups.
In separate bivariate logistic regression analyses we studied the extent to which the association between Gram-negative bacteraemia and use of vancomycin depended on each of the other factors that were statistically significantly associated in the univariate analyses. Table 3 shows that in a bivariate logistic model, none of the other variables had a major influence on the association between vancomycin use and the occurrence of Gram-negative bacteraemia. This association remained positive and statistically significant with each of the adjustments. The odds ratio for use of vancomycin then

TABLE 4. Multivariate logistic regression showing relative risk of vancomycin use and Gram-negative bacteraemia with various adjustments

Model	Vancomycin given with	OR	95% CI
Model 1	Aminoglycosides, cephalosporins, other antibiotics, dexamethasone, antacids	3.97	1.39 to 11.31
Model 2	Surgical intervention, central venous catheter, parenteral nutrition	6.70	2.53 to 17.75
Model 3	Aminoglycosides, cephalosporins, other antibiotics, dexamethasone, antacids, surgical intervention, central venous catheter, parenteral nutrition	3.88	1.34 to 11.21

Values are Odds Ratios (OR) with 95% Confidence Intervals (CI) indicating the relative risk of vancomycin use for gram-negative bacteraemia, allowing for the effects of the other variables provided in the respective models.

ranged from OR = 5.94, 95% CI: 2.22 – 15.90, when adjusted for use of other antibiotics, to OR = 8.14, 95% CI: 3.10 – 21.38, when adjusted for the mean TISS 28 score, while all other odds ratios in between that range were statistically significant (data not shown).

In subsequent multivariate logistic regression models all variables concerning drug use and invasive procedures that showed statistically significant univariate associations were simultaneously included. The results are shown in table 4. A first model with vancomycin adjusted for other drug use, including other antibiotics, yielded a somewhat lower odds ratio for vancomycin. It decreased less in a second model with vancomycin adjusted for invasive procedures. The odds ratio of vancomycin again decreased when a full multivariate model was used, (OR = 3.88, 95% CI: 1.34 to 11.21). Thus, adjustment for other drug use lowered the association more than adjustment for invasive procedures.

We further assessed whether the effect of vancomycin differed within users of other antibiotics (table 5), indicating among, for

TABLE 5. Results of univariate logistic regression with an indicator for the presence of Gram-negative bacteraemia as dependent variable and vancomycin use as independent variable, restricted to users of other antibiotics

Restricted to users of	OR	95% CI	OR*	95% CI*
Antibiotics (n = 131)	6.16	2.26 to 16.77	5.65	2.01 to 15.94
Penicillins (n = 78)	5.10	1.23 to 21.09	5.68	1.24 to 25.95
Aminoglycosides (n = 58)	2.67	0.60 to 11.91	4.16	0.76 to 22.65
Cephalosporins (n = 39)	5.10	1.11 to 23.37	3.59	0.65 to 19.76
Other antibiotics (n = 42)	2.63	0.59 to 11.65	2.40	0.60 to 19.15

* Adjusted for indicators of surgical intervention, central venous catheter, parenteral nutrition.

instance, users of penicillin (n=78) the risk of Gram-negative bacteraemia in users of vancomycin as compared with non-users of vancomycin. When restricted to users of antibiotics in general (n=131), vancomycin still showed an OR = 6.16, 95% CI: 2.27 to 16.75. Similar results were found when analysis was restricted to use of penicillins and cephalosporins. When restricted to use of aminoglycosides or the category called other antibiotics the odds ratios decreased somewhat. The effect of vancomycin also persisted within the domain of users of dexamethasone and antacids (data not shown). Further adjustment for invasive procedures did not materially affect these associations.

Subsequently, we looked at the effect of vancomycin used in combination with each of the other antibiotics on Gram-negative bacteraemia, with non-users of such combinations as the respective reference groups. Vancomycin combined with penicillin showed an OR = 6.03, 95% CI: 1.57 to 23.19; with aminoglycosides: OR = 4.43, 95% CI: 1.09 to 18.07; with cephalosporins: OR = 6.85, 95% CI: 1.82 to 25.84; and with other antibiotics: OR = 6.85, 95% CI: 1.82 to 25.84. Table 6 shows that the effects of vancomycin combined with the other antibiotics did not differ much from the univariate effect of vancomycin on Gram-negative bacteraemia. In contrast, when

TABLE 6. Effect of vancomycin used in combination with other antibiotics on Gram-negative bacteraemia, with non-users of such combinations as reference groups

Vancomycin in combination with	OR	95% CI
Penicillin	6.03	1.57 to 23.19
Aminoglycosides	4.43	1.09 to 18.07
Cephalosporins	6.85	1.82 to 25.84
Other antibiotics	6.85	1.82 to 25.84

we restricted the data to users of vancomycin only (table 7), there was no effect observed of other antibiotics on the occurrence of Gram-negative bacteraemia, while in non-vancomycin users the effects were similar to those in the

TABLE 7. Results of univariate logistic regression with an indicator for presence of Gram-negative bacteraemia as dependent variable and use of various antibiotics as independent variables, by use of vancomycin and by use of a central venous catheter

Variable	Vancomycin			
	Yes (n=25)		No (n=305)	
	OR	95% CI	OR	95% CI
Vancomycin				
Penicillins	0.73	0.12 to 4.59	1.45	0.81 to 2.60
Aminoglycosides	0.46	0.07 to 2.99	2.20	1.17 to 4.15
Cephalosporins	0.90	0.14 to 5.65	1.56	0.69 to 3.57
Other antibiotics	0.90	0.14 to 5.65	3.35	1.55 to 7.21
Variable	**Central venous catheter**			
	Yes (n=150)		No (n=180)	
	OR	95% CI	OR	95% CI
Vancomycin	5.57	1.72 to 18.04	10.95	2.12 to 56.49
Penicillins	1.27	0.62 to 2.58	1.70	0.75 to 3.86
Aminoglycosides	1.31	0.63 to 2.72	3.36	1.27 to 8.93
Cephalosporins	2.92	1.14 to 7.46	1.37	0.45 to 4.14
Other antibiotics	4.09	1.65 to 10.16	2.77	0.96 to 7.94

overall analysis (see table 2). One indication for use of vancomycin is when a central venous catheter is suspected to be infected. Table 7 also shows the associations between vancomycin and other antibiotics and Gram-negative bacteraemia separately in those who had had a central venous catheter and in those who had not. The overall effect of vancomycin was modified by the presence of a central venous catheter. Of patients who did not have central venous catheters but had Gram-negative bacteraemia (n=44), 38 (82,6%) were immune-compromised in the broadest sense, 3 had a cardiopulmonary diagnosis and 3 had other diagnoses.The overall effect of vancomycin on Gram-negative bacteraemia clearly persisted when restricted to children who had had this indication for vancomycin, but was even stronger among those who had not.

The positive association between vancomycin and Gram-negative bacteraemia might be related to specific routine procedures within wards or with disease severity. Table 8 shows that within paediatric and neonatal intensive care units the associations remained strongly positive, although confidence intervals were wide. In general wards a positive association remained that was close to the univariate effect. Restriction of analyses to those who had ultimately died and those who had not, again yielded associations that were very similar to the univariate effect of vancomycin. None of the other antibiotics was clearly associated with Gram-negative bacteraemia among those who died (data not shown). We further looked at whether specific diagnoses could explain the association between vancomycin use and Gram-negative bacteraemia. When diagnosis was entered as a confounder in the model, we found OR = 13.88, 95% CI: 4.36 to 44.13 for vancomycin use. Gram-negative bacteraemia was more common with some diagnoses than others. Compared with cardiologic, pulmonic, neurologic diagnoses and congenital malformations, diagnoses in the fields of infectiology, hematology/oncology, gastro-enterology, neonatology and

nephrology had a much higher chance of Gram-negative bacteraemia (OR = 6.71, 95% CI: 3.10 to 14.52) (table 1). When we used an arbitrary cut of point of diagnoses with more than or lower than 50% Gram-negative bacteraemia, the effects of vancomycin were in the same positive direction and possibly stronger among diagnoses with lower prevalence of Gram-negative bacteraemia (table 8). Similar findings were obtained when diagnoses were grouped as immunocompromised, cardiopulmonary and other (data not shown).

TABLE 8. Results of univariate logistic regression with an indicator for presence of Gram-negative bacteraemia as dependent variable and use of vancomycin as independent variable, by ward, vital status, and diagnosis

Variable	N	OR	95% CI
Ward			
Intensive care	61	13.05	1.46 to 116.98
Neonatal intensive care	131	14.10	1.64 to 121.20
General wards	138	5.20	1.43 to 18.91
Vital status			
Dead	53	6.48	0.75 to 55.80
Alive	277	6.59	2.17 to 20.02
Relative frequency of Gram-negative bacteraemia			
> 50% (diagnoses infection, hematology/oncology, gastro-enterology, neonatology, nephrology)	235	8.91	2.50 to 31.73
< 50% (diagnoses cardiology, pulmonology, congenital disease, neurology)	90	26.33	4.34 to 159.74

Discussion

In our study on clinical risk indicators for Gram-negative bacteraemia we found positive associations between use of antibiotics, other drugs and indicators of intensity of care. Our study shows an strong positive and independent association between the empirical use of vancomycin and the existence of Gram-negative bacteraemia.
Before further interpreting our data, some methodological issues concerning our study need to be addressed. Using bacteriologic registry data we obtained solid outcome data in which it is very unlikely that misclassification has occurred. The original intent of this study was to identify risk indicators for Gram-negative bacteraemia from which an easily usable clinical risk score could be constructed. This to some extent directed the way in which exposure data were collected. Assessment of risk indicators was performed in retrospect. As exposure assessment from medical files could not be blinded for the bacteriologic outcome we chose to use those categories (yes/no) that were least vulnerable to interpretation. There was much variation in patient characteristics and medical backgrounds, but the most important factors were collected. Given the original goals of the study data collected about antibiotics were confined to their use or not. We did not gather data on Gram-positive bacteraemia, as we consider negative blood cultures the optimal reference group given our research question. We used, only those risk indicators that were noted in patients' charts prior to the physician's knowledge of the results of blood cultures. With respect to antibiotics this means that the present results pertain only to their empiric use.
In our analyses, we attempted to assess, whether the association between vancomycin use and Gram-negative bacteraemia was genuine or biased.[10] Use of vancomycin showed the highest positive association with Gram-negative bacteraemia and it was the only antibiotic that remained positively associated with Gram-negative bacteraemia in a

multivariate analysis. The univariate positive associations between the other antibiotics and Gram-negative bacteraemia might be explained by the fact that they were prescribed for suspected Gram-negative bacteraemia. The finding with vancomycin, however, is surprising because vancomycin is not indicated for Gram-negative bacteraemia.[11] One explanation might be that vancomycin is empirically used in combination with other antibiotics as broad antibiotic coverage for suspected bacteraemia. A positive association for vancomycin might then just be the result of being combined with another antibiotic used because of suspicion of Gram-negative bacteraemia. However, this effect persisted when we analysed in only those who used other antibiotics. Overall, taken into account that some of these restrictions yielded small numbers of patients, there was a consistent tendency for positive associations between vancomycin and Gram-negative bacteraemia within users of other antibiotics. Similarly, vancomycin combined with each of the other antibiotics showed clear positive associations, while among those using vancomycin other antibiotics were not associated with Gram-negative bacteraemia. Although the analysis was based on small numbers of patients, this may indicate that the positive associations found with antibiotic combinations including vancomycin were largely due to the exclusive effect of vancomycin.

Another explanation might be that vancomycin was used for specific indications such as a central venous catheter. If vancomycin is (routinely) used as empiric antibiotic coverage with central venous catheters, one might find a spurious association between vancomycin and Gram-negative bacteraemia. This would in fact only be due to severe infectious disease, predominantly caused by Gram-negative bacteria, inducing the use of central venous catheters, in turn inducing the use of vancomycin. However, the association between vancomycin use and Gram-negative bacteraemia was even stronger when restricted to children without central

venous catheters than in children with central venous catheters. This is an argument against such a spurious association.

The patients in our study had rather different backgrounds. One might argue that the association between vancomycin and Gram-negative bacteraemia has to do with that heterogeneity. It is conceivable that this association is induced by specific routinely performed prescriptions or procedures among specific groups of children. However, our analysis indicated that the association held within specific wards and within categories indicating severeness of disease (e.g., those who died and those who did not). Although Gram-negative bacteraemia was more frequent with some diagnoses than others, our results do not indicate that diagnosis was a confounder. The association seemed even stronger with diagnoses in which Gram-negative bacteraemia is least frequent (table 7).

Another possible confounding factor could be exposure time defined as the time between admission and infection. Longer exposure time might be associated with an increased risk of getting vancomycin prescribed as well as with more severe disease such as Gram-negative bacteraemia. However, there was no relation between exposure time and Gram-negative bacteraemia. A model with vancomycin and exposure time as independent variables did not alter the odds ratio for vancomycin as compared with the univariate model with vancomycin.

The existence of an association between empiric use of vancomycin and the occurrence of Gram-negative bacteraemia has been the subject of previous studies, although data are very scarce and we have not found data in the literature that would provide a definite answer in either direction. Antecedent administration of antibiotics and number of ICU admissions are associated with colonization by Gram-negative bacilli.[12] Ideally, in order to find a causal relation between use of vancomycin and Gram-negative bacteraemia, one would use

a design in which empiric use of vancomycin would be random allocated to children suspected of bacteraemia. In a retrospective study on the effects of empirical use of vancomycin paste in oncology patients such an association was found to be absent.[13] However, in one trial in febrile neutropenic children with cancer a randomized comparison of vancomycin versus amikacin was made, in which vancomycin use was associated, although not statistically significant, with increased frequency of secondary Gram-negative bacteraemia.[14] Another trial in 747 febrile granulocytopenic adult patients with cancer in which vancomycin was added to empiric combination antibiotic therapy no significant difference occurred between these groups.[15] There has to our knowledge been no later reporting of such an adverse effect of vancomycin, one reason perhaps being that most randomised studies with vancomycin did not pertain to its empiric use.[16-18] Our study is in agreement with the finding of Viscoli et al.[14] We feel that the association between empiric vancomycin use and Gram-negative bacteraemia may well be genuine and causal as it is quite strong and consistent and insensitive to various adjustments and restrictions in the dataanalysis. While emerging resistance against vancomycin is a very important problem in itself,[19-22] our data additionally indicate Gram-negative bacteraemia to be an important adverse consequence of its empiric use. Our results should be confirmed in larger randomized prospective studies. Meanwhile, one could justify particular caution in of empirical use of vancomycin.

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General discussion

Since their discovery antibiotics have considerably changed the epidemiology and prognosis of bacterial infectious diseases. Complications of frequent bacterial infections such as otitis media have become uncommon and the mortality and morbidity of severe infections as meningitis and osteomyelitis have been reduced dramatically. Antibiotics were considered miracle drugs during the second half of this century and the number of new agents that has been developed in the decades following the discovery of penicillin is striking.

Antibiotics are among the most frequently prescribed drugs, in adults as well as in children.[1] Soon after their introduction in clinical practice, it was recognised that antibiotics were overused and misused.[2] Studies in hospitals show that in more than half of the cases for which antibiotics are prescribed there was no need for the prescription, an inappropriate agent was chosen or the dose was incorrect.[3] Antibiotics account for up to 50% of the pharmacy budget in some hospitals. The rising costs of health care together with the governmental urgency in most countries to reduce or control these costs make it necessary to rationalise antimicrobial related expenditure. Therefore it is necessary to increase our knowledge concerning the actual use of antibiotics, the associated costs and the prescribing behaviour of doctors.

Until now limited information is available on the use of antibiotics in children. Only a small number of studies have reported on the use of antibiotics in paediatrics. The most commonly used parameter for use of antibiotics in adults, the Daily Defined Doses, has been described only once for a paediatric population.[4] A combination of other more indirect variables is used more often.[5-12] Not much attention has been paid to the costs of antibiotics in relation to prescribing patterns.[13] The studies mentioned in this thesis are focused on these aspects of the use of antibiotics in paediatrics.

We presented the first study of antibiotic expenditure in a children's hospital. It shows that a rough analysis of costs of antibiotics results is an incomplete view of the real antibiotic expenditure. The reason is that in the interpretation of these costs are not included detailed specifications of costs of antibiotics related to generic class, changes in retail price, changes in patient characteristics, or changes in hospital policies regarding formularies. Increasing costs in health care could be linked to the use of more expensive antibiotics.

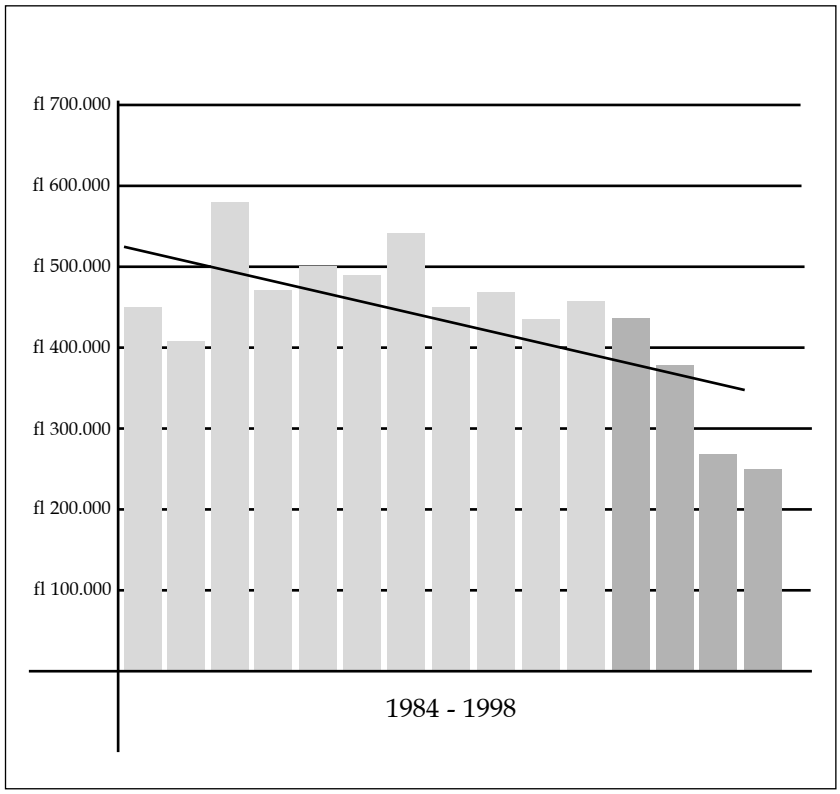

FIGURE 1. Antibiotic expenditure in Beatrix Children's Hospital (1984 - 1998).

Disclosure on itself of antibiotic-related expenditures resulted in a decrease in antibiotic expenditure over the years of the study (figure 1). Directing the attention of doctors towards their prescription attitudes, even without directly requiring a change in attitude during our study probably caused this beneficial effect.

Next to analysis of the antibiotic costs a detailed description of the actual use of antibiotics in daily practice in paediatrics was carried out. Results as percentage of antibiotic use, division of antibiotic prescription as described in the literature were confirmed by our data. Mostly antibiotics were prescribed on an empirical basis, without convincing evidence to confirm the diagnosis of a bacterial infection. It is possible that in a number of cases antibiotics would have been discontinued earlier or would not have been given at all if more accurate diagnostic procedures had been available to prove a bacterial infection. However, sometimes it is legitimate to start empirical antibiotic therapy in unproven but suspected bacterial diseases in childhood, e.g. in febrile infants less than 3 months old, or children with meningitis and a negative Gram-stain of the cerebrospinal fluid.

As suspected we found a lack of uniformity in prescribing antibiotics by several groups of paediatricians. After the introduction of an authorised formulary, in which the empiric treatment of the most common infectious diseases in paediatrics are described, a significant increase of uniformity in prescribing behaviour was found as well as a more corresponding therapy with the formulary (table 1). However, a strictly enforced formulary is only one possible successful strategy. Other strategies to improve the prescribing patterns of antibiotics probably resulting in significant savings and in a significant impact on a physician's prescribing patterns are for example the use of a separate antibiotic order form, implementation of strict guidelines according to diagnostic algorithms, or computer-assisted antimicrobial therapy. Next to this continuing education in antibiotics and its consequences

TABLE 1. Number of chosen antibiotic classes for each case, with in parentheses, the number of respondents for the particular case

The first column was before introduction of the formulary, the next columns after introduction of the formulary. The following antibiotic classes were defined: penicillins, cephalosporins, aminoglycosides, sulphonamides, vancomycin, quinolones, metronidazole, and all different combinations of these individual classes. And the percentages of chosen therapy corresponding with the therapy named in the introduced formulary.

Case number and description	Paediatricians and residents		Same therapy as in formulary
	Before (n = 50)	After (n = 29)	After
1. a child of three weeks old with bacterial meningitis	15 (45)	4 (24)	71%
2. a four year old girl with a clinically and radiologically proven bacterial pneumonia	8 (47)	2 (22)	91%
3. a seven year old boy with sinusitis	5 (44)	2 (22)	86%
4. a five year old girl with pyelonefritis	12 (43)	3 (22)	86%
5. a four year old child with bilateral otitis media	3 (47)	3 (23)	61%
6. a premature infant, with respiratory distress and sepsis	20 (45)	3 (22)	82%
7. a twelve year old girl with high fever, hypotension, tachycardia and bloody diarrhoea	18 (36)	5 (16)	17%
8. an eight year old boy with osteomyelitis of the ankle	10 (43)	4 (21)	67%
9. an eight year old girl with atypical pneumonia	6 (43)	1 (23)	65%
10. a three year old girl with bacterial meningitis	12 (47)	2 (22)	86%
11. a four year old girl with endocarditis	17 (30)	2 (12)	92%
12. a two year old girl with infected eczema	8 (41)	3 (18)	33%
13. a nine year old boy with septic arthritis	10 (36)	4 (15)	7%

is of great importance.[14-17] Further research on the success of different programs in optimising antibiotic therapy, while safeguarding patient outcome, and curtailing the antibiotic budget is warranted.

Another very important problem related at least partially to inappropriate prescription of antibiotics is the emergence of resistance. Antibiotics not only exert a therapeutic effect but also alter the ecology of the microflora of the body and the environment.[18] The development of resistant micro-organisms was recognised by Paul Ehrlich as a potential problem during his early studies of organic arsenicals almost 100 years ago.[2] Multiple-drug-resistant micro-organisms derived through the transfer among species of plasmids or transduction by bacteriophages are an amplification of this problem. A causal relationship between antibiotic usage and development of resistance of micro-organisms in hospitals has been suggested on the basis of consistent associations of the emergence of resistant strains with concurrent variations in antibiotic use in populations over time.[19] Several groups have presented evidence that control of antibiotic use can result in reversal of the bacterial population to sensitive micro-organisms.[20-22] However Toltzis indicated that antibiotic restriction policies in an ICU failed to diminish the size of the endemic reservoir of antibiotic-resistant Gram-negative rods, and suggested that such policies in the absence of broader efforts to limit antibiotic use will have little impact.[23] Other important issues like the widespread use of antibiotics in the community and veterinary exposure of antibiotics in livestock will need to be addressed simultaneously.

Although the initial aim of this study was to decrease the rate of emergence of resistance it was impossible to measure this in the available time-frame. Moreover, a lack of uniformity in defining resistance, variations in susceptibility test methods (and interpretation of the results), potential study selection biases, and variations in infection control measures in the hospital were confounding variables.[24]

As we all know and described before an important and causing relationship exists between antibiotic use and antibiotic resistance. Therefore we performed a study to discover risk factors in the development of Gram-negative bacteraemia, on of the life threatening symptoms in paediatrics. This study shows an unexpectedly strong positive and independent association between the empirical use of vancomycin and the existence of Gram-negative bacteraemia. (Chapter 6) This is surprising because vancomycin is not indicated for Gram-negative bacteraemia. Selective antibiotic pressure against Gram-positive micro-organisms could cause a shift in colonisation resistance favouring the multiplication and translocation of Gram-negative micro-organisms. This study demonstrated unexpected epidemiological phenomena connected with the use of broad-spectrum antibiotic therapy in the hospital.

In conclusion antibiotics are responsible for a high percentage of the health care costs.[3] About 35% of all hospitalised patients receive one or even more courses of antibiotics during their admission. This could be shown for adults as well as for the paediatric population.[5-7,25-28] Until now only a few studies have been performed concerning use of antibiotics in a paediatric population. To our knowledge this thesis is the first collection of studies concerning most aspects of the use of antibiotics and prescribing behaviour in paediatrics. As shown in this study saving money by using less expensive drugs, a higher uniformity in prescribing behaviour, a more rational use of antibiotics and getting people aware of the emergence of resistance could be the result. Most important and most difficult is to get doctors aware of the consequences of antibiotic use and misuse.[3,29,30] In order to improve antibiotic prescribing a more strict and more uniform policy is warranted. This policy should be based on local sensitivity patterns and should be revised regularly. Some recently performed studies showed an association between the prior use of antibiotics and the development of resistance.[31-34]

Because of these emergent threats it is necessary to be informed continuously about the use of antibiotics in the hospital. This monitoring of antibiotic use should be associated with continuous feedback and education of each prescribing doctor. Infectious disease specialists, medical microbiologists, pharmacists or ideally a combination of these professionals should be made responsible for these tasks. A decrease in health care costs and especially a diminishing of antibiotic expenditure will only be attained by continuous monitoring antibiotic usage, and antibiotic-related costs, and increasing awareness of prescribers of these results. Several intervention strategies could be used to change the prescribing behaviour of doctors.[35,36] According to the literature effective change strategies were reminders, patient-mediated interventions, outreach visits, sessions with opinion leaders, and multifaceted activities. Audit with feedback and educational materials were less effective and formal Continuous Medication Education conferences or activities, without enabling or practice-reinforcing strategies, had relatively little impact.[36] Studies with these different methods should be performed to come to the best solution for changing prescribing behaviour of doctors and streamlining antibiotic therapy. It would be wise and more effective to make plans on a regional, national or even international level. For the future the most important problem is the emergence of resistance. Antimicrobial resistance results in increased morbidity, mortality, and costs of health care. Several societies have described guidelines or statements for the prevention of antimicrobial resistance.[37-39] Again appropriate antimicrobial stewardship that includes optimal selection, dose, and duration of treatment, as well as control of antibiotic use will be of paramount importance.[37] A multidisciplinary, system-oriented approach, catalysed by hospital leadership or even by governmental leadership, is required to address this urgent problem.[38] For example in the Netherlands an Antibiotic Policy Foundation called Stichting Werkgroep Antibiotica Beleid (SWAB) is founded to optimize

antibiotic therapy in the Netherlands.[40] One of the SWAB projects is the development of national guidelines for the use of antibiotics in hospitals.[40-43] These guidelines are prepared by a committee of experts and reviewed by external consultants: infectious disease specialists, medical microbiologists and pharmacists. The SWAB hopes that these guidelines will make the prevention of antibiotic resistance a major factor in the choice of the antibiotic. Streamlining antibiotic therapy is an important tool in this respect. These are important challenges at the beginning of the 21st century. In this century more research should be performed in antibiotic use and its possible consequences for all medical specialties using or prescribing antibiotics during a continuous period.

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Summary of the studies

Since the introduction of penicillins in 1941 these drugs had been used increasingly over the ensuing years. In paediatrics antibiotics are of the most frequently prescribed drugs and widespread misuse has been described. Nowadays we are dealing with large problems of rising expenditures and the emergence of antibiotic resistance. Several professional organizations promote a more prudent overall use of antibiotics. One of the responsible factors is the prescribing by doctors.
We wanted to know how doctors are prescribing antibiotics in our paediatric hospital. A higher uniformity in antibiotic prescribing could result in a decrease in antibiotic expenditures and after all could possible block the further development of resistance.
Therefore we started in 1995 a research project concerning antibiotic use in paediatrics. Several methods are available to get the necessary information.

Chapter one contains a concise review of the literature including definitions of the major problems of the use of antibiotics in paediatrics. After a detailed description of the use, overuse and abuse of antibiotics more emphasis was put on the relation between prescribing and development of resistance. Finally some possible strategies for the future were disclosed. We focused on the necessity to implement these strategies very soon in order to have a reasonable chance to slow the pace with which we are moving towards the post-antibiotic era.

In **chapter two** a study is presented concerning the use of antibiotics by means of analysing the total antibiotic expenditure during the study period. Over a 10-year period

we analysed antibiotic costs by using pharmacy surveys of antibiotic costs and prescriptions. No increase in costs was found but a dramatic shift in antibiotic prescription patterns was observed, although the total antibiotic expenditure did not increase significantly. A remarkable shift occurred from the use of less expensive penicillins to newer, resistance-inducing and more expensive cephalosporins and vancomycin. This could not be explained by shifts in resistance patterns of isolated micro-organisms. A remarkable increase in the number of admissions or hospitalization days did not occur, although a shift to a higher intensity of medical care could not be ruled out.
The total cost of antibiotics is often used by hospital boards to monitor budgets and motivate personnel for a change in prescribing attitudes. It is shown here that due to several factors as marketing techniques and price cuts, this parameter is useless for monitoring antibiotic use in the hospital. It is necessary to study prescription patterns of antibiotics over several years, in order to study clinically, economically and microbiologically important shifts and relate these prescription patterns to shifts in the patient populations. More accurate indicators as Daily Defined Doses per 1000 hospital days should be used, but this parameter is only practical in adult medicine. To our knowledge until now no equivalent accurate parameter exists for children.

In **chapter three** a study is presented in which we analysed the lack of uniformity in empiric antibiotic therapy between paediatricians end paediatric residents. Which we assessed with the help of questionnaires with 13 clear clinical cases. Considerable variability was found in empiric antibiotic therapy between paediatricians and paediatric residents in the northern part of the Netherlands. This variability was evident for selected generic classes of antibiotics as well as for dose and duration of therapy. Highest variability was found in infections of the central nervous system and lowest variability

in respiratory tract infections. In literature more agreement could be found in the therapy of central nervous system infections and less agreement in treatment of children with respiratory tract infections. For the purpose of this study we were mostly interested in the agreement between doctors within one hospital and less in the scientifically correct choice of antibiotics. We conclude that in order to optimise patient care, to achieve a reduction in health care costs and to reduce the emergence of drug resistance, antibiotics should be used rationally. Therefore an urgent need for a more appropriate selection and use of antibiotics exists. Clear formularies are warranted for optimal clinical decision making resulting in the choice of the best available product at an adequate dose for an reasonable period of time. The formulary should be based on the knowledge of local trends in antimicrobial resistance. Enforcing the guidelines of the formulary should be accompanied by a continuous commitment of all prescribers. Finally a feedback system in which infectious disease specialists and hospital epidemiologists should have a central role.

In **chapter four** we presented a study concerning the use of antibiotics in a paediatric university hospital. A high percentage (35%) of all hospitalised children received antibiotics. Over 50% of all antibiotic prescriptions were started on an empirical basis, without confirmation of a bacterial infection. Especially children admitted to intensive care units and young children are at risk of receiving multiple courses of antibiotics. In this study attention was focused on the characteristics of the population receiving antibiotics. Moreover the indication of antibiotic prescription was studied. Our results are comparable with data found in studies reported in the literature, performed more than 15 years ago. Until now no studies have been published on the difference of antibiotic prescriptions on different paediatric units. In our study a significant difference could be found in percentage of

antibiotic prescriptions and the route of administration (more intravenous antibiotics in the Intensive Care unit) for children admitted to the intensive care unit compared with patients admitted on the medium care. Likewise a significant difference in number of antibiotic courses could be found between the former and latter group. The highest number of antibiotic prescriptions was made for children in the youngest age group (between 0 and 2 years). No uniformity in dose and duration of antibiotic therapy was found. Overall we may conclude that over the study period a shift to the use of more expensive and broader spectrum antibiotics was seen for all groups. In order to improve antibiotic prescribing in a hospital a more strict and more uniform policy is warranted. This policy should be based on local sensitivity patterns and should be revised yearly.

In **chapter five** we presented the results of a study concerning the prescribing pattern and the acquaintance of doctors of antibiotics. It was important to know if the daily use of antibiotics agreed with the prescription patterns of doctors and their knowledge of antibiotics. These items were studied by using a semi-structured interview for thirty paediatricians. Next to this we analysed the consequences of the introduction of an antibiotic formulary on the uniformity in antibiotic prescribing. Two months after the introduction of an authorised antibiotic formulary analyses were performed to get informed about the presence of uniformity in prescribing behaviour of paediatricians and the use of antibiotics in daily clinical practice in a paediatric university hospital. These data were compared with data found in earlier studies (as described in chapter 3 and 4). A remarkable shift towards more uniformity in theoretical prescribing behaviour could be found. On the other hand this could not be confirmed with the results found for antibiotic use in daily clinical practice. Almost the same data were found as presented in earlier studies. Another remarkable finding was the level of

acquaintance with 11 most commonly prescribed or used antibiotics. This analysis showed that a very high percentage of prescribing paediatricians was not familiar with most important items of most commonly prescribed antibiotics in current practice. The conclusion of this chapter was the introduction of an authorised antibiotic formulary solely is not enough to achieve a significant change in antibiotic prescribing behaviour in a hospital although it can induce a learning effect. It should always be accompanied with continuous feedback and ongoing education programs about antibiotics and its possible consequences.

After we studied the antibiotic costs, uniformity in antibiotic prescribing pattern and the use of antibiotics in daily practice, before and after the introduction of an antibiotic formulary, we wanted to get informed about the emergence of resistance. The duration of the research project made an extensive analysis of data concerning resistance impossible. It is commonly known that there is an important relationship between the use of antibiotics and the development of resistance. Therefore we presented in **chapter six** a study on clinical risk indicators for the development of Gram-negative bacteraemia. Gram-negative bacteraemia is a severe symptom presenting in children and always leading to the use of antibiotics. Positive associations between on the one hand use of antibiotics, other drugs and indicators of intensity of care and on the other hand the risk for Gram-negative bacteraemia could be found. This study shows an unexpectedly strong positive and independent association between the empirical use of vancomycin and the existence of Gram-negative bacteraemia.
The original intent of this study was to obtain risk indicators for Gram-negative bacteraemia from which an easily usable clinical risk score can be constructed. Assessment of risk indicators was performed in retrospect. In our analyses, we have attempted to assess, within the limits of our data, whether the association between vancomycin use and Gram-

negative bacteraemia was genuine or biased. Use of vancomycin showed the highest positive association with Gram-negative bacteraemia and it was the only antibiotic that remained positively associated with Gram-negative bacteraemia in a multivariate analysis. Although based on small numbers of patients, this may indicate that the positive associations found with antibiotic combinations including vancomycin are largely due to the exclusive effect of vancomycin.
Ideally, in order to find a causal relation between use of vancomycin and Gram-negative bacteraemia, one would use a design in which empirical use of vancomycin would be randomly allocated to children suspected of bacteraemia. Although our results should ideally be confirmed in larger randomised studies, it is felt that they justify particular caution in case of empirical use of vancomycin.
In conclusion, we find that among children suspected of bacteraemia there are several drugs and clinical procedures that indicate increased risk of Gram-negative bacteraemia. Empirical use of vancomycin is strongly and independently associated with Gram-negative bacteraemia, while its use is not indicated for Gram-negative micro-organisms. Our study indicates that the safety of using vancomycin solely on the basis of suspicion of bacteraemia in children may not be warranted.

This thesis has tried to give an overview of important aspects in the use of antibiotics in paediatrics and its possible consequences for now and the future.
For the future, further research could be performed for the in our study analysed data (antibiotic expenditure, presence of uniformity, use of antibiotics in daily practice and development of resistance). Not only in the department of paediatrics, but for each specialism, in which antibiotics were used and prescribed. It should be performed
during a long period because a continuing registration and

analysis is necessary as illustrated in this thesis.
The use of vancomycin and the entity as risk factor for the development of a Gram-negative bacteraemia gave rise to the performance of a lot of new research. At first the reproducibility in the current clinic and other clinics. Another possibility is to try to rebuild the situation in an animal, as a method for testing our hypothesis.
These and other research possibilities could learn us more about the use of antibiotics, the possible consequences and how to deal with these consequences in the future.

Nederlandstalige samenvatting
voor de niet-geneeskundige lezer

Sinds de introductie van antibiotica in het begin van de jaren dertig wordt er op grote schaal gebruik van gemaakt. Al sinds jaar en dag hebben antibiotica een geweldige reputatie; in de afgelopen halve eeuw hebben deze middelen veel levens gespaard en aan veel mensen de gezondheid teruggegeven. Binnen de kindergeneeskunde is het een van de meest voorgeschreven medicijnen. Diverse in het verleden uitgevoerde studies lieten zien dat ongeveer 35% van de in het ziekenhuis opgenomen kinderen antibiotica kregen voorgeschreven.
Echter door het enorme en veelal onjuiste gebruik is het nu helaas steeds meer de beurt aan de bacterie. Vandaag de dag zijn infecties steeds moeilijker te behandelen, wat eens een droom was, is nu tot een nachtmerrie geworden, steeds meer bacteriën worden ongevoelig voor bepaalde antibiotica en dat terwijl er geen nieuwe antibiotica ontwikkeld worden en we dit de komende 10 jaar ook niet hoeven te verwachten. Naast beschreven wereldwijde problematiek maakt ook de kostenstijging en gebrek aan uniformiteit in voorschrijfgedrag het van essentieel belang om rationeler en zorgvuldiger gebruik te maken van antibiotica. Vanuit diverse professionele organisaties wordt dit al reeds enige jaren gestimuleerd. Ook binnen onze kliniek werd het belang hiervan en de noodzaak hiertoe duidelijk.
Dit was een reden om in 1995 van start te gaan met een onderzoeksproject naar het antibioticabeleid in de Beatrix Kinderkliniek te Groningen.
De gedachte bestaat, dat een verbetering van het antibioticumbeleid zich zou moeten richten op een uniformer voorschrijfgedrag, waardoor de kosten voor antibioticagebruik beperkt kunnen worden en de resistentieontwikkeling in de hand te houden. Deze gedachten en bijbehorende

uitwerkingen worden beschreven in dit proefschrift en zullen hieronder per hoofdstuk uitgelegd worden.

Hoofdstuk één bevat een volledig overzicht van de literatuur inclusief definities van de belangrijkste problemen van het gebruik van antibiotica en de mogelijke oplossingen.
Na een gedetailleerde beschrijving van het gebruik, overgebruik en misbruik van antibiotica wordt meer aandacht besteed aan de relatie tussen voorschrijfgedrag en ontwikkeling van resistentie. Tenslotte worden enkele mogelijke strategieën, als een verlaging van de antibioticakosten, verhoging van de uniformiteit in voorschrijfgedrag en een beperking van de resistentie ontwikkeling uit de doeken gedaan. De noodzaak wordt uitgesproken om deze mogelijke strategieën spoedig te implementeren om op deze manier een redelijke kans te maken om het tempo te vertragen waarmee we richting het postantibiotische tijdperk gaan, waarin we uiteindelijk de infectieziekten niet meer kunnen behandelen met de voorheen beschikbare en gebruikelijke antibiotica.

In **hoofdstuk twee** wordt de eerste studie gepresenteerd. Om inzicht te krijgen in het antibioticagebruik en de daarmee gepaard gaande kosten zal een analyse hiervan moeten plaatsvinden. Om kostenverlaging te bereiken is allereerst inzicht nodig in de huidige antibioticakosten. Het gebruik van antibiotica over de periode 1984-1994 in de Kinderkliniek wordt weergegeven door het analyseren van de totale antibioticakosten middels gegevens van de apotheek over deze periode.
Een opvallende verschuiving vond plaats van het gebruik van minder dure penicillines naar de nieuwere, meer resistentie inducerende en duurdere cefalosporines en vancomycine. Deze verschuiving kon niet verklaard worden door een verschuiving in resistentiepatronen van de geïsoleerde micro-organismen. Ook was er niet een enorme stijging in het aantal

opnames of opname dagen opgetreden, alhoewel een verschuiving naar een intensievere zorg niet uitgesloten kon worden. Ondanks deze verschuiving in het voorschrijfpatroon van antibiotica waren de totale kosten niet gestegen. De totale kosten van het antibioticagebruik worden vaak door het ziekenhuisbestuur gebruikt om budgetten te beoordelen en personeel te motiveren voor een verandering in voorschrijfgedrag. Er kon aangetoond worden, dat door verschillende factoren als marketing technieken en prijsverlagingen, deze parameter niet te gebruiken is voor het beoordelen van antibioticagebruik in het ziekenhuis. Het is nodig om gedetailleerde voorschrijfpatronen van antibiotica over verloop van enkele jaren te bestuderen, om klinisch, economisch en microbiologisch belangrijke verschuivingen te bestuderen en deze voorschrijfpatronen te relateren aan verschuivingen in patiënten populaties. Nauwkeuriger indicatoren als Daily Defined Doses (DDD, een internationaal gestandaardiseerde dagelijks dosis voor ieder antibiotica) per 1000 opnamedagen zouden gebruikt moeten worden maar deze parameter is alleen praktisch in de geneeskunde voor volwassenen omdat in de kindergeneeskunde op lichaamsgewicht wordt gedoseerd. Voor zover we hebben kunnen nagaan bestaat tot op heden nog geen gelijkwaardig nauwkeurige parameter voor kinderen.

In **hoofdstuk drie** wordt een studie gepresenteerd, waarin de aan- of afwezigheid in uniformiteit in empirische antibiotica therapie tussen kinderartsen en assistenten in de kindergeneeskunde wordt bestudeerd. (Onder empirische antibiotica keuze wordt verstaan, er bestaat een verdenking op een bepaalde ziekte maar dit kan niet bevestigd worden middels aanvullende diagnostiek of microbiologische kweken) De uniformiteit in antibioticakeuze wordt bestudeerd middels een enquête met dertien duidelijke en meest voorkomende ziektebeelden in de kindergeneeskunde. Na analyse van de resultaten valt een grote variabiliteit op in empirische

antibiotica therapie tussen kinderartsen en assistenten in het noordelijk deel van Nederland. Deze variabiliteit was duidelijk voor de geselecteerde generische klassen van antibiotica, evenals voor de dosis en duur van de therapie. De grootste variabiliteit werd gevonden voor centraal zenuw stelsel infecties en de minste variabiliteit voor luchtweginfecties, alhoewel in de literatuur juist meer overeenstemming gevonden werd in therapie van centraal zenuw stelsel infecties en minder overeenstemming in de behandeling van kinderen met luchtweginfecties. Voor het doel van deze studie waren we het meest geïnteresseerd in de overeenstemming tussen dokters binnen een ziekenhuis en minder in de wetenschappelijk juiste keuze van antibiotica. We kunnen concluderen dat om patiëntenzorg te optimaliseren, tot een reductie in de kosten voor de gezondheidszorg te komen en om de verdere ontwikkeling van resistentie te beperken, antibiotica rationeel gebruikt moeten worden. Daarom bestaat er een dringende behoefte aan een uniformere selectie en gebruik van antibiotica. Duidelijke formularia zijn noodzakelijk voor een optimale klinische beleidsbepaling, die resulteert in de keuze van het best beschikbare product in een adequate dosis voor een redelijke duur van therapie. Het formularium zou gebaseerd moeten zijn op de kennis van lokale trends in antimicrobiële resistentie. Om de richtlijnen van het formularium kracht bij te zetten moet de introductie van een formularium samen gaan met een continue educatie van alle voorschrijvers. Ten slotte zal een feedback systeem nodig zijn tijdens het voorschrijven van antibiotica, waarin artsen gespecialiseerd in infectieziekten en ziekenhuisepidemiologen een centrale rol innemen.

In **hoofdstuk vier** presenteren we een studie, die over het gebruik van antibiotica in de dagelijkse praktijk gaat. Een hoog percentage (35%) van alle opgenomen kinderen ontvangt antibiotica. Meer dan 50% van alle antibiotica voorschriften wordt gestart op een empirische basis. Er bestaat een klinische

verdenking op een infectie maar dit wordt niet bevestigd middels aanvullende diagnostiek of kweken. In het bijzonder kinderen die opgenomen worden op Intensive Care afdelingen, en jonge kinderen hebben een grote kans om meerdere antibiotica kuren te krijgen gedurende de opname. In deze studie was de aandacht gericht op de karakteristieken van de kinderen, die antibiotica ontvingen. Daarnaast hebben we de indicatie van antibiotica prescriptie bestudeerd. Onze resultaten zijn vergelijkbaar met data gevonden in studies, die meer dan 15 jaar geleden gerapporteerd zijn. Tot op heden zijn geen studies gepubliceerd over het verschil in antibiotica voorschriften en de wijzen van toediening tussen verschillende kindergeneeskundige afdelingen. In onze studie hebben wij een significant verschil gevonden in het percentage antibiotica voorschriften en de wijze van toediening (meer intraveneuze antibiotica op the Intensive Care afdeling) voor kinderen opgenomen op de Intensive Care afdeling vergeleken met patiënten opgenomen op de Medium Care afdeling. Een vergelijkbaar significant verschil in aantal antibiotica kuren kon gevonden worden tussen de eerste en de laatste groep. Het grootst aantal antibiotica voorschriften werd gemaakt voor kinderen in de jongste leeftijdgroep (tussen 0 en 2 jaren). Er bleek geen uniformiteit in dosis en duur van antibiotische therapie te zijn. In het algemeen kunnen we concluderen, dat over de studieperiode een verschuiving naar het gebruik van duurdere en breedspectrum antibiotica werd gevonden voor alle groepen. Om het voorschrijven van antibiotica te verbeteren in een ziekenhuis is een strikter en uniformer beleid van het grootste belang. Dit beleid zal gebaseerd moeten zijn op lokale gevoeligheidspatronen en zal jaarlijks gereviseerd moeten worden.

In **hoofdstuk vijf** presenteren we de resultaten van een studie betreffende het voorschrijfpatroon en het kennisniveau met betrekking tot antibiotica. Dit is van belang om te evalueren of het gebruik van antibiotica in de dagelijkse praktijk

overeenkomt met hetgeen dokters op papier voorschrijven en wat hun kennis van antibiotica is. Daarom hebben we gebruik gemaakt van een semi-gestructureerd interview gehouden bij dertig kinderartsen. Tevens hebben wij geanalyseerd of invoer van een formularium gevolgen had voor eerder beschreven uniformiteit in antibioticagebruik. Twee maanden na de introductie van het formularium werd een analyse verricht naar de aan- of afwezigheid van uniformiteit in voorschrijfgedrag van kinderartsen en het gebruik van antibiotica in de dagelijkse klinische praktijk in een academische kinderafdeling. Deze data werden vergeleken met data gevonden in eerder uitgevoerde studies (als beschreven in hoofdstuk 3 en 4). Een belangrijke verschuiving naar meer uniformiteit in voorschrijfgedrag werd gevonden. De resultaten voor het antibioticagebruik in de dagelijkse klinische praktijk zijn nauwelijks veranderd. Bijna dezelfde resultaten werden gevonden als in eerdere uitgevoerde studie. Een andere opmerkelijke bevinding was het kennisniveau van kinderartsen van 11 veel voorgeschreven of gebruikte antibiotica. Deze analyse toonde, dat een erg hoog percentage van de voorschrijvende kinderartsen niet vertrouwd was met de belangrijkste karakteristieken van de meest voorgeschreven antibiotica in de dagelijkse praktijk. De conclusie van dit hoofdstuk is dan ook, dat de introductie van een antibiotica formularium alleen niet voldoende is om een significante verandering te bereiken in voorschrijfgedrag in een ziekenhuis, alhoewel het een leereffect kan induceren. De introductie of implementatie hiervan zal altijd gepaard moeten gaan met continue feedback bij het voorschrijven van antibiotica en voortdurende bij- en nascholing over antibiotica en de vele mogelijke gevolgen.

Nadat we de kosten, de uniformiteit in voorschrijfgedrag en het gebruik van antibiotica in de dagelijkse klinische praktijk bestudeerd hebben, zowel voor als na de introductie van het formularium, wilden we onze aandacht richten op de

resistentieontwikkeling . De duur van het onderzoek maakte een uitvoerige analyse van resistentie gegevens echter onmogelijk. Bekend is, dat er een belangrijke relatie bestaat tussen antibioticagebruik en resistentieontwikkeling. Dit is er een reden van, dat we in de volgende studie, gepresenteerd in **hoofdstuk zes**, naar klinische risico indicatoren voor het ontwikkelen van een Gram-negatieve bacteriemie (een voorkomen van een bacterie in de bloedbaan gepaard gaande met ernstige ziekteverschijnselen) hebben gekeken. Gram-negatieve bacteriemie is een ernstig symptoom voorkomend bij kinderen en leidt altijd tot het gebruik van antibiotica. Er werden positieve associaties tussen aan de ene kant gebruik van antibiotica, andere medicijnen en indicatoren van intensiteit van zorg en aan de andere kant het voorkomen van Gram-negatieve bacteriemie gevonden. Deze studie laat een onverwachte sterk positieve en onafhankelijke associatie zien tussen het empirisch gebruik van vancomycine en het bestaan van Gram-negatieve bacteriemie.
Hiervoor kunnen we mogelijke verklaringen bedenken, echter deze zijn alle hypothetisch en zullen middels verder onderzoek verder uitgewerkt moeten worden.
De oorspronkelijke opzet van de studie was om risico indicatoren te herkennen voor Gram-negatieve bacteriemie, waarvan een gemakkelijke en bruikbare klinische risico score kan worden geconstrueerd. Het bepalen van risicofactoren werd retrospectief uitgevoerd. In onze analyses hebben we getracht te bepalen - binnen de grenzen van onze data - of de associatie tussen vancomycine gebruik en Gram-negatieve bacteriemie echt was of gebiased. Het gebruik van vancomycine liet een significant positieve associatie met Gram-negatieve bacteriemie zien en het was het enige antibioticum dat positief geassocieerd bleef met Gram-negatieve bacteriemie in een multivariaat analyse. Alhoewel het gebaseerd is op kleine aantallen patiënten, mag dit een aanwijzing zijn, dat de positieve associaties gevonden met antibiotica combinaties inclusief vancomycine grotendeels het

gevolg zijn van het exclusieve effect van vancomycine. Alhoewel onze resultaten idealiter bevestigd zouden moeten worden in grotere, gerandomiseerde studies, is het gerechtvaardigd om te menen dat bijzondere voorzichtigheid in acht genomen moet worden in het geval van empirisch gebruik van vancomycine.
Concluderend, hebben we gevonden dat onder kinderen verdacht van bacteriemie verschillende medicijnen en klinische procedures belangrijk zijn omdat ze een verhoogd risico betekenen voor het ontwikkelen van een Gram-negatieve bacteriemie. Empirisch gebruik van vancomycine is sterk en onafhankelijk geassocieerd met Gram-negatieve bacteriemie, terwijl het gebruik niet geïndiceerd is voor Gram-negatieve micro-organismen. Onze studie toont aan, dat de veiligheid van het gebruik van vancomycine alleen op basis van de verdenking van een bacteriemie bij kinderen niet geoorloofd is.

Dit proefschrift heeft getracht een overzicht te geven van de belangrijkste aspecten van antibioticagebruik in de kindergeneeskunde en de mogelijke gevolgen hiervan voor nu en de toekomst.
In de toekomst zal verder onderzoek gedaan moeten worden naar de in ons onderzoek benoemde parameters (kosten, uniformiteit, dagelijks gebruik en resistentieontwikkeling). Niet alleen binnen de kindergeneeskunde, maar binnen ieder specialisme waar antibiotica wordt gebruikt en voorgeschreven. Dit zal niet voor een korte periode moeten gelden maar er zal sprake moeten zijn van een continue registratie en analyse van deze data. Pas dan zullen we binnen de gezondheidszorg een zo optimaal mogelijk gebruik kunnen maken van de huidige aanwezige antibiotica. Nieuw ontwikkelde antibiotica zullen een duidelijker plaats krijgen, als een ieder ervan overtuigd is zorgvuldig ermee om te gaan. Het gebruik van vancomycine en de entiteit als risicofactor voor het ontwikkelen van een Gram-negatieve bacteriemie geeft aanleiding tot het verrichten van tal van onderzoeken.

Allereerst of we deze data kunnen reproduceren binnen een andere kliniek. Daarnaast of we in diermodel een zelfde situatie kunnen nabootsen. Mogelijk dat we hierdoor een van de mogelijke hypothesen kunnen bevestigen. Waarin gesteld wordt dat er een vermindering van de kolonisatie met Gram-positieven door vancomycine optreedt waardoor Gram-negatieven zich op darm niveau versterken en vervolgens in de bloedbaan voorkomen en zich vermeerderen.
Deze en andere onderzoeksmogelijkheden zullen ons meer leren over het gebruik van antibiotica en de mogelijke gevolgen voor de toekomst en hoe met deze gevolgen om te gaan.

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